CSA296844

Organizacion CSA Ltda

1/4

RF

Industria y Comercio

SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
INVENTARIO
04

Delegatura de Propiedad Industrial

División de Nuevas Creciones

PCT

SOLICITUD
PATENTE DE INVENCIÓN

21. **EXPEDIENTE No.** 09-418

54. **TÍTULO** Activadores Novedosos de Glucocinasa y metodos de Uso de los mismos.

51. **CLASIFICACIÓN INTERNACIONAL**

71. **SOLICITANTE** Bristol-Myers SQUIBB COMPANY

DOMICILIO ESTADOS UNIDOS DE AMERICA

74. **APODERADO** ALVARO CORREA ORDOÑEZ
C.C. 79.143.366 de USAQUEN

22. **BOGOTÁ, D. C.,**

FV: 06-02-2009

FORMA P-10)

PETITORIO

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 09-000418- -00000-0000
Fecha: 2009-01-05 16:46:19 Dep: 2020 NUECREACIONI
Tra: 11 PATENTEIYII Eve: 378 FASENACIONALI
Act: 411 PRESENTACION Folios: 849

Industria y Comercio
SUPERINTENDENCIA

FORMULARIO ÚNICO DE SOLICITUD DE PATENTE
PCT
ENTRADA EN FASE NACIONAL

(1) SOLICITUD DE :

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

(2) SOLICITANTE (71)

Nombre: **BRISTOL-MYERS SQUIBB COMPANY**

Dirección: P.O. Box 4000, Route 206 and ProvinceLine Road, Princeton, New Jersey 08543-4000, Estados Unidos de América

Nacionalidad o Domicilio: Estados Unidos de América

Lugar de Constitución:

Teléfono: Fax:

E-Mail

IDENTIFICACION

C.C. [ ] NIT [ ]

C.E. [ ] Otro [ ]

Cual

Número

(3) REPRESENTANTE O APODERADO

Nombre: ALVARO CORREA ORDOÑEZ

Dirección: Avenida 82 No. 10-62 Piso 6

Teléfono: 6341500 Fax: 3762211

E-Mail: office.bogota@bakernet.com

IDENTIFICACION

C.C. [X] NIT [ ]

C.E. [ ] Otro [ ]

Cual

Número 79.143.366 Usaquén TP 28281

(4) INVENTOR (ES) (72)

Nombre: **RYONO, Dennis E. ; CHENG, Peter T.W. ; BOLTON, Scott A. ;CHEN, Sean S; SHI, Yan ; MENG, Wei; TINO, Joseph A; ZHANG, Hao; SULSKY, Richard B**

Dirección: 28 Marion Road West, Princenton, New Jersey 08540, Estados Unidos de America; c/o Bristol-Myers Squibb Company, 311 Pennington-Rocky Hill Road, Pennington, New Yersey 08534, Estados Unidos de América; c/o Bristol-Myers Squibb Company, 311 Pennington-Rocky Hill Road, Pennington, New Yersey 08534, Estados Unidos de América; c/o Bristol-Myers Squibb Company, 311 Pennington-Rocky Hill Road, Pennington, New Yersey 08534, Estados Unidos de América; c/o Bristol-Myers Squibb Company, 311 Pennington-Rocky Hill Road, Pennington, New Yersey 08534, Estados Unidos de América; c/o Bristol-Myers Squibb Company, 311 Pennington-Rocky Hill Road, Pennington, New Yersey 08534, Estados Unidos de América; c/o Bristol-Myers Squibb Company, 311 Pennington-Rocky Hill Road, Pennington, New Yersey 08534, Estados Unidos de América; c/o Bristol-Myers Squibb Company, 311 Pennington-Rocky Hill Road, Pennington, New Yersey 08534, Estados Unidos de América;

Nacionalidad o Domicilio: Estados Unidos de América

(5) PCT (85)

Solicitud Internacional No. PCT/US2007/072708 Fecha 03.07.2007

Publicación Internacional No. WO/2008/005964 Fecha 10.01.2008

(6) Título (54) ACTIVADORES NOVEDOSOS DE GLUCOCINASA Y METODOS DE USO DE LOS MISMOS

(7) Clasificación Internacional (51) C07F 9/32 ; A61K 31/675; A61P 3/00; C07F 9/40

(8) Prioridad SI [X] NO [ ]	(33) País de Origen	(32) Fecha	(31) Número de Solicitud
	US	06.07.2006	60/818,912
	US	28.06.2007	11/769,964

9 Comprobante de pago No.

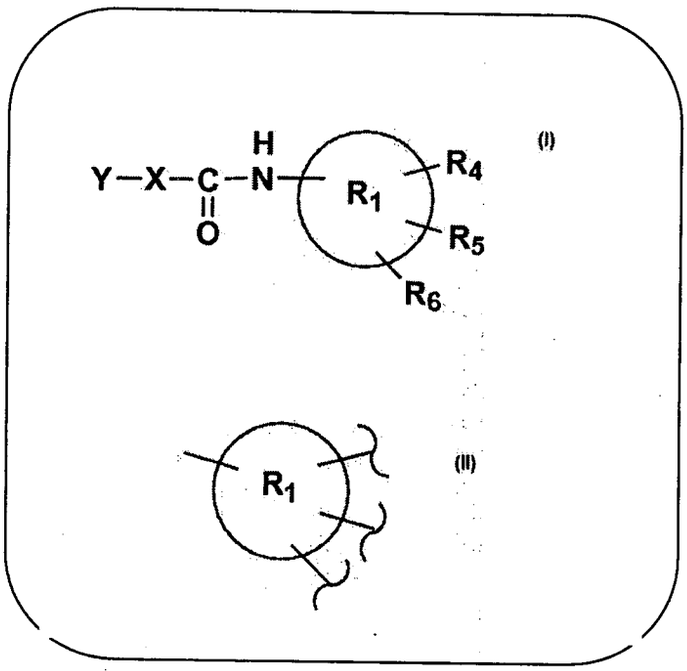
	Fecha
08-92,256	Nov-25-2008
08-100,645	Dic-26-2008
08-86,680	Nov-4-2008
08-100,315	Dic-26-2008
08-95,751	Dic-10-2008

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

(10) ANEXOS

- [X] Comprobante de pago de la tasa de presentación de la solicitud
- [X] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica
- [X] Poderes, si fuere el caso
- [ ] Documento de cesión del inventor al solicitante o a su causante
- [ ] Declaraciones
- [X] Copia de la solicitud internacional. (Resumen, 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
- [X] 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.
- [ ] Otros: Extractos, Forma IB 304.

(11) FIGURA CARATERISTICA



(12) Solicito la concesión de la patente,

NOMBRE: ALVARO CORREA ORDOÑEZ

FIRMA:

C.C. 79.143.366 de Usaquén T.P. 20.281

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

000103

2008/021

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 08 - 92,256
FECHA : NOVIEMBRE 25 DE 2008

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 09-000418- -00000-0000
Fecha: 2009-01-05 16:46:19 Dep: 2020 NUECREACIONI
Tra: 11 PATENTEIYII Eve: 378 FASENACIONALI
Act: 411 PRESENTACION Folios: 849

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
BAKER & MCKENZIE	CONSIGNACION	BANCO DE BOGOTA	062754387	102237936	25/11/2008	35,764,000.00

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

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

SON: QUINIENTOS UN MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

POD-4002

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

PODER OTORGADO POR BRISTOL-MYERS SQUIBB COMPANY

APOSTILLA

1. PAÍS: ESTADOS UNIDOS DE AMÉRICA

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

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

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

CERTIFICADO

5. EN TRENTON, NUEVA JERSEY

6. EL 28 DE JUNIO DE 2007

7. POR BRADLEY ABELOW, TESORERO DE NUEVA JERSEY

8. N° A295716

9. SELLO (APARECE ADHERIDO SELLO DORADO)

10. FIRMA (FIRMADO) BRADLEY ABELOW

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

Dado y suscrito el 30 de mayo de 2007

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

JAIME A. GARAVITO B

COMO NOTARIO ONCE DE ESTE CÍRCULO HAGO CONSTAR QUE ESTA FOTOCOPIA ES COPIA FIEL DEL ORIGINAL QUE HE TENIDO A LA VISTA

31 DIC 2006

BOGOTÁ, D.C. - COLOMBIA

ZULMA NAVARRO DE BAUTISTA

NOTARIA ONCE (11)

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

CERTIFICACIÓN NOTARIAL

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

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

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

[Firmado] SALLY B. HANSEN, Notario Público

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

[Aparece sello realzado]

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

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

BOGDM5 # 82106

JAIME A. GARAVITO
TRADUCTOR E INTÉRPRETE OFICIAL
Res. 034 de Enero 11 de
MINISTERIO DE JUSTICIA

COMO NOTARIO ONCE (11) DEL CÍRCULO HAGO CONSTAR QUE LA PRESENTE FOTOCOPIA COINCIDE CON EL ORIGINAL QUE TUVE A LA VISTA
31 OCT 2008
BOGOTÁ, D.C. - COLOMBIA
ZULMA NAVARRO DE BAUTISTA
NOTARIA ONCE (11)

APOSTILLE

(CONVENTION DE LA HAYE DU 5 OCTOBRE 1961)

1. COUNTRY: UNITED STATES OF AMERICA

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

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

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

CERTIFIED

5. AT TRENTON, NEW JERSEY

6. THE 28TH DAY OF JUNE 2007

7. BY: Bradley Abelow, NEW JERSEY TREASURER

8. NO. A295716

9. SEAL/STAMP:

10. SIGNATURE

Bradley Abelow

ESTE
FOTOCOPIA CONCUERDA CON EL
ORIGINAL QUE SE LE PRESENTÓ A LA VISTA
3 DIC 2008
BOGOTÁ, D.C. - COLOMBIA
ZULMA NAVARRO DE BAUTISTA
NOTARIA ONCE (11)

BAKER & MCKENZIE

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

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

POWER OF ATTORNEY

The undersigned.

BRISTOL–MYERS SQUIBB COMPANY

domiciled in

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

declares that it hereby grants to

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

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

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

Done and subscribed in

On the 30 day of May of 2007

Signature of the person issuing the Power

Anastasia P. Winslow
Senior Patent Counsel

PODER DE ABOGADO

La abajo firmada,

BRISTOL–MYERS SQUIBB COMPANY

domiciliada en

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

declara por el presente que otorga a

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

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

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

Dado y firmado en

A los 30 días del mes de mayo de 2007

Firma de la persona que firma el Poder

COMO NOTARIO ONCE DE ESTE CIRCULO HAGO CONSTAR QUE ESTA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
30 OCT 2008
BOGOTA, D.C. - COLOMBIA
ZULMA NAVARRO DE BAUTISTA
NOTARIA ONCE (11)

NOTARIAL CERTIFICATION

On this 30 day of May 2007, the undersigned Notary

CERTIFIES

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

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

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

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

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

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

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

CERTIFICACION NOTARIAL

A los 30 días del mes de mayo de 2007, el suscrito Notario

DA FE

1 Que Anastasia P. Winslow
mayor y domiciliado en Princeton, NJ Estados Unidos de América
suscribió de su puño y letra el documento que antecede.

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

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

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

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

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

El Notario Público

COMO NOTARIO DE ESTE CIRCULO HA CONSTATADO QUE ÉSTA COINCIDE CON EL ORIGINAL A LA VISTA
31 DIC 2008
BOGOTÁ, D.C. - COLOMBIA
ZULA NAVARRO DE SCUTTI
NOTARIA ONCE (11)

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
10 January 2008 (10.01.2008)

PCT

(10) International Publication Number
WO 2008/005964 A2

(51) International Patent Classification:
C07F 9/32 (2006.01) *A61K 31/675* (2006.01)
C07F 9/40 (2006.01) *A61P 3/00* (2006.01)

(21) International Application Number:
PCT/US2007/072708

(22) International Filing Date: 3 July 2007 (03.07.2007)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/818,912 6 July 2006 (06.07.2006) US
11/769,964 28 June 2007 (28.06.2007) US

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

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **RYONO, Dennis E.** [US/US]; 28 Marion Road West, Princeton, NJ 08540 (US). **CHENG, Peter T.W.** [US/US]; c/o Bristol-Myers Squibb Company, 311 Pennington-Rocky Hill Road, Pennington, NJ 08534 (US). **BOLTON, Scott A.** [US/US]; c/o Bristol-Myers Squibb Company, 311 Pennington-Rocky Hill Road, Pennington, NJ 08534 (US). **CHEN, Sean S.** [US/US]; c/o Bristol-Myers Squibb Company, 311 Pennington-Rocky Hill Road, Pennington, NJ 08534 (US). **SHI, Yan** [US/US]; c/o Bristol-Myers Squibb Company, 311 Pennington-Rocky Hill Road, Pennington, NJ 08534 (US). **MENG, Wei** [CN/US]; c/o Bristol-Myers Squibb Company, 311 Pennington-Rocky Hill Road, Pennington, NJ 08534 (US). **TINO, Joseph A.** [US/US]; c/o Bristol-Myers Squibb Company, 311 Pennington-Rocky Hill Road, Pennington, NJ 08534 (US). **ZHANG, Hao** [CN/US]; c/o Bristol-Myers Squibb Company, 311 Pennington-Rocky Hill Road, Pennington, NJ 08534 (US). **SULSKY, Richard B.** [US/US]; c/o Bristol-Myers Squibb Company, 311 Pennington-Rocky Hill Road, Pennington, NJ 08534 (US).

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

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

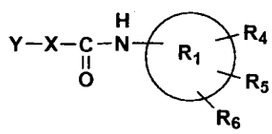
(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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))*

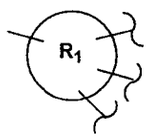
Published:
— *without international search report and to be republished upon receipt of that report*

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

(54) Title: NOVEL GLUCOKINASE ACTIVATORS AND METHODS OF USING SAME



(I)



(II)

(57) Abstract: Compounds are provided which are phosphonate and phosphinate activators and thus are useful in treating diabetes and related diseases and have the structure of Formula (I), wherein Formula (II) is a heteroaryl ring; R_4 is $-(CH_2)_n$-Z-$(CH_2)_m$-$PO(OR_7)(OR_8)$, $-(CH_2)_n$Z-$(CH_2)_m$-$PO(OR_7)R_9$, $-(CH_2)_n$-Z-$(CH_2)_m$-$OPO(OR_7)R_9$, $-(CH_2)_n$Z-$(CH_2)_m$-$OPO(R_9)(R_{10})$, or $-(CH_2)_n$Z-$(CH_2)_m$-$PO(R_9)(R_{10})$; R_5 and R6 are independently selected from H, alkyl and halogen; Y is $R_7(CH_2)_s$ or is absent; and X, n, Z, m, R_4, R_5, R_6, R_7, and s are as defined herein; or a pharmaceutically acceptable salt thereof. A method for treating diabetes and related diseases employing the above compounds is also provided.

WO 2008/005964 A2

NOVEL GLUCOKINASE ACTIVATORS AND METHODS OF USING SAME

[0001] This application claims a benefit of priority from U.S. Provisional Application No. 60/818,912, filed July 6, 2006, the entire disclosure of which is herein incorporated by reference.

FIELD OF THE INVENTION

[0002] The present invention relates to novel phosphonate and phosphinate compounds which are activators of the enzyme glucokinase and thus are useful in treating diabetes, and to a method for treating diabetes, especially Type II diabetes, using such compounds.

BACKGROUND OF THE INVENTION

[0003] The enzyme glucokinase (GK), which is mainly found in pancreatic β-cells and liver parenchymal cells, catalyzes the conversion of glucose to glucose-6-phosphate, which is the first step in the metabolism of glucose. Glucokinase is also a rate-controlling enzyme for glucose metabolism in pancreatic β-cells and liver parenchymal cells, which play an important role in whole-body glucose homeostasis.

[0004] Liag, Y. et al., (Biochem. J., **1995**, 309:167-173) report the finding that Type II (maturity-onset) diabetes of the young (MODY-2) is caused by loss of function mutations in the glucokinase gene, which suggests that glucokinase also functions as a glucose sensor in humans. Thus, compounds that activate glucokinase and thus increase the sensitivity of the glucokinase sensor system and thereby cause increase in insulin secretion will be useful in the treatment of hyperglycemia and Type II diabetes.

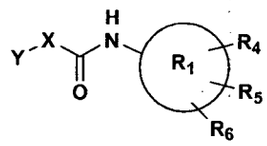
[0005] Glucokinase activators have been demonstrated to be effective in enhancing: 1) the effect of glucose on insulin release from isolated rat and human pancreatic islets, and 2) the glucose induction of pancreatic islet glucokinase in isolated cultured rat islets (e.g. Matschinsky, F.M. et al., Diabetes, **2006**, 55:1, and ("Glucokinase and Glycemic Disease, from Basics to Novel Therapeutics", published by Karger, **2004**; F.M. Matschinsky and M.A. Magnuson, eds., Ch. 6, pp. 360-378). In diabetic animal model studies, glucokinase activators have been demonstrated to

stimulate insulin release, enhance glycogen synthesis and reduce hepatic glucose production in pancreatic clamp studies. Importantly, glucokinase activators have been demonstrated to dose-dependently lower blood glucose levels in different standard animal models of type 2 diabetes, such as the ob/ob mouse, db/db mouse and Zucker in acute single-dose studies and also effectively improved the glucose excursion in both normal C57/BL6J and ob/ob mice in oral glucose tolerance tests (e.g. in "Glucokinase and Glycemic Disease, from Basics to Novel Therapeutics", published by Karger, **2004**; F.M. Matschinsky and M.A. Magnuson, eds., Ch. 6, pp. 360-378 as well as Fyfe, M.C. et al., Diabetologia, **2007**, 50:1277).

[0006] Glucokinase activators have also demonstrated antidiabetic efficacy in chronic animal models of type II diabetes. For instance, in a 9-day study in ob/ob mice, a glucokinase activator improved the overall glucose profile while showing comparable antihyperglycemic effects in oral glucose tolerance tests at the beginning and end of the study (Fyfe, M.C. et al., Diabetologia, **2007**, 50:1277). In another instance, in a chronic 40-week study, a glucokinase activator prevented the development of hyperglycemia in diet-induced obese mice which were glucose intolerant. The diet-induced obese mice treated with a glucokinase activator showed marked improvement in the glucose excursion in an oral glucose tolerance test at the end of the study relative to the control group ("Glucokinase and Glycemic Disease, from Basics to Novel Therapeutics", published by Karger, **2004**; F.M. Matschinsky and M.A. Magnuson, eds., Ch. 6, pp. 360-378).

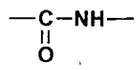
SUMMARY OF THE INVENTION

[0007] In accordance with one aspect of the invention, compounds are provided having the structure I



I

wherein

R_1 is a heteroaryl substituted by R_4 and optionally substituted with one or two substituents R_5 and/or R_6, wherein the heteroaryl possesses a nitrogen atom adjacent to the atom joining said heteroaryl group to  ;

R_4 is $-(CH_2)_n-Z-(CH_2)_m-PO(OR_7)(OR_8)$,

or $-(CH_2)_nZ-(CH_2)_m-PO(OR_7)R_9$,

or $-(CH_2)_n-Z-(CH_2)_m-O-PO(OR_7)R_9$,

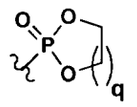
or $-(CH_2)_nZ-(CH_2)_m-O-PO-(R_9)R_{10}$,

or $-(CH_2)_nZ-(CH_2)_m-PO(R_9)R_{10}$;

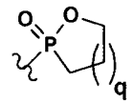
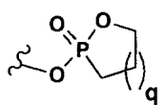
R_7 and R_8 are the same or different and are independently selected from hydrogen and alkyl;

R_9 and R_{10} are the same or different and are independently selected from alkyl, aryl, arylalkyl, heteroaryl and heteroarylalkyl, any of which may be optionally substituted;

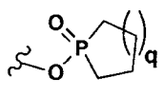
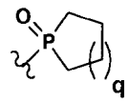
additionally, R_7 and R_8 can be cyclized into a ring

 where q = 1-3 ;

similarly, R_7 and R_9 can be cyclized into a ring

 where q = 1-3, or  where q = 1-3;

similarly, R_9 and R_{10} can be cyclized into a ring

 where q = 1-3, or  where q = 1-3 ;

Z is selected from a bond, alkylene and alkenylene, each of which may be optionally substituted (e.g. hydroxy, alkoxy, aminoalkyl, aminoaralkyl, aminoheteroaralkyl, aminoaryl, aminoheteroaryl or carboxy);

m is 0, 1 or 2;

n is 0, 1 or 2;

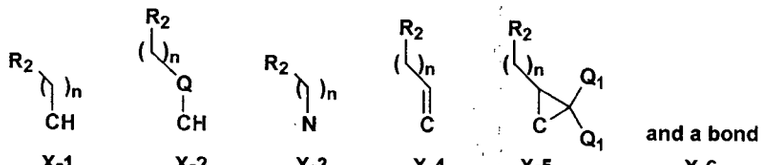
and Z may be O, S, SO_2 when

m is 1 or 2,

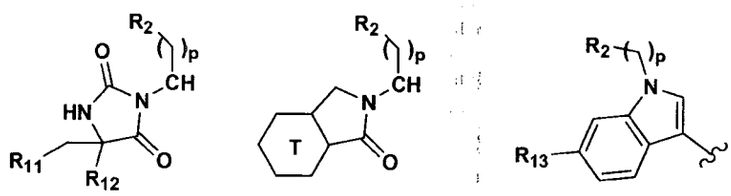
n is 0, 1, or 2;

R_5 and R_6 are the same or different and are independently selected from hydrogen, alkyl, halogen or carboxyl, or is absent;

X is selected from



and when Y is absent, X is selected from



R_2 is selected from hydrogen, alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, alkynyl, and alkenyl (all of which may be optionally substituted);

p is 0 or 1;

Q is selected from O, $S(O)_q$ and CO, where q is 0, 1 or 2;

Q_1 is selected from hydrogen and fluorine;

R_{11} is selected from hydrogen, lower alkyl, cycloalkyl, aryl and heteroaryl;

R_{12} is selected from hydrogen, and lower alkyl, or R_{11} and R_{12} together with the carbon atom to which they are attached form a cycloalkyl ring of 5 to 7 carbon atoms;

R_{13} is selected from halo, nitro, amino, cyano, methyl, trifluoromethyl, hydroxy, methoxy, trifluoromethoxy, methylthio, methylsulfinyl and methylsulfonyl;

T is selected from aryl and heteroaryl, each of which may be optionally substituted;

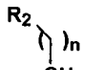
Y is R_3-$(CH_2)_s$-, or is absent;

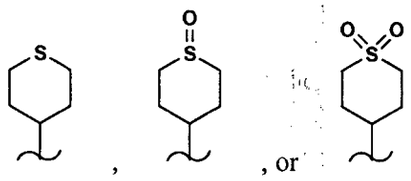
where R_3 is aryl or heteroaryl, each of which may be optionally substituted;

s is 0 or 1;

all stereoisomers thereof, a prodrug ester thereof or a pharmaceutically acceptable salt thereof.

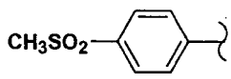
[0008] Preferably in compounds of formula I

X is  where more preferably n is 1, and R_2 is a cycloalkyl, preferably cyclopentyl or cyclohexyl, or R_2 is a heterocyclyl group such as cycloalkyl with an embedded hetero atom such as an oxygen atom or a sulfur atom, for example tetrahydropyran, tetrahydrofuran,



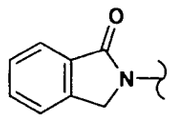
preferably tetrahydropyran;

Y is aryl or heteroaryl or is absent, still more preferably aryl, more preferably phenyl, still more preferably



;

or X is a bond and Y is



;

R_4 is $(CH_2)_n$-Z-$(CH_2)_m$-$PO(OR_7)(OR_8)$ wherein Z is alkylene or alkenylene, wherein n is 0, m is 0 and Z is a bond, $-CH_2-$, $-CH_3-CH=CH-$, $-CH_2CH_2-$ or  ;

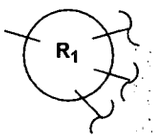
and

R_5 and R_6 are each H;

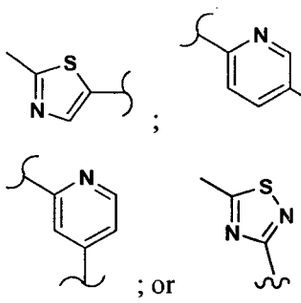
R_7 is H or alkyl; and

R_8 is H or alkyl.

[0009] The moiety

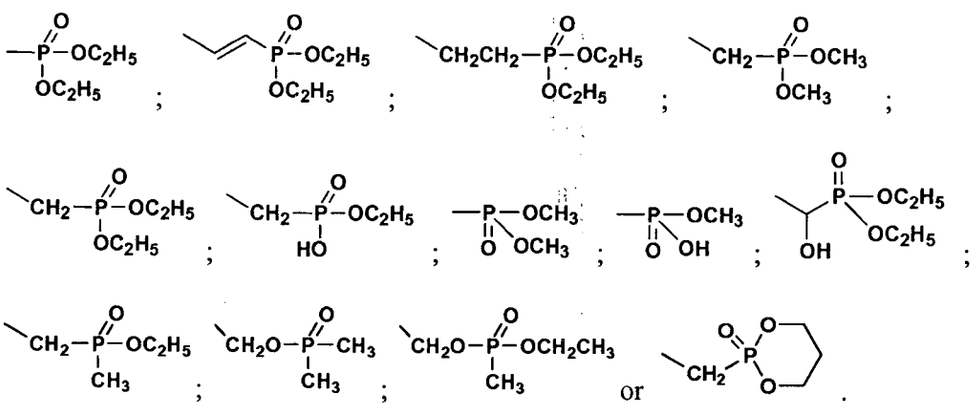


is preferably

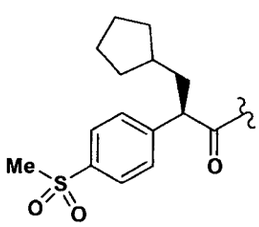


; or

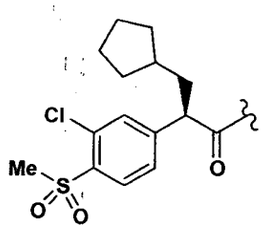
[0010] R_4 is more preferably



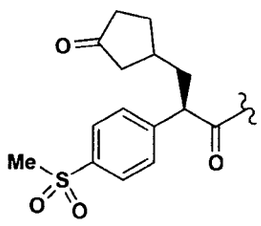
[0011] Preferred embodiments of Y-X-CO- wherein X is X-1 include, but are not limited to:



(a) ,

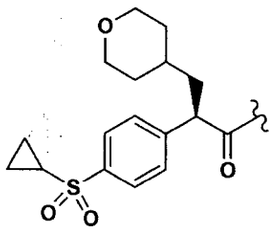


(b) ,



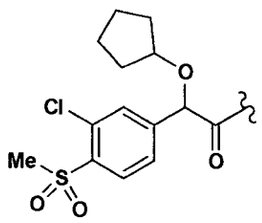
(c)

, and



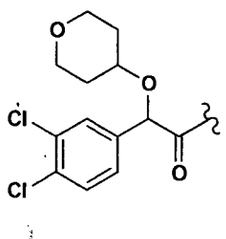
(d)

[0012] Preferred embodiments of Y-X-CO- wherein X = X-2 include, but are not limited to:



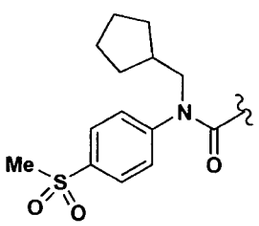
(e)

and



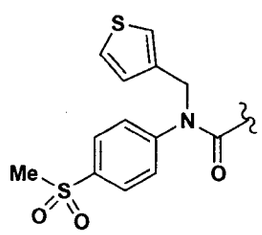
(f)

[0013] Preferred embodiments of Y-X-CO- wherein X = X-3 include, but are not limited to:



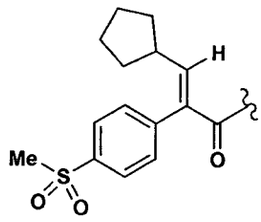
(g)

and

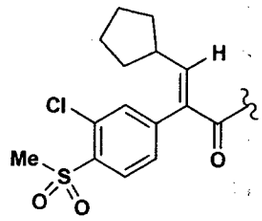


(h)

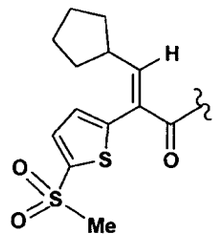
[0014] Preferred embodiments of Y-X-CO- wherein X = X-4 include, but are not limited to:



(i) ,

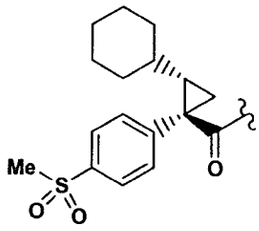


(j) , and

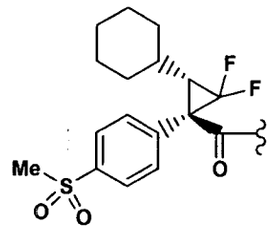


(k) .

[0015] Preferred embodiments of Y-X-CO- wherein X = X-5 include, but are not limited to:

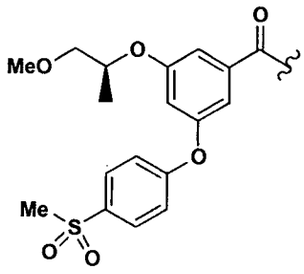


(l) and

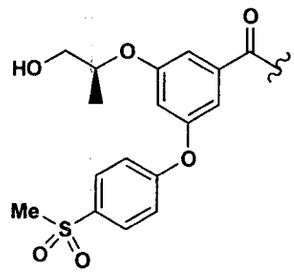


(m) .

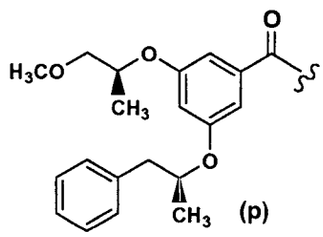
[0016] Preferred embodiments of Y-X-CO- wherein X = X-6 (wherein X is a bond) include, but are not limited to:



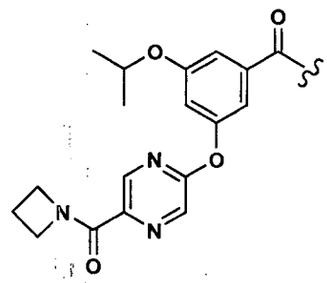
(n) ,



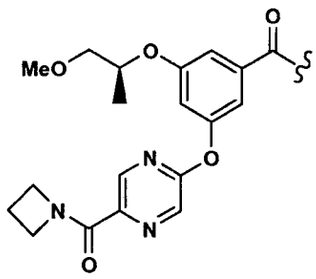
(o) ,



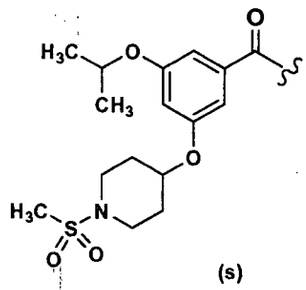
(p)



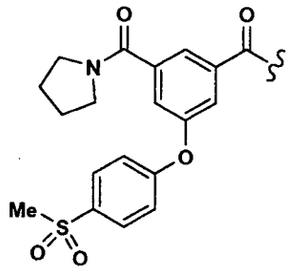
(q)



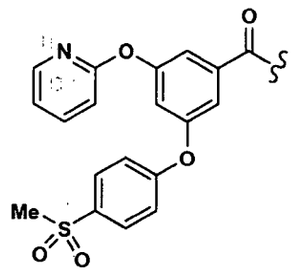
(r)



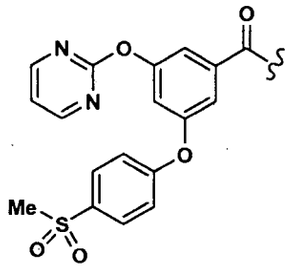
(s)



(t)

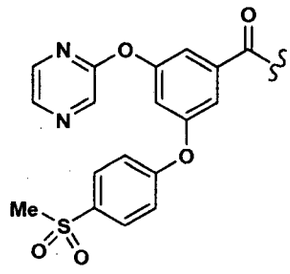


(u)



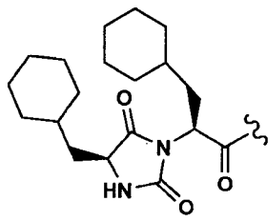
(v)

, and

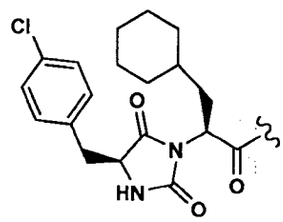


(w)

[0017] Preferred embodiments of Y-X-CO- wherein X = X-7 include, but are not limited to:

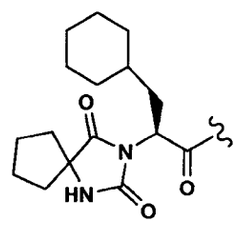


(x)



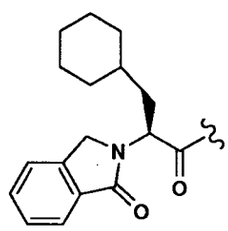
(y)

, and



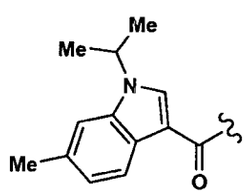
(z)

[0018] Preferred embodiments of Y-X-CO- wherein X = X-8 include, but are not limited to:



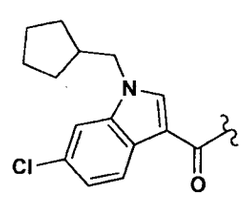
(aa)

[0019] Preferred embodiments of Y-X-CO- wherein X = X-9 include, but are not limited to:



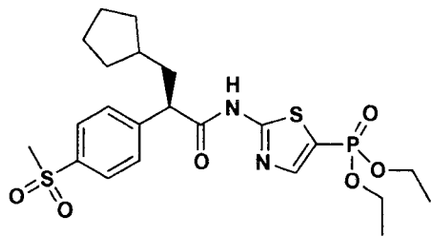
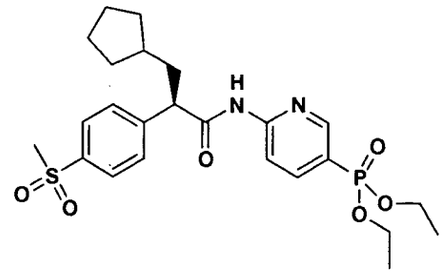
(ab)

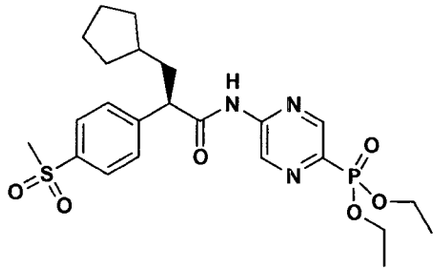
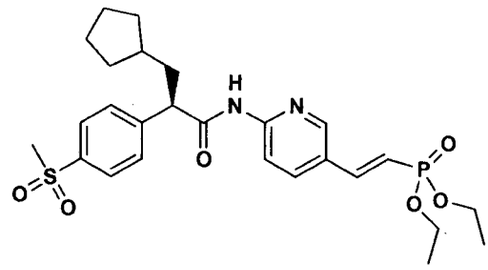
and

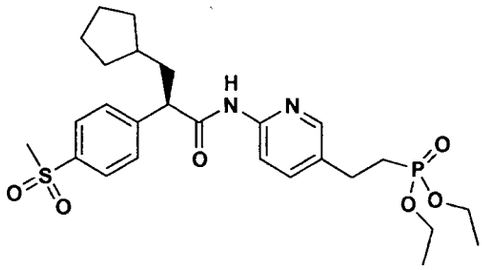
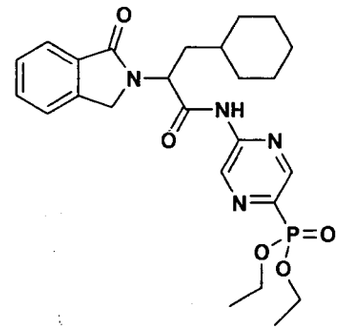


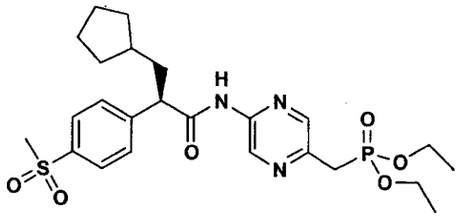
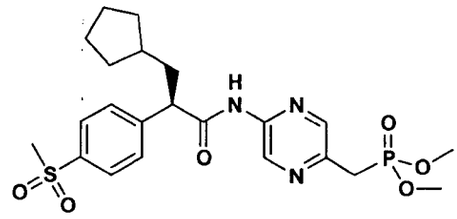
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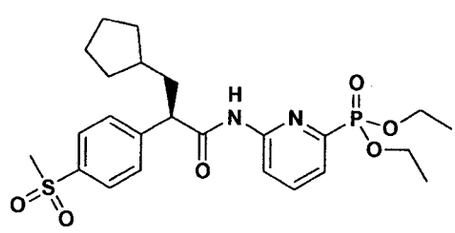
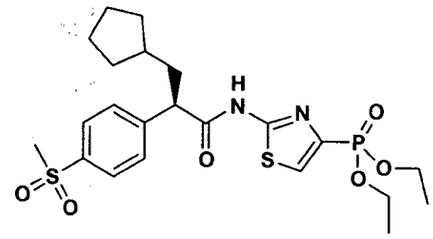
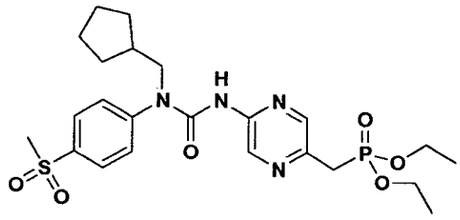
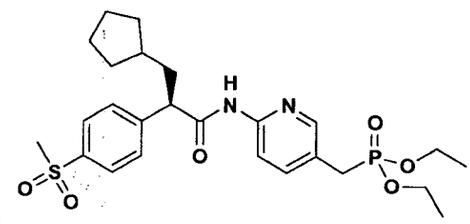
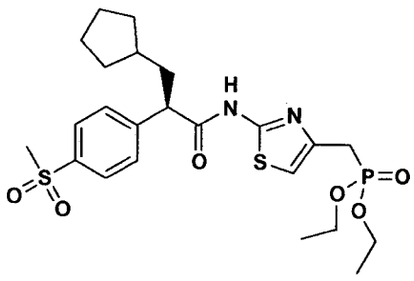
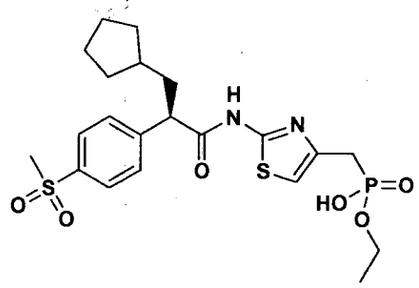
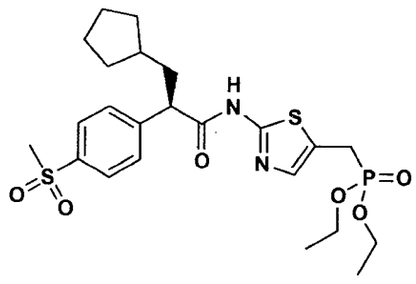
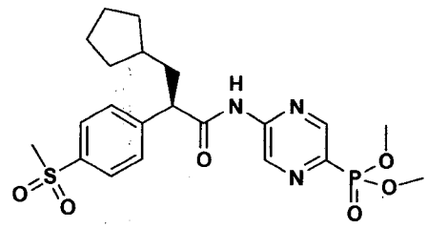
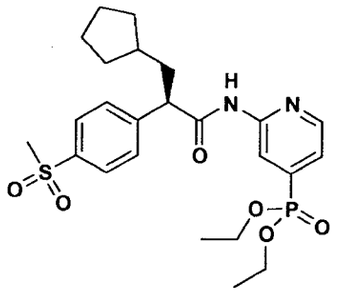
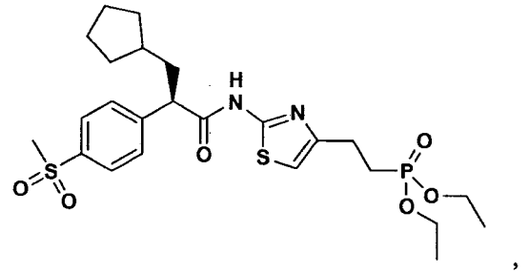
[0020] Examples of preferred compounds in accordance with the present invention include, but are not limited to, the following:

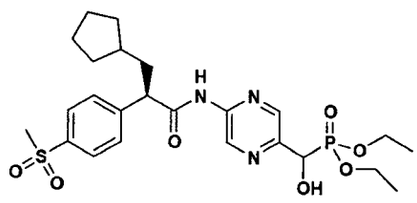
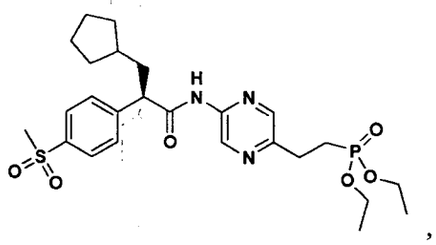

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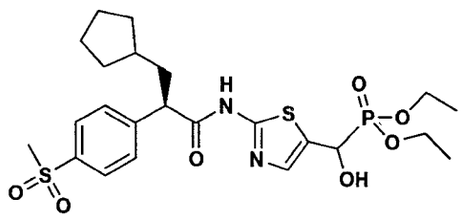
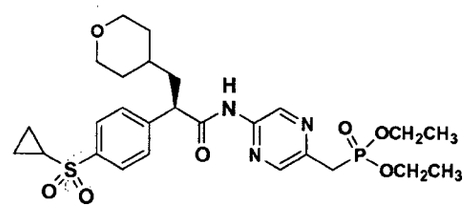

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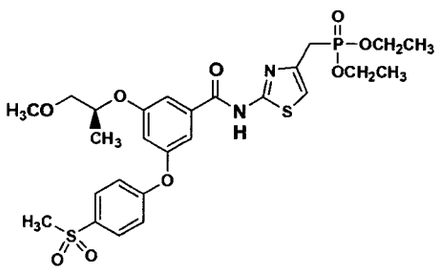
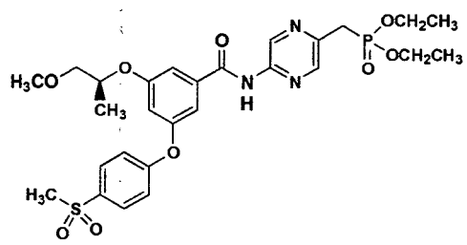

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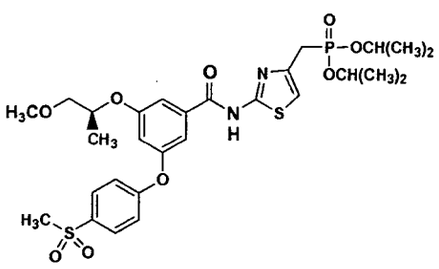
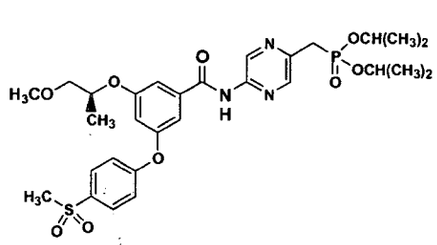

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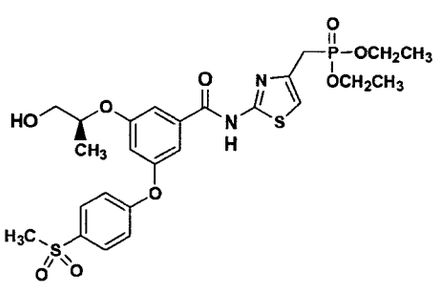
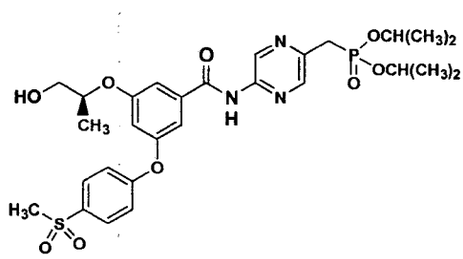

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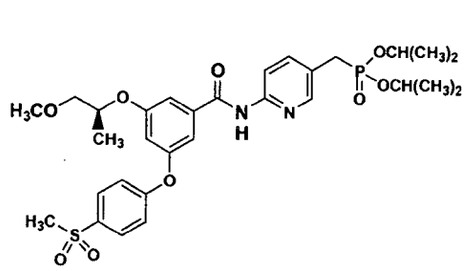
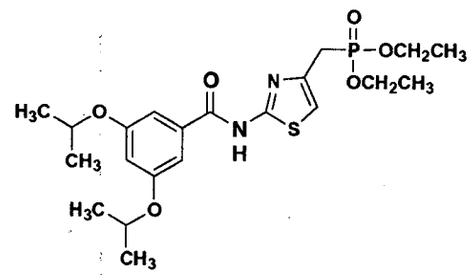

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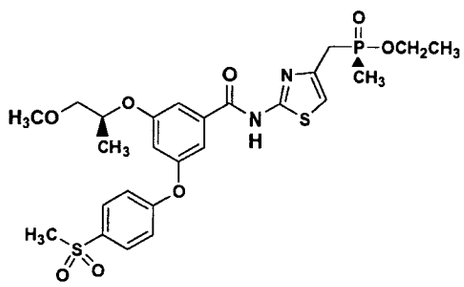
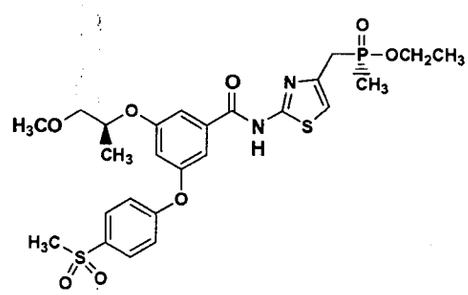

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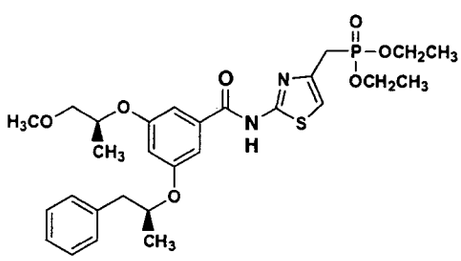
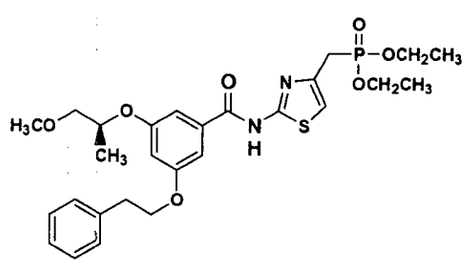

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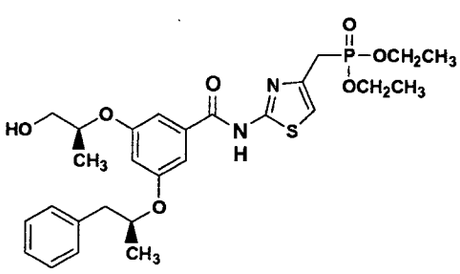
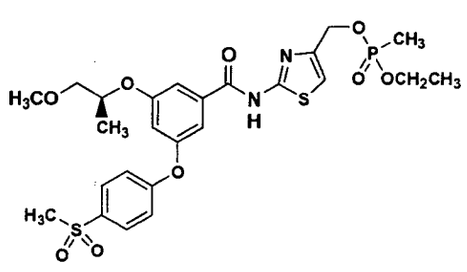

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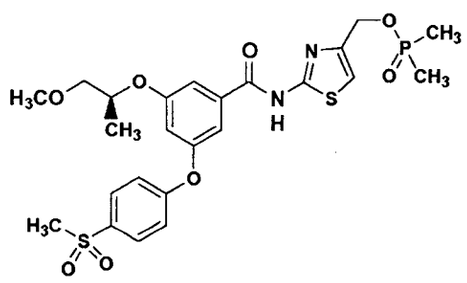
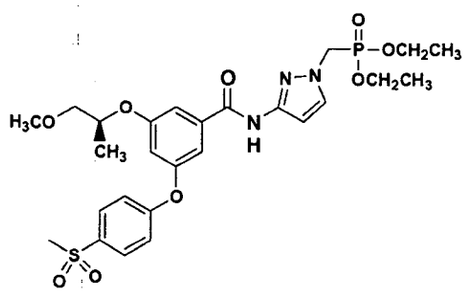

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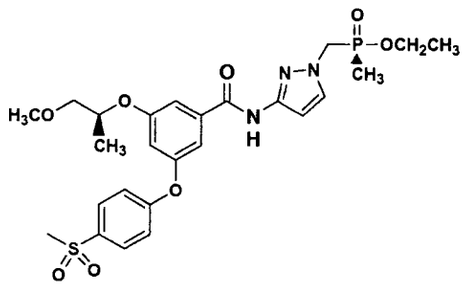
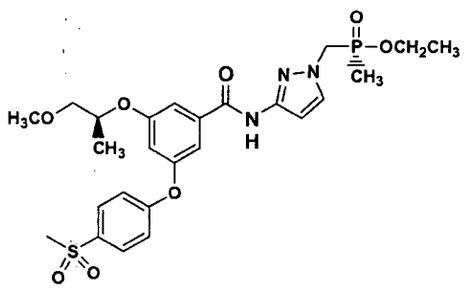

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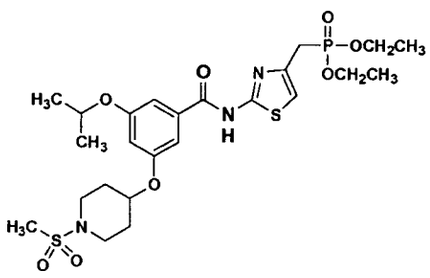
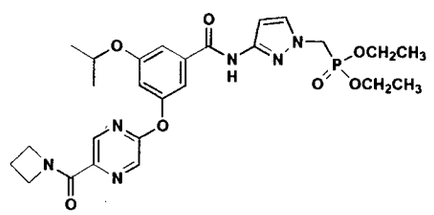

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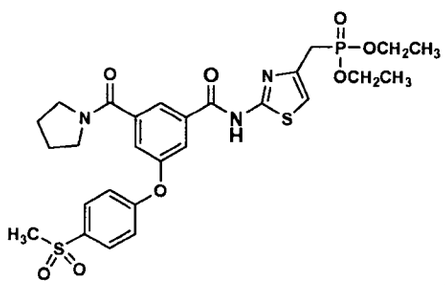
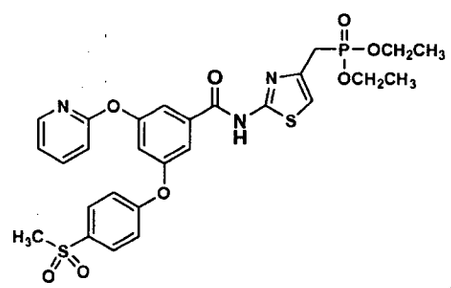

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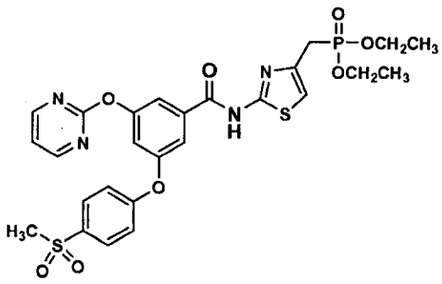

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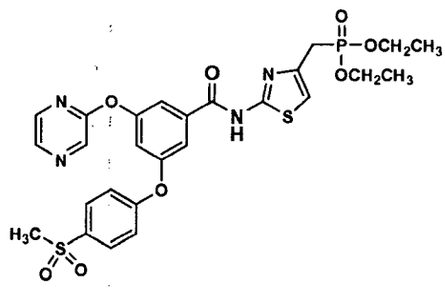

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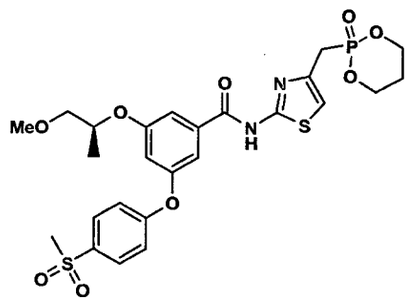

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[0021] The compounds of the present invention activate or enhance the activity of the enzyme glucokinase. Consequently, the compounds of the present invention may be used in the treatment of multiple diseases or disorders associated with a deficit of glucokinase, such as diabetes and related conditions, microvascular complications associated with diabetes, the macrovascular complications associated with diabetes, cardiovascular diseases, Metabolic Syndrome and its component conditions, and other maladies. Examples of diseases or disorders associated with deficit in activity of the enzyme glucokinase that can be prevented, inhibited, or treated according to the present invention include, but are not limited to, diabetes, hyperglycemia, impaired glucose tolerance, insulin resistance, hyperinsulinemia, retinopathy, neuropathy, nephropathy, delayed wound healing, atherosclerosis and its sequelae, abnormal heart function, myocardial ischemia, stroke, Metabolic Syndrome, hypertension, obesity, dyslipidemia, hyperlipidemia, hypertriglyceridemia, hypercholesterolemia, low HDL, high LDL, non-cardiac ischemia, infection, cancer, vascular restenosis, pancreatitis, neurodegenerative disease, lipid disorders, cognitive impairment and dementia, bone disease, HIV protease associated lipodystrophy, and glaucoma.

[0022] The present invention provides for compounds of formula I, pharmaceutical compositions employing such compounds, and for methods of using such compounds. In particular, the present invention provides a pharmaceutical composition containing a therapeutically effective amount of a compound of formula I, alone or in combination with a pharmaceutically acceptable carrier.

[0023] Further, in accordance with the present invention, a method is provided for preventing, inhibiting, or treating the progression or onset of diseases or disorders associated with deficit in the activity of the enzyme glucokinase, such as defined above and hereinafter, wherein a therapeutically effective amount of a compound of formula I is administered to a mammalian, i.e., human, patient in need of treatment.

[0024] The compounds of the invention can be used alone, in combination with other compounds of the present invention, or in combination with one or more other therapeutic agent(s).

[0025] Further, the present invention provides a method for preventing, inhibiting, or treating the diseases as defined above and hereinafter, wherein a therapeutically effective amount of a combination of a compound of formula I and another compound of formula I and/or at least one other type of therapeutic agent, is administered to a mammalian, i.e., human, patient in need of treatment.

[0026] In another embodiment, compounds of the present invention are selected from the compounds exemplified in the examples.

[0027] In another embodiment, the present invention relates to pharmaceutical compositions which include of a therapeutically effective amount of a compound of the present invention, alone or, optionally, in combination with a pharmaceutically acceptable carrier and/or one or more other agent(s).

[0028] In another embodiment, the present invention relates to methods of enhancing the activity of the enzyme glucokinase which includes the step of administering to a mammalian patient, for example, a human patient, in need thereof a therapeutically effective amount of a compound of the present invention, alone, or optionally, in combination with another compound of the present invention and/or at least one other type of therapeutic agent.

[0029] In another embodiment, the present invention relates to a method for preventing, inhibiting, or treating the progression or onset of diseases or disorders

associated with deficit in the activity of the enzyme glucokinase which includes the step of administering to a mammalian patient, for example, a human patient, in need of prevention, inhibition, or treatment a therapeutically effective amount of a compound of the present invention, alone, or, optionally, in combination with another compound of the present invention and/or at least one other type of therapeutic agent.

[0030] Examples of diseases or disorders associated with the deficit in activity of the enzyme glucokinase that can be prevented, inhibited, or treated according to the present invention include, but are not limited to, are those diseases or disorders set out above.

[0031] In another embodiment, the present invention relates to a method for preventing, inhibiting, or treating the progression or onset of diabetes, hyperglycemia, obesity, dyslipidemia, hypertension, and cognitive impairment which includes the step of administering to a mammalian patient, for example, a human patient, in need of prevention, inhibition, or treatment a therapeutically effective amount of a compound of the present invention, alone, or, optionally, in combination with another compound of the present invention and/or at least one other type of therapeutic agent.

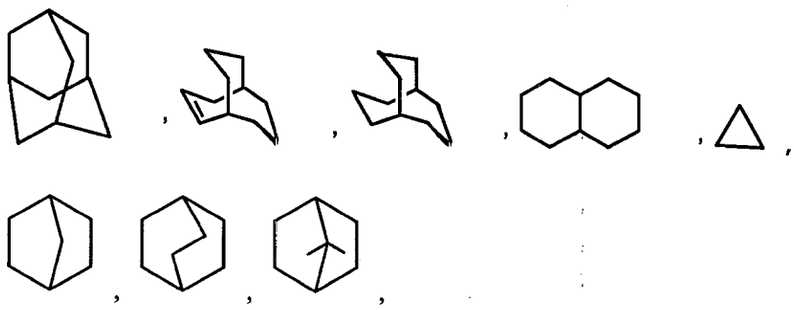
[0032] In still another embodiment, the present invention relates to a method for preventing, inhibiting, or treating the progression or onset of diabetes, which includes the step of administering to a mammalian patient, for example, a human patient, in need of prevention, inhibition, or treatment a therapeutically effective amount of a compound of the present invention, alone, or, optionally, in combination with another compound of the present invention and/or at least one other type of therapeutic agent.

[0033] In yet still another embodiment, the present invention relates to a method for preventing, inhibiting, or treating the progression or onset of hyperglycemia which includes the step of administering to a mammalian patient, for example, a human patient, in need of prevention, inhibition, or treatment a therapeutically effective amount of a compound of the present invention, alone, or, optionally, in combination with another compound of the present invention and/or at least one other type of therapeutic agent.

[0034] In another embodiment, the present invention relates to a method for preventing, inhibiting, or treating the progression or onset of obesity which includes the step of administering to a mammalian patient, for example, a human patient, in

from same groups as R_a and R_b but is not hydrogen. Each group R_a and R_b when other than hydrogen, and each R_c group optionally has up to three further substituents attached at any available carbon or nitrogen atom of R_a, R_b, and/or R_c, said substituent(s) being the same or different and are independently selected from the group consisting of (C_{1-6})alkyl, (C_{2-6})alkenyl, hydroxy, halogen, cyano, nitro, CF_3, $O(C_{1-6}alkyl)$, OCF_3, C(=O)H, $C(=O)(C_{1-6}alkyl)$, CO_2H, $CO_2(C_{1-6}alkyl)$, $NHCO_2(C_{1-6}alkyl)$, $-S(C_{1-6}alkyl)$, $-NH_2$, $NH(C_{1-6}alkyl)$, $N(C_{1-6}alkyl)_2$, $N(CH_3)_3^+$, $SO_2(C_{1-6}alkyl)$, $C(=O)(C_{1-4}alkylene)NH_2$, $C(=O)(C_{1-4}alkylene)NH(alkyl)$, $C(=O)(C_{1-4}alkylene)N(C_{1-4}alkyl)_2$, C_{3-7}cycloalkyl, phenyl, benzyl, phenylethyl, phenyloxy, benzyloxy, naphthyl, a four to seven membered heterocylo, or a five to six membered heteroaryl. When a substituted alkyl is substituted with an aryl, heterocyclo, cycloalkyl, or heteroaryl group, said ringed systems are as defined below and thus may have zero, one, two, or three substituents, also as defined below.

[0041] Unless otherwise indicated, the term "cycloalkyl" as employed herein alone or as part of another group includes saturated or partially unsaturated (containing 1 or 2 double bonds) cyclic hydrocarbon groups containing 1 to 3 rings, including monocyclic alkyl, bicyclic alkyl (or bicycloalkyl), and tricyclic alkyl, containing a total of 3 to 20 carbons forming the ring, preferably 3 to 10 carbons, forming the ring and which may be fused to 1 or 2 aromatic rings as described for aryl, which includes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclodecyl and cyclododecyl, cyclohexenyl,



any of which groups may be optionally substituted with 1 to 4 substituents such as halogen, alkyl, alkoxy, hydroxy, aryl, aryloxy, arylalkyl, cycloalkyl, alkylamido, alkanoylamino, oxo, acyl, arylcarbonylamino, amino, nitro, cyano, thiol, and/or alkylthio, and/or any of the substituents for alkyl.

[0042] Unless otherwise indicated, the term "lower alkenyl" or "alkenyl" as used herein by itself or as part of another group refers to straight or branched chain radicals of 2 to 20 carbons, preferably 2 to 12 carbons, and more preferably 1 to 8 carbons in the normal chain, which include one to six double bonds in the normal chain, such as vinyl, 2-propenyl, 3-butenyl, 2-butenyl, 4-pentenyl, 3-pentenyl, 2-hexenyl, 3-hexenyl, 2-heptenyl, 3-heptenyl, 4-heptenyl, 3-octenyl, 3-nonenyl, 4-decenyl, 3-undecenyl, 4-dodecenyl, 4,8,12-tetradecatrienyl, and the like, and which may be optionally substituted with 1 to 4 substituents, namely, halogen, haloalkyl, alkyl, alkoxy, alkenyl, alkynyl, aryl, arylalkyl, cycloalkyl, amino, hydroxy, heteroaryl, cycloheteroalkyl, alkanoylamino, alkylamido, arylcarbonyl-amino, nitro, cyano, thiol, alkylthio, and/or any of the alkyl substituents set out herein.

[0043] Unless otherwise indicated, the term "lower alkynyl" or "alkynyl" as used herein by itself or as part of another group refers to straight or branched chain radicals of 2 to 20 carbons, preferably 2 to 12 carbons and more preferably 2 to 8 carbons in the normal chain, which include one triple bond in the normal chain, such as 2-propynyl, 3-butynyl, 2-butynyl, 4-pentynyl, 3-pentynyl, 2-hexynyl, 3-hexynyl, 2-heptynyl, 3-heptynyl, 4-heptynyl, 3-octynyl, 3-nonynyl, 4-decynyl,3-undecynyl, 4-dodecynyl, and the like, and which may be optionally substituted with 1 to 4 substituents, namely, halogen, haloalkyl, alkyl, alkoxy, alkenyl, alkynyl, aryl, arylalkyl, cycloalkyl, amino, heteroaryl, cycloheteroalkyl, hydroxy, alkanoylamino, alkylamido, arylcarbonylamino, nitro, cyano, thiol, and/or alkylthio, and/or any of the alkyl substituents set out herein.

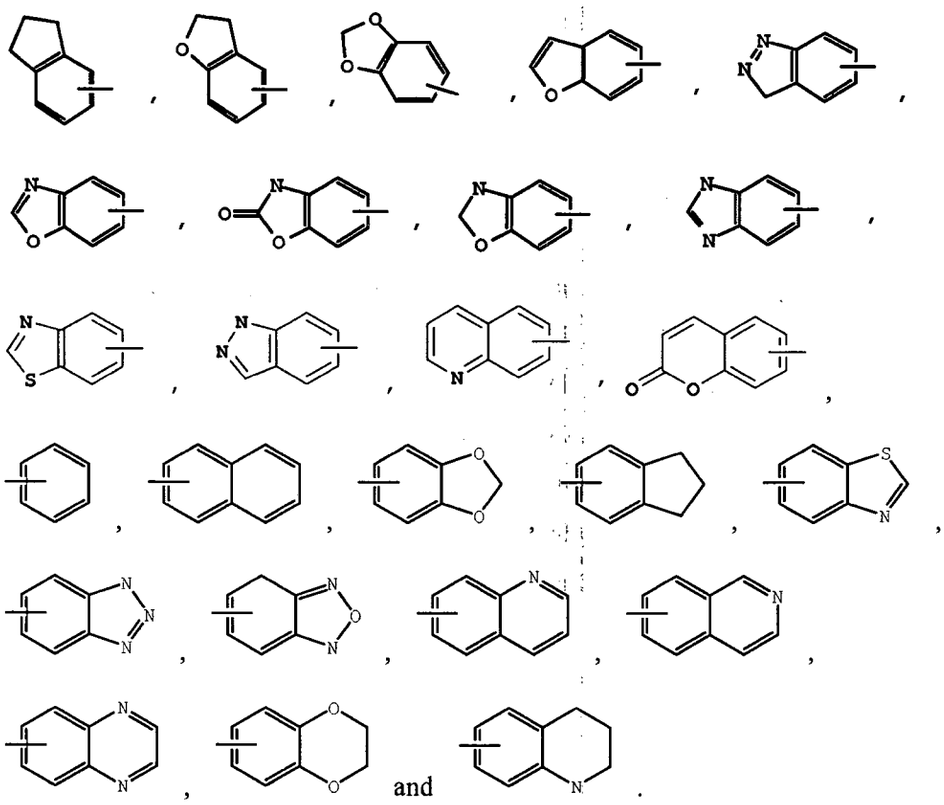
[0044] Where alkyl groups as defined above have single bonds for attachment to other groups at two different carbon atoms, they are termed "alkylene" groups and may optionally be substituted as defined above for "alkyl".

[0045] Where alkenyl groups as defined above and alkynyl groups as defined above, respectively, have single bonds for attachment at two different carbon atoms, they are termed "alkenylene groups" and "alkynylene groups", respectively, and may optionally be substituted as defined above for "alkenyl" and "alkynyl".

[0046] The term "halogen" or "halo" as used herein alone or as part of another group refers to chlorine, bromine, fluorine, and iodine as well as CF_3, with chlorine or fluorine being preferred.

[0047] Unless otherwise indicated, the term "aryl" as employed herein alone or as part of another group refers to monocyclic and bicyclic aromatic groups containing 6 to 10 carbons in the ring portion (such as phenyl, biphenyl or naphthyl, including 1-naphthyl and 2-naphthyl) and may optionally include 1 to 3 additional rings fused to a carbocyclic ring or a heterocyclic ring (such as aryl, cycloalkyl, heteroaryl, or cycloheteroalkyl rings)

for example



and

The aryl group may be optionally substituted through available carbon atoms with 1, 2, or 3 substituents, for example, hydrogen, halo, haloalkyl, alkyl, haloalkyl, alkoxy, haloalkoxy, alkenyl, trifluoromethyl, trifluoromethoxy, alkynyl, cycloalkyl-alkyl, cycloalkyl, cycloheteroalkyl, cycloheteroalkylalkyl, aryl, heteroaryl, arylalkyl, aryloxy, aryloxyalkyl, arylalkoxy, arylthio, arylazo, heteroarylalkyl, heteroarylalkenyl, heteroarylheteroaryl, heteroaryloxy, hydroxy, nitro, cyano, amino, substituted amino wherein the amino includes 1 or 2 substituents (which are alkyl, aryl, or any of the other aryl compounds mentioned in the definitions), thiol,

alkylthio, arylthio, heteroarylthio, arylthioalkyl, alkoxyarylthio, alkylcarbonyl, arylcarbonyl, alkyl-aminocarbonyl, arylaminocarbonyl, alkoxycarbonyl, aminocarbonyl, alkylcarbonyloxy, arylcarbonyloxy, alkylcarbonylamino, arylcarbonylamino, arylsulfinyl, arylsulfinylalkyl, arylsulfonylamino, or arylsulfonaminocarbonyl, OR_a, SR_a, (=S), $-NR_aR_b$, $-N(alkyl)_3^+$, $-NR_aSO_2$, $-NR_aSO_2R_c$, $-SO_2R_c$ - $SO_2NR_aR_b$, $-SO_2NR_aC(=O)R_b$, SO_3H, $-PO(OH)_2$, $-C(=O)R_a$, $-CO_2R_a$, $-C(=O)NR_aR_b$, $-C(=O)(C_{1-4}alkylene)NR_aR_b$, $-C(=O)NR_a(SO_2)R_b$, $-CO_2(C_{1-4}alkylene)NR_aR_b$, $-NR_aC(=O)R_b$, $-NR_aCO_2R_b$, or $-NR_a(C_{1-4}alkylene)CO_2R_b$, wherein R_a, R_b and R_c are as defined above for substituted alkyl groups, and are also in turn optionally substituted as recited above. Additionally, two substituents attached to an aryl, particularly a phenyl group, may join to form a further ring such as a fused or spiro-ring, *e.g.*, cyclopentyl or cyclohexyl, or fused heterocyclo or heteroaryl. When an aryl is substituted with a further ring (or has a second ring fused thereto), said ring in turn is optionally substituted with one to two of (C_{1-4})alkyl, (C_{2-4})alkenyl, halogen, hydroxy, cyano, nitro, CF_3, $O(C_{1-4}alkyl)$, OCF_3, $C(=O)H$, $C(=O)(C_{1-4}alkyl)$, CO_2H, $CO_2(C_{1-4}alkyl)$, $NHCO_2(C_{1-4}alkyl)$, $-S(C_{1-4}alkyl)$, $-NH_2$, $NH(C_{1-4}alkyl)$, $N(C_{1-4}alkyl)_2$, $N(C_{1-4}alkyl)_3^+$, $SO_2(C_{1-4}alkyl)$, $C(=O)(C_{1-4}alkylene)NH_2$, $C(=O)(C_{1-4}alkylene)NH(alkyl)$, and/or $C(=O)(C_{1-4}alkylene)N(C_{1-4}alkyl)_2$.and/or any of the alkyl substituents set out herein.

[0048] Unless otherwise indicated, the term "lower alkoxy", "alkoxy", "aryloxy" or "aralkoxy" as employed herein alone or as part of another group includes any of the above alkyl, aralkyl, or aryl groups linked to an oxygen atom.

[0049] Unless otherwise indicated, the term "amino" as employed herein alone or as part of another group refers to amino that may be substituted with one or two substituents, which may be the same or different, such as alkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl, cycloalkyl, cycloalkylalkyl, haloalkyl, hydroxyalkyl, alkoxyalkyl, or thioalkyl. These substituents may be further substituted with a carboxylic acid and/or any of the R_3 groups or substituents for R_3 as set out above. In addition, the amino substituents may be taken together with the nitrogen atom to which they are attached to form 1-pyrrolidinyl, 1-piperidinyl, 1-azepinyl, 4-morpholinyl, 4-thiamorpholinyl, 1-

piperazinyl, 4-alkyl-1-piperazinyl, 4-arylalkyl-1-piperazinyl, 4-diarylalkyl-1-piperazinyl, 1-pyrrolidinyl, 1-piperidinyl, or 1-azepinyl, optionally substituted with alkyl, alkoxy, alkylthio, halo, trifluoromethyl, or hydroxy.

[0050] Unless otherwise indicated, the term "lower alkylthio," "alkylthio," "arylthio," or "aralkylthio" as employed herein alone or as part of another group includes any of the above alkyl, aralkyl, or aryl groups linked to a sulfur atom.

[0051] Unless otherwise indicated, the term "lower alkylamino," "alkylamino," "arylamino," or "arylalkylamino" as employed herein alone or as part of another group includes any of the above alkyl, aryl, or arylalkyl groups linked to a nitrogen atom.

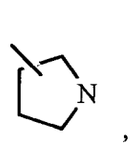
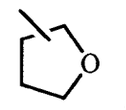
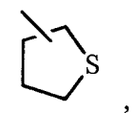
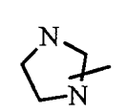
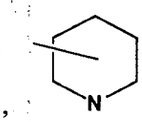
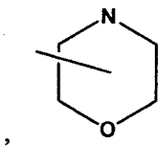
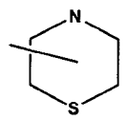
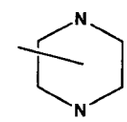
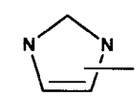
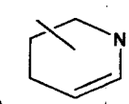
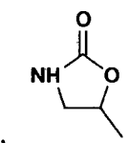
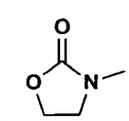
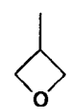
[0052] The term "acyl" alone or as part of another group refers to a carbonyl group linked to an organic radical, more particularly, the group $C(=O)R_e$, as well as the bivalent groups $-C(=O)-$ or $-C(=O)R_e-$, which are linked to organic radicals. The group R_e can be selected from alkyl, alkenyl, alkynyl, aminoalkyl, substituted alkyl, substituted alkenyl, or substituted alkynyl, as defined herein, or when appropriate, the corresponding bivalent group, *e.g.*, alkylene, alkenylene, and the like.

[0053] The term "heterocyclo" or "heterocyclic" or "heterocyclyl" or "cycloheteroalkyl" refers to substituted and unsubstituted non-aromatic 3 to 7 membered monocyclic groups, 7 to 11 membered bicyclic groups, and 10 to 15 membered tricyclic groups, in which at least one of the rings has at least one heteroatom (O, S, or N) (also referred to as cycloheteroalkyl or heterocycloalkyl). Each ring of the heterocyclo group containing a heteroatom can contain one or two oxygen or sulfur atoms and/or from one to four nitrogen atoms provided that the total number of heteroatoms in each ring is four or less, and further provided that the ring contains at least one carbon atom. The fused rings completing bicyclic and tricyclic groups may contain only carbon atoms and may be saturated, partially saturated, or unsaturated. The nitrogen and sulfur atoms may optionally be oxidized and the nitrogen atoms may optionally be quaternized. The heterocyclo group may be attached at any available nitrogen or carbon atom. The heterocyclo ring may contain zero, one, two, or three substituents selected from the group consisting of halogen, trifluoromethyl, trifluoromethoxy, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, nitro, cyano, oxo (=O), OR_a, SR_a, (=S), $-NR_aR_b$, $-N(alkyl)_3^+$,

$-NR_aSO_2$, $-NR_aSO_2R_c$, $-SO_2R_c$ $-SO_2NR_aR_b$, $-SO_2NR_aC(=O)R_b$, SO_3H, $-PO(OH)_2$, $-C(=O)R_a$, $-CO_2R_a$, $-C(=O)NR_aR_b$, $-C(=O)(C_{1-4}alkylene)NR_aR_b$, $-C(=O)NR_a(SO_2)R_b$, $-CO_2(C_{1-4}alkylene)NR_aR_b$, $-NR_aC(=O)R_b$, $-NR_aCO_2R_b$, $-NR_a(C_{1-4}alkylene)CO_2R_b$, =N-OH, =N-O-alkyl, aryl, cycloalkyl, heterocyclo, and/or heteroaryl, wherein R_a, R_b, and R_c are as defined above for substituted alkyl groups, and are also in turn optionally substituted as recited above. When a heterocyclo is substituted with a further ring, said ring in turn is optionally substituted with one to two of (C_{1-4})alkyl, (C_{2-4})alkenyl, halogen, hydroxy, cyano, nitro, CF_3, $O(C_{1-4}alkyl)$, OCF_3, C(=O)H, $C(=O)(C_{1-4}alkyl)$, CO_2H, $CO_2(C_{1-4}alkyl)$, $NHCO_2(C_{1-4}alkyl)$, $-S(C_{1-4}alkyl)$, $-NH_2$, $NH(C_{1-4}alkyl)$, $N(C_{1-4}alkyl)_2$, $N(C_{1-4}alkyl)_3^+$, $SO_2(C_{1-4}alkyl)$, $C(=O)(C_{1-4}alkylene)NH_2$, $C(=O)(C_{1-4}alkylene)NH(alkyl)$, and/or $C(=O)(C_{1-4}alkylene)N(C_{1-4}alkyl)_2$.

[0054] Exemplary monocyclic groups include azetidinyl, pyrrolidinyl, oxetanyl, imidazolinyl, oxazolidinyl, isoxazolinyl, thiazolidinyl, isothiazolidinyl, tetrahydrofuranyl, piperidyl, piperazinyl, 2-oxopiperazinyl, 2-oxopiperidyl, 2-oxopyrrolodinyl, 2-oxoazepinyl, azepinyl, 4-piperidonyl, tetrahydropyranyl, morpholinyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiamorpholinyl sulfone, 1,3-dioxolane, and tetrahydro-1,1-dioxothienyl, and the like. Exemplary bicyclic heterocyclo groups include quinuclidinyl.

[0055] Preferred heterocyclo groups in compounds of formula (I) include













and 

which optionally may be substituted.

[0056] The term "heteroaryl" alone or as part of another group refers to substituted and unsubstituted aromatic 5 or 6 membered monocyclic groups, 9 or 10 membered bicyclic groups, and 11 to 14 membered tricyclic groups which have at least one heteroatom (O, S or N) in at least one of the rings. Each ring of the heteroaryl group containing a heteroatom can contain one or two oxygen or sulfur atoms and/or from one to four nitrogen atoms provided that the total number of heteroatoms in each ring is four or less and each ring has at least one carbon atom. The fused rings completing the bicyclic and tricyclic groups may contain only carbon atoms and may be saturated, partially saturated, or unsaturated, and may include aryl, cycloalkyl, heteroaryl or cycloheteroaryl. The nitrogen and sulfur atoms may optionally be oxidized and the nitrogen atoms may optionally be quaternized. Heteroaryl groups which are bicyclic or tricyclic must include at least one fully aromatic ring but the other fused ring or rings may be aromatic or non-aromatic. The heteroaryl group may be attached at any available nitrogen or carbon atom of any ring. The heteroaryl ring system may contain zero, one, two or three substituents which may be any of the substituents set out for alkyl and can be selected from the group consisting of halogen, trifluoromethyl, trifluoromethoxy, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, nitro, cyano, OR_a, SR_a, (=S), $-NR_aR_b$, $-N(alkyl)_3^+$, $-NR_aSO_2$, $-NR_aSO_2R_c$, $-SO_2R_c$ $-SO_2NR_aR_b$, $-SO_2NR_aC(=O)R_b$, SO_3H, $-PO(OH)_2$, $-C(=O)R_a$, $-CO_2R_a$, $-C(=O)NR_aR_b$, $-C(=O)(C_{1-4}alkylene)NR_aR_b$, $-C(=O)NR_a(SO_2)R_b$, $-CO_2(C_{1-4}alkylene)NR_aR_b$, $-NR_aC(=O)R_b$, $-NR_aCO_2R_b$, $-NR_a(C_{1-4}alkylene)CO_2R_b$, aryl, cycloalkyl, heterocyclo, and/or heteroaryl, wherein R_a, R_b and R_c are as defined above for substituted alkyl groups, and are also in turn optionally substituted as recited above. When a heteroaryl is substituted with a further ring, said ring in turn is optionally substituted with one to two of (C_{1-4})alkyl, (C_{2-4})alkenyl, halogen, hydroxy, cyano, nitro, CF_3, $O(C_{1-4}alkyl)$, OCF_3, C(=O)H, $C(=O)(C_{1-4}alkyl)$, CO_2H, $CO_2(C_{1-4}alkyl)$, $NHCO_2(C_{1-4}alkyl)$, $-S(C_{1-4}alkyl)$, $-NH_2$, $NH(C_{1-4}alkyl)$, $N(C_{1-4}alkyl)_2$, $N(C_{1-4}alkyl)_3^+$, $SO_2(C_{1-4}alkyl)$, $C(=O)(C_{1-4}alkylene)NH_2$, $C(=O)(C_{1-4}alkylene)NH(alkyl)$, and/or $C(=O)(C_{1-4}alkylene)N(C_{1-4}alkyl)_2$.

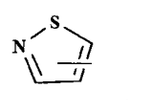
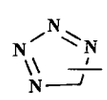
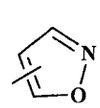
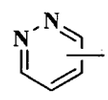
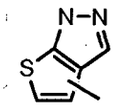
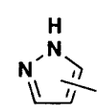
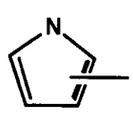
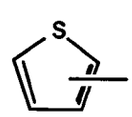
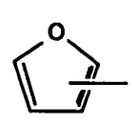
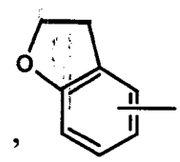
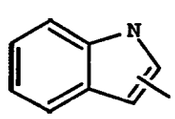
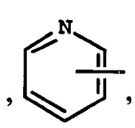
[0057] Exemplary monocyclic heteroaryl groups include pyrrolyl, pyrazolyl, pyrazolinyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, thiadiazolyl, isothiazolyl,

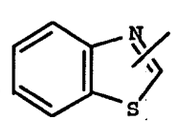
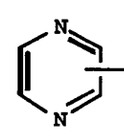
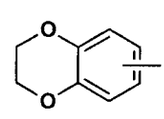
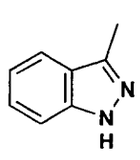
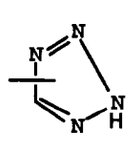
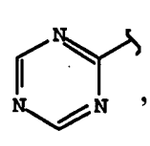
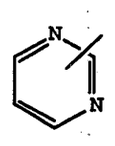
furanyl, thienyl, oxadiazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazinyl and the like.

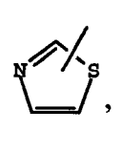
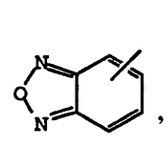
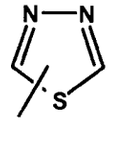
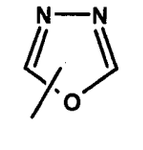
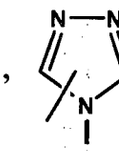
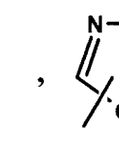
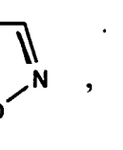
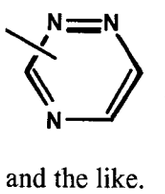
[0058] Exemplary bicyclic heteroaryl groups include indolyl, benzothiazolyl, benzodioxolyl, benzoxazolyl, benzothienyl, quinolinyl, tetrahydroisoquinolinyl, isoquinolinyl, benzimidazolyl, benzopyranyl, indolizinyl, benzofuranyl, chromonyl, coumarinyl, benzopyranyl, cinnolinyl, quinoxalinyl, indazolyl, pyrrolopyridyl, furopyridyl, dihydroisoindolyl, tetrahydroquinolinyl and the like.

[0059] Exemplary tricyclic heteroaryl groups include carbazolyl, benzidolyl, phenanthrollinyl, acridinyl, phenanthridinyl, xanthenyl and the like.

[0060] In compounds of formula (I), preferred heteroaryl groups include


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and the like.

[0061] The term " heterocyclylalkyl" or "heterocycloalkyl" or "cycloheteroalkylakyl" as used herein alone or as part of another group refers to heterocyclyl groups as defined above linked through a C atom or heteroatom to an alkyl chain.

[0062] The term "heteroarylalkyl" or "heteroarylalkenyl" as used herein alone or as part of another group refers to a heteroaryl group as defined above linked through a C atom or heteroatom to an alkyl chain, alkylene, or alkenylene as defined above.

[0063] The term "cyano" as used herein, refers to a -CN group.

[0064] The term "nitro" as used herein, refers to an $-NO_2$ group.

[0065] The term "hydroxy" as used herein, refers to an -OH group.

[0066] Unless otherwise indicated, when reference is made to a specifically-named aryl (*e.g.*, phenyl), cycloalkyl (*e.g.*, cyclohexyl), heterocyclo (*e.g.*, pyrrolidinyl) or heteroaryl (*e.g.*, imidazolyl), unless otherwise specifically indicated the reference is intended to include rings having 0 to 3, preferably 0-2, substituents selected from those recited above for the aryl, cycloalkyl, heterocyclo and/or heteroaryl groups, as appropriate.

[0067] The term "heteroatoms" shall include oxygen, sulfur and nitrogen.

[0068] The term "carbocyclic" means a saturated or unsaturated monocyclic or bicyclic ring in which all atoms of all rings are carbon. Thus, the term includes cycloalkyl and aryl rings. The carbocyclic ring may be substituted in which case the substituents are selected from those recited above for cycloalkyl and aryl groups.

[0069] When the term "unsaturated" is used herein to refer to a ring or group, the ring or group may be fully unsaturated or partially unsaturated.

[0070] Throughout the specification, groups and substituents thereof may be chosen by one skilled in the field to provide stable moieties and compounds and compounds useful as pharmaceutically-acceptable compounds and/or intermediate compounds useful in making pharmaceutically-acceptable compounds.

[0071] The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

[0072] As used herein, "pharmaceutically acceptable salts" refer to derivatives of the disclosed compounds wherein the parent compound is modified by making acid or base salts thereof.

[0073] The terms pharmaceutically acceptable "salt" and "salts" may refer to basic salts formed with inorganic and organic bases. Such salts include ammonium salts; alkali metal salts, such as lithium, sodium, and potassium salts (which are preferred); alkaline earth metal salts, such as calcium and magnesium salts; salts with organic bases, such as amine like salts (e.g., dicyclohexylamine salt, benzathine, N-methyl-D-glucamine, and hydrabamine salts); and salts with amino acids like arginine, lysine, and the like; and zwitterions, the so-called "inner salts." Nontoxic, pharmaceutically acceptable salts are preferred, although other salts are also useful, e.g., in isolating or purifying the product.

[0074] The term pharmaceutically acceptable "salt" and "salts" also includes acid addition salts. These are formed, for example, with strong inorganic acids, such as mineral acids, for example sulfuric acid, phosphoric acid, or a hydrohalic acid such as HCl or HBr, with strong organic carboxylic acids, such as alkanecarboxylic acids of 1 to 4 carbon atoms which are unsubstituted or substituted, for example, by halogen, for example acetic acid, such as saturated or unsaturated dicarboxylic acids, for example oxalic, malonic, succinic, maleic, fumaric, phthalic, or terephthalic acid, such as hydroxycarboxylic acids, for example ascorbic, glycolic, lactic, malic, tartaric, or citric acid, such as amino acids, (for example aspartic or glutamic acid or lysine or arginine), or benzoic acid, or with organic sulfonic acids, such as (C_1-C_4) alkyl or arylsulfonic acids, which are unsubstituted or substituted, for example by halogen, for example methanesulfonic acid or p-toluenesulfonic acid.

[0075] The pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in *Remington's*

Pharmaceutical Sciences, 17th ed., Mack Publishing Company, Easton, PA, 1985, p. 1418, the disclosure of which is hereby incorporated by reference.

[0076] Throughout the specification, groups and substituents thereof may be chosen by one skilled in the field to provide stable moieties and compounds and compounds useful as pharmaceutically-acceptable compounds and/or intermediate compounds useful in making pharmaceutically-acceptable compounds.

[0077] Any compound that can be converted in vivo to provide the bioactive agent (i.e., the compound of formula I) is a prodrug within the scope and spirit of the invention.

[0078] The term "prodrug" denotes a compound which, upon administration to a subject, undergoes chemical conversion by metabolic or chemical processes to yield a compound of the formula, and/or a salt and/or solvate thereof. For example, compounds containing a carboxy group can form physiologically hydrolyzable esters which serve as prodrugs by being hydrolyzed in the body to yield formula compounds *per se*. Such prodrugs are preferably administered orally since hydrolysis in many instances occurs principally under the influence of the digestive enzymes. Parenteral administration may be used where the ester *per se* is active, or in those instances where hydrolysis occurs in the blood.

[0079] The term "prodrugs" as employed herein includes esters and carbonates formed by reacting one or more hydroxyls of compounds of formula I with alkyl, alkoxy, or aryl substituted acylating agents employing procedures known to those skilled in the art to generate acetates, pivalates, methylcarbonates, benzoates, and the like.

[0080] Various forms of prodrugs are well known in the art and are described in:

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

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

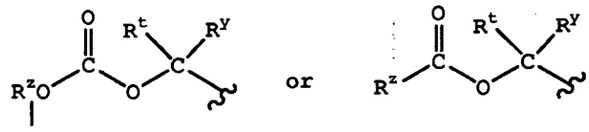
c) *A Textbook of Drug Design and Development*, P. Krogsgaard–Larson and H. Bundgaard, eds. Ch. 5, pp. 113-191 (Harwood Academic Publishers, 1991); and

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

Said references are incorporated herein by reference.

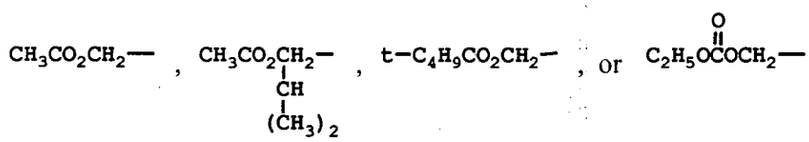
[0081] Examples of physiologically hydrolyzable esters of compounds of formula (I) include C_{1-6}alkylbenzyl, 4-methoxybenzyl, indanyl, phthalyl, methoxymethyl, C_{1-6}alkanoyloxy-C_{1-6}alkyl, *e.g.* acetoxymethyl, pivaloyloxymethyl, or propionyloxymethyl, C_{1-6}alkoxycarbonyloxy-C_{1-6}alkyl, *e.g.* methoxycarbonyl-oxymethyl or ethoxycarbonyloxymethyl, glycyloxymethyl, phenylglycyloxymethyl, (5-methyl-2-oxo-1,3-dioxolen-4-yl)-methyl, and other well known physiologically hydrolyzable esters used, for example, in the penicillin and cephalosporin arts. Such esters may be prepared by conventional techniques known in the art.

[0082] Prodrug ester examples include the following groups: (1-alkanoyloxy)alkyl such as,

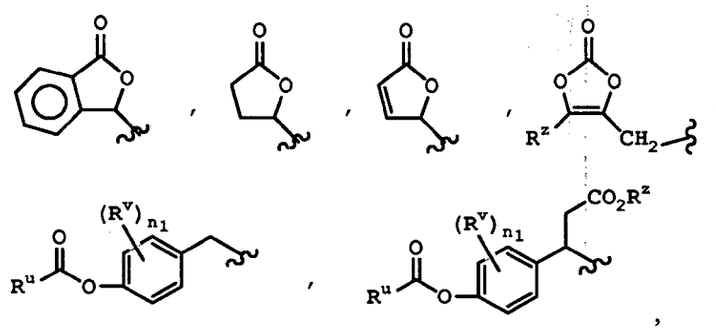


wherein R^z, R^t, and R^y are H, alkyl, aryl, or arylalkyl; however, R^zO cannot be HO.

[0083] Examples of such prodrug esters include



[0084] Other examples of suitable prodrug esters include



wherein R^z can be H, alkyl (such as methyl or t-butyl), arylalkyl (such as benzyl) or aryl (such as phenyl); R^v is H, alkyl, halogen or alkoxy, R^u is alkyl, aryl, arylalkyl, or alkoxyl, and n_1 is 0, 1, or 2.

[0085] The term "tautomer" refers to compounds of the formula I and salts thereof that may exist in their tautomeric form, in which hydrogen atoms are transposed to other parts of the molecules and the chemical bonds between the atoms of the molecules are consequently rearranged. It should be understood that the all tautomeric forms, insofar as they may exist, are included within the invention.

[0086] In addition, compounds of the formula I are, subsequent to their preparation, preferably isolated and purified to obtain a composition containing an amount by weight equal to or greater than 99% formula I compound ("substantially pure" compound I), which is then used or formulated as described herein. Such "substantially pure" compounds of the formula I are also contemplated herein as part of the present invention.

[0087] All stereoisomers of the compounds of the instant invention are contemplated, either in admixture or in pure or substantially pure form. The compounds of the present invention can have asymmetric centers at any of the carbon atoms including any one of the R substituents and/or exhibit polymorphism. Consequently, compounds of formula I can exist in enantiomeric, or diastereomeric forms, or in mixtures thereof. The processes for preparation can utilize racemates, enantiomers, or diastereomers as starting materials. When diastereomeric or enantiomeric products are prepared, they can be separated by conventional methods for example, chromatographic or fractional crystallization.

[0088] "Stable compound" and "stable structure" are meant to indicate a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent. The present invention is intended to embody stable compounds.

[0089] "Therapeutically effective amount" is intended to include an amount of a compound of the present invention alone or an amount of the combination of compounds claimed or an amount of a compound of the present invention in combination with other active ingredients effective to treat or prevent diabetes and/or obesity.

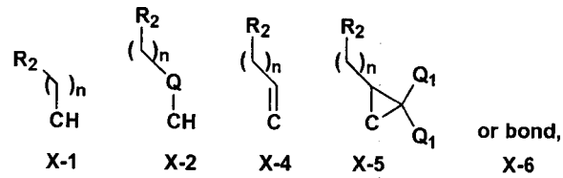
[0090] As used herein, "treating" or "treatment" cover the treatment of a disease-state in a mammal, particularly in a human, and include: (a) preventing the disease-state from occurring in a mammal, in particular, when such mammal is predisposed to

the disease-state but has not yet been diagnosed as having it; (b) inhibiting the disease-state, i.e., arresting its development; and/or (c) relieving the disease-state, i.e., causing regression of the disease state.

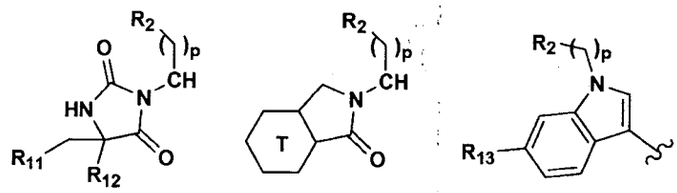
SYNTHESIS

[0091] Compounds of formulae I and Ia may be prepared as shown in the following reaction schemes and the description thereof, as well as relevant literature procedures that may be used by one skilled in the art. Exemplary reagents and procedures for these reactions appear hereinafter and in the working Examples. Protection and deprotection in the Schemes below may be carried out by procedures generally known in the art (see, for example, Greene, T.W. and Wuts, P.G.M., Protecting Groups in Organic Synthesis, 3rd Edition, 1999 [Wiley]).

[0092] The synthesis of amide compounds of formula I wherein X =

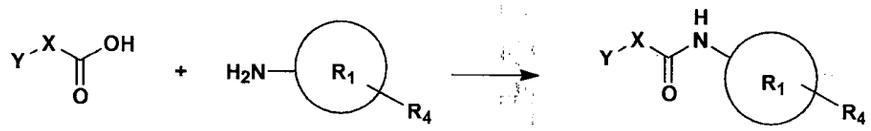


and when Y is absent,



is described in Scheme 1. The carboxylic acid 1 is coupled with amine 2 followed standard literature conditions, such as: (1) the use of oxalyl chloride with catalytic DMF to form the acid chloride intermediate followed by subsequent reaction with amine 2 in the presence of an amine base; or (2) the treatment of a mixture of 1 and 2 with a coupling reagent such as DEPBT (Li et al., *Org. Lett.*, **1999**, 1:91). Where the heteroaromatic ring R_1 is depicted in Scheme 1 and in all subsequent schemes described below, the optional ring substituents R_5 and R_6 may be present.

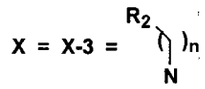
SCHEME 1



1 2 I

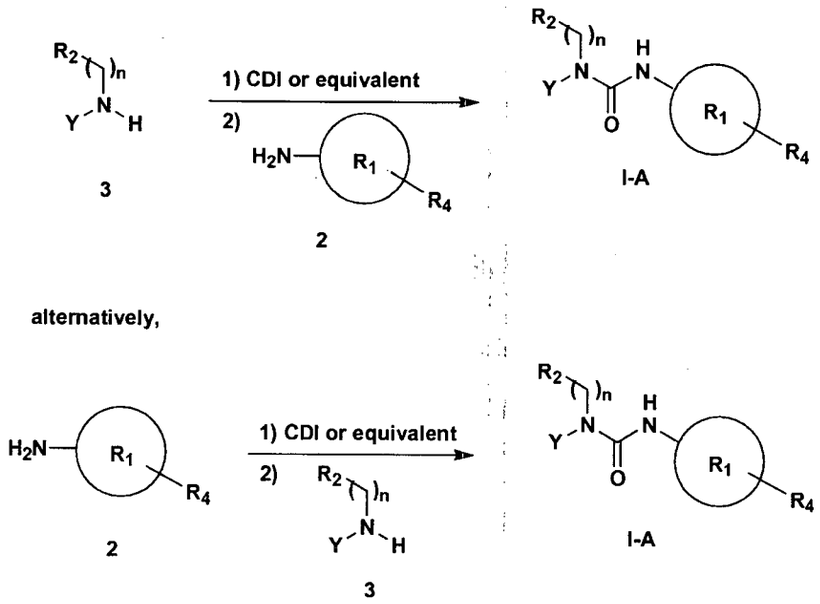
[0093] Procedures for the synthesis of pertinent examples of carboxylic acid 1 can be found in the literature (references include, but are not limited to, the following PCT Intl. Applications: for X-1, WO 2000/058293, WO 2001/083465, WO 2001/085706, WO 2001/085707, WO 2002/046173, WO 2003/095438, WO 2004/052869, WO 2004/072031, WO 2004/063194, WO 2004/072066, WO 2005/103021, WO 2006/016194, WO 2006/016174, WO 2006/016178; for X-2, WO 2002/008209, WO 2004/063194; for X-4, WO 2001/044216, WO 2004/072031, WO 2004/072066, WO 2004/063194, WO 2002/014312, WO 2005/103021, WO 2006/016194; for X-5, WO 2004/063179; for X-6, WO 2003/000262, WO 2003/000267, WO 2003/080585, WO 2003/015774, WO 2004/045614, WO 2004/046139, WO 2004/076420, WO 2005/121110; WO 2006/040528, WO 2006/040529, WO 2006/125972, WO 2007/007040, WO 2007/007041, WO 2007/007042, WO 2007/0017649; for X-7, WO 2001/083478; for X-8, WO 2002/048106; for X-9, WO 2004/031179.

[0094] The synthesis of urea compounds of formula I wherein



is described in Scheme 2. The amine 3 may be treated with a reagent such as carbonyldiimidazole, 4-nitrophenylchloroformate, phosgene, or a phosgene derivative such as diphosgene or triphosgene, followed by the addition of amine 2 to afford the desired urea product of formula I. Alternatively, amine 2 may be first treated with a reagent such as carbonyldiimidazole (or other like reagents as described above), followed by addition of amine 3 to provide ureas of formula I-A.

SCHEME 2



[0095] Procedures for the synthesis of pertinent examples of amine 3 are available in the literature (references include PCT Int. Applications WO2003/055482 and WO2004/002481; and Castellano et al., *Bioorg. Med. Chem. Lett.* **2005**, 15:1501).

[0096] Scheme 3 describes a general approach to the synthesis of amine 2A wherein

$R_4 = -(CH_2)_n-Z-(CH_2)_m-PO(OR_7)(OR_8)$

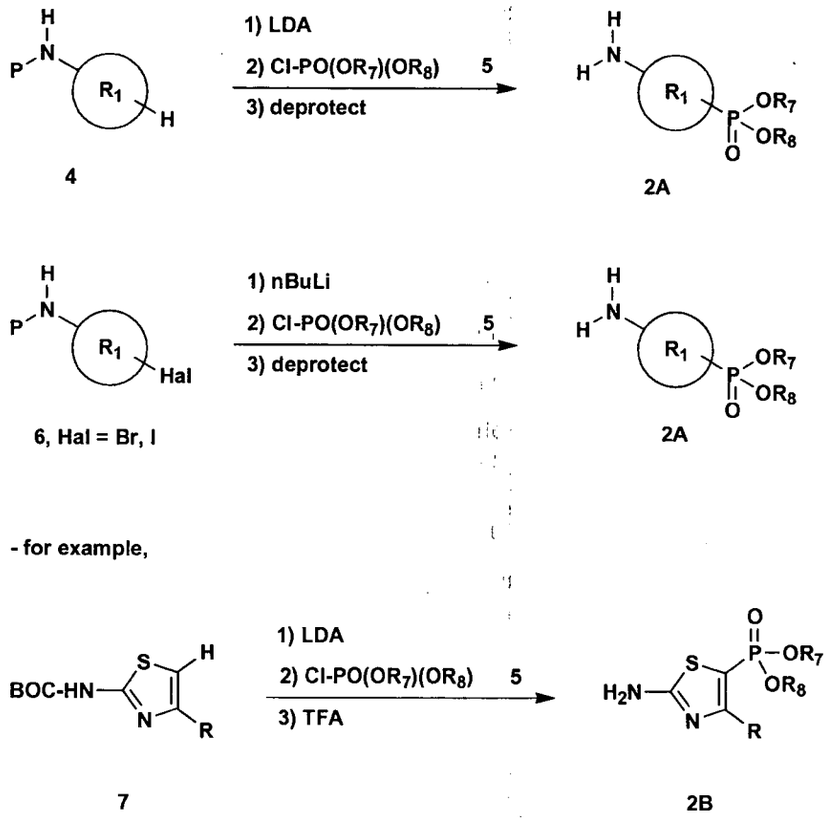
Z = bond

m and n = 0

i.e., where the resulting phosphonate group is directly attached to the heteroaromatic ring, R_1. A protected amino-substituted heteroaryl 4 with a suitably activated hydrogen substituent is deprotonated with a strong base such as LDA or n-butyllithium. The resulting anion is reacted with a dialkylchlorophosphate 5 resulting in direct attachment of the phosphonate group to R_1. Removal of the protecting groups provides amine 2A. Alternatively, the halo-substituted heteroaryl 6 can also be converted to the same anionic intermediate via halogen-metal exchange by reaction with a base such as n-butyllithium. This approach can also be extended to the synthesis of phosphinic acids by the use of a reagent such as N,N-diethylchloromethylphosphonamide to react with the anion intermediate (Rumthao et

al., *Bioorg. Med. Chem. Lett.*, **2004**, 14:5165-5170). As an example, the protected thiazole amine 7 may be deprotonated as shown in Scheme 3 using a base such as LDA or n-BuLi and phosphonylated as described to give, after deprotection, the 5-phosphonate-substituted thiazole amine 2B (South et al., *J. Het. Chem.*, **1991**, 28:1017).

SCHEME 3

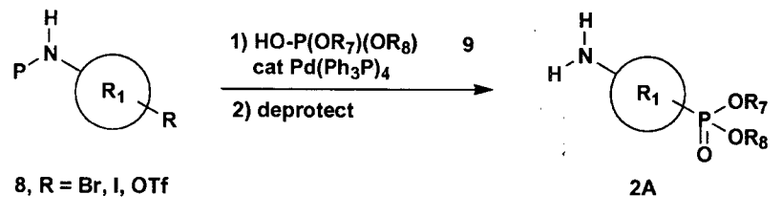


[0097] The reactions described in Scheme 3 above and Schemes 4, 5, 6, 7 and 8 below may also be conducted on compounds wherein the group Y-X-CO- has already been acylated to the amine 2 and where the chemistry is allowed by compatible structure in Y-X-CO- and/or the use of appropriate protecting groups.

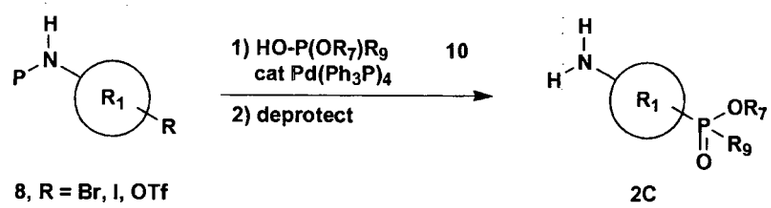
[0098] Scheme 4 describes another approach to the synthesis of amine 2A. The protected heteroaryl amine 8 containing a substituent such as bromo, iodo or triflate is coupled to dialkylphosphite 9 in the presence of a catalytic amount of palladium(0)

catalyst, such as tetrakis-triphenylphosphine palladium(0) to provide, after deprotection, the phosphonate substituted heteroaryl amine 2A (Hirao et al., *Synthesis*, **1981**, 56-57). The use of the reagent 10 in this reaction provides the corresponding phosphinate 2C (Rumthao et al., *Bioorg. Med. Chem. Lett.*, **2004**, 14:5165-5170). As an example, the reaction between the bromo pyridine 11 and dialkylphosphite 9 catalyzed by $Pd(Ph_3P)_4$ provides the phosphonylated pyridine compound I-B. Compound 11 is obtained by coupling acid 1 to 5-bromo-2-aminopyrazine in the manner described in Scheme 1.

SCHEME 4

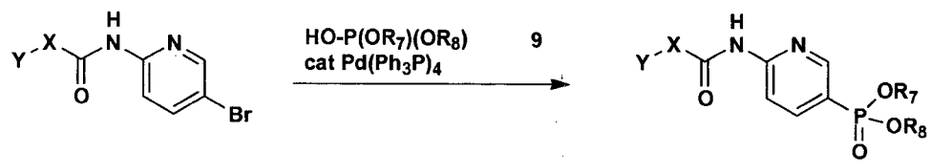


8, R = Br, I, OTf 2A



8, R = Br, I, OTf 2C

- for example,



11 I-B

[0099] Scheme 5 describes the synthesis of compounds of formula I in which

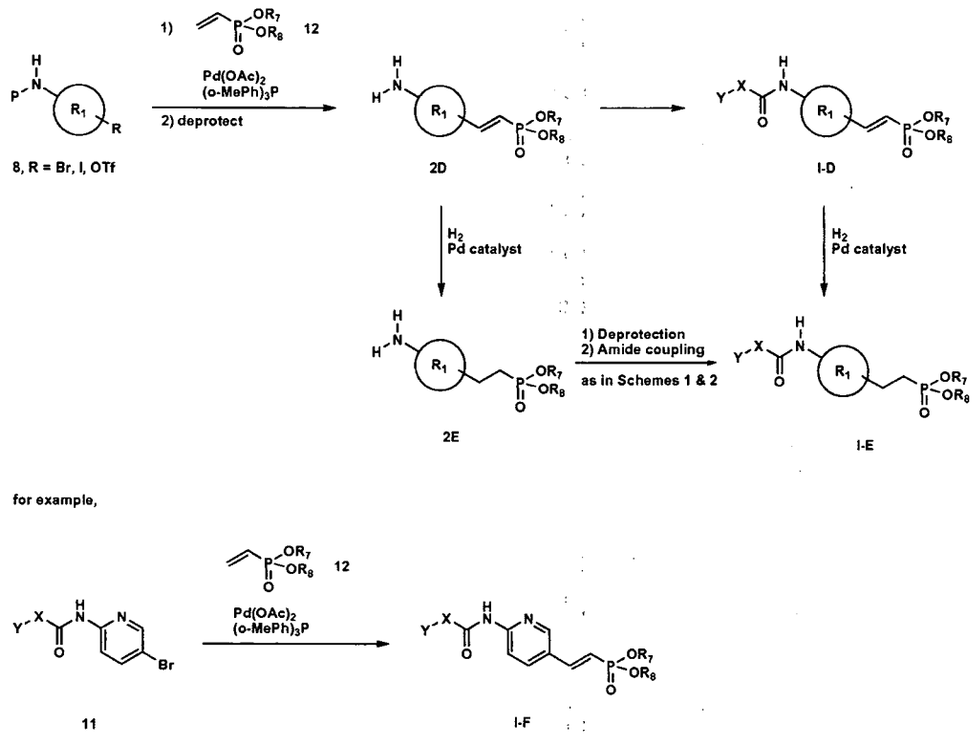
$R_4 = -(CH_2)_n-Z-(CH_2)_m-PO(OR_7)(OR_8)$

Z = alkene or ethylene

m and n = 0

thus connecting the phosphonate group to the heteroaromatic ring with a two-carbon linker. A suitably protected heteroaryl amine 8 is coupled to vinyl phosphonate 12 in the presence of catalytic amounts of a Pd(II) catalyst such as $Pd(OAc)_2$ and phosphine ligand such as tri-o-tolylphosphine to give a protected vinyl phosphonate intermediate product (Xu et al., *Synthesis*, **1983**, 556-558). Removal of protecting groups yields the vinyl phosphonate amine 2D which is converted to I-D, the corresponding compound of formula I wherein Z = alkene (vinyl) by the manner described in Schemes 1 and 2. Hydrogenation in the presence of catalytic Pd(0) of 2D and 1D provides the corresponding ethylene (two-carbon) linked phosphonate compounds, 2E and 1-E. As mentioned earlier, these transformations can be conducted on a fully elaborated intermediate such as described conversion of aminopyrazine amide 11 to the vinyl phosphonate substituted pyrazine product I-F.

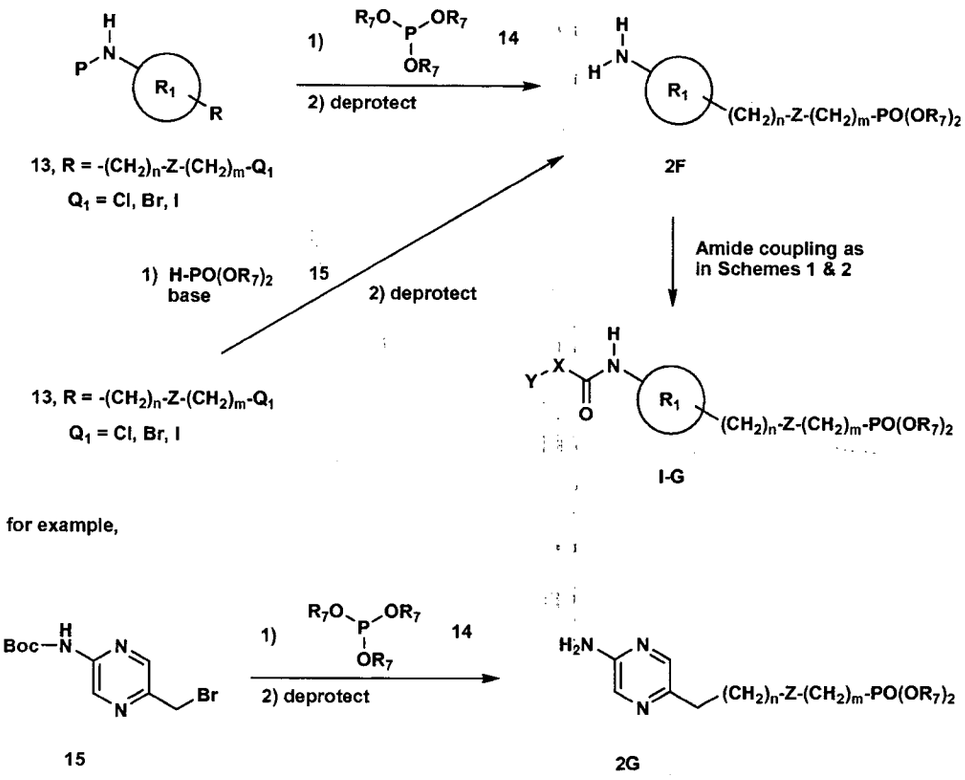
SCHEME 5



[00100] Scheme 6 describes the synthesis of compounds of formula I in which the phosphonate or phosphinate groups in R_4 are incorporated using the Arbusov (Engel,

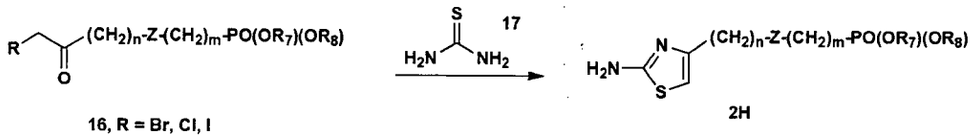
R., Handbook of Organophosphorus Chemistry, 1992 [Marcel Dekker]) or Michaelis-Becker (Engel, R., Handbook of Organophosphorus Chemistry, 1992 [Marcel Dekker]) reactions. In the Arbusov reaction, the alkyl halide 13 is heated with the trialkylphosphite 14 to yield, after removal of protecting groups, amine 2F. Amine 2F is converted to compounds of formula IG by means described in Schemes 1 and 2. When carried out using $R_9P(OR_7)_2$ instead of the trialkylphosphite 14, the corresponding phosphinic ester product is obtained (i.e., where $R_4 = -(CH_2)_n-Z-(CH_2)_m-PO-(R_9)(OR_7)$ (Kapustin et al., *Org. Lett.*, **2003**, 5:3053-3057). In the Michaelis-Becker reaction, compound 13 is reacted with dialkylphosphite 15 in the presence of base to yield, after removal of protecting groups, amine 2F. Amine 2F can be converted to compounds of formula I-G by means described in Schemes 1 and 2. As an example, the Boc-protected 5-bromomethylpyrazine can heated with trialkylphosphite 14 to give, after removal of the Boc group, the phosphonomethyl-substituted pyrazine amine 2G, which can be converted to compounds of formula I as described above.

SCHEME 6.

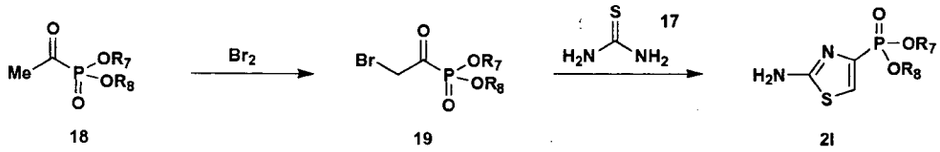


[00101] Scheme 7 describes the synthesis compounds of formula I in which the R_1 heteroaromatic ring is a thiazole. In this scheme, the phosphonate or phosphinate group in incorporated into an acyclic precursor to the formation of the heteroaromatic ring. In a standard Hantzsch thiazole synthesis, haloketone 16 is reacts with thiourea 17 to form the 4-substituted, 2-aminothiazole 2H. As an example, acetylphosphonic acid 18 is treated with bromine to form the α-haloketone 19. The reaction of 19 with thiourea 17 affords the 5-phosphono-2-aminothiazole 2I (Ohler et al., *Chem. Ber.*, **1984**, 117:3034-3047). The aminothiazoles 2H and 2I may be converted to compounds of formula I by means described in Scheme 1 and 2.

SCHEME 7



for example,



[00102] Scheme 8 describes the synthesis of compounds of formula I in which

R_4 = -$(CH_2)_n$-Z-(CH_2)m-$PO(OR_7)(OR_8)$

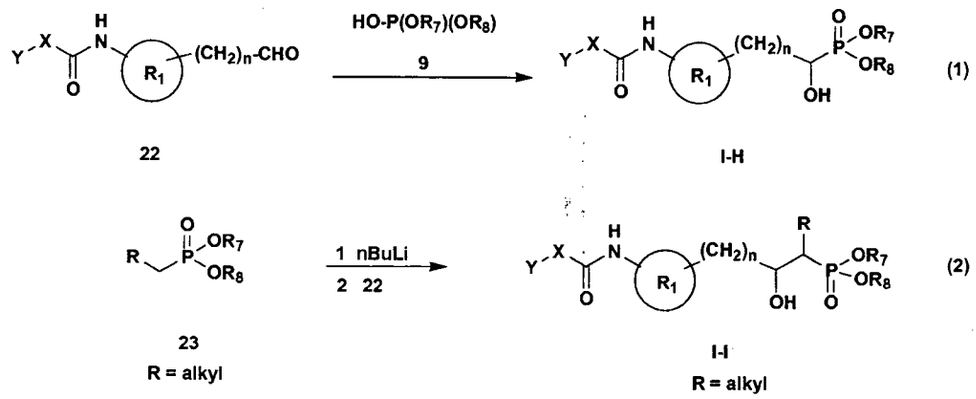
Z = CH(OH)

m = 0, 1

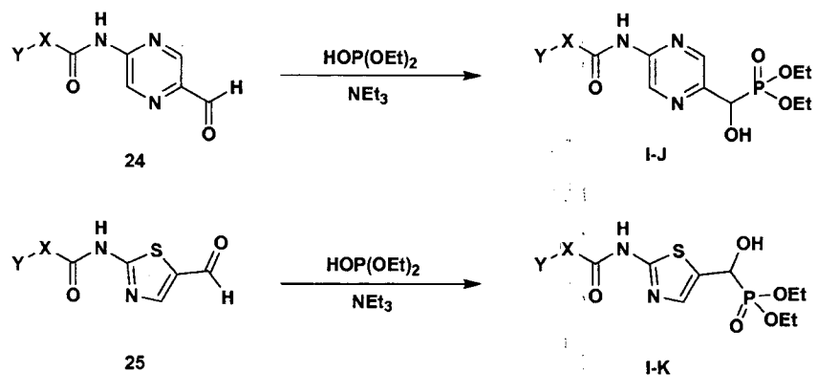
n = 0, 1, 2

i.e., compounds in which R_4 contains a hydroxy-substituted methylene [Z = CH(OH)] positioned between the heteroaromatic ring R_1 and the phosphonate group. In equation (1), reaction of dialkylphosphite 9 with aldehyde 22 in the presence of a base such as triethylamine or DBN gives the hydroxyphosphonate product I-H (Caplan et al., *J. Chem. Soc. Perkin I*, **2000**, 3:421-437), representing a compound of formula I in which Z = CH(OH), n = 0,1,2 and m = 0. In equation (2), alkyl phosphonate 23 is treated with a base such as n-BuLi, followed by addition of aldehyde 22 gives the hydroxyphosphonate product I-I (Mikolajczyk et al., *Synthesis*, **1984**, 691-694), representing a compound of formula I in which Z = CH(OH), n = 0, 1, 2 and m = 1. As examples, the pyrazine 24 and thiazole 25 are converted as shown to the corresponding hydroxyphosphonates, I-J and I-K.

SCHEME 8



for example,



[00103] Scheme 9 describes the synthesis of compounds of formula I in which

$R_4 = -(CH_2)_n\text{-}Z\text{-}(CH_2)_m\text{-}PO(OR_7)(OR_8)$

$Z = CH(OR_9)$

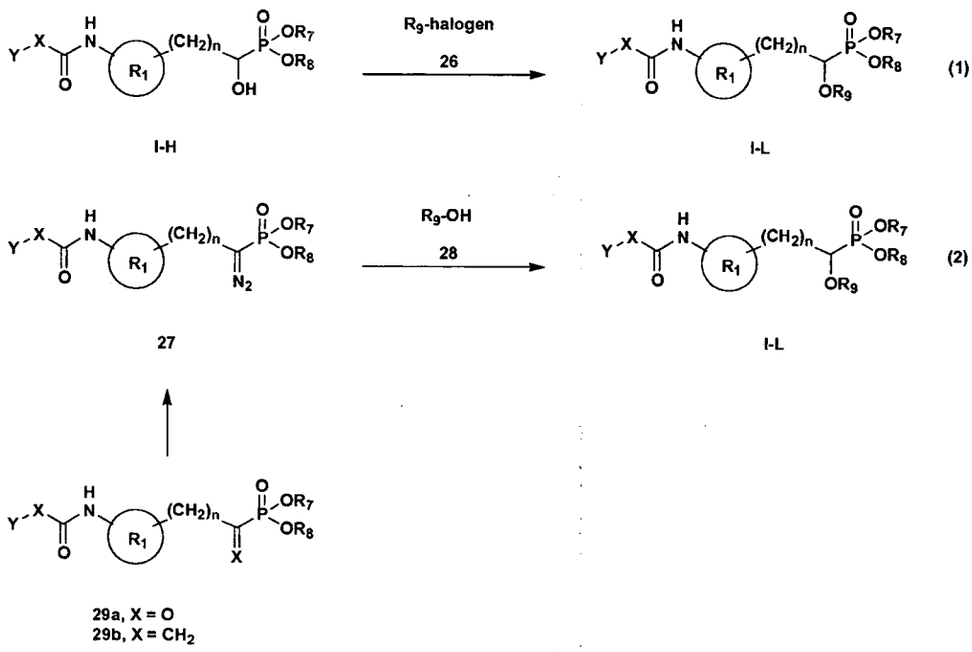
$m = 0$

$n = 0, 1, 2$

i.e., compounds in which R_4 contains a alkoxy-substituted methylene [$Z = CH(OR_9)$] positioned between the heteroaromatic ring R_1 and the phosphonate group. In equation (1), the hydroxyl phosphonate products of Scheme 8 may be alkylated with suitable active alkyl halides 26 to give the alpha-alkoxy phosphonates I-L (Wrobleski et al., *Tetrahedron Asymmetry*, **2002**, 13:845-850). Alternatively, equation (2) depicts the rhodium-catalyzed insertion reaction of alcohols 28 with alpha-diazo phophonates 27 which also provides compounds I-L (Cox, G. et al., *Tetrahedron*,

1994, 50:3195-3212; Moody, C. et al., *Tetrahedron Asymmetry*, **2001**, 12:1657-1661). The preparation of alpha-diazo phosphonates 28 has been described by direct diazo transfer to the corresponding ketone 29a (Regitz, M., *Tetrahedron Lett.*, **1968**, 9:3171-3174). Alternatively, the diazo phosphonates 28 can be obtained via base-catalyzed decomposition of the alpha-toluenesulfonylhydrazides derived from the corresponding keto phosphonates 29b (Marmor, R. et al., *J. Org. Chem.*, **1971**, 36:128-136). The alpha-keto phosphonates 29a may be synthesized directly from alpha-hydroxy phosphonates (I-H) by oxidation using a reagent such as CrO_3 (Kaboudin, B. et al., Tetrahedron Lett., **2000**, 41:3169-2171). Alternatively, the Arbusov reaction between an acid chloride and trialkylphosphite yields the corresponding alpha-keto phosphonate (Marmor, R., et al., *J. Org. Chem.*, **1971**, 36:128-136). Methods for the synthesis of phosphonates such as 29a have been described above.

SCHEME 9



[00104] Scheme 10 describes the synthesis of compounds of formula I in which

$R_4 = -(CH_2)_n-Z-(CH_2)_m-PO(OR_7)(OR_8)$

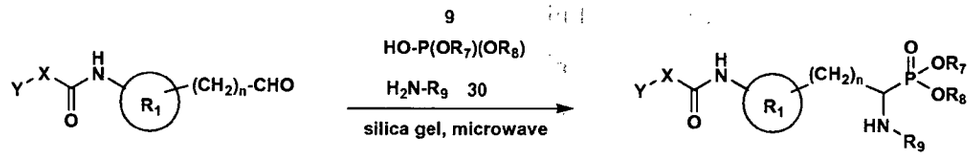
$Z = CH(NHR_9)$

m = 0

n = 0, 1, 2

i.e., compounds in which R_4 contains an amino-substituted methylene [Z = $CH(NHR_9)$] positioned between the heteroaromatic ring R_1 and the phosphonate group. In Scheme 10, aldehyde 22 can be reacted with a dialkylphosphite 9 and amine 30 to give the alpha-amino substituted phosphonate I-M by conducting the reaction in the presence of silica gel and microwave irradiation (Zhan et al., *Chem. Lett.*, **2005**, 34:1042-1043). Other methods involve preformation of the corresponding imine resulting from condensation of the aldehyde 22 and amine 30, which is followed by reaction with the dialkylphosphite 9 in the presence of various catalysts such as Lewis acids (Laschat and Kunz, *Synthesis*, **1992**, 90). Furthermore, other catalysts may be used for the one-pot synthesis described in Scheme 10 (for example, use of SmI_2 is described in Xu et al., *Eur. J. Org. Chem.*, **2003**, 4728).

SCHEME 10

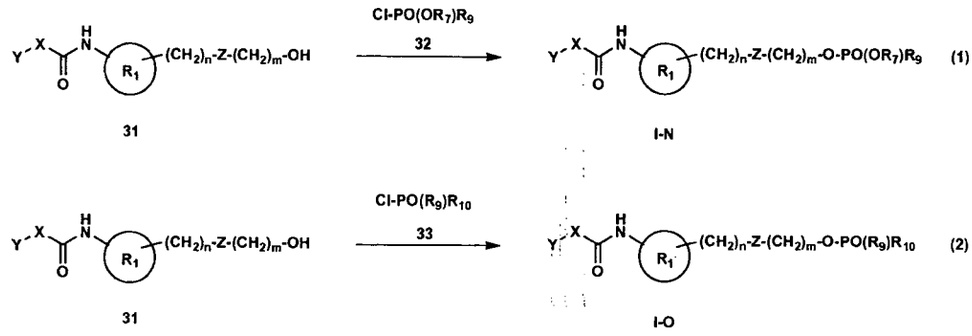


[00105] Scheme 11 describes the synthesis of compounds of formula I in which $R_4 = -(CH_2)_n-Z-(CH_2)_m-O-PO(OR_7)R_9$ and $-(CH_2)_nZ-(CH_2)_m-O-PO-R_9R_{10}$.

[00106] Reaction of the alcohol precursor 31 with the a phosphonyl chloride 32 or phosphinyl chloride 33 in the presence of a base such as pyridine or triethylamine yields the phosphonate compound I-N (equation 1) or the phosphinate compound I-O (equation 2). In addition to the reaction shown for the synthesis of phosphonates I-N, other methods include the direct esterification of a phosphonic acid or the use of the Mitsunobu reaction (Saady et al., *Tetrahedron Lett.*, **1995**, 36:2239-2242). The preparation of phosphinic esters of dimethylphosphinic acid (I-O wherein R_9 and R_{10} = Me) has been described using dimethylphosphinyl chloride and tetrazole in the

presence of pyridine to produce an intermediate phosphinyl tetrazolide (PCT Intl. Application WO 2000/078763).

SCHEME 11



[00107] Scheme 12 describes the synthesis of compounds of formula I in which

$R_4 = -(CH_2)_n-Z-(CH_2)_m-O-PO(OR_7)R_9$

and $-(CH_2)_nZ-(CH_2)_m-O-PO-(R_9)R_{10}$,

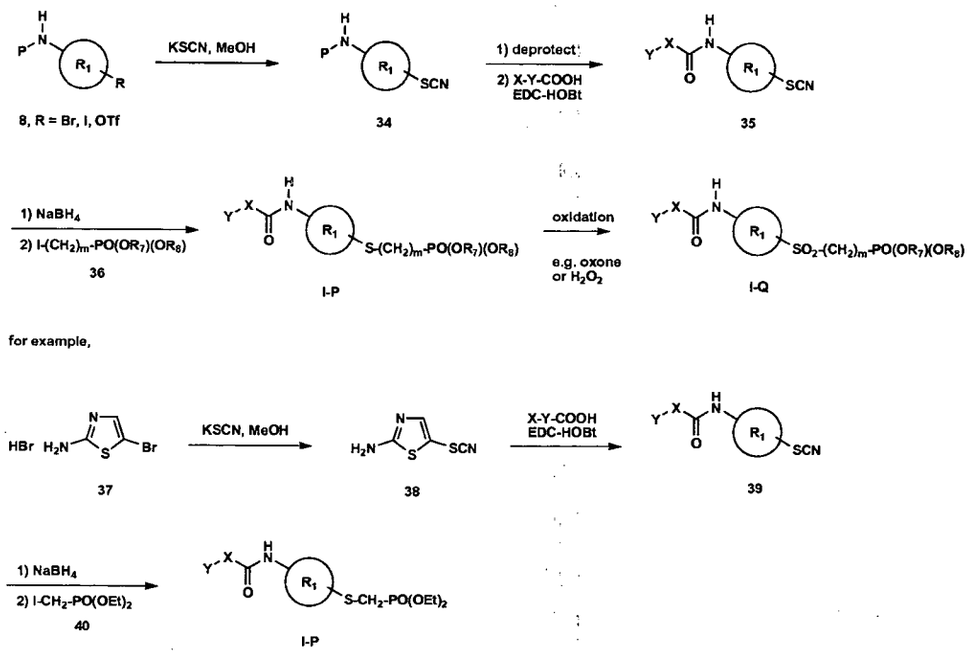
and Z = S or SO_2,

and m = 1 or 2,

and n = 0, 1 or 2.

[00108] Reaction of a suitably activated halogen-substituted heteroaromatic intermediate 8 with potassium thiocyanate gives the thiocyanate intermediate 34. At this point, protecting groups may be removed and the resulting amino heteroaromatic compound coupled with acid 1 using standard means such as EDC-HOBt to give intermediate 35. Treatment of thiocyanate 35 with $NaBH_4$ yields the corresponding thiol intermediate which is alkyated with the substituted halide 36 to give compounds of formula I wherein Z = S (I-P). Treatment of the product I-P with oxidizing agents such as hydrogen peroxide or oxone gives compounds of formula I wherein Z = SO_2 (I-Q). As an example, treatment of the HBr salt of 2-amino-5-bromothiazole (37) with, for instance, potassium thiocyanate, affords thiocyanate 38. The amino-thiocyanate product is acylated with acid 1 using standard means to give the amide 39. Reduction of the thiocyanate group of 39 with a reagent such as $NaBH_4$, followed by alkylation of the resulting free thiol with iodomethyl phosphonate 40 gives phosphonate compounds of formula I where Z = S, m = 1 and n = 0 (I-P).

SCHEME 12



[00109] Scheme 13 describes the synthesis of compounds of formula I in which

$R_4 = -(CH_2)_n-Z-(CH_2)_m-O-PO(OR_7)R_9$

and $-(CH_2)_nZ-(CH_2)_m-O-PO-(R_9)R_{10}$,

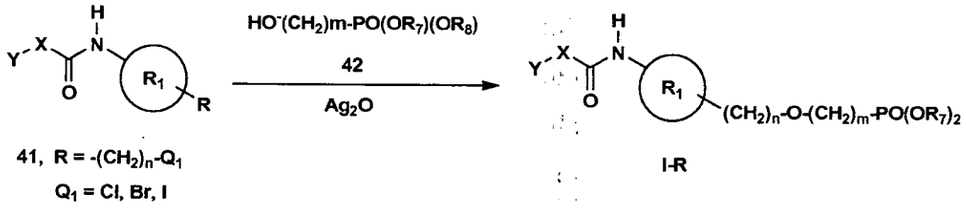
and Z = O,

and m = 1 or 2,

and n = 0, 1 or 2.

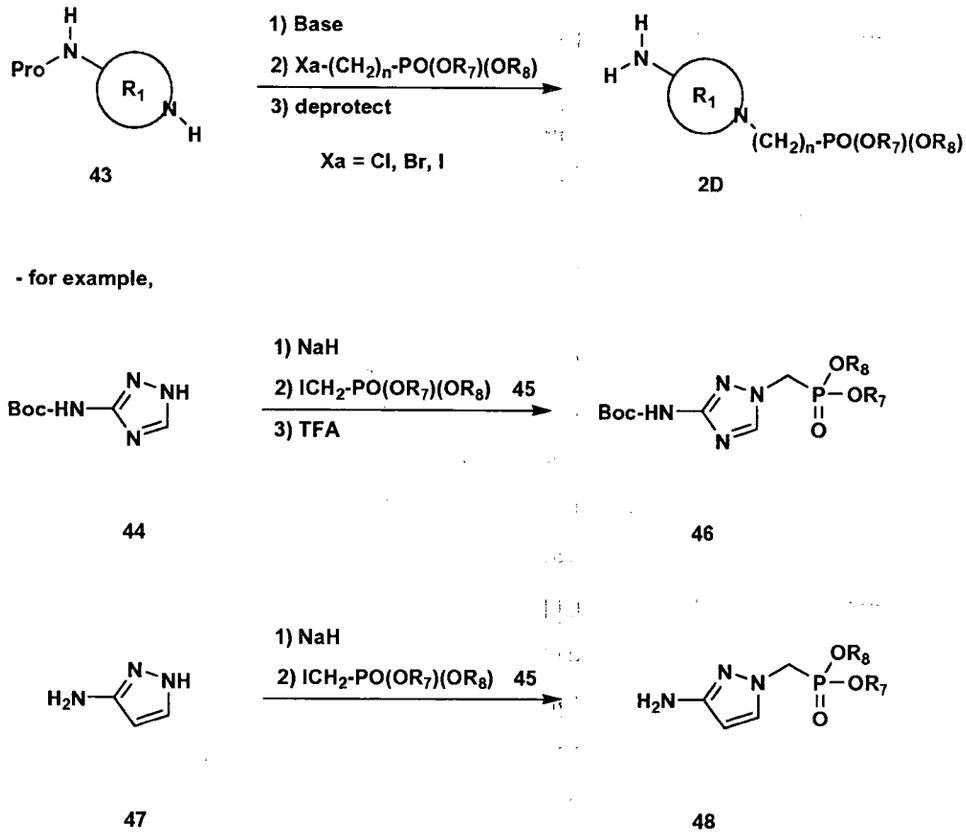
[00110] Reaction of a suitably activated halogen-substituted heteroaromatic intermediate 41 with the hydroxy substituted phosphonate intermediate 42 in the presence of silver oxide yields I-R, the phosphonate compound of formula I in which Z = O, m = 1 or 2, and n = 0, 1 or 2 (Flor et al., *J. Med. Chem.*, **1999**, 42:2633-2640).

SCHEME 13



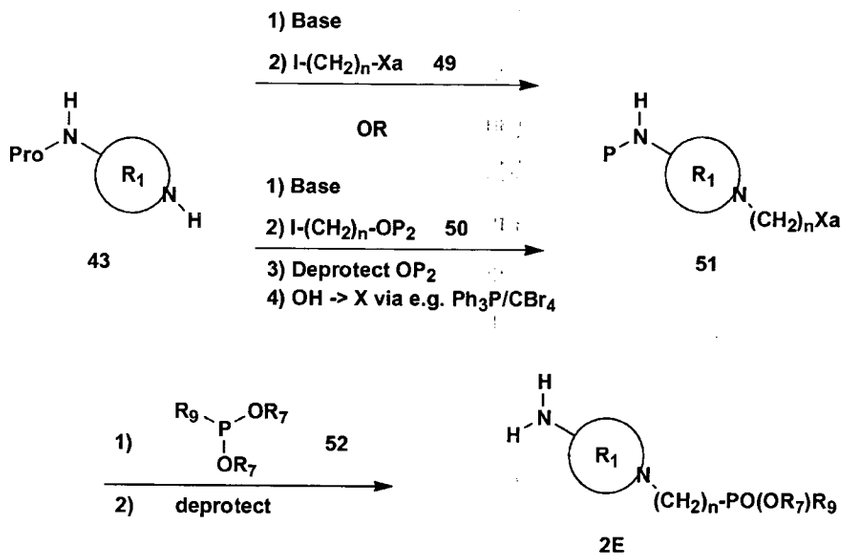
[00111] Scheme 14 describes a general synthesis of amine 2D, where the phosphonate or phosphinate moiety (here illustrated by a phosphonate) is linked to the heterocycle R1 by a nitrogen atom rather than a carbon atom. A protected (Pro)amino-heterocyle such as 43 can be deprotonated with a base followed by alkylation with an appropriate halide containing the phosphonate/phosphinate moiety followed by deprotection to give amine 2D. This is illustrated by the example of the N-Boc protected triazole 44, which is deprotonated with a base (e.g. NaH), then alkylated with an iodomethyl phosphonate 45. Deprotection of the N-Boc group then furnishes the aminotriazole phosphonate 46. On the other hand, in certain cases, the amino-heterocycle does not need to be protected, as illustrated in the case of the pyrazole 47, which can be deprotonated with a base such as KOtBu and alkylated preferentially on the ring nitrogen with electrophiles such as an iodomethyl phosphonate 45 to form product 48.

SCHEME 14



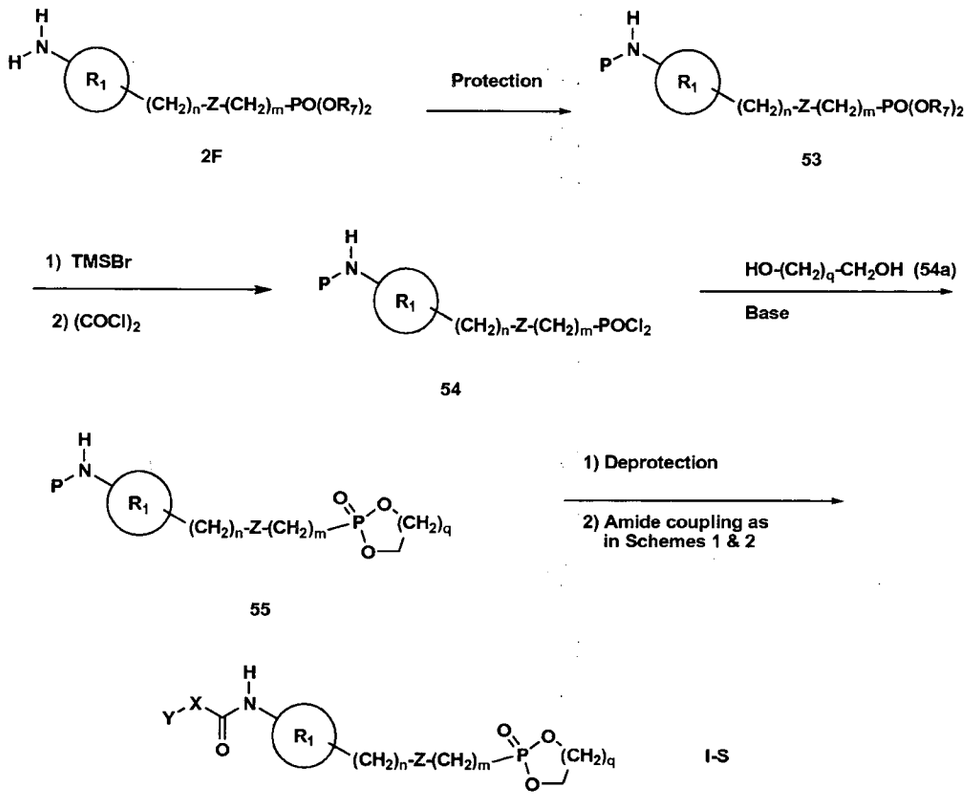
[00112] An alternative representative approach to N-alkylated phosphonates/phosphinates is shown in Scheme 15. Amine 43 can be deprotonated with an appropriate base and reacted with an iodide such as 49 (containing a functional group Xa, e.g. Cl, Br, OTs) to give the N-alkylated heterocycle 51. Alternatively, amine can be reacted with an iodide such as 50 (containing e.g., a protected hydroxyl group OP_2, which can subsequently be deprotected and converted to a halide via known methods, e.g. Ph_3P/CBr_4) to provide the N-alkylated heterocycle 51. This intermediate then can be reacted with either a trialkyl phosphate (Arbusov reaction) as described in Scheme 6 to provide a phosphonate, or, as shown here. When halide 51 is reacted with the phosphonite 52, the product is the corresponding phosphinic ester 2E (reference: Kapustin et al., *Org. Lett.*, **2003**, 5:3053-3057).

SCHEME 15



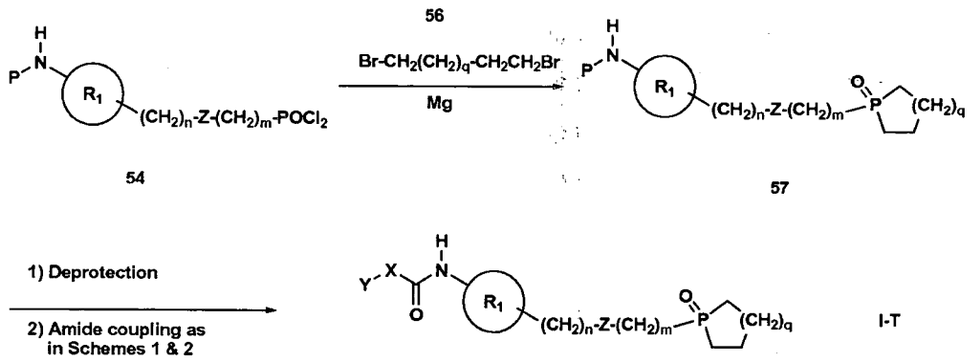
[00113] Scheme 16 describes the synthesis of compounds of formula I-S which contain cyclic phosphonate esters. The phosphonate diester of intermediate amine 2F is protected (e.g. as a tert-butyl carbamate or as a benzyl carbamate) to give the phosphonate 53, which is dealkylated with an agent such as bromotrimethylsilane. The resulting bis-trimethylsilyl phosphonic acid ester is reacted directly with oxalyl chloride to give the phosphoryl dichloride 54. Intermediate 54 is converted to the desired cyclic phosphonate 55 by reaction with an appropriate diol 54a in the presence of a base (reference: Notter et al., *Bioorg. Med. Chem. Lett.*, **2007**, 17:113-117) . Deprotection of 55 gives the corresponding amine, which is then readily converted to compounds of formula I-S by the methods previously described in Schemes 1 and 2.

SCHEME 16



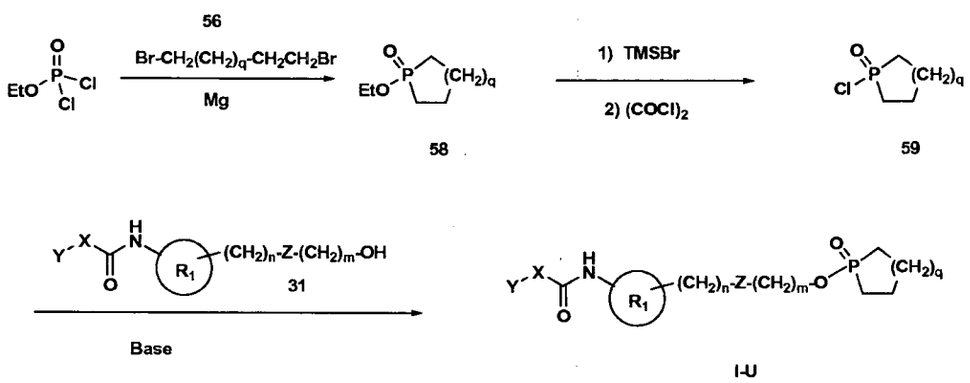
[00114] Similarly, Scheme 17 describes the synthesis of compounds of formula I-T which contain cyclic phosphine oxides. The phosphoryl dichloride 54 can be reacted with a Grignard reagent formed from a dibromide 56 and magnesium to provide the cyclic phosphine oxide 57 (ref: R. Polniaszek et. al., *J. Org. Chem.*, **1991**, 56:3137-3146). Deprotection of 57 gives the corresponding amine, which is then converted to compounds of formula I-T by the methods previously described in Schemes 1 and 2.

SCHEME 17



[00115] Scheme 18 describes the synthesis of compounds of formula I-U which contain cyclic phosphinates. Ethyl dichlorophosphate is reacted with a Grignard reagent formed from a dibromide 56 and magnesium to give the cyclic phosphinate ester 58 (ref: R. Polniaszek et. al., *J. Org. Chem.*, **1991**, 56:3137-3146). Ester 58 is dealkylated (e.g. with bromotrimethylsilane). The resulting trimethylsilyl phosphonic acid ester is reacted directly with a chlorinating agent (e.g. oxalyl chloride) to give the phosphoryl chloride 59, which is then reacted with alcohol 31 in the presence of a base to give compounds of formula I-U.

SCHEME 18



UTILITIES AND COMBINATIONS

A. Utilities

[00116] The compounds of the present invention possess activity as enhancers of activity of the enzyme glucokinase, and, therefore, may be used in the treatment of diseases associated with glucokinase activity.

[00117] Accordingly, the compounds of the present invention can be administered to mammals, preferably humans, for the treatment of a variety of conditions and disorders, including, but not limited to, treating, preventing, or slowing the progression of diabetes and related conditions, microvascular complications associated with diabetes, macrovascular complications associated with diabetes, cardiovascular diseases, Metabolic Syndrome and its component conditions, and other maladies. Consequently, it is believed that the compounds of the present invention may be used in preventing, inhibiting, or treating diabetes, hyperglycemia, impaired glucose tolerance, insulin resistance, hyperinsulinemia, retinopathy, neuropathy, nephropathy, delayed wound healing, atherosclerosis and its sequelae, abnormal heart function, myocardial ischemia, stroke, Metabolic Syndrome, hypertension, obesity, dyslipidemia, hyperlipidemia, hypertriglyceridemia, hypercholesterolemia, low HDL, high LDL, non-cardiac ischemia, infection, cancer, vascular restenosis, pancreatitis, neurodegenerative disease, lipid disorders, cognitive impairment and dementia, bone disease, HIV protease associated lipodystrophy, and glaucoma.

[00118] Metabolic Syndrome or "Syndrome X" is described in Ford, et al., *J. Am. Med. Assoc.*, **2002**, 287:356-359 and Arbeeny et al., *Curr. Med. Chem. - Imm., Endoc. & Metab. Agents*, **2001**, 1:1-24.

B. Combinations

[00119] The present invention includes within its scope pharmaceutical compositions comprising, as an active ingredient, a therapeutically effective amount of at least one of the compounds of formula I, alone or in combination with a pharmaceutical carrier or diluent. Optionally, compounds of the present invention can be used alone, in combination with other compounds of the invention, or in

combination with one or more other therapeutic agent(s), e.g., an antidiabetic agent or other pharmaceutically active material.

[00120] The compounds of the present invention may be employed in combination with other enhancers of activity of glucokinase or one or more other suitable therapeutic agents useful in the treatment of the aforementioned disorders including: anti-diabetic agents, anti-hyperglycemic agents, anti-hyperinsulinemic agents, anti-retinopathic agents, anti-neuropathic agents, anti-nephropathic agents, anti-atherosclerotic agents, anti-infective agents, anti-ischemic agents, anti-hypertensive agents, anti-obesity agents, anti-dyslipidemic agents, anti-hyperlipidemic agents, anti-hypertriglyceridemic agents, anti-hypercholesterolemic agents, anti-ischemic agents, anti-cancer agents, anti-cytotoxic agents, anti-restenotic agents, anti-pancreatic agents, lipid lowering agents, appetite suppressants, memory enhancing agents, and cognitive agents.

[00121] Examples of suitable anti-diabetic agents for use in combination with the compounds of the present invention include insulin and insulin analogs: LysPro insulin, inhaled formulations comprising insulin; glucagon-like peptides; sulfonylureas and analogs: chlorpropamide, glibenclamide, tolbutamide, tolazamide, acetohexamide, glypizide, glyburide, glimepiride, repaglinide, meglitinide; biguanides: metformin, phenformin, buformin; alpha2-antagonists and imidazolines: midaglizole, isaglidole, deriglidole, idazoxan, efaroxan, fluparoxan; other insulin secretagogues: linogliride, insulinotropin, exendin-4, BTS-67582, A-4166; thiazolidinediones (PPARgamma agonists): ciglitazone, pioglitazone, troglitazone, rosiglitazone; non-thiazolidinedione PPAR-gamma agonists; selective PPARgamma modulators (SPPARMs; e.g. metaglidasen from Metabolex); PPAR-alpha agonists; PPAR alpha/gamma dual agonists; PPAR delta agonists, PPARalpha/gamma/delta pan agonists; SGLT2 inhibitors; dipeptidyl peptidase-IV (DPP4) inhibitors; aldose reductase inhibitors; RXR agonists: JTT-501, MX-6054, DRF2593, LG100268; fatty acid oxidation inhibitors: clomoxir, etomoxir; α-glucosidase inhibitors: precose, acarbose, miglitol, emiglitate, voglibose, MDL-25,637, camiglibose, MDL-73,945; beta-agonists: BRL 35135, BRL 37344, Ro 16-8714, ICI D7114, CL 316,243, TAK-667, AZ40140; phosphodiesterase inhibitors, both cAMP and cGMP type: sildenafil, L686398: L-386,398; amylin antagonists: pramlintide, AC-137; lipoxygenase

inhibitors: masoprocal; somatostatin analogs: BM-23014, seglitide, octreotide; glucagon antagonists: BAY 276-9955; insulin signaling agonists, insulin mimetics, PTP1B inhibitors: L-783281, TER17411, TER17529; gluconeogenesis inhibitors: GP3034; somatostatin analogs and antagonists; antilipolytic agents: nicotinic acid, acipimox, WAG 994; glucose transport stimulating agents: BM-130795; glucose synthase kinase inhibitors: lithium chloride, CT98014, CT98023; and galanin receptor agonists.

[00122] Other suitable thiazolidinediones include Mitsubishi's MCC-555 (disclosed in U.S. Patent No. 5,594,016), Glaxo-Wellcome's farglitazar (GI-262570), englitazone (CP-68722, Pfizer), or darglitazone (CP-86325, Pfizer), isaglitazone (MIT/J&J), JTT-501 (JPNT/P&U), L-895645 (Merck), R-119702 (Sankyo/WL), NN-2344 or balaglitazone (Dr. Reddy/NN), or YM-440 (Yamanouchi).

[00123] Suitable PPAR alpha/gamma dual agonists include muraglitazar (Bristol-Myers Squibb), tesaglitazar (Astra/Zeneca), naveglitazar (Lilly/Ligand); AVE-0847 (Sanofi-Aventis); TAK-654 (Takeda), as well as those disclosed by Murakami et al, "A Novel Insulin Sensitizer Acts As a Coligand for Peroxisome Proliferation – Activated Receptor Alpha (PPAR alpha) and PPAR gamma; Effect of PPAR alpha Activation on Abnormal Lipid Metabolism in Liver of Zucker Fatty Rats", Diabetes 47:1841-1847 (1998), WO 01/21602 and U.S. 6,414,002, the disclosure of which is incorporated herein by reference, employing dosages as set out therein, which compounds designated as preferred are preferred for use herein. Suitable PPARdelta agonists include, for example, GW-501516 (Glaxo). Suitable PPARalpha/gamma/ delta pan agonists include, for example, GW-677954 (Glaxo).

[00124] Suitable alpha2 antagonists also include those disclosed in WO 00/59506, employing dosages as set out herein.

[00125] Suitable SGLT2 inhibitors include T-1095, phlorizin, WAY-123783, and those described in WO 01/27128.

[00126] Suitable DPP4 inhibitors include saxagliptin (Bristol-Myers Squibb), vildagliptin (Novartis) and sitagliptin (Merck) as well as those disclosed in WO 99/38501, WO 99/46272, WO 99/67279 (PROBIODRUG), WO 99/67278 (PROBIODRUG), WO 99/61431 (PROBIODRUG), NVP-DPP728A (1-[[[2-[(5-cyanopyridin-2-yl)amino]ethyl]amino]acetyl]-2-cyano-(S)-pyrrolidine) (Novartis) as

disclosed by Hughes et al, Biochemistry, 38(36):11597-11603, 1999, TSL-225 (tryptophyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid) as disclosed by Yamada et al., Bioorg. & Med. Chem. Lett., 8:1537-1540 (1998), 2-cyanopyrrolidides and 4-cyanopyrrolidides, as disclosed by Ashworth et al., Bioorg. & Med. Chem. Lett., Vol. 6, No. 22, pp. 1163-1166 and 2745-2748 (1996), employing dosages as set out in the above references.

[00127] Suitable aldose reductase inhibitors include those disclosed in WO 99/26659.

[00128] Suitable meglitinides include nateglinide (Novartis) or KAD1229 (PF/Kissei).

[00129] Examples of glucagon-like peptide-1 (GLP-1) include GLP-1(1-36) amide, GLP-1(7-36) amide, GLP-1(7-37) (as disclosed in U.S. Patent No. 5,614,492 to Habener), as well as AC2993 (Amylin), and LY-315902 (Lilly).

[00130] Other anti-diabetic agents that can be used in combination with compounds of the invention include ergoset and D-chiroinositol.

[00131] Suitable anti-ischemic agents include, but are not limited to, those described in the Physician's Desk Reference and NHE inhibitors, including those disclosed in WO 99/43663.

[00132] Examples of suitable anti-infective agents are antibiotic agents, including, but not limited to, those described in the Physicians' Desk Reference.

[00133] Examples of suitable lipid lowering agents for use in combination with the compounds of the present invention include one or more MTP inhibitors, HMG CoA reductase inhibitors, squalene synthetase inhibitors, fibric acid derivatives, ACAT inhibitors, lipoxygenase inhibitors, cholesterol absorption inhibitors, ileal Na^+/bile acid cotransporter inhibitors, upregulators of LDL receptor activity, bile acid sequestrants, cholesterol ester transfer protein inhibitors (e.g., torcetrapib (Pfizer)), and/or nicotinic acid and derivatives thereof.

[00134] MTP inhibitors which may be employed as described above include those disclosed in U.S. Patent No. 5,595,872, U.S. Patent No. 5,739,135, U.S. Patent No. 5,712,279, U.S. Patent No. 5,760,246, U.S. Patent No. 5,827,875, U.S. Patent No. 5,885,983, and U.S. Patent No. 5,962,440.

[00135] The HMG CoA reductase inhibitors which may be employed in combination with one or more compounds of formula I include mevastatin and related compounds, as disclosed in U.S. Patent No. 3,983,140, lovastatin, (mevinolin) and related compounds, as disclosed in U.S. Patent No. 4,231,938, pravastatin, and related compounds, such as disclosed in U.S. Patent No. 4,346,227, simvastatin, and related compounds, as disclosed in U.S. Patent Nos. 4,448,784 and 4,450,171. Other HMG CoA reductase inhibitors which may be employed herein include, but are not limited to, fluvastatin, disclosed in U.S. Patent No. 5,354,772; cerivastatin, as disclosed in U.S. Patent Nos. 5,006,530 and 5,177,080; atorvastatin, as disclosed in U.S. Patent Nos. 4,681,893, 5,273,995, 5,385,929 and 5,686,104; atavastatin (Nissan/Sankyo's nisvastatin (NK-104)), as disclosed in U.S. Patent No. 5,011,930; visastatin (Shionogi-Astra/Zeneca (ZD-4522)) as disclosed in U.S. Patent No. 5,260,440; and related statin compounds disclosed in U.S. Patent No. 5,753,675; pyrazole analogs of mevalonolactone derivatives, as disclosed in U.S. Patent No. 4,613,610; indene analogs of mevalonolactone derivatives, as disclosed in PCT application WO 86/03488; 6-[2-(substituted-pyrrol-1-yl)alkyl)pyran-2-ones and derivatives thereof, as disclosed in U.S. Patent No. 4,647,576; Searle's SC-45355 (a 3-substituted pentanedioic acid derivative) dichloroacetate; imidazole analogs of mevalonolactone, as disclosed in PCT application WO 86/07054; 3-carboxy-2-hydroxy-propane-phosphonic acid derivatives, as disclosed in French Patent No. 2,596,393; 2,3-disubstituted pyrrole, furan and thiophene derivatives, as disclosed in European Patent Application No. 0221025; naphthyl analogs of mevalonolactone, as disclosed in U.S. Patent No. 4,686,237; octahydronaphthalenes, such as disclosed in U.S. Patent No. 4,499,289; keto analogs of mevinolin (lovastatin), as disclosed in European Patent Application No.0142146 A2; and quinoline and pyridine derivatives, as disclosed in U.S. Patent Nos. 5,506,219 and 5,691,322.

[00136] Preferred hypolipidemic agents are pravastatin, lovastatin, simvastatin, atorvastatin, fluvastatin, cerivastatin, atavastatin, and ZD-4522.

[00137] In addition, phosphinic acid compounds useful in inhibiting HMG CoA reductase, such as those disclosed in GB 2205837, are suitable for use in combination with the compounds of the present invention.

[00138] The squalene synthetase inhibitors suitable for use herein include, but are not limited to, α-phosphono-sulfonates disclosed in U.S. Patent No. 5,712,396, those disclosed by Biller et al., J. Med. Chem., 1988, Vol. 31, No. 10, pp. 1869-1871, including isoprenoid (phosphinyl-methyl)phosphonates, as well as other known squalene synthetase inhibitors, for example, as disclosed in U.S. Patent No. 4,871,721 and 4,924,024 and in Biller, S.A., Neuenschwander, K., Ponpipom, M.M., and Poulter, C.D., Current Pharmaceutical Design, 2:1-40 (1996).

[00139] In addition, other squalene synthetase inhibitors suitable for use herein include the terpenoid pyrophosphates disclosed by P. Ortiz de Montellano et al, J. Med. Chem., **1977**, 20:243-249, the farnesyl diphosphate analog A and presqualene pyrophosphate (PSQ-PP) analogs as disclosed by Corey and Volante, J. Am. Chem. Soc., **1976**, 98:1291-1293, phosphinylphosphonates reported by McClard, R.W. et al, J.A.C.S., **1987**, 109:5544 and cyclopropanes reported by Capson, T.L., Ph.D. dissertation, June, 1987, Dept. Med. Chem. U of Utah, Abstract, Table of Contents, pp. 16, 17, 40-43, 48-51, Summary.

[00140] The fibric acid derivatives which may be employed in combination with one or more compounds of formula I include fenofibrate, gemfibrozil, clofibrate, bezafibrate, ciprofibrate, clinofibrate, and the like, probucol, and related compounds, as disclosed in U.S. Patent No. 3,674,836, probucol and gemfibrozil being preferred, bile acid sequestrants, such as cholestyramine, colestipol and DEAE-Sephadex (Secholex®, Policexide®), as well as lipostabil (Rhone-Poulenc), Eisai E-5050 (an N-substituted ethanolamine derivative), imanixil (HOE-402), tetrahydrolipstatin (THL), istigmastanylphosphorylcholine (SPC, Roche), aminocyclodextrin (Tanabe Seiyoku), Ajinomoto AJ-814 (azulene derivative), melinamide (Sumitomo), Sandoz 58-035, American Cyanamid CL-277,082 and CL-283,546 (disubstituted urea derivatives), nicotinic acid, acipimox, acifran, neomycin, p-aminosalicylic acid, aspirin, poly(diallylmethylamine) derivatives, such as disclosed in U.S. Patent No. 4,759,923, quaternary amine poly(diallyldimethylammonium chloride) and ionenes, such as disclosed in U.S. Patent No. 4,027,009, and other known serum cholesterol lowering agents.

[00141] The ACAT inhibitor which may be employed in combination with one or more compounds of formula I include those disclosed in Drugs of the Future 24:9-15

(1999), (Avasimibe); "The ACAT inhibitor, Cl-1011 is effective in the prevention and regression of aortic fatty streak area in hamsters", Nicolosi et al, Atherosclerosis (Shannon, Irel). (1998), 137(1):77-85; "The pharmacological profile of FCE 27677: a novel ACAT inhibitor with potent hypolipidemic activity mediated by selective suppression of the hepatic secretion of ApoB100-containing lipoprotein", Ghiselli, Giancarlo, Cardiovasc. Drug Rev. (1998), 16(1):16-30; "RP 73163: a bioavailable alkylsulfinyl-diphenylimidazole ACAT inhibitor", Smith, C., et al, Bioorg. Med. Chem. Lett. (1996), 6(1):47-50; "ACAT inhibitors: physiologic mechanisms for hypolipidemic and anti-atherosclerotic activities in experimental animals", Krause et al, Editor(s): Ruffolo, Robert R., Jr.; Hollinger, Mannfred A., Inflammation: Mediators Pathways (1995), 173-98, Publisher: CRC, Boca Raton, Fla.; "ACAT inhibitors: potential anti-atherosclerotic agents", Sliskovic et al, Curr. Med. Chem. (1994), 1(3):204-25; "Inhibitors of acyl-CoA:cholesterol O-acyl transferase (ACAT) as hypocholesterolemic agents. 6. The first water-soluble ACAT inhibitor with lipid-regulating activity. Inhibitors of acyl-CoA:cholesterol acyltransferase (ACAT). 7. Development of a series of substituted N-phenyl-N'-[(1-phenylcyclopentyl)methyl]ureas with enhanced hypocholesterolemic activity", Stout et al, Chemtracts: Org. Chem. (1995), 8(6):359-62, or TS-962 (Taisho Pharmaceutical Co. Ltd.).

[00142] The hypolipidemic agent may be an upregulator of LD2 receptor activity, such as MD-700 (Taisho Pharmaceutical Co. Ltd) and LY295427 (Eli Lilly).

[00143] Examples of suitable cholesterol absorption inhibitors for use in combination with the compounds of the invention include SCH48461 (Schering-Plough), as well as those disclosed in Atherosclerosis 115:45-63 (1995) and J. Med. Chem. 41:973 (1998).

[00144] Examples of suitable ileal Na^+/bile acid cotransporter inhibitors for use in combination with the compounds of the invention include compounds as disclosed in Drugs of the Future, 24:425-430 (1999).

[00145] The lipoxygenase inhibitors which may be employed in combination with one or more compounds of formula I include 15-lipoxygenase (15-LO) inhibitors, such as benzimidazole derivatives, as disclosed in WO 97/12615, 15-LO inhibitors, as disclosed in WO 97/12613, isothiazolones, as disclosed in WO 96/38144, and 15-LO

inhibitors, as disclosed by Sendobry et al "Attenuation of diet-induced atherosclerosis in rabbits with a highly selective 15-lipoxygenase inhibitor lacking significant antioxidant properties", Brit. J. Pharmacology (1997) 120:1199-1206, and Cornicelli et al, "15-Lipoxygenase and its Inhibition: A Novel Therapeutic Target for Vascular Disease", Current Pharmaceutical Design, 1999, 5:11-20.

[00146] Examples of suitable anti-hypertensive agents for use in combination with the compounds of the present invention include beta adrenergic blockers, calcium channel blockers (L-type and T-type; e.g. diltiazem, verapamil, nifedipine, amlodipine and mybefradil), diuretics (e.g., chlorothiazide, hydrochlorothiazide, flumethiazide, hydroflumethiazide, bendroflumethiazide, methylchlorothiazide, trichloromethiazide, polythiazide, benzthiazide, ethacrynic acid tricrynafen, chlorthalidone, furosemide, musolimine, bumetanide, triamtrenene, amiloride, spironolactone), renin inhibitors, ACE inhibitors (e.g., captopril, zofenopril, fosinopril, enalapril, ceranopril, cilazopril, delapril, pentopril, quinapril, ramipril, lisinopril), AT-1 receptor antagonists (e.g., losartan, irbesartan, valsartan), ET receptor antagonists (e.g., sitaxsentan, atrsentan, and compounds disclosed in U.S. Patent Nos. 5,612,359 and 6,043,265), Dual ET/AII antagonist (e.g., compounds disclosed in WO 00/01389), neutral endopeptidase (NEP) inhibitors, vasopepsidase inhibitors (dual NEP-ACE inhibitors) (e.g., omapatrilat and gemopatrilat), and nitrates.

[00147] Examples of suitable anti-obesity agents for use in combination with the compounds of the present invention include a cannabinoid receptor 1 antagonist or inverse agonist, a beta 3 adrenergic agonist, a lipase inhibitor, a serotonin (and dopamine) reuptake inhibitor, a thyroid receptor beta drug, and/or an anorectic agent.

[00148] Cannabinoid receptor 1 antagonists and inverse agonists which may be optionally employed in combination with compounds of the present invention include rimonabant, SLV 319, and those discussed in D. L. Hertzog, Expert Opin. Ther. Patents, **2004**, 14:1435-1452.

[00149] The beta 3 adrenergic agonists which may be optionally employed in combination with compounds of the present invention include AJ9677 (Takeda/Dainippon), L750355 (Merck), or CP331648 (Pfizer,) or other known beta 3

agonists, as disclosed in U.S. Patent Nos. 5,541,204, 5,770,615, 5,491,134, 5,776,983, and 5,488,064, with AJ9677, L750,355, and CP331648 being preferred.

[00150] Examples of lipase inhibitors which may be optionally employed in combination with compounds of the present invention include orlistat or ATL-962 (Alizyme), with orlistat being preferred.

[00151] The serotonin (and dopamine) reuptake inhibitor which may be optionally employed in combination with a compound of formula I may be sibutramine, topiramate (Johnson & Johnson), or axokine (Regeneron), with sibutramine and topiramate being preferred.

[00152] Examples of thyroid receptor beta compounds which may be optionally employed in combination with compounds of the present invention include thyroid receptor ligands, such as those disclosed in WO 97/21993 (U. Cal SF), WO 99/00353 (KaroBio), and WO 00/039077 (KaroBio), with compounds of the KaroBio applications being preferred.

[00153] The anorectic agent which may be optionally employed in combination with compounds of the present invention include dexamphetamine, phentermine, phenylpropanolamine, or mazindol, with dexamphetamine being preferred.

[00154] Other compounds that can be used in combination with the compounds of the present invention include CCK receptor agonists (e.g., SR-27895B); galanin receptor antagonists; MCR-4 antagonists (e.g., HP-228); leptin or mimentics; 11-beta-hydroxysteroid dehydrogenase type-1 inhibitors; urocortin mimetics, CRF antagonists, and CRF binding proteins (e.g., RU-486, urocortin).

[00155] Further, the compounds of the present invention may be used in combination with anti-cancer and cytotoxic agents, including but not limited to alkylating agents such as nitrogen mustards, alkyl sulfonates, nitrosoureas, ethylenimines, and triazenes; antimetabolites such as folate antagonists, purine analogues, and pyrimidine analogues; antibiotics such as anthracyclines, bleomycins, mitomycin, dactinomycin, and plicamycin; enzymes such as L-asparaginase; farnesyl-protein transferase inhibitors; 5α reductase inhibitors; inhibitors of 17β-hydroxy steroid dehydrogenase type 3; hormonal agents such as glucocorticoids, estrogens/antiestrogens, androgens/antiandrogens, progestins, and luteinizing hormone-releasing hormone antagonists, octreotide acetate; microtubule-disruptor

agents, such as ecteinascidins or their analogs and derivatives; microtubule-stabilizing agents such as taxanes, for example, paclitaxel (Taxol®), docetaxel (Taxotere®), and their analogs, and epothilones, such as epothilones A-F and their analogs; plant-derived products, such as vinca alkaloids, epipodophyllotoxins, taxanes; and topiosomerase inhibitors; prenyl-protein transferase inhibitors; and miscellaneous agents such as hydroxyurea, procarbazine, mitotane, hexamethylmelamine, platinum coordination complexes such as cisplatin and carboplatin; and other agents used as anti-cancer and cytotoxic agents such as biological response modifiers, growth factors; immune modulators; and monoclonal antibodies. Additional anti-cancer agents are disclosed in EP 1177791. The compounds of the invention may also be used in conjunction with radiation therapy.

[00156] Examples of suitable memory enhancing agents, anti-dementia agents, or cognitive agents for use in combination with the compounds of the present invention include, but are not limited to, donepezil, rivastigmine, galantamine, memantine, tacrine, metrifonate, muscarine, xanomelline, deprenyl, and physostigmine.

[00157] The aforementioned patents and patent applications are incorporated herein by reference.

[00158] The above other therapeutic agents, when employed in combination with the compounds of the present invention may be used, for example, in those amounts indicated in the Physicians' Desk Reference, as in the patents set out above, or as otherwise determined by one of ordinary skill in the art.

[00159] The compounds of formula I can be administered for any of the uses described herein by any suitable means, for example, orally, such as in the form of tablets, capsules, granules, or powders; sublingually; bucally; parenterally, such as by subcutaneous, intravenous, intramuscular, or intrasternal injection, or infusion techniques (e.g., as sterile injectable aqueous or non-aqueous solutions or suspensions); nasally, including administration to the nasal membranes, such as by inhalation spray; topically, such as in the form of a cream or ointment; or rectally such as in the form of suppositories; in dosage unit formulations containing non-toxic, pharmaceutically acceptable vehicles or diluents.

[00160] In carrying out the method of the invention for treating diabetes and related diseases, a pharmaceutical composition will be employed containing the

compounds of formula I, with or without other antidiabetic agent(s) and/or antihyperlipidemic agent(s) and/or other type therapeutic agents in association with a pharmaceutical vehicle or diluent. The pharmaceutical composition can be formulated employing conventional solid or liquid vehicles or diluents and pharmaceutical additives of a type appropriate to the mode of desired administration, such as pharmaceutically acceptable carriers, excipients, binders, and the like. The compounds can be administered to a mammalian patient, including humans, monkeys, dogs, etc. by an oral route, for example, in the form of tablets, capsules, beads, granules, or powders. The dose for adults is between 0.25 and 2,000 mg per day, preferably between 1 and 500 mg, which can be administered in a single dose or in the form of individual doses from 1-4 times per day.

[00161] A typical capsule for oral administration contains compounds of structure I (250 mg), lactose (75 mg), and magnesium stearate (15 mg). The mixture is passed through a 60 mesh sieve and packed into a No. 1 gelatin capsule.

[00162] A typical injectable preparation is produced by aseptically placing 250 mg of compounds of structure I into a vial, aseptically freeze-drying and sealing. For use, the contents of the vial are mixed with 2 mL of physiological saline, to produce an injectable preparation.

ABBREVIATIONS

[00163] The following abbreviations are employed in the Examples and elsewhere herein:

Ph = phenyl

Bn = benzyl

t-Bu = tertiary butyl

i-Bu = iso-butyl

Me = methyl

Et = ethyl

Pr = propyl

iPr = isopropyl

Bu = butyl

AIBN = 2,2'-Azobisisobutyronitrile

TMS = trimethylsilyl

$TMSCHN_2$ = (trimethylsilyl)diazomethane

$TMSN_3$ = trimethylsilyl azide

TBS = tert-butyldimethylsilyl

FMOC = fluorenylmethoxycarbonyl

Boc or BOC = tert-butoxycarbonyl

Cbz = carbobenzyloxy or carbobenzoxy or benzyloxycarbonyl

THF = tetrahydrofuran

Et_2O = diethyl ether

hex = hexanes

EtOAc = ethyl acetate

DMF = dimethyl formamide

MeOH = methanol

EtOH = ethanol

DCM = dichloromethane

i-PrOH = isopropanol

DMSO = dimethyl sulfoxide

DME = 1,2 dimethoxyethane

DMA = N,N-dimethylacetylamide

DCE = 1,2 dichloroethane

HMPA = hexamethyl phosphoric triamide

HOAc or AcOH = acetic acid

TFA = trifluoroacetic acid

DIEA or DIPEA or i-Pr_2NEt or Hunig's Base = diisopropylethylamine

TEA or Et_3N = triethylamine

NMM = N-methyl morpholine

NBS = N-bromosuccinimide

NCS = N-chlorosuccinimide

DMAP = 4-dimethylaminopyridine

DEPBT = 3-diethoxyphosphoryloxy-1,2,3-benzotriazin-4[3H]-one

mCPBA = 3-chloroperoxybenzoic acid

$NaBH_4$ = sodium borohydride

$NaBH(OAc)_3$ = sodium triacetoxyborohydride

NaN_3 = sodium azide

DIBALH = diisobutyl aluminum hydride

$LiAlH_4$ = lithium aluminum hydride

n-BuLi = n-butyllithium

Oxone® = monopersulfate

Pd/C = palladium on carbon

$PXPd_2$ = Dichloro(chlorodi-*tert*-butylphosphine)palladium (II) dimer or $[PdCl_2(t\text{-}Bu)_2PCl]_2$

PtO_2 = platinum oxide

KOH = potassium hydroxide

NaOH = sodium hydroxide

LiOH = lithium hydroxide

$LiOH.H_2O$ = lithium hydroxide monohydrate

HCl = hydrochloric acid

H_2SO_4 = sulfuric acid

H_2O_2 = hydrogen peroxide

Al_2O_3 = aluminum oxide

K_2CO_3 = potassium carbonate

Cs_2CO_3 = cesium carbonate

$NaHCO_3$ = sodium bicarbonate

$ZnBr_2$ = zinc bromide

$MgSO_4$ = magnesium sulfate

Na_2SO_4 = sodium sulfate

KSCN = potassium thiocyanate

NH_4Cl = Ammonium chloride

DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene

EDC (or EDC.HCl) or EDCI (or EDCI.HCl) or EDAC = 3-ethyl-3'-(dimethylamino)propyl- carbodiimide hydrochloride (or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride)

HOBT or $HOBT.H_2O$ = 1-hydroxybenzotriazole hydrate

HOAT = 1-Hydroxy-7-azabenzotriazole

PyBOP reagent or BOP reagent = benzotriazol-1-yloxy-tris (dimethylamino) phosphonium hexafluorophosphate

$NaN(TMS)_2$ = sodium hexamethyldisilazide or sodium bis(trimethylsilyl)amide

Ph_3P = triphenylphosphine

$Pd(OAc)_2$ = Palladium acetate

$(Ph_3P)_4Pd^o$ = tetrakis triphenylphosphine palladium

$Pd_2(dba)_3$ = tris(dibenzylacetone)dipalladium

DPPF = 1,1'-Bis(diphenylphosphino)ferrocene

HATU = 2-(7-aza-1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate, 2-(3H-[1,2,3]triazolo[4,5-b]pyridin-3-yl)-1,1,3,3-tetramethylisouronium hexafluorophosphate(V)

DEAD = diethyl azodicarboxylate

DIAD = diisopropyl azodicarboxylate

Cbz-Cl = benzyl chloroformate

CAN = ceric ammonium nitrate

SAX = Strong Anion Exchanger

SCX = Strong Cation Exchanger

H_2 = hydrogen

Ar = argon

N_2 = nitrogen

Equiv = equivalent(s)

min = minute(s)

h or hr = hour(s)

L = liter

mL = milliliter

µL = microliter

g = gram(s)

mg = milligram(s)

mol = moles

mmol = millimole(s)

meq = milliequivalent

RT or R.T. = room temperature

AT = ambient temperature

sat or sat'd = saturated

aq. = aqueous

TLC = thin layer chromatography

HPLC = high performance liquid chromatography

HPLC R_t = HPLC retention time

LC/MS = high performance liquid chromatography/mass spectrometry

MS or Mass Spec = mass spectrometry

NMR = nuclear magnetic resonance

NMR spectral data: s = singlet; d = doublet; m = multiplet; br = broad; t = triplet

mp = melting point

EXAMPLES

[00164] The following working Examples serve to better illustrate, but not limit, some of the preferred embodiments of the present invention.

GENERAL

[00165] The term HPLC refers to a Shimadzu high performance liquid chromatography with one of following methods:

Method A: YMC or Phenomenex C18 5 micron 4.6 X 50mm column using a 4 minute gradient of 0-100% solvent B [90% MeOH:10% H_2O:0.2% H_3PO_4] and 100-0% solvent A [10% MeOH:90% H_2O:0.2% H_3PO_4] with 4 mL/min flow rate and a 1 min. hold, an ultra violet (uv) detector set at 220 nm.

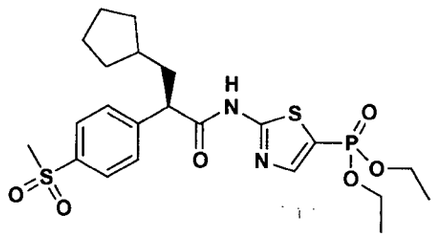
Method B: Phenomenex S5 ODS 4.6 x 30 mm column, gradient elution 0-100% B/A over 2 min (solvent A = 10% MeOH/H_2O containing 0.1% TFA, solvent B = 90% MeOH/H_2O containing 0.1% TFA), flow rate 5 mL/min, UV detection at 220 nm.

Method C: YMC S7 ODS 3.0 x 50 mm column, gradient elution 0-100% B/A over 2 min (solvent A = 10% MeOH/H_2O containing 0.1% TFA, solvent B = 90% MeOH/H_2O containing 0.1% TFA), flow rate 5 mL/min, UV detection at 220 nm.

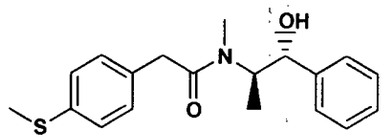
[00166] The term prep HPLC refers to an automated Shimadzu HPLC system using a mixture of solvent A (10% MeOH/90%H_2O/0.2%TFA) and solvent B (90% MeOH/10%H_2O/0.2% TFA). The preparative columns are packed with YMC or Phenomenex ODS C18 5 micron resin or equivalent.

[00167] The following Examples are illustrative of preferred compounds of the invention.

EXAMPLE 1

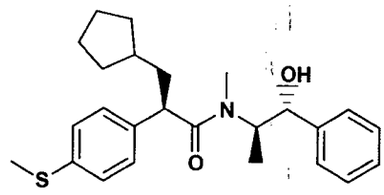


A.



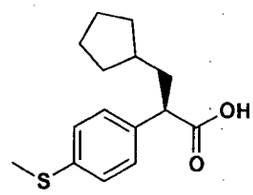
[00168] Trimethylacetyl chloride (3.83 mL; 31.1 mmol) was added dropwise to a -10°C mixture of 4-methylthio-phenylacetic acid (5.40 g; 29.6 mmol) and K_2CO_3 (12.3 g; 88.8 mmol) in acetone (40 mL), while maintaining the temperature at < -10°C. After 10 min at -10°C, the reaction was warmed to 0°C. After 10 min at 0°C, the reaction was cooled to -10°C. (1R, 2R)–(-)– pseudoephedrine (7.34 g; 44.4 mmol) was added. After 10 min at -10°C, the reaction mixture was allowed to warm to RT. After 4 h, the reaction was partitioned between EtOAc (60 mL) and H_2O (30 mL). The aqueous phase was extracted with EtOAc (30 mL). All organic phases were combined, washed with brine (30 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was recrystallized from warm EtOAc / hexanes to afford Part A compound (7.3 g; 75%) as a crystalline solid.

B.



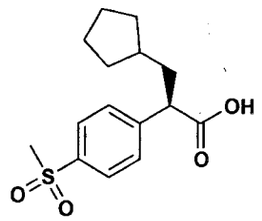
[00169] A solution of Part A compound (7.0 g; 21.27 mmol) in THF (51 mL) was added over 45 min to a -70°C solution of $LiN(TMS)_2$ (44.7 mL of a 1.0 M solution in THF; 44.7 mmol) while keeping the internal temperature below -65°C. After addition the reaction mixture was stirred at -70°C for 15 min and then allowed to warm to 0°C. After 20 min at 0°C the reaction was re-cooled to -70°C. A solution of cyclopentylmethyl iodide (6.70 g; 31.91 mmol) in DMPU (5.4 mL; 44.68 mmol) was added. The reaction was stirred at -70°C for 30 min and then allowed to warm to RT. After 20 h the reaction mixture was quenched by addition of sat. aqueous NH_4Cl (20 mL). The solution was extracted with EtOAc (175 mL). The organic phase was isolated, washed with sat. NH_4Cl (50 mL) and brine (50 mL), dried ($MgSO_4$) and concentrated. The crude product was purified by flash chromatography (SiO_2; continuous gradient from 0 to 90% solvent B over 75 min, where solvent A = hexanes and solvent B = EtOAc) to give Part B compound (6.94 g; 79%).

C.



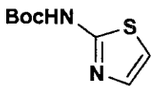
[00170] A solution of Part B compound (5.44 g; 13.22 mmol) in 1,4 dioxane (24 mL) was treated with 9 N aqueous H_2SO_4 (15 mL). The reaction mixture was then heated at 105°C. After 20 h heating was stopped and the solution was cooled to RT. H_2O (100 mL) was added to precipitate the product. The solid was isolated by filtration and dried *in vacuo* to give Part C compound (3.40 g; 97%).

D.



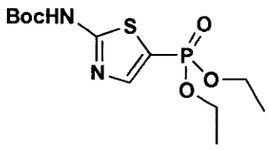
[00171] Oxone® (17.64 g; 28.70 mmol) was added to a mixture of Part C compound (3.30 g; 12.48 mmol) in 2-propanol (90 mL) and H_2O (45 mL). After 20 h at RT the 2-propanol was removed *in vacuo*. The aqueous solution was extracted with EtOAc (175 mL). The organic phase was washed with H_2O (50 mL) and brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give Part D compound (3.60 g; 97%) as a white solid. (Part D compound was prepared by a slight modification of the procedure found in Patent WO 02/46173).

E.



[00172] Di-tert-butyl dicarbonate (2.40 g; 11.00 mmol) was added to a solution of 2-aminothiazole (1.00 g; 9.99 mmol) in THF (5 mL). TEA (1.67 mL; 11.98 mmol) was added followed by a catalytic amount of 4-DMAP (2.0 mg). After 4 h the reaction mixture was concentrated *in vacuo*. The residue was partitioned between EtOAc (20 mL) and 0.1 N aqueous HCl (15 mL).The organic phase was washed with brine (15 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was chromatographed (SiO_2; continuous gradient from 0 to 100% solvent B over 25 min; hold at 100% solvent B for 5 min, where solvent A = hexanes and solvent B = EtOAc) to give Part E compound (0.77 g; 39%) as a white solid.

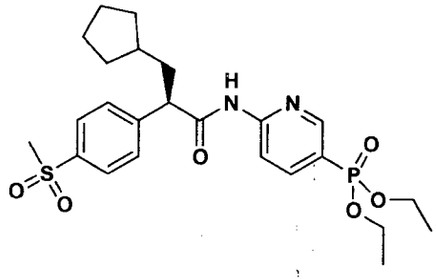
F.



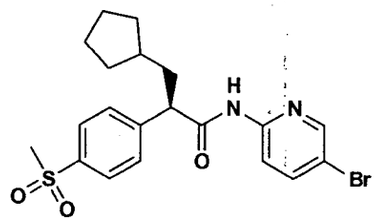
[00173] A -78°C solution of LDA (1.44 mL of a 2.0 M solution in THF/heptane/ethylbenzene; 2.88 mmol) was cannulated into a -78°C solution of Part

$NaHCO_3$ (2 x 2 mL) and brine (2 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was dissolved in DCM (3 mL). The solution was stirred with aminomethylated polystyrene resin (40 mg; to remove unreacted activated ester) for 20 min and then filtered. The filtrate was concentrated *in vacuo*. The residue was purified by preparative HPLC (YMC reverse phase ODS-A-5u 30 x 100 mm column; flow rate = 40 mL/min, 10 to 100% solvent B over 12 min, hold to 16 min, where solvent A = 90:10:0.1 H_2O:MeOH:TFA and solvent B = 90:10:0.1 MeOH:H_2O:TFA) to give the title compound (15 mg; 37%) as a colorless solid. $[M + H]^+ = 515.2$; ^1H NMR (400 MHz, CD_3OD): δ 1.19 (m, 2H), 1.33 (m, 6H), 1.50 (m, 2H), 1.64 (m, 3H), 1.80 (m, 2H), 1.89 (m, 1H), 2.23 (m, 1H), 3.10 (s, 3H), 4.00 (t, 1H), 4.12 (m, 4H), 7.69 (d, 2H), 7.89 (d, J = 4.8 Hz, 1H), 7.93 (d, 2H).

EXAMPLE 2



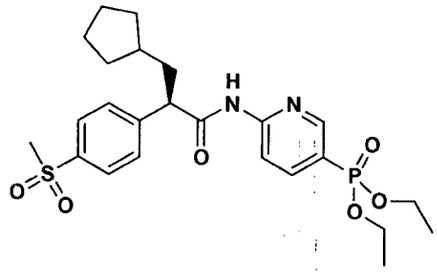
A.



[00176] Oxalyl chloride (2.0 M in DCM) (0.68 mL; 1.35 mmol) was added to a mixture of Example 1 Part D compound (200 mg; 0.68 mmol) in DCM (1 mL). DMF (5 μL) was added. Gas evolution occurred. After 2 h at RT the reaction mixture was concentrated *in vacuo*. The residue was stripped from $CHCl_3$ (2 X 2 mL), then was dissolved in DCM (2.5 mL). The solution was cooled to 0°C and 2-amino-5-bromopyridine (175 mg; 1.01 mmol) was added followed by pyridine (82 uL; 1.01

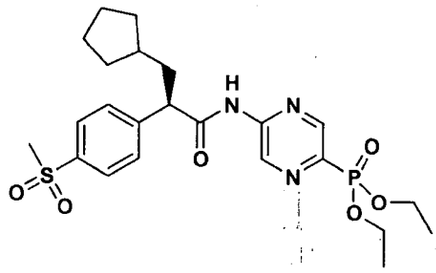
mmol). The reaction mixture was stirred at RT for 16 h, then was concentrated *in vacuo*. The residue was partitioned between EtOAc (5 mL) and 0.1 N aqueous HCl (4 mL). The organic phase was washed with brine (4 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The crude product was chromatographed (SiO_2; continuous gradient from 0 to 80% solvent B over 18 min, where solvent A = hexanes and solvent B = EtOAc) to give Part A compound (250 mg; 82%).

B.



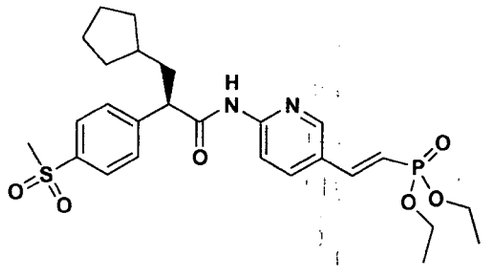
[00177] THF (degassed) (0.50 mL) was added to Part A compound (28.9 mg; 0.064 mmol) and $(Ph_3P)_4Pd°$ (14.8 mg; 0.013 mmol). $H(O)P(OEt)_2$ (10.3 μL; 0.079 mmol) was added followed by TEA (13.7 μL; 0.098 mmol). The vessel was capped and the reaction mixture was heated at 75°C for 9 h, then was cooled to RT and concentrated *in vacuo*. The crude product was purified by preparative HPLC (YMC reverse phase ODS-A-5u 30 x 100 mm column; flow rate = 40 mL/min, 20 to 100% solvent B over 12 min, hold at 100% solvent B for 17 min, where solvent A = 90:10:0.1 H_2O:MeOH:TFA and solvent B = 90:10:0.1 MeOH:H_2O:TFA) to give title compound (18 mg; 55%) as an amorphous solid. $[M + H]^+ = 509.2$; ^1H NMR (400 MHz, CD_3OD): δ 1.19 (m, 2H), 1.32 (t, 6H), 1.51 (m, 2H), 1.64 (m, 3H), 1.84 (m, 3H), 2.22 (m, 1H), 3.09 (s, 3H), 4.02 (t, 1H), 4.12 (m, 4H), 7.70 (d, 2H), 7.92 (d, 2H), 8.08 (ddd, 1H), 8.26 (dd, 1H), 8.60 (dd, 1H).

EXAMPLE 3



[00178] The title compound (14.3 mg; 44%; yellow amorphous solid) was synthesized from 5-bromo-2-pyrazinamine employing the procedure described in Example 2. $[M + H]^+ = 510.2$; ^1H NMR (400 MHz, CD_3OD): δ 1.19 (m, 2H), 1.33 (t, 6H), 1.51 (m, 2H), 1.64 (m, 3H), 1.84 (m, 3H), 2.22 (m, 1H), 3.09 (s, 3H), 4.03 (t, 1H), 4.21 (m, 4H), 7.71 (d, 2H), 7.92 (d, 2H), 8.71 (s, 1H), 9.59 (s, 1H).

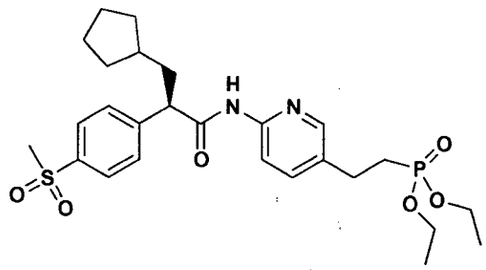
EXAMPLE 4



[00179] CH_3CN (150 μL) was added to a mixture of Example 2 Part A compound (30 mg; 0.066 mmol), $Pd(OAc)_2$ (0.30 mg; 0.0013 mmol) and tri-o-tolylphosphine (0.80 mg; 0.0026 mmol). Diethyl vinylphosphate (10.7 uL; 0.083 mmol) was added followed by TEA (27.7 uL; 0.199 mmol). The reaction mixture was heated at 95°C for 4 h, then was cooled to RT. The solution was partitioned between EtOAc (3 mL) and brine (2 mL). The organic phase was dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed (SiO_2; continuous gradient from 0 to 100% solvent B over 12 min, hold at 100% for 8 min, where solvent A = hexanes and solvent B = EtOAc) to give the title compound (24 mg; 68%) as an amorphous solid. $[M + H]^+ = 535.3$; ^1H NMR (400 MHz, $CDCl_3$): δ 1.15 (m, 2H), 1.36 (t, 6H), 1.48 (m, 2H), 1.61 (m, 3H), 1.74 (m, 2H), 1.92 (m, 1H), 2.23 (m, 1H), 3.05 (s, 3H), 3.68 (t, 1H), 4.14 (m,

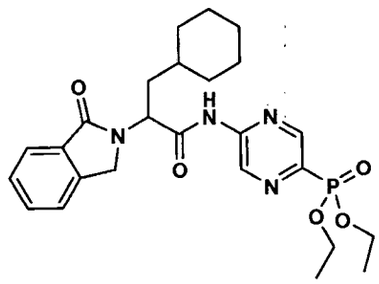
4H), 6.25 (t,1H), 7.42 (d, J = 22.4 Hz, 2H), 7.59 (d, 2H), 7.85 (dd, 1H), 7.92 (d, 2H), 8.23 (s, 1H), 8.24 (d, 2H), 8.31 (d, 1H).

EXAMPLE 5

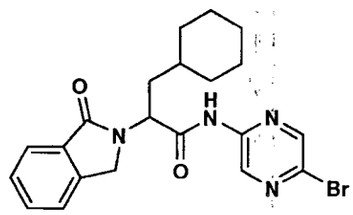


[00180] 10% Pd/C (5 mg) was added to a solution of Example 4 compound (20 mg; 0.037 mmol) in MeOH (0.30 mL). A H_2 atmosphere was introduced via balloon. After 8 h the reaction mixture was filtered. The catalyst was rinsed with MeOH (1.5 mL) and the combined filtrates were concentrated *in vacuo*. The crude product was chromatographed (SiO_2; continuous gradient from 0 to 100% solvent B over 6 min, hold at 100% solvent B for 15 min, where solvent A = hexanes and solvent B = EtOAc) to give the title compound (14.5 mg; 73%) as a colorless solid. $[M + H]^+$ = 537.2; ^1H NMR (400 MHz, $CDCl_3$): δ 1.13 (m, 2H), 1.31 (t, 6H), 1.47 (m, 2H), 1.61 (m, 2H), 1.74 (m, 3H), 1.90 (m, 1H), 2.00 (m, 2H), 2.21 (m, 1H), 2.87 (m, 2H), 3.05 (s, 3H), 3.65 (t, 1H), 4.10 (m, 4H), 7.56 (dd, 1H), 7.58 (d, 2H), 7.90 (d, 2H), 8.08 (d, 1H), 8.13 (d, 1H), 8.20 (s, 1H).

EXAMPLE 6

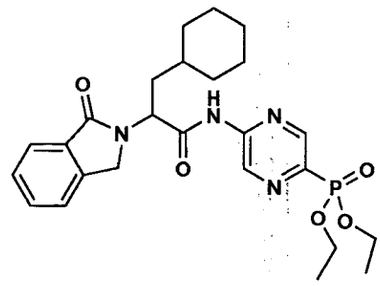


A.



[00181] To a 0°C solution of (S)-3-Cyclohexyl-2-(1-oxo-1,3-dihydroisoindol-2-yl)-propionic acid (144 mg, 0.5 mmol, prepared as described in WO 2002/048106) and oxalyl chloride (0.38 mL of a 2 M solution in DCM; 0.75 mmol) in DCM (1 mL) under Ar was added DMF (1 drop). After 30 min, the reaction was allowed to warm to RT and was stirred at RT for 4 h. Volatiles were removed *in vacuo*; the crude acid chloride was re-dissolved in DCM (3 mL). 5-Bromo-2-aminopyrazine (130 mg, 0.75 mmol) and pyridine (0.061 mL, 0.75 mmol) were added to the acid chloride solution cooled in an ice bath under Ar. The reaction mixture was allowed to warm to room temperature overnight, then was diluted with DCM (6 mL) and rinsed with 0.5 N aqueous HCl (1 mL, 2x), water (1 mL), sat. aqueous $NaHCO_3$ (1 mL), brine (1 mL), then dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed (40 g SiO_2, 0-50% EtOAc-hexanes gradient) gave 188 mg (84%) of racemic Part A compound.

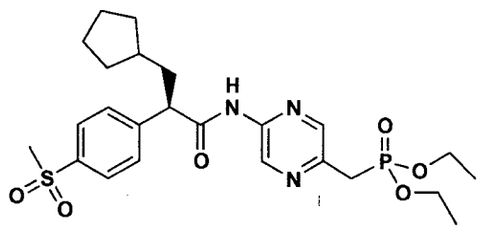
B.



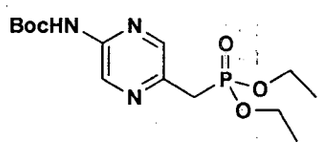
[00182] THF (degassed) (0.40 mL) was added to a reaction flask containing Part A compound (25.0 mg; 0.056 mmol) and $(Ph_3P)_4Pd(0)$(12.9 mg; 0.011 mmol). Diethyl phosphite (8.72 uL; 0.068 mmol) was added followed by TEA (10.9 uL; 0.078 mmol). The reaction vessel was capped and the reaction mixture was heated at 85°C for 6 h, then cooled to RT and concentrated *in vacuo*. The residue was partitioned between EtOAc (2 mL) and brine (1.5 mL). The organic phase was isolated, dried

($MgSO_4$) concentrated *in vacuo*. The crude product was purified by preparative HPLC (YMC reverse phase ODS-A-5u 30 x 100 mm column; flow rate = 40 mL/min., 45 to 100% solvent B over 12 min, hold to 16 min, where solvent A = 90:10:0.1 H_2O:MeOH:TFA and solvent B = 90:10:0.1 MeOH:H_2O:TFA) to give title compound (8 mg; 29%; colorless solid) as a racemic mixture. $[M + H]^+ = 501.3$; ^1H NMR (400 MHz, $CDCl_3$): δ 1.00 (m, 2H), 1.20 (m, 4H), 1.35 (m, 6H), 1.65 (m, 3H), 1.85 (m, 3H), 2.05 (m, 1H), 4.22 (m, 4H), 4.54 (q, 2H), 5.23 (t, 1H), 7.50 (m, 3H), 7.60 (dd, 1H), 7.92 (d, 1H), 8.75 (s, 1H), 9.52 (s, 1H), 9.62 (s, 1H).

EXAMPLE 7

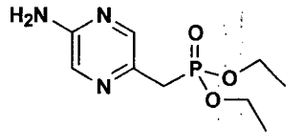


A.



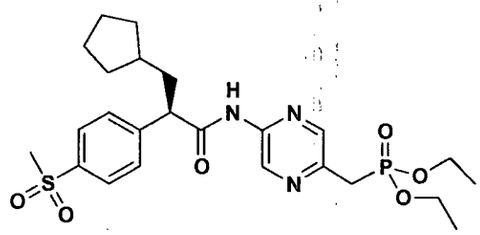
[00183] $(EtO)_3P$ (0.60 mL; 3.47 mmol) was added to a reaction flask containing a solution of tert-butyl 5–(bromomethyl) pyrazin-2-ylcarbamate (*Bioorg. Med. Chem. Lett.*, **2002**, 12:1203-1208) (125 mg; 0.434 mmol) in THF (1.0 mL). The reaction vessel was capped and the reaction mixture was heated at 80°C for 16 h, then was cooled to RT and concentrated *in vacuo*. The crude product was chromatographed (SiO_2; continuous gradient from 0 to 100% solvent B over 8 min, hold at 100% solvent B for 8 min, where solvent A = hexanes and solvent B = EtOAc) to give Part A compound (145 mg; 96%).

B.



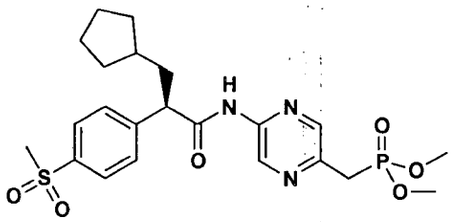
[00184] TFA (0.30 mL) was added to a cold (0°C) solution of Part A compound (144 mg; 0.417 mmol) in DCM (1.2 mL). The reaction mixture was then stirred at RT for 16 h, then was concentrated *in vacuo*. The residue was partitioned between EtOAc (4 mL) and sat. aqueous $NaHCO_3$ (3 mL). The organic phase was isolated, washed with brine (3 mL), dried ($MgSO_4$), and concentrated *in vacuo* to give Part B compound (51 mg; 50%).

C.



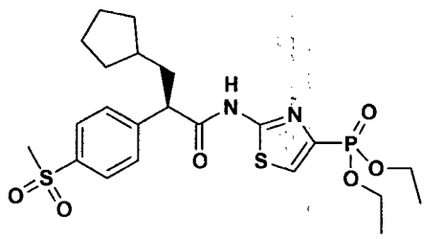
[00185] Oxalyl chloride (0.84 uL of a 2.0 M solution in DCM; 0.168 mmol) was added to a mixture of Example 1 Part D compound (25 mg; 0.084 mmol) in DCM (0.15 mL). DMF (5 μL) was added. Gas evolution occurred. After 1.5 h at RT the reaction mixture was concentrated *in vacuo*. The residue was stripped from $CHCl_3$ (2 X 0.8 mL). The crude acid chloride was then dissolved in DCM (0.25 mL). Part B compound (24.8 mg; 0.101 mmol) was added followed by pyridine (10.2 uL; 0.126 mmol). After stirring for 16 h at RT the reaction was concentrated *in vacuo*. The residue was partitioned between EtOAc (4 mL) and brine (2 mL). The organic phase was dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by preparative HPLC (YMC reverse phase ODS-A-5u 30 x 100 mm column; flow rate = 40 mL/min, 10 to 100% solvent B over 12 min, hold to 16 min, where solvent A = 90:10:0.1 H_2O:MeOH:TFA and solvent B = 90:10:0.1 MeOH:H_2O:TFA) to give the title compound (18 mg; 41%) as an amorphous solid. $[M + H]^+ = 524.4$; ^1H NMR (400 MHz, CD_3OD): δ 1.18 (m, 2H), 1.27 (t, 6H), 1.51 (m, 2H), 1.64 (m, 2H), 1.72 (m, 1H), 1.83 (m, 3H), 2.22 (m, 1H), 3.09 (s, 3H), 3.46 (d, 2H), 4.00 (t, 1H), 4.09 (m, 4H), 7.70 (d, 2H), 7.92 (d, 2H), 8.32 (s, 1H), 9.30 (s, 1H).

EXAMPLE 8

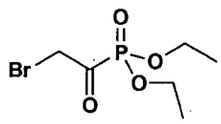


[00186] The title compound (11 mg; 19%; colorless solid) was synthesized from trimethylphosphite employing the sequence described for the synthesis of Example 7. $[M + H]^+ = 496.3$; ^1H NMR (400 MHz, CD_3OD): δ 1.19 (m, 2H), 1.51 (m, 2H), 1.64 (m, 2H), 1.72 (m, 1H), 1.84 (m, 3H), 2.23 (m, 1H), 3.09 (s, 3H), 3.50 (d, 2H), 3.73 (s, 3H), 3.76 (s, 3H), 4.00 (t, 1H), 7.69 (d, 2H), 7.91 (d, 2H), 8.31 (s, 1H), 9.29 (s, 1H).

EXAMPLE 9

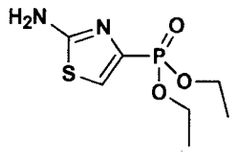


A.



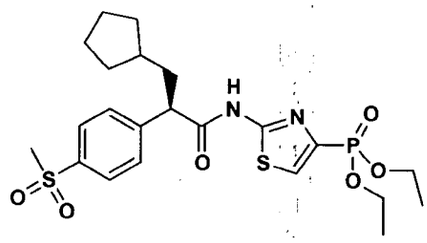
[00187] A solution of bromine (145 uL; 2.82 mmol) in CCl_4 (5 mL) was added dropwise to a 0°C solution of acetyl-phosphonic acid di-ethyl ester (0.508 g; 2.82 mmol) in CCl_4 (5 mL). The reaction mixture was then stirred at RT for 2 h, then was concentrated *in vacuo*. The residue was chromatographed (SiO_2; continuous gradient from 0 to 100% solvent B over 10 min, hold at 100% solvent B for 10 min, where solvent A = hexanes and solvent B = EtOAc) to give Part A compound (250 mg; 34%).

B.



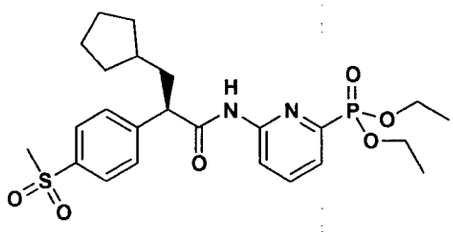
[00188] Thiourea (43.9 mg; 0.577 mmol) was added to a solution of Part A compound (135 mg 0.52 mmol) in EtOH (1.0 mL). The reaction mixture was stirred at RT for 48 h, then was concentrated *in vacuo*. The residue was partitioned between EtOAc (5 mL) and sat. aqueous $NaHCO_3$ (3 mL). The organic phase was isolated, washed with brine (3 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed (SiO_2; continuous gradient from 0 to 100% solvent B over 2 min, hold at 100% solvent B for 10 min, where solvent A = hexanes and solvent B = EtOAc) to give Part B compound (22 mg; 18%).

C.

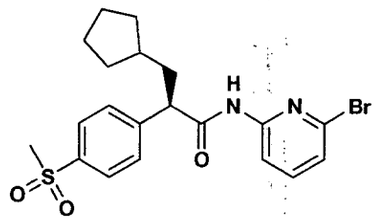


[00189] DEPBT (50 mg; 0.168 mmol) was added to a stirred solution of Example 1 Part D compound (25 mg; 0.084 mmol) and Part B compound (21.9 mg; 0.093 mmol) in THF (0.40 mL). DIPEA (28.4 uL; 0.168 mmol) was added. After 96 h at RT the reaction mixture was concentrated *in vacuo*. The residue was dissolved in EtOAc (3 mL). The EtOAc solution was washed with brine (2 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude product was purified by preparative HPLC (YMC reverse phase ODS-A-5u 30 x 100 mm column; flow rate = 40 mL/min, 20 to 100% solvent B over 12 min, hold to 15 min, where solvent A = 90:10:0.1 H_2O:MeOH:TFA and solvent B = 90:10:0.1 MeOH:H_2O:TFA) to give title compound (13 mg; 30%) as a white solid. $[M + H]^+ = 515.2$; ^1H NMR (400 MHz, CD_3OD): δ 1.18 (m, 2H), 1.31 (m, 6H), 1.51 (, 2H), 1.64 (m, 3H), 1.81 (m, 2H), 1.88 (m, 1H), 2.23 (m, 1H), 3.10 (s, 3H), 3.96 (t, 1H), 4.14 (m, 4H), 7.68 (d, 2H), 7.86 (d, J = 4.95 Hz, 1H),7.93 (d, 2H).

EXAMPLE 10

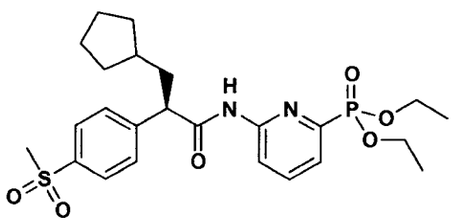


A.



[00190] DEPBT (162 mg; 0.540 mmol) was added to a stirred solution of Example 1 Part D compound (80 mg; 0.270 mmol) and 2-amino-6-bromopyridine (51.4 mg; 0.297 mmol) in THF (1.0 mL). DIPEA (91.0 uL; 0.540 mmol) was added. After 48 h at RT more 2-amino-6-bromopyridine (93.0 mg; 0.537 mmol) was added. After an additional 48 h the reaction mixture was concentrated *in vacuo*. The residue was partitioned between EtOAc (6 mL) and 0.1 N aqueous HCl (3 mL). The organic phase was washed with brine (3 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by preparative HPLC (YMC reverse phase ODS-A-5u 30 x 100 mm column; flow rate = 40 mL/min, 35 to 100% solvent B over 10 min, hold to 13 min, where solvent A = 90:10:0.1 H_2O:MeOH:TFA and solvent B = 90:10:0.1 MeOH:H_2O:TFA) to give Part A compound (16 mg; 13%).

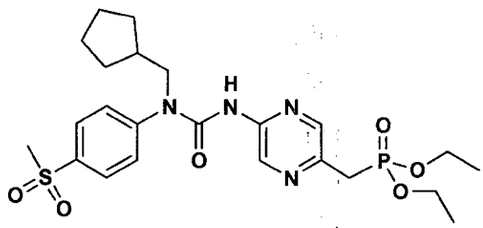
B.



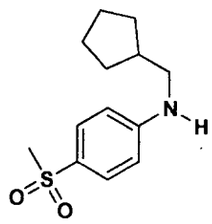
[00191] THF (degassed) (0.50 mL) was added to a reaction flask containing Part A compound (14.0 mg; 0.031 mmol) and $(Ph_3P)_4Pd(0)$(7.2 mg; 0.006 mmol). Diethyl

phosphite (4.8 uL; 0.037 mmol) was added followed by Et_3N (6.0 μL; 0.043 mmol). The reaction vessel was capped and the reaction mixture was heated at 75°C for 12 h, then was cooled to RT. The reaction mixture was concentrated *in vacuo*. The crude product was purified by preparative HPLC (YMC reverse phase ODS-A-5u 20 x 100 mm column; flow rate = 40 mL/min., 20 to 100% solvent B over 12 min, hold to 15 min, where solvent A = 90:10:0.1 H_2O:MeOH:TFA and solvent B = 90:10:0.1 MeOH:H_2O:TFA) to give the title compound (3.6 mg; 23%) as a colorless solid. $[M + H]^+$ = 509.3; ^1H NMR (400 MHz, CD_3OD): δ 1.20 (m, 2H), 1.33 (m, 6H), 1.53 (m, 2H), 1.65 (m, 2H),1.72 (m, 1H), 1.83 (m, 3H), 2.22 (m, 1H), 3.09 (s, 3H), 4.01 (t, 1H), 4.19 (m, 4H), 7.61 (t, 1H), 7.71 (d, 2H), 7.91 (m, 3H), 8.32 (d, 1H).

EXAMPLE 11

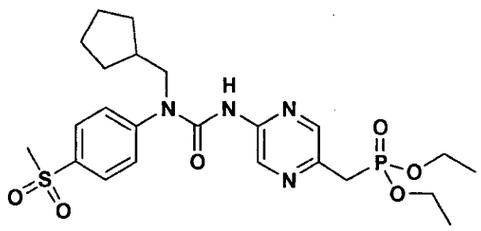


A.



[00192] To a 0°C mixture of 4-methylsulfonylaniline, hydrochloride (1.06 g, 5.10 mmol), cyclopentane carboxaldehyde (0.5 g, 5.10 mmol), and Et_3N (1 mL, 7.14 mmol) in 20 mL of dichloroethane was added $NaBH(OAc)_3$ (1.51 g, 7.14 mmol). The reaction was allowed to warm to RT and stirred at RT for two days, then was treated with excess sat. aqueous $NaHCO_3$. The aqueous layer was extracted with EtOAc. The organic extract was rinsed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography (120 g silica gel, continuous gradient from 0-100% EtOAc-hexanes) gave Part A compound (904 mg, 70% yield).

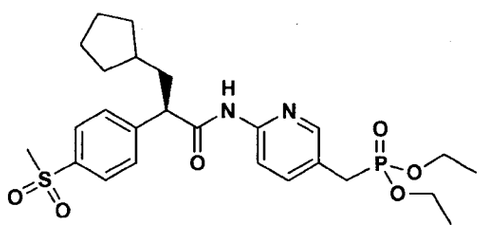
B.



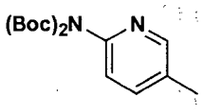
[00193] **Part 1:** 4-Nitrophenylchloroformate (49.3 mg; 0.245 mmol) was added to a cold (0°C) solution of Example 7 Part B compound (60 mg; 0.245 mmol). Pyridine 20.8 µL; 0.257 mmol) was added. The reaction mixture was stirred at RT for 1 h, then was concentrated *in vacuo* to give the crude carbamate.

[00194] **Part 2:** The crude carbamate was dissolved in CH_3CN (1.0 mL). Part A compound (62 mg; 0.245 mmol) was added. The reaction mixture was heated at 40°C for 2 h, then was cooled to RT and concentrated *in vacuo*. The crude product was chromatographed (SiO_2; continuous gradient from 0 to 100% solvent B over 4 min, switch to solvent C, hold at 100% solvent C for 8 min, where solvent A = hexanes, solvent B = EtOAc and solvent C = 10% MeOH in EtOAc) to give title compound (30 mg; 23% - two steps) as an amorphous solid. $[M + H]^+ = 525.3$; ^1H NMR (400 MHz, CD_3OD): δ 1.28 (t, 8H), 1.54 (m, 2H), 1.67 (m, 4H), 2.10 (m, 1H), 3.17 (s, 3H), 3.45 (d, 2H), 3.83 (d, 2H), 4.09 (m, 4H), 7.65 (d, 2H), 8.05 (d, 2H), 8.19 (s, 1H), 9.12 (s, 1H).

EXAMPLE 12

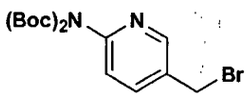


A.



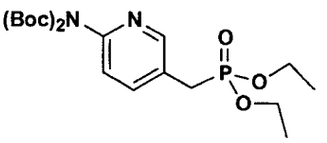
[00195] DIPEA (8.05 mL; 46.24 mmol) was added to a cold (0°C) solution of 2-amino-5-picoline (2.50 g; 23.12 mmol) in DCM (30 mL). A solution of di-tert-butyl dicarbonate (12.61 g; 57.80 mmol) in DCM (17 mL) was added followed by 4-DMAP (2.82 g; 23.12 mmol). The reaction mixture was then stirred at RT for 16 h, then was concentrated *in vacuo* to half volume. The solution was diluted with EtOAc (125 mL). The organic solution was washed with sat. aqueous NH_4Cl (3 x 45 mL), brine (45 mL), sat. aqueous $NaHCO_3$ (2 x 45 mL) and brine (45 mL). The solution was then dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was chromatographed (SiO_2; continuous gradient from 15 to 20 % EtOAc in hexanes) to give Part A compound (2.70 g; 38%).

B.



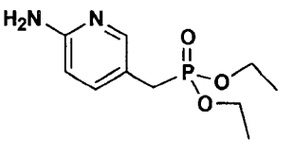
[00196] N-bromosuccinimide (1.56 g; 8.76 mmol) was added to a solution of Part A compound (2.70 g; 8.76 mmol) in CCl_4 (40 mL). Benzoyl peroxide (0.21 g; 0.88 mmol) was added. The reaction mixture was heated to reflux (80°C) for 7 h, then was cooled to RT. The reaction mixture was filtered and the filtrate was concentrated *in vacuo*. The crude product was chromatographed (SiO_2; 5 % EtOAc in DCM) to give Part B compound (1.48 g; 44%). (*Bioorg. Med. Chem. Lett*, **2004**, 14:2227-2231).

C.



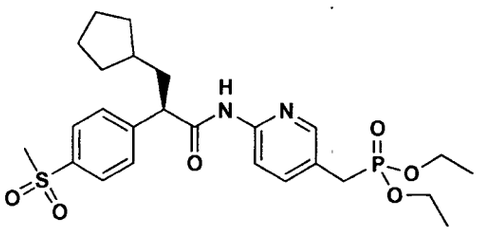
[00197] Triethylphosphite (1.2 mL; 6.97 mmol) was added to a solution of Part B compound (0.45 g; 1.16 mmol) in THF (2.5 mL). The reaction vessel was capped and the reaction mixture was heated at 80°C for 16 h, then was cooled to RT. The solution was concentrated *in vacuo*. The crude product was chromatographed (SiO_2; continuous gradient from 0 to 100% solvent B over 8 min, hold at 100% solvent B for 6 min, where solvent A = hexanes and solvent B = EtOAc) to give Part C compound (0.52 g; 100%).

D.



[00198] TFA (1.5 mL) was added to a cold (0°C) solution of Part C compound (0.52 g; 1.17 mmol) in DCM (3 mL). The reaction mixture was then stirred at RT for 3 h, then was concentrated *in vacuo*. The residue was partitioned between $CHCl_3$ (10 mL) and sat. aqueous $NaHCO_3$ (8 mL). The aqueous phase was extracted with $CHCl_3$ (8 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to give Part D compound (0.25 g; 88%).

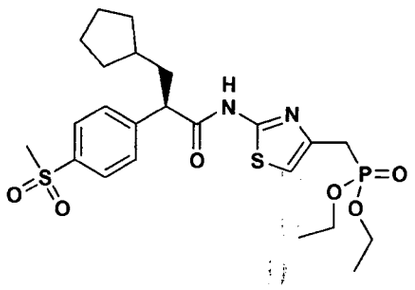
E.



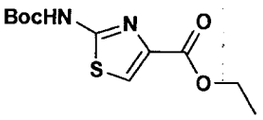
[00199] Oxalyl chloride (2.0 M in DCM) (104 µL; 0.208 mmol) was added to a 0°C solution of Example 1 Part D compound (30.9 mg; 0.104 mmol) in DCM (0.3 mL). DMF (5 µL) was added. Gas evolution occurred. After 1 h at RT the reaction mixture was concentrated *in vacuo*. The residue was stripped from $CHCl_3$ (2 x 1 mL). The crude acid chloride was dissolved in DCM (0.42 mL). Part D compound (25.5 mg; 0.104 mmol) was added followed by pyridine (12.6 uL; 0.156 mmol). After stirring for 16 h the reaction was concentrated *in vacuo*. The residue was partitioned between EtOAc (5 mL) and brine (4 mL). The organic phase was dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by preparative HPLC (YMC reverse phase ODS-A-5u 30 x 100 mm column; flow rate = 40 mL/min, 20 to 100% solvent B over 15 min, hold to 20 min, where solvent A = 90:10:0.1 H_2O:MeOH:TFA and solvent B = 90:10:0.1 MeOH:H_2O:TFA) to give the title compound (19 mg; 34%) as an amorphous solid. $[M + H]^+ = 523.4$; ^1H NMR (400 MHz, CD_3OD): δ 1.20 (m, 2H), 1.27 (t, 6H), 1.51 (m, 2H), 1.65 (m, 2H), 1.71 (m, 1H), 1.85 (m, 3H), 2.21 (m,

1H), 3.10 (s, 3H), 3.30 (d, 2H), 3.98 (t, 1H), 4.07 (m, 4H), 7.70 (d, 2H), 7.92 (m, 4H), 8.23 (s, 1H).

EXAMPLE 13

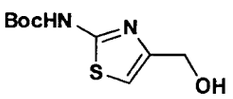


A.



[00200] A solution of di-tert-butyl dicarbonate (11.3 g; 51.83 mmol) in THF (50 mL) was added to a cold (0°C) solution of ethyl 2-aminothiazole-4-carboxylate (8.59 g; 49.36 mmol) in THF (150 mL). TEA (7.57 mL; 54.30 mmol) was added followed by a catalytic amount of 4-DMAP (30 mg). The reaction mixture was stirred at RT for 16 h, then was concentrated *in vacuo*. The residue was portioned between EtOAc (300 mL) and 0.5 N aqueous HCl (250 mL). The organic phase was washed with brine (150 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give Part A compound (12.38 g; yield given below in Part B). The crude product was used in the next step without further purification.

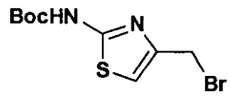
B.



[00201] A solution of $LiAlH_4$ (1.0 M in THF) (48.0 mL; 48.0 mmol) was added to a cold (0°C) solution of Part A compound (12.38 g; 45.3 mmol) in THF (130 mL). After 3 h at 0°C the reaction was carefully quenched by dropwise addition of H_2O (5 mL). After 10 min, 5 N aqueous NaOH (2.5 mL) was added. After another 10 min,

the solution was concentrated *in vacuo*. The residue was partitioned between EtOAc (300 mL) and H_2O (200 mL). The aqueous phase was extracted with EtOAc (100 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was chromatographed (SiO_2; continuous gradient from 0 to 100% solvent B over 16 min, hold at 100% solvent B for 5 min, where solvent A = hexanes and solvent B = EtOAc) to give Part B compound (8.67 g; 67% - two steps).

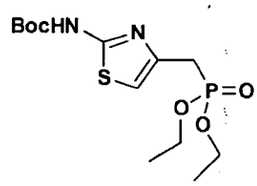
C.



[00202] **Method 1:** A solution of methanesulfonyl chloride (318 μL; 4.10 mmol) in DCM (3 mL) was slowly added to a 0°C solution of Part B compound (900 mg; 3.91 mmol) and TEA (600 μL; 4.30 mmol) in DCM (10 mL). After 25 min of stirring the reaction mixture was diluted with acetone (13 mL). LiBr (2.03 g; 23.46 mmol) was added. The reaction was stirred at RT for 1 h, then was diluted with sat. aqueous NH_4Cl (20 mL) and extracted with Et_2O (2 x 40 mL). The combined organic extracts were washed with sat. aqueous NH_4Cl (2 x 20 mL) and brine (20 mL). The solution was dried ($MgSO_4$) and concentrated *in vacuo* to give Part C compound (1.03 g; 89%). The crude product was taken forward without further purification.

[00203] **Method 2:** N-Boc thiourea (428 mg; 2.427 mmol) was added to a solution of 1,3– dibromoacetone (524 mg; 2.427 mmol) in acetone (9.7 mL). After 24 h at RT the reaction mixture was concentrated *in vacuo* to give Part C compound (0.78 g; Quant.) as a brown foam. The crude product was taken forward without further purification.

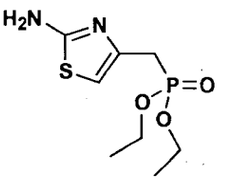
D.



[00204] Triethyl phosphite (3.6 mL; 20.96 mmol) was added to a solution of Part C compound (878 mg; 2.99 mmol) in THF (6 mL). The reaction vessel was capped and

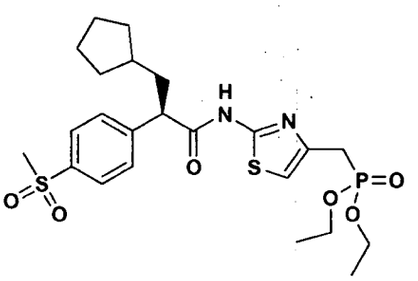
the reaction mixture was heated at 80°C for 16 h, then was cooled to RT. The solution was concentrated *in vacuo*. The crude product was chromatographed (SiO_2; continuous gradient from 0 to 100% solvent B over 8 min, hold at 100% solvent B for 10 min, where solvent A = hexanes and solvent B = EtOAc) to give Part D compound (0.86 g; 82%).

E.



[00205] TFA (3.0 mL) was added to a 0°C solution of Part D compound (0.86 g; 2.45 mmol) in DCM (7 mL). The reaction mixture was stirred at RT for 2.5 h, then was concentrated *in vacuo*. The residue was partitioned between EtOAc (15 mL) and sat. aqueous $NaHCO_3$ (10 mL). The aqueous phase was extracted with EtOAc (10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to give Part E compound (488 mg; 80%). ^1H NMR (400 MHz, $CDCl_3$) δ 6.17 (1 H, d, J=3.95 Hz), 5.85 (2 H, br. s.), 3.92 - 4.05 (4 H, m), 3.08 (2 H, d, J=21.09 Hz), 1.18 (6 H, t, J=7.03 Hz).

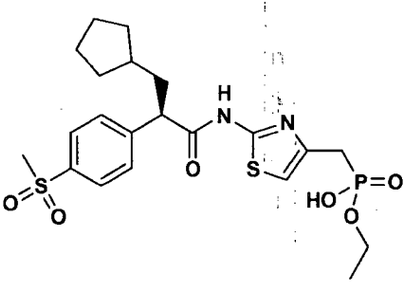
F.



[00206] Oxalyl chloride (2.0 M in DCM) (0.63 mL; 1.26 mmol) was added to a 0°C mixture of Example 1 Part D compound (250 mg; 0.844 mmol) in DCM (2.5 mL). DMF (10 uL) was added. Gas evolution occurred. After 1.5 h at RT the reaction mixture was concentrated *in vacuo*. The residue was stripped from $CHCl_3$ (2 x 3 mL). The crude acid chloride was dissolved in DCM (3.0 mL). Part E compound (253 mg;

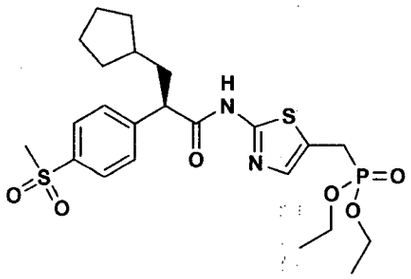
1.013 mmol) was added followed by pyridine (205 uL; 2.532 mmol). After 2 h at RT the reaction was concentrated *in vacuo*. The residue was partitioned between EtOAc (15 mL) and 0.5 N aqueous HCl (10 mL). The organic phase was washed with 0.5 N aqueous HCl (10 mL) and brine (10 mL). The solution was dried ($MgSO_4$), and concentrated *in vacuo*. The crude product was chromatographed (SiO_2; continuous gradient from 0 to 100% solvent B over 3 min, hold at 100% solvent B for 14 min, where solvent A = hexanes and solvent B = EtOAc) to give the title compound (0.40 g; 89%) as an amorphous solid. $[M + H]^+ = 529.2$; ^1H NMR (400 MHz, CD_3OD): δ 1.18 (m, 2H), 1.26 (t, 6H), 1.51 (m, 2H), 1.64 (m, 3H), 1.83 (m, 3H), 2.22 (m, 1H), 3.09 (s, 3H), 3.31 (d, 2H), 3.95 (t, 1H), 4.07 (m, 4H), 6.89 (d, J = 4.03Hz, 1H), 7.67 (d, 2H), 7.92 (d, 2H).

EXAMPLE 14

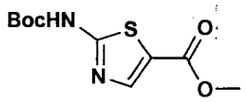


[00207] 1 N aqueous NaOH (136 uL; 0.136 mmol) was added to a solution of Example 13 Part F compound (50.5 mg; 0.096 mmol) in EtOH (100 μL). The reaction mixture was heated at 80°C for 48 h, then was cooled to RT and concentrated *in vacuo*. The crude product was purified by preparative HPLC (YMC reverse phase ODS-A-5u 30 x 100 mm column; flow rate = 40 mL/min, 10 to 100% solvent B over 16 min, hold to 20 min, where solvent A = 90:10:0.1 H_2O:MeOH:TFA and solvent B = 90:10:0.1 MeOH:H_2O:TFA) to give the title compound (12.5 mg; 26%) as an amorphous solid. $[M + H]^+ = 501.1$; ^1H NMR (400 MHz, $CDCl_3$): δ 1.13 (m, 2H), 1.30 (t, 3H), 1.48 (m, 2H), 1.60 (m, 3H), 1.78 (m, 2H), 1.90 (m, 1H), 2.23 (m, 1H), 3.04 (s, 3H), 3.28 (d, 2H), 4.05 (m, 3H), 6.68 (d, 1H), 7.68 (d, 2H), 7.88 (d, 2H).

EXAMPLE 15

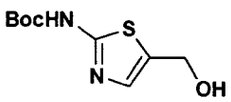


A.



[00208] A solution of di-tert-butyl dicarbonate (1.66 g; 7.59 mmol) in THF (10 mL) was added to a 0°C solution of methyl 2-aminothiazole-5-carboxylate (1.20 g; 7.59 mmol) in THF (20 mL). TEA (1.11 mL; 7.97 mmol) was added followed by a catalytic amount of 4-DMAP (10 mg). The reaction mixture was then stirred at RT for 20 h, then was concentrated *in vacuo*. The residue was partitioned between EtOAc (80 mL) and 0.2 N aqueous HCl (40 mL). The organic phase was washed with brine (40 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give Part A compound (1.70 g; yield given below in Part B). The crude product was taken forward without further purification.

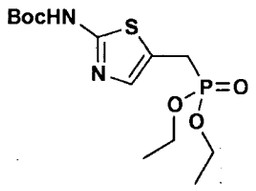
B.



[00209] A solution of $LiAlH_4$ (7.60 mL of a 1.0 M solution in THF); 7.60 mmol) was added to a 0°C solution of Part A compound (1.70 g; 6.58 mmol) in THF (30 mL). The reaction mixture was stirred at RT for 1 h, then was cooled to 0°C and carefully quenched by dropwise addition of H_2O (0.76 mL). After 10 min, 5 N aqueous NaOH (0.38 mL) was added. After another 10 min, the solution was filtered through a pad of Celite and the filtrate was concentrated *in vacuo*. The crude product was chromatographed (SiO_2; continuous gradient from 0 to 100% solvent B over 13

min, hold at 100% solvent B for 6 min, where solvent A = hexanes and solvent B = EtOAc) to give Part B compound (0.80 g; 46% - two steps).

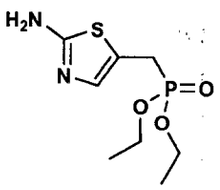
C.



[00210] **Part 1:** Thionyl chloride (253 μL; 3.47 mmol) was added to a 0°C mixture of Part B compound (200 mg; 0.869 mmol) in DCM (0.40 mL). The reaction mixture was stirred at 0°C for 2 h then was concentrated vacuo to give the crude chloride.

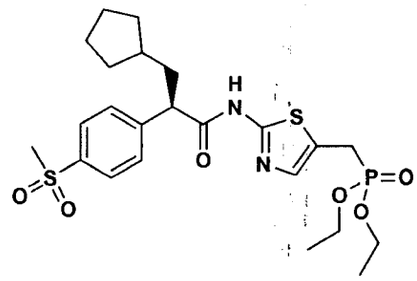
[00211] **Part 2:** The crude chloride was dissolved in THF (3.0 mL). $(EtO)_3P$ (1.20 mL; 6.95 mmol) was added. The reaction mixture was heated at 80°C for 16 h, then was cooled to RT and concentrated *in vacuo*. The crude product was chromatographed (SiO_2; continuous gradient from 0 to 100% solvent B over 8 min, switch to solvent C, hold at 100% solvent C for 7 min, where solvent A = hexanes, solvent B = EtOAc and solvent C = 3% MeOH in EtOAc) to give Part C compound (270 mg; 89% - two steps).

D.



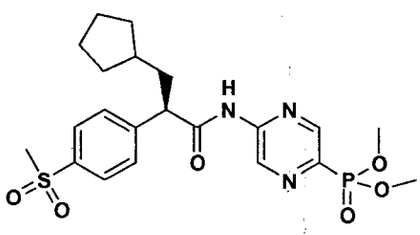
[00212] TFA (0.80 mL) was added to a 0°C solution of Part C compound (0.31 g; 0.885 mmol) in DCM (2.4 mL). The reaction mixture was stirred at RT for 3 h then was concentrated *in vacuo*. The residue was partitioned between $CHCl_3$ (10 mL) and sat. aqueous $NaHCO_3$ (10 mL). The aqueous phase was extracted with $CHCl_3$ (10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to give Part D compound (198 mg; 89%).

E.

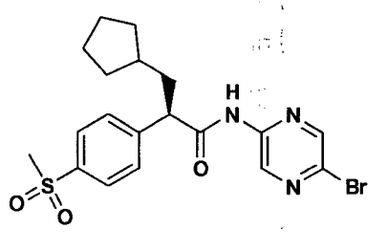


[00213] Oxalyl chloride (2.0 M in DCM) (101 uL; 0.202 mmol) was added to a 0°C mixture of Example 1 Part D compound (40 mg; 0.135 mmol) in DCM (0.35 mL). DMF (6 uL) was added. Gas evolution occurred. The reaction mixture was then stirred at RT for 1.5 h then was concentrated *in vacuo*. The residue was stripped from $CHCl_3$ (2 X 1 mL). The crude acid chloride was dissolved in DCM (0.45 mL). Part D compound (47.3 mg; 0.189 mmol) was added followed by pyridine (33.0 uL; 0.405 mmol). After 4 h at RT the reaction was concentrated *in vacuo*. The residue was partitioned between EtOAc (6 mL) and brine (4 mL). The organic phase was dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by preparative HPLC (YMC reverse phase ODS-A-5u 30 x 100 mm column; flow rate = 40 mL/min, 15 to 100% solvent B over 10 min, hold to 15 min, where solvent A = 90:10:0.1 H_2O:MeOH:TFA and solvent B = 90:10:0.1 MeOH:H_2O:TFA) to give the title compound (46 mg; 65%) as a white solid. $[M + H]^+$ = 529.1; ^1H NMR (400 MHz, CD_3OD): δ 1.18 (m, 2H), 1.29 (t, 6H), 1.49 (m, 2H), 1.63 (m, 3H), 1.80 (m, 3H), 2.22 (m, 1H), 3.09 (s, 3H), 3.43 (d, 2H), 3.96 (t, 1H), 4.09 (m, 4H), 7.26 (d, J = 4.4Hz, 1H), 7.67 (d, 2H), 7.92 (d, 2H).

EXAMPLE 16

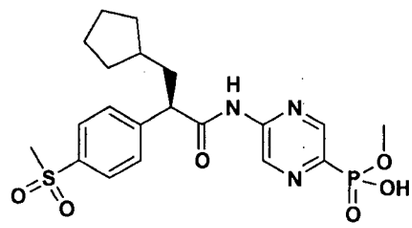


A.



[00214] Oxalyl chloride (169 μL of a 2 M solution in DCM; 0.338 mmol) was added to a mixture of Example 1 Part D compound (50 mg; 0.169 mmol) in DCM (0.35 mL). The solution was cooled to 0°C. DMF (5 uL) was added. Gas evolution occurred. After 2 h at RT the reaction mixture was concentrated *in vacuo*. The residue was stripped from $CHCl_3$ (2 X 1 mL). The crude acid chloride was dissolved in DCM (0.5 mL). 5-bromo-2-pyrazinamine (44 mg; 0.253 mmol) was added followed by pyridine (20.5 uL; 0.253 mmol). The reaction mixture was stirred at RT for 3 h, then was concentrated *in vacuo*. The residue was partitioned between EtOAc (6 mL) and brine (4 mL). The organic phase was dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was chromatographed (SiO_2; continuous gradient from 0 to 30% solvent B over 30 min, then 30% to 65% solvent B over 5 min, then hold at 65% solvent B for 5 min, where solvent A = hexanes and solvent B = EtOAc) to give Part A compound (64 mg; 84%).

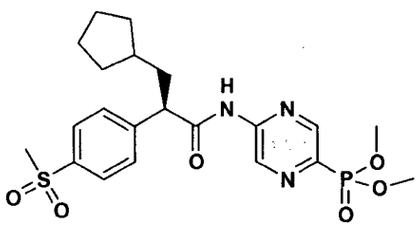
B.



[00215] A solution of Part A compound (44 mg; 0.097 mmol) in THF (degassed) (0.50 mL) was added to a reaction flask containing $(Ph_3P)_4Pd(0)$(22.4 mg; 0.019 mmol). $(MeO)_3P$ (11.6 μL; 0.126 mmol) was added followed by TEA (21.6 μL; 0.155 mmol). The reaction vessel was capped and the reaction mixture was heated at 75°C for 6 h, then was cooled to RT and concentrated *in vacuo*. The crude product was purified by preparative HPLC (YMC reverse phase ODS-A-5u 30 x 100 mm

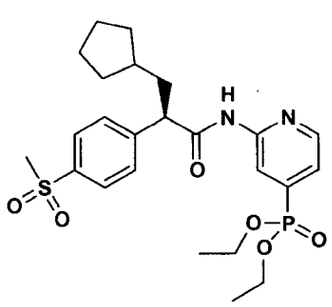
column; flow rate = 40 mL/min, 15 to 100% solvent B over 10 min, hold to 13 min, where solvent A = 90:10:0.1 H_2O:MeOH:TFA and solvent B = 90:10:0.1 MeOH:H_2O:TFA) to give Part B compound (17 mg; 38%).

C.



[00216] $TMSCHN_2$ (2.0 M in hexane) (73 μL; 0.145 mmol) was added to a mixture of Part B compound (17 mg; 0.036 mmol) in Et_2O (75 μL) and THF (250 μL). After stirring at RT for 1 h the reaction mixture was concentrated *in vacuo*. The crude product was purified by preparative HPLC (YMC reverse phase ODS-A-5u 20 x 100 mm column; flow rate = 20 mL/min., 20 to 100% solvent B over 10 min, hold to 15 min, where solvent A = 90:10:0.1 H_2O:MeOH:TFA and solvent B = 90:10:0.1 MeOH:H_2O:TFA) to give the title compound (9 mg; 51%) as a colorless solid. $[M + H]^+ = 482.2$; ^1H NMR (400 MHz, CD_3OD): δ 1.19 (m, 2H), 1.51 (m, 2H), 1.64 (m, 3H), 1.83 (m, 3H), 2.22 (m, 1H), 3.09 (s, 3H), 3.83 (d, 3H), 3.86 (d, 3H), 4.04 (t, 1H), 7.70 (d, 2H), 7.92 (d, 2H), 8.71 (s, 1H), 9.59 (s, 1H).

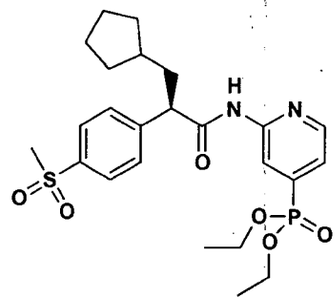
EXAMPLE 17



A.

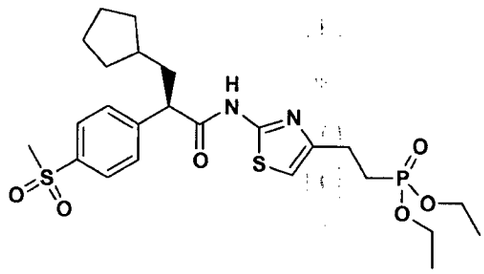
occurred. After 2 h at RT the reaction mixture was concentrated *in vacuo*. The residue was stripped from $CHCl_3$ (2 X 1 mL). The crude acid chloride was then dissolved in DCM (0.5 mL). Part B compound (53 mg; 0.253 mmol) was added followed by pyridine (49 uL; 0.606 mmol). The reaction mixture was stirred at RT for 2 h then was concentrated *in vacuo*. The residue was partitioned between EtOAc (8 mL) and brine (4 mL). The organic phase was dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was chromatographed (SiO_2; continuous gradient from 0 to 100% solvent B over 10 min, where solvent A = hexanes and solvent B = EtOAc) to give Part C compound (72 mg; 79%).

D.

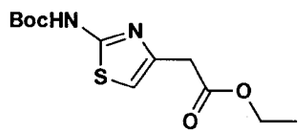


[00220] A solution of Part C compound (66 mg; 0.146 mmol) in THF (degassed) (0.38 mL) was added to a reaction flask containing $(Ph_3P)_4Pd(0)$(34 mg; 0.029 mmol). $H(O)P(OEt)_2$ (21 µL; 0.161 mmol) was added followed by TEA (24.4 µL; 0.175 mmol). The reaction vessel was capped and the reaction mixture was heated at 75°C for 16 h, then was cooled to RT and concentrated *in vacuo*. The crude product was purified by preparative HPLC (YMC reverse phase ODS-A-5u 30 x 100 mm column; flow rate = 40 mL/min, 35 to 100% solvent B over 12 min, hold to 14 min, where solvent A = 90:10:0.1 H_2O:MeOH:TFA and solvent B = 90:10:0.1 MeOH:H_2O:TFA) to give the title compound (49 mg; 66%) as a white solid. $[M + H]^+ = 509.1$; ^1H NMR (400 MHz, CD_3OD): δ 1.19 (m, 2H), 1.34 (m, 6H), 1.52 (m, 2H), 1.65 (m, 3H), 1.84 (m, 3H), 2.23 (m, 1H), 3.09 (s, 3H), 4.01 (t, 1H), 4.16 (m, 4H), 7.38 (dd, 1H), 7.71 (d, 2H), 7.92 (d, 2H), 8.47 (m, 2H).

EXAMPLE 18

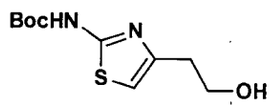


A.



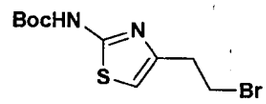
[00221] A solution of di-tert-butyl dicarbonate (1.03 g; 4.73 mmol) in toluene (15 mL) was added to a reaction vessel containing (ethyl 2-(2-aminothiazol-4-yl) acetate (0.80 g; 4.30 mmol). The reaction mixture was heated at 85°C for 24 h, then was cooled to RT and concentrated *in vacuo* to give Part A compound (1.14 g; quant. yield). The crude compound was carried forward without further purification.

B.



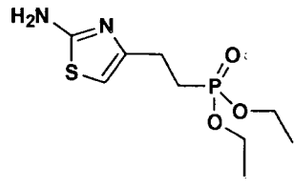
[00222] A solution of $LiAlH_4$ (4.30 mL of a 1 M solution in THF; 4.40 mmol) was added to a 0°C solution of crude Part A compound (1.14 g; 3.98 mmol) in THF (13 mL). The reaction mixture was stirred at 0°C for 2 h, then was carefully quenched by dropwise addition of sat. aqueous NH_4Cl (0.6 mL). The solution was partitioned between EtOAc (20 mL) and brine (10 mL). The organic phase was washed with brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was chromatographed (SiO_2; continuous gradient from 0 to 100% solvent B over 8 min, hold at 100% solvent B for 8 min, where solvent A = hexanes and solvent B = EtOAc) to give Part B compound (0.42 g; 43%).

C.



[00223] A solution of CH_3SO_2Cl (140 µL; 1.81 mmol) in DCM (1.7 mL) was added to a 0°C solution of Part B compound (0.42 g; 1.72 mmol) and TEA (264 uL; 1.89 mmol) in DCM (4.0 mL). After 30 min at 0°C the reaction mixture was diluted with acetone (5.7 mL). LiBr (896 mg; 10.32 mmol) was added. The reaction was stirred at RT for 1 h, then was partitioned between Et_2O (10 mL) and sat. aqueous NH_4Cl (10 mL). The organic phase was washed with sat. aqueous NH_4Cl (10 mL) and brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give Part C compound (0.50 g; 94%).

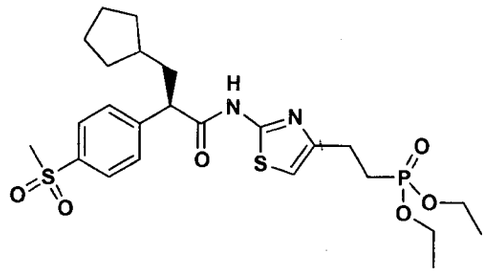
D.



[00224] **Part 1:** Part C compound (0.50 g; 1.63 mmol) was dissolved in neat $(EtO)_3P$ (1.0 mL). The reaction mixture was heated at 130°C for 2 h; at this point analytical HPLC showed multiple peaks. The reaction was cooled to RT and concentrated *in vacuo*. The crude product was chromatographed (SiO_2; continuous gradient from 0 to 100% solvent B over 7 min, switch to solvent C, hold at 100% solvent C for 7 min, where solvent A = hexanes, solvent B = EtOAc and solvent C = 3% MeOH in EtOAc). The compound was not pure at this point (65% purity).

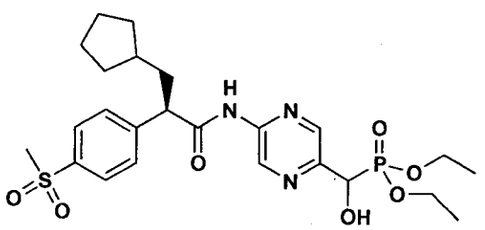
[00225] **Part 2:** To a 0°C solution of the impure intermediate from Part 1 in DCM (0.8 mL) was added TFA (0.4 mL). The reaction was allowed to warm to RT and stirred at RT for 2 h, then was concentrated *in vacuo*. The residue was partitioned between EtOAc (10 mL) and sat. aqueous $NaHCO_3$ (10 mL). The organic phase was dried ($MgSO_4$) and concentrated *in vacuo* to give Part D compound (73 mg; 17% - two steps). (65% purity).

E.

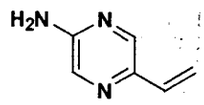


[00226] Oxalyl chloride (2.0 M in DCM) (78 μL; 0.155 mmol) was added to a mixture of Example 1 Part D compound (33 mg; 0.111 mmol) in DCM (0.25 mL). The solution was cooled to 0°C. DMF (7 μL) was added. Gas evolution occurred. After 1.5 h at RT the reaction mixture was concentrated *in vacuo*. The residue was stripped from $CHCl_3$ (2 X 0.8 mL). The crude acid chloride was dissolved in DCM (0.25 mL). Part D compound (38 mg; 0.144 mmol) was added followed by pyridine (27 uL; 0.333 mmol). The reaction mixture was stirred at RT for 2 h, then was concentrated *in vacuo*. The residue was partitioned between EtOAc (8 mL) and 0.5 N aqueous HCl (4 mL). The organic phase was washed with brine (4 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The crude product was purified by preparative HPLC (YMC reverse phase ODS-A-5u 30 x 100 mm column; flow rate = 40 mL/min, 20 to 100% solvent B over 10 min, hold to 14 min, where solvent A = 90:10:0.1 H_2O:MeOH:TFA and solvent B = 90:10:0.1 MeOH:H_2O:TFA) to give title compound (29 mg; 48%) as an amorphous solid. $[M + H]^+ = 543.0$; ^1H NMR (400 MHz, CD_3OD): δ 1.19 (m, 2H), 1.27 (t, 6H), 1.50 (m, 2H), 1.63 (m, 3H), 1.81 (m, 3H), 2.20 (m, 3H), 2.87 (m, 2H), 3.09 (s, 3H), 3.95 (t, 1H), 4.06 (m, 4H), 6.77 (s, 1H), 7.67 (d, 2H), 7.92 (d, 2H).

EXAMPLE 19

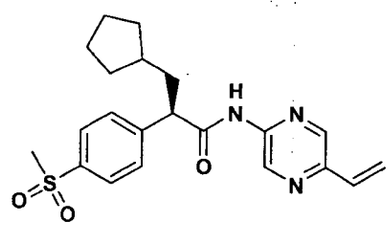


A.



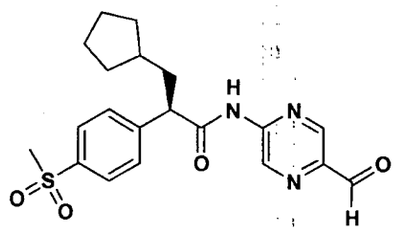
[00227] DMF (20 mL) was added to a reaction flask containing 5-bromo-2-pyrazinamine (1.00 g; 5.75 mmol), $(Ph_3P)_4Pd(0)$ (199 mg; 0.173 mmol) and LiCl (853 mg; 20.13 mmol). DIPEA (2.50 mL; 14.38 mmol) was added followed by tributyl (vinyl)tin (2.52 mL; 8.62 mmol). The reaction mixture was heated at 120°C for 4 h, then was cooled to RT. A solution of aqueous sat. KF (20 mL) was added. After stirring for 16 h the mixture was diluted with EtOAc (80 mL) and filtered through Celite. The filtrate was washed with H_2O (80 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was chromatographed (SiO_2; continuous gradient from 0 to 100% solvent B over 13 min, hold at 100% for 4 min, where solvent A = hexanes and solvent B = EtOAc) to give Part A compound (0.41 g; 59%).

B.



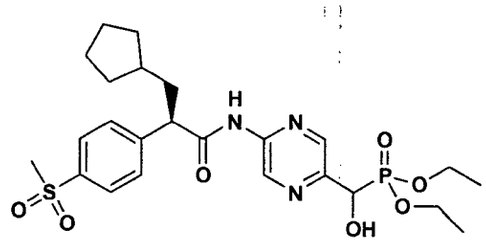
[00228] Oxalyl chloride (127 µL of a 2 M solution in DCM; 0.253 mmol) was added to a mixture of Example 1 Part D compound (50 mg; 0.169 mmol) in DCM (0.5 mL). The solution was cooled to 0°C. DMF (7 µL) was added. Gas evolution occurred. After 1.5 h at RT the reaction mixture was concentrated *in vacuo*. The residue was stripped from $CHCl_3$ (2 X 1 mL). The crude acid chloride was then dissolved in DCM (0.6 mL). Part A compound (24.5 mg; 0.202 mmol) was added followed by pyridine (41 uL; 0.507 mmol). The reaction mixture was stirred at RT for 1.5 h, then was concentrated *in vacuo*. The crude product was chromatographed (SiO_2; continuous gradient from 0 to 100% solvent B over 12 min, hold at 100% solvent B for 3 min, where solvent A = hexanes and solvent B = EtOAc) to give Part B compound (70 mg; 100%).

C.



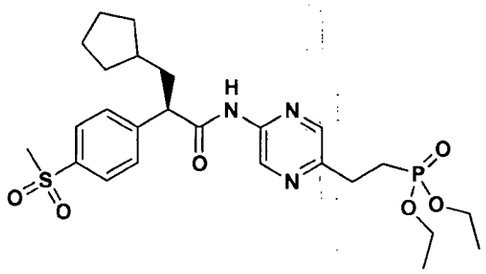
[00229] Acetic acid (15 μL) was added to a solution of Part B compound (70 mg; 0.175 mmol) in DCM (0.50 mL). The solution was cooled to -78°C (dry ice/acetone). Ozone was bubbled through the solution until it turned light blue (~4 min). The dry ice/acetone bath was removed and the reaction was allowed to warm to RT. After 5 min of stirring at RT the solution was diluted with DCM (3 mL). Sat. aqueous $NaHCO_3$ (3 mL) was added (emulsion formed). The mixture was concentrated *in vacuo* to remove DCM. The aqueous solution was then extracted with EtOAc (4 mL). The organic phase was dried ($MgSO_4$) and concentrated *in vacuo* to give Part C compound (55 mg; 78%).

D.

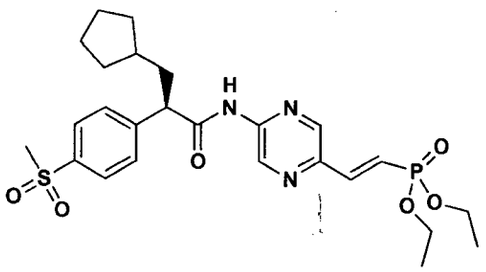


[00230] Diethyl phosphite (8.0 μL; 0.062 mmol) was added to a solution of Part C compound (25 mg; 0.062 mmol) in THF (0.30 mL). TEA (8.68 uL; 0.062 mmol) was then added. After 8 h at RT the solution was concentrated *in vacuo*. The crude product was purified by preparative HPLC (YMC reverse phase ODS-A-5u 30 x 100 mm column; flow rate = 40 mL/min, 15 to 100% solvent B over 15 min, hold to 20 min, where solvent A = 90:10:0.1 H_2O:MeOH:TFA and solvent B = 90:10:0.1 MeOH:H_2O:TFA) to give the title compound (15 mg; 45%; amorphous solid) as a 1:1 mixture of diastereomers. $[M + H]^+$ = 540.2; ^1H NMR (400 MHz, $CDCl_3$): δ 1.15 (m, 2H), 1.31 (m, 6H), 1.48 (m, 2H), 1.62 (m, 3H), 1.78 (m, 2H), 1.93 (m, 1H), 2.22 (m, 1H), 3.88 (m, 1H), 4.20 (m, 4H), 5.13 (dd, 1H), 7.63 (d, 2H), 7.89 (d, 2H), 8.34 (d, 1H), 9.11 (d, 1H), 9.43 (s, 1H).

EXAMPLE 20

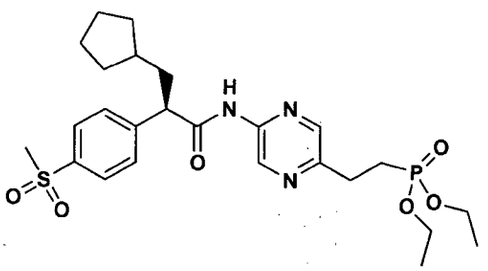


A.



[00231] A solution of Example 19 Part C compound (26 mg; 0.065 mmol) in DCM (150 uL) was added to a solution of $CH_2(PO_3Et_2)_2$ (16.2 μL; 0.065 mmol) in 5 N aqueous NaOH (150 μL). After 1 h at RT the reaction mixture was partitioned between DCM (3 mL) and H_2O (2 mL). The organic phase was dried ($MgSO_4$) and concentrated *in vacuo* to give Part A compound (35 mg; 100%).

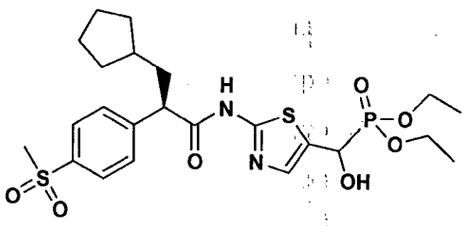
B.



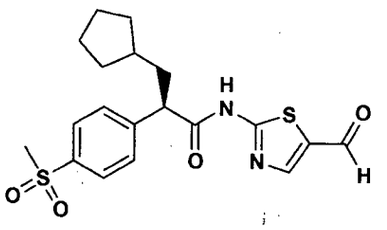
[00232] 10% Pd/C (3 mg) was added to a solution of Part A compound (35 mg; 0.065 mmol) in MeOH (0.30 mL). A H_2 atmosphere was introduced via balloon. After 6 h the reaction mixture was filtered and the filtrate was concentrated *in vacuo*. The crude product was purified by preparative HPLC (YMC reverse phase ODS-A-5u 30

x 100 mm column; flow rate = 40 mL/min, 20 to 100% solvent B over 11 min, hold to 15 min, where solvent A = 90:10:0.1 H_2O:MeOH:TFA and solvent B = 90:10:0.1 MeOH:H_2O:TFA) to give title compound (11 mg; 31%) as an amorphous solid. $[M + H]^+ = 538.2$; ^1H NMR (400 MHz, $CDCl_3$): δ 1.15 (m, 2H), 1.30 (m, 8H), 1.48 (m, 2H), 1.61 (m, 3H), 1.76 (m, 2H), 1.93 (m, 1H), 2.22 (m, 3H), 3.05 (s, 3H), 3.74 (m, 1H), 4.09 (m, 4H), 7.61 (d, 2H), 7.92 (d, 2H), 8.08 (s, 1H), 8.29 (s, 1H), 9.44 (s, 1H).

EXAMPLE 21

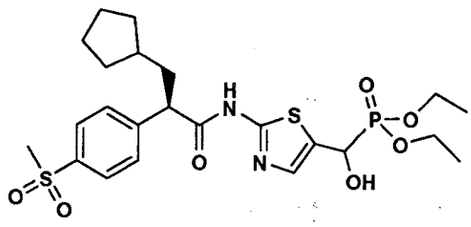


A.



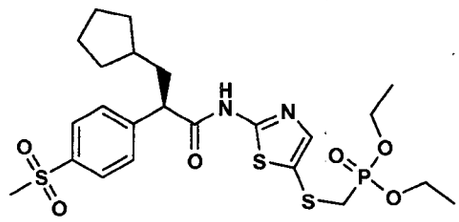
[00233] Oxalyl chloride (203 μL of a 2 M solution in DCM; 0.406 mmol) was added to a 0°C mixture of Example 1 Part D compound (80 mg; 0.270 mmol) in DCM (0.70 mL). DMF (10 uL) was added. Gas evolution occurred. The reaction mixture was stirred at RT for 1.5 h, then was concentrated *in vacuo*. The residue was stripped from $CHCl_3$ (2 x 2 mL). The crude acid chloride was dissolved in DCM (0.90 mL). 2-amino-5-formylthiazole (45.0 mg; 0.351 mmol) was added followed by pyridine (66.0 uL; 0.810 mmol). After 16 h at RT the reaction was concentrated *in vacuo*. The crude product was chromatographed (SiO_2; continuous gradient from 0 to 100% solvent B over 6 min, hold at 100% solvent B for 8 min, where solvent A = hexanes and solvent B = EtOAc) to give Part A compound (27 mg; 25%).

B.

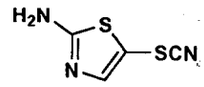


[00234] $H(O)P(OEt)_2$ (8.9 μL; 0.069 mmol) was added to a solution of Part A compound (27 mg; 0.066 mmol) in THF (0.30 mL). TEA (9.6 μL; 0.069 mmol) was added. The reaction mixture was stirred at RT for 20 h, after which more $H(O)P(OEt)_2$ (8.89 uL; 0.069 mmol) and TEA (9.62 uL; 0.069 mmol) were added along with THF (0.10 mL). After 20 h the reaction was heated at 45°C for 16 h, then was cooled to RT. After two weeks at RT the residue which had formed was purified by preparative HPLC (YMC reverse phase ODS-A-5u 30 x 100 mm column; flow rate = 40 mL/min, 15 to 100% solvent B over 20 min, where solvent A = 90:10:0.1 H_2O:MeOH:TFA and solvent B = 90:10:0.1 MeOH:H_2O:TFA) to give the title compound (27 mg; 75%; amorphous solid) as a 1:1 mixture of diastereomers. $[M + H]^+$ = 540.2; ^1H NMR (400 MHz, $CDCl_3$): δ 1.16 (m, 2H), 1.32 (m, 6H), 1.49 (m, 2H), 1.62 (m, 3H), 1.78 (m, 2H), 1.95 (m, 1H), 2.24 (m, 1H), 3.04 (s, 3H), 4.01 (t, 1H), 4.21 (m, 4H), 5.18 (d, 1H), 7.37 (s, 1H), 7.65 (d, 2H), 7.91 (d, 2H).

EXAMPLE 22



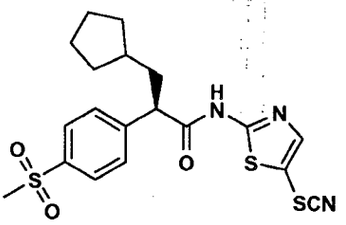
A.



[00235] To a solution of 2-amino-5-bromothiazole hydrobromide (10.0 g, 38.4 mmol) in MeOH (50 mL) was added KSCN (15.0 g, 160 mmol). The reaction mixture was stirred at RT for 18 h, then was concentrated *in vacuo*, and H_2O (40 mL)

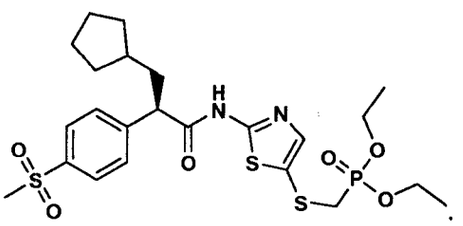
was added to the residue. The mixture was adjusted to pH 12 with 1N aqueous NaOH. A precipitate was formed, which was collected by suction filtration, and washed with H_2O (3 x) and Et_2O (3 x). The solid was dried *in vacuo* for 18 h to give Part A compound as a brown solid (2.8 g, 47%).

B.



[00236] To a solution of Part A thiocyanate (800 mg, 5.09 mmol) and Example 1D (1.51 g, 5.09 mmol) in THF (20 mL) was added DEPBT (3.05 g, 10.18 mmol) and iPr_2NEt (1.8 mL, 10.18 mmol). The reaction mixture was stirred at RT for 18 h, then was concentrated *in vacuo*. The residue was taken up in EtOAc and brine, and extracted with EtOAc (3x). The combined organic extracts were washed with 1N aqueous HCl, H_2O, 5% aqueous $NaHCO_3$, H_2O, and brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was chromatographed (SiO_2; continuous gradient 10% EtOAc/Hex to 100% EtOAc/Hexane) to give Part B compound (927 mg, 42%) as an orange solid.

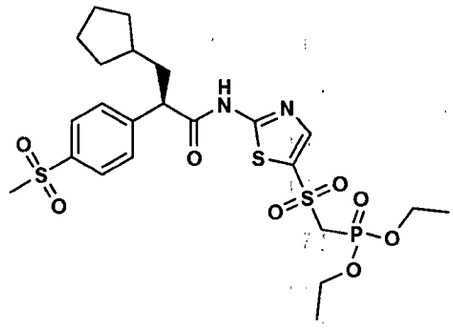
C.



[00237] To a 0°C solution of thiocyanate B (50 mg, 0.11 mmol) in absolute EtOH (2 mL) was added $NaBH_4$ (7 mg, 0.22 mmol). The mixture was stirred at 0°C for 1 h, after which excess $NaBH_4$ was cautiously quenched with acetone (0.5 mL). The mixture was warmed to RT, and was added to a flask charged with $ICH_2PO_3Et_2$ (41 mg, 0.15 mmol). The reaction was stirred at RT for 18 h, then was concentrated *in*

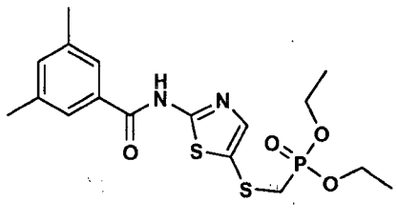
vacuo. The residue was purified by preparative HPLC (Phenomenex Luna 5u C18 21.2 x 100 mm column; detection at 220 nm; flow rate = 20 mL/min; continuous gradient from 70% A to 100% B over 8 min + 7 min hold time at 100% B, where A = 90:10:0.1 H_2O:MeOH:TFA and B = 90:10:0.1 MeOH:H_2O:TFA) to provide the title compound (25.1 mg, 39% yield) as an off white lyophilate. $[M + H]^+ = 561.1$; ^1H NMR (400 MHz, DMSO-D6): δ 7.83 (d, *J*=8.4, 2H), 7.58 (d, *J*=8.3, 2H), 7.51 (s, 1H), 3.92 (m, 5H), 3.15 (s, 2H), 3.12 (s, 3H), 2.09-1.36 (m, 11H), 1.12 (m, 6H).

EXAMPLE 23

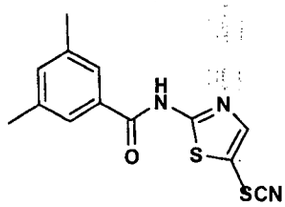


[00238] To a solution of Example **22** compound (20 mg, 0.04 mmol) in MeOH (1 mL) and THF (1 mL) was added *p*-toluenesulfonyl imidazole (24 mg, 0.11 mmol), 30% aqueous H_2O_2 (0.02 mL, 0.14 mmol), and 1N aqueous NaOH (1.0 mL). The reaction was stirred at RT for 3 h, then was concentrated *in vacuo*. The residue was purified by preparative HPLC (Phenomenex Luna 5u C18 21.2 x 100 mm column; detection at 220 nm; flow rate = 20 mL/min; continuous gradient from 70% A to 100% B over 8 min + 7 min hold time at 100% B, where A = 90:10:0.1 H_2O:MeOH:TFA and B = 90:10:0.1 MeOH:H_2O:TFA) to provide the title compound (12 mg, 57% yield) as a white lyophilate. $[M + H]^+ = 593.2$; ^1H NMR (400 MHz, DMSO-D6): δ 8.00 (s, 1H), 7.84 (d, *J*=8.4, 2H), 7.59 (d, *J*=8.4, 2H), 4.08-3.94 (m, 5H), 3.13 (s, 2H), 3.10 (s, 3H), 2.02-1.10 (m, 11H), 1.10-1.06 (m, 6H).

EXAMPLE 24

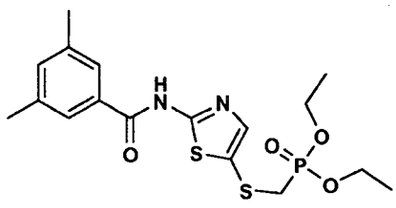


A.



[00239] To a solution of 3,5-dimethylbenzoic acid (800 mg, 5.3 mmol) in CH_2Cl_2 (20 mL)was added oxalyl chloride (0.51 mL, 5.8 mmol) and DMF (0.1 mL). The reaction mixture was stirred at RT for 2 h, then was concentrated *in vacuo*. The residue was taken up in THF (20 mL), and Example 22 Part A amine (922 mg, 5.8 mmol) and pyridine (0.86 mL, 10.6 mmol) were added. The mixture was stirred at RT for 18 h, then was diluted with EtOAc (60 mL), washed with H_2O and brine, and extracted with EtOAc (2x). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed (10% EtOAc/Hex to 100% EtOAc/Hexane) to give Part A compound (770 mg, 51% yield) as a brown solid.

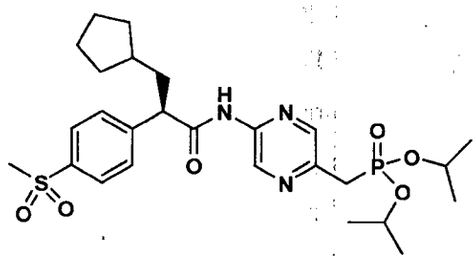
B.



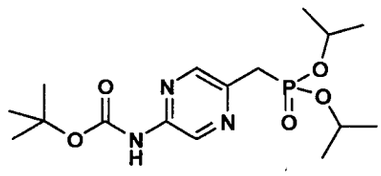
[00240] To a 0°C solution of Part A compound (50 mg, 0.17 mmol) in absolute EtOH (2 mL) was added $NaBH_4$ (13 mg, 0.35 mmol), and the mixture was stirred for 1 h at 0°C. The excess $NaBH_4$ was quenched with acetone (0.5 mL), and the mixture was warmed to RT. The mixture was added to a flask charged with $ICH_2PO_3Et_2$ (62 mg, 0.22 mmol). The reaction was stirred at RT for 18 h, then was concentrated *in*

vacuo. The residue was purified by preparative HPLC (Phenomenex Luna 5μm C18 21.2 x 100 mm column; detection at 220 nm; flow rate = 20 mL/min; continuous gradient from 70% A to 100% B over 8 min + 7 min hold time at 100% B, where A = 90:10:0.1 H_2O:MeOH:TFA and B = 90:10:0.1 MeOH:H_2O:TFA) to provide the title compound (22.4 mg, 32% yield) as a white solid. $[M + H]^+ = 415.1$; ^1H NMR (400 MHz, DMSO-D6): δ 7.71 (s, 1H), 7.66 (s, 2H), 7.27 (s, 1H), 4.02 (m, 4H), 3.27 (s, 2H), 2.34 (s, 6H), 1.21 (m, 6H).

EXAMPLE 25

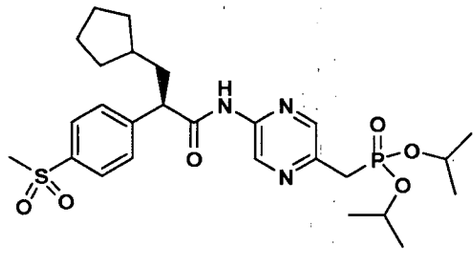


A.



[00241] A mixture of tert-butyl 5-(bromomethyl)pyrazin-2-ylcarbamate (399 mg, 1.23 mmol) and $(iPrO)_3P$ (2 mL) was heated at 100°C overnight. The reaction mixture was cooled to RT, then was chromatographed (120 g SiO_2; continuous gradient from 0-50% EtOAc in DCM, followed by a continuous gradient from 0-10% MeOH in DCM) to give 399 mg (86% yield) of Part A compound as a light yellow solid (88% purity by HPLC). $[M + H]^+ = 374.3$; ^1H-NMR (400 MHz, $CDCl_3$): δ 9.18 (s, 1H), 8.24 (s, 1H), 7.32 (s, 1H), 4.67 (m, 2H), 3.33 (d, 2H), 1.54 (s, 9H), 1.25 -1.30 (m, 12H).

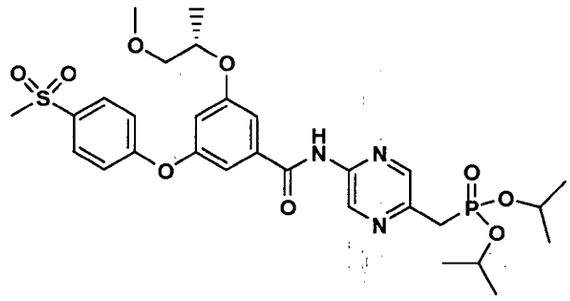
B.



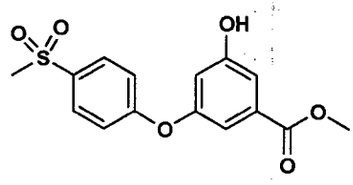
[00242] A 0°C solution of Part A compound (200 mg, 0.535 mmol) in DCM (1 mL) was treated with 1 mL of 4N aqueous HCl in dioxane under Ar. The reaction mixture was allowed to warm to RT overnight, then was concentrated *in vacuo*. The residue was dissolved in water (5 mL) and extracted with Et_2O to remove an impurity. The aqueous solution was basified with 1 N aqueous NaOH and extracted with DCM (3 x 2 mL). The combined organic extracts were rinsed with brine, dried ($MgSO_4$), and concentrated *in vacuo* to provide 103 mg (71% yield) of diisopropyl (5-aminopyrazin-2-yl)methylphosphonate as a yellow, waxy solid. $[M + H]^+ = 274.3$. This material was used directly in the next step without further purification.

[00243] Example **1D** acid was converted to the corresponding acid chloride using oxalyl chloride (as described in Example 2 Part A). The acid chloride was transferred with two 0.3 mL portions of DCM into a 0°C mixture of the above amine (45 mg, 0.165 mmol) and pyridine (53.4 µL, 0.66 mmol) in DCM (0.7 mL) under Ar. The reaction was allowed to warm to RT overnight, then was extracted with DCM (5 mL). The organic extract was washed with 2 mL each of 0.1N aqueous HCl, water, and brine, was dried ($MgSO_4$), and concentrated *in vacuo* to afford 142 mg of crude product. The crude material was chromatographed (40 g SiO_2; continuous gradient from 10-100% EtOAc in DCM) to give the title compound (25.6 mg, 28% yield) as a colorless oil. $[M + H]^+ = 552.4$; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 9.40 (s, 1H), 8.24 (s, 2H), 7.93 (d, 2H), 7.61 (d, 2H), 4.68 (m, 2H), 3.74 (m, 1H), 3.34 (d, 2H), 3.05 (s, 3H), 2.22 (m, 1H), 1.95 (m, 1H), 1.10 – 2.83 (m, 9H), 1.25 – 1.29 (m, 12H).

EXAMPLE 26

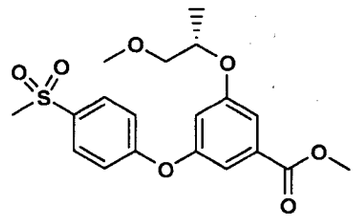


A.



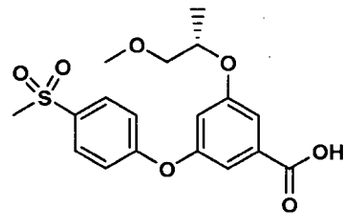
[00244] To a rapidly stirred mixture of methyl 3,5-dihydroxybenzoate (38 g, 0.226 mol) and K_2CO_3 (47.7 g, 0.345 mol) in DMF (150 mL) heated at 120°C under Ar was added a solution of 1-fluoro-4-(methylsulfonyl)benzene (20 g, 0.115 mol) in DMF (50 mL) over 3 h. After heating at 120°C overnight, the reaction mixture was cooled to RT, diluted with DMF (300 mL), and then treated with Celite® as a filter aid. The heterogeneous reaction mixture was filtered, and the filter cake was thoroughly rinsed with more DMF. The combined filtrates were concentrated *in vacuo*, and the residue was partitioned between 1N aqueous HCl (200 mL) and EtOAc (250 mL). A further 100 mL of water was added. The aqueous layer was extracted with EtOAc (200 mL), and the combined organic extracts were rinsed with water and brine (250 mL each), and dried ($MgSO_4$). Volatiles were removed *in vacuo*. The residue was chromatogaphed in 3 portions. Each portion was absorbed onto SiO_2 (~20 g) and chromatographed (330 g SiO_2; elution with a continuous gradient of 0-20% EtOAc in CH_2Cl_2 followed by isocratic 20% EtOAc: CH_2Cl_2) to give Part A compound (14.77 g; combined yield of 40%) as a white solid. $[M + H]^+ = 323.0$; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.89 (d, 2H), 7.33 (s, 1H), 7.22 (s, 1H), 7.11 (dd, 2H), 6.89 (d, 1H), 3.89 (s, 3H), 3.07 (s, 3H).

B.



[00245] To a 5°C mixture of Part A compound (5 g, 15.5 mmol), (R)-(-)-1-methoxy-2-propanol (2 mL, 20.4 mmol) and polymer-supported Ph_3P (13.4 g of 3 mmol/g, 40.2 mmol) in THF (175 mL) was added dropwise a solution of DIAD (4.5 mL, 23.2 mmol) in THF (25 mL) over 25 min under Ar (internal temperature maintained at ≤ 5°C). The reaction mixture was allowed to warm to RT overnight, and was then filtered. The solids were thoroughly washed with THF and CH_2Cl_2. The combined filtrates were concentrated *in vacuo*, re-dissolved in CH_2Cl_2 and divided in 2 equal portions. The first portion was chromatographed (330 g SiO_2; elution with a continuous gradient of 0-10% EtOAc in CH_2Cl_2 over 40 min) to give 2.53 g of pure Part B compound as a colorless oil. Impure product fractions from this column were combined with the rest of the crude product and this mixture was chromatographed as above on 330 g SiO2, but with a continuous gradient from 0-8% EtOAc in CH_2Cl_2 to give Part B compound (3.02 g) as a colorless oil. The combined yield of Part B compound was 5.55 g (90%). $[M+H]^+ = 395.0$; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.90 (d, 2H), 7.48 (s, 1H), 7.30 (s, 1H), 7.11 (dd, 2H), 6.86 (d, 1H), 4.61 (m, 1H), 3.90 (s, 3H), 3.49-3.62 (m, 2H), 3.40 (s, 3H), 3.07 (s, 3H), 1.32 (d, 3H).

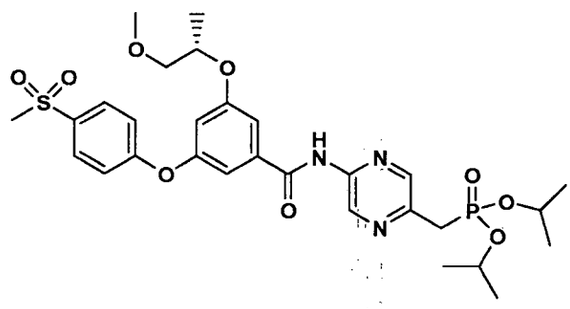
C.



[00246] To a 0°C solution of Part B compound (4.24 g, 10.75 mmol) in THF (50 mL) and water (15 mL) was added LiOH.H_2O (1.287 g, 53.7 mmol). The reaction mixture was allowed to warm to RT overnight (reaction complete by LC/MS). The reaction mixture was concentrated *in vacuo* and 50 mL of H_2O was added; the

solution was acidified with 5N aqueous HCl. The mixture was extracted with EtOAc (2 x 100 mL). The combined EtOAc extracts were washed with brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo* to provide Part C compound (3.95 g, 96.5% yield) as a colorless glass. $[M + H]^+ = 381.1$; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.91 (d, 2H), 7.52 (s, 1H), 7.35 (s, 1H), 7.13 (dd, 2H), 6.90 (s, 1H), 4.61 (m, 1H), 3.52-3.64 (m, 2H), 3.42 (s, 3H), 3.07 (s, 3H), 1.33 (d, 3H).

D.

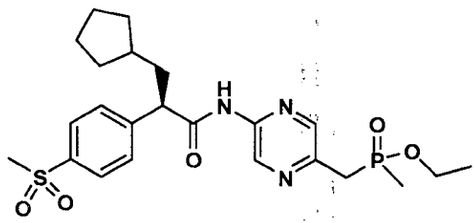


[00247] To a 0°C solution of Example **25A** compound (199 mg, 0.533 mmol) in DCM (1 mL) was added TFA (1 mL) under Ar. The reaction mixture was allowed to warm to RT. After 5.5 h, the reaction mixture was concentrated *in vacuo* and partitioned between 0.5N aqueous HCl and Et_2O (4 mL each). The aqueous layer was basified with solid K_2CO_3, then extracted with DCM (3x). The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo* to provide 108 mg (74%) of diisopropyl (5-aminopyrazin-2-yl)methylphosphonate isolated as a yellow solid. $[M + H]^+ = 274.3$.

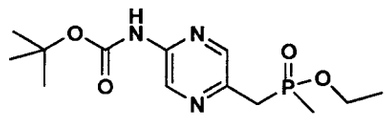
[00248] The Part C acid (32 mg, 0.0841 mmol) was converted to the corresponding acid chloride using oxalyl chloride (as described in Example 2 Part A). The crude acid chloride was transferred with two portions (0.2 mL each) of DCM to a mixture of diisopropyl (5-aminopyrazin-2-yl)methylphosphonate (25.3 mg, 0.0926 mmol) and pyridine (27.2 μL, 0.370 mmol) in DCM (0.4 mL) cooled to 0°C under Ar. The reaction was allowed to warm to RT overnight. The reaction mixture was then extracted with DCM (4 mL), washed with 2 mL each of 0.5N aqueous HCl, water, sat. aqueous $NaHCO_3$ and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The crude product (47 mg) was chromatographed (12 g SiO_2; elution with a continuous gradient from 15 to 100% EtOAc in DCM) to provide 17.6 mg (30%) of the title

compound as a colorless oil. $[M + H]^+ = 636.3$; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 9.57 (s, 1H), 8.46 (s, 1H), 8.34 (s, 1H), 7.93 (d, 2H), 7.36 (s, 1H), 7.18 (s,1H), 7.17 (d, 2H), 6.87 (s, 1H), 4.60 – 4.75 (m, 3H), 3.52 – 3.63 (m, 2H), 3.41 (s, 3H), 3.39 (d, 2H), 3.08 (s, 3H), 1.25 – 1.36 (m, 15H).

EXAMPLE 27 (Isomer A) and EXAMPLE 28 (Isomer B)

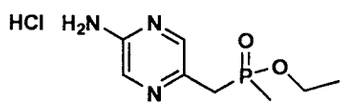


A.



[00249] A mixture of tert-butyl 5-(bromomethyl)pyrazin-2-ylcarbamate (300 mg, 1.04 mmol) and diethyl methylphosphonite (0.2 mL) in THF (0.2 mL) was heated overnight at 100°C , then cooled to RT and dissolved in EtOAc (15 mL). The solution was washed with water (3 x 5 mL) and brine (5 mL), was dried ($MgSO_4$), and concentrated *in vacuo*. The crude product (279 mg) was chromatographed (SiO_2; 80 g; elution with a continuous gradient from 0 – 100% EtOAc in DCM) to give Part A compound (114 mg) as a waxy white solid, which still contained some by-product from the diethyl methylphosphonite reagent. $[M + H]^+ = 316.3$.

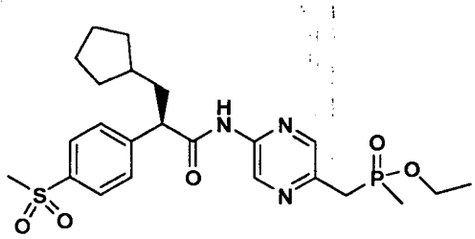
B.



[00250] A 0°C solution of Part A compound (114 mg, 0.361 mmol) in DCM (1 mL) was treated with 4N HCl in dioxane (1 mL). The reaction was allowed to warm to RT overnight, then was diluted with Et_2O to fully precipitate the desired product HCl salt and decanted. This process was repeated several times to yield Part B

compound (82 mg; 90%) as a white solid. LC/MS showed the correct $[M + H]^+$ = 216.3 for the free amine.

C.



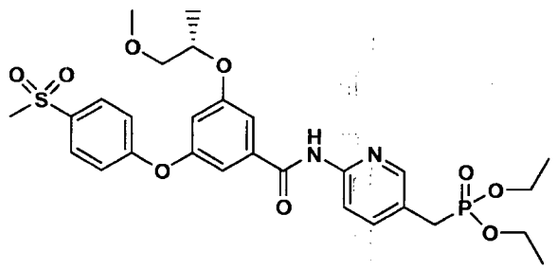
[00251] Example 1 Part D compound (91.9 mg, 0.310 mmol) was converted to the corresponding acid chloride using oxalyl chloride (as described in Example 2 Part A). The crude acid chloride was dissolved in a minimal volume of DCM and added to a 0°C mixture of Part B compound (52 mg, 0.242 mmol) and pyridine (78.2 µL, 0.968 mmol) in DCM (1 mL) under Ar. The reaction was allowed to warm to RT overnight, then was diluted with DCM (7 mL) and washed with two 2 mL portions of 0.5N aqueous HCl, water, sat. aqueous $NaHCO_3$ and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The crude material (150 mg) was chromatographed (40 g SiO_2; elution with a continuous gradient from 0 to 100% EtOAc in DCM, followed by a continuous gradient from 0-10% MeOH in DCM) to give the product diastereomers (43 mg) as a mixture. Preparative reverse phase HPLC on a YMC ODS-A 5µ 30x100 mm column (elution with a continuous 40-100% gradient from 90:10:0.1 to 10:90:0.1, water:MeOH:TFA) gave 17.9 mg of a faster-eluting isomer A and 18.3 mg of the slower-eluting isomer B. Each of the above samples was dissolved in 6 mL of DCM and rinsed with 2 mL of sat. aqueous $NaHCO_3$ to remove TFA. The DCM solutions were rinsed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to give the desired Isomers A and B.

[00252] Isomer A (Example 27) was obtained as 16.8 mg of a colorless glass. $[M + H]^+$ = 494.4; ^{1}H-NMR (400 MHz, CD_3OD): δ 9.31 (s, 1H), 8.31 (s, 1H), 7.92 (m, 2H), 7.72 (m, 2H), 3.96 – 4.12 (m, 3H), 3.44 (d, 2H), 3.30 (s, 3H), 2.18 – 2.26 (m, 1H), 1.13 – 1.89 (m, 9H), 1.56 (d, 3H), 1.27 (m, 3H).

[00253] Isomer B (Example 28) was obtained as 15.6 mg of a colorless glass: $[M + H]^+$ = 494.4; ^{1}H-NMR (400 MHz, CD_3OD): δ 9.31 (s, 1H), 8.31 (s, 1H), 7.91 (m,

2H), 7.70 (m, 2H), 3.97 – 4.12 (m, 3H), 3.44 (d, 2H), 3.30 (s, 3H), 2.16 – 2.26 (m, 1H), 1.13 – 1.88 (m, 9H), 1.54 (d, 3H), 1.28 (m, 3H).

EXAMPLE 29

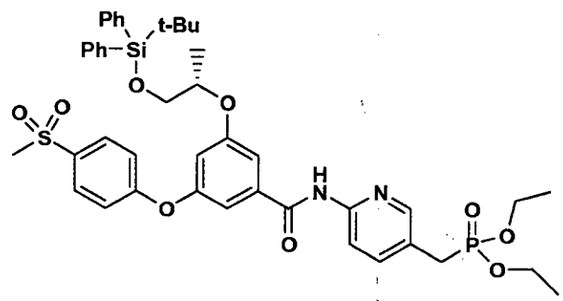


[00254] EDC (19.7 mg, 0.100 mmol) was added to a 0°C mixture of the Example **26C** acid (34.6 mg, 0.091 mmol), HOAT (14.8 mg, 0.109 mmol), diethyl (6-aminopyridin-3-yl)methylphosphonate (24.4 mg, 0.100 mmol) and Et_3N (12.6 μL, 0.091 mmol) in 0.7 mL of DCM under Ar. The reaction mixture was allowed to warm to RT overnight. An additional 12 mg of amine was added and stirring was continued for 4 days. The reaction was extracted with 3 mL of DCM and washed with 1 mL each of 0.5N aqueous HCl, water, sat. aqueous $NaHCO_3$ and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The crude product (34 mg) was purified by preparative reverse phase HPLC on a 30 x 100 mm Phenomenex Axia Luna 5μ C18 column (continuous gradient from 30-100% 90:10:0.1 to 10:90:0.1, water:CH_3CN: TFA) to provide 29 mg of desired product. This material was dissolved in 3 mL of DCM and washed with two 1 mL portions of sat. aqueous $NaHCO_3$, brine and dried ($MgSO_4$). Concentration *in vacuo* provided 20.8 mg (38% yield) of the title compound as a colorless oil. $[M + H]^+ = 607.3$; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.54 (s, 1H), 8.30 (d, 1H), 8.20 (s, 1H), 7.91 (d, 2H), 7.72 (d, 1H), 7.34 (s, 1H), 7.12 – 7.17 (m, 3H), 6.85 (s, 1H), 4.62 (m, 1H), 4.06 (m, 4H), 3.50 – 3.62 (m, 2H), 3.41 (s, 3H), 3.11 (d, 2H), 3.08 (s, 3H), 1.23 – 1.35 (m, 9H).

methyl 3-hydroxy-5-(4-(methylsulfonyl)phenoxy)benzoate (240 mg, 0.744 mmol) and polymer-supported Ph_3P (1.6 mmol/g load, 1.2 g, 1.92 mmol) in 10 mL of THF under Ar. The reaction was allowed to warm to RT. After 3 hours at RT, the reaction was filtered and the resin thoroughly rinsed with THF and DCM. The combined filtrates were concentrated *in vacuo*. The residue was chromatographed (SiO_2; 40 g; continuous gradient from 0-40% EtOAc in hexane) to give partially purified product (contained some reduced DIAD by ^{1}H-NMR) which was used in the next step without further purification.

[00257] $LiOH.H_2O$ (93 mg, 2.22 mmol) was added to a 0°C mixture of the methyl ester from above (nominally 0.744 mmol) in 4 mL of THF and 1 mL of water. The reaction was allowed to warm to RT overnight. Analytical HPLC indicated that ~16% of the starting material remained, so more $LiOH.H_2O$ (31 mg) was added. After an additional 4.5 h, the reaction mixture was concentrated *in vacuo*, then was partitioned between water and EtOAc (15 mL each). The aqueous layer was extracted with 15 mL of EtOAc. The combined organic extracts were washed with 10% aqueous $KHSO_4$ (10 mL), 10 mL each of water and brine, dried ($MgSO_4$) and concentrated *in vacuo* to give Part B compound (402 mg, 90% yield), which still contained some reduced DIAD. ^{1}H NMR (400 MHz, $CDCl_3$) partial assignments: δ 7.90 (d, 2H), 7.63 (d, 4H), 7.46 (s, 1H), 7.30 – 7.43 (m, 7H), 7.10 (d, 2H), 6.82 (s, 1H), 4.58 (m, 1H), 3.77 (dd, 2H), 3.06 (s, 3H), 1.01 (s, 9H).

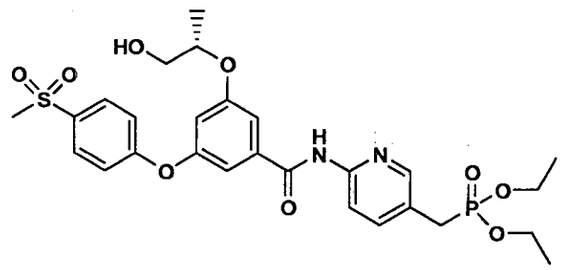
C.



[00258] EDC (26.1 mg, 0.136 mmol) was added to a 0°C mixture of Part B compound (75 mg, 0.124 mmol), HOAT (20.2 mg, 0.149 mmol), diethyl (6-aminopyridin-3-yl)methylphosphonate (39.3 mg, 0.161 mmol) and Et_3N (19 μL, 0.136 mmol) in 1.5 mL of DCM under Ar. After 5 days, LC/MS analysis showed a

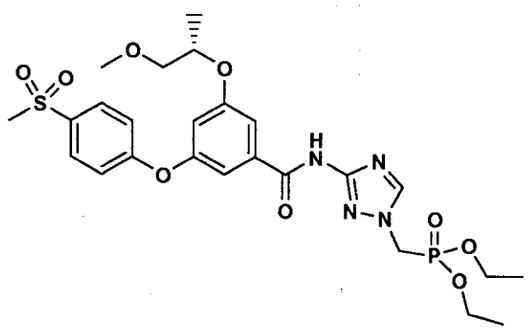
ca. 62:9 ratio of desired product to the HOAT ester of the Part B acid. After another 24 h, the reaction mixture was diluted with 7 mL of DCM and washed with 2 mL each of 0.5N aqueous HCl, water, sat. aqueous $NaHCO_3$ and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The crude product (85 mg) was chromatographed (12 g SiO_2; elution with a continuous gradient from 0-5% MeOH to DCM) to provide Part C compound (46 mg; 45%) as a colorless oil. $[M + H]^+ = 831.4$; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.57 (s,1H), 8.31 (d, 1H), 8.21 (s, 1H), 7.90 (d, 2H), 7.74 (d, 1H), 7.63 (m, 4H), 7.32 – 7.43 (m, 6H), 7.28 (s, 1H), 7.07 – 7.14 (m, 3H), 6.79 (s, 1H), 4.59 (m, 1H), 4.08 (m, 4H), 3.78 (dd, 2H), 3.12 (d, 2H), 3.07 (s, 3H), 1.33 (d, 3H), 1.25 – 1.30 (m, 6H), 1.02 (s, 9H).

D.

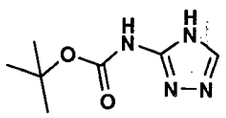


[00259] To a 0°C solution of Part C compound (46 mg, 0.0553 mmol) in 1.5 mL of THF under Ar was added Bu_4NF (0.11 mL of a 1M solution in THF, 0.11 mmol). The reaction was allowed to warm to RT. After 4 hr, the reaction mixture was concentrated *in vacuo* and partitioned between 6 mL of EtOAc and 2 mL of water. The organic extract was washed with 2 mL each of water and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue (44 mg) was purified by preparative reverse phase HPLC on a 30x100 mm Phenomenex Axia Luna 5μ C18 column (linear 20-100% gradient from 90:10:0.1 to 10:90:0.1, water:CH_3CN:TFA). The purified material was dissolved in DCM (6 mL) and washed with 2 mL each of sat. aqueous $NaHCO_3$ and brine, dried ($MgSO_4$) and concentrated *in vacuo* to yield the title compound (25 mg; 76%) as a colorless oil. $[M + H]^+ = 593.2$; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.85 (s,1H), 8.31 (d, 1H), 8.17 (s, 1H), 7.92 (d, 2H), 7.72 (d, 1H), 7.34 (s, 1H), 7.16 (s, 1H), 7.12 (d, 2H), 6.81 (s, 1H), 4.58 (m, 1H), 4.07 (m, 4H), 3.77 (m, 2H), 3.08 (s, 3H), 1.27 (m, 6H).

EXAMPLE 31

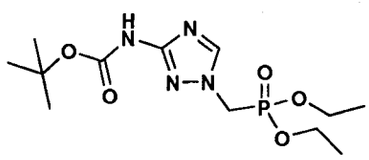


A.



[00260] To a RT slurry of 3-amino-1,2,4-triazole (1.0 g, 11.9 mmol)in hexanes (20 mL) was added TMEDA (0.07 g, 0.6 mmol) and di-*tert*-butyl dicarbonate (3.89 g, 17.8 mmol). The reaction mixture was stirred at RT for 24 h, poured into sat. aqueous $NaHCO_3$ (150 mL) and the product was extracted with EtOAc (2 x 25 mL). The organic extracts were combined, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed (SiO_2: continuous gradient from 0% EtOAc/Hexane to 100% EtOAc/Hex) to give the desired Part A compound (1.33 g, 61% yield) as a white solid. $[M + H]^+ = 185.0$; ^1H NMR (400 MHz, $CDCl_3$): δ 7.48 (s, 1H), 1.66 (s, 9H)

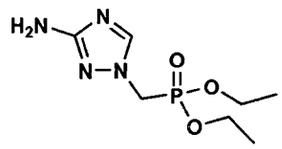
B.



[00261] To a 0°C solution of Part A compound (0.500g, 2.71 mmol) in DMF (5 mL) was added 60% NaH in oil (0.119 g, 2.99 mmol), in 1 portion, and the resultant slurry was stirred at 0°C for 1 h. $ICH_2PO_3Et_2$ (0.830 g, 2.99 mmol) was added, and

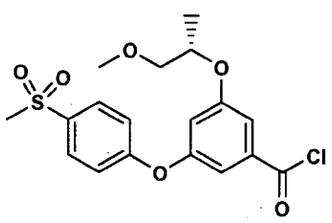
the reaction mixture was stirred overnight at RT. The reaction mixture was poured into brine (35 mL); and extracted with EtOAc (4 x 25 mL); the combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by preparative HPLC (Phenomenex Luna AXIA 30 x 100 mm column; detection at 220 nm; flow rate=40 mL/min.; continuous gradient from 100% A to 100% B over 15 min. + 2 min. hold at 100% B, where A=90:10 H_2O:MeOH and B=90:10 MeOH: H_2O) to provide the Part B compound (0.059 g, 6.5% yield) as a white solid. [M + H]=335.1; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.59 (s, 1H), 8.24 (d, *J*=1.76 Hz, 1H), 4.75 (d, *J*=11.87 Hz, 2H), 4.10-4.00 (m, 4H), 1.42 (s, 9H) 1.21 (t, *J*=7.03 Hz, 6H).

C.



[00262] To a RT solution of Part B compound (0.059 g, 0.177 mmol) in CH_2Cl_2 (1 mL) was added TFA (2.04 mL, 3.13 mmol). The reaction mixture was stirred at RT for 2 h, then was concentrated *in vacuo*. The residue was purified by preparative HPLC (Phenomenex Luna 21.2 x 100 mm column; detection at 220 nm; flow rate=20 mL/min.; continuous gradient from 100% A to 100% B over 15 min. + 2 min. hold at 100% B, where A=90:10:0.1 H_2O:MeOH:TFA and B=90:10:0.1 MeOH: H_2O:TFA) to provide Part C compound (0.050 g, 81% yield) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (s, 1H), 6.78 (s, 2H), 4.43 (d, *J*=13.62 Hz, 2H), 4.24-4.15 (m, 4H), 1.32-1.38 (m, 6H).

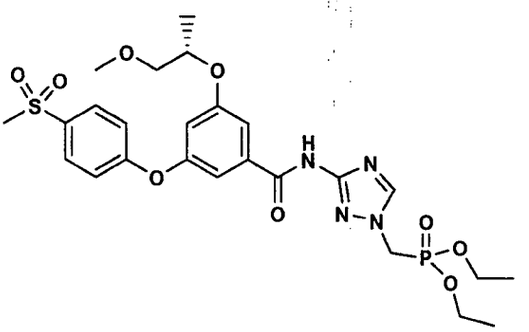
D.



[00263] To a RT solution of Example 26 Part C compound (0.023 g, 0.060 mmol) in CH_2Cl_2 (1 mL) were added oxalyl chloride (10.6 µL, 0.121 mmol) and DMF (0.9

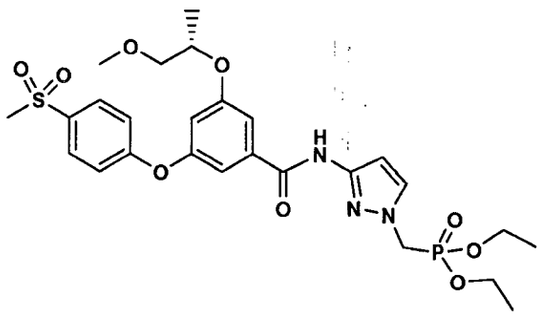
μL, 0.012 mmol) and the reaction mixture was stirred at RT for 1 h. Volatiles were removed *in vacuo* to provide crude Part D compound (0.060 g) as a yellow oil.

E.

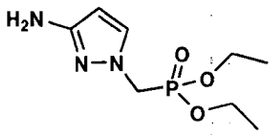


[00264] To a RT solution of crude Part D compound (0.060 g, 0.24 mmol) in CH_2Cl_2 (1 mL) were added a solution of Part C compound (0.031 g, 0.090 mmol) and pyridine (0.019 mL, 0.241 mmol) in CH_2Cl_2 (1 mL). The reaction mixture was stirred at RT overnight, then was partitioned between sat. aqueous $NaHCO_3$ (1 mL) and EtOAc (2 mL); the organic phase was washed with sat. aqueous $NaHCO_3$ (1 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by preparative HPLC (Phenomenex Luna AXIA 21.2 x 100 mm column; detection at 220 nm; flow rate=40 mL/min.; continuous gradient from 100% A to 100% B over 15 min. + 2 min. hold at 100% B, where A=90:10 H_2O:MeOH and B=90:10 MeOH: H_2O) to provide the title compound (0.007 g, 19.0% yield) as a white solid. $[M + H]^+ = 597.3$; ^1H NMR (400 MHz, $CDCl_3$): δ 9.65 (s, 1H), 8.42 (d, *J*=1.76 Hz 1H), 7.92 (t, *J*=1.76 Hz, 1H), 7.90 (t, *J*=1.76 Hz, 7.45 (t, J=1.75 Hz, 1H), 7.32 (t, *J*=1.76 Hz 1H), 7.15 (t, *J*=1.76 1H), 7.14 (t, *J*=1.76 Hz), 6.88 (t, *J*=2.19 Hz 1H), 4.80-4.75 (m, 1H), 4.70 (d, *J*=13.18 Hz, 2H), 4.29-4.19 (m, 4H), 3.64-3.54 (m, 2H), 3.42 (s, 3H), 3.07 (s, 3H), 1.35 (t, *J*=7.03, 9H).

EXAMPLE 32

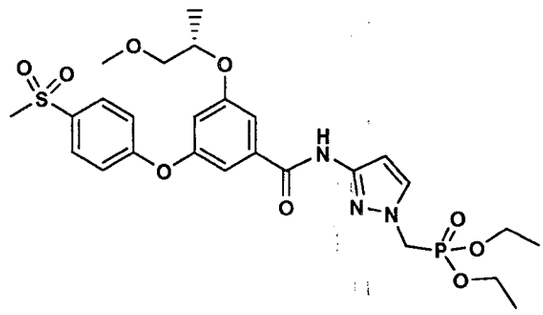


A.



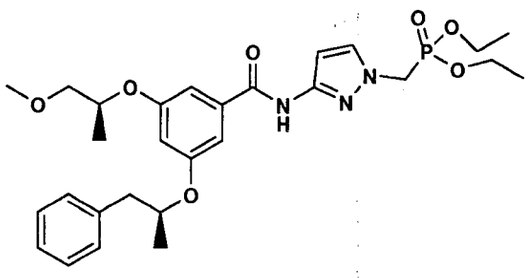
[00265] To a 0°C solution of 1H-pyrazol-3-amine (1.00g, 12.03 mmol) in DMF (25 mL) was added potassium *tert*-butoxide (2.70 g, 24.07 mmol) and the reaction mixture was stirred at 0°C for 1 h. $ICH_2PO_3Et_2$ (3.35 g, 12.03 mmol) was added, and the reaction mixture was stirred at 0°C for 1.5 h, then was allowed to warm to RT and stirred at RT overnight. Volatiles were removed *in vacuo*, and the residue was partitioned between brine (30 mL) and EtOAc (30 mL). The product was extracted with EtOAc (5 x 30 mL); the combined organic extracts were dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by preparative HPLC (Phenomenex Luna AXIA 5 µm C18 30 x 100 mm column; detection at 220 nm; flow rate=40 mL/min.; continuous gradient from 100% A to 20% B over 25 min. + 2 min. hold at 20% B, where A=90:10 H_2O:MeCN and B=90:10 MeCN: H_2O) to provide the Part A compound (0.470 g, 16.8% yield) as a pale yellow oil. $[M + H]^+ = 233.9$; ^1H NMR (400 MHz, $CDCl_3$): δ 7.29 (s, 1H), 5.66 (d, *J*=2.20 Hz, 1H), 4.36 (d, *J*=11.55 Hz, 2H), 4.10 (m, 4H), 3.76 (s, 2H) 1.29 (t, *J*=7.15 Hz, 6H).

B.

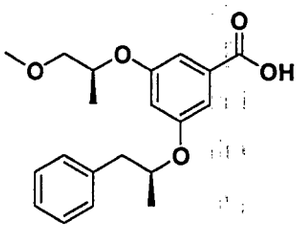


[00266] To a RT solution of Example 26 Part C compound (0.16 g, 0.421 mmol) in DMF (8 mL) were added EDAC (0.161 g, 0.841 mmol), HOAT (0.114 g, 0.841 mmol), and iPr_2NEt (0.185 mL, 1.05 mmol), and the reaction mixture was stirred at RT for 30 min. A solution of Part A compound (0.123 g, 0.526 mmol) in DMF (2 mL) was added and the reaction mixture was stirred at RT overnight, then poured into H_2O (40 mL). The mixture was extracted with EtOAc (2 x 15 mL); the combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by preparative HPLC (Phenomenex Luna 5 μ C18 30 x 100 mm column; detection at 220 nm; flow rate=40 mL/min.; continuous gradient from 100% A to 1000% B over 25 min. + 10 min. hold at 100% B, where A=90:10 H_2O:MeCN and B=90:10 MeCN: H_2O) to provide the title compound (0.149 g, 59.4% yield) as a white solid. $[M + H]^+ = 596.3$; ^1H NMR (400 MHz, $CDCl_3$): δ 8.98 (s, 1H), 7.92 (t, *J*=1.65 Hz, *J*=3.3 Hz 1H), 7.90 (t, *J*=2.70 Hz, *j*=2.2 Hz, 1H) 7.47 (d, *J*=2.2 Hz, 1H), 7.35 (t, *J*=1.65 Hz, 1H), 7.20 (t, J=2.2 Hz,1H), 7.14 (t, *J*=2.75 Hz, *J*=2.2 Hz, 1H),7.12 (t, *J*=2.75 Hz, *J*=2.20 Hz, 6.90 (d, *J*=2.20 Hz, 1H), 6.82 (t, *J*=2.20 Hz, 1H), 4.67-4.59 (m, 1H), 4.51 (d, *J*=12.09 Hz, 2H), 4.13-4.03 (m, 4H), 3.58 (dd, *J*= 10.44 Hz, *J*= 6.05 Hz, 1H), 3.51 (dd, *J*=10.44 Hz, *J*=3.85 Hz, 1H), 3.40 (s, 3H), 3.08 (s, 3H), 1.33 (d, J=6.05 Hz, 3H), 1.27 (t, *J*=7.14 Hz, 6H).

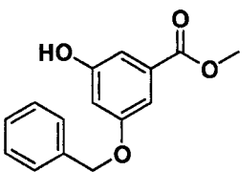
EXAMPLE 33



A.

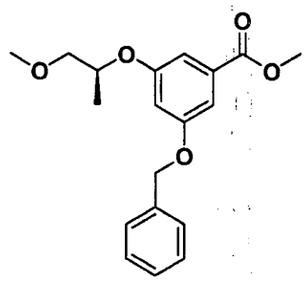


i.



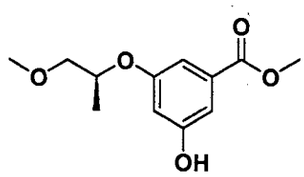
[00267] To a solution of methyl 3,5-dihydroxybenzoate (10.0 g, 59.5 mmol) in DMF (60.0 mL) under Ar was added K_2CO_3 (12.4 g, 89.7 mmol) at RT. Benzyl bromide (10.0 mL, 84.2 mmol; filtered through basic Al_2O_3 prior to use) was added slowly over 10 min. The reaction mixture was stirred for 12 h at RT and then carefully quenched with sat. aqueous NH_4Cl (50 mL), followed by H_2O (350 mL). The aqueous suspension was extracted with CH_2Cl_2 (1x30 mL, 2x50 mL). The combined organic extracts were washed with H_2O (100 mL) and brine, dried [$MgSO_4$] and concentrated *in vacuo* to give the crude product (27.0 g) as a golden-colored oil. The crude material was chromatographed (product eluted during the 30% EtOAc/hexane portion of a stepwise gradient (10-50% EtOAc/hexane) to yield Part A(i) compound (4.6 g, 30%) as a cream-colored powder.

ii.



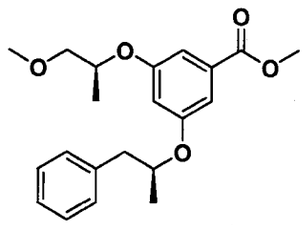
[00268] To a 0°C solution of Part A(i) compound (1.0 g, 3.9 mmol) in THF (16.8 mL) were successively added (R)-(-)-1-methoxy-2-propanol (0.5 g, 5.8 mmol) and Ph_3P (1.5 g, 5.8 mmol), followed by slow addition of DIAD (1.1 mL, 5.8 mmol). The reaction mixture was warmed to RT and stirred at RT for 2 days. The reaction mixture was diluted with H_2O and extracted with Et_2O. The organic layer was dried [$MgSO_4$] and concentrated *in vacuo* to give a thick, pale, yellow oil. This crude material was chromatographed (product eluted during the 10% EtOAc/hexane portion of a stepwise gradient of 10-30% EtOAc/hexane) to give Part A(ii) compound (1.1 g, 85% yield) as a colorless oil.

iii.



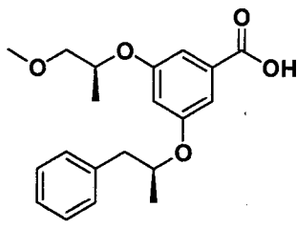
[00269] A flask containing Part A(ii) compound (1.2 g, 3.6 mmol) in MeOH (45.4 mL) was evacuated and flushed with Ar. In one portion, 10% Pd/C (0.38 g, 0.36 mmol) was added. The mixture was stirred under an atmosphere of H_2 for 12 h at RT, then was filtered through Celite®, which was washed with EtOAc. The combined filtrates were concentrated *in vacuo* to give Part A(iii) compound (0.81 g, 93% yield) as a yellow oil.

iv.



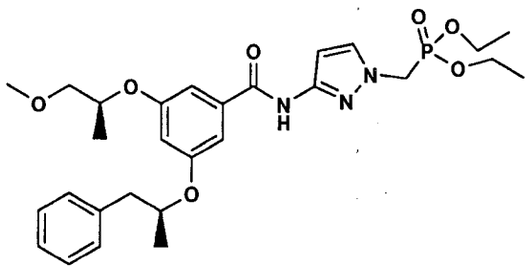
[00270] To a 0°C solution of Part A(iii) compound (0.14 g, 0.59 mmol) in THF (2.9 mL) were added Ph_3P (0.4 g, 1.3 mmol) and (R)-1-phenylpropan-2-ol (0.2 g, 1.3 mmol) under Ar. The reaction mixture was stirred for 5 min at 0°C, then DIAD (0.3 mL, 1.3 mmol) was added dropwise. The reaction mixture was stirred at RT for 12 h, then was diluted with H_2O and extracted with EtOAc (2x). The combined organic extracts were washed with 1N aqueous NaOH and brine, dried [$MgSO_4$] and concentrated *in vacuo* to give a pale yellow oil (1.0 g). This crude material was chromatographed (product eluted during the 10% EtOAc/hexane portion of a stepwise gradient from 5-20% EtOAc/hexane) to give Part A(iv) compound (0.17 g, 81% yield) as a near-colorless oil.

v.



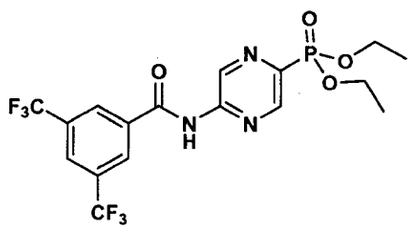
[00271] To a solution of Part A(iv) compound (0.17g, 0.5 mmol) in THF (1.8 mL) and H_2O (0.6 mL) was added $LiOH.H_2O$ (0.02 g, 0.52 mmol) at RT. The reaction mixture was stirred at 45°C for 1 h; an additional portion of $LiOH.H_2O$ was added, and stirring was continued at 45°C. The starting material was consumed after 6 h, and the reaction was cooled to RT. Volatiles were removed *in vacuo*, and the remaining aqueous layer was acidified to pH 2 with 0.5 N aqueous HCl, then was extracted with EtOAc (3x). The combined organic extracts were washed with brine, dried [$MgSO_4$] and concentrated *in vacuo* to give crude Part A(v) compound (0.16 g, 86%) as a pale-yellow oil.

B.

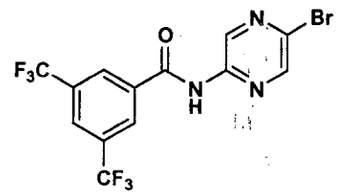


[00272] To a RT solution of Part A(v) compound (0.030 g, 0.087 mmol) in DMF (1.5 mL) was added EDAC (0.033 g, 0.174 mmol), HOAt (0.024 g, 0.174 mmol), and DIEA (0.038 mL, 0.218 mmol). The reaction mixture was stirred at RT for 30 min, after which a solution of Example 32 Part A compound (0.025 g, 0.109 mmol) in DMF (0.5 mL) was added. The reaction mixture was stirred at RT overnight, then was poured into water (7 mL); the mixture was extracted with EtOAC (2 x 10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by preparative HPLC (Phenomenex Luna AXIA 100A 5 μ C18 column; detection at 220 nm; flow rate=40 mL/min.; continuous gradient from 100% A to 100% B over 25 min. + 2 min. hold at 100% B, where A=90:10 H_2O:MeCN and B=90:10 MeCN: H_2O) to provide the title compound (0.027 g, 56.3% yield) as a clear oil. $[M + H]^+$ = 560.4; ^1H NMR (400 MHz, $CDCl_3$): δ 8.59 (s, 1H), 7.44-7.46 (m, 1H), 7.32-7.19 (m, 5H), 7.00 (t, *J*=1.65 Hz, 1H), 6.97 (t, *J*=2.2 Hz, 1H), 6.91 (d, *J*=2.2 Hz, 1H), 6.63 (t, *J*=2.2 Hz, 1H), 4.65-4.53 (m, 2H), 4.44 (d, *J*=11.54 Hz, 2H), 4.14-4.04 (m, 4H), 3.56 (dd, *J*=9.9 Hz, J=5.5 Hz,1H), 3.49 (dd,*J*=9.89 Hz, *J*=3.84 Hz, 1H), 3.41 (s, 3H), 3.06 (dd, *J*=13.74 Hz, *J*=6.04 Hz, 1H), 2.85 (dd, *J*=13.74 Hz, *J*=6.04 Hz, 1H), 1.26 (m, 12H).

EXAMPLE 34

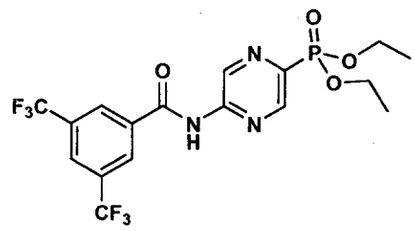


A.



[00273] To a 0°C solution of 3,5-bis(trifluoromethyl)benzoic acid (129 mg, 0.50 mmol) in CH_2Cl_2 (1 mL) was added oxalyl chloride (0.375 mL, 0.75 mmol, 2M in CH_2Cl_2) and DMF (1 drop). The reaction was stirred at 0°C for 30 min and was then warmed to RT and was stirred for 4 h. The mixture was concentrated *in vacuo*. To a solution of the acid chloride residue in CH_2Cl_2 (3 mL) was added 5-bromopyrazin-2-amine (130 mg, 0.75 mmol) and pyridine (0.061 mL, 0.75 mmol). The reaction was stirred at RT for 18 h and was diluted with CH_2Cl_2 (6 mL), and was washed with 0.5 N aqueous HCl (1 mL, 2x), water (1 mL), sat. aqueous $NaHCO_3$ (1 mL), and Brine. The organic layer was dried (MgSO4), filtered, and concentrated in vacuo. The residue was chromatographed (SiO_2) to provide the Part A compound (40 mg, 19% yield) as a white solid.

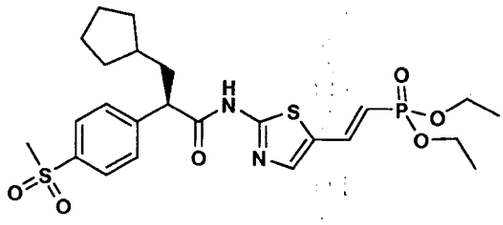
B.



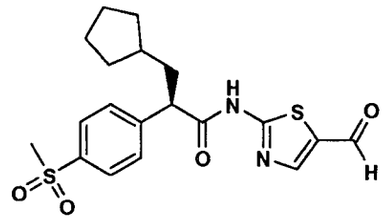
[00274] THF (degassed)(0.40 mL) was added to Part A compound (25.0 mg; 0.060 mmol) and $(Ph_3P)_4Pd^o$ (13.9 mg; 0.012 mmol). $H(O)P(OEt)_2$ (9.33 µL; 0.072 mmol) was added followed by TEA (11.7 µL; 0.084 mmol). The reaction mixture was heated at 85°C for 5 h, then was cooled to RT and partitioned between EtOAc (3 mL) and brine (3 mL). The organic phase was dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by preparative HPLC (YMC reverse phase ODS-A-5µm 30 x 100 mm column; flow rate = 40 mL/min, 45 to 100% solvent B over 12 min,

hold to 15 min, where solvent A = 90:10:0.1 H_2O:MeOH:TFA and solvent B = 90:10:0.1 MeOH:H_2O:TFA) to give the title compound (11.6 mg; 41%) as a light yellow solid. $[M + H]^+ = 472.2$; ^1H NMR (400 MHz, $CDCl_3$): δ 1.37 (t, 6H), 4.27 (m, 4H), 8.12 (s, 1H), 8.53 (s, 2H), 8.82 (s, 1H), 9.53 (s, 1H), 9.80 (s, 1H).

EXAMPLE 35

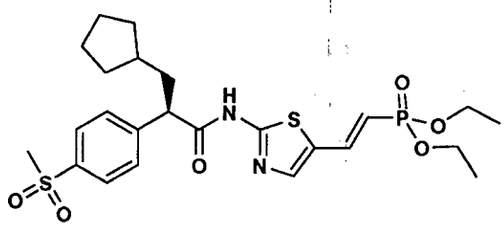


A.



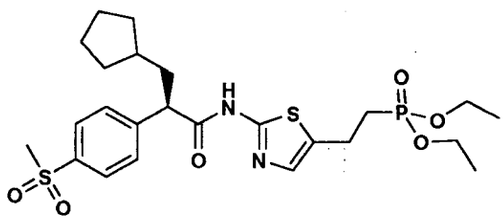
[00275] DIPEA (66 μL; 0.378 mmol) was added to a stirred solution of Example 1 Part D compound (80 mg; 0.270 mmol), 2-amino-5-formylthiazole (43.3 mg; 0.338 mmol) and HOAt (44.0 mg; 0.324 mmol) in DMF (1.0 mL). EDAC (62.0 mg; 0.324 mmol) was added. After 3 h at RT, the reaction mixture was partitioned between EtOAc (8 mL) and H_2O (8 mL). The organic phase was washed with 1N aqueous HCl (5 mL), sat. aqueous $NaHCO_3$ (5 mL) and brine (5 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was chromatographed (SiO_2; continuous gradient from 0 to 100% EtOAc in hexanes over 11 min, hold at 100% EtOAc for 4 min) to give Part A compound (81 mg; 74%) as a foam.

B.



[00276] $CH_2(PO_3Et)_2$ (59.4 μL; 0.239 mmol) was added to a mixture of powdered LiCl (10.13 mg; 0.239 mmol) in CH_3CN (1.0 mL). DBU (35.7 μL; 0.239 mmol) was added followed by a solution of Part A compound (81.0 mg; 0.199 mmol) in CH_3CN (1.0 mL). After 24 h at RT more $CH_2(PO_3Et)_2$ (9.92 μL; 0.040 mmol), DBU (5.96 μL; 0.040 mmol) and LiCl (1.7 mg; 0.040 mmol) were added. After 72 h the reaction mixture was concentrated *in vacuo*. The residue was partitioned between EtOAc (8 mL) and 0.2 N aqueous HCl (8 mL). The organic phase was washed with brine (6 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was chromatographed (SiO_2; continuous gradient from 0% to 100% EtOAc in hexanes over 6 min, switched to 2% MeOH in EtOAC and held for 8 min) to give the title compound (67 mg; 62%) as a colorless solid. $[M + H]^+ = 541.1$; ^1H NMR (400 MHz, $CDCl_3$)(19:1, E/Z): δ 1.15 (m, 2H), 1.37 (m, 6H), 1.48 (m, 2H), 1.66 (m, 3H), 1.78 (m, 2H), 1.92 (m, 1H), 2.27 (m, 1H), 3.03 (s, 3H), 4.12 (m, 5H), 5.88 (dd, J = 17.3 Hz, 1H), 7.58 (s, 1H), 7.66 (d, 2H), 7.89 (d, 2H), 8.14 (dd, J = 17.1 Hz, 1H).

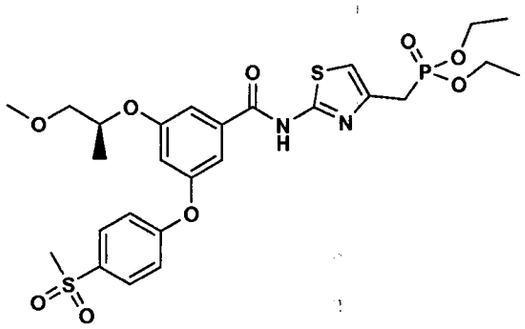
EXAMPLE 36



[00277] 20% $Pd(OH)_2$ (16 mg) was added to a solution of Example 35 compound (35 mg; 0.065 mmol) in MeOH (0.40 mL). A H_2 (g) atmosphere was introduced via balloon. After 48 h of stirring, the reaction mixture was filtered. The catalyst was rinsed with MeOH (1.5 mL), EtOAc (1.5 mL) and $CHCl_3$ (1.5 mL) and the combined filtrates were concentrated *in vacuo*. The crude product was purified by preparative

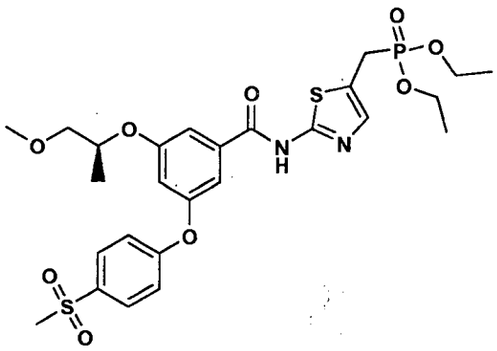
HPLC (YMC reverse phase ODS-A-5u 20 x 100 mm column; flow rate = 20 mL/min, 15 to 100% solvent B over 10 min, hold to 12 min, where solvent A = 90:10:0.1 H_2O:MeOH:TFA and solvent B = 90:10:0.1 MeOH:H_2O:TFA) to provide the title compound (18 mg; 51%). $[M + H]^+ = 543.2$; ^1H NMR (400 MHz, CD_3OD): δ1.19 (m, 2H), 1.29 (t, 6H), 1.51 (m, 2H), 1.64 (m, 3H), 1.80 (m, 3H), 2.17 (m, 3H), 3.05 (m, 2H), 3.09 (s, 3H), 3.96 (t, 1H), 4.07 (m, 4H), 7.20 (s, 1H), 7.67 (d, 2H), 7.92 (d, 2H).

EXAMPLE 37



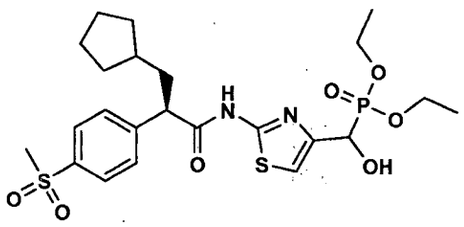
[00278] DIPEA (387 μL; 2.22 mmol) was added to a cold (0°C) solution of Example 26 Part C compound (704 mg; 1.85 mmol), Example 13 Part E compound (556 mg; 2.22 mmol) and HOAt (302 mg; 2.22 mmol)in DMF (7.4 mL). EDAC (426 mg; 2.22 mmol) was added. After 24 h at RT, the reaction mixture was partitioned between EtOAc (100 mL) and H_2O (75 mL). The organic phase was washed with 0.5 N aqueous HCl (50 mL), sat. aqueous $NaHCO_3$ (50 mL) and brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by preparative HPLC (YMC reverse phase ODS-A-5u 30 x 250 mm column; flow rate = 30 mL/min, 15 to 100% solvent B over 25 min, hold to 30 min, where solvent A = 90:10:0.1 H_2O:CH_3CN:TFA and solvent B = 90:10:0.1 CH_3CN:H_2O:TFA). The product was purified by preparative HPLC a second time using the same conditions but using MeOH instead of CH_3CN to give the title compound (778 mg; 69%) as a white foam. $[M + H]^+ = 613.2$; ^1H NMR (400 MHz, $CDCl_3$): δ 1.26 (t, 6H), 1.35 (d, 3H), 3.08 (s, 3H), 3.34 (d, 2H), 3.41 (s, 3H), 3.55 (m, 2H), 4.08 (m, 4H), 4.69 (m, 1H), 6.88 (s, 2H), 7.14 (d, 2H), 7.30 (s, 1H), 7.48 (s, 1H), 7.92 (d, 2H).

EXAMPLE 38

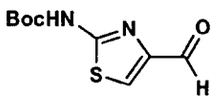


[00279] The title compound (39 mg; 78%; yellow solid) was synthesized from Example 15 Part D compound employing the procedure described for Example 37. $[M + H]^+ = 613.3$; ^1H NMR (400 MHz, $CDCl_3$): δ 1.34 (m, 9H), 3.08 (s, 3H), 3.28 (d, 2H), 3.41 (s, 3H), 3.59 (m, 2H), 4.15 (m, 4H), 4.84 (m, 1H), 6.93 (s, 1H), 7.15 (d, 2H), 7.34 (d, 1H), 7.40 (s, 1H), 7.63 (s, 1H), 7.92 (d, 2H).

EXAMPLE 39



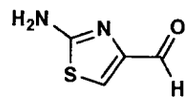
A.



[00280] A solution of Example 13 Part B compound (0.94 g; 4.08 mmol) in DCM (8 mL) was added dropwise to a 0°C solution of Dess-Martin periodinane (1.82 g; 4.28 mmol) in DCM (8 mL). After 20 h at RT, the reaction was diluted with DCM (4 mL) and 1.0 N aqueous NaOH (6 mL). After stirring for 10 min, the mixture was filtered through Celite®. The organic phase was washed with brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed (SiO_2;

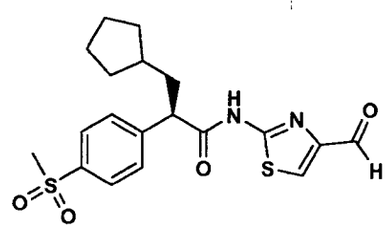
continuous gradient from 0 to 50% EtOAc in hexanes over 12 min, hold at 50% EtOAc in hexanes for 8 min) to give Part A compound (0.65 g; 70%) as a white solid.

B.



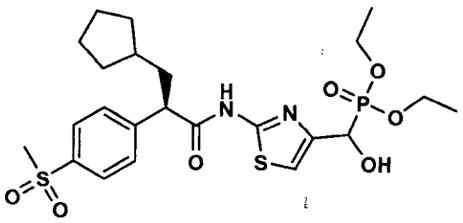
[00281] TFA (2.0 mL) was added to a 0°C solution of Part A compound (0.64 g; 2.80 mmol) in DCM (4.0 mL). After 20 h at RT the reaction mixture was concentrated *in vacuo*. The residue was partitioned between EtOAc (10 mL) and sat. aqueous $NaHCO_3$ (8 mL). The aqueous phase was isolated and extracted with EtOAc (5 x 8 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to give Part B compound (0.30 g; 83%) as a yellow solid.

C.



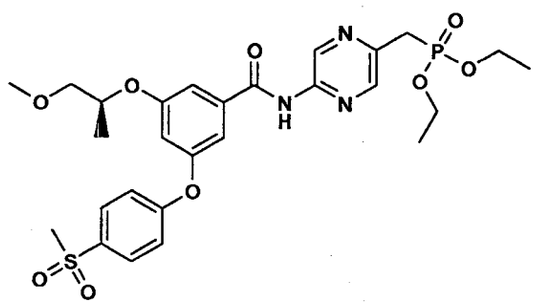
[00282] DIPEA (88.7 µL; 0.509 mmol) was added to a stirred solution of Example 1 Part D compound (130 mg; 0.439 mmol), Part B compound (67.4 mg; 0.526 mmol) and HOAt (69.3 mg; 0.509 mmol) in DMF (1.5 mL). EDAC (97.6 mg; 0.509 mmol) was added. After 20 h stirring at RT the reaction mixture was partitioned between EtOAc (12 mL) and H_2O (12 mL). The organic phase was washed with 0.5 N aqueous HCl (8 mL), sat. aqueous $NaHCO_3$ (8 mL) and brine (8 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was chromatographed (SiO_2; continuous gradient from 0 to 80% EtOAc in hexanes over 13 min, hold at 80% EtOAC in hexanes for 3 min) to give Part C compound (100 mg; 56%) as a yellow foam.

D.



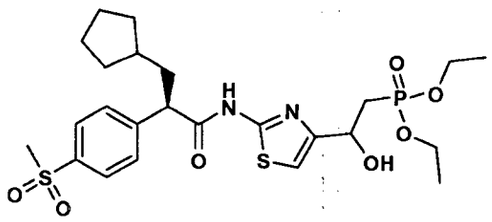
[00283] $H(O)P(OEt)_2$ (10.0 μL; 0.078 mmol)was added to Part C compound (30.0 mg; 0.074 mmol) followed by pyridine (6.6 μL; 0.081 mmol). The reaction mixture was heated at 70°C for 5 h, then cooled to RT. After 48 h more $H(O)P(OEt)_2$ (10.0 μL; 0.078 mmol) and pyridine (10.0 μμL; 0.123 mmol) were added and heating at 70°C was continued. After 7 h the reaction was cooled to RT and diluted with EtOAc (3 mL), washed with 1.0 N aqueous HCl (1.5 mL) and brine (1.5 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was chromatographed (SiO_2; continuous gradient from 0 to 100% EtOAc in hexanes over 3 min, switch to 3% MeOH in EtOAc and hold for 8 min). The product was then purified by preparative HPLC (YMC reverse phase ODS-A-5u 20 x 100 mm column; flow rate = 20 mL/min, 10 to 100% solvent B over 10 min, hold to 12 min, where solvent A = 90:10:0.1 H_2O:MeOH:TFA and solvent B = 90:10:0.1 MeOH:H_2O:TFA) to give the title compound (14 mg; 35%) as a light yellow solid (diastereomeric mixture). $[M + H]^+$ = 545.2; ^1H NMR (400 MHz, $CDCl_3$): δ1.13 (m, 2H), 1.28 (m, 6H), 1.49 (m, 2H), 1.60 (m, 3H), 1.76 (m, 2H), 1.96 (m, 1H), 2.23 (m, 1H), 3.04 (s, 3H), 4.01 (t, 1H), 4.16 (m, 4H), 5.18 (dd, 1H), 7.03 (d, 1H), 7.65 (d, 2H), 7.90 (d, 2H).

EXAMPLE 40

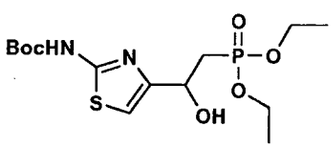


[00284] Oxalyl chloride (2.0 M in DCM) (45.0 µL; 0.091 mmol) was added to a solution of Oxalyl chloride (2.0 M in DCM) (45.0 µL; 0.091 mmol) was added to a solution of Example 26 Part C compound (23.0 mg; 0.060 mmol) in DCM (0.20 mL). DMF (5 µL) was added. Gas evolution occurred. The reaction mixture was stirred at RT for 1 h, then was concentrated *in vacuo*. The residue was stripped from DCM (2 X 1 mL). The crude acid chloride was dissolved in DCM (0.25 mL). Example 7 Part B compound (16.2 mg; 0.066 mmol) was added followed by pyridine (14.6 µL; 0.180 mmol). After 20 h at RT the reaction was concentrated *in vacuo*. The residue was partitioned between EtOAc (4 mL) and 0.5 N aqueous HCl (3 mL). The organic phase was washed with sat. aqueous $NaHCO_3$ (3 mL) and brine (3 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by preparative HPLC (YMC reverse phase ODS-A-5u 30 x 100 mm column; flow rate = 40 mL/min, 15 to 100% solvent B over 12 min, hold to 14 min, where solvent A = 90:10:0.1 H_2O:MeOH:TFA and solvent B = 90:10:0.1 MeOH:H_2O:TFA) to give the title compound (13 mg; 36%) as a white solid. $[M + H]^+ = 608.2$; ^1H NMR (400 MHz, $CDCl_3$): δ 1.32 (m, 9H), 3.07 (s, 3H), 3.40 (s, 3H), 3.44 (d, 2H), 3.57 (q, 2H), 4.13 (m, 4H), 4.63 (m, 1H), 6.88 (s, 1H), 7.16 (d, 2H), 7.19 (s, 1H), 7.35 (s, 1H), 7.93 (d, 2H), 8.32 (s, 1H), 8.53 (s, 1H), 9.59 (s, 1H).

EXAMPLE 41



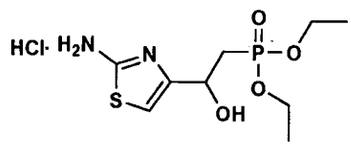
A.



[00285] nBuLi (575 µL of a 1.6 M solution in hexanes; 0.920 mmol) was added dropwise to a cold (-78°C) solution of $Me(O)P(OEt)_2$ (134 µL; 0.920 mmol) in THF

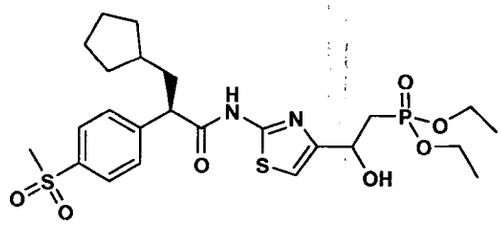
(0.30 mL). After 20 min a solution of Example 39 Part A compound (100 mg; 0.438 mmol) in THF (0.70 mL) was added dropwise. After 1 h at -78°C, the reaction was quenched by addition of AcOH (63 µL; 1.10 mmol). The reaction was warmed to RT and concentrated using a stream of Ar. The residue was partitioned between EtOAc (5 mL) and brine (4 mL). The organic phase was dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was chromatographed (SiO_2; continuous gradient from 0 to 100% EtOAc in hexanes over 8 min, switch to 4% MeOH in EtOAc and hold for 6 min) to give Part A compound (104 mg; 62%) as a syrup.

B.



[00286] HCl (100 µL of a 4.0 N solution in 1,4 dioxane) was added to Part A compound (104 mg; 0.273 mmol). After 20 h, the reaction mixture was concentrated *in vacuo* to give Part B compound (64 mg; 75%) as an oil, which was used in the next step without further purification.

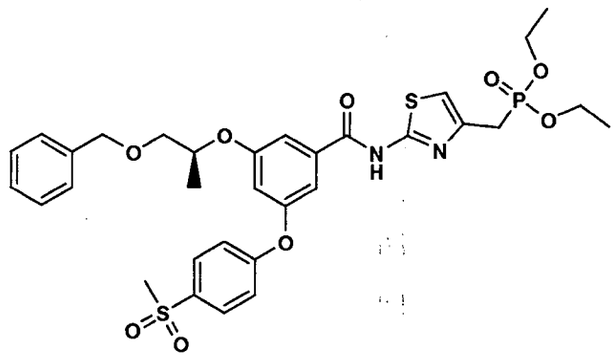
C.



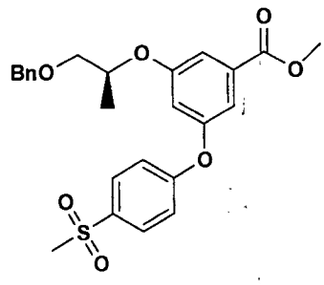
[00287] DIPEA (56.0 µL; 0.324 mmol) was added to a stirred solution of Example 1 Part D compound (32.0 mg; 0.108 mmol), Part B compound (48.0 mg; 0.151 mmol) and HOAt (16.9 mg; 0.124 mmol) in DMF (0.42 mL). EDAC (23.8 mg; 0.124 mmol) was added. After 2 h at RT the reaction mixture was partitioned between EtOAc (4 mL) and 0.5 N aqueous HCl (3 mL). The organic phase was washed with sat. aqueous $NaHCO_3$ (3 mL) and brine (3 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by preparative HPLC (YMC reverse phase ODS-A-5u 20 x 100 mm column; flow rate = 20 mL/min, 15 to 100% solvent B over 12 min, hold to

14 min, where solvent A = 90:10:0.1 H_2O:MeOH:TFA and solvent B = 90:10:0.1 MeOH:H_2O:TFA) to give the title compound (27 mg; 45%) as a white solid. [M + H]$^+$ = 559.3; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.15 (m, 2H), 1.27 (m, 3H), 1.35 (t, 3H), 1.49 (m, 2H), 1.62 (m, 3H), 1.78 (m, 2H), 1.95 (m, 1H), 2.25 (m, 1H), 2.41 (m, 2H), 3.04 (s, 3H), 4.03 (t, 1H), 4.16 (m, 4H), 5.19 (t, 1H), 6.93 (s, 1H), 7.65 (d, 2H), 7.90 (d, 2H).

EXAMPLE 42



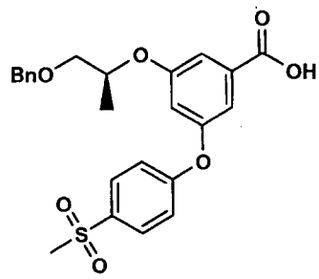
A.



[00288] To a cold (internal temperature maintained at ≤ 5°C) solution of Example 26A (3.7 g, 11.5 mmol), (R)-(-)-1-benzyloxy-2-propanol (2.5 g, 15 mmol), and polymer-supported Ph_3P (30 g of 1 mmol/g, 30 mmol) in THF (150 mL) under N_2 (g) was added dropwise over 15 min a solution of DIAD (3.4 mL, 17.3 mmol). The reaction mixture was warmed to RT and was stirred for 18 h, then filtered. The solids were thoroughly washed with THF and CH_2Cl_2. The combined filtrates were concentrated *in vacuo*. The mixture was chromatographed (SiO_2; EtOAc/Hexane 1:1) to give Part A compound (6.0 g, 110%) as a colorless oil. [M + H]=471.2; ^{1}H NMR

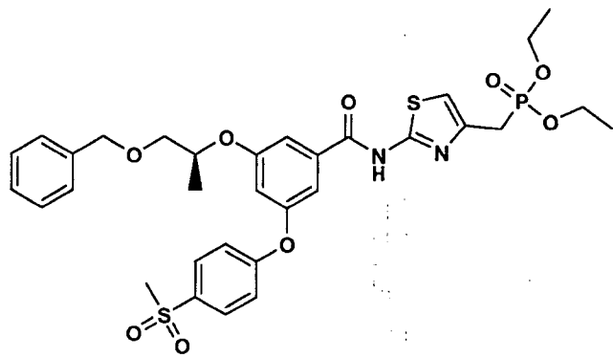
(400 MHz, $CDCl_3$) δ 7.90 (2 H, d, J=8.79 Hz), 7.48 (1 H, s), 7.27 - 7.37 (6 H, m), 7.09 (2 H, d, J=8.79 Hz), 6.83 - 6.89 (1 H, m), 4.60 - 4.69 (1 H, m), 4.58 (2 H, s), 3.90 (3 H, s), 3.54 - 3.70 (2 H, m), 3.06 (3 H, s), 1.34 (3 H, d, J=6.15 Hz).

B.



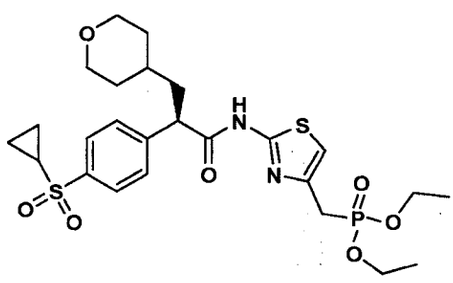
[00289] A solution of Part A (6 g, 13 mmol), LiOH (1.6 g, 39 mmol), and H_2O (50 mL) in THF (20 mL) was stirred at RT for 3 h, then was concentrated *in vacuo*. The aqueous solution was washed with Et_2O (15 mL x 4), acidified to pH 4 with concentrated HCl, and was extracted with EtOAc (50 mL). The organic layer was washed with H_2O, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give Part B compound (5 g, 95%) as a white solid. [M + H]=457.2; ^1H NMR (400 MHz, $CDCl_3$) δ 7.91 (2 H, d, J=8.79 Hz), 7.52 (1 H, s), 7.27 - 7.38 (6 H, m), 7.11 (2 H, d, J=8.79 Hz), 6.90 (1 H, t, J=2.20 Hz), 4.61 - 4.70 (1 H, m), 4.59 (2 H, s), 3.56 - 3.70 (2 H, m), 3.07 (3 H, s), 1.35 (3 H, d, J=6.59 Hz).

C.

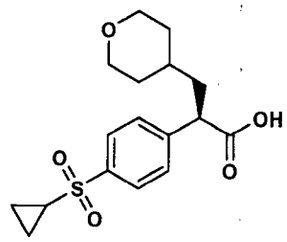


[00290] DIPEA (22.0 μL; 0.127 mmol) was added to a 0°C solution of Part C compound (50 mg; 0.110 mmol), Example 13 Part E compound (33.0 mg; 0.131 mmol) and HOAt (17.0 mg; 0.127 mmol) in DMF (0.44 mL), followed by EDAC (24.0 mg; 0.127 mmol). After 24 h at RT the reaction mixture was partitioned between EtOAc (7 mL) and 0.5 N aqueous HCl (5 mL). The organic phase was washed with sat. aqueous $NaHCO_3$ (5 mL) and brine (5 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was chromatographed (SiO_2; continuous gradient from 0 to 100% EtOAc in hexanes over 12 min, hold at 100% EtOAc for 4 min). The product was further purified by dissolving in MeOH (1 mL) and loading onto a 0.5g SAX (strong anion exchange) column. The column was eluted with MeOH (4 mL). The filtrate was concentrated to give the title compound (50 mg; 67%) as a light yellow residue. $[M + H]^+ = 689.3$; ^1H NMR (400 MHz, $CDCl_3$): δ 1.26 (t, 6H), 1.34 (m, 3H), 3.08 (s, 3H), 3.34 (d, 2H), 3.62 (m, 2H), 4.06 (m, 4H), 4.58 (s, 2H), 4.68 (m, 1H), 6.85 (s, 1H), 6.88 (s, 1H), 7.14 (d, 2H), 7.20 (s, 1H), 7.27 (m, 5H), 7.39 (s, 1H), 7.92 (d, 2H).

EXAMPLE 43

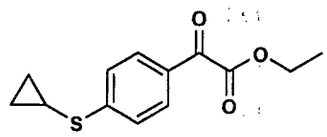


A.



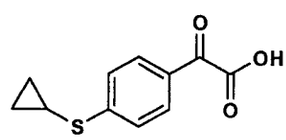
[00291] Note: The following procedure was adapted from WO 2006/016178 and WO 2006/016174.

i.



[00292] To a 0°C suspension of NH_4Cl (8.44 g, 63.3 mmol) in DCM (40 mL) was added ethyl 2-chloro-2-oxoacetate (5.53 mL, 49.7 mmol) over 10 min. The reaction was stirred at 0°C for 30 min. Cyclopropyl phenyl sulfide (6.5 mL, 45.2 mmol) was then added over a period of 45 min, keeping the temperature at 0°C. [Note: when sulfide was added, reaction immediately turned deep purple/red in color]. The reaction was allowed to warm to RT and was stirred at RT for 18 h. Ice water (100 mL) was slowly added to the mixture at 0°C. The organic phase was washed with H_2O (2x), sat. aqueous $NaHCO_3$ (2x), and again with H_2O. The organic layer was dried [$MgSO_4$] and concentrated *in vacuo* to give crude Part A(i) compound (6.1 g, 54%) as a yellow oil.

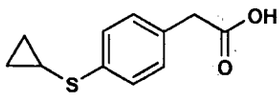
ii.



[00293] A solution of Part A(i) compound(6.1 g, 24.37 mmol) in toluene (50 mL) was heated to 50°C with stirring. 3N aqueous NaOH (9.75 mL, 29.2 mmol) was

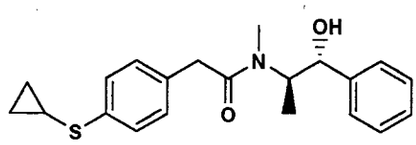
added dropwise while keeping the temperature at ≤60°C. After the addition was complete, the reaction was stirred at 50°C for 4 h, then was cooled to RT and neutralized by cautious addition of conc HCl (0.821 mL, 26.8 mmol). The reaction was stirred at RT for 18 h. The organic phase was concentrated *in vacuo* to give crude Part A(ii) compound (6.0g, 111%) as a yellow solid.

iii.



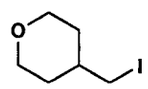
[00294] To $NH_2NH_2.H_2O$ (5.89 mL, 121 mmol) at -78°C was added Part A(ii) compound (5.4 g, 24.30 mmol) in one portion, and the reaction was heated to 80°C with stirring, then was cooled to RT. KOH (0.818 g, 14.58 mmol) was added; the reaction was stirred at RT for several minutes, and then a second portion of KOH (0.818 g, 14.58 mmol) was added. The reaction was stirred at RT for several minutes, and then a third portion of KOH (0.818 g, 14.58 mmol) was added. The reaction again was stirred at RT for several minutes, and a fourth portion of KOH (0.818 g, 14.58 mmol) was added. The reaction was then heated at 100°C with stirring for 18 h. The reaction was cooled to RT and diluted with H_2O. The reaction mixture was partitioned between Et_2O and H_2O. The layers were separated, and the aqueous layer was transferred to a round bottom flask. The organic layer was washed with H_2O, and the combined aqueous layers were treated with heptane (~50 mL), and the mixture was stirred vigorously. The stirred solution was treated dropwise with concentrated HCl (11.66 mL, 384 mmol) over 30 min at 0°C. The suspension was warmed to RT and was stirred at RT for several hours. A yellow precipitate formed and was filtered off; this material was washed with 1N aqueous HCl and heptane, then was dried *in vacuo* for 48 h. Part A(iii) compound (3.7g, 73% yield) was thus isolated as a pale yellow solid.

iv.

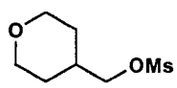


[00295] Part A(iii) compound was stripped from toluene (2x). To a -10°C mixture of Part A(iii) compound (3.7 g, 17.76 mmol) and K_2CO_3 (7.37 g, 53.3 mmol) in anhydrous acetone (50 mL) was added dropwise trimethylacetyl chloride (2.297 mL, 18.65 mmol) while maintaining the temperature at ≤-10°C. The reaction was stirred at -10°C for 30 min, then warmed to 0°C for 1 h and finally warmed to RT for 30 min. The mixture was recooled to -10°C and was treated with (1R, 2R)-(-)-pseudoephedrine (4.40 g, 26.6 mmol). The reaction was stirred at -10°C for 1h, then was warmed to 25°C and stirred for 18 h at 25°C. The reaction was quenched with H_2O (25 mL) and extracted with EtOAc. The organic phase was washed with 1N aqueous HCl, dried ($MgSO_4$) and concentrated *in vacuo* to give crude Part D compound. Crude Part D compound was dissolved in CH_2Cl_2 and chromatographed (SiO_2; 120g; gradient from 30% EtOAc/Hexane to 100% EtOAc). The combined fractions were concentrated *in vacuo* to give Part A(iv) compound (1.16g, 18.4% yield) as a white solid.

v.



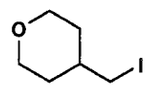
a.



[00296] To a solution of tetrahydropyran-4-MeOH (5.0 g, 43 mmol) in CH_2Cl_2 (30 mL) was added Et_3N (7.2 mL, 51.6 mmol). The mixture was cooled to 0°C, and methanesulfonyl chloride (4.0 mL, 51.6 mmol) was added. The mixture was stirred at 0°C for several hours, then was slowly warmed to RT. The reaction was stirred at RT for 18 h, then was concentrated *in vacuo*. The residue was taken up in EtOAc and

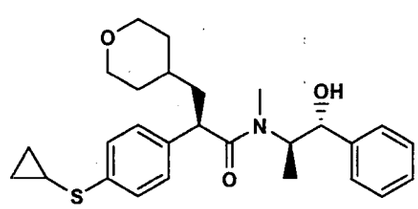
was washed with sat. $NaHCO_3$. The organic layer was dried [$MgSO_4$] and concentrated *in vacuo* to give the mesylate Part A(v)(a) compound (8.3 g, quantitative yield) as a white, needle-like solid.

b.



[00297] A mixture of the mesylate Part A(v)(a) compound (8.3 g, 43.0 mmol) and NaI (12.8 g, 85.5 mmol) was refluxed at 65°C in acetone (100 mL) for 18 h, then was cooled to RT and filtered. The filter cake was washed with acetone. The combined filtrates were concentrated *in vacuo*, and the residue was partitioned between Et_2O and water. The aqueous layer was extracted with Et_2O (3x). The combined organic extracts were washed with 10% aqueous $Na_2S_2O_3$ and water, dried [$MgSO_4$] and concentrated *in vacuo* to give Part A(v)(b) compound (7.1 g, 74% yield) as a yellow oil.

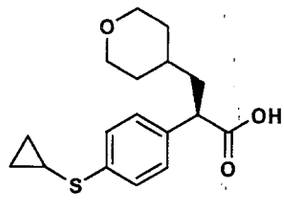
vi.



[00298] All starting materials were evaporated with toluene several times and all glassware was dried in an oven overnight. To a -78°C solution of LiHMDS (5.91 mL, 5.91 mmol) in THF (15 mL) was added dropwise a solution of Part A(iv) compound(1.0 g, 2.81 mmol) in THF (15 mL) over 15 min. The reaction was stirred at -78°C for 15 min, then was warmed to 0°C for 45 min and recooled to -78°C. Distilled DMPU (0.714 mL, 5.91 mmol) was added and the reaction was stirred at -78°C for ~15 min, after which Part A(v) iodide (0.954 g, 4.22 mmol) was added. The reaction was stirred at -78°C for 1h, then was slowly warmed to RT and stirred for 18 h. The reaction was quenched with sat. aqueous NH_4Cl (~10 mL) and diluted with EtOAc. The mixture was washed with H_2O. The aqueous layer was extracted

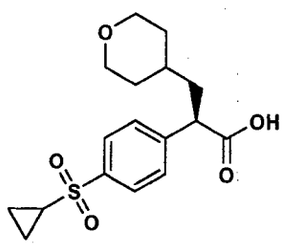
with EtOAc, and the combined organic extracts were washed with brine, dried [$MgSO_4$] and concentrated *in vacuo* to give Part A(vi) compound (1.3 g, 100%) as a yellow oil.

vii.



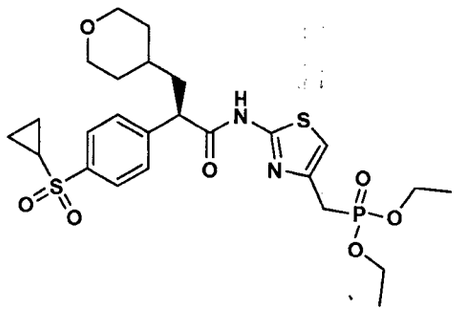
[00299] A solution of Part A(vi) compound (1.3 g, 2.87 mmol) and 9N concentrated H_2SO_4 (10.4 mL, 94 mmol) in dioxane (20 mL) was refluxed at 110°C for 18 h, then was cooled to RT. The solution was diluted with EtOAc (50 mL) and washed with H_2O (40 mL x 2) and brine (20 mL). The organic layer was dried [$MgSO_4$] and concentrated *in vacuo* to give Part A(vii) compound (1.17 g, 133% yield) as a yellow, sticky oil.

viii.



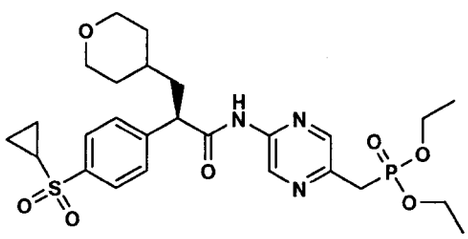
[00300] To a solution of Part A(vii) compound (0.9 g, 2.94 mmol) in isopropanol (20 mL) and water (10 mL) was added oxone (4.15 g, 6.76 mmol). The reaction was stirred at RT for 18 h, then was filtered, and the filtrate was concentrated *in vacuo*. The residue was taken up in EtOAc and was washed with H_2O and brine. The organic layer was dried [$MgSO_4$] and concentrated *in vacuo* to give Part A(viii) compound (0.9 g, 91% yield) as a pale yellow foam.

B.



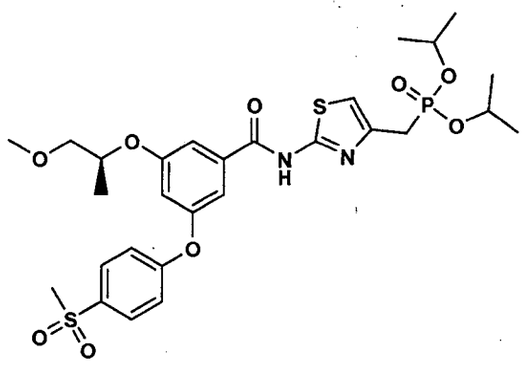
[00301] Oxalyl chloride (58.0 μL of a 2.0 M solution in DCM; 0.116 mmol) was added to a solution of Part A compound (26.0 mg; 0.077 mmol) in DCM (0.25 mL). DMF (5 μL) was added. Gas evolution occurred. The reaction mixture was stirred at RT for 1 h, then was concentrated *in vacuo*. The residue was stripped from DCM (2 X 1 mL). The crude acid chloride was dissolved in DCM (0.32 mL). Example 13 Part E compound (23.0 mg; 0.092 mmol) was added followed by pyridine (18.7 μL; 0.231 mmol). After 20 h at RT the reaction was concentrated *in vacuo*. The residue was partitioned between EtOAc (4 mL) and 0.5 N aqueous HCl (3 mL). The organic phase was washed with sat. aqueous $NaHCO_3$ (3 mL) and brine (3 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by preparative HPLC (YMC reverse phase ODS-A-5μm 30 x 100 mm column; flow rate = 40 mL/min, 15 to 100% solvent B over 16 min, hold to 20 min, where solvent A = 90:10:0.1 H_2O:MeOH:TFA and solvent B = 90:10:0.1 MeOH:H_2O:TFA) to give the title compound (17 mg; 39%) as a light yellow solid. $[M + H]^+ = 571.4$; ^1H NMR (400 MHz, $CDCl_3$): δ 1.04 (m, 2H), 1.33 (m, 11H), 1.63 (m, 2H), 1.87 (m, 1H), 2.21 (m, 1H), 2.46 (m, 1H), 3.28 (m, 4H), 3.92 (m, 2H), 4.02 (t, 1H), 4.11 (m, 4H), 6.88 (d, 1H), 7.61 (d, 2H), 7.88 (d, 2H).

EXAMPLE 44

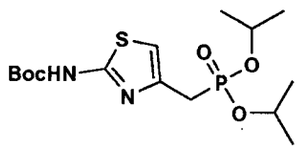


[00302] The title compound (22 mg; 51%; light yellow solid) was synthesized from Example 7 Part B compound and Example 43 Part A(viii) compound employing the procedure for the synthesis of Example 43 compound. $[M + H]^+ = 566.4$; ^1H NMR (400 MHz, $CDCl_3$): δ 1.05 (m, 2H), 1.34 (m, 10H), 1.48 (m, 1H), 1.67 (m, 2H), 1.79 (m, 1H), 2.22 (m, 1H), 2.46 (m, 1H), 3.35 (m, 4H), 3.92 (d, 2H), 4.04 (t, 1H), 4.14 (m, 4H), 7.62 (d, 2H), 7.85 (d, 2H), 8.20 (s, 1H), 9.34 (s, 1H), 9.36 (s, 1H).

EXAMPLE 45

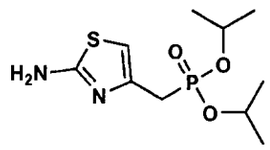


A.



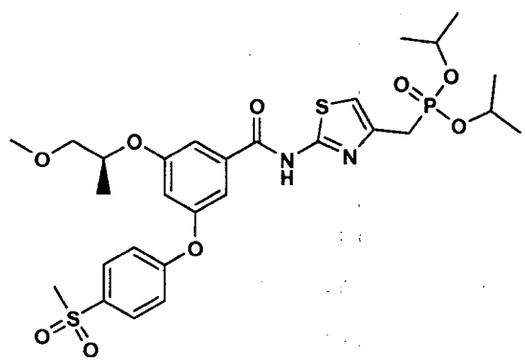
[00303] $(iPrO)_3P$ (2.02 mL; 8.20 mmol) was added to a vessel containing Example 13 Part C compound (600 mg; 2.05 mmol). The reaction vessel was capped and the mixture was heated at 85°C for 16 h, then cooled to RT. The solution was directly chromatographed (SiO_2; continuous gradient from 0 to 100% EtOAc in hexanes over 7 min, switched to 4% MeOH in EtOAc and held for 12 min) to give Part A compound (607 mg; 78%) as a viscous solid.

B.



[00304] TFA (2.0 mL) was added to a 0°C solution of Part A compound (559 mg; 1.48 mmol) in DCM (4 mL). The reaction mixture was allowed to warm to RT and stirred at RT for 2 h, then was concentrated *in vacuo*. The residue was partitioned between EtOAc (15 mL) and sat. aqueous $NaHCO_3$ (10 mL). The aqueous phase was extracted with EtOAc (10 mL). The combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give Part B compound (0.41 g; 100%) as a yellow solid.

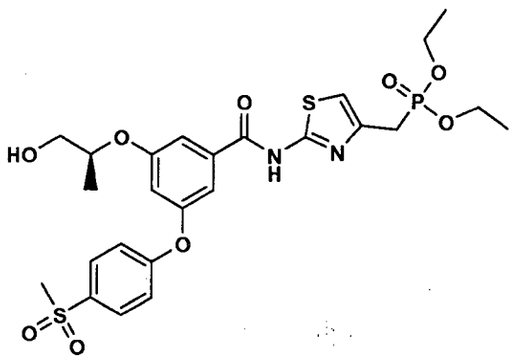
C.



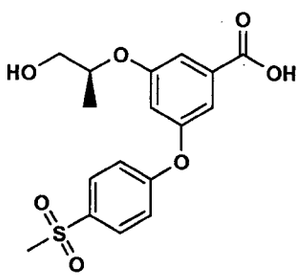
[00305] DIPEA (81.3 μL; 0.467 mmol) was added to a solution of Part B compound (135.6 mg; 0.487 mmol), Example 26 Part C compound (154.5 mg; 0.406 mmol) and HOAt (63.6 mg; 0.467 mmol)in DMF (1.5 mL). EDAC (89.5 mg; 0.467 mmol) was added. After 48 h at RT the reaction mixture was partitioned between EtOAc (15 mL) and H_2O (12 mL). The organic phase was washed with 0.5 N aqueous HCl (10 mL), sat. aqueous $NaHCO_3$ (10 mL) and brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by preparative HPLC (YMC reverse phase ODS-A-5u 30 x 250 mm column; flow rate = 30 mL/min, 20 to 100% solvent B over 18 min, held to 25 min, where solvent A = 90:10:0.1 H_2O:MeOH:TFA and solvent B = 90:10:0.1 MeOH:H_2O:TFA) to give the title compound (0.24 g; 92%) as a light yellow solid. $[M + H]^+ = 641.3$; ^1H NMR (400 MHz, $CDCl_3$): δ1.25 (m,

6H), 1.31 (m, 9H), 3.08 (s, 3H), 3.27 (d, 2H), 3.41 (s, 3H), 3.58 (m, 2H), 4.71 (m, 2H), 4.80 (m, 1H), 6.92 (s, 1H), 6.99 (s, 1H), 7.15 (d, 2H), 7.37 (s, 1H), 7.58 (s, 1H), 7.92 (d, 2H).

EXAMPLE 46

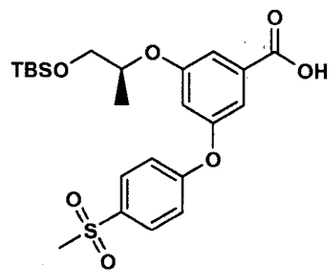


A.



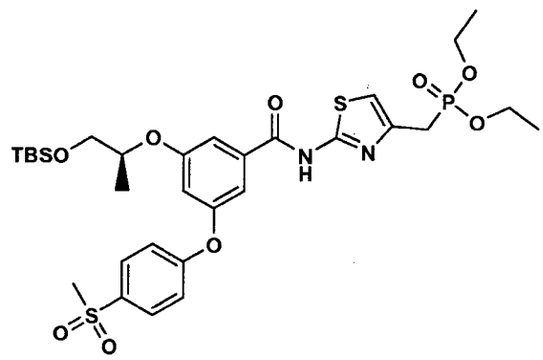
[00306] A mixture of 10% Pd/C (100 mg) and Example 42 Part B compound (1.03 g; 2.26 mmol) in EtOAc (6 mL) was stirred under an H_2 atmosphere for 8 h, after which the reaction mixture was filtered. The catalyst was rinsed with MeOH (10 mL) and the combined filtrates were concentrated *in vacuo* to give Part A compound (0.82 g; 99%).

B.



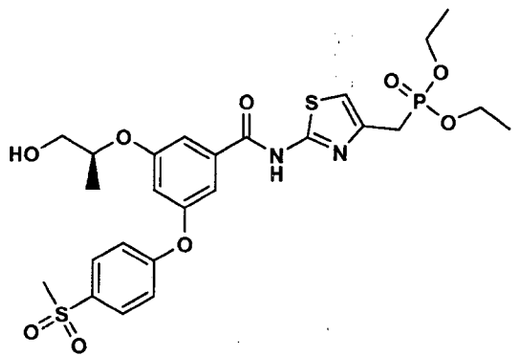
[00307] A solution of TBSCl (1.01 g; 6.71 mmol) in DMF (6 mL) was added to Part A compound (0.82 g; 2.24 mmol), followed by imidazole (0.91 g; 13.43 mmol). After 20 h the reaction mixture was partitioned between EtOAc (50 mL) and sat. aqueous NH_4Cl (50 mL). The organic phase was washed with sat. aqueous NH_4Cl (25 mL) and brine (25 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was chromatographed (SiO_2; continuous gradient from 0 to 100% EtOAc in hexanes over 14 min, hold at 100% EtOAc for 4 min) to give Part B compound (725 mg; 68%) as a white foam.

C.



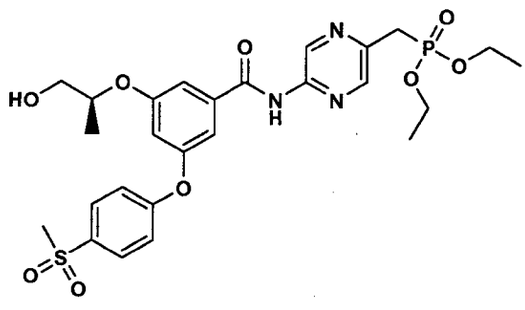
[00308] DIPEA (14.5 μL; 0.083 mmol) was added to a RT solution of Part B compound (30.8 mg; 0.064 mmol), Example 13 Part E compound (21.6 mg; 0.086 mmol) and HOAt (10.9 mg; 0.080 mmol) in DMF (0.33 mL). EDAC (15.3 mg; 0.080 mmol) was then added. After 48 h at RT the reaction mixture was partitioned between EtOAc (3 mL) and H_2O (3 mL). The organic phase was washed with brine (30 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give Part C compound (53 mg; 100%) as a syrup. The crude product was used in the next step without further purification.

D.

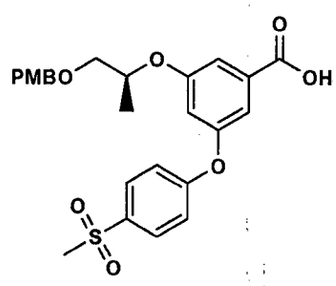


[00309] TBAF (1.0 M in THF) (152 μL; 0.152 mmol) was added to a 0°C solution of Part C compound (54 mg; 0.76 mmol) in THF (0.22 mL). The reaction was allowed to warm to RT and stirred for 2 h at RT, then was concentrated *in vacuo*. The residue was partitioned between EtOAc (2.5 mL) and brine (2.5 mL). The organic phase was dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by preparative HPLC (YMC reverse phase ODS-A-5u 30 x 100 mm column; flow rate = 40 mL/min, 10 to 100% solvent B over 10 min, hold to 13 min, where solvent A = 90:10:0.1 H_2O:MeOH:TFA and solvent B = 90:10:0.1 MeOH:H_2O:TFA) to give the title compound (23 mg; 51%) as a colorless syrup. $[M + H]^+ = 599.3$; ^1H NMR (400 MHz, $CDCl_3$): δ 1.33 (m, 9H), 3.07 (s, 3H), 3.33 (d, 2H),3.79 (q, 2H), 4.15 (m, 4H), 4.82 (m, 1H), 6.93 (s, 1H), 7.05 (d, 1H), 7.15 (d, 2H), 7.44 (s, 1H), 7.70 (s, 1H), 7.92 (d, 1H).

EXAMPLE 47

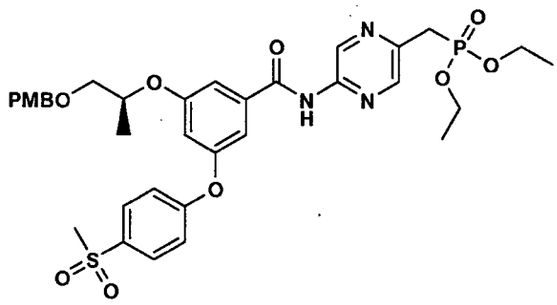


A.



[00310] Powdered KOH (141 mg; 2.51 mmol) was added to a solution of Example 46 Part B compound (0.41 g; 1.12 mmol) in DMSO-D6 (2.5 mL). A solution of 4-methoxybenzyl bromide (0.47 g; 2.35 mmol) in DMSO-D6 (1 mL) was added. After 2 h H_2O (0.5 mL) was added. After 30 min the solution was partitioned between EtOAc (20 mL) and H_2O (20 mL). The organic phase was dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was chromatographed (SiO_2; continuous gradient from 0 to 70% EtOAc in hexanes over 13 min, held at 70% EtOAc for 4 min) to give Part A compound (195 mg; 33%).

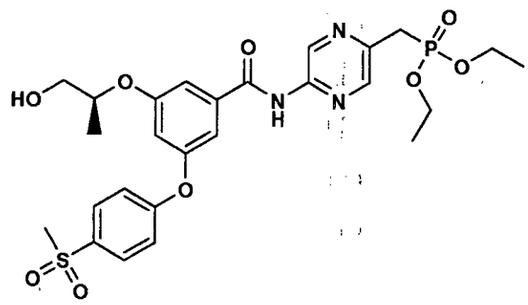
B.



[00311] Oxalyl chloride (2.0 M in DCM) (72 μL; 0.144 mmol) was added to a 0°C solution of Part A compound (43.9 mg; 0.096 mmol) in DCM (0.33 mL). DMF (5 μL) was added. Gas evolution occurred. After stirring for 1.5 h at RT the solution was concentrated *in vacuo*. The residue was stripped from $CHCl_3$ (2 mL). The crude acid chloride was dissolved in DCM (0.40 mL). Example 7 Part B compound (29.4 mg; 0.120 mmol) was added followed by pyridine (23.3 uL; 0.288 mmol). After 14 h at RT the reaction was concentrated *in vacuo*. The residue was partitioned between EtOAc (3 mL) and 0.5 N aqueous HCl (2 mL). The organic phase was washed with sat. aqueous $NaHCO_3$ (2 mL) and brine (2 mL), dried ($MgSO_4$) and concentrated *in*

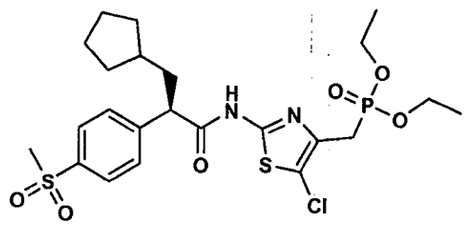
vacuo. The crude product was chromatographed (SiO_2; continuous gradient from 0 to 100% EtOAc in hexanes over 13 min, switched to 3% MeOH in EtOAc and held for 7 min) to give Part B compound (28 mg; 40%).

C.



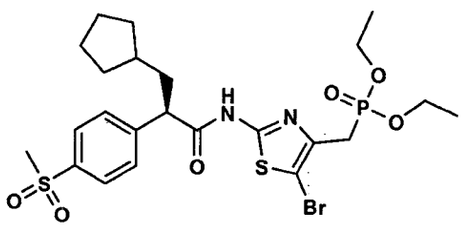
[00312] DDQ (9.4 mg; 0.041 mmol) was added to a solution of Part B compound (28 mg; 0.039 mmol) in DCM (400 µL) and H_2O (25 µL). After stirring for 1 h at RT the mixture was concentrated *in vacuo*. The residue was partitioned between EtOAc (3 mL) and sat. aqueous $NaHCO_3$ (2 mL). The organic phase was washed with sat. aqueous $NaHCO_3$ (2 mL) and brine (2 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by preparative HPLC (YMC reverse phase ODS-A-5u 30 x 100 mm column; flow rate = 40 mL/min, 10 to 100% solvent B over 10 min, hold to 14 min, where solvent A = 90:10:0.1 H_2O:ACN:TFA and solvent B = 90:10:0.1 ACN:H_2O:TFA) to give 20 mg of a syrup. The material was further chromatographed to remove aldehyde contaminant (SiO_2; elute with 100% EtOAc to remove aldehyde, then switch to 5% MeOH in EtOAc to elute product) to give the title compound (12 mg; 52%) as a colorless syrup. $[M + H]^+ = 594.3$; ^1H NMR (400 MHz, $CDCl_3$): δ1.29 (m, 9H), 2.29 (s, 1H), 3.08 (s, 3H), 3.42 (d, 2H), 3.77 (m, 2H), 4.11 (m, 4H), 4.59 (m, 1H), 6.86 (s, 1H), 7.14 (d, 2H), 7.19 (s, 1H), 7.37 (s, 1H), 7.93 (d, 2H), 8.30 (s, 1H), 8.68 (s, 1H), 9.57 (s, 1H).

EXAMPLE 48



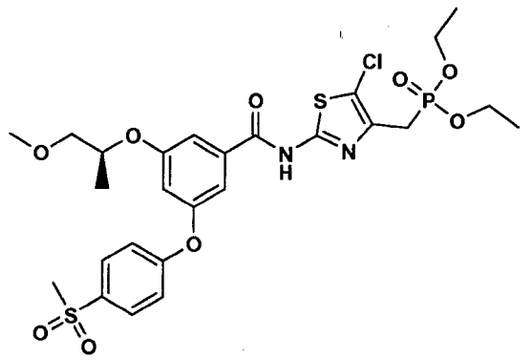
[00313] NCS (13.1 mg; 0.098 mmol) was added to a solution of Example 13 compound (52.0 mg; 0.098 mmol) in MeOH (0.5 mL) at RT and stirred at RT for 48 h. Volatiles were removed *in vacuo*. The residue was purified by preparative HPLC (YMC reverse phase ODS-A-5u 30 x 100 mm column; flow rate = 40 mL/min, 20 to 100% solvent B over 12 min, hold to 18 min, where solvent A = 90:10:0.1 H_2O:MeOH:TFA and solvent B = 90:10:0.1 MeOH:H_2O:TFA) to give the title compound (42 mg; 76%) as a white solid. $[M + H]^+ = 563.3$; ^1H NMR (400 MHz, $CDCl_3$): δ1.13 (m, 2H), 1.29 (m, 6H), 1.48 (m, 2H), 1.60 (m, 3H), 1.74 (m, 2H), 1.92 (m, 1H), 2.20 (m, 1H), 3.06 (s, 3H), 3.33 (d, 2H), 3.84 (t, 1H), 4.11 (m, 4H), 7.59 (d, 2H), 7.89 (d, 2H).

EXAMPLE 49



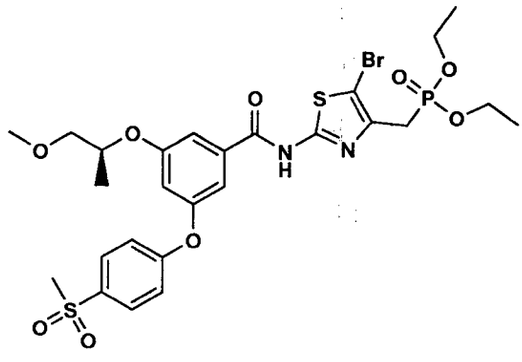
[00314] The title compound (23 mg; 69%; white solid) was synthesized employing the same procedure as for the synthesis of Example 48, except that NBS was used instead of NCS. The bromination reaction was complete within 1 h. $[M + H]^+ = 607.3$; ^1H NMR (400 MHz, $CDCl_3$): δ1.13 (m, 2H), 1.28 (m, 6H), 1.48 (m, 2H), 1.59 (m, 3H), 1.76 (m, 2H), 1.92 (m, 1H), 2.20 (m, 1H), 3.06 (s, 3H), 3.31 (d, 2H), 3.83 (t, 1H), 4.09 (m, 4H), 7.59 (d, 2H), 7.89 (d, 2H).

EXAMPLE 50



[00315] NCS (8.55 mg; 0.064 mmol) was added to a solution of Example 37 compound (39.0 mg; 0.064 mmol) in MeOH (0.4 mL). After 48 h at RT the reaction mixture was concentrated *in vacuo*. The crude product was purified by preparative HPLC (YMC reverse phase ODS-A-5u 30 x 100 mm column; flow rate = 40 mL/min, 25 to 100% solvent B over 10 min, hold to 13 min, where solvent A = 90:10:0.1 H_2O:MeOH:TFA and solvent B = 90:10:0.1 MeOH:H_2O:TFA) to give the title compound (27 mg; 66%) as a white solid. $[M + H]^+ = 647.2$; ^1H NMR (400 MHz, $CDCl_3$): δ 1.29 (t, 6H), 1.35 (d, 3H), 3.09 (s, 3H), 3.29 (d, 2H), 3.41 (s, 3H), 3.56 (q, 2H), 4.10 (m, 4H), 4.65 (m, 1H), 6.89 (s, 1H), 7.15 (d, 2H), 7.19 (s, 1H), 7.36 (s, 1H), 7.94 (d, 2H).

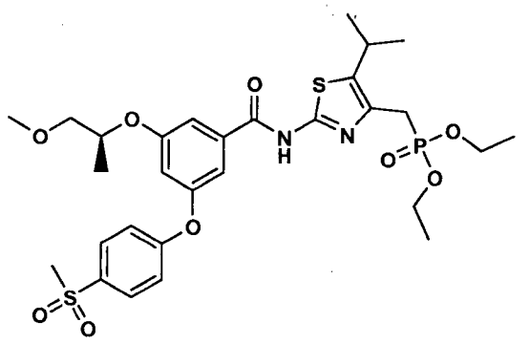
EXAMPLE 51



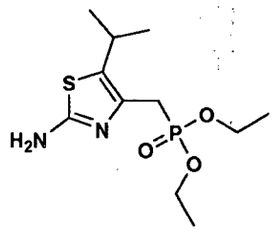
[00316] The title compound (32 mg; 78%; white solid) was synthesized employing the same procedure as described for the synthesis of Example 50, except that NBS was used instead of NCS. The bromination reaction was complete within 1 h. $[M + H]^+ = 691.3$; ^1H NMR (400 MHz, $CDCl_3$): δ 1.29 (t, 6H), 1.34 (d, 3H), 3.09 (s, 3H),

3.33 (d, 2H), 3.41 (s, 3H), 3.55 (q, 2H), 4.09 (m, 4H), 4.65 (m, 1H), 6.89 (s, 1H), 7.14 (d, 2H), 7.21 (s, 1H), 7.38 (s, 1H), 7.94 (d, 2H).

EXAMPLE 52

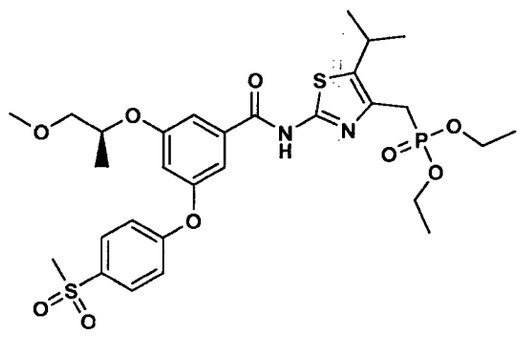


A.



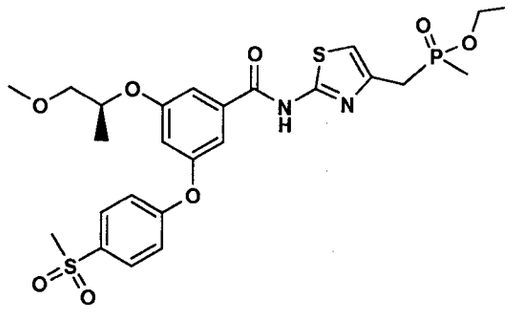
[00317] Compound A (120 mg; 16% for 5 steps; soft white solid) was synthesized from methyl 2-amino-5-isopropyl-1,3-thiazole-4-carboxylate employing the same procedure used to prepare Example 13 Part E compound.

B.

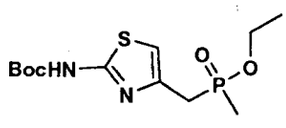


[00318] DIPEA (19.2 μL; 0.110 mmol) was added to a solution of Part A compound (33.6 mg; 0.115 mmol), Example 26 Part C compound (36.4 mg; 0.096 mmol) and HOAt (15.0 mg; 0.110 mmol)in DMF (0.35 mL), followed by EDAC (21.1 mg; 0.110 mmol). After 24 h at RT the reaction mixture was partitioned between EtOAc (15 mL) and 0.5 N aqueous HCl (10 mL). The organic phase was washed with sat. aqueous $NaHCO_3$ (10 mL) and brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by preparative HPLC (YMC reverse phase ODS-A-5u 30 x 100 mm column; flow rate = 40 mL/min, 15 to 100% solvent B over 10 min, hold to 12 min, where solvent A = 90:10:0.1 H_2O:ACN:TFA and solvent B = 90:10:0.1 ACN:H_2O:TFA) to give the title compound (49 mg; 75%) as a colorless residue. $[M + H]^+ = 655.3$; ^1H NMR (400 MHz, $CDCl_3$): δ 1.29 (t, 6H), 1.35 (m, 9H), 3.07 (s, 3H), 3.28 (d, 2H), 3.31 (m, 1H), 3.41 (s, 3H), 3.57 (m, 2H), 4.13 (m, 4H), 4.84 (m, 1H), 6.92 (s, 1H), 7.15 (d, 2H), 7.38 (s, 1H), 7.62 (s, 1H), 7.92 (d, 2H).

EXAMPLE 53



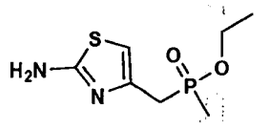
A.



[00319] Diethyl methylphosphonite (690 mg; 5.07 mmol) was added to a solution of Example 13 Part C compound (496 mg; 1.69 mmol) in THF (0.5 mL). The reaction mixture was heated at 75°C for 16 h, then was cooled to RT. The solution was directly loaded onto a 12 g SiO_2 column and the crude product was chromatographed

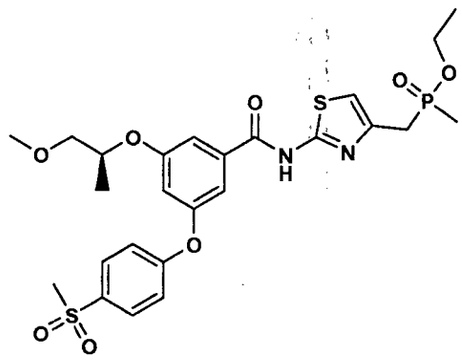
(continuous gradient from 0 to 100% EtOAc in hexanes over 4 min, switched to 5% MeOH in EtOAc and held for 10 min) to give Part A compound (493 mg; 91%) as a light yellow solid.

B.



[00320] TFA (2.0 mL) was added to a 0°C solution of Part A compound (768 mg; 2.40 mmol) in DCM (6 mL). The reaction mixture was stirred at RT for 3 h, then was concentrated *in vacuo*. The residue was partitioned between EtOAc (15 mL) and sat. aqueous $NaHCO_3$ (10 mL). The aqueous phase was extracted with EtOAc (2 x 10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to give Part B compound (203 mg; 38%).

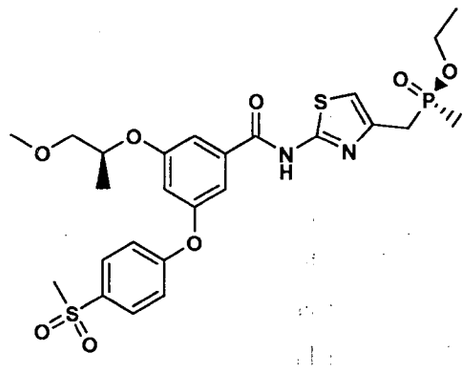
C.



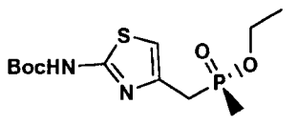
[00321] DIPEA (228 µL; 1.31 mmol) was added to a solution of Part B compound (369 mg; 1.67 mmol), Example 26 Part C compound (415 mg; 1.09 mmol) and HOAt (178 mg; 1.31 mmol) in DMF (4.0 mL). EDAC (251 mg; 1.31 mmol) was added. After 48 h at RT the reaction mixture was partitioned between EtOAc (15 mL) and H_2O (12 mL). The organic phase was washed with 0.5 N aqueous HCl (10 mL), sat. aqueous $NaHCO_3$ (10 mL) and brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was chromatographed (SiO_2; continuous gradient from 0 to 100% EtOAc in hexanes over 6 min, switch to 1% MeOH in EtOAc and hold for 4

min, then switched to 4% MeOH in EtOAc and hold for 10 min) to give title compound (354 mg; 56%) as a white solid (diastereomeric mixture). $[M + H]^+$ = 583.3; ^1H NMR (400 MHz, $CDCl_3$): δ 1.34 (m, 6H), 1.50 (d, 3H), 3.08 (s, 3H), 3.32 (m, 1H), 3.41 (s, 3H), 3.57 (m, 3H), 4.06 (m, 2H), 4.76 (m, 1H), 6.89 (s, 2H), 7.15 (d, 2H), 7.44 (s, 1H), 7.61 (s, 1H), 7.92 (d, 2H).

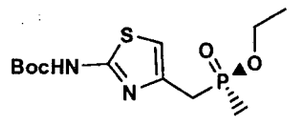
EXAMPLE 54



A.



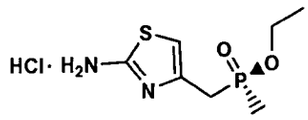
Isomer 1



Isomer 2

[00322] The two isomers of Example 53 Part A compound (2.6 g; 8.12 mmol) were separated by chiral preparative HPLC (ChiralPak AD, 5 x 50 cm column, 20μ, isocratic at 15% of 50/50 MeOH:EtOH; 85% heptane, 50 mL/min for 2 h). The material was purified in three runs. Isomer 1 had a retention time of 38 min and isomer 2 had a retention time of 52 min. Fractions containing isomer 1 were concentrated *in vacuo* to give 1.07 g (82%) of a glassy solid. Fractions containing isomer 2 were concentrated *in vacuo* to give 1.09 g (84%) of a glassy solid.

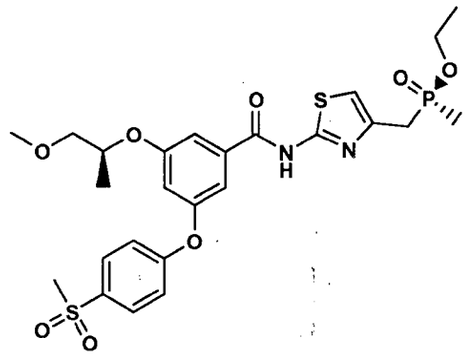
B.



Isomer 2

[00323] HCl (6.0 mL of a 4.0 N solution in 1,4 dioxane) was added to Part A compound isomer 2 (1.05 g; 3.28 mmol). After stirring at RT for 5 h, the reaction mixture was concentrated *in vacuo*. The residue was dissolved in H_2O (20 mL), frozen and lyophilized. The lyophilate was dissolved in MeOH (25 mL) and concentrated *in vacuo* to give Part B compound (0.85 g; 100%) as a white foam.

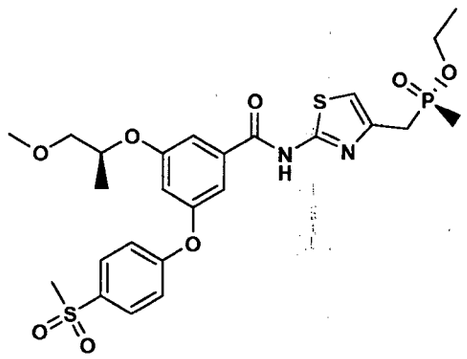
C.



[00324] DIPEA (1.45 mL; 8.28 mmol) was added to a solution of Part B compound (0.85 g; 3.31 mmol), Example 26 Part C compound (1.05 g; 2.76 mmol) and HOAt (526 mg; 3.86 mmol)in DMF (10.0 mL). EDAC (741 mg; 3.86 mmol) was added. After 72 h at RT the reaction mixture was partitioned between EtOAc (140 mL) and H_2O (120 mL). The organic phase was washed with 0.5 N aqueous HCl (100 mL), sat. aqueous $NaHCO_3$ (100 mL) and brine (80 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was divided into 4 portions and purified by preparative HPLC (YMC reverse phase ODS-A-5u 30 x 250 mm column; flow rate = 30 mL/min, 20 to 100% solvent B over 20 min, hold to 25 min, where solvent A = 90:10:0.1 H_2O:MeOH:TFA and solvent B = 90:10:0.1 MeOH:H_2O:TFA). The product was purified by preparative HPLC a second time using same conditions but using CH_3CN instead of MeOH to give the title compound (920 mg; 57%) as a white solid. $[M + H]^+ = 583.0$; ^1H NMR (400 MHz, $CDCl_3$): δ 1.33 (m, 6H), 1.45 (d, 3H),

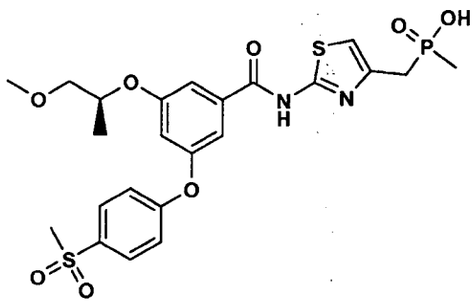
3.07 (s, 3H), 3.34 (m, 1H), 3.40 (s, 3H), 3.55 (q, 2H), 3.86 (m, 1H), 4.05 (m, 2H), 4.70 (m, 1H), 6.77 (d, 1H), 6.86 (s, 1H), 7.14 (d, 2H), 7.49 (s, 1H), 7.62 (s, 1H), 7.91 (d, 2H).

EXAMPLE 55



[00325] The title compound (133 mg, 44% crude yield, white solid) was prepared from Example 54 Part A Isomer 1 employing the procedure set forth in Example 54. $[M + H]^+ = 583.2$; ^1H NMR (400 MHz, $CDCl_3$): δ 1.33 (m, 6H), 1.45 (d, 3H), 3.07 (s, 3H), 3.32 (m, 1H), 3.40 (s, 3H), 3.55 (q, 2H), 3.77 (m, 1H), 4.06 (m, 2H), 4.70 (m, 1H), 6.77 (d, 1H), 6.86 (s, 1H), 7.14 (d, 2H), 7.47 (s, 1H), 7.59 (s, 1H), 7.91 (d, 2H).

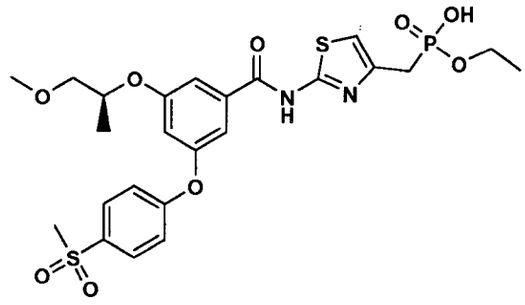
EXAMPLE 56



[00326] 2.0 N aqueous NaOH (81 μL; 0.162 mmol) was added to a mixture of Example 55 compound (31.5 mg; 0.054 mmol) in EtOH (70 μL) and THF (70 μL). After 16 h the mixture was partitioned between EtOAc (2 mL) and 0.5 N aqueous HCl (1 mL). The organic phase was washed with brine (1 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give title compound (27.4 mg; 91%) as a white solid. $[M + H]^+ = 555.0$; ^1H NMR (400 MHz, $CDCl_3$): δ 1.28 (d, 3H), 1.37 (d, 3H), 3.10 (s, 3H),

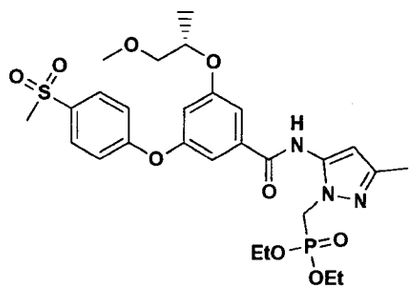
3.21 (d, 2H), 3.43 (s, 3H), 3.59 (q, 2H), 4.77 (m, 1H), 6.74 (s, 1H), 6.92 (s, 1H), 7.20 (d, 2H), 7.70 (s, 1H), 7.77 (s, 1H), 7.93 (d, 2H).

EXAMPLE 57

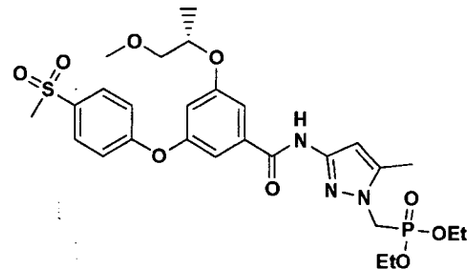


[00327] 2.5 N aqueous NaOH (131 μL; 0.328 mmol) was added to a solution of Example 37 compound (67 mg; 0.109 mmol) in MeOH (130 μL) and THF (130 μL). The solution was heated at 50°C for 20 h, then was cooled to RT and partitioned between EtOAc (4 mL) and 1.0 N aqueous HCl (2 mL). The organic phase was washed with brine (2 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by preparative HPLC (YMC reverse phase ODS-A-5μm 30 x 100 mm column; flow rate = 40 mL/min, 15 to 100% solvent B over 10 min, hold to 12 min, where solvent A = 90:10:0.1 H_2O:ACN:TFA and solvent B = 90:10:0.1 ACN:H_2O:TFA) to give a white solid. The material was purified by preparative HPLC a second time (same conditions as above but using MeOH in place of ACN) to give title compound (30 mg; 47%) as a white solid. $[M + H]^+ = 585.0$; ^1H NMR (400 MHz, CD_3OD): δ 1.30 (m, 6H), 3.12 (s, 3H), 3.28 (d, 2H), 3.37 (s, 3H), 3.56 (m, 2H), 4.05 (m, 2H), 4.71 (m, 1H), 6.96 (m, 2H), 7.24 (d, 2H), 7.31 (s, 1H), 7.48 (s, 1H), 7.97 (d, 2H).

EXAMPLES 58 AND 59

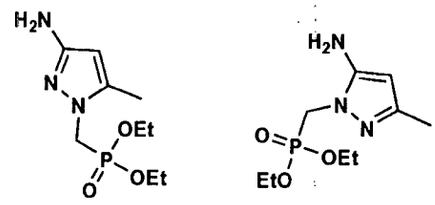


58



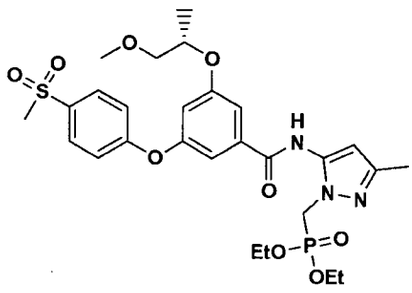
59

A.

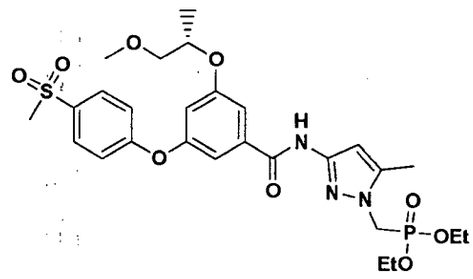


[00328] To a stirred 0°C solution of 5-methyl-1H-pyrazol-3-amine (260 mg, 2.68 mmol) in DMF (4 mL) was added KOtBu (601 mg, 5.35 mmol). The reaction was stirred at 0°C for 30 min, and then $ICH_2PO_3Et_2$ (1116 mg, 4.02 mmol) was added dropwise. The reaction was stirred at 0°C for 1 h, then was warmed to RT and stirred at RT for 18 h. Volatiles were removed *in vacuo* at 50°C. The residue was partitioned between EtOAc and brine. The aqueous layer was extracted with EtOAc (4x), and the combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to give a brown oil. The crude residue was purified by preparative HPLC (Luna 5u 21.2 x 100 mm column; flow rate = 20 mL/min, 0 to 100% solvent B over 12 min, hold to 15 min, where solvent A = 90:10:0.1 H_2O:MeOH:TFA and solvent B = 90:10:0.1 MeOH:H_2O:TFA) to afford the Part A compounds (1:1 mixture, 80 mg, 12%) as a white solid.

B.



58



59

[00329] To a RT solution of Example 26C acid (0.110 g, 0.288 mmol) in DMF (4.5 mL), was added EDC (0.110 g, 0.576 mmol), HOAT (0.078 g, 0.576 mmol), and DIEA (0.088 mL, 0.5004 mmol). The homogeneous yellow solution was stirred at 25°C for 30 min. A solution of Part A compound (0.100g, 288 mmol) in DIEA (0.088 mL, 0.5004 mmol) and DMF (1.5 mL) was added, and the homogeneous yellow reaction mixture was stirred at 25°C for 2 h, then was poured into water (15 mL). The mixture was extracted with EtOAc (10 mL); the organic phase was dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by preparative HPLC (Phenomenex Luna 5 μ C18 30 x 250 mm column; detection at 220 nm; flow rate=20 mL/min.; continuous gradient from 100% A to 100% B over 30 min. + 7 min. hold at 100% B, where A=90:10 H_2O:MeOH and B=90:10 MeOH: H_2O) to provide a yellow foam (a mixture of the two regioismers).

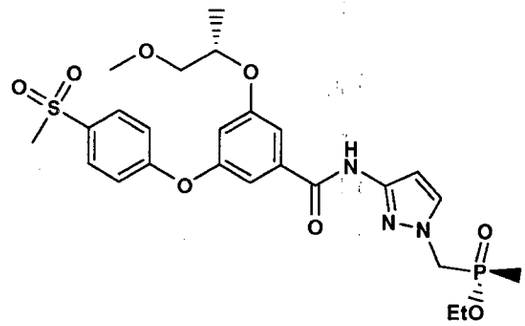
[00330] The regioisomers were separated by chiral preparative HPLC (5 cm x 50 cm AD column, detection at 220 nm, isocratic 50:50 EtOH:MeOH mobile phase, 50 mL/min. flow) to provide the title compound 58 (27 mg, 15.2 % yield) as a tan solid and the title compound 59 (64mg, 36.3 % yield) as an off-white solid.

[00331] **Example 58:** $[M + H]^+ = 610.4$; ^1H NMR (400 MHz, $CDCl_3$) δ10.56 (s, 1H), 7.91 (d, *J*=8.79 Hz, 2H), 7.52 (t, *J*=1.75, 1.76 Hz, 1H), 7.37 (t, *J*=1.75,1.32 Hz, 1H), 7.15 (d, *J*=8.79 Hz, 2H), 6.83 (t, *J*=2.20 Hz, 1H), 6.44 (s, 1H), 4.64-4.74 (m, 1H), 4.50 (d, *J*=10.55 Hz, 2H), 3.97-4.17 (m, 4H), 3.49-3.64 (m, 2H), 3.42 (s, 3H), 3.07 (s, 3H), 2.26 (s, 3H), 1.36 (d, *J*=6.15 Hz, 3H), 1.27 (t, *J*=7.03 Hz, 6H).

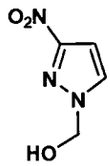
[00332] **Example 59:** $[M + H]^+ = 610.4$; ^1H NMR (400 MHz, $CDCl_3$) δ 8.6 (s, 1H),. 7.92 (d, *J*=8.79 Hz, 2H), 7.31 (t, *J*=1.76 Hz, 1H), 7.12-7.17 (m, 3H), 6.83 (t,

J=2.19, 1.76 Hz, 1H), 6.66 (s, 1H), 4.57-4.69 (m, 1H), 4.37 (d, *J*=11.42 Hz, 2H), 4.01-4.15 (m, 4H), 3.48-3.63 (m, 2H), 3.42 (s, 3H), 3.09 (s, 3H), 2.34 (s, 3H), 1.34 (d, *J*=6.59 Hz, 3H), 1.29 (t, *J*=7.03 Hz, 6H).

EXAMPLE 60

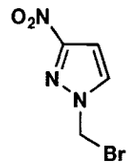


A.



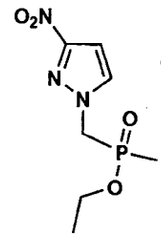
[00333] To a suspension of 3-nitro-1H-pyrazole (1.00 g, 8.84 mmol) in water (31 mL) was added formaldehyde (37 wt % in water, 1.317 mL, 17.69 mmol). The reaction mixture was stirred at RT for 48 h (after 2 h the reaction mixture became a homogeneous pale yellow solution). The reaction mixture was diluted with sat. aqueous $NaHCO_3$ (20 mL) and extracted with CH_2Cl_2 (4 x 40 mL) and EtOAc (3 x 50 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to provide Part A compound (1.26 g, 99% yield) as a white solid. ^1H NMR (400 MHz, CD_3OD) δ 7.69 (d, *J*=2.20 Hz, 1H),. 6.95 (d, *J*=2.75 Hz, 1H), 5.62 (d, *J*=7.70 Hz, 2H), 4.40 (t, *J*=7.70, 7.69 Hz, 1H).

B.



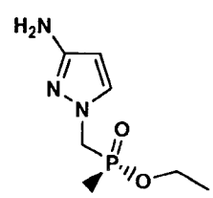
[00334] To a 75°C solution of Part A compound (1.809 g, 12.64 mmol) in MeCN (54 mL) was added PBr_3 (1.788 mL, 18.96 mmol) dropwise over 10 min. The reaction mixture was stirred at 75°C for 15 min, then was cooled to RT and filtered. The filter cake was washed with CH_3CN (2 x 2 mL), and the combined filtrates were concentrated *in vacuo*. The residue was partitioned between EtOAc (50 mL) and sat. aqueous $NaHCO_3$ (30 mL). The organic phase was washed with brine (20 mL), dried ($MgSO_4$), and concentrated *in-vacuo*. The residue was chromatographed (SiO_2: continuous gradient 0% EtOAc/Hexane to 70% EtOAc/Hex) to provide Part B compound (1.693 g, 65% yield) as a pale yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ7.80 (d, *J*=2.20 Hz, 1H), 7.01 (d, *J*=2.75 Hz, 1H), 5.98 (s, 2H).

C.

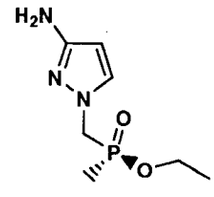


[00335] To a solution of Part B compound (1.7366 g, 8.43 mmol) in THF (4 mL) was added $CH_3P(OEt)_2$ (1.377 g, 10.12 mmol). The reaction mixture was stirred at 75°C for 15 h. Additional $CH_3P(OEt)_2$ (0.53 g, 3.89 mmol) was added, and the reaction mixture was stirred at 75°C for 24 h, then was cooled to RT. Volatiles were removed *in vacuo*, and the residue was chromatographed (SiO_2: continuous gradient from 0% MeOH/CH_2Cl_2 to 15% MeOH/CH_2Cl_2) to provide Part C compound (1.56 g, 80% yield) as an orange oil. $[M + H]^+ = 234.1$; ^1H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J*=3.30 Hz, 1H), 6.96 (d, *J*=2.75 Hz, 1H), 4.63 (d, *J*=9.34 Hz, 2H), 4.03-4.20 (m, 4H), 1.57 (d, *J*=14.85 Hz, 3H), 1.30-1.37 (m, 6H).

D.



D1



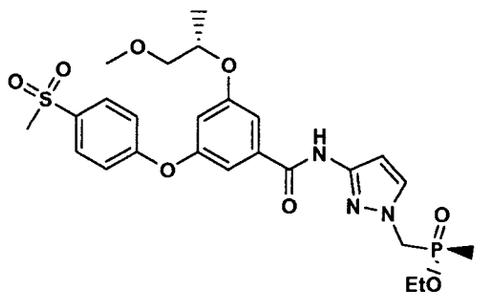
D2

[00336] To a solution of Part C compound (1.60 g, 6.86 mmol) in MeOH (190 mL) was added 10% Pd/C (0.730 g, 0.686 mmol). The reaction mixture was stirred under an H_2(g) atmosphere for 3 h. The reaction mixture was filtered through Celite®, and the filtrate was concentrated *in vacuo*. The individual stereoisomers were separated on a Chiralcel OJ column (5 cm x 50 cm, isocratic conditions: 40% IPA in heptane, detection at 220 nm, 50 mL/min. flow) to provide isomer D1 (0.59 g, 42.3% yield) as an off-white solid and isomer D2 (0.56 g, 40% yield) as a tan solid.

[00337] **Isomer D1:** $[M + H]^+ = 204.1$; ^1H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, *J*=2.19 Hz, 1H), 5.66 (d, *J*=2.20 Hz, 1H), 4.32 (d, *J*=8.79 Hz, 2H), 4.02-4.17 (m, 2H), 3.59-3.81 (s, 2H), 1.48 (d, *J*=14.50 Hz, 3H), 1.33 (t, *J*=7.03 Hz, 3H), specific rotation=48.5°.

[00338] **Isomer D2:** $[M + H]^+ = 204.1$; ^1H NMR (400 MHz, $CDCl_3$) δ 7.21-7.27 (m, 1H), 5.62-5.70 (m, 1H), 4.32 (d, *J*=8.79 Hz, 2H), 4.01-4.19 (m, 2H), 3.55-3.81 (s, 2H), 1.48 (d, *J*=14.50 Hz, 3H), 1.33 (t, *J*=7.03 Hz, 3H), specific rotation=-49.6°.

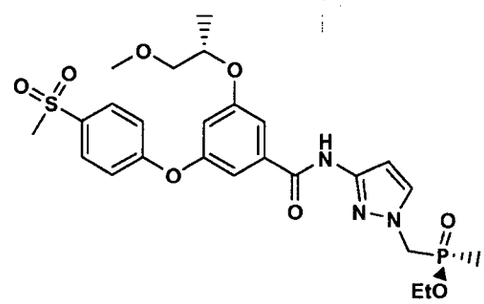
E.



[00339] To a RT solution of Example 26 Part C compound (0.120 g, 0.315 mmol) in DMF (6 mL) was added EDAC (0.121 g, 0.631 mmol), HOAT (0.086 g, 0.631 mmol), and DIEA (0.165 mL, 0.946 mmol). The reaction mixture was stirred at RT

for 30 min and Part D1 compound (0.064 g, 0.315 mmol) was added. The reaction mixture was stirred at RT for 18 h. The reaction mixture was poured into water (40 mL) and the mixture was extracted with EtOAc (3 x 15 mL). The combined organic extracts were concentrated *in vacuo*. The residue was purified by preparative HPLC (Phenomenex Luna 5 μm C18 30 x 100 mm column; detection at 220 nm; flow rate=40 mL/min; continuous gradient from 100% A to 100% B over 20 min. + 2 min. hold at 100% B, where A=90:10:0.1 H_2O:MeOH:TFA and B=90:10:0.1 MeOH: H_2O:TFA) to provide the title compound (0.121 g, 68.1% yield) as a white solid. [M + H]$^+$ = 566.3; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.24 (s, 1H), 7.91 (d, *J*=8.78 Hz 2H), 7.46 (d, *J*=1.76 Hz, 1H), 7.38 (t, *J*=1.76 Hz, 1H), 7.23 (t, J=1.76 Hz,1H), 7.13 (d, *J*=8.79 Hz, 2H), 6.96 (d, *J*=2.19 Hz, 1H), 6.84 (t, *J*=2.20 Hz, 1H), 4.73-4.63 (m, 1H), 4.56 (dd, *J*=16.25, 8.35 Hz, 1H), 4.46 (dd, *J*=15.82, 8.35, 9.67 Hz, 1H), 4.20-4.05 (m, 2H), 3.63-3.50 (m, 2H), 3.42 (s, 3H), 3.08 (s, 3H), 1.51 (d, J=14.5 Hz, 3H), 1.39-1.29 (m, 6H).

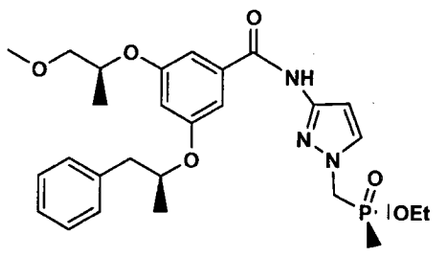
EXAMPLE 61



[00340] To a RT solution of Example 26C acid (0.120 g, 0.315 mmol) in DMF (6 mL) was added EDAC (0.121 g, 0.631 mmol), HOAT (0.086 g, 0.631 mmol), and DIEA (0.165 mL, 0.946 mmol). The reaction mixture was stirred at RT for 30 min and Example 60 Part D2 compound (0.064 g, 0.315 mmol) was added. The reaction mixture was stirred at RT for 18 h, then was poured into water (40 mL). The mixture was extracted with EtOAc (3 x 15 mL); the combined organic extracts were concentrated *in vacuo*. The residue was purified by preparative HPLC (Phenomenex Luna 5 μm C18 30 x 100 mm column; detection at 220 nm; flow rate=40 mL/min.; continuous gradient from 100% A to 100% B over 20 min. + 2 min. hold at 100% B,

where A=90:10:0.1 H_2O:MeOH:TFA and B=90:10:0.1 MeOH: H_2O:TFA) to provide the title compound (0.117 g, 65.4% yield) as a white solid. $[M + H]^+ = 566.3$; ^1H NMR (400 MHz, $CDCl_3$): δ 9.19 (s, 1H), 7.92 (d, *J*=9.22 Hz 2H), 7.46 (d, *J*=1.76 Hz, 1H), 7.37 (t, *J*=1.76 Hz, 1H), 7.22 (t, *J*=1.76 Hz,1H), 7.13 (d, *J*=8.78 Hz, 2H), 6.96 (d, *J*=2.63 Hz, 1H), 6.85 (t, *J*=2.20 Hz, 1H), 4.72-4.62 (m, 1H), 4.56 (dd, *J*=16.25, 8.35 Hz, 1H), 4.46 (dd, *J*=15.82, 8.35, 9.67 Hz, 1H), 4.19-4.05 (m, 2H), 3.63-3.50 (m, 2H), 3.42 (s, 3H), 3.08 (s, 3H), 1.51 (d, J=14.5 Hz, 3H), 1.38-1.29 (m, 6H).

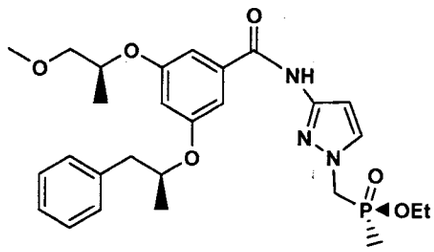
EXAMPLE 62



[00341] To a RT solution of Example 33 Part A acid ((0.030 g, 0.087 mmol) in DMF (2.0 mL) was added EDAC (0.033 g, 0.174 mmol), HOAt (0.024 g, 0.174 mmol) and DIEA (0.046 mL, 0.261 mmol). The reaction mixture was stirred at RT for 30 min, after which Example 60 Part D1 compound (0.018 g, 0.087 mmol) was added. The reaction mixture was stirred at RT for 18 h, then was poured into water (20 mL). The mixture was extracted with EtOAc (2 x 10 mL); the combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by preparative HPLC (Phenomenex Luna 5 μ C18 21.2 x 100 mm column; detection at 220 nm; flow rate=40 mL/min.; continuous gradient from 100% A to 100% B over 15 min. + 2 min. hold at 100% B, where A=90:10:0.1 H_2O:MeOH:TFA and B=90:10:0.1 MeOH: H_2O:TFA) to provide the title compound (0.034 g, g, 74.8% yield) as a tacky off-white solid. $[M + H]^+ = 530.4$; ^1H NMR (400 MHz, $CDCl_3$): δ 9.16 (s, 1H), 7.45 (d, *J*=1.65 Hz, 1H), 7.32-7.18 (m, 5H), 7.06 (t, *J*=1.65 Hz, 1H), 7.03 (t, *J*=1.65 Hz, 1H), 6.98 (d, *J*=2.19 Hz, 1H), 6.64 (t, *J*=2.2 Hz, 1H), 4.69-4.56 (m, 2H), 4.55- 4.40 (m, 2H), 4.18-4.04 (m, 2H), 3.57 (dd, *J*=10.45 Hz, *J*=6.04 Hz, 1H), 3.50 (dd, *J*=9.89 Hz, *J*=3.85 Hz, 1H), 3.41 (s, 3H), 3.06 (dd, *J*=13.74 Hz,

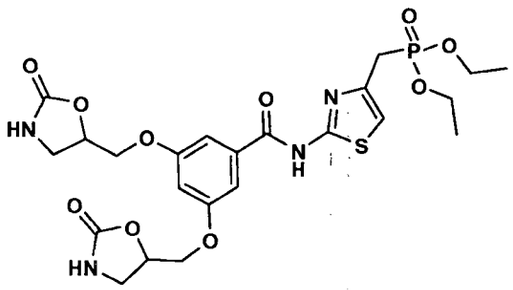
J=6.04 Hz, 1H), 2.86 (dd, *J*=13.75 Hz, *J*=6.05 Hz, 1H), 1.53 (d, *J*=14.84 Hz, 3H), 1.35-1.27 (m, 9H).

EXAMPLE 63

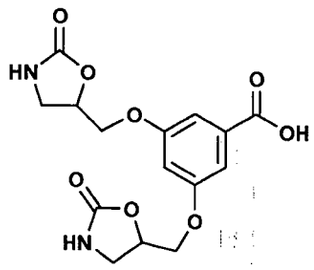


[00342] To a RT solution of Example 33 Part A acid ((0.030 g, 0.087 mmol) in DMF (2.0 mL) was added EDAC (0.033 g, 0.174 mmol), HOAt (0.024 g, 0.174 mmol) and DIEA (0.046 mL, 0.261 mmol). The reaction mixture was stirred at RT for 30 min, after which Example 60 Part D2 compound (0.018 g, 0.087 mmol) was added. The reaction was stirred at RT for 18 h, then was poured into water (20 mL). The mixture was extracted with EtOAc (2 x 10 mL) and the combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by preparative HPLC (Phenomenex Luna 5 μ C18 21.2 x 100 mm column; detection at 220 nm; flow rate=40 mL/min.; continuous gradient from 100% A to 100% B over 15 min. + 2 min. hold at 100% B, where A=90:10:0.1 H_2O:MeOH:TFA and B=90:10:0.1 MeOH: H_2O:TFA) to provide the title compound (0.03626 g, 79% yield) as a tacky white solid. $[M + H]^+ = 530.4$; ^1H NMR (400 MHz, $CDCl_3$): δ 9.17 (s, 1H), 7.45 (d, *J*=2.20 Hz, 1H), 7.32-7.17 (m, 5H), 7.06 (t, *J*=2.2 Hz, 1H), 7.03 (t, *J*=2.2 Hz, 1H), 6.98 (d, *J*=2.19 Hz, 1H), 6.64 (t, *J*=2.2 Hz, 1H), 4.70-4.57 (m, 2H), 4.54- 4.40 (m, 2H), 4.17-4.03 (m, 2H), 3.57 (dd, *J*=9.90 Hz, *J*=6.04 Hz, 1H), 3.50 (dd, *J*=10.44 Hz, *J*=3.38 Hz, 1H), 3.41 (s, 3H), 3.06 (dd, *J*=13.74 Hz, *J*=6.59 Hz, 1H), 2.85 (dd, *J*=13.75 Hz, *J*=6.05 Hz, 1H), 1.52 (d, *J*=14.29 Hz, 3H), 1.36-1.26 (m, 9H).

EXAMPLE 64

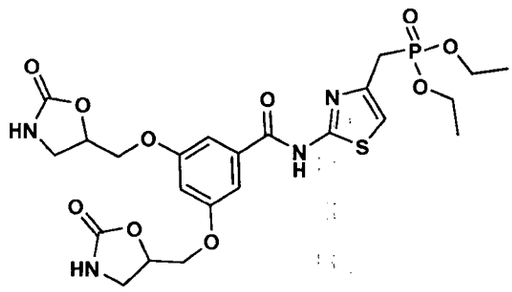


A.



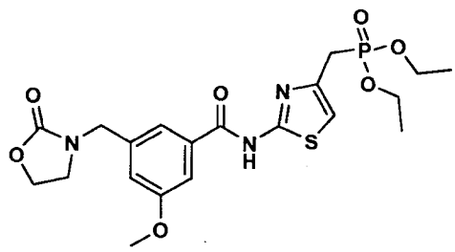
[00343] A mixture of methyl 3,5-dihydroxybenzoate (350 mg, 2.082 mmol), 5-(chloromethyl) oxazolidin-2-one (1.0 g, 7.38 mmol), and K_2CO_3 (5.75 g, 41.6 mmol) in DMF (10 mL) was stirred at 80°C for 18 h, then was cooled to RT and filtered. The filter cake was washed with EtOAc, and the combined filtrates were concentrated *in vacuo* to give a brown oil. The crude methyl bis-alkylated benzoate was dissolved in THF (1 mL), and aqueous 1N NaOH (1 mL, 1.00 mmol) was added. The mixture was stirred at RT for 18 h, then concentrated *in vacuo*. The residue was acidified with TFA and then purified by preparative HPLC (Phenomenex AXIA 5u C18 30 x 100 mm column; detection at 220 nm; flow rate = 40 mL/min; continuous gradient from 30% A to 100% B over 10 min + 1 min hold time at 100% B, where A = 90:10:0.1 H_2O:MeOH:TFA and B = 90:10:0.1 MeOH:H_2O:TFA) to give Part A compound (83 mg, 9% yield) as a red solid. $[M + H]^+ = 353.1$; ^1H NMR (400 MHz, MEOH-d_4) δ 3.56 (dd, J=8.79, 6.60 Hz, 2 H) 3.75 (t, J=9.07 Hz, 2 H) 4.10 - 4.30 (m, 4 H) 4.96 - 5.07 (m, 2 H) 6.77 - 6.85 (m, 0 H) 7.22 (d, J=2.75 Hz, 2 H).

B.

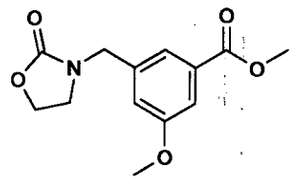


[00344] A mixture of Part A compound (13 mg, 0.037 mmol), Example 13 Part E compound (23 mg, 0.037 mmol), HOAt (10 mg, 0.072 mmol), EDCI (20 mg, 0.500 mmol) and DIPEA (0.2 mL, 1.148 mmol) in DMF (0.5 mL) was stirred at 21°C for 18 h. The reaction mixture was diluted with EtOAc (1 mL) and washed with 1N aqueous HCl (1mL). The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by preparative HPLC (Phenomenex AXIA 5u C18 30 x 100 mm column; detection at 220 nm; flow rate = 40 mL/min; continuous gradient from 30% A to 100% B over 10 min + 1 min hold time at 100% B, where A = 90:10:0.1 H_2O:MeOH:TFA and B = 90:10:0.1 MeOH:H_2O:TFA) to give the title compound (12.5 mg, 58.0 % yield) as a white solid. $[M + H]^+$ = 585.3; ^1H NMR (400 MHz, $CDCl_3$) δ 1.33 (t, J=7.15 Hz, 6 H) 3.35 (d, J=21.44 Hz, 2 H) 3.63 (dd, J=8.25, 6.60 Hz, 2 H) 3.79 (t, J=8.79 Hz, 2 H) 4.11 - 4.20 (m, 4 H) 4.21 - 4.37 (m, 4 H) 4.96 - 5.04 (m, 2 H) 5.76 (br. s., 2 H) 6.80 (br. s., 1 H) 7.04 (d, J=3.85 Hz, 1 H) 7.44 (s, 2 H).

EXAMPLE 65

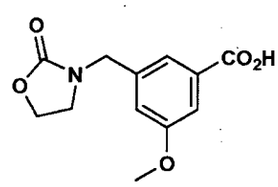


A.



[00345] A suspension of NaH (70 mg of a 60% suspension in oil, 1.750 mmol) in THF (3 mL) was stirred at 0°C under N_2 (g) for 15 min. The reaction was cooled to -30°C and oxazolidin-2-one (125 mg, 1.436 mmol) was added. The mixture was stirred at -30°C for 30 min, then was warmed to RT and stirred for 30 min. The mixture was cooled to -30°C again and a solution of methyl 3-(bromomethyl)-5-methoxybenzoate (200 mg, 0.772 mmol) in THF (2 mL) was added. The mixture was stirred at RT for 5 days, then was cooled to -30°C and sat. aqueous NH_4Cl (1 mL) was added. The aqueous layer was back-extracted with EtOAc (2 x 5mL), and the combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was chromatographed [SiO_2; EtOAc/Hexane (1:1)] to give Part A compound 184 mg, 90% yield) as a clear oil. $[M + H]^+ = 266.01$; ^1H NMR (500 MHz, $CDCl_3$) δ 3.46 (t, J=7.70 Hz, 2 H) 3.85 (s, 3 H) 3.92 (s, 3 H) 4.33 (t, J=7.70 Hz, 2 H) 4.44 (s, 2 H) 7.05 (s, 1 H) 7.50 (s, 1 H) 7.54 (s, 1 H).

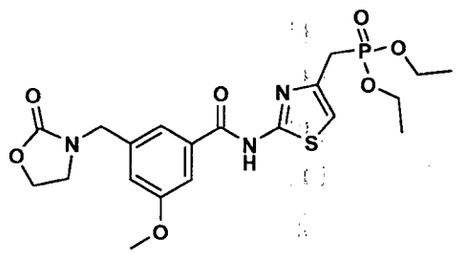
B.



[00346] A mixture of Part A compound (50 mg, 0.188 mmol), and NaOH (1 mL, 1.00 mmol) in THF (2 mL) was stirred at RT for 2h, then was acidified with 1N aqueous HCl (0.5 mL). The mixture was filtered and concentrated *in vacuo*; the residue was purified by preparative HPLC (Phenomenex AXIA 5u C18 30 x 100 mm column; detection at 220 nm; flow rate = 40 mL/min; continuous gradient from 30% A to 100% B over 10 min + 1 min hold time at 100% B, where A = 90:10:0.1 H_2O:MeOH:TFA and B = 90:10:0.1 MeOH:H_2O:TFA) to give Part B compound as a white solid (42 mg, 0.167 mmol, 89 %). $[M + H]^+ = 251.98$; ^1H NMR (400 MHz,

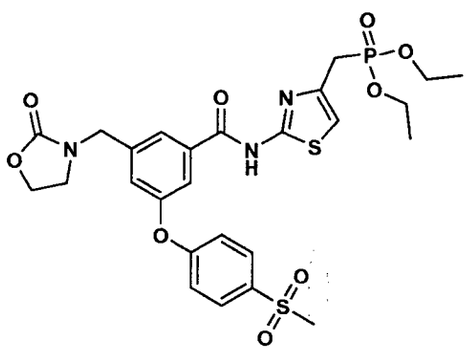
CD_3OD) δ 3.53 (t, J=8.24 Hz, 2 H), 3.84 (s, 3 H), 4.34 (t, J=8.24 Hz, 2 H), 4.44 (s, 2 H), 7.09 (t, J=1.65 Hz, 1 H), 7.49 (dd, J=2.75, 1.10 Hz, 1 H), 7.55 (s, 1 H).

C.

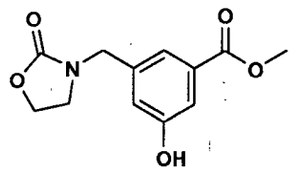


[00347] A mixture of Part B compound (12 mg, 0.048 mmol), Example 13 Part E compound (11.95 mg, 0.048 mmol), HOAt (10 mg, 0.072 mmol), DIPEA (0.2 mL, 1.148 mmol) and EDCI (20 mg, 0.500 mmol) in DMF (0.5 mL) was stirred at RT in for 18 h, then was diluted with EtOAc (1 mL) and washed with 1N aqueous HCl (1 mL). Volatiles were removed *in vacuo*. The crude residue was purified by preparative HPLC (Phenomenex AXIA 5u C18 30 x 100 mm column; detection at 220 nm; flow rate = 40 mL/min; continuous gradient from 30% A to 100% B over 10 min + 1 min hold time at 100% B, where A = 90:10:0.1 H_2O:MeOH:TFA and B = 90:10:0.1 MeOH:H_2O:TFA) to give the title compound as a clear oil (20 mg, 87 % yield). $[M + H]^+$ = 483.99; ^1H NMR (400 MHz, $CDCl_3$) δ 1.33 (t, J=7.15 Hz, 6 H), 3.36 (d, J=21.44 Hz, 2 H), 3.52 (s, J=8.24, 8.24 Hz, 2 H), 3.91 (s, 3 H), 4.12 - 4.22 (m, J=7.35, 7.35, 7.28, 7.15 Hz, 4 H) 4.33 (t, J=8.25 Hz, 2 H), 4.46 (s, 2 H), 7.05 (d, J=3.30 Hz, 1 H), 7.17 (s, 1 H), 7.66 (s, 1 H), 7.68 (d, J=2.20 Hz, 1 H).

EXAMPLE 66

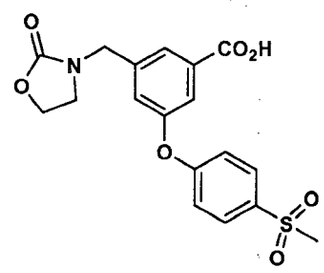


A.



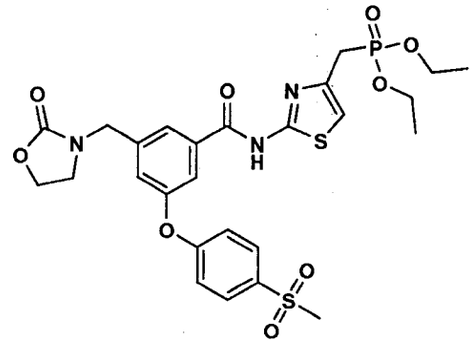
[00348] To a 0°C solution of Example 64 Part B compound (177 mg, 0.667 mmol) in DCM (1 mL) was added BBr_3 (1 mL, 1.000 mmol). The reaction was stirred at 0°C for 24 h, after which volatiles were removed *in vacuo*. The residue was dissolved in MeOH (3 mL), and the pH was adjusted to pH~4 with sat. aqueous $NaHCO_3$. Solids were removed by filtration, and the filtrate was concentrated *in vacuo*. The residue was purified by preparative HPLC (Phenomenex AXIA 5u C18 30 x 100 mm column; detection at 220 nm; flow rate = 40 mL/min; continuous gradient from 30% A to 100% B over 10 min + 1 min hold time at 100% B, where A = 90:10:0.1 H_2O:MeOH:TFA and B = 90:10:0.1 MeOH:H_2O:TFA) to give the Part A compound (67 mg, 40% yield) as a white solid. $[M + H]^+ = 252.19$; ^1H NMR (400 MHz, CD_3OD) δ 3.52 (t, J=8.24 Hz, 2 H), 3.88 (s, 3 H), 4.34 (t, J=8.24 Hz, 2 H), 4.40 (s, 2 H), 6.97 (s, 1 H), 7.36 (s, 1 H), 7.42 (s, 1 H).

B.



[00349] A solution of Part A compound (67 mg, 0.267 mmol), 1-fluoro-4-(methylsulfonyl) benzene (50 mg, 0.287 mmol), and K_2CO_3 (300 mg, 2.171 mmol) in DMF (3 mL) was stirred at 100°C in a sealed tube for 18 h, then was cooled to RT. Solids were filtered off, and the filtrate was concentrated *in vacuo*. The residue was acidified with TFA and then purified by preparative HPLC (Phenomenex AXIA 5µm C18 30 x 100 mm column; detection at 220 nm; flow rate = 40 mL/min; continuous gradient from 30% A to 100% B over 10 min + 1 min hold time at 100% B, where A = 90:10:0.1 H_2O:MeOH:TFA and B = 90:10:0.1 MeOH:H_2O:TFA) to give Part B compound (73mg, 69.9% yield) as a white solid. $[M + H]^+ = 392.01$; ^1H NMR (400 MHz, CD_3OD) δ 3.12 (s, 3 H), 3.57 (t, J=8.24 Hz, 2 H), 4.36 (t, J=8.24 Hz, 2 H), 4.50 (s, 2 H), 7.20 (d, J=8.79 Hz, 2 H), 7.32 (s, 1 H), 7.63 (s, 1 H), 7.84 (s, 1 H), 7.96 (d, J=8.79 Hz, 2 H).

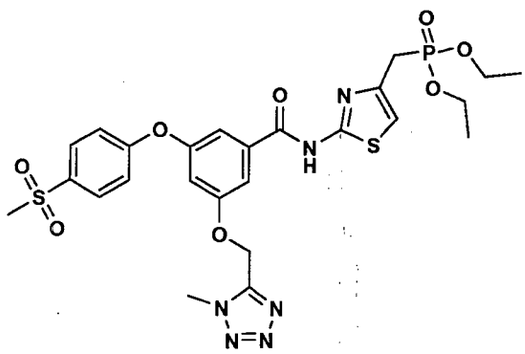
C.



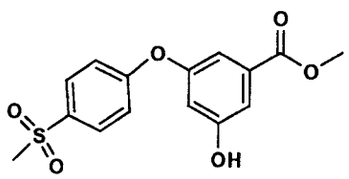
[00350] A mixture of Part B compound (15 mg, 0.038 mmol), Example 13 Part E compound (9.59 mg, 0.038 mmol), HOAt (10 mg, 0.072 mmol), EDCI (20 mg, 0.500 mmol), and DIPEA (0.2 mL, 1.148 mmol) in DMF (0.5 mL) was stirred at 25°C for

18 h. The mixture was diluted with EtOAc (1 mL) and washed with 1N aqueous HCl (1 mL). The organic phase was dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by preparative HPLC (Phenomenex AXIA 5u C18 30 x 100 mm column; detection at 220 nm; flow rate = 40 mL/min; continuous gradient from 30% A to 100% B over 10 min + 1 min hold time at 100% B, where A = 90:10:0.1 H_2O:MeOH:TFA and B = 90:10:0.1 MeOH:H_2O:TFA) to give the title compound (17mg, 70% yield) as a white solid. $[M + H]^+$ = 624.2; ^1H NMR (400 MHz, $CDCl_3$) (1.32 (t, J=7.15 Hz, 6 H), 3.07 (s, 3 H), 3.33 (d, J=21.44 Hz, 2 H), 3.64 (t, J=7.70 Hz, 2 H), 4.15 (dd, J=8.25, 7.15 Hz, 4 H), 4.35 (t, J=8.24 Hz, 2 H), 4.51 (s, 2 H), 7.05 (d, J=3.85 Hz, 1 H), 7.14 (d, J=8.79 Hz, 2 H), 7.40 (s, 1 H), 7.76 (t, J=1.65 Hz, 1 H), 7.89 - 7.96 (m, 3 H).

EXAMPLE 67



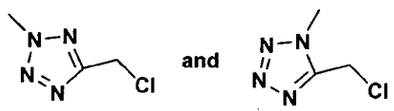
A.



[00351] A mixture of methyl 3,5-dihydroxybenzoate (10 g, 59.5 mmol) and K_2CO_3 (13 g, 94 mmol) in DMF (50 mL) was stirred at 120°C for 2 h. A solution of 1-fluoro-4-(methylsulfonyl) benzene (5 g, 28.7 mmol) in DMF (10 mL) was added, and the reaction was stirred at 120°C for another 24 h. The reaction mixture was filtered, and the resulting filter cake was rinsed with DMF (50 mL). The combined filtrates

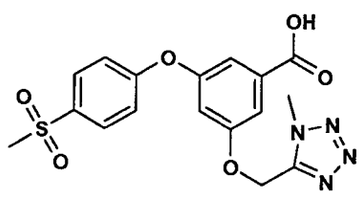
were concentrated *in vacuo*. The residue was partitioned between EtOAc (100 mL) and 1N aqueous HCl (100 mL). The aqueous layer was extracted with EtOAc (50 mL x 3), and the combined organic extracts were washed with water, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude residue was chromatographed (SiO_2; EtOAc/Hexane 1:3) to give Part A compound (4 g, 43% yield) as yellow solid. $[M + H]^+ = 323.0$; ^1H NMR (400 MHz, $CDCl_3$) δ 3.08 (s, 3 H), 3.91 (s, 3 H), 6.13 (s, 1 H), 6.80 (t, J=2.20 Hz, 1 H), 7.11 (d, J=8.79 Hz, 2 H), 7.27 - 7.28 (m, 1 H), 7.41 - 7.44 (m, 1 H), 7.91 (d, J=8.79 Hz, 2 H).

B.

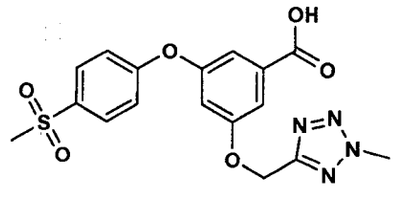


[00352] To a stirred solution of 5-(chloromethyl)-2H-tetrazole (0.5 g, 4.22 mmol) in Et_2O (5 mL) was added dropwise a solution of CH_2N_2 in Et_2O (5 mL) prepared from 1-methyl-3-nitro-1-nitrosoguanidine (700 mg, 4.76 mmol) and 40% aqueous KOH (4 g, 28.5 mmol, 10 mL water) at 0°C. The reaction solution was maintained at 0°C during the addition, and the reaction was stirred at RT for 1 h and was then concentrated using a stream of air. Residual solvent was removed *in vacuo* to give the Part B isomeric compounds as yellow oils (400 mg, 71.5 % yield).

C.



C1



C2

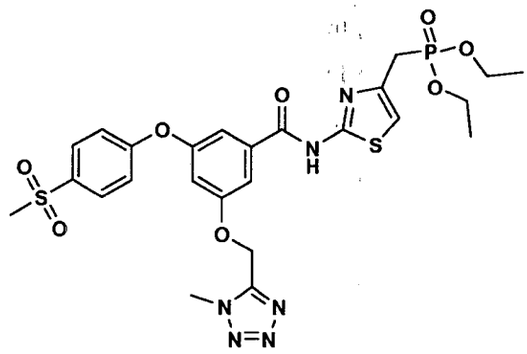
[00353] A mixture of Part A compound (100 mg, 0.310 mmol), Part B compound (41.1 mg, 0.310 mmol), and K_2CO_3 (300 mg, 2.17 mmol) was stirred at 100°C in a sealed tube for 18 h, then was cooled to RT. The reaction mixture was diluted with EtOAc (5 mL) and washed with H_2O (5 mL x 2); the organic layer was dried (Na_2SO_4) and concentrated *in vacuo* to give a yellow oil. This crude methyl ester was

stirred in 1N aqueous NaOH (0.5 mL, 0.500 mmol) and THF (1 mL) for 2 h. The reaction was concentrated *in vacuo* and was acidified with TFA. The two isomers were separated by preparative HPLC (Phenomenex AXIA 5u C18 30 x 100 mm column; detection at 220 nm; flow rate = 40 mL/min; continuous gradient from 30% A to 100% B over 10 min + 1 min hold time at 100% B, where A = 90:10:0.1 H_2O:MeOH:TFA and B = 90:10:0.1 MeOH:H_2O:TFA) to give Part C1 compound (40 mg, 31% yield) as a white solid and Part C2 compound (72 mg, 57% yield) as a white solid.

[00354] **Part C1 Compound:** $[M + H]^+ = 405.1$; ^1H NMR (400 MHz, DMSO-d6) δ 3.22 (s, 3 H), 4.13 (s, 3 H), 5.63 (s, 2 H), 7.20 - 7.28 (m, 4 H), 7.49 (s, 1 H), 7.95 (d, J=8.79 Hz, 2 H), 13.35 (s, 1 H).

[00355] **Part C2 Compound:** $[M + H]^+ = 405.1$; ^1H NMR (400 MHz, DMSO-d6) δ 3.21 (s, 3 H), 4.38 (s, 3 H), 5.47 (s, 2 H), 7.18 (d, J=5.50 Hz, 2 H), 7.24 (d, J=8.79 Hz, 2 H), 7.44 (s, 1 H), 7.94 (d, J=8.79 Hz, 2 H), 13.30 (s, 1 H).

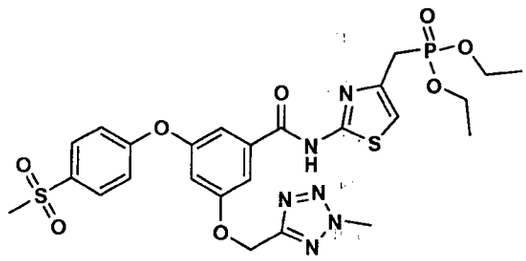
D.



[00356] A mixture of Part C1 compound (12 mg, 0.030 mmol), Example 13 Part E compound (7.43 mg, 0.030 mmol), HOAt (10 mg, 0.072 mmol), EDCI (20 mg, 0.500 mmol), and DIPEA (0.2 mL, 1.148 mmol) in DMF (0.5 mL) was stirred at 25°C for 18 h. The reaction mixture was diluted with EtOAc (1 mL) and washed with 1N aqueous HCl (1 mL). The organic layer was dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by preparative HPLC (Phenomenex AXIA 5μm C18 30 x 100 mm column; detection at 220 nm; flow rate = 40 mL/min; continuous gradient from 30% A to 100% B over 10 min + 1 min hold time at 100% B, where A

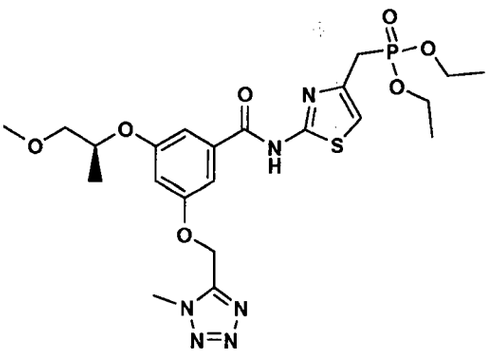
= 90:10:0.1 H_2O:MeOH:TFA and B = 90:10:0.1 MeOH:H_2O:TFA) to give the title compound (12 mg, 64% yield) as a white solid. $[M + H]^+$ = 636.99; ^1H NMR (400 MHz, $CDCl_3$) δ 1.30 (t, J=6.87 Hz, 6 H), 3.08 (s, 3 H), 3.29 (d, J=21.44 Hz, 2 H), 4.08 - 4.17 (m, J=7.56, 7.56, 7.42, 7.15 Hz, 4 H), 4.18 (s, 3 H), 5.56 (s, 2 H), 6.98 (s, 1 H), 7.03 (d, J=3.30 Hz, 1 H), 7.15 (d, J=8.79 Hz, 2 H), 7.50 (s, 1 H), 7.80 (s, 1 H), 7.94 (d, J=8.79 Hz, 2 H).

EXAMPLE 68

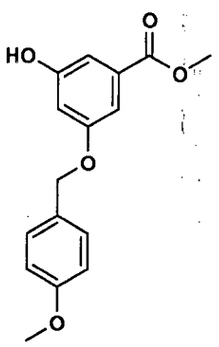


[00357] A mixture of Example 67 Part C2 Compound (12 mg, 0.030 mmol), Example 13 Part E compound (7.43 mg, 0.030 mmol), HOAt (10 mg, 0.072 mmol), DIPEA (0.2 mL, 1.148 mmol), and EDCI (0.500 mL, 0.500 mmol) in DMF (0.5 mL) was stirred at 25°C for 18 h. The reaction mixture was diluted with EtOAc (1 mL) and washed with 1N aqueous HCl (1 mL). The organic layer was dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by preparative HPLC (Phenomenex AXIA 5μm C18 30 x 100 mm column; detection at 220 nm; flow rate = 40 mL/min; continuous gradient from 30% A to 100% B over 10 min + 1 min hold time at 100% B, where A = 90:10:0.1 H_2O:MeOH:TFA and B = 90:10:0.1 MeOH:H_2O:TFA) to give the title compound (10 mg, 53% yield) as a white solid. $[M + H]^+$ = 637.00; ^1H NMR (400 MHz, $CDCl_3$) δ 1.30 (t, J=7.15 Hz, 6 H), 3.07 (s, 3 H), 3.32 (d, J=21.44 Hz, 2 H), 4.07 - 4.17 (m, J=7.35, 7.35, 7.28, 7.15 Hz, 4 H), 4.39 (s, 3 H), 5.48 (s, 2 H), 6.97 - 7.02 (m, 2 H), 7.15 (d, J=8.79 Hz, 2 H), 7.49 (s, 1 H), 7.78 (s, 1 H), 7.93 (d, J=8.79 Hz, 2 H).

EXAMPLE 69

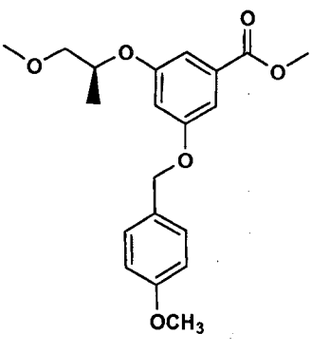


A.



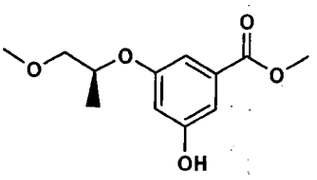
[00358] A mixture of 1-(bromomethyl)-4-methoxybenzene (2.151 mL, 14.92 mmol), methyl 3,5-dihydroxybenzoate (5 g, 29.7 mmol), and K_2CO_3 (12.33 g, 89 mmol) in MeCN (100 mL) was stirred at 80°C for 3 days. The reaction was diluted with water (50 mL), acidified with 12N HCl (30 mL) to pH~2, and extracted with EtOAc (20 mL x 3). The combined organic extracts were washed with water, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was chromatographed (SiO_2: EtOAc/Hexane 1:3) to give Part A compound (3.0 g, 35% yield) as a white solid. ^1H NMR (400 MHz, $CDCl_3$) δ 3.82 (s, 3 H), 3.90 (s, 3 H), 5.00 (s, 2 H), 5.14 (s, 1 H), 6.66 (t, J=2.20 Hz, 1 H), 6.92 (d, J=8.35 Hz, 2 H), 7.10 - 7.16 (m, 1 H), 7.22 - 7.29 (m, 1 H), 7.35 (d, J=8.35 Hz, 2 H).

B.



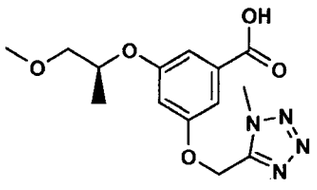
[00359] To a 0°C solution of Ph_3P (1.820 g, 6.94 mmol), Part A compound (1 g, 3.47 mmol), and (R)-1-methoxypropan-2-ol (0.365 mL, 4.16 mmol) in dry THF (5 mL) was added DIAD (1.012 mL, 5.20 mmol). The reaction was stirred at RT for 18 h. Volatiles were removed *in vacuo*, and the residue was chromatographed (SiO_2; EtOAc/Hexane, 1:5) to give crude Part B compound (1.7 g, 136%), which was used in the next step without further purification.

C.

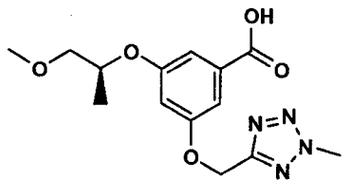


[00360] A solution of crude Part B compound (1.75 g, 4.86 mmol) and TFA (3 mL, 38.9 mmol) in dry DCM (5 mL) was stirred at RT for 2 h. Volatiles were removed *in vacuo*, and the residue was chromatographed (SiO_2; EtOAc/Hexane 1:5) to give Part C compound (407 mg, 35%) as a clear oil. $[M + H]^+ = 241.27$; ^1H NMR (400 MHz, $CDCl_3$) δ 1.29 (d, J=6.05 Hz, 3 H), 3.41 (s, 3 H), 3.47 - 3.62 (m, 2 H), 3.88 (s, 3 H), 4.51 - 4.62 (m, 1 H), 4.95 (br. s., 1 H), 6.65 (s, 1 H), 7.13 (dd, J=5.22, 1.37 Hz, 2 H).

D.



D1



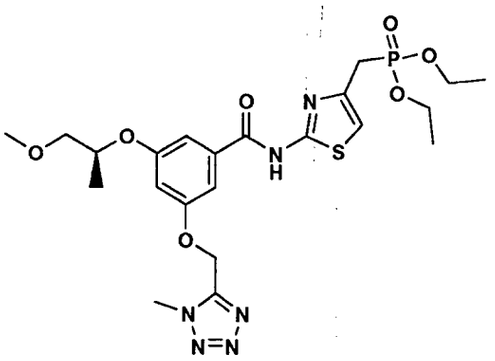
D2

[00361] A mixture of Part C compound (300 mg, 1.249 mmol), Example 67 Part B compound (166 mg, 1.249 mmol), and K_2CO_3 (300 mg, 2.171 mmol) in DMF (3 mL) was stirred at 100°C in a sealed tube for 18 h, then was cooled to RT. Solids were filtered off, and the filtrate was concentrated *in vacuo*. The residue was acidified with TFA and the two isomers were separated by preparative HPLC (Phenomenex AXIA 5u C18 30 x 100 mm column; detection at 220 nm; flow rate = 40 mL/min; continuous gradient from 30% A to 100% B over 10 min + 1 min hold time at 100% B, where A = 90:10:0.1 H_2O:MeOH:TFA and B = 90:10:0.1 MeOH:H_2O:TFA) to give Part D1 compound (160 mg, 40% yield) as a white solid and Part D2 compound (33 mg, 8.2% yield) as a white solid.

[00362] **Part D1 compound:** $[M + H]^+ = 323.15$; ^1H NMR (400 MHz, $CDCl_3$) δ 1.31 (d, J=6.05 Hz, 3 H), 3.43 (s, 3 H), 3.50 - 3.64 (m, 2 H), 4.18 (s, 3 H), 4.57 - 4.67 (m, 1 H), 5.47 (s, 2 H), 6.82 (t, J=2.47 Hz, 1 H), 7.30 (dd, J=2.20, 1.10 Hz, 1 H), 7.35 (s, 1 H).

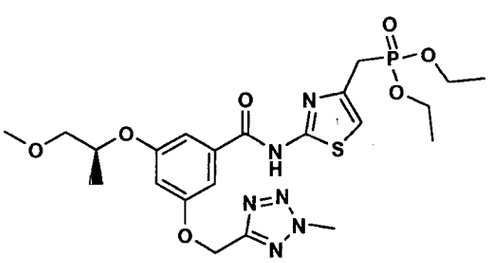
[00363] **Part D2 compound:** $[M + H]^+ = 323.18$; ^1H NMR (400 MHz, $CDCl_3$) δ 1.32 (d, J=6.05 Hz, 3 H), 3.42 (s, 3 H), 3.48 - 3.62 (m, 2 H), 4.39 (s, 3 H), 4.55 - 4.64 (m, 1 H), 5.35 (s, 2 H), 6.86 (t, J=2.47 Hz, 1 H), 7.34 (s, 1 H), 7.37 (dd, J=2.20, 1.10 Hz, 1 H).

E.



[00364] A mixture of Part D1 compound (15 mg, 0.047 mmol), Example 13 Part E compound (11.65 mg, 0.047 mmol), HOAt (10 mg, 0.072 mmol), EDCI (20 mg, 0.500 mmol), and DIPEA (0.2 mL, 1.148 mmol) in DMF (0.5 mL) was stirred at 25°C for 18 h. The reaction mixture was diluted with EtOAc (1 mL) and washed with 1N aqueous HCl (1 mL). The organic phase was dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by preparative HPLC(Phenomenex AXIA 5u C18 30 x 100 mm column; detection at 220 nm; flow rate = 40 mL/min; continuous gradient from 30% A to 100% B over 10 min + 1 min hold time at 100% B, where A = 90:10:0.1 H_2O:MeOH:TFA and B = 90:10:0.1 MeOH:H_2O:TFA) to give the title compound (13 mg, 50% yield) as a white solid. $[M + H]^+ = 555.3$; ^1H NMR (400 MHz, $CDCl_3$) δ 1.28 - 1.35 (m, 9 H), 3.29 - 3.36 (m, 2 H), 3.40 (s, 3 H), 3.49 - 3.61 (m, 2 H), 4.09 - 4.19 (m, 7 H), 4.74 (td, J=6.19, 3.79 Hz, 1 H), 5.49 (s, 2 H), 6.84 (t, J=2.15 Hz, 1 H), 7.03 (d, J=3.54 Hz, 1 H), 7.47 (t, J=1.77 Hz, 1 H), 7.49 (dd, J=2.02, 1.52 Hz, 1 H).

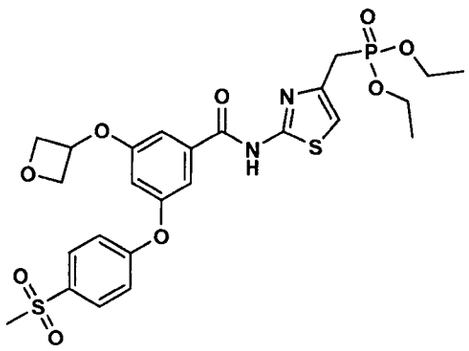
EXAMPLE 70



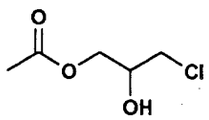
[00365] The title compound (10 mg; 58% yield; colorless oil) was synthesized employing the procedure described in Example 69 Part E, except that Example 69

Part D2 was used in the sequence instead of Example 69 Part D1. $[M + H]^+ = 555.3$; ^1H NMR (400 MHz, $CDCl_3$) δ 1.25 - 1.37 (m, 9 H), 3.26 - 3.37 (m, 2 H), 3.40 (s, 3 H), 3.47 - 3.62 (m, 2 H), 4.06 - 4.19 (m, 4 H), 4.38 (s, 3 H), 4.71 (td, J=6.19, 4.04 Hz, 1 H), 5.40 (s, 2 H), 6.86 (t, J=2.27 Hz, 1 H), 6.98 (d, J=3.54 Hz, 1 H), 7.40 (d, J=1.52 Hz, 1 H), 7.45 (d, J=1.52 Hz, 1 H).

EXAMPLE 71

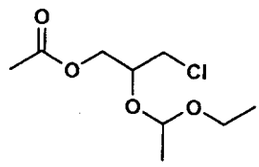


A.



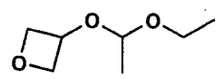
[00366] To a solution of $FeCl_3$ (100mg, 0.62 mmol) in HOAc (68.8 mL, 1202 mmol) was added 2-(chloromethyl)oxirane (111.2 g, 1202 mmol) with stirring, over a 10-min period. The mixture was heated at 70°C with stirring for 24 h, then was cooled to RT and filtered to give Part A compound (183 g, 100% yield) as a yellow oil. ^1H NMR (400 MHz, $CDCl_3$) (2.11 (s, 3 H), 3.57 - 3.66 (m, 2 H), 4.05 - 4.12 (m, 1 H), 4.21 (t, J=4.83 Hz, 2 H).

B.



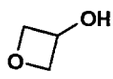
[00367] To crude Part A compound (183 g, 1202 mmol) was added pTsOH (1 g, 5.26 mmol), followed by dropwise addition of ethyl vinyl ether (118 mL, 1232 mmol) over a period of 2 h. The flask was cooled to maintain a reaction temperature of 35-37°C. After the addition was complete, the mixture was heated at 40-45°C for 18 h, then cooled to RT to give crude Part B compound (270 g, 100 %) as a red liquid.

C.



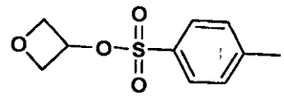
[00368] To a 110°C solution of NaOH (110 g, 2750 mmol) in water (110 mL) was added Part B compound (270 g, 1202 mmol) over a 1.5 h period. The reaction mixture was refluxed for another 4 h, then was cooled to RT and washed with water (110 mL). The aqueous layer was extracted with DCM (110 mL), and the combined organic extracts were concentrated *in vacuo* to give a brown oil. Distillation (bp = 45-50°C @ 0.5 mm Hg) gave Part C compound (15 g, 8.5%) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.15 (t, J=7.15 Hz, 3 H), 1.25 (d, J=5.50 Hz, 3 H), 3.44 (dd, J=9.34, 7.15 Hz, 1 H), 3.56 (q, J=7.15 Hz, 1 H), 4.55 - 4.84 (m, 4 H).

D.



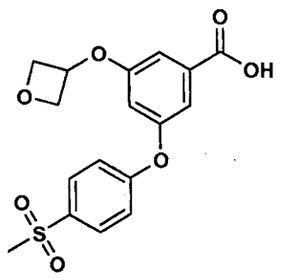
[00369] A solution of Part C compound (15 g, 103 mmol) in MeOH (5.26 mL, 125 mmol) was cooled to 15-18°C, and p-TsOH (100 mg, 0.581 mmol) was added with stirring. The reaction mixture was stirred for 45 min, after which $NaHCO_3$ (50 mg, 0.595 mmol) was added. Distillation at 35-40°C (0.1 mmHg) gave crude Part D compound (7.0 g, 95%) as a clear oil.

E.



[00370] To a well-stirred 50°C solution of Part D compound (7 g, 94 mmol) and p-TsCl (12.8 g, 67.1 mmol) in water (15 mL) was added dropwise a solution of NaOH (2.69 g, 67.1 mmol) in water (15 mL). The reaction was heated for 1 h at 50°C, then cooled to RT and toluene (10 mL) was added. The aqueous layer was extracted with toluene (5 mL x 2). The combined organic extracts were washed with conc NH_4OH (3x) and water (2x), then concentrated *in vacuo*. Hexane (50 mL) was added to the residue and a solid was formed, which was collected by filtration and then was dried *in vacuo* for 1 h to give Part E compound (10 g, 65% yield) as a white solid. $[M + H]^+ = 229.1$; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 2.46 (s, 3 H), 4.64 - 4.75 (m, 4 H), 5.27 - 5.34 (m, 1 H), 7.37 (d, J=8.25 Hz, 2 H), 7.78 (d, J=8.25 Hz, 2 H).

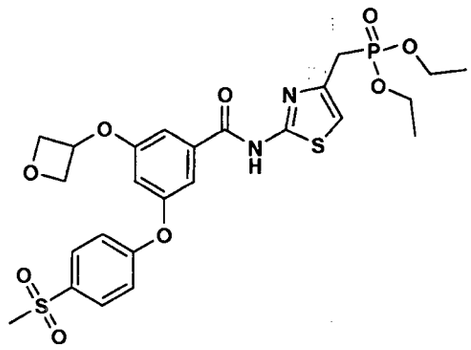
F.



[00371] A mixture of Example 67 Part A compound (450 mg, 1.396 mmol), Part E compound (500 mg, 2.190 mmol), and K_2CO_3 (2.7 g, 19.54 mmol) in DMF (5 mL) was stirred in a sealed tube at 110°C for 18 h, then was cooled to RT. The reaction was filtered, the solids were washed with DMF, and the combined filtrates were concentrated *in vacuo*. The residue was neutralized with TFA and purified by preparative HPLC(Phenomenex AXIA 5u C18 30 x 100 mm column; detection at 220 nm; flow rate = 40 mL/min; continuous gradient from 30% A to 100% B over 10 min + 1 min hold time at 100% B, where A = 90:10:0.1 H_2O:MeOH:TFA and B = 90:10:0.1 MeOH:H_2O:TFA) to give the Part F compound (220 mg, 42% yield) as a white solid. $[M + H]^+ = 365.2$; ^1H NMR (400 MHz, $CDCl_3$) δ 3.08 (s, 3 H), 4.78 (dd,

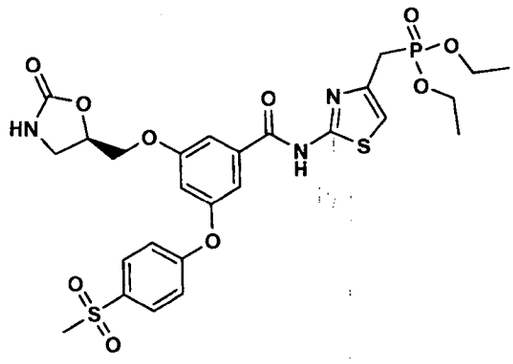
J=7.15, 4.95 Hz, 2 H), 5.02 (t, J=6.87 Hz, 2 H), 5.23 - 5.31 (m, 1 H), 6.75 (t, J=1.92 Hz, 1 H), 7.13 (d, J=8.79 Hz, 2 H), 7.18 (s, 1 H), 7.39 (s, 1 H), 7.93 (d, J=8.24 Hz, 2 H).

G.

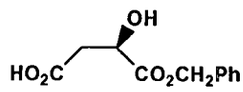


[00372] A mixture of Part F compound (14 mg, 0.038 mmol), Example 13 Part E compound (9.62 mg, 0.038 mmol), HOAt (10 mg, 0.072 mmol), EDCI (20 mg, 0.500 mmol) and DIPEA (0.2 mL, 1.148 mmol) in DMF (0.5 mL) was stirred at 40°C for 18h, then was cooled to RT. The reaction mixture was partitioned between EtOAc (1mL) and 1N aqueous HCl (1 mL). The organic layer was dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by preparative HPLC (Phenomenex AXIA 5µm C18 30 x 100 mm column; detection at 220 nm; flow rate = 40 mL/min; continuous gradient from 30% A to 100% B over 10 min + 1 min hold time at 100% B, where A = 90:10:0.1 H_2O:MeOH:TFA and B = 90:10:0.1 MeOH:H_2O:TFA) to give the title compound (13 mg, 55.6% yield) as a white solid. $[M + H]^+$ = 597.2; ^1H NMR (400 MHz, $CDCl_3$) δ 1.28 (t, J=7.03 Hz, 6 H), 3.08 (s, 3 H), 3.34 (d, J=21.09 Hz, 2 H), 4.04 - 4.16 (m, 4 H), 4.75 (dd, J=7.47, 4.83 Hz, 2 H), 5.05 (t, J=6.81 Hz, 2 H), 5.36 - 5.45 (m, J=5.49, 5.38, 5.33, 5.33 Hz, 1 H), 6.82 (t, J=2.20 Hz, 1 H), 6.96 (d, J=3.52 Hz, 1 H), 7.15 (d, J=8.79 Hz, 2 H), 7.24 (s, 1 H), 7.42 (s, J=1.76, 1.76 Hz, 1 H), 7.94 (d, J=9.23 Hz, 2 H).

EXAMPLE 72

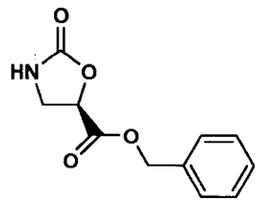


A.



[00373] Pre-cooled TFAA (25 mL, 177 mmol) at 0°C was added to D-malic acid (5 g, 37.3 mmol) with stirring. The suspension was stirred for 2 h at RT, then was concentrated *in vacuo*. Dry benzyl alcohol (25 mL, 240 mmol) was added and the solution was stirred overnight at RT. Volatiles (benzyl alcohol and TFAA) were removed *in vacuo*. The residue was chromatographed [SiO_2; EtOAc/Hexane (1:1 + 0.5%TFA)] to give Part A compound (7.9 g, 94% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.80 - 2.96 (m, 2 H), 4.55 (dd, J=6.19, 4.42 Hz, 1 H), 5.24 (s, 2 H), 7.30 - 7.38 (m, 5 H); [a]=+12.19 @ 1.4% w/v in DMF at 589 nm.

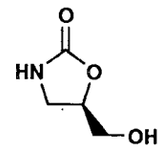
B.



[00374] To a solution of the Part A compound (7.9 g, 35.2 mmol) and Et_3N (5.6 mL, 40.2 mmol) in Toluene (120 mL) was slowly added Ph_2PON_3 (8.64 mL, 40.0 mmol) over ~30 min. The reaction mixture was refluxed for 2 h, stirred at 70°C for 2 h, then cooled to RT and stirred at RT for 3 days. Volatiles were removed *in vacuo*;

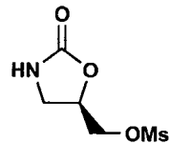
the residue was dissolved in water and extracted with EtOAc (20 mL x 3). The combined organic extracts were washed with sat. aqueous $NaHCO_3$, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was chromatographed [SiO_2; EtOAc/Hexane (1:1)] to give Part B compound (2.28 g, 27.5 % yield) as a pale solid. $[M + H]^+$ = 222.16; ^1H NMR (400 MHz, $CDCl_3$) δ 3.58 - 3.73 (m, 1 H), 3.86 (t, J=9.35 Hz, 1 H), 5.02 (dd, J=9.60, 5.56 Hz, 1 H), 5.24 (d, J=1.77 Hz, 2 H), 6.40 (br. s., 1 H), 7.36 (s, 5 H); [a]=-4.56 @ 1.2% w/v in DMF at 589 nm.

C.



[00375] To a 0°C suspension of Part B compound (2.28 g, 10.31 mmol) in EtOH (50 mL) was slowly added $NaBH_4$ (0.390 g, 10.31 mmol). The mixture was stirred for 3 h at 0 °C, then was warmed to RT and sat. aqueous NH_4Cl (2 mL) was added. The reaction was stirred for 30 min, then the solids were filtered off, and the filtrate was concentrated *in vacuo*. The residue was chromatographed (SiO_2; EtOAc/MeOH, 5:1) to give Part C compound (0.966 g, 80 % yield) as a white solid. ^1H NMR (400 MHz, DMSO-d6) δ 3.20 (t, J=7.70 Hz, 1 H), 3.41 - 3.57 (m, 3 H), 4.52 (dt, J=15.39, 4.67 Hz, 1 H), 5.06 (t, J=5.77 Hz, 1 H), 7.39 (br. s., 1 H); [a] = -33.11 @ 1.1% w/v in EtOH at 589 nm.

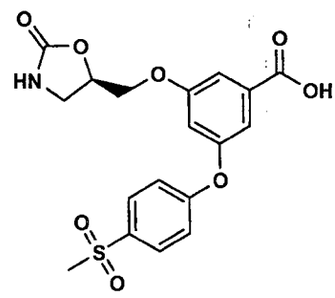
D.



[00376] To a -5 °C solution of Part C compound (966 mg, 8.25 mmol) and pyridine (10 mL, 124 mmol) in DCM (15 mL) was slowly added MsCl (0.8 mL, 10.27 mmol) over 1 h. After 3 h, the volatiles were removed *in vacuo* at a minimal temperature. The residue was chromatographed (SiO_2; CH_2Cl_2/MeOH 95:5 v/v) to give Part D compound (1.5 g, 93 % yield) as a colorless solid. ^1H NMR (400 MHz, DMSO-d6) δ

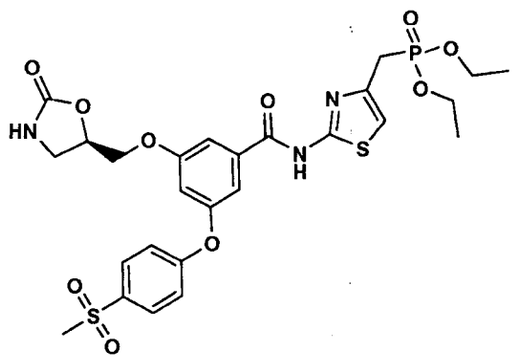
3.21 - 3.27 (m, 4 H), 3.58 (t, J=9.34 Hz, 1 H), 4.28 - 4.35 (m, 1 H), 4.36 - 4.43 (m, 1 H), 4.80 - 4.88 (m, 1 H), 7.63 (br. s., 1 H); [a]= -33.93 @ 0.55% w/v in EtOH at 589 nm.

E.



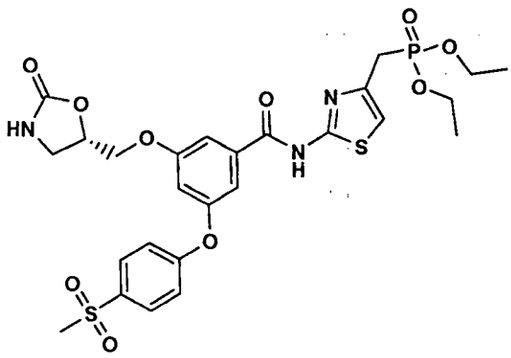
[00377] A mixture of Example 26 Part A compound (400 mg, 1.241 mmol), Part D compound (242 mg, 1.241 mmol), and K_2CO_3 (2.7 g, 19.54 mmol) in DMF (5 mL) was stirred in a sealed tube at 110°C for 18 h, then was cooled to RT and filtered. The filtrate was concentrated *in vacuo*. The residue was neutralized with TFA and then purified by preparative HPLC (Phenomenex AXIA 5u C18 30 x 100 mm column; detection at 220 nm; flow rate = 40 mL/min; continuous gradient from 30% A to 100% B over 10 min + 1 min hold time at 100% B, where A = 90:10:0.1 H_2O:MeOH:TFA and B = 90:10:0.1 MeOH:H_2O:TFA) to give the Part E compound (260 mg, 51.4 % yield) as a white solid. $[M + H]^+ = 408.1$; ^1H NMR (400 MHz, CD_3OD) δ 3.12 (s, 3 H), 3.55 (dd, J=9.01, 6.37 Hz, 1 H), 3.75 (t, J=9.23 Hz, 1 H), 4.17 - 4.24 (m, 1 H), 4.26 - 4.33 (m, 1 H), 4.97 - 5.05 (m, 1 H), 6.98 (t, J=2.20 Hz, 1 H), 7.19 (d, J=8.79 Hz, 2 H), 7.30 (s, 1 H), 7.47 (s, 1 H), 7.95 (d, J=9.23 Hz, 2 H); [a]= -23.97 @ 1.4% w/v in MeOH at 589 nm.

F.



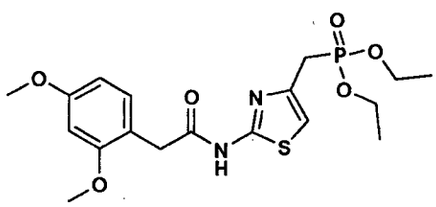
[00378] A mixture of Part E compound (20 mg, 0.049 mmol), Example 13 Part E compound (12.29 mg, 0.049 mmol), HOAt (10 mg, 0.072 mmol), EDCI (20 mg, 0.500 mmol), and DIPEA (0.2 mL, 1.148 mmol) in DMF (0.5 mL) was stirred at 25°C for 18 h. Volatiles were removed *in vacuo* and the residue was purified by preparative HPLC (Phenomenex AXIA 5µm C18 30 x 100 mm column; detection at 220 nm; flow rate = 40 mL/min; continuous gradient from 30% A to 100% B over 10 min + 1 min hold time at 100% B, where A = 90:10:0.1 H_2O:MeOH:TFA and B = 90:10:0.1 MeOH:H_2O:TFA) to give the title compound (17 mg, 51.4 % yield) as a white solid. $[M + H]^+$ = 640.3; ^1H NMR (400 MHz, $CDCl_3$) δ 1.31 (td, J=7.07, 5.05 Hz, 6 H), 3.07 (s, 3 H), 3.32 (d, J=21.22 Hz, 2 H), 3.64 (dd, J=8.84, 6.32 Hz, 1 H), 3.82 (t, J=8.97 Hz, 1 H), 4.07 - 4.18 (m, 4 H), 4.38 (d, J=4.55 Hz, 2 H), 4.96 - 5.06 (m, 1 H), 6.12 (br. s., 1 H), 6.93 (t, J=2.27 Hz, 1 H), 6.99 (d, J=3.79 Hz, 1 H), 7.15 (d, J=8.84 Hz, 2 H), 7.50 (dd, J=2.15, 1.39 Hz, 1 H), 7.71 (t, J=1.77 Hz, 1 H), 7.92 (d, J=8.84 Hz, 2H); e.e.=98.2% (Chiralpak AS, 250 X 4.6 mm ID; 10 µm, RT, 60% (50/50 MeOH-EtOH): 40% Heptane, 1 mL/min).

EXAMPLE 73



[00379] The title compound (22 mg; 58% yield; white solid) was synthesized from L-malic acid employing the same procedure as described in Example 72. $[M + H]^+$ = 640.3; ^1H NMR (400 MHz, $CDCl_3$) δ 1.33 (t, J=7.07 Hz, 6 H), 3.07 (s, 3 H), 3.38 (d, J=21.47 Hz, 2 H), 3.64 (dd, J=8.84, 6.57 Hz, 1 H), 3.81 (t, J=8.97 Hz, 1 H), 4.17 (dd, J=8.21, 7.20 Hz, 3 H), 4.29 - 4.37 (m, 1 H), 4.40 - 4.48 (m, 1 H), 4.99 - 5.08 (m, 1 H), 5.91 (br. s., 1 H), 6.96 (t, J=2.15 Hz, 1 H), 7.06 (d, J=3.79 Hz, 1 H), 7.15 (dq, J=8.84, 4.80 Hz, 1 H), 7.51 (dd, 1 H), 7.71 (t, J=1.52 Hz, 1 H), 7.93 (dq, J=8.84, 4.80 Hz, 1 H); e.e.=99.9% (Chiralpak AS, 250 X 4.6 mm ID; 10 μm, RT, 60% (50/50 MeOH-EtOH): 40% Heptane, 1 mL/min)

EXAMPLE 74

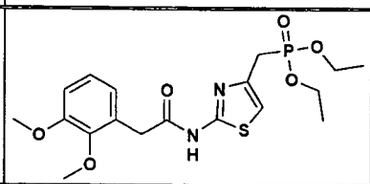
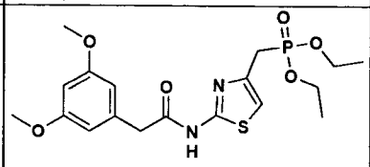
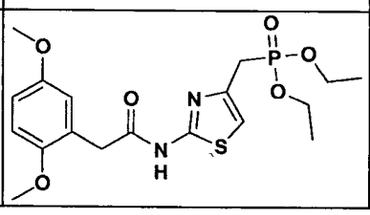


[00380] A mixture of 2-(2,4-dimethoxyphenyl) acetic acid (20 mg, 0.12 mmol), Example 13 Part E compound (25 mg, 0.1 mmol), HOAt (20 mg, 0.015 mmol), EDCI (25 mg, 0.500 mmol), and DIPEA (0.2 mL, 1.148 mmol) in DMF (0.5 mL) was stirred at 25°C for 18 h. The reaction mixture was concentrated *in vacuo*, and the residue was purified by preparative HPLC (Phenomenex AXIA 5μm C18 30 x 100 mm column; detection at 220 nm; flow rate = 40 mL/min; continuous gradient from 30% A to 100% B over 10 min + 1 min hold time at 100% B, where A = 90:10:0.1 H_2O:MeOH:TFA and B = 90:10:0.1 MeOH:H_2O:TFA) to give the title compound

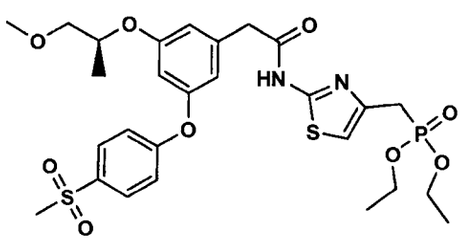
(2.6 mg, 6 % yield) as a yellow oil. $[M + H]^+ = 429.4$; ^1H NMR (400 MHz, $CDCl_3$) δ 1.31 (t, J=7.03 Hz, 6 H), 3.25 - 3.34 (d, J=21.53 Hz, 2 H), 3.79 (s, 3 H), 3.80 (s, 3 H), 3.83 (s, 2 H), 4.09 - 4.18 (m, 4 H), 6.46 - 6.50 (m, 2 H), 6.91 (d, J=3.52 Hz, 1 H), 7.15 (d, 1 H);

EXAMPLES 75 TO 77

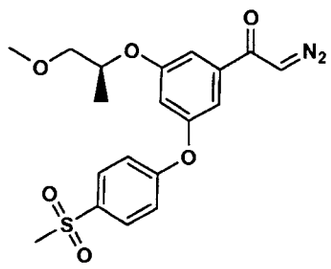
[00381] The following examples were prepared in the same manner as Example 74:

Example #	Structure	$[M + H]^+$	1H NMR (400 MHz, $CDCl_3$)	Yield and Description
75		429.4	δ 1.29 (t, *J*=7.03 Hz, 6 H), 3.27 (d, *J*=21.09 Hz, 2 H), 3.83 - 3.91 (m, 8 H), 4.04 - 4.17 (m, 4 H), 6.83 - 6.93 (m, 3 H), 7.01 - 7.08 (m, 1 H)	8.3 mg (19% yield); yellow oil
76		429.4	(1.27 (t, J=7.03 Hz, 6 H), 3.25 (d, J=21.09 Hz, 2 H), 3.75 - 3.78 (m, 2 H), 3.79 (s, 6 H), 4.02 - 4.12 (m, 4 H), 6.40 - 6.43 (m, 1 H), 6.47 (d, J=2.20 Hz, 2 H), 6.82 (none, 1H)	8.6 mg (20% yield); yellow oil
77		429.4	δ 1.29 (t, *J*=7.03 Hz, 6 H), 3.23 - 3.31 (m, 2 H), 3.77 (s, 3 H), 3.82 (s, 5 H), 4.06 - 4.14 (m, 4 H), 6.82 - 6.87 (m, 4 H)	8.3 mg (19% yield); yellow oil

EXAMPLE 78

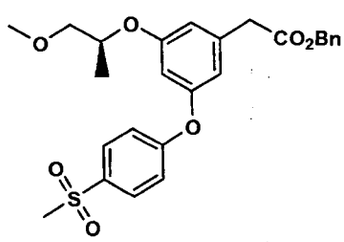


A.



[00382] A solution of Example 26C acid (146mg, 0.384 mmol) and $(COCl)_2$ (2 mL of a 2M solution in DCM, 4 mmol) in DCM (2 mL) was stirred at RT for 18 h, then was concentrated *in vacuo*. The crude acid chloride was taken up in Et_2O (5 mL) and was added dropwise to a 0°C solution of CH_2N_2 in Et_2O (5 mL) prepared from 1-methyl-3-nitro-1-nitrosoguanidine (735 mg, 5 mmol) and 40% aqueous KOH (0.8 g, 15 mmol, 2 mL water) at 0°C. The reaction mixture was stirred at RT for 1 h and was concentrated under a stream of air; residual solvent were removed *in vacuo*. The residue was chromatographed (SiO_2; EtOAc/Hexane 5:1) to give Part A compound (130 mg, 84 % yield) as a yellow oil. $[M + H]^+ = 405.2$; ^1H NMR (400 MHz, $CDCl_3$) δ 1.28 (d, J=6.15 Hz, 3 H), 3.03 (s, 3 H), 3.36 (s, 3 H), 3.43 - 3.57 (m, 2 H), 4.51 - 4.62 (m, 1 H), 5.86 (s, 1 H), 6.79 (t, J=2.20 Hz, 1 H), 6.99 (s, 1 H), 7.08 (d, J=8.79 Hz, 2 H), 7.15 (s, 1 H), 7.87 (d, 2 H).

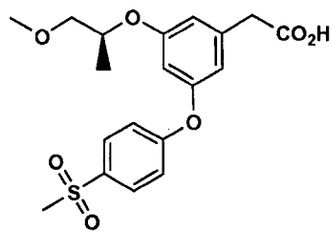
B.



[00383] To a -25 °C solution of Part A compound (130 mg, 0.321 mmol) and BnOH (0.5 mL, 5 mmol) in dry THF (2 mL) was added over 15 min a solution of $PhCO_2Ag$ (206.1mg, 0.9 mmol) in Et_3N (1.67 mL, 12 mmol). The reaction mixture was stirred at RT for 5 h in the dark. The reaction was filtered through Celite®; the filtrate was concentrated *in vacuo*, and the residue was chromatographed [SiO_2; EtOAc/Hexane(2:1)] to give Part B compound (130mg, 83.6%) as a clear oil. [M +

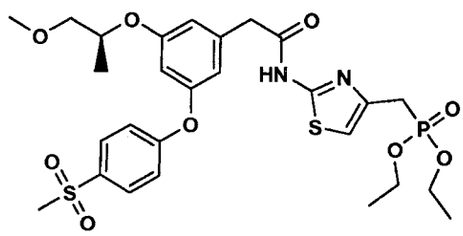
H]$^+$ = 485.2; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28 (d, *J*=6.15 Hz, 3 H), 3.05 (s, 3 H), 3.39 (s, 3 H), 3.44 - 3.50 (m, 1 H), 3.52 - 3.58 (m, 1 H), 3.62 (s, 2 H), 4.45 - 4.54 (m, 1 H), 5.14 (s, 2 H), 6.56 (t, *J*=2.20 Hz, 1 H), 6.59 (t, *J*=1.76 Hz, 1 H), 6.73 (d, *J*=1.76 Hz, 1 H), 7.08 (d, *J*=9.23 Hz, 2 H), 7.28 - 7.38 (m, 5 H), 7.86 (d, *J*=8.79 Hz, 2 H).

C.



[00384] A solution of Part B compound (130 mg, 0.268 mmol) and 10% Pd-C (20 mg) in EtOAc (10 mL) was stirred under H_2 (g; 60 psi) for 18 h. The catalyst was removed by filtration and the filtrate was concentrated *in vacuo* to give Part C compound (86 mg, 81.4%) as a clear oil. [M + H]$^+$ = 395.1; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28 (d, *J*=6.15 Hz, 3 H), 3.05 (s, 3 H), 3.38 (s, 3 H), 3.44 - 3.51 (m, 1 H), 3.51 - 3.57 (m, 1 H), 3.58 (s, 2 H), 4.46 - 4.56 (m, 1 H), 6.55 (t, *J*=2.20 Hz, 1 H), 6.58 (s, 1 H), 6.72 (s, 1 H), 7.09 (d, *J*=8.79 Hz, 2 H), 7.87 (d, 2 H).

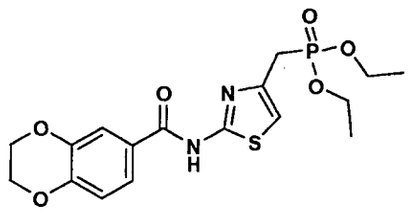
D.



[00385] A solution of Part C compound (43 mg, 0.109 mmol) and $(COCl)_2$ (3.0 mL of a 2M solution in DCM, 6 mmol) in DCM (3 mL) was stirred at RT for 18 h, then was concentrated *in vacuo*. The crude acid chloride was taken up in DCM (2 mL) and was added over 15 min to a 0°C solution of Example 13 Part E compound (37 mg, 0.148 mmol) and pyridine (0.2 mL, 2.5 mmol) in DCM (3 mL). The reaction was stirred at 0°C for 30 min, then was concentrated *in vacuo*. The residue was purified

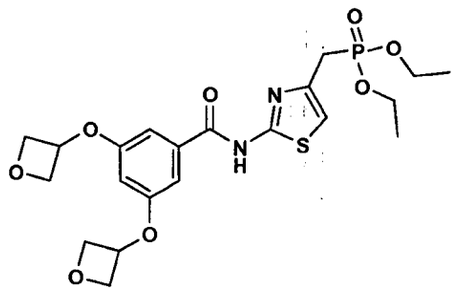
by preparative HPLC (Phenomenex AXIA 5μm C18 30 x 100 mm column; detection at 220 nm; flow rate = 40 mL/min; continuous gradient from 30% A to 100% B over 10 min + 1 min hold time at 100% B, where A = 90:10:0.1 H_2O:MeOH:TFA and B = 90:10:0.1 MeOH:H_2O:TFA) to give the title compound (20 mg, 29% yield) as a yellow oil. $[M + H]^+ = 627.3$; ^1H NMR (400 MHz, $CDCl_3$) δ 1.21 - 1.34 (m, 6 H), 3.06 (s, 3 H), 3.23 - 3.34 (m, 2 H), 3.38 (s, 3 H), 3.44 - 3.51 (m, 1 H), 3.51 - 3.59 (m, 1 H), 3.77 (s, 2 H), 4.03 - 4.15 (m, 4 H), 4.46 - 4.58 (m, 1 H), 6.58 (t, *J*=2.20 Hz, 1 H), 6.64 (s, 1 H), 6.79 (s, 1 H), 6.85 (d, *J*=3.52 Hz, 1 H), 7.11 (d, *J*=8.79 Hz, 2 H), 7.88 (d, 2 H).

EXAMPLE 79

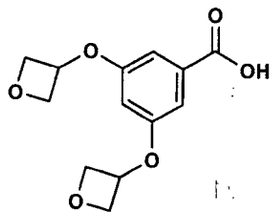


[00386] A solution of 2,3-dihydrobenzo[b][1,4]dioxine-6-carboxylic acid (20 mg, 0.11 mmol), Example 13 Part E compound (20 mg, 0.083 mmol), HOAt (20 mg, 0.147 mmol), EDCI (40 mg, 0.21 mmol), and DIPEA (40mg, 0.31 mmol) in DMF (1 mL) was stirred at 25°C for 18 h. The reaction mixture was concentrated *in vacuo*, and the residue was purified by preparative HPLC (Phenomenex AXIA 5u C18 30 x 100 mm column; detection at 220 nm; flow rate = 40 mL/min; continuous gradient from 30% A to 100% B over 10 min + 1 min hold time at 100% B, where A = 90:10:0.1 H_2O:MeOH:TFA and B = 90:10:0.1 MeOH:H_2O:TFA) to give the title compound (8.2 mg, 24 % yield) as a white solid. $[M + H]^+ = 413.3$; ^1H NMR (400 MHz, $CDCl_3$) δ 1.29 (t, J=7.03 Hz, 6 H), 3.27 - 3.36 (d, J=21.09 Hz, 2 H), 4.06 - 4.16 (m, 4 H), 4.28 - 4.37 (m, 4 H), 6.94 (d, J=3.52 Hz, 1 H), 6.99 (d, J=8.35 Hz, 1 H), 7.64 - 7.71 (m, 2 H).

EXAMPLE 80

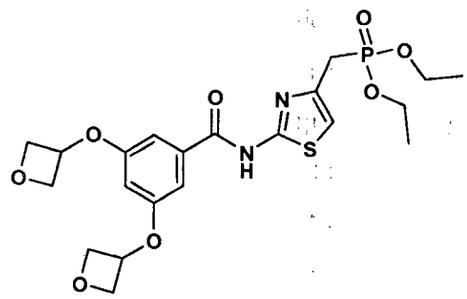


A.



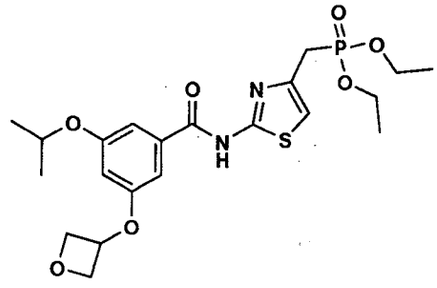
[00387] A mixture of methyl 3,5-dihydroxybenzoate (200 mg, 1.189 mmol), Example 71 Part E compound (600 mg, 2.63 mmol), and K_2CO_3 (2 g, 14.47 mmol) in DMF (10 mL) was stirred in a sealed tube at 115°C for 18 h, then was cooled to RT. Solids were removed by filtration and were washed with DMF. The combined filtrates were concentrated *in vacuo*. The residue was neutralized with TFA and was purified by preparative HPLC (Phenomenex AXIA 5u C18 30 x 100 mm column; detection at 220 nm; flow rate = 40 mL/min; continuous gradient from 30% A to 100% B over 10 min + 1 min hold time at 100% B, where A = 90:10:0.1 H_2O:MeOH:TFA and B = 90:10:0.1 MeOH:H_2O:TFA) to give Part A compound (60 mg, 19.0 %) as a white solid. $[M + H]^+ = 267.2$; ^1H NMR (400 MHz, CD_3OD) δ 4.68 (dd, J=7.15, 4.95 Hz, 4 H), 5.02 (t, J=6.60 Hz, 4 H), 5.26 - 5.35 (m, 2 H), 6.46 (t, J=2.20 Hz, 1 H), 6.98 (d, J=2.20 Hz, 2 H).

B.

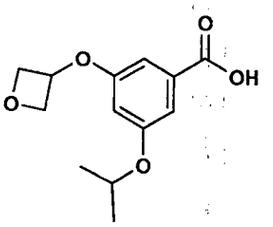


[00388] A mixture of Part A compound (21 mg, 0.079 mmol), Example 13 Part E compound (19.74 mg, 0.079 mmol), HOAt (20 mg, 0.145 mmol), EDCI (20 mg, 0.500 mmol), and DIPEA (0.2 mL, 1.148 mmol) in DMF (0.5 mL) was stirred at 25°C for 18 h, then was concentrated *in vacuo*. The residue was purified by preparative HPLC (Phenomenex AXIA 5u C18 30 x 100 mm column; detection at 220 nm; flow rate = 40 mL/min; continuous gradient from 30% A to 100% B over 10 min + 1 min hold time at 100% B, where A = 90:10:0.1 H_2O:MeOH:TFA and B = 90:10:0.1 MeOH:H_2O:TFA) to give the title compound (25 mg, 63.6 % yield) as a white solid. $[M + H]^+$ = 499.3; ^1H NMR (400 MHz, $CDCl_3$) (7.09 (2 H, d), 7.03 (1 H, d, J=3.30 Hz), 6.54 (1 H, t, J=2.20 Hz), 5.31 - 5.39 (2 H, m), 5.04 (4 H, t, J=6.60 Hz), 4.74 (4 H, dd, J=7.70, 4.95 Hz), 4.10 - 4.19 (4 H, m), 3.36 (1 H, s), 3.31 (1 H, s), 1.32 (6 H, t, J=6.87 Hz).

EXAMPLE 81

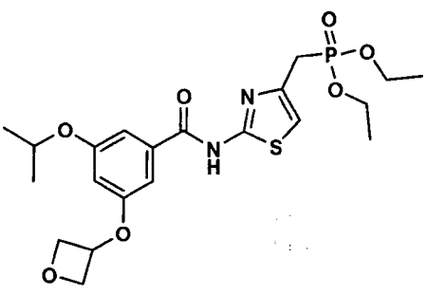


A.



[00389] A mixture of methyl 3-hydroxy-5-isopropoxybenzoate (100 mg, 0.476 mmol), Example 71 Part E compound (180 mg, 0.789 mmol), and K_2CO_3 (1 g, 7.24 mmol) in DMF (5 mL) was stirred in a sealed tube at 115°C for 18 h, then was cooled to RT. Solids were filtered off and washed with DMF. The combined filtrates were concentrated *in vacuo*. The residue was neutralized with TFA and purified by preparative HPLC (Phenomenex AXIA 5µm C18 30 x 100 mm column; detection at 220 nm; flow rate = 40 mL/min; continuous gradient from 30% A to 100% B over 10 min + 1 min hold time at 100% B, where A = 90:10:0.1 H_2O:MeOH:TFA and B = 90:10:0.1 MeOH:H_2O:TFA) to give Part A compound (100 mg, 83 % yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35 (d, J=6.05 Hz, 6 H), 4.59 (dt, J=12.09, 6.05 Hz, 1 H), 4.77 (dd, J=7.42, 5.22 Hz, 2 H), 5.01 (t, J=6.60 Hz, 2 H), 5.19 - 5.27 (m, 1 H), 6.52 (t, J=2.47 Hz, 1 H), 6.94 (s, 1 H), 7.27 (s, 1 H).

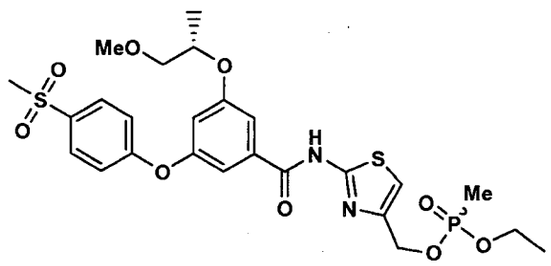
B.



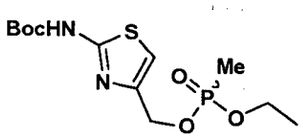
[00390] A mixture of Part A compound (21 mg, 0.083 mmol), Example 13 Part E compound (20.83 mg, 0.083 mmol), HOAt (20 mg, 0.145 mmol), EDCI (20 mg, 0.500 mmol), and DIPEA (0.2 mL, 1.148 mmol) in DMF (0.5 mL) was stirred at 25°C for 18 h, then was concentrated *in vacuo*. The residue was neutralized with TFA and was purified by preparative HPLC (Phenomenex AXIA 5µm C18 30 x 100 mm column; detection at 220 nm; flow rate = 40 mL/min; continuous gradient from

30% A to 100% B over 10 min + 1 min hold time at 100% B, where A = 90:10:0.1 H_2O:MeOH:TFA and B = 90:10:0.1 MeOH:H_2O:TFA) to give the title compound (28 mg, 0.058 mmol, 69.4 % yield) as a clear wax. $[M + H]^+ = 485.3$; ^1H NMR (400 MHz, $CDCl_3$) δ 7.31 (1 H, t, J=1.52 Hz), 6.96 - 7.01 (2 H, m), 6.56 (1 H, t, J=2.27 Hz), 5.28 - 5.35 (1 H, m, J=5.53, 5.53, 5.49, 5.43 Hz), 5.03 (2 H, t, J=6.95 Hz), 4.64 - 4.78 (3 H, m), 4.13 (4 H, dd, J=8.21, 7.20 Hz), 3.36 (1 H, s), 3.30 (1 H, s), 1.35 (6 H, d, J=6.06 Hz), 1.30 (6 H, t, J=7.07 Hz).

EXAMPLE 82

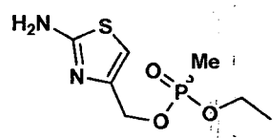


A.



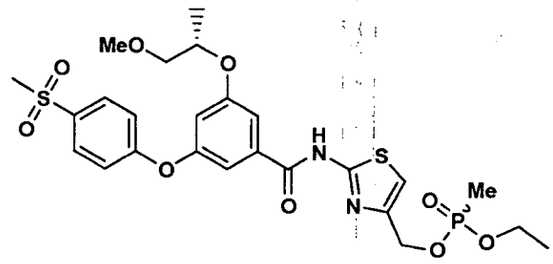
[00391] To a solution of tert-butyl 4-(chloromethyl)thiazol-2-ylcarbamate (249 mg, 1.00 mmol) and $CH_3P(OEt)_2$ (124.2 mg, 1.00 mmol) in MeCN (4.0 mL) under Ar at RT was added 18-crown-6 (52.9 mg, 0.2 mmol), K_2CO_3 (138.2 mg, 1.00 mmol), and $(n\text{-}Bu)_4NI$ (74.0 mg, 0.20 mmol). The reaction mixture was heated at 55°C for 2 h, then cooled to RT and quenched with saturated aqueous $NaHCO_3$. The mixture was extracted with EtOAc (2x). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residual oil was chromatographed (SiO_2; continuous gradient from 0% EtOAc/Hexane to 100% EtOAc/Hexane) to provide Part A compound (171 mg, 51% material balance, 90% purity by HPLC) as a colorless oil.

B.



[00392] To a RT solution of Example 82 Part A compound (171 mg, ~0.51 mmol) in CH_2Cl_2 (1.5 mL) [Note: the flask was fitted with a $CaCl_2$-filled drying tube to protect from atmospheric moisture] was added TFA (0.5 mL). The reaction was stirred at RT for 14 h, then was concentrated *in vacuo* and then stripped from CH_2Cl_2. The oily residue was used without further purification or characterization for Part C.

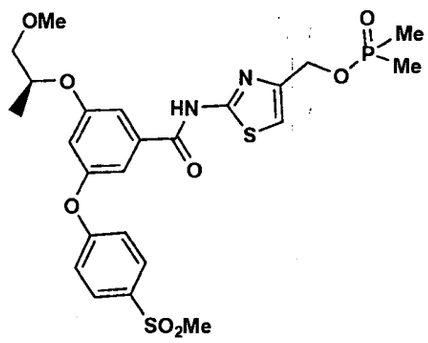
C.



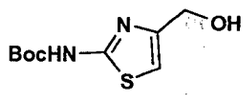
[00393] A RT solution of Example 26 Part C acid (193.4 mg, 0.51 mmol) in CH_2Cl_2 (2.0 mL) [Note: the flask was fitted with a $CaCl_2$-filled drying tube to protect from atmospheric moisture] was treated with oxalyl chloride (0.305 mL of a 2 M solution in CH_2Cl_2, 0.61 mmol) and DMF (0.020 mL). The reaction mixture was stirred at RT for 2 h, then was concentrated *in vacuo*, and re-dissolved in CH_2Cl_2 (2 mL). To this RT solution under Ar was added a solution of Part B compound in CH_2Cl_2 (2 mL), followed by Et_3N (0.213 mL, 1.53 mmol). After 15 h at RT, the reaction mixture was diluted with CH_2Cl_2 and washed with sat. aqueous $NaHCO_3$. The organic extract was dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by preparative HPLC (Phenomenex Luna 5u C18 30 x 250 mm column; detection at 220 nm; flow rate = 30 mL/min; continuous gradient from 20% B to 100% B over 20 min + 5 min hold time at 100% B, where A = 90:10:0.1 H_2O: CH_3CN:TFA and B = 10:90:0.1 H_2O:CH_3CN:TFA) to provide the title compound (33 mg, 11%) as a colorless thick oil. $[M + H]^+$ = 599.2; ^1H NMR (400 MHz, $CDCl_3$): δ 11.23 (br s, 1H), 7.92 (d, *J*=8.8 Hz, 2H), 7.57 (t, *J*=1.6 Hz, 1H), 7.47 (t, *J*=1.6 Hz, 1H), 7.13 (d, *J*=8.8 Hz, 2H), 6.95 (s, 1H), 6.87 (t, *J*=2.2 Hz, 1H), 5.22 (m, 2H), 4.68 (m, 1H), 4.05 (m, 2H), 3.56 (ddd, *J*=6.6, 10.5, 30.3 Hz, 2H), 3.39 (s, 1H), 3.09 (s,

1H), 1.51 (dd, *J*=13.7, 17.6 Hz, 3H), 1.34 (d, *J*=6.6 Hz, 3H), 1.27 (dt, *J*=2.2, 7.2 Hz, 3H).

EXAMPLE 83

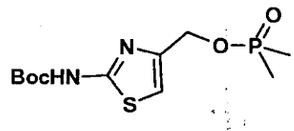


A.



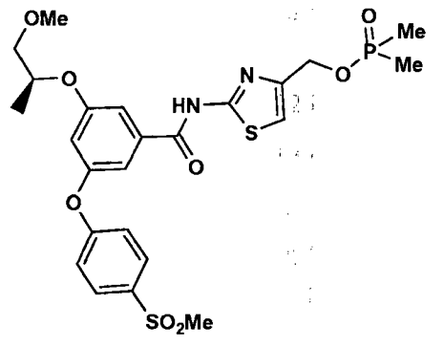
[00394] To a stirred solution of ethyl 2-(tert-butoxycarbonylamino) thiazole-4-carboxylate (2.24 g, 8.23 mmol) in CH_2Cl_2 (25 mL) under Ar at -78°C was added a solution of DiBALH (25.5 mL, 1.0 M in CH_2Cl_2, 25.5 mmol) at such a rate as to keep the temperature ≤-65°C. The reaction was stirred for 20 min at -65°C, then was allowed to warm to -30°C. After 30 min, the reaction mixture was quenched with 1 M sodium potassium tartrate solution (30 mL), warmed to RT and stirred for 2 h at RT. The mixture was filtered through Celite®, which was washed with CH_2Cl_2. The combined filtrates were dried (Na_2SO_4), and concentrated *in vacuo*. The resulting oil was chromatographed (SiO_2; continuous gradient from 0% EtOAc/Hexane to 100% EtOAc/Hexane) to provide Part A compound (1.66 g, 88% yield) as an amorphous white solid.

B.



[00395] To a 0°C solution of Part A compound (310 mg, 1.35 mmol) in CH_2Cl_2 (5 mL) under Ar was added dimethylphosphinic chloride (182 mg, 1.62 mmol), and then Et_3N (0.244 mL, 1.75 mmol) over 2 min. The reaction was allowed to warm to RT and stirred at RT for 14 h, then was diluted with EtOAc. The mixture was washed with 1% aqueous HCl and brine. The organic phase was dried ($MgSO_4$) and concentrated *in vacuo* to give Part B compound as a colorless oil (413 mg, 100% crude). This material was used in the next step without further purification.

C.

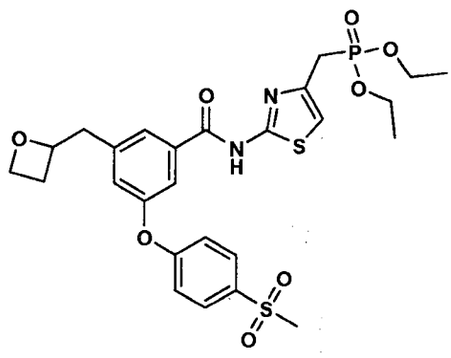


[00396] **C1:** To a stirred solution of Part B compound (410 mg, 1.34 mmol) in CH_2Cl_2 (3 mL) at RT [Note: the flask was fitted with a $CaCl_2$-filled drying tube to protect from atmospheric moisture] was added TFA (1 mL). The reaction was stirred for 14 h at RT, and the reaction mixture was concentrated *in vacuo* and re-dissolved in MeOH (5 mL). The solution was passed through 2 StratroSpheres™ PL-HCO_3 MP SPE cartridges (0.9 meq capacity), and the eluant was evaporated *in vacuo* to provide Part C1 compound. The resulting colorless oil (225 mg) was re-dissolved in CH_2Cl_2 (2 mL). One half (by weight) of this solution was used without further characterization for Part C2.

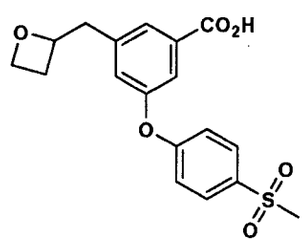
[00397] **C2:** To a stirred slurry of Example 26 Part C compound (152 mg, 0.40 mmol) and HOAt (54.5 mg, 0.40 mmol) in CH_2Cl_2 (2.4 mL) at RT under Ar was added EDC (76.3 mg, 0.40 mmol). A clear solution soon formed. After 30 min, the

solution of Part C1 compound in CH_2Cl_2 from C1 was added, followed by iPr_2NEt (0.028 mL, 0.20 mmol) and DMAP (5 mg, 0.04 mmol). The reaction was stirred for 16 h at RT, then was quenched with sat. aqueous NH_4Cl and extracted twice with EtOAc. The combined organic extracts were dried (Na_2SO_4) and evaporated *in vacuo* to give an orange oil. The residue was purified by preparative HPLC (Phenomenex AXIA Luna 5u 30 x 75 mm column; detection at 220 nm; flow rate = 40 mL/min; continuous gradient from 0% B to 100% B over 10 min + 10 min hold time at 60% B, where A = 90:10:0.1 H_2O: CH_3CN:TFA and B = 10:90:0.1 H_2O:CH_3CN:TFA) to provide the title compound (28.9 mg, 13% yield) as a waxy white solid. $[M + H]^+$ = 569.0; ^1H NMR(400 MHz, $CDCl_3$) δ 11.75 (br s, 1H), 7.92 (d, *J*=8.8 Hz, 2H), 7.63 (t, *J*=2.2 Hz, 1H), 7.49 (t, *J*=1.9 Hz, 1H), 7.14 (d, *J*=8.8 Hz, 2H), 6.94 (s, 1H), 6.87 (t, *J*= 2.2 Hz, 1H), 5.20 (d, *J*=7.7 Hz, 2H), 4.70 (m, 1H), 3.55 (ddd, *J*=6.0, 9.9, 30.2 Hz, 2H), 3.40 (s, 1H), 3.08 (s, 1H), 1.53 (dd, *J*=2.8, 14.3 Hz, 6H), 1.33 (d, *J*=6.6 Hz, 3H).

EXAMPLE 84

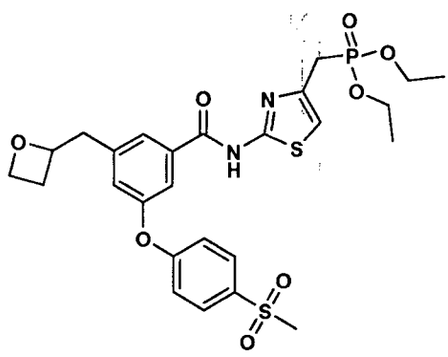


A.



[00398] To a 0°C solution of Example 26 Part A compound (100 mg, 0.310 mmol), Ph_3P (150 mg, 0.572 mmol), and oxetan-2-ylmethanol (40 mg, 0.454 mmol) in THF (5 mL) was added DIAD (0.2 mL, 1.029 mmol). The reaction was stirred at RT for 18h, and volatiles were removed *in vacuo*. The residue was chromatographed (EtOAc/Hexane, 1:1) to give the crude methyl ester. To a solution of this material in MeOH (1 mL) was added 1N aqueous NaOH (1 mL). The reaction was stirred at RT for 2 h and then acidified with TFA and concentrated *in vacuo*. The residue was purified by preparative HPLC (Phenomenex AXIA 5u C18 30 x 100 mm column; detection at 220 nm; flow rate = 40 mL/min; continuous gradient from 30% A to 100% B over 10 min + 1 min hold time at 100% B, where A = 90:10:0.1 H_2O:MeOH:TFA and B = 90:10:0.1 MeOH:H_2O:TFA) to give Part A compound (40 mg, 34.1 % yield) as a white solid. $[M + H]^+$ = 377.2; ^1H NMR (400 MHz, $CDCl_3$) δ 2.66 - 2.88 (m, 2 H), 3.08 (s, 3 H), 4.20 (d, J=3.85 Hz, 2 H), 4.66 - 4.81 (m, 2 H), 5.16 - 5.25 (m, 1 H), 6.92 (t, J=2.47 Hz, 1 H), 7.11 (d, J=8.79 Hz, 2 H), 7.36 (d, J=2.20 Hz, 1 H), 7.52 (dd, J=2.20, 1.10 Hz, 1 H), 7.92 (d, J=8.79 Hz, 2 H).

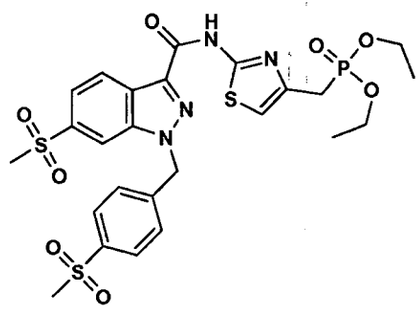
B.



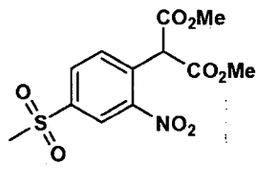
[00399] A mixture of Part A compound (15 mg, 0.040 mmol), Example 13 Part E compound (20 mg, 0.080 mmol), HOAt (20 mg, 0.145 mmol), EDCI (40 mg, 1.000 mmol) and DIPEA (0.2 mL, 1.148 mmol) in DMF (0.5 mL) was stirred at 25°C for 18 h. The reaction mixture was concentrated *in vacuo*, and the crude residue was purified by preparative HPLC (Phenomenex AXIA 5u C18 30 x 100 mm column; detection at 220 nm; flow rate = 40 mL/min; continuous gradient from 30% A to 100% B over 10 min + 1 min hold time at 100% B, where A = 90:10:0.1 H_2O:MeOH:TFA and B = 90:10:0.1 MeOH:H_2O:TFA) to provide the title compound

(9.8 mg, 0.016 mmol, 39.7 % yield) as a white solid. $[M + H]^+ = 611.3$; ^1H NMR (400 MHz, $CDCl_3$) δ 7.93 (2 H, d, *J*=8.79 Hz), 7.59 (1 H, s), 7.39 (1 H, s), 7.15 (2 H, d, *J*=8.79 Hz), 6.94 - 6.98 (2 H, m), 5.12 - 5.20 (1 H, m), 4.62 - 4.78 (2 H, m), 4.22 - 4.32 (2 H, m), 4.06 - 4.17 (4 H, m, *J*=7.35, 7.35, 7.28, 7.15 Hz), 3.32 (2 H, d, *J*=20.89 Hz), 3.08 (3 H, s), 2.64 - 2.86 (2 H, m), 1.30 (6 H, t, *J*=6.87 Hz).

EXAMPLE 85

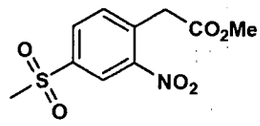


A.



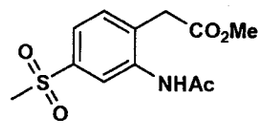
[00400] To a solution of KOtBu (17.1 mL, 17.1 mmol) in t-BuOH (10 mL) was added dropwise dimethyl malonate (2.0 mL, 17.1 mmol). To the resulting mixture was added a warm solution of 1-chloro-4-(methylsulfonyl) 2-nitrobenzene (2.0 g, 8.6 mmol) in t-BuOH (10 mL). The reaction mixture was heated at reflux for 15 h, then was cooled to RT and diluted with EtOAc (50 mL), washed with water and brine (30 mL each), dried ($MgSO_4$) and concentrated *in vacuo* to provide Part A compound (2.8 g, 100%).

B.



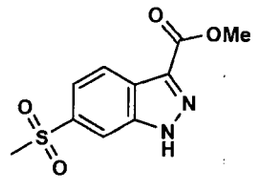
[00401] To a solution of Part A compound (2.8 g, 8.6 mmol) in DMSO (10 mL) was added NaCl (1.0 g, 17.1 mmol) and water (2 mL, 111 mmol). The mixture was heated at 120°C for 5 h, then was cooled to RT and diluted with EtOAc (50 mL). The organic layer was washed with water and brine (35 mL each), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed (SiO_2; 30 min gradient from 100% to 0% hexane/EtOAc) to provide Part B compound (863 mg, 37% yield over 2 steps).

C.



[00402] To a solution of Part B compound (830 mg, 3.0 mmol) and Ac_2O (2.0 mL, 21.6 mmol) in toluene (10 mL) was slowly added 10% Pd/C (200 mg, 1.7 mmol). The reaction was stirred under an atmosphere of H_2 (g) (1 atm) at RT for 4 h. The catalyst was filtered off and washed with toluene (2x). The combined filtrates were concentrated *in vacuo* to provide crude Part C compound (398 mg, 46%).

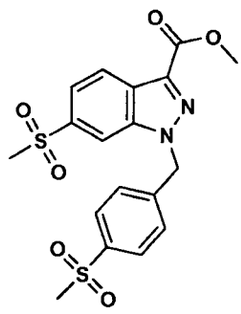
D.



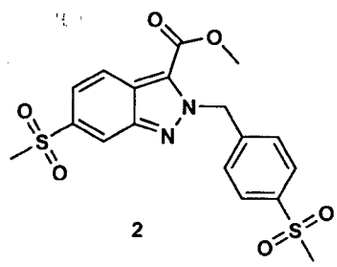
[00403] To a 90-95°C solution of Part C compound (398 mg, 1.4mmol) in AcOH (6 mL) was added dropwise t-butyl nitrite (0.18 mL, 1.5 mmol). The reaction was stirred at 95°C for 30 min. The reaction was cooled to RT and was diluted with EtOAc (30 mL). The organic layer was washed with water (15 mL) and brine (15 mL), dried ($MgSO_4$), and concentrated *in vacuo* until a solid precipitated. This solid

precipitate was collected by filtration and washed with toluene to give Part D compound (280 mg, 79% yield), which was used in the next step without further purification.

E.



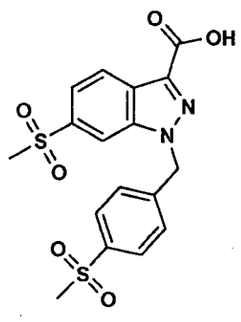
1



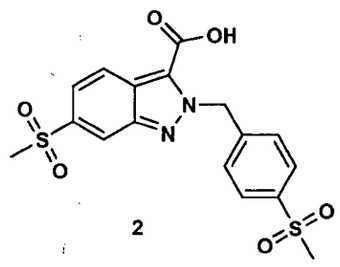
2

[00404] To a solution of Part D compound (30 mg, 0.12 mmol) in CH_3CN (1.5 mL) was added 1-(chloromethyl)-4-(methylsulfonyl) benzene (72.4 mg, 0.35 mmol), K_2CO_3 (48.9 mg, 0.35 mmol), and $(n\text{-}Bu)_4NI$ (3.5 mg, 9.4 μmol). The reaction was stirred at 80°C for 3 h, then cooled to RT. Solids were filtered off and washed with acetone. The combined filtrates were concentrated *in vacuo* to afford a mixture of the Part E compounds.

F.



1

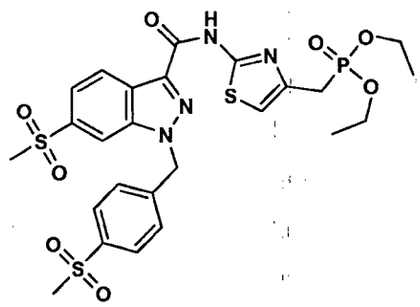


2

[00405] To a solution of Part E compounds (0.12 mmol theoretical yield) in THF (1 mL) was added 1N aqueous NaOH (0.4 mL, 0.40 mmol). The reaction was stirred at RT for 15 h., then was diluted with EtOAc (4 mL) and acidified with 1N aqueous HCl (0.45 mL). The organic layer was washed with brine, dried ($MgSO_4$) and

concentrated *in vacuo*. The crude mixture was purified by preparative HPLC (Phenomenex Luna AXIA 30x100 mm column; detection at 220 nm; flow rate = 25 mL/min; continuous gradient from 60% A to 100% B over 10 min, where A = 90:10:0.1 H_2O:MeOH:TFA and B = 90:10:0.1 MeOH:H_2O:TFA) to provide Part F1 compound (15.2 mg, 32% yield over 2 steps) and Part F2 compound (9.0 mg, 19% yield over 2 steps).

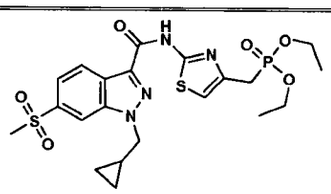
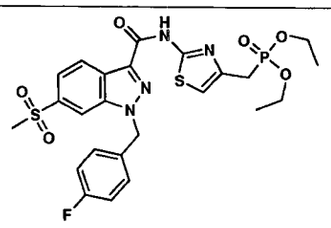
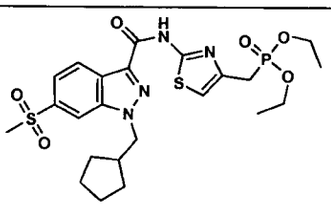
G.

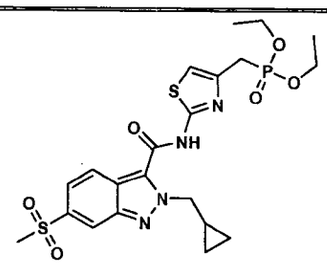
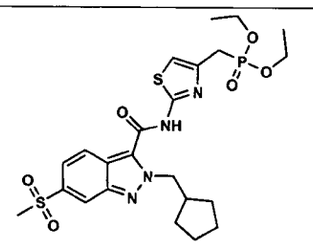
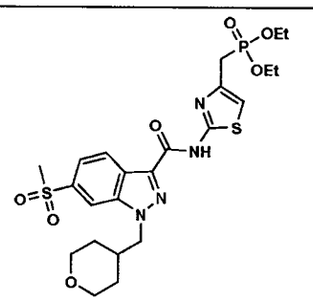
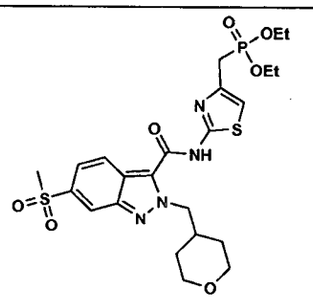


[00406] To a solution of Part F1 compound (7 mg, 0.02 mmol) in CH_2Cl_2 (0.8 mL) was added oxalyl chloride (0.03 mL of a 2M solution in DCM, 0.05 mmol) and DMF (1.3 µL, 0.02 mmol). The reaction was stirred at RT for 1 h, then was concentrated *in vacuo*. The residue was taken up in THF (0.4 mL) and added to a solution of Example 13 Part E compound (17.2 mg, 0.07 mmol) and $NaHCO_3$ (7.2 mg, 0.09 mmol) in THF/H_2O (1:1, 0.8 mL). The reaction was stirred at RT for 2 h, then was diluted with EtOAc (4 mL) and water (1 mL). The organic layer was concentrated *in vacuo*. The residue was purified by preparative HPLC (Phenomenex Luna AXIA 30x100 mm column; detection at 220 nm; flow rate = 40 mL/min; continuous gradient from 70% A to 100% B over 10 min, where A = 90:10:0.1 H_2O:MeOH:TFA and B = 90:10:0.1 MeOH:H_2O:TFA) to provide the title compound (0.63 mg, 5.7% yield) as a white solid. $[M + H]^+ = 641.2$; ^1H NMR (400 MHz, $CDCl_3$) δ 8.63 (1 H, d, *J*=8.35 Hz), 8.21 (1 H, s), 7.96 (2 H, d, *J*=8.35 Hz), 7.90 (1 H, d, *J*=8.35 Hz), 7.63 (2 H, d, *J*=8.35 Hz), 6.94 - 7.04 (1 H, m), 5.81 (2 H, s), 4.05 - 4.21 (4 H, m), 3.35 (2 H, d, *J*=21.09 Hz), 3.16 (3 H, s), 3.05 (3 H, s), 1.33 (6 H, t, *J*=7.03 Hz).

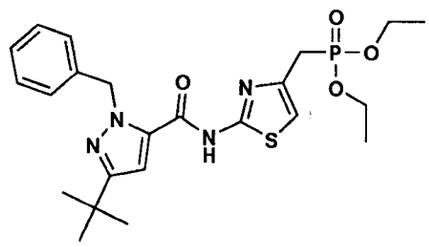
EXAMPLES 86 TO 92

[00407] The following Examples were synthesized from Example 85 Part D compound by employing the general synthetic route described for the preparation of Example 85 compound from Example 85 Part D compound.

Example #	Structure	$[M + H]^+$	^1H NMR	Yield and Description
86		527.0	(400 MHz, $CDCl_3$) δ 8.62 (1 H, d, *J*=8.79 Hz), 8.24 (1 H, s), 7.86 (1 H, d, *J*=8.35 Hz), 6.94 (1 H, d, *J*=3.95 Hz), 4.41 (2 H, d, *J*=7.03 Hz), 4.04 - 4.21 (4 H, m), 3.35 (2 H, d, *J*=21.09 Hz), 3.16 (3 H, s), 1.41 - 1.52 (1 H, m), 1.32 (6 H, t, *J*=7.03 Hz), 0.66 - 0.75 (2 H, m), 0.50 - 0.58 (2 H, m)	4.0 mg (24% yield), white solid
87		581.1	(400 MHz, $CDCl_3$) δ 8.62 (1 H, d, *J*=7.91 Hz), 8.18 (1 H, s), 7.79 - 7.89 (1 H, m), 7.34 (2 H, dd, *J*=8.57, 5.05 Hz), 7.06 (2 H, t, *J*=8.57 Hz), 6.92 (1 H, d, *J*=3.52 Hz), 5.67 (2 H, s), 4.02 - 4.20 (4 H, m), 3.34 (2 H, d, *J*=21.09 Hz), 3.13 (3 H, s), 1.31 (6 H, t, *J*=7.03 Hz)	8.5 mg (37% yield), grey solid
88		555.1	(500 MHz, $CDCl_3$) δ 8.60 (1 H, d, *J*=7.70 Hz), 8.22 (1 H, s), 7.85 (1 H, d, *J*=7.15 Hz), 6.96 (1 H, d, *J*=3.85 Hz), 4.46 (2 H, d, *J*=7.15 Hz), 4.06 - 4.21 (4 H, m), 3.35 (2 H, d, *J*=20.89 Hz), 3.17 (3 H, s), 2.62 - 2.75 (1 H, m), 1.68 - 1.81 (4 H, m), 1.57 - 1.68 (2 H, m), 1.34 - 1.43 (2 H, m), 1.32 (6 H, t, *J*=7.15 Hz)	8.5 mg (40% yield), white solid

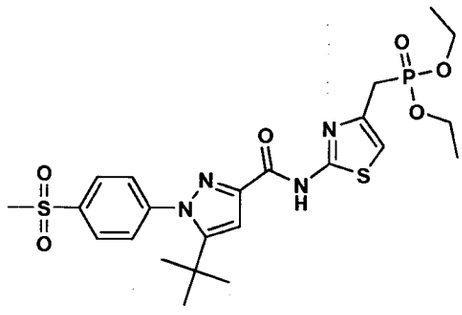
Example #	Structure	$[M + H]^+$	^1H NMR	Yield and Description
89		527.0	(500 MHz, $CDCl_3$) δ ppm 8.56 (1 H, s), 8.05 (1 H, d, *J*=8.80 Hz), 7.75 (1 H, d, *J*=9.35 Hz), 7.07 (1 H, d, *J*=3.30 Hz), 4.77 (2 H, d, *J*=7.15 Hz), 4.08 - 4.24 (4 H, m), 3.38 (2 H, d, *J*=21.44 Hz), 3.12 (3 H, s), 1.46 - 1.63 (1 H, m), 1.26 - 1.37 (6 H, m), 0.51 - 0.65 (4 H, m)	3.0 mg (21% yield), oil
90		555.1	(500 MHz, $CDCl_3$) δ 8.54 (1 H, s), 8.06 (1 H, d, *J*=8.80 Hz), 7.74 (1 H, d, *J*=9.35 Hz), 7.05 (1 H, d, *J*=3.30 Hz), 4.87 (2 H, d, *J*=7.70 Hz), 4.09 - 4.21 (4 H, m), 3.36 (2 H, d, *J*=21.44 Hz), 3.12 (3 H, s), 2.56 - 2.71 (1 H, m), 1.64 - 1.76 (4 H, m), 1.51 - 1.63 (2 H, m), 1.35 - 1.43 (2 H, m), 1.32 (6 H, t, *J*=7.15 Hz)	3.5 mg (29% yield), oil
91		571.3	(500 MHz, $CDCl_3$) δ 8.57 (1 H, d, *J*=8.25 Hz), 8.22 (1 H, s), 7.88 (1 H, d, *J*=9.90 Hz), 7.04 (1 H, d, *J*=3.85 Hz), 4.43 (2 H, d, *J*=7.15 Hz), 4.12 - 4.24 (4 H, m), 4.01 (2 H, dd, *J*=11.55, 2.75 Hz), 3.43 - 3.49 (2 H, m), 3.40 (2 H, d, *J*=21.44 Hz), 3.18 (3 H, s), 2.51 - 2.68 (1 H, m), 1.43 - 1.64 (4 H, m), 1.34 (6 H, t, *J*=7.15 Hz)	10.5 mg (37% yield), grey solid
92		571.3	(500 MHz, $CDCl_3$) δ 8.55 (1 H, s), 8.04 (1 H, d, *J*=8.80 Hz), 7.76 (1 H, d, *J*=10.45 Hz), 7.12 (1 H, d, *J*=3.85 Hz), 4.81 (2 H, d, *J*=7.15 Hz), 4.13 - 4.28 (4 H, m), 3.99 - 4.08 (2 H, m), 3.33 - 3.48 (4 H, m), 3.13 (3 H, s), 2.32 - 2.53 (1 H, m), 1.48 - 1.65 (4 H, m), 1.36 (6 H, t, *J*=6.87 Hz)	4.8 mg (24 % yield), yellow oil

EXAMPLE 93

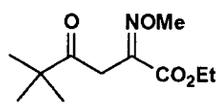


[00408] To a solution of Example 13 Part E compound (50 mg, 0.20 mmol) in DCM (1 mL) was added 1-benzyl-3-tert-butyl-1H-pyrazole-5-carbonyl chloride (71.9 mg, 0.26 mmol) and pyridine (0.02 mL, 0.26 mmol). The reaction was stirred at RT for 16 h, then was concentrated *in vacuo*. The residue was purified by preparative HPLC (Phenomenex Luna AXIA 30x100 mm column; detection at 220 nm; flow rate = 40 mL/min; continuous gradient from 50% A to 100% B over 10 min, where A = 90:10:0.1 H_2O:MeOH:TFA and B = 90:10:0.1 MeOH:H_2O:TFA) to give the title compound (64 mg, 65% yield) as an oil. $[M + H]^+$ = 491.1; ^1H NMR (400 MHz, $CDCl_3$) δ 7.31 (1 H, s), 7.17 - 7.30 (5 H, m), 6.96 (1 H, d, *J*=3.52 Hz), 5.81 (2 H, s), 4.05 - 4.19 (4 H, m), 3.31 (2 H, d, *J*=21.09 Hz), 1.36 (9 H, s), 1.29 (6 H, t, *J*=7.03 Hz).

EXAMPLE 94

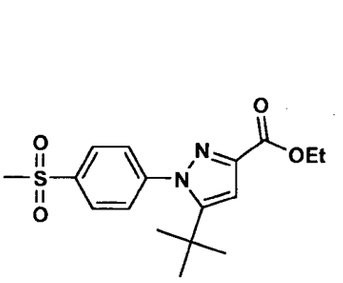


A.

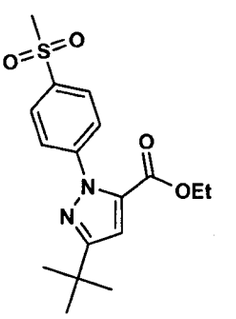


[00409] To a solution of ethyl trimethylacetopyruvate (205 mg, 1.02 mmol) in dry EtOH (1 mL) was added O-methylhydroxylamine hydrochloride (90 mg, 1.07 mmol) and 3A mol. sieves. The reaction was stirred at RT for 15 h, then was filtered and washed with EtOH. The filtrated was concentrated *in vacuo*, and the residue was partitioned between Et_2O and sat. aqueous $NaHCO_3$. The Et_2O layer was washed with water and brine, dried ($MgSO_4$) and concentrated *in vacuo* to give Part A compound (176 mg, 75%) as a red-orange oil.

B.



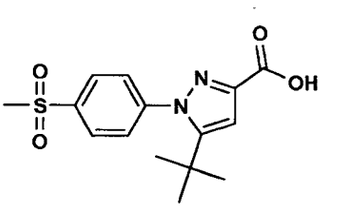
1



2

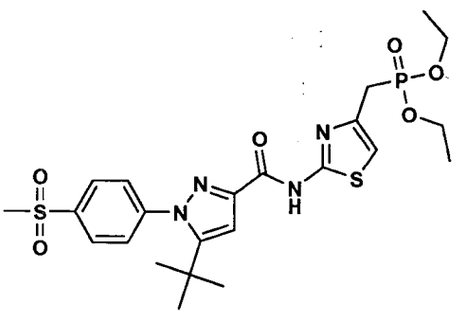
[00410] To a solution of Part A compound (176 mg, 0.77 mmol) in AcOH:EtOH (1.5 mL) was added (4-(methylsulfonyl)phenyl)hydrazine (286 mg, 1.54 mmol). The reaction was stirred at 90°C for 10 h, then was cooled to RT. The reaction mixture was concentrated *in vacuo*, and the residue was partitioned between EtOAc and 0.2 N aqueous HCl. The organic layer was washed with water and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed (SiO_2; 15 min gradient from 0% EtOAc/Hexanes to 100% EtOAc/Hexanes) to provide Part B1 compound (214 mg, 80%) and Part B2 compound (20 mg, 7%).

C.



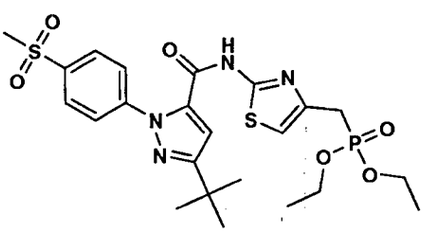
[00411] To a solution of the Part B1 compound (23 mg, 0.07 mmol) in THF (1 mL) was added 1N aqueous NaOH. The mixture was stirred at RT for 15 h, then was diluted with EtOAc (4 mL) and acidified with 1N aqueous HCl (0.5 mL). The organic layer was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to give crude Part C compound (23 mg, 109% recovery).

D.



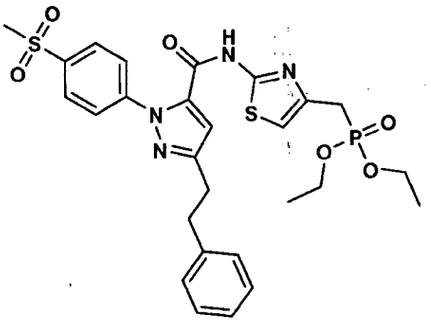
[00412] To a solution of Part C compound (21.3 mg, 0.07 mmol)in DMF (1 mL) was added Example 13 Part E compound (33.0 mg, 0.13mmol), EDCI (25.3 mg, 0.13 mmol), HOBT (20.2 mg, 0.13 mmol), and Hunig's Base (0.034 mL, 0.20 mmol). The reaction mixture was stirred at RT for 4 days and was purified directly by preparative HPLC (Phenomenex Luna AXIA 30x100 mm column; detection at 220 nm; flow rate = 40 mL/min; continuous gradient from 50% A to 100% B over 10 min, where A = 90:10:0.1 H_2O:MeOH:TFA and B = 90:10:0.1 MeOH:H_2O:TFA) to provide the title compound (14 mg, 38% yield) as a yellow oil. $[M + H]^+ = 555.1$; ^1H NMR (500 MHz, $CDCl_3$) δ 8.11 (2 H, d), 7.71 (2 H, d, J=8.25 Hz), 6.99 (1 H, s), 6.98 (1 H, d, J=3.85 Hz), 4.10 - 4.18 (4 H, m), 3.98 (1 H, s), 3.35 (2 H, d, J=21.44 Hz), 3.13 (3 H, s), 1.30 (6 H, t, J=7.15 Hz), 1.27 (9 H, s).

EXAMPLE 95

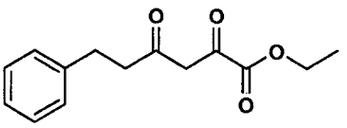


[00413] The title compound (10 mg, 32% yield, brown solid) was synthesized from Example 94 Part B2 compound using the procedure employed in Example 94. $[M + H]^+ = 555.1$; ^1H NMR (500 MHz, $CDCl_3$) δ 8.04 (2 H, d, J=8.80 Hz), 7.68 (2 H, d, J=8.80 Hz), 7.49 (1 H, s), 7.01 (1 H, d, J=3.85 Hz), 4.15 - 4.22 (4 H, m), 3.37 (2 H, d, J=21.44 Hz), 3.11 (3 H, s), 1.40 (9 H, s), 1.34 (6 H, t, J=6.87 Hz).

EXAMPLE 96

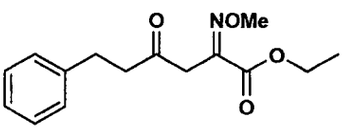


A.



[00414] To a 0°C solution of benzylacetone (0.54 mL, 3.6 mmol) and diethyl oxalate (0.53 mL, 3.9 mmol) in dry EtOH (6 mL) was added NaOEt (0.31 mL, 3.9 mmol). The reaction was slowly warmed to RT and stirred for 15 h at RT, then was diluted with EtOAc (20 mL) and washed with brine. The organic layer was dried ($MgSO_4$) and concentrated *in vacuo* to provide Part A compound (0.65 g, 73% yield) as a yellow oil.

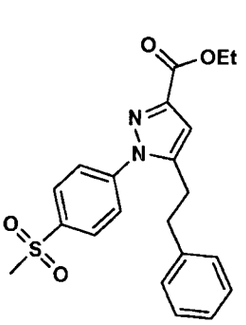
B.



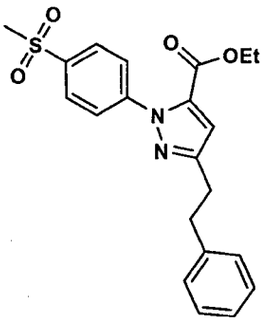
[00415] To a solution of the Part A compound (0.65 g, 2.6 mmol) in dry EtOH (5 mL) was added O-methylhydroxylamine hydrochloride (0.31 g, 3.7 mmol) and 3A

mol.sieves (2 g). The reaction was stirred at RT for 15 h, then was filtered and washed with EtOH. The combined filtrates were concentrated *in vacuo*, and the residue was partitioned between Et_2O and sat. aqueous $NaHCO_3$. The Et_2O layer was washed with water and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed (SiO_2; 16 min gradient from 0% EtOAc/Hexanes to 100% EtOAc/Hexanes) to provide Part B compound (117 mg, 16%).

C.



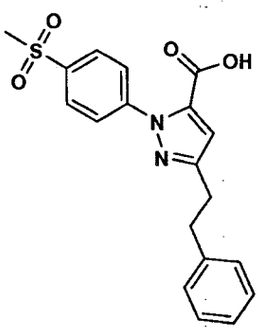
1



2

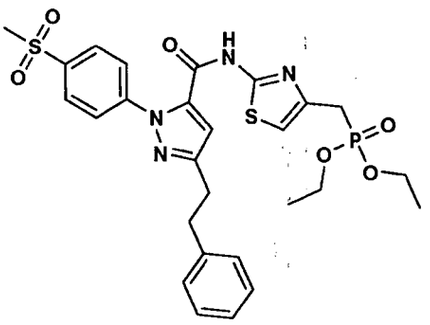
[00416] To a solution of Part B compound (117 mg, 0.42 mmol) in AcOH:EtOH (1.5 mL) was added (4-(methylsulfonyl)phenyl)hydrazine (157 mg, 0.84 mmol). The reaction was stirred at 100°C for 10 h, then was cooled to RT and concentrated *in vacuo*. The residue was partitioned between EtOAc and 0.2N aqueous HCl. The organic layer was washed with water and brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was chromatographed (SiO_2; 22 min continuous gradient from 0% EtOAc/Hexanes to 100% EtOAc/Hexanes) to give Part C1 compound (20 mg, 12%) and Part C2 compound (95 mg, 57%).

D.



[00417] To a solution of Part C2 compound (28 mg, 0.07 mmol) in THF (1 mL) was added aqueous NaOH (0.3 mL of a 1 M solution, 0.30 mmol). The reaction was stirred at RT for 15 h, then was diluted with EtOAc (4 mL) and acidified with 1N aqueous HCl (0.5 mL). The organic layer was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to give Part D compound (29 mg, 111% crude).

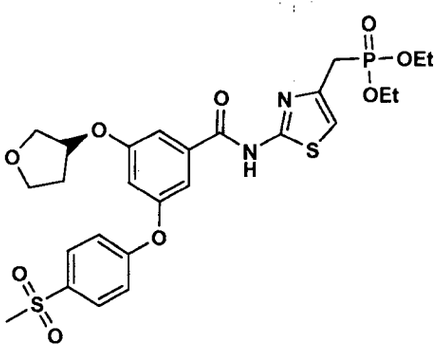
E.



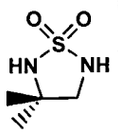
[00418] To a solution of the Part D compound (25.9 mg, 0.07 mmol) in DMF (1 mL) was added Example 13 Part E compound (35.0 mg, 0.14 mmol), EDCI (26.8 mg, 0.14 mmol), HOBT (21.4 mg, 0.14 mmol) and Hunig's Base (0.037 mL, 0.21 mmol). The reaction was stirred at RT for 2 days, then was concentrated *in vacuo*. The residue was purified directly by preparative HPLC (Phenomenex Luna AXIA 30x100 mm column; detection at 220 nm; flow rate = 40 mL/min; continuous gradient from 50% A to 100% B over 10 min, where A = 90:10:0.1 H_2O:MeOH:TFA and B = 90:10:0.1 MeOH:H_2O:TFA) to provide the title compound (7 mg, 17% yield) as a grey solid. $[M + H]^+$ = 603.0; ^1H NMR (500 MHz, $CDCl_3$) δ 8.04 (2 H, d, *J*=8.80 Hz), 7.67 (2 H, d, *J*=8.25 Hz), 7.18 - 7.36 (5 H, m), 7.14 (1 H, br. s.), 6.90 (1 H, s),

4.01 - 4.17 (4 H, m), 3.32 (2 H, d, *J*=21.44 Hz), 3.00 - 3.15 (7 H, m), 1.22 - 1.35 (6 H, m).

EXAMPLE 97

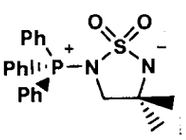


A.



[00419] To a refluxing solution of sulfamide (6.09 mL; 102.0 mmol) in anhydrous pyridine (109.0 mL) was added dropwise 2-methylpropane-1,2-diamine (10.7 mL; 102.0 mmol) over 30 min via syringe pump. The reaction mixture was refluxed for 16 h, then was cooled to RT and concentrated *in vacuo*. The residue was triturated with hexanes until the filtrate was nearly colorless. The resulting solid was dried *in vacuo* to give Part A compound (14.89 g, 97%) as a beige solid.

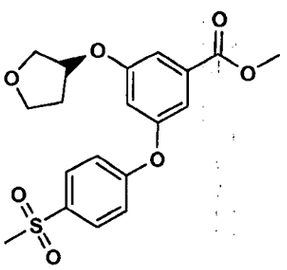
B.



[00420] To a stirred solution of Ph_3P (26.0 g; 99.0 mmol) and Part A compound (14.89 g; 99.0 mmol) in anhydrous THF (300 mL) was added DIAD (19.3 mL; 99.0 mmol) dropwise over 5 min under Ar. The reaction mixture was stirred at RT for 16 h. The resulting off-white solid was filtered off, washed with anhydrous THF and

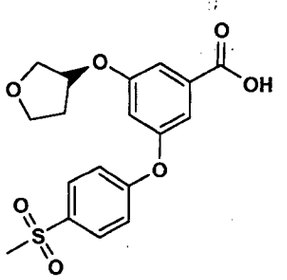
anhydrous Et_2O, then dried *in vacuo* to give Part B compound (36.68 g, 90%) as an off-white solid.

C.



[00421] To a suspension of Part B compound (1.4 g, 3.5 mmol) in DCM (6 mL) was added a solution of Example 26A compound (141 mg, 0.44 mmol) and (R)-(-)-3-hydroxytetrahydrofuran (0.08 mL, 1.0 mmol) in toluene (2 mL). The reaction was stirred at RT for 15 h, then was diluted with EtOAc, and washed with water and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was chromatographed (SiO_2; 19 min gradient from 0% EtOAc/Hexanes to 100% EtOAc/0% Hexanes) to provide Part C compound (254 mg, 148 % yield).

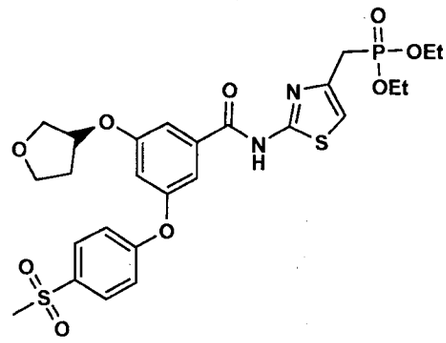
D.



[00422] To a mixture of the Part C compound (254 mg, 0.65 mmol) in THF (2 mL) was added 1N aqueous NaOH (1 mL, 1.0 mmol). The reaction was stirred at RT for 15 h, then was diluted with EtOAc (6 mL) and acidified with 1N aqueous HCl (0.5 mL). The organic layer was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by preparative HPLC (Phenomenex Luna AXIA 30x100 mm column; detection at 220 nm; flow rate = 40 mL/min; continuous gradient from 70% A to 100% B over 10 min, where A = 90:10:0.1 H_2O:MeOH:TFA

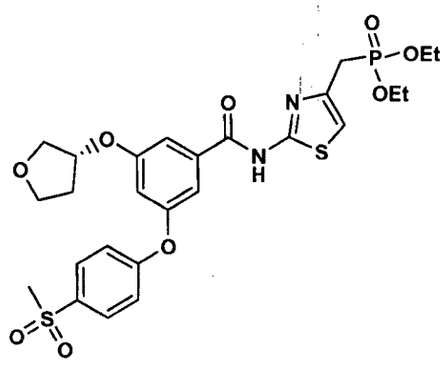
and B = 90:10:0.1 MeOH:H_2O:TFA) to give the Part D compound (90 mg, 54% yield over 2 steps) as a colorless oil.

E.



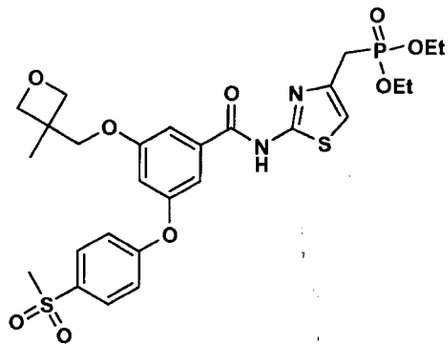
[00423] To a solution of Part D compound (43.0 mg, 0.11 mmol) in DMF (1 mL) was added Example 13 Part E compound (56.9 mg, 0.23 mmol), EDCI (43.6 mg, 0.23 mmol), HOBT (34.8 mg, 0.23 mmol), and Hunig's Base (0.059 mL, 0.34 mmol). The reaction was stirred at RT for 24 h and was purified directly by preparative HPLC (Phenomenex Luna AXIA 30x100 mm column; detection at 220 nm; flow rate = 40 mL/min; continuous gradient from 70% A to 100% B over 10 min, where A = 90:10:0.1 H_2O:MeOH:TFA and B = 90:10:0.1 MeOH:H_2O:TFA) to provide the title compound (36 mg, 52% yield) as a white solid. $[M + H]^+$ = 611.3; ^1H NMR (500 MHz, $CDCl_3$) δ 7.94 (2 H, d, *J*=8.80 Hz), 7.63 (1 H, s), 7.49 (1 H, s), 7.16 (2 H, d, *J*=8.80 Hz), 7.07 (1 H, d, *J*=3.85 Hz), 6.91 (1 H, s), 5.22 - 5.33 (1 H, m), 4.12 - 4.24 (4 H, m), 3.85 - 4.08 (4 H, m), 3.37 (2 H, d, *J*=20.89 Hz), 3.08 (3 H, s), 2.08 - 2.41 (2 H, m), 1.34 (6 H, t, *J*=7.15 Hz).

EXAMPLE 98



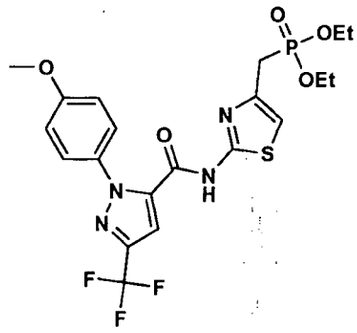
[00424] The title compound (10 mg, 16% yield, white solid) was prepared from (S)-(+)-3-hydroxytetrahydrofuran employing the same procedure as described for the synthesis of Example 97 compound. $[M + H]^+ = 611.3$; ^1H NMR (500 MHz, $CDCl_3$) δ 7.94 (2 H, d, *J*=8.80 Hz), 7.57 (1 H, s), 7.44 (1 H, s), 7.16 (2 H, d, *J*=8.80 Hz), 7.00 (1 H, d, *J*=3.30 Hz), 6.89 (1 H, s), 5.15 - 5.26 (1 H, m), 4.06 - 4.19 (4 H, m), 3.86 - 4.06 (4 H, m), 3.32 (2 H, d, *J*=20.89 Hz), 3.08 (3 H, s), 2.06 - 2.39 (2 H, m), 1.30 (6 H, t, *J*=7.15 Hz).

EXAMPLE 99



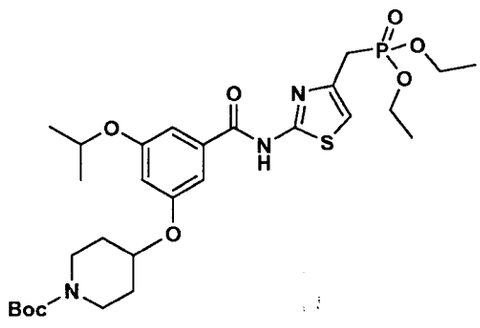
[00425] The title compound (24 mg, 42% yield, white solid) was prepared from 3-Methyl-3-Oxetane-methanol employing the same procedure as described for the synthesis of Example 97 compound. $[M + H]^+ = 625.3$; ^1H NMR (500 MHz, $CDCl_3$) δ 7.94 (2 H, d, *J*=8.80 Hz), 7.70 (1 H, s), 7.51 (1 H, s), 7.13 - 7.20 (2 H, m), 7.07 (1 H, d, *J*=3.30 Hz), 6.97 (1 H, s), 4.70 (2 H, d, *J*=6.05 Hz), 4.51 (2 H, d, *J*=6.05 Hz), 4.13 - 4.26 (6 H, m), 3.98 (1 H, s), 3.38 (2 H, d, *J*=21.44 Hz), 3.08 (3 H, s), 1.47 (3 H, s), 1.34 (6 H, t, *J*=7.15 Hz).

EXAMPLE 100

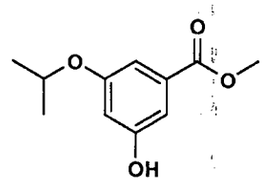


[00426] To a solution of 1-(4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxylic acid (61 mg, 0.213 mmol) [see WO 1998/57937] in DMF (1 ml), was added Example 13 Part E compound (107 mg, 0.426 mmol), EDC (82 mg, 0.426 mmol), HOBT (65.3 mg, 0.426 mmol), and DIPEA (0.111 ml, 0.639 mmol). The reaction mixture was stirred at RT for 4 days. The reaction mixture was purified directly by preparative HPLC (Phenomenex Luna AXIA 30x100 mm column; detection at 220 nm; flow rate = 40 mL/min; continuous gradient from 50% B to 100% B over 10 min, where A = 90:10:0.1 H_2O:MeOH:TFA and B = 90:10:0.1 MeOH:H_2O:TFA) to provide the title compound (13 mg, 12% yield) as a grey solid. $[M + H]^+$ = 519.0; ^1H NMR (400 MHz, $CDCl_3$) δ 7.59 (1 H, s), 7.33 - 7.46 (2 H, m), 6.91 - 7.02 (2 H, m), 6.80 (1 H, d, *J*=3.52 Hz), 3.99 - 4.15 (4 H, m), 3.86 (3 H, s), 3.51 (2 H, d, *J*=21.53 Hz), 1.26 (6 H, t, *J*=7.03 Hz).

EXAMPLE 101

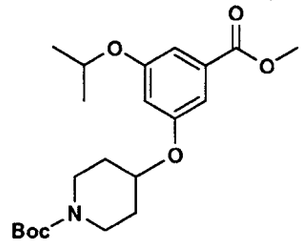


A.



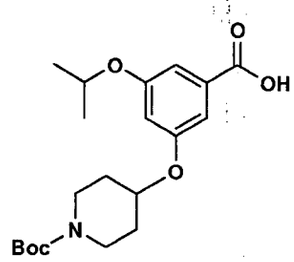
[00427] To a solution of methyl 3,5-dihydroxybenzoate (2.7 g, 16.06 mmol) in CH_3CN (35 mL) was added K_2CO_3 (2.70 g, 19.54 mmol), followed by slow addition of 2-bromopropane (1.975 g, 16.06 mmol). The reaction mixture was heated to 80°C for 3 days. The reaction mixture was diluted with water and extracted with EtOAc (3x). The combined organic layer was washed H_2O and brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2; continuous gradient 15% EtOAc/Hex to 60% EtOAc/Hexane) to give Part A compound (1.22 g, 36% yield) as yellow solid. $[M + H]^+ = 211.0$; ^1H NMR (400 MHz, $CDCl_3$) δ 1.33 (d, J=6.15 Hz, 6 H), 3.89 (s, 3 H), 4.51 - 4.62 (m, 1 H), 5.21 (s, 1 H), 6.59 (t, J=2.42 Hz, 1 H), 7.08 - 7.12 (m, 1 H), 7.13 - 7.17 (m, 1 H).

B.



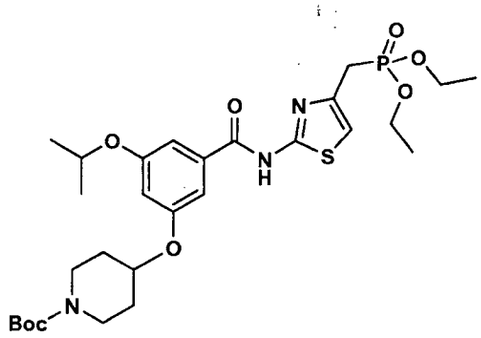
[00428] To a solution of Part A compound (300 mg, 1.427 mmol) and tert-butyl 4-hydroxypiperidine-1-carboxylate (1.15 g, 5.7 mmol) in toluene (2 mL) was added a suspension of Example 97B compound (2.34g, 5.7mmol) in DCM (2 mL). The reaction mixture was stirred at RT for 3 h, then was concentrated *in vacuo*. The residue was chromatographed (SiO_2; continuous gradient from 10% EtOAc/Hex to 60% EtOAc/Hexane) to give Part B compound (490 mg, 87%) as a light yellow solid. $[M + H]^+ = 294.0$; ^1H NMR (500 MHz, $CDCl_3$) δ 1.32 (d, *J*=6.05 Hz, 6 H), 1.45 (s, 9 H), 1.66 - 1.78 (m, 2 H), 1.85 - 1.96 (m, 2 H), 3.26 - 3.38 (m, 3 H), 3.62 - 3.72 (m, 3 H), 3.86 - 3.90 (m, 3 H), 4.44 - 4.51 (m, 1 H), 4.52 - 4.62 (m, 1 H), 6.61 (t, *J*=2.20 Hz, 1 H), 7.10 - 7.19 (m, 2 H).

C.



[00429] To a 0°C solution of Part B compound (490mg, 1.245 mmol) in THF/water (1/1, 4 mL) was added $LiOH.H_2O$ (209 mg, 4.98 mmol). The mixture was stirred at RT for 18 h, then was diluted with EtOAc and acidified with 1N aqueous HCl to pH~4-5. The aqueous layer was extracted with EtOAc (2x). The combined organic extracts were washed with 1N aqueous HCl, H_2O, and brine, dried ($MgSO_4$) and concentrated *in vacuo* to provide Part C compound (440 mg, 93% yield) as a white solid. $[M + H]^+ = 561.1$.

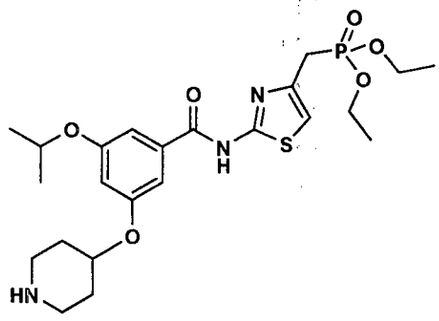
D.



[00430] To a solution of Part C compound (200mg, 0.527 mmol) and Example 13 Part E compound (132 mg, 0.527 mmol) (buffered with DIEA) in DCM/DMF (1/1) were successively added HOAT (201 mg, 1.476 mmol), EDCI (202 mg, 1.054 mmol), and DIEA (641 µL, 3.69 mmol). The reaction mixture was stirred at RT for 18 h, then was diluted with DCM. The organic layer was washed with water (2x) and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed (SiO_2; continuous gradient 0% DCM/MeOH to 5% DCM/MeOH) to give the title compound (140 mg, 43% yield) as a white solid. $[M + H]^+ = 612$; ^1H NMR (500

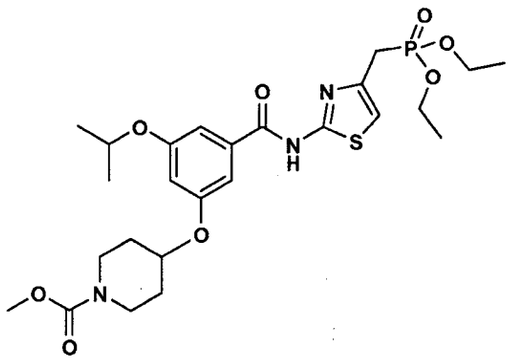
MHz, $CDCl_3$) δ 1.26 (t, *J*=7.15 Hz, 6 H), 1.33 (d, *J*=6.05 Hz, 6 H), 1.45 (s, 9 H), 1.63 (s, 2 H), 1.67 - 1.80 (m, 2 H), 1.92 (dd, *J*=12.65, 3.85 Hz, 2 H), 3.21 - 3.39 (m, 4 H), 3.63 - 3.76 (m, 2 H), 4.00 - 4.14 (m, 4 H), 4.44 - 4.53 (m, 1 H), 4.53 - 4.62 (m, 1 H), 6.63 (t, *J*=2.20 Hz, 1 H), 6.84 (d, *J*=3.85 Hz, 1 H), 8.00 (s, 1 H).

EXAMPLE 102



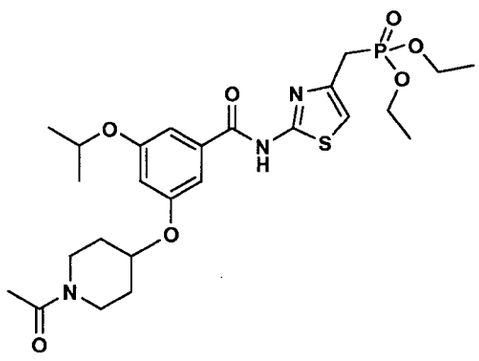
[00431] To a solution of Example 101 compound (15mg, 0.025mmol) in DCM (0.5 mL) was added TFA (0.15 mL). The reaction mixture was stirred at RT for 2 h, then was concentrated *in vacuo*. The residue was purified by preparative HPLC (Phenomenex AXIA 5u C18 30 x 100 mm column; detection at 220 nm; flow rate = 40 mL/min; continuous gradient from 35% B to 100% B over 10 min, where A = 90:10:0.1 H_2O:MeOH:TFA and B = 90:10:0.1 MeOH:H_2O:TFA) give the title compound (11 mg, 85% yield) as a white solid. $[M + H]^+ = 512$; ^1H NMR (500 MHz, $CDCl_3$) δ 1.29 (t, *J*=7.15 Hz, 6 H), 1.33 (d, *J*=5.50 Hz, 6 H), 2.08 - 2.16 (m, 2 H), 2.16 - 2.26 (m, 2 H), 3.22 (d, *J*=9.90 Hz, 2 H), 3.30 (d, *J*=21.44 Hz, 2 H), 3.35 (d, *J*=7.70 Hz, 2 H), 4.02 - 4.17 (m, 4 H), 4.60 - 4.73 (m, 1 H), 4.82 (s, 1 H), 6.69 (t, *J*=2.20 Hz, 1 H), 6.96 (d, *J*=3.30 Hz, 1 H), 7.36 (d, *J*=8.80 Hz, 2 H), 9.37 (s, 1 H), 9.47 (s, 1 H).

EXAMPLE 103



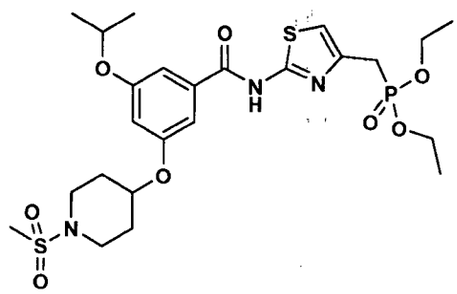
[00432] To a solution of Example 102 compound (30 mg, 0.059 mmol) in THF (1 mL) and sat. aqueous $NaHCO_3$ (1 mL) was added methyl chloroformate (6.77 μL, 0.088 mmol). The reaction mixture was stirred at RT for 18 h, then was diluted with EtOAc. The aqueous layer was extracted with EtOAc (2x), and the combined organic extracts were concentrated *in vacuo*. The residue was purified by preparative HPLC (Phenomenex AXIA 5u C18 30 x 100 mm column; detection at 220 nm; flow rate = 40 mL/min; continuous gradient from 35% B to 100% B over 10 min, where A = 90:10:0.1 H_2O:MeOH:TFA and B = 90:10:0.1 MeOH:H_2O:TFA) to give the title compound (16mg, 48% yield) as a white solid. $[M + H]^+$ = 570.3; ^1H NMR (500 MHz, $CDCl_3$) δ 1.30 (t, *J*=7.15 Hz, 6 H), 1.33 (d, *J*=6.05 Hz, 6 H), 1.76 (s, 2 H), 1.91 (s, 2 H), 3.31 (d, *J*=20.89 Hz, 2 H), 3.31 (d, *J*=20.89 Hz, 2 H), 3.44 (s, 2 H), 3.66 (d, *J*=5.50 Hz, 2 H), 3.69 (s, 3 H), 4.10 - 4.17 (m, 4 H), 4.64 - 4.75 (m, 2 H), 6.69 (t, *J*=2.20 Hz, 1 H), 7.01 (d, *J*=3.30 Hz, 1 H), 7.33 (dd, *J*=4.67, 1.92 Hz, 2 H).

EXAMPLE 104



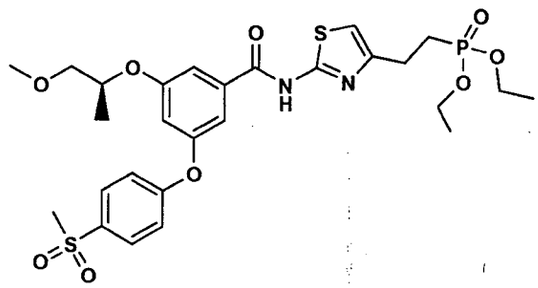
[00433] To a solution of Example 102 compound (30 mg, 0.059 mmol) in DCM (1 mL) was added pyridine (0.1 mL) and acetyl chloride (6.90 mg, 0.088 mmol). The reaction was stirred at RT for 18 h, then was diluted with EtOAc. The aqueous layer was extracted with EtOAc (2x), and the combined organic extracts were concentrated *in vacuo*. The residue was purified by preparative HPLC (Phenomenex AXIA 5u C18 30 x 100 mm column; detection at 220 nm; flow rate = 40 mL/min; continuous gradient from 35% B to 100% B over 10 min, where A = 90:10:0.1 H_2O:MeOH:TFA and B = 90:10:0.1 MeOH:H_2O:TFA) to give the title compound (22 mg, 68% yield) as a white solid. $[M + H]^+ = 554.4$; ^1H NMR (500 MHz, $CDCl_3$) δ 1.34 (t, *J*=7.15 Hz, 6 H), 1.36 (d, *J*=6.05 Hz, 6 H), 1.79 - 2.04 (m, 4 H), 2.17 (s, 3 H), 3.36 (d, *J*=21.44 Hz, 2 H), 3.43 - 3.54 (m, 1 H), 3.63 - 3.86 (m, 3 H), 4.12 - 4.24 (m, 4 H), 4.68 - 4.86 (m, 2 H), 6.73 (s, 1 H), 7.06 (d, *J*=3.30 Hz, 2 H), 7.39 (s, 2 H).

EXAMPLE 105



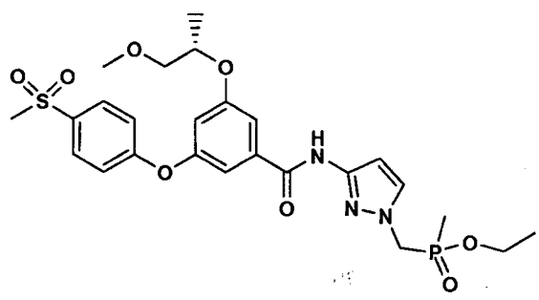
[00434] A solution of Example 102 compound (50 mg, 0.098 mmol) and Et_3N (10 mg, 0.098 mmol) in DCM (0.5 mL) was added to a solution of methanesulfonyl chloride (11.20 mg, 0.098 mmol) in DCM (0.5mL). The reaction was stirred at RT for 18 h, then was diluted with EtOAc. The aqueous layer was extracted with EtOAc (2x), and the combined organic extracts were concentrated *in vacuo*. The residue was purified by preparative HPLC (Phenomenex AXIA 5μm C18 30 x 100 mm column; detection at 220 nm; flow rate = 40 mL/min; continuous gradient from 35% B to 100% B over 10 min , where A = 90:10:0.1 H_2O:MeOH:TFA and B = 90:10:0.1 MeOH:H_2O:TFA) to give the title compound (19.5 mg, 34% yield) as a colorless oil. $[M + H]^+ = 590.3$; ^1H NMR (500 MHz, $CDCl_3$) δ 1.28-1.38 (m,12H), 1.93-2.10 (m, 4 H), 2.97(s, 3H), 3.29-3.40 (m, 6 H), 4.12 - 4.22(m, 4 H), 4.68 - 4.75 (m, 2 H), 6.70 (t, *J*=2.20 Hz, 1 H), 7.03(d, *J*=3.85 Hz, 1 H), 7.337 (d, 1.10 Hz, 2 H).

EXAMPLE 106



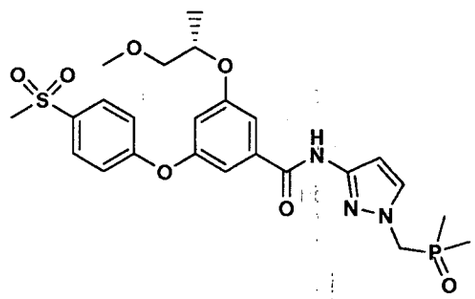
[00435] To a solution of Example 26 Part C compound (25.0 mg; 0.066 mmol), Example 18 Part D compound (20.9 mg; 0.079 mmol), and HOAt (10.3 mg; 0.076 mmol) in DMF (0.25 mL) were successively added DIPEA (13.2 μL; 0.076 mmol) and EDAC (14.6 mg; 0.076 mmol). The reaction was stirred at RT for 20 h, then was partitioned between EtOAc (4 mL) and H_2O (3 mL). The organic layer was washed with 0.5 N aqueous HCl (3 mL), sat. aqueous $NaHCO_3$ (3 mL), and brine (3 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by preparative HPLC (YMC reverse phase ODS-A-5μm 20 x 100 mm column; flow rate = 20 mL/min, 15 to 100% solvent B over 10 min, hold to 14 min, where solvent A = 90:10:0.1 H_2O:MeOH:TFA and solvent B = 90:10:0.1 MeOH:H_2O:TFA) to give the title compound (22.0 mg; 54%) as a light yellow solid. $[M + H]^+ = 627.1$; ^1H NMR (400 MHz, $CDCl_3$): δ 1.34 (m, 9H), 2.19 (m, 2H), 3.07 (m, 5H), 3.41 (s, 3H), 3.57 (m, 2H), 4.12 (m, 4H), 4.89 (m, 1H), 6.81 (s, 1H), 6.94 (s, 1H), 7.15 (d, 2H), 7.44 (s, 1H), 7.69 (s, 1H), 7.92 (d, 2H).

EXAMPLE 107

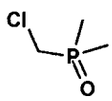


[00436] The title compound (20 mg, 65% yield, white solid) was prepared from racemic-ethyl (3-amino-1H-pyrazol-1-yl)methyl(methyl) phosphinate employing the same general sequence as used to prepare Example 58. $[M + H]^+ = 566.3$; ^1H NMR (400 MHz, CD_3OD): δ 1.33 (d, J = 6.6 Hz, 3H), 1.34 (t, J = 6.6 Hz, 3H), 1.57 (d, J = 14.3 Hz, 3H), 3.01 (s, 3H), 3.42 (s, 3H), 3.53-3.63 (m, 2H), 4.08-4.21 (m, 2H), 4.52 (dd, J = 2.4, 6.0 Hz, 2H), 4.71 (m, 1H), 6.86 (d, J = 2.2 Hz, 1H), 7.03 (s, 1H), 7.14 (d, J = 8.8 Hz, 2H), 7.24 (s, 1H), 7.39 (s, 1H), 7.52 (d, J = 2.2 Hz, 1H), 7.91 (d, J = 8.8 Hz, 2H).

EXAMPLE 108

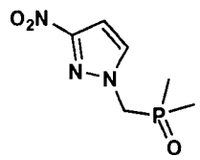


A.



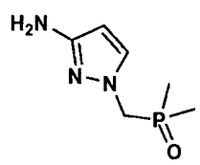
[00437] To a stirred 10°C solution of chloromethyl(methyl)phosphinic chloride (2 g, 13.61 mmol) in Et_2O (10 mL) was added dropwise MeMgBr (4.54 mL of a 3 M solution in Et_2O, 13.61 mmol). The reaction turned cloudy and gummy, then was slowly warmed to RT for 1 h. Volatiles were removed *in vacuo* and the residue was carefully quenched with sat. aqueous $NaHCO_3$ and extracted with $CHCl_3$ (4×). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. To the resulting clear oil was added hexanes (50 mL); a white precipitate formed. The precipitated was filtered to collect the white solid (crystalline, fine needles) as Part A compound (360 mg, 21%).

B.



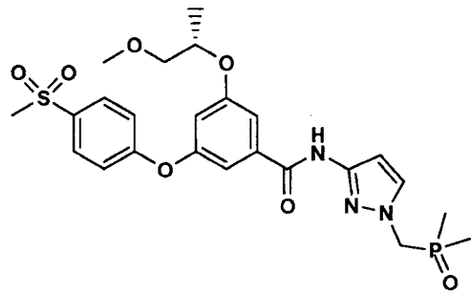
[00438] To a stirred solution of 3-nitro-1H-pyrazole (45 mg, 0.398 mmol) in DMF (2 mL) was added K_2CO_3 (70 mg, 0.506 mmol) and Part A compound (70 mg, 0.553 mmol). The reaction was stirred at 75°C for 16 h, then was cooled to RT and partitioned between EtOAc and saturated aqueous NH_4Cl. The aqueous layer was extracted with $CHCl_3$ (10×), and the combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to give Part B compound (50 mg, 62% yield) as a white solid.

C.



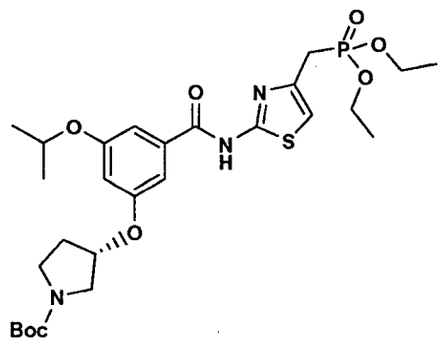
[00439] To a stirred solution of Part B compound (50 mg, 0.246 mmol) in MeOH (3 mL) was added Pd/C (26.2 mg, 0.025 mmol). The reaction was stirred under an atmosphere of H_2 (balloon) for 1 h, then was filtered through Celite® and concentrated *in vacuo* to give Part C compound (35 mg, 82%) as a light yellow oil.

D.

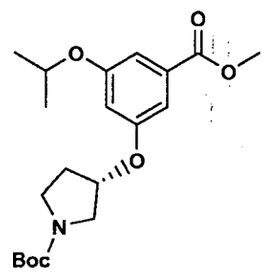


[00440] To a stirred solution of Example 26 Part C acid (77 mg, 0.202 mmol) in DMF (2 mL) was added HOBT (55.0 mg, 0.404 mmol), EDC (77 mg, 0.404 mmol), and Hunig's Base (0.106 mL, 0.606 mmol). The reaction was stirred at RT for 30 min, after which Part C compound (35 mg, 0.202 mmol) was added. The reaction was stirred at RT for 20 h, then was partitioned between 1N aqueous HCl and CH_2Cl_2. The organic phase was washed with sat. aqueous NH_4Cl and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by preparative HPLC (Luna 5μm 21.2 x 100 mm column; flow rate = 20 mL/min, 0 to 100% solvent B over 12 min, hold to 15 min, where solvent A = 90:10:0.1 H_2O:MeOH:TFA and solvent B = 90:10:0.1 MeOH:H_2O:TFA) to give the title compound (59 mg, 55% yield) as a white solid. $[M + H]^+$ = 536.3; ^1H NMR (400 MHz, CD_3OD): δ 1.31 (d, J = 6.9 Hz, 3H), 1.64 (d, J = 13.2 Hz, 6H), 2.99 (s, 3H), 3.40 (s, 3H), 3.48-3.61 (m, 2H), 4.60 (d, J = 6.6 Hz, 2H), 4.68 (m, 1H), 6.84 (s, 1H), 6.96 (d, J = 2.2 Hz, 1H), 7.11 (d, J = 8.8 Hz, 2H), 7.21 (s, 1H), 7.34 (s, 1H), 7.52 (d, J = 2.2 Hz, 1H), 7.88 (d, J = 8.8 Hz, 2H).

EXAMPLE 109

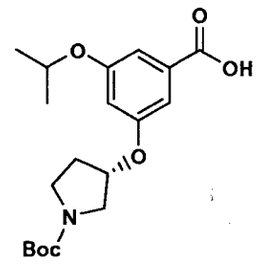


A.



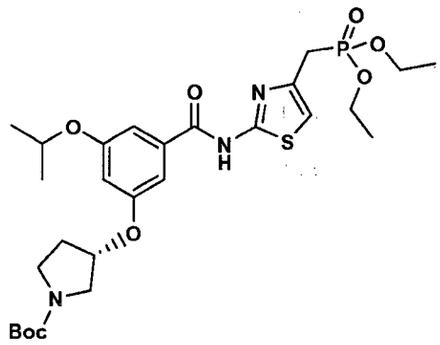
[00441] To a solution of Example 101 Part A compound (300 mg, 1.427 mmol) and (R) tert-butyl-3-hydroxypyrrolidine-carboxylate (534m g, 2.85 mmol) in toluene (2 mL) was added a suspension of Example 97 Part B compound (1.17g, 2.85 mmol) in DCM (2 mL). The reaction mixture was stirred at RT for 3 h, then was concentrated *in vacuo*. The residue was chromatographed (SiO_2; continuous gradient 10% EtOAc/Hex to 60% EtOAc/Hexane) to give Part A compound (500 mg, 92%) as a white solid. $[M + H]^+ = 402$; ^1H NMR (400 MHz, $CDCl_3$) δ 1.25 (d, *J*=6.15 Hz, 6 H), 1.39 (d, *J*=7.47 Hz, 9 H), 1.95 - 2.22 (m, 2 H), 3.25 - 3.46 (m, 4 H), 3.47 - 3.58 (m, 1 H), 3.82 (s, 3 H), 4.61 - 4.73 (m, 1 H), 5.07 (s, 1 H), 6.76 (t, *J*=2.42 Hz, 1 H), 7.00 (s, 1 H), 7.03 (s, 1 H).

B.



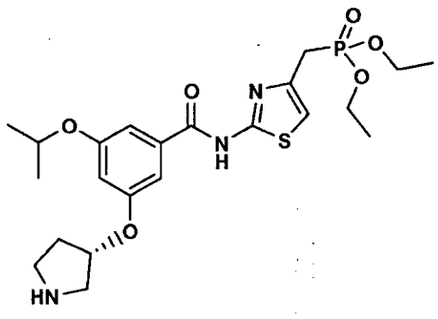
[00442] To a 0°C solution of Part A compound (500 mg, 1.318 mmol) in THF/water (1/1, 4 mL) was added $LiOH.H_2O$ (270 mg, 6.59 mmol). The mixture was stirred at RT for 18 h, then was diluted with EtOAc and acidified with 1N aqueous HCl to pH~4-5. The aqueous layer was extracted with EtOAc (2x). The combined organic extracts were washed with 1N aqueous HCl, H_2O, and brine, dried ($MgSO_4$) and concentrated *in vacuo* to provide Part B compound (480 mg, 100% yield) as a white solid. MS $[M - H]^- = 364.4$.

C.



[00443] To a solution of Part B compound (200 mg, 0.547 mmol) and Example 13 Part E compound (137 mg, 0.547 mmol) in DCM/DMF (1/1; buffered with DIEA) were successively added HOAT (208 mg, 1.53mmol), EDCI (210 mg, 1.094 mmol), and DIPEA (665 μL, 3.83 mmol). The reaction mixture was stirred at RT for 18 h, then was diluted with DCM. The organic phase was washed with water (2x) and brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was chromatographed (SiO_2; continuous gradient from 0% DCM/MeOH to 5% DCM/MeOH) to give the title compound (160 mg, 49% yield) as a white solid. $[M + H]^+ = 598.3$; ^1H NMR (500 MHz, $CDCl_3$) δ 1.26 (t, J=7.15 Hz, 6 H), 1.33 (d, J=6.05 Hz, 6 H,) 1.45 (s, 9 H), 1.64 (s, 2 H), 2.02 - 2.24 (m, 2 H), 3.28 (d, J=21.44 Hz, 2 H), 3.41 - 3.70 (m, 4 H), 4.01 - 4.16 (m, 4 H), 4.51 - 4.63 (m, 1 H), 6.98 (s, 1 H), 7.03 (s, 1 H), 9.71 (s, 1 H).

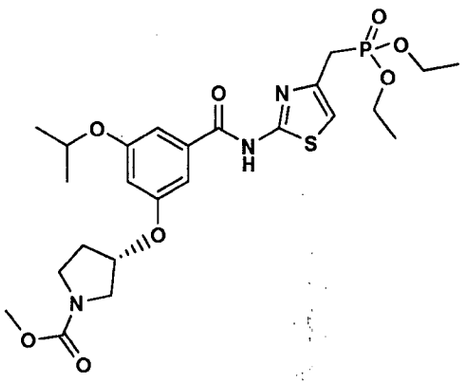
EXAMPLE 110



[00444] The title compound (10.4 mg, 71% yield, white solid) was prepared from Example 109 compound employing the same general sequence as used to prepare Example 102. $[M + H]^+ = 498.0$; ^1H NMR (500 MHz, $CDCl_3$) δ 1.24 - 1.29 (m, 6 H),

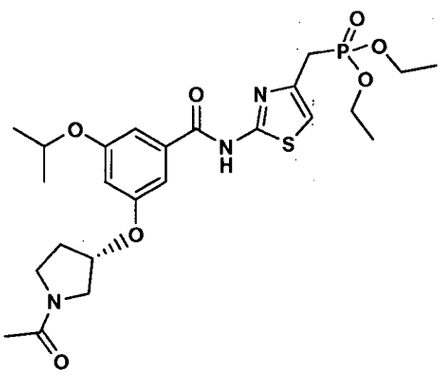
1.32 (d, *J*=6.05 Hz, 6 H), 2.22 - 2.44 (m, 2 H), 3.26 (d, *J*=21.44 Hz, 2 H), 4.01 - 4.16 (m, 4 H), 4.58 - 4.70 (m, 1 H), 5.24 (s, 1 H), 6.66 (s, 1 H), 6.93 (d, *J*=3.30 Hz, 1 H), 7.29 (s, 1 H), 7.33 (s, 1 H), 9.81 (s, 1 H), 10.30 (s, 1 H).

EXAMPLE 111



[00445] The title compound (22.5 mg, 68% yield, colorless oil) was prepared from Example 110 compound employing the same general sequence as used to prepare Example 103. $[M + H]^+ = 556.3$; ^1H NMR (500 MHz, $CDCl_3$) δ 1.29 - 1.35 (m, 12 H), 2.13 (s, 1 H), 2.20 (s, 1 H), 3.35 (d, *J*=21.44 Hz, 2 H), 3.48 - 3.65 (m, *J*=28.04 Hz, 4 H), 3.70 (d, *J*=11.55 Hz, 4 H), 4.13 - 4.20 (m, 4 H), 4.64 - 4.74 (m, 1 H), 5.14 (s, 1 H), 6.66 (t, *J*=1.92 Hz, 1 H), 7.03 (d, *J*=3.30 Hz, 1 H), 7.31 - 7.41 (m, 2 H).

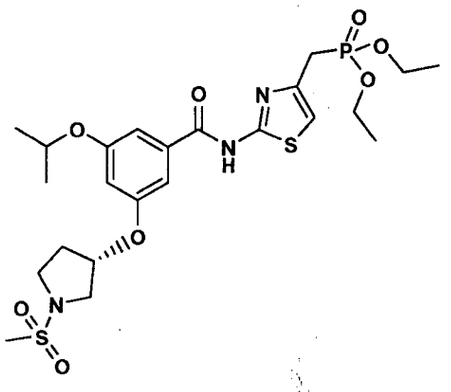
EXAMPLE 112



[00446] The title compound (24 mg, 74% yield, light yellow oil) was prepared from Example 110 compound employing the same general sequence as used to prepare Example 104. $[M + H]^+ = 540.4$; ^1H NMR (500 MHz, $CDCl_3$) δ 1.32 - 1.35

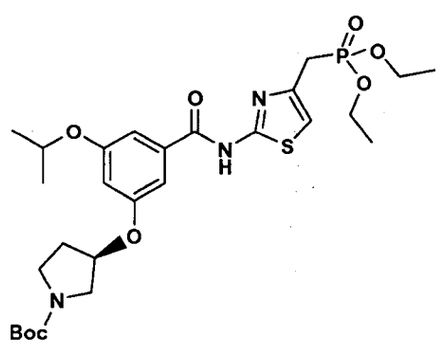
(m, 6 H), 1.35 - 1.39 (m, 6 H), 2.09 - 2.20 (m, *J*=23.09 Hz, 3 H), 2.21 - 2.43 (m, 2 H), 3.37 (d, *J*=21.44 Hz, 2 H), 3.55 - 3.92 (m, 4 H), 4.13 - 4.24 (m, 4 H), 4.66 - 4.76 (m, 1 H), 5.19 - 5.30 (m, 1 H), 6.67 - 6.72 (m, 1 H), 7.07 (d, *J*=3.85 Hz, 1 H), 7.39 (s, 1 H), 7.40 - 7.44 (m, 1 H).

EXAMPLE 113



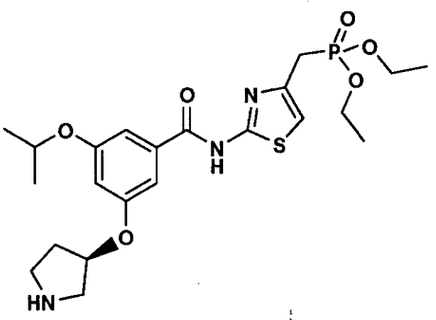
[00447] The title compound (28 mg, 43% yield, white solid) was prepared from Example 110 compound employing the same general sequence as used to prepare Example 105. $[M + H]^+ = 576.3$; ^1H NMR (500 MHz, $CDCl_3$) δ 1.32 (t, *J*=7.15 Hz, 6 H), 1.35 (dd, *J*=6.05, 1.10 Hz, 6 H), 2.17 - 2.37 (m, 2 H), 2.83 (s, 3 H), 3.34 (d, *J*=20.89 Hz, 2 H), 3.42 - 3.52 (m, 1 H), 3.54 - 3.71 (m, 3 H), 4.11 - 4.23 (m, 4 H), 4.65 - 4.77 (m, 1 H), 5.16 (s, 1 H), 6.64 (t, *J*=2.20 Hz, 1 H), 7.35 (s, 1 H), 7.41 (d, *J*=3.30 Hz, 1 H).

EXAMPLE 114



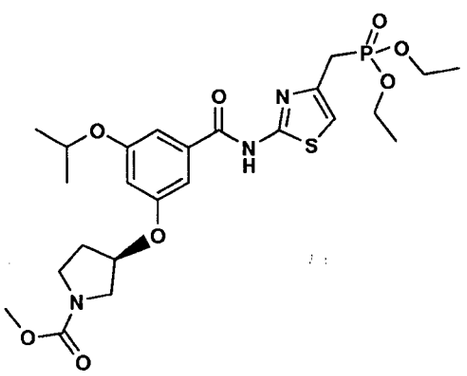
[00448] The title compound (176 mg, 32% yield, white solid) was prepared from (S) tert-butyl-3-hydroxypyrrolidine-carboxylate employing the same general sequence as used to prepare Example 109. $[M + H]^+ = 598.4$; ^1H NMR (500 MHz, $CDCl_3$) δ 1.26 (t, *J*=7.15 Hz, 6 H), 1.34 (d, *J*=5.50 Hz, 6 H), 1.45 (s, 9 H), 1.63 (s, 2 H), 2.00 - 2.27 (m, 2 H), 3.28 (d, *J*=20.89 Hz, 2 H), 3.39 - 3.70 (m, 4 H), 3.99 - 4.18 (m, 4 H), 4.50 - 4.66 (m, 1 H), 4.91 (s, 1 H), 6.59 (s, 1 H), 6.84 (s, 1 H), 6.96 - 7.10 (m, 2 H).

EXAMPLE 115



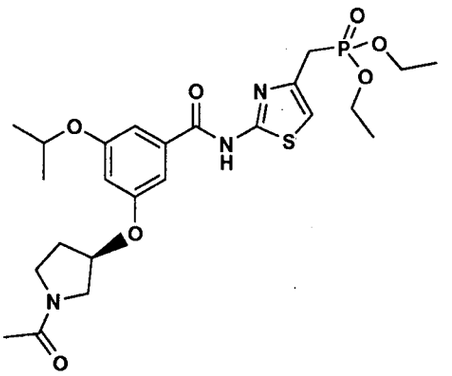
[00449] The title compound (13.4 mg, 67% yield, white solid) was prepared from Example 114 compound employing the same general sequence as used to prepare Example 110. $[M + H]^+ = 498.3$; ^1H NMR (500 MHz, $CDCl_3$) δ 1.22 - 1.28 (m, 6 H), 1.32 (d, *J*=6.05 Hz, 6 H), 2.24 - 2.40 (m, 2 H), 3.24 (d, *J*=21.44 Hz, 2 H), 3.41 - 3.69 (m, 4 H), 3.97 - 4.13 (m, 4 H), 4.56 - 4.69 (m, 1 H), 5.22 (s, 1 H), 6.64 (t, *J*=2.20 Hz, 1 H), 6.89 (d, *J*=3.85 Hz, 1 H), 7.28 (s, 1 H), 7.32 (s, 1 H).

EXAMPLE 116



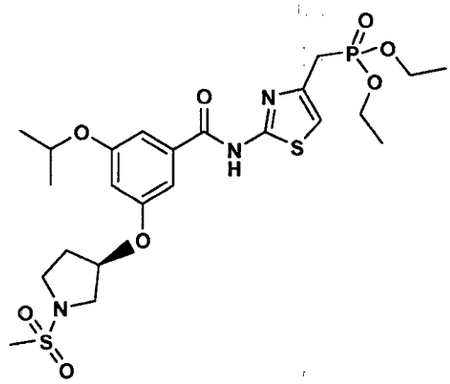
[00450] The title compound (32.5 mg, 83% yield, colorless oil) was prepared from Example 115 compound employing the same general sequence as used to prepare Example 111. $[M + H]^+ = 554$; ^1H NMR (500 MHz, $CDCl_3$) δ 1.29 - 1.32 (m, 6 H), 1.33 (d, *J*=5.50 Hz, 6 H), 2.05 - 2.28 (m, 2 H), 3.35 (d, *J*=21.44 Hz, 2 H), 3.45 - 3.74 (m, 7 H), 4.11 - 4.22 (m, 4 H), 4.65 - 4.74 (m, 1 H), 5.14 (s, 1 H), 6.66 (t, *J*=1.92 Hz, 1 H), 7.03 (d, *J*=3.30 Hz, 1 H), 7.33 (s, 1 H), 7.38 (s, 1 H).

EXAMPLE 117



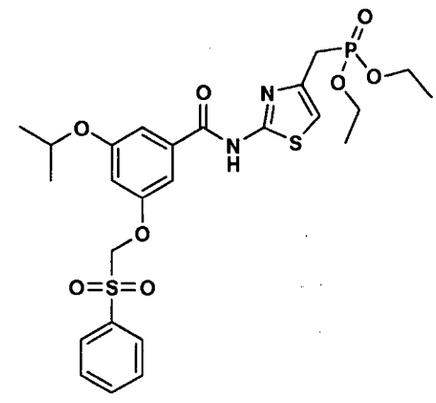
[00451] The title compound (28.5 mg, 75% yield, light yellow oil) was prepared from Example 115 compound employing the same general sequence as used to prepare Example 112. $[M + H]^+ = 540.2$; ^1H NMR (500 MHz, $CDCl_3$) δ 1.29 - 1.32 (m, 6 H), 1.32 - 1.36 (m, 6 H), 2.12 (d, *J*=23.09 Hz, 3 H), 2.19 - 2.39 (m, 2 H), 3.34 (d, *J*=21.44 Hz, 2 H), 3.55 - 3.88 (m, 4 H), 4.11 - 4.21 (m, 4 H), 4.64 - 4.73 (m, 1 H), 5.17 - 5.28 (m, 1 H), 6.64 - 6.69 (m, 1 H), 7.04 (d, *J*=2.75 Hz, 1 H), 7.35 (d, *J*=1.10 Hz, 1 H), 7.39 (d, *J*=9.35 Hz, 1 H).

EXAMPLE 118

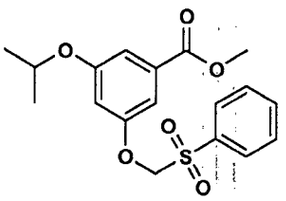


[00452] The title compound (12 mg, 30% yield, light yellow oil) was prepared from Example 115 compound employing the same general sequence as used to prepare Example 113. $[M + H]^+ = 576.2$; ^1H NMR (500 MHz, $CDCl_3$) δ 1.31 - 1.34 (m, 6 H), 1.36 (d, *J*=6.05 Hz, 6 H), 2.08 - 2.39 (m, 2 H), 2.85 (s, 3 H), 3.37 (d, *J*=21.44 Hz, 2 H), 3.44 - 3.54 (m, 1 H), 3.56 - 3.72 (m, 3 H), 4.13 - 4.25 (m, 4 H), 4.68 - 4.80 (m, 1 H), 5.18 (s, 1 H), 6.66 (s, 1 H), 7.07 (d, *J*=3.30 Hz, 1 H), 7.37 (s, 1 H), 7.43 (s, 1 H).

EXAMPLE 119

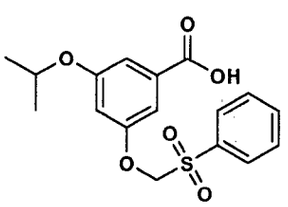


A.



[00453] To a RT solution of Example 101 Part A ester (94.7 mg, 0.450 mmol) in MeCN (2.2 mL) under Ar was added 1,4,7,10,13,16-hexaoxacyclooctadecane (16 mg, 0.061 mmol), K_2CO_3 (178 mg, 1.288 mmol), and bromomethyl phenyl sulfone (120 mg, 0.510 mmol). The mixture was heated at 70°C for 6 h, then at 90°C for 4 h. DMF (1 mL) was added, and the reaction was heated at 115°C for 24 h. After 24 hours, more bromomethyl phenyl sulphone (90 mg, 0.382 mmol) was added, and the reaction was stirred at 115°C for 3 days, then cooled to RT and stirred at RT for 2 days. The dark brown mixture was partitioned between EtOAc and saturated aqueous $NaHCO_3$. The organic layer was washed with saturated aqueous $NaHCO_3$, water, and brine, dried (Na_2SO_4), and concentrated *in vacuo*. The residue was chromatographed (SiO_2, 12 g, eluting from 0-10%, then 35% EtOAc:hexanes, finally flushing with 100% EtOAc) to give impure Part A compound (70 mg) as an oil. The residue was further purified by preparative HPLC (Phenomenex AXIA Luna 5μ, 75x30mm, detection at 220 nm; flow rate = 40 mL/min; continuous gradient from 40% A to 100% B over 15 min +3 min hold time at 100% B, where A = 90:10:0.1 H_2O:CH_3CN:TFA and B = 90:10:0.1 CH_3CN:H_2O:TFA) to give Part A compound (9.2 mg, 5.5%) as an oily solid.

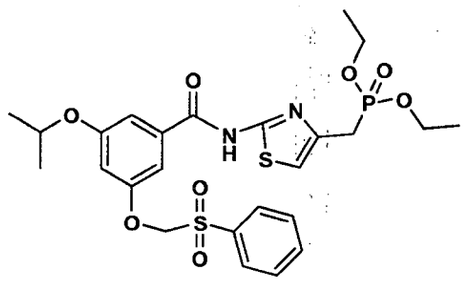
B.



[00454] To a RT solution of Part A compound (9 mg, 0.025 mmol) in THF (0.2 mL) and MeOH (0.1 mL) under Ar was added 4N aqueous LiOH (0.062 mL, 0.247 mmol). The reaction was stirred at RT for 8 h, then was stored at -20°C for 18 h.

After warming to RT and diluting with EtOAc, volatiles were removed *in vacuo* to give a colorless solid. The residue was suspended in water, brought to pH 1 with 1N aqueous HCl (0.3 mL), and the aqueous layer was extracted with EtOAc (2x). The combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated *in vacuo* to give Part B compound (10.6 mg, >100% recovery) as a colorless solid.

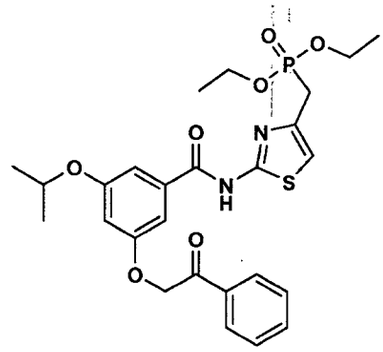
C.



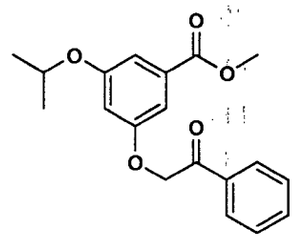
[00455] To Part B acid (8.76 mg, 0.025 mmol) was added a RT solution of Example 13 Part E amine (21 mg, 0.084 mmol) in CH_2Cl_2 (0.800 mL) under Ar. To the resulting mixture was added iPr_2NEt (0.030 mL, 0.175 mmol) followed by addition of HATU (14.2 mg, 0.037 mmol). The solution was stirred at RT for 18 h, after which another portion of Example 13 Part E amine (15 mg, 0.06 mmol) was added, and stirring was continued at RT for 18 h. The reaction was partitioned between EtOAc and saturated aqueous $NaHCO_3$ after stirring for 15 min. The organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by preparative HPLC (Phenomenex Luna 5μm 21.2x100mm column, detection at 220 nm; flow rate = 20 mL/min; continuous gradient from 60% A to 100% B over 10 min +2 min hold time at 100% B, where A = 90:10:0.1 H_2O:MeOH:TFA and B = 90:10:0.1 MeOH:H_2O:TFA). This material was further purified by preparative HPLC (Phenomenex Luna, 5micron 21.2x100mm, detection at 220 nm; flow rate = 20 mL/min; continuous gradient from 35% A to 100% B over 10 min +2 min hold time at 100% B, where A = 90:10:0.1 H_2O:MeOH:TFA and B = 90:10:0.1 MeOH:H_2O:TFA). The material was finally purified by passing through a MeOH-treated cartridge of Polymer Lab StratoSpheres TM SPE PL-HCO3 MP SPE resin (500 mg), washing well with MeOH. The filtrate was concentrated *in vacuo* and the

resulting solid dissolved in CH_2Cl_2/MeOH, filtered, and concentrated *in vacuo* to give the title compound (5 mg, 34%) as a tan solid. $[M + H]^+ = 583.3$; ^1H NMR (400 MHz, $CDCl_3$) δ 1.27 (t, *J*=6.87 Hz, 6 H), 1.33 (d, *J*=6.05 Hz, 6 H), 3.33 (d, *J*=20.89 Hz, 2 H), 4.07 (td, *J*=7.15, 4.40 Hz, 4 H), 4.55 – 4.58 (m, 1 H), 5.11 (s, 2 H), 6.67 (s, 1 H), 6.83 (d, *J*=3.30 Hz, 1 H), 7.08 (s, 1 H), 7.16 (s, 1 H), 7.59 (t, *J*=7.70 Hz, 2 H), 7.69 (t, *J*=7.15 Hz, 1 H), 7.97 (d, *J*=7.15 Hz, 2 H).

EXAMPLE 120

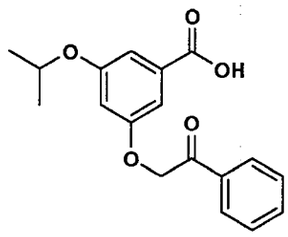


A.



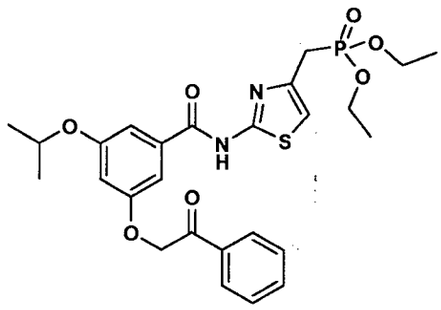
[00456] To a 0°C solution of Example 101 Part A compound (183.9 mg, 0.875 mmol) in DMPU (4.5 mL) under Ar was added NaH (35.0 mg of a 60% dispersion in oil, 0.875 mmol). To the resulting solution was added 2-bromoacetophenone (174 mg, 0.875 mmol). The reaction was stirred at 0°C for several min and then warmed to RT and stirred at RT for 1.5 h. More 2-bromoacetophenone (39 mg, 0.19 mmol) was added, and the reaction was stirred at RT for 1 h. The reaction was quenched with water and EtOAc was added. The organic layer was washed with water (2x) and brine (1x), dried (Na_2SO_4), and concentrated *in vacuo*. The residue was chromatographed (SiO_2, 12 g, eluting from 0-5% EtOAc:CH_2Cl_2, then flushing with 90% EtOAc) to give Part A compound (274 mg, 95%) as a yellow oil.

B.



[00457] To a RT solution of Part A compound (101.4 mg, 0.309 mmol) in TF (2.4 mL) under Ar was added water (0.6 mL), followed by $LiOH.H_2O$ (54.7 mg, 1.304 mmol). The reaction was stirred at RT for 18 h, and aqueous LiOH (0.2 mL of a 4 M solution, 0.8 mmol) was added. After stirring for 5.5 h, MeOH (0.5 mL) was added; stirring was continued at RT for 2.5 h and the reaction was stored at -20°C for 18 h. After warming to RT, the reaction was stirred for another 4.5 h. Volatiles were removed *in vacuo* to give an orange aqueous mixture, which was acidified with 1N aqueous HCl (1.9 mL), then was partitioned between EtOAc and water. The organic layer was washed with water and brine, dried (Na_2SO_4) and concentrated *in vacuo* to give crude Part B compound (88 mg, 49%) as a yellow oil.

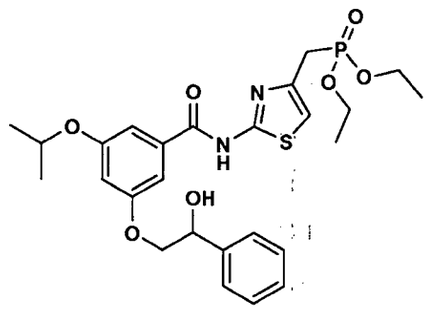
C.



[00458] To a RT solution of Part B acid (≤88 mg, ≤0.280 mmol) in CH_2Cl_2 (1.4 mL) under Ar were successively added HATU (166 mg, 0.437 mmol), DIPEA (0.34 mL, 1.952 mmol) and a solution of Example 13 Part E compound (162 mg, 0.445 mmol) in CH_2Cl_2 (0.6 mL). The reaction was stirred at RT for 65 h, then was partitioned between EtOAc and sat. aqueous $NaHCO_3$. The organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4) and concentrated *in*

vacuo. The residue was purified by preparative HPLC (YMC ODS S5 30x250mm column, detection at 220 nm; flow rate = 25 mL/min; continuous gradient from 50% A to 100% B over 20 min +5 min hold time at 100% B, where A = 90:10:0.1 H_2O:CH_3CN:TFA and B = 90:10:0.1 CH_3CN:H_2O:TFA) to give the title compound (33 mg, 22%) as a gummy, yellow solid. $[M + H]^+$ = 545.3; ^1H NMR (400 MHz, CD_3OD): δ 1.28 (t, *J*=7.15 Hz, 6 H), 1.34 (d, *J*=6.05 Hz, 6 H), 3.36 (d, *J*=16.49 Hz, 2 H), 4.04 - 4.14 (m, 4 H), 4.64 – 4.86 (m, 1 H), 5.55 (s, 2 H), 6.78 – 6.80 (m, 1 H), 6.95 – 6.97 (m, 1 H), 7.18 – 7.21 (m, 2 H), 7.50 – 7.58 (t, *J*=7.97 Hz 2 H), 7.65 – 7.70 (m, 1 H), 8.07 (d, *J*=7.15 Hz, 2 H).

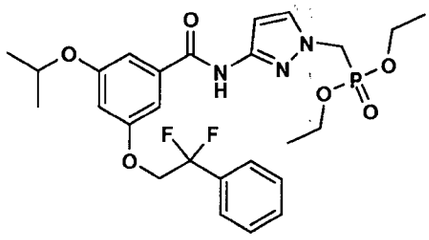
EXAMPLE 121



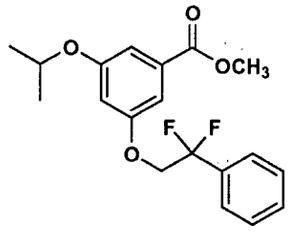
[00459] To a 0°C solution of Example 120 ketone (28 mg, 0.051 mmol) in MeOH (1 mL) under Ar was added $NaBH_4$ (10 mg, 0.264 mmol). After 15 minutes, the reaction was allowed to warm to RT and stirred at RT for 4 h. The mixture was stored at -20°C for 18 h, then was treated with pH 3 aqueous phosphate buffer, allowed to warm to RT and stirred at RT for 40 min. Volatiles were removed *in vacuo*, and the resulting aqueous mixture was partitioned between water, phosphate buffer and EtOAc. The organic layer was washed with water and brine, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by preparative HPLC (Phenomenex AXIA Luna 5μm 75x30mm, detection at 220 nm; flow rate = 40 mL/min; continuous gradient from 40% A to 100% B over 15 min +3 min hold time at 100% B, where A = 90:10:0.1 H_2O:CH_3CN:TFA and B = 90:10:0.1 CH_3CN:H_2O:TFA) to give two fractions containing the desired title compound. Both fractions were passed through a MeOH-treated cartridge of Polymer Lab StratoSpheres TM SPE PL-HCO3 MP SPE resin (500mg), washing well with MeOH.

The filtrates were concentrated *in vacuo*, and the resulting solids were dissolved in CH_2Cl_2/MeOH, and concentrated *in vacuo* to give the title compound (17 mg, 60%) as a tan solid. $[M + H]^+ = 549.2$; $[M - H]^- = 547.2$; ^1H NMR (400 MHz, CD_3OD): δ 1.28 (t, *J*=6.87 Hz, 6 H), 1.33 (d, *J*=6.05 Hz, 6 H), 3.35 (d, *J*=20.89 Hz, 2 H), 4.05 - 4.17 (m, 6 H), 4.63 - 4.69 (m, 1 H), 5.02 – 5.07 (m, 1 H), 6.71 – 6.73 (m, 1 H), 6.95 (d, *J*=3.85 Hz, 1 H), 7.13 -7.15 (m, 2 H), 7.27 -7.30 (m, 1 H), 7.37 (t, *J*=7.42 Hz, 2 H), 7.48 (d, *J*=7.15 Hz, 2 H).

EXAMPLE 122

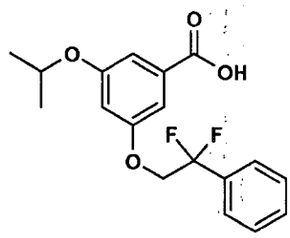


A.



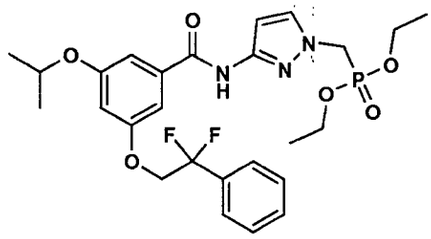
[00460] To a RT solution of Example 120 Part A compound (53.7 mg, 0.164 mmol) in CH_2Cl_2 (0.5 mL) under Ar was added bis-(2-methoxyethyl)aminosulfur trifluoride (0.3 mL, 1.627 mmol). The orange solution was stirred at RT under Ar for 18 h, then was diluted with CH_2Cl_2 and added carefully to a stirred mixture of ice and sat. aqueous $NaHCO_3$. The mixture was stirred for 1 h, then was partitioned between CH_2Cl_2 and sat. aqueous $NaHCO_3$. The aqueous layer was extracted CH_2Cl_2 (2x), and the combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated *in vacuo* to give crude Part A ester (54.4 mg, 95% recovered) as a yellow oil.

B.



[00461] To a RT solution of Part A ester (54.4 mg, 0.155 mmol) in THF (0.8 mL) and MeOH (0.4 mL) under Ar was added 4N aqueous LiOH (0.35 mL, 1.4 mmol). The reaction was stirred at RT for 6 h, and the volatiles were removed *in vacuo*. The orange aqueous mixture was acidified with 1N aqueous HCl (1.5 mL). The resulting mixture was partitioned between water and EtOAc. The organic layer was washed with water and brine, dried (Na_2SO_4) and concentrated *in vacuo* to give Part B compound (46.7 mg, 89% recovered) as a yellow oily solid.

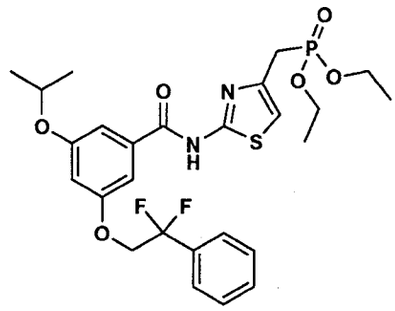
C.



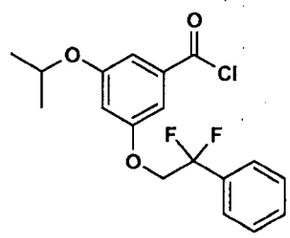
[00462] To a RT solution of Part B compound (21.2 mg, 0.063 mmol) in CH_2Cl_2 (0.6 mL) under Ar were successively added HATU (34 mg, 0.089 mmol), iPr_2NEt (35 µL, 0.201 mmol), and a solution of Example 32 Part A amine (20.6 mg, 0.088 mmol) in CH_2Cl_2 (0.3 mL). The reaction was stirred for 41 h at RT, then was diluted with CH_2Cl_2, saturated aqueous $NaHCO_3$, and EtOAc, then stirred for 15 min and partitioned between EtOAc and aqueous $NaHCO_3$. The aqueous layer was extracted with EtOAc (2x), and the combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by preparative HPLC (YMC ODS 30x250mm column, detection at 220 nm; flow rate = 25 mL/min; continuous gradient from 50% A to 100% B over 25 min +7 min hold time at 100% B, where A = 90:10:0.1 H_2O:CH_3CN:TFA and B = 90:10:0.1 CH_3CN:H_2O:TFA) to give slightly impure title compound (34.3 mg) as a colorless oil. The residue was purified further by preparative HPLC (Phenomenex AXIA 5micron C18 30x100mm

column, detection at 220 nm; flow rate = 40 mL/min; continuous gradient from 60% A to 100% B over 10 min +5 min hold time at 100% B, where A = 90:10:0.1 H_2O:MeOH:TFA and B = 90:10:0.1 MeOH:H_2O:TFA) to give the title compound (25 mg, 59%, TFA salt) as a colorless oil. $[M + H]^+$ = 552.2; $[M - H]^-$ = 550.3; ^1H NMR (400 MHz, $CDCl_3$): δ 1.28 (t, *J*=7.15 Hz, 6 H), 1.32 (d, *J*=6.05 Hz, 6 H), 4.04 - 4.14 (m, 4 H), 4.37 - 4.48 (m, 4 H), 4.59 (dt, *J*=12.09, 6.05 Hz, 1 H), 6.60 (s, 1 H), 6.94 (s, 1 H), 7.01 (s, 1 H), 7.08 (s, 1 H), 7.43 – 7.49 (m, 4 H), 7.55 - 7.61 (m, 2 H), 9.10 (s, 1 H), ^{19}F NMR (400 MHz, CDCl3): δ -75.98, -103.82, -103.86.

EXAMPLE 123

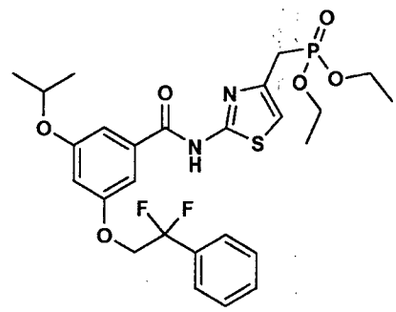


A.



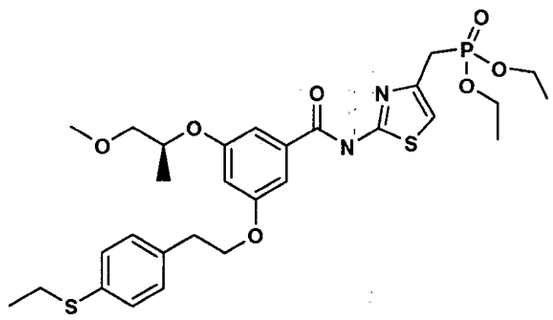
[00463] To a 0°C solution of Example 122 Part B acid (46.7 mg, 0.139 mmol) in CH_2Cl_2 (1.5 mL) under Ar were successively added dropwise oxalyl chloride (250 µL of a 2M solution in 2 M in CH_2Cl_2; 0.5 mmol,) and DMF (15 µL). After 15 min, the reaction was allowed to warm to RT and the yellow reaction was stirred at RT for 3 h. Volatiles were removed *in vacuo* to give Part A compound (68.8 mg, >100% recovery) as an orange oily solid.

B.

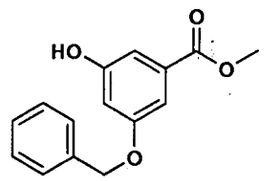


[00464] To a 0°C solution of Example 13 Part E amine (36.7 mg, 0.147 mmol) in THF (0.4 mL) under Ar were successively added iPr_2NEt (120 μL, 0.689 mmol), a solution of Part A compound (24.7 mg, 0.0695 mmol) in CH_2Cl_2 (0.4 mL) and finally DMAP (1.7 mg, 0.014 mmol). The reaction was allowed to warm to RT and stirred for 20 h at RT, then was diluted with water and combined with the crude reaction mixture from a similar experiment using Part A acid chloride (24.7 mg, 0.0695 mmol) and Example 13 Part E amine (36.7 mg, 0.147 mmol). The combined reaction mixtures were partitioned between dilute aqueous $NaHCO_3$ and CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2 (2x), and the combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was initially purified by preparative HPLC (YMC ODS 30x250mm column, detection at 220 nm; flow rate = 25 mL/min; continuous gradient from 50% A to 100% B over 30 min +7 min hold time at 100% B, where A = 90:10:0.1 H_2O:CH3CN:TFA and B = 90:10:0.1 CH_3CN:H_2O:TFA). The residue was dissolved in MeOH and passed through a MeOH treated cartridge of Polymer Lab StratoSpheres TM SPE PL-HCO_3 MP SPE (500 mg) resin, washing well with MeOH. The filtrate was concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2/MeOH, filtered, and concentrated *in vacuo* to give the title compound (5.6 mg, 7%) as a tan gummy solid. $[M + H]^+$ = 569.3; $[M - H]^-$ = 567.3; ^1H NMR (400 MHz, $CDCl_3$): δ 1.24 (t, *J*=7.15 Hz, 6 H), 1.30 (d, *J*=6.05 Hz, 6 H), 3.28 (d, *J*=20.89 Hz, 2 H), 3.98 - 4.09 (m, 4 H), 4.36 (t, *J*=12.37 Hz, 2 H), 4.53 (dt, *J*=12.09, 6.05 Hz, 1 H), 6.57 (s, 1 H), 6.77 (d, *J*=3.30 Hz, 1 H), 7.02 (s, 1 H), 7.09 (s, 1 H), 7.41 - 7.49 (m, 3 H), 7.51 - 7.59 (m, 2 H), 8.01 (d, *J*=7.15 Hz, 1 H); ^{19}F NMR (400 MHz, CDCl3): δ -103.73, -103.76, -103.80.

EXAMPLE 124

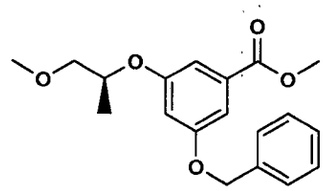


A.



[00465] To a solution of methyl-3,5-dihydroxy benzoate (10.00 g; 59.5 mmol) in DMF (60.0 mL) under Ar was added K_2CO_3 (12.4 g; 89.7 mmol), followed by the slow addition of benzyl bromide (10.0 mL; 84.2 mmol) over 10 min. The reaction mixture was stirred at 25°C for 16 h, then was quenched with sat. aqueous NH_4Cl (50 mL) and water (350 mL). The aqueous suspension was extracted with CH_2Cl_2 (3 x 50mL). The combined organic extracts were washed with water and brine, dried ($MgSO_4$), and concentrated *in vacuo*. The crude product was chromatographed (SiO_2; stepwise gradient from 10-20-30-50% solvent B , where solvent A = hexanes and solvent B = EtOAc) to give Part A compound (4.599 g; 30%) as an off-white powder.

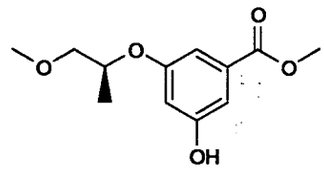
B.



[00466] To a 0°C solution of Part A compound (3.130 g; 12.12 mmol) in THF (52.7 mL) were added (R)-1-methoxypropan-2-ol (1.64 g; 18.18mmol) and Ph_3P (4.77 g; 18.18 mmol), followed by the slow addition of DIAD (3.53 mL; 18.18 mmol)

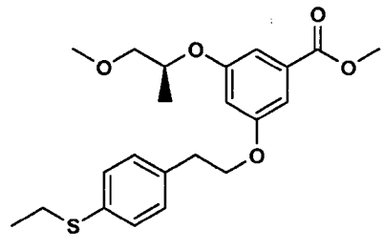
via syringe pump. The reaction mixture was stirred at 25°C for 16 h under Ar, then was diluted with water and extracted with EtOAc (3x). The combined organic extracts were washed with 1N aqueous NaOH and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was chromatographed (SiO_2; stepwise gradient from 5-10-30-50% solvent B, where solvent A = hexanes and solvent B = EtOAc) to give Part B compound (2.892 g; 53%) as a clear, colorless oil.

C.



[00467] A flask containing Part B compound (2.892 g; 8.75 mmol) in MeOH (109 mL) was evacuated and flushed with Ar. 10% Pd/C (0.931 g; 0.875 mmol) was added followed by evacuation of the flask and refilling with H_2 (g; 1 atmosphere). The reaction was stirred for 2 days under H_2. The reaction mixture was filtered and the catalyst was washed with EtOAc. The combined filtrates were concentrated *in vacuo* to give Part C compound (2.075 g; 83%) as a clear, colorless oil.

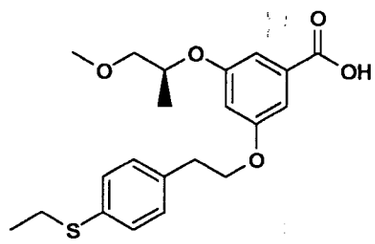
D.



[00468] To a 0°C solution of Part C compound (0.125 g; 0.519 mmol) in THF (2.60 mL) were added 2-(4-(ethylthio)phenyl)ethanol (0.208 g; 1.142 mmol) and Ph_3P (0.299 g; 1.142 mmol), followed by the slow addition of DIAD (0.222 mL; 1.142 mmol). The reaction mixture was stirred at 25°C for 16 h under Ar. The reaction mixture was diluted with water and extracted with EtOAc (3x). The combined organic extracts were washed with 1N aqueous NaOH and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed (SiO_2; stepwise gradient

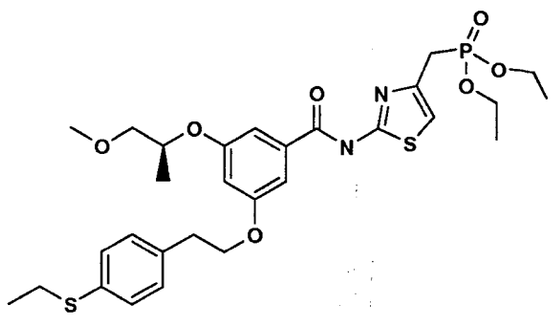
from 5-10-20-30-50% solvent B, where solvent A = hexanes and solvent B = EtOAc) to give Part D compound (0.121 g; 49%) as a clear, yellow oil.

E.



[00469] To a solution of Part D compound (0.1208 g; 0.299 mmol) in THF (2.47 mL) and water (0.25 mL) was added $LiOH.H_2O$ (0.014 g; 0.597 mmol). The reaction mixture was stirred at 45°C for 1 h in a sealed vial, then an additional equivalent of $LiOH.H_2O$ was added. The reaction mixture was stirred at 45°C for 16 h, then was cooled to RT. Volatiles were removed *in vacuo*, and the remaining aqueous solution was acidified with 0.5N aqueous HCl to pH < 2. The aqueous layer was re-extracted with EtOAc (3x). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to give Part E compound (0.1082 g; 76%) as a clear, colorless oil.

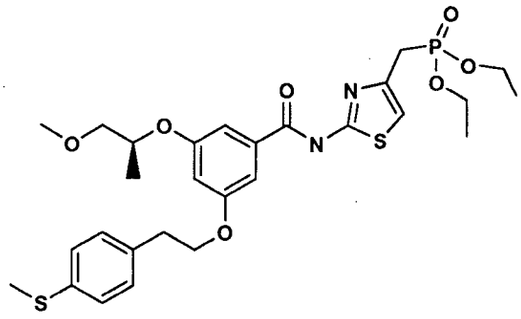
F.



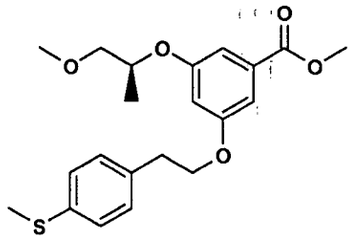
[00470] To a solution of Part E compound (0.160 g; 0.411 mmol) in DMF (2.05 mL) were added HOAT (0.064 g; 0.47 mmol), Example 13 Part E compound (0.123 g; 0.493 mmol), and DIPEA (0.08 mL; 0.47 mmol), and lastly, EDCI (0.091 g; 0.47 mmol). The reaction mixture was stirred at 25°C for 16 h. Water was added, and the mixture was extracted with EtOAc (3x). The combined organic extracts were washed

with sat. aqueous NH_4Cl, sat. aqueous $NaHCO_3$, and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by preparative HPLC (YMC reverse phase ODS-5u 30 x 100 mm column; flow rate = 40 mL/min, 25 to 100% solvent B over 12 min, where solvent A = 90:10:0.1 H_2O: CH_3CN:TFA and solvent B = 90:10:0.1 CH_3CN:H_2O:TFA) to give the title compound (80.4 mg; 31%) as a clear, colorless oil. $[M + H]^+ = 623.2$.

EXAMPLE 125

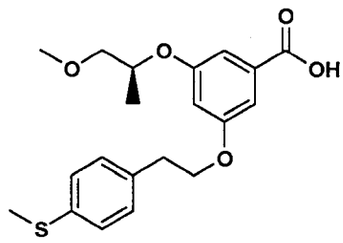


A.



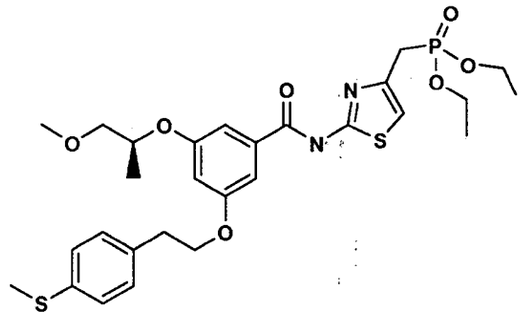
[00471] To a 0°C solution of Example 124 Part C compound (0.125 g; 0.519 mmol) in THF (2.60 mL) was added 2-(4-(methylthio)phenyl)ethanol (0.208 g; 1.142 mmol) and Ph_3P (0.299 g; 1.142 mmol), followed by the slow addition of DIAD (0.222 mL; 1.142 mmol). The reaction mixture was stirred at 25°C for 16 h under Ar, then was diluted with water and extracted with EtOAc (3x). The combined organic extracts were washed with 1N aqueous NaOH and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was chromatographed (SiO_2; step gradient from 5-10-20-30-50% solvent B, where solvent A = hexanes and solvent B = EtOAc) to give Part A compound (0.121 g; 49%) as a clear, yellow oil.

B.



[00472] To a solution of Part A compound (0.1208 g; 0.299 mmol) in THF (2.47 mL) and water (0.25 mL) was added $LiOH.H_2O$ (0.014 g; 0.597 mmol). The reaction mixture was stirred at 45°C for 1 h in a sealed vial, then an additional equivalent of LiOH was added. The reaction mixture was stirred at 45°C for 16 h, then was cooled to RT. Volatiles were removed *in vacuo*, and the remaining aqueous solution was acidified with 0.5N aqueous HCl to pH <2. The aqueous layer was re-extracted with EtOAc (3x). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to give Part B compound (0.1082 g; 76%) as a clear, colorless oil.

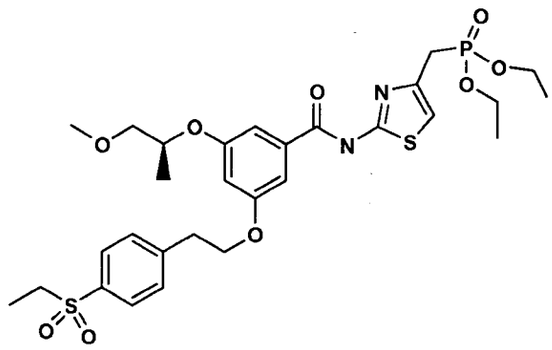
C.



[00473] To a solution of Example 13 Part E compound (0.13 g; 0.51 mmol) in DMF (2.13 mL) were added HOAT (0.067 g; 0.49 mmol), Part B compound (0.16 g; 0.43 mmol), DIPEA (0.63 mL; 0.49 mmol), and, lastly, EDCI (0.094 g; 0.49 mmol). The reaction mixture was stirred at 25°C for 16 h. Water was added, and the mixture was extracted with EtOAc (3x). The combined organic extracts were washed with sat. aqueous NH_4Cl, sat. aqueous $NaHCO_3$, and brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by preparative HPLC (YMC reverse phase ODS-5u 30 x 100 mm column; flow rate = 40 mL/min, 25 to 100% solvent B over 12 min,

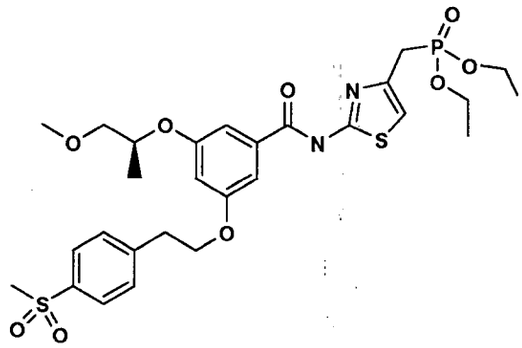
where solvent A = 90:10:0.1 H_2O: CH_3CN:TFA and solvent B = 90:10:0.1 CH_3CN:H_2O:TFA) to give the title compound (47.0 mg; 17%) as a clear, colorless oil. $[M + H]^+ = 609.1$.

EXAMPLE 126



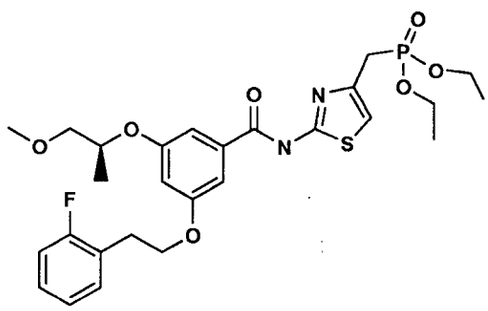
[00474] To Example 124 Part F compound (0.04 g; 0.07 mmol) in iPrOH (1.46 mL) and water (0.73 mL) was added oxone (0.09 g; 0.15 mmol). The reaction mixture was stirred for 16 h at 25°C, then was filtered and extracted with EtOAc. The filtrate was partitioned between water and brine. The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by preparative HPLC (YMC reverse phase ODS-5u 30 x 100 mm column; flow rate = 40 mL/min, 25 to 100% solvent B over 12 min, where solvent A = 90:10:0.1 H_2O:CH_3CN:TFA and solvent B = 90:10:0.1 CH_3CN:H_2O:TFA) to give the title compound (48.0 mg; 55%) as a white solid. $[M + H]^+ = 655.3$; ^1H NMR (400 MHz, $CDCl_3$): δ 1.16 - 1.29 (m, 12 H), 2.98 - 3.08 (m, *J*=7.33, 7.33, 7.33 Hz, 2 H), 3.08 - 3.18 (m, *J*=6.32, 6.32 Hz, 2 H), 3.22 (s, 1 H), 3.28 (s, 1 H), 3.33 (s, 3 H), 3.41 - 3.54 (m, 2 H), 4.01 - 4.13 (m, 4 H), 4.24 (t, *J*=6.32 Hz, 2 H), 4.61 - 4.70 (m, *J*=10.17, 6.32 Hz, 1 H), 6.64 - 6.70 (m, 1 H), 6.93 - 6.97 (m, *J*=3.30 Hz, 1 H), 7.29 (d, *J*=17.59 Hz, 2 H), 7.42 (d, *J*=8.24 Hz, 2 H), 7.78 (d, *J*=8.25 Hz, 2 H).

EXAMPLE 127

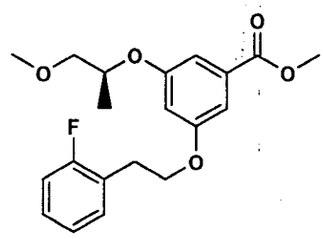


[00475] To Example 125 Part C compound (0.04 g; 0.07 mmol) in iPrOH (1.46 mL) and water (0.73 mL) was added oxone (0.09 g; 0.15 mmol). The reaction mixture was stirred for 16 h at 25°C, then was filtered and rinsed with EtOAc. The filtrate was washed with water and brine, dried ($MgSO_4$) and concentrated *in vacuo.* The residue was purified by preparative HPLC (YMC reverse phase ODS-5u 30 x 100 mm column; flow rate = 40 mL/min, 25 to 100% solvent B over 12 min, where solvent A = 90:10:0.1 H_2O: CH_3CN:TFA and solvent B = 90:10:0.1 CH_3CN:H_2O:TFA) to give the title compound (14.2 mg; 33%) as a white solid. $[M + H]^+ = 641.3$; ^1H NMR (400 MHz, $CDCl_3$): δ 1.21 - 1.30 (m, *J*=7.42, 7.42 Hz, 9 H), 2.97 (s, 3 H), 3.12 (t, *J*=6.05 Hz, 2 H), 3.26 (s, 1 H), 3.29 - 3.36 (m, 4 H), 3.41 - 3.55 (m, 2 H), 4.03 - 4.16 (m, 4 H), 4.25 (t, *J*=6.32 Hz, 2 H), 4.60 - 4.72 (m, 1 H), 6.62 - 6.71 (m, 1 H), 6.91 - 7.01 (m, *J*=3.85 Hz, 1 H), 7.32 (d, *J*=16.49 Hz, 2 H), 7.43 (d, *J*=8.25 Hz, 2 H), 7.81 (d, *J*=8.24 Hz, 2 H).

EXAMPLE 128

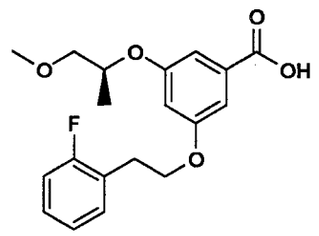


A.



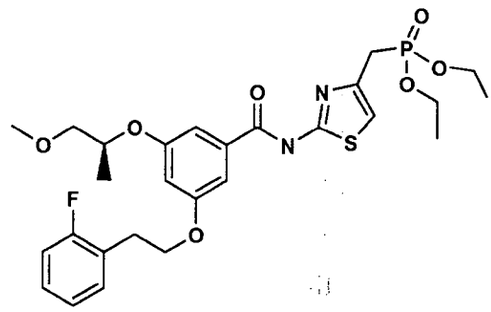
[00476] To Example 124 Part C compound (0.100g; 0.416 mmol) was added 2-(2-fluorophenyl) ethanol (0.24 g; 1.67 mmol in toluene; 2.08 mL), followed by a suspension of Example 97 Part B compound (0.68 g; 1.67 mmol) in CH_2Cl_2 (7.6 mL). The reaction mixture was stirred for 16 h at 25°C, then was diluted with water and extracted with EtOAc (3x). The combined organic extracts were washed with 1N aqueous NaOH and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was chromatographed (SiO_2; step gradient from 10-20-30% solvent B , where solvent A = hexanes and solvent B = EtOAc) to give Part A compound (0.146 g; 90%).

B.



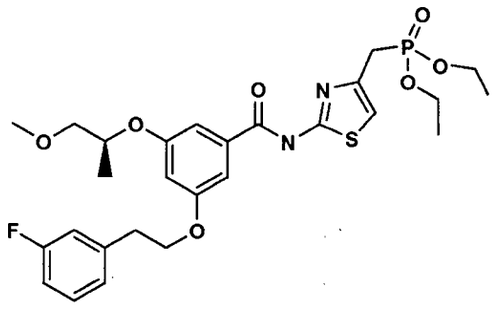
[00477] To a solution of Part A compound (0.100 g; 0.27 mmol) in THF (2.23 mL) and water (0.22 mL) was added $LiOH.H_2O$ (0.013 g; 0.54 mmol). The reaction mixture was stirred at 45°C for 1 h in a sealed vial, then an additional equivalent of $LiOH.H_2O$ was added. The reaction mixture was stirred at 45°C for 16 h, then cooled to RT. Volatiles were removed *in vacuo* and the remaining aqueous solution was acidified with 0.5N aqueous HCl to pH <2. The aqueous layer was re-extracted with EtOAc (3x). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to give Part B compound (0.107 g; 100%).

C.

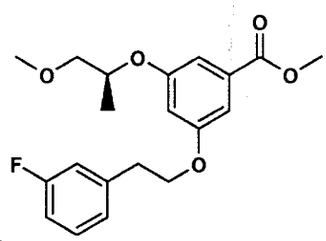


[00478] To a solution of Example 13 Part E compound (0.073 g; 0.29 mmol) in DMF (1.21 mL) were added HOAT (0.038 g; 0.278 mmol), Part B compound (0.084 g; 0.242 mmol), and DIPEA (0.049 mL; 0.278 mmol) and, lastly, EDCI (0.053 g; 0.278 mmol). The reaction mixture was stirred at 25°C for 16 h. Water was added, and the mixture was extracted with EtOAc (3x). The combined organic extracts were washed with sat. aqueous NH_4Cl, sat. aqueous $NaHCO_3$, and brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by preparative HPLC (YMC reverse phase ODS-5μm 30 x 100 mm column; flow rate = 40 mL/min, 25 to 100% solvent B over 12 min, where solvent A = 90:10:0.1 H_2O:CH_3CN:TFA and solvent B = 90:10:0.1 CH_3CN:H_2O:TFA) to give the title compound (69.7 mg; 49%) as a clear, colorless oil. $[M + H]^+$ = 581.5; ^1H NMR (400 MHz, $CDCl_3$) δ 1.21 - 1.26 (m, 9 H), 3.06 (t, *J*=6.87 Hz, 2 H), 3.21 (s, 1 H), 3.26 (s, 1 H), 3.31 - 3.35 (m, 3 H), 3.41 - 3.53 (m, 2 H), 3.98 - 4.10 (m, 4 H), 4.18 (t, *J*=6.60 Hz, 2 H), 4.61 - 4.71 (m, 1 H), 6.63 - 6.70 (m, 1 H), 6.84 - 7.06 (m, 3 H), 7.10 - 7.17 (m, 1 H), 7.18 - 7.25 (m, *J*=12.64 Hz, 3 H), 7.26 - 7.30 (m, 1 H).

EXAMPLE 129

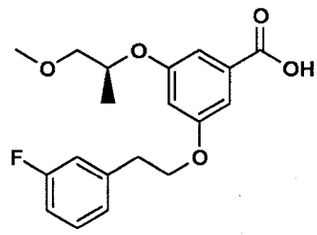


A.



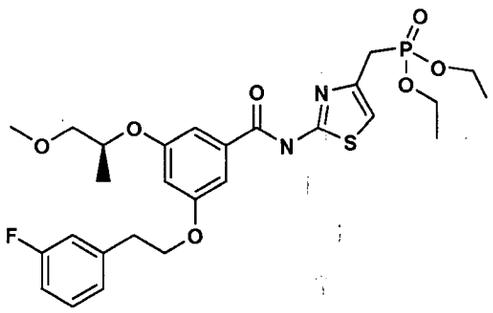
[00479] To Example 124 Part C compound (0.100g; 0.416 mmol) were added 2-(3-fluorophenyl)ethanol (0.24 g; 1.67 mmol in toluene (2.08 mL) followed by a suspension of Example 97 Part B compound (0.68 g; 1.67 mmol) in CH_2Cl_2 (7.6 mL). The reaction mixture was stirred for 16 h at 25°C, then was diluted with water and extracted with EtOAc (3x). The combined organic extracts were washed with 1N aqueous NaOH and brine, dried ($MgSO_4$), and concentrated *in vacuo*. The crude product was chromatographed (SiO_2; step gradient from 10-20-30% solvent B, where solvent A = hexanes and solvent B = EtOAc) to give Part A compound (0.146 g; 90%).

B.



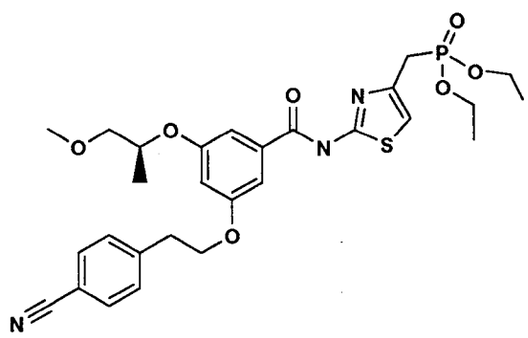
[00480] To a solution of Part A compound (0.100 g; 0.27 mmol) in THF (2.23 mL) and water (0.22 mL) was added $LiOH.H_2O$ (0.013 g; 0.54 mmol). The reaction mixture was stirred at 45°C for 1 h in a sealed vial, then an additional equivalent of $LiOH.H_2O$ was added. The reaction mixture was stirred at 45°C for 16 h, then was cooled to RT. Volatiles were removed *in vacuo*, and the remaining aqueous solution was acidified with 0.5N aqueous HCl to pH < 2. The aqueous layer was re-extracted with EtOAc (3x). The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo* to give Part B compound (0.107 g; 100%).

C.

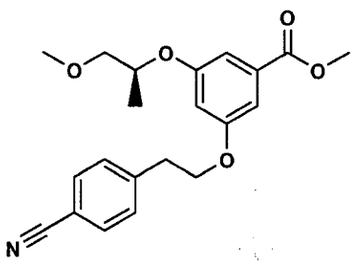


[00481] To a solution of Example 13 Part E compound (0.092 g; 0.37 mmol) in DMF (1.54 mL) were added HOAT (0.038 g; 0.35 mmol) Part B compound (0.107 g; 0.308 mmol), DIPEA (0.062 mL; 0.35 mmol) and, lastly, EDCI (0.068 g; 0.35 mmol). The reaction mixture was stirred at 25°C for 16 h. Water was added, and the mixture was extracted with EtOAc (3x). The combined organic extracts were washed with sat. aqueous NH_4Cl, sat. aqueous $NaHCO_3$, and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by preparative HPLC (YMC reverse phase ODS-5µm 30 x 100 mm column; flow rate = 40 mL/min, 25 to 100% solvent B over 12 min, where solvent A = 90:10:0.1 H_2O:CH_3CN:TFA and solvent B = 90:10:0.1 CH_3CN:H_2O:TFA) to give the title compound (78.5 mg; 44%) as a clear, colorless oil. $[M + H]^+$ = 581.1; ^1H NMR (400 MHz, $CDCl_3$) δ 1.17 - 1.28 (m, 9 H), 3.01 (t, *J*=6.32 Hz, 2 H), 3.24 (s, 1 H), 3.26 - 3.36 (m, 4 H), 3.42 - 3.54 (m, 2 H), 4.00 - 4.14 (m, 4 H), 4.19 (t, *J*=6.32 Hz, 2 H), 4.62 - 4.73 (m, 1 H), 6.64 - 6.70 (m, 1 H), 6.79 - 6.88 (m, *J*=8.52, 8.52 Hz, 1 H), 6.88 - 7.02 (m, 3 H), 7.12 - 7.22 (m, 1 H), 7.25 - 7.30 (m, 1 H), 7.28 (s, 1 H), 7.33 (s, 1 H), 7.31 - 7.36 (m, 1 H).

EXAMPLE 130

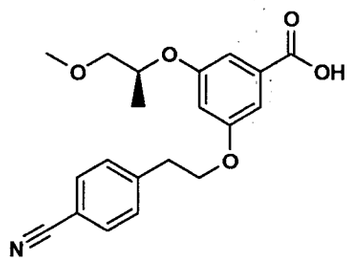


A.



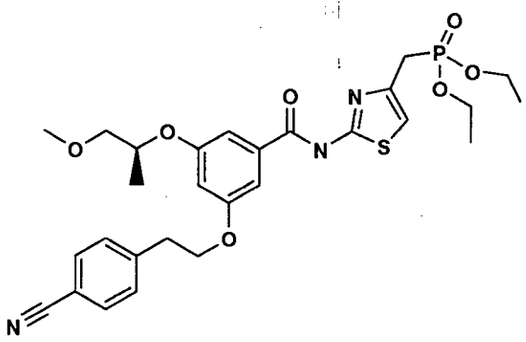
[00482] To Example 124 Part C compound (0.100g; 0.416 mmol) was added 4-(2-hydroxyethyl) benzonitrile (0.09 g; 0.62 mmol in toluene (2.08 mL) followed by a suspension of Example 97 Part B compound (0.26 g; 0.62 mmol) in CH_2Cl_2 (7.14 mL). The reaction mixture was stirred for 16 h at 25°C, then was diluted with water and extracted with EtOAc (3x). The combined organic extracts were washed with 1N aqueous NaOH and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was chromatographed (SiO_2; stepwise gradient from 5-10-20% solvent B , where solvent A = hexanes and solvent B = EtOAc) to give Part A compound (0.100 g; 63%).

B.



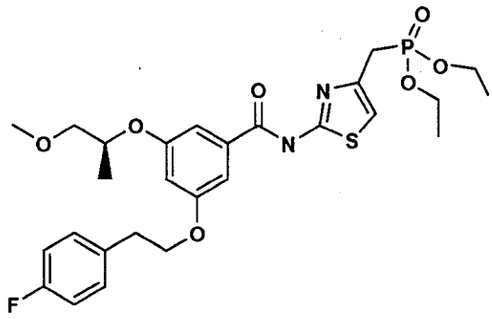
[00483] To a solution of Part A compound (0.15 g; 0.40 mmol) in THF (3.27 mL) and water (0.33 mL) was added $LiOH.H_2O$ (0.019 g; 0.79 mmol). The reaction mixture was stirred at 45°C for 1 h in a sealed vial, then an additional equivalent of LiOH was added. The reaction mixture was stirred at 45°C for 16 h, then was cooled to RT. Volatiles were removed *in vacuo*, and the remaining aqueous solution was acidified with 0.5N aqueous HCl to pH <2. The aqueous layer was re-extracted with EtOAc (3x). The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo* to give Part B compound (0.140 g; 85%).

C.

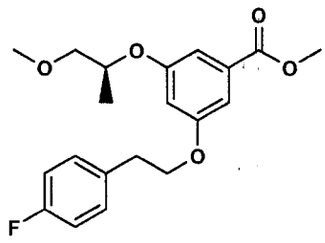


[00484] To a solution of Example 13 Part E compound (0.114 g; 0.454 mmol) in DMF (1.89 mL) were added HOAT (0.059 g; 0.44 mmol), Part B compound (0.134 g; 0.378 mmol), DIPEA (0.076 mL; 0.35 mmol), and, lastly, EDCI (0.083 g; 0.435 mmol). The reaction mixture was stirred at 25°C for 16 h. Water was added, and the mixture was extracted with EtOAc (3x). The combined organic extracts were washed with sat. aqueous NH_4Cl, sat. aqueous $NaHCO_3$, and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by preparative HPLC (YMC reverse phase ODS-5u 30 x 100 mm column; flow rate = 40 mL/min, 25 to 100% solvent B over 12 min, where solvent A = 90:10:0.1 H_2O:CH_3CN:TFA and solvent B = 90:10:0.1 CH_3CN:H_2O:TFA) to give the title compound (86.5 mg; 39%) as a tacky, clear, white solid. $[M + H]^+$ = 588.1; ^1H NMR (400 MHz, $CDCl_3$): δ 1.18 - 1.27 (m, 9 H), 3.07 (t, *J*=6.32 Hz, 2 H), 3.20 (s, 1 H), 3.25 (s, 1 H), 3.33 (s, 3 H), 3.40 - 3.53 (m, 2 H), 3.97 - 4.09 (m, 4 H), 4.19 (t, *J*=6.32 Hz, 2 H), 4.55 - 4.66 (m, *J*=3.85 Hz, 1 H), 6.63 (s, 1 H), 6.84 - 6.90 (m, *J*=3.30 Hz, 1 H), 7.17 - 7.21 (m, *J*=3.85 Hz, 1 H), 7.24 (s, 1 H), 7.33 (d, *J*=8.25 Hz, 2 H), 7.53 (d, *J*=8.25 Hz, 2 H).

EXAMPLE 131

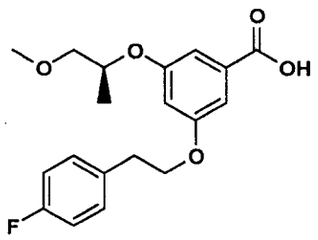


A.



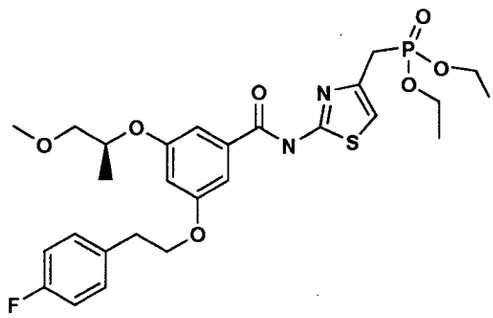
[00485] To Example 124 Part C compound (0.100g; 0.416 mmol) were added a solution of 2-(4-flurorophenyl)ethanol (0.58 g; 4.16 mmol) in toluene (2.18 mL) and a suspension of Example 97 Part B compound (1.71 g; 4.16 mmol) in CH_2Cl_2 (7.60 mL). The reaction mixture was stirred for 16 h at 25°C, then was diluted with water and extracted with EtOAc (3x). The combined organic extracts were washed with 1N aqueous NaOH and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was chromatographed (SiO_2; step gradient from 5-10-15-20% solvent B, where solvent A = hexanes and solvent B = EtOAc) to give Part A compound (0.137 g; 86%).

B.



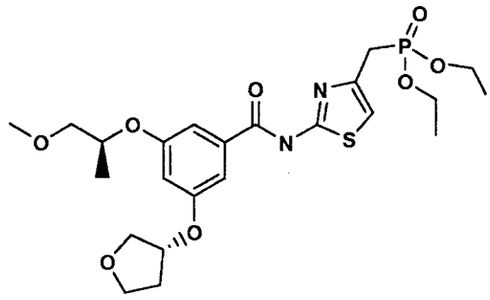
[00486] To a solution of Part A compound (0.14 g; 0.38 mmol) in THF (3.27 mL) and water (0.33 mL) was added $LiOH.H_2O$ (0.010 g; 0.38 mmol). The reaction mixture was stirred at 45°C for 1 h in a sealed vial, then an additional equivalent of LiOH was added. The reaction mixture was stirred at 45°C for 16 h, then was cooled to RT. Volatiles were removed *in vacuo*, and the remaining aqueous solution was acidified with 0.5N aqueous HCl to pH less than 2. The aqueous layer was re-extracted with EtOAc (3x). The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo* to give Part B compound (0.122 g; 78%).

C.

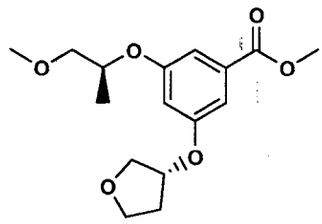


[00487] To a solution of Example 13 Part E compound (0.106 g; 0.422 mmol) in DMF (1.76 mL) were added HOAT (0.055 g; 0.404 mmol), Part B compound (0.122 g; 0.351 mmol), DIPEA (0.071 mL; 0.404 mmol), and, lastly, EDCI (0.077 g; 0.404 mmol). The reaction mixture was stirred at 25°C for 16 h. Water was added, and the mixture was extracted with EtOAc (3x). The combined organic extracts were washed with sat. aqueous NH_4Cl, sat. aqueous $NaHCO_3$, and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by preparative HPLC (YMC reverse phase ODS-5u 30 x 100 mm column; flow rate = 40 mL/min, 25 to 100% solvent B over 12 min, where solvent A = 90:10:0.1 H_2O:CH_3CN:TFA and solvent B = 90:10:0.1 CH_3CN:H_2O:TFA) to give the title compound (80.0 mg; 39%) as a clear, pale yellow oil. $[M + H]^+$ = 581.2; ^1H NMR (400 MHz, $CDCl_3$): δ 1.21 - 1.33 (m, 9 H), 3.06 (t, 2 H), 3.25 (s, 1 H), 3.31 (s, 1 H), 3.39 (s, 3 H), 3.45 - 3.60 (m, 2 H), 4.00 - 4.15 (m, 4 H), 4.19 (t, 2 H), 4.60 - 4.70 (m, 1 H), 6.65 - 6.72 (m, 1 H), 6.88 - 6.94 (m, 1 H), 6.99 (t, 2 H), 7.13 - 7.27 (m, 4 H), 11.77 (s, 1 H).

EXAMPLE 132

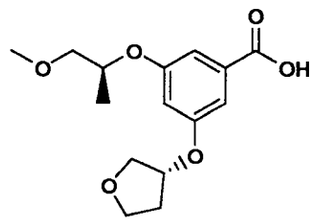


A.



[00488] To a cold solution (0°C) of Example 124 Part C compound (0.100 g; 0.416 mmol) in THF (2.08 mL) were added (S)-(+)-3-Hydroxytetrahydrofuran (0.074 mL; 0.916 mmol) and Ph_3P (0.24 g; 0.916 mmol), followed by the slow addition of DIAD (0.178 mL; 0.916mmol). The reaction mixture was stirred at 25°C for 16 h under at atmosphere of Ar. The reaction mixture was diluted with water and extracted with EtOAc (3x). The combined organic extracts were washed with 1N aqueous NaOH and brine, dried ($MgSO_4$), and concentrated *in vacuo*. The crude product was chromatographed (SiO_2; stepwise gradient from 10-15-20% solvent B, where solvent A = hexanes and solvent B = EtOAc) to give Part A compound (0.105 g; 75%).

B.



[00489] To a solution of Part A compound (0.105 g; 0.337 mmol) in THF (2.79 mL) and water (0.279 mL) was added $LiOH.H_2O$ (0.028 g; 0.674 mmol). The reaction

PATENTE DE INVENCION

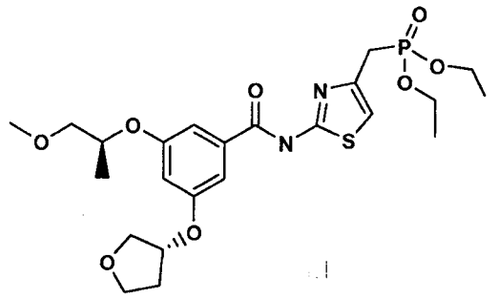
Organizacion y
Digitalizacion CSA Ltda

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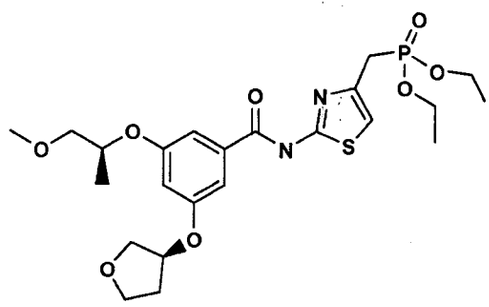
mixture was stirred at 45°C for 1 h in a sealed vial, then an additional equivalent of LiOH was added. The reaction mixture was stirred at 45°C for 16 h, then was cooled to RT. Volatiles were removed *in vacuo*, and the remaining aqueous solution was acidified with 0.5N aqueous HCl to pH < 2. The aqueous layer was re-extracted with EtOAc (3x). The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo* to give Part B compound (0.0964 g; 97%).

C.

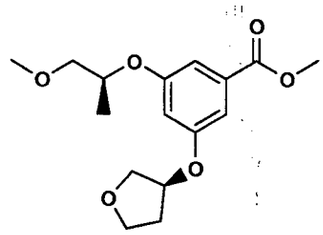


[00490] To a solution of Example 13 Part E compound (0.098 g; 0.390 mmol) in DMF (1.63 mL) were added HOAT (0.051 g; 0.374 mmol), Part B compound (0.096 g; 0.325 mmol), DIPEA (0.065 mL; 0.374 mmol), and, lastly, EDCI (0.072 g; 0.374 mmol). The reaction mixture was stirred at 25°C for 16 h. Water was added, and the mixture was extracted with EtOAc (3x). The combined organic extracts were washed with sat.aqueous NH_4Cl, sat. aqueous $NaHCO_3$, and brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by preparative HPLC (YMC reverse phase ODS-5u 30 x 100 mm column; flow rate = 40 mL/min, 25 to 100% solvent B over 12 min, where solvent A = 90:10:0.1 H_2O:CH_3CN:TFA and solvent B = 90:10:0.1 CH_3CN:H_2O:TFA) to give the title compound (84.3 mg; 49%) as a clear, colorless oil. $[M + H]^+$ = 529.1; ^1H NMR (400 MHz, $CDCl_3$): δ 1.19 - 1.34 (m, 9 H), 2.06 - 2.30 (m, 2 H), 3.25 (s, 1 H), 3.30 (s, 1 H), 3.39 (s, 3 H), 3.43 - 3.61 (m, 2 H), 3.84 - 4.00 (m, 4 H), 4.00 - 4.13 (m, 4 H), 4.54 - 4.64 (m, 1 H), 4.91 - 5.00 (m, 1 H), 6.62 - 6.70 (m, 1 H), 6.80 - 6.88 (m, *J*=3.85 Hz, 1 H), 7.06 (s, 1 H), 7.13 (s, 1 H), 10.53 (s, 1 H).

EXAMPLE 133

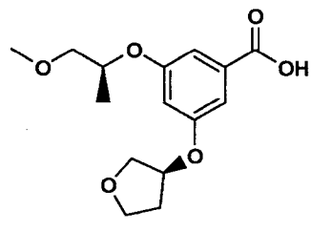


A.



[00491] To a 0°C solution of Example 124 Part C compound (0.100 g; 0.416 mmol) in THF (2.08 mL) were added (R)-(-)-3-hydroxytetrahydrofuran (0.033 mL; 0.416 mmol) and Ph_3P (0.24 g; 0.916 mmol), followed by the slow addition of DIAD (0.178 mL; 0.916mmol). The reaction mixture was stirred at 25°C for 16 h under Ar, then was diluted with water and extracted with EtOAc (3x). The combined organic extracts were washed with 1N aqueous NaOH and brine, dried ($MgSO_4$), and concentrated *in vacuo*. The crude product was chromatographed (SiO_2; stepwise gradient from 10-15-20% solvent B, where solvent A = hexanes and solvent B = EtOAc) to give Part A compound (0.088 g; 62%).

B.

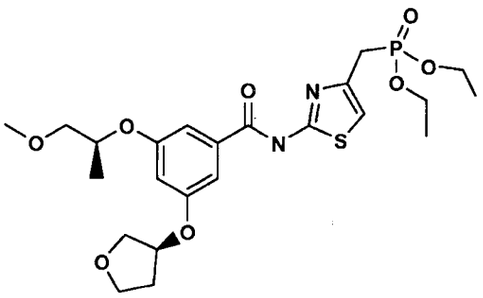


[00492] To a solution of Part A compound (0.088 g; 0.282 mmol) in THF (2.33 mL) and water (0.233 mL) was added $LiOH.H_2O$ (0.024 g; 0.565 mmol). The reaction

000275

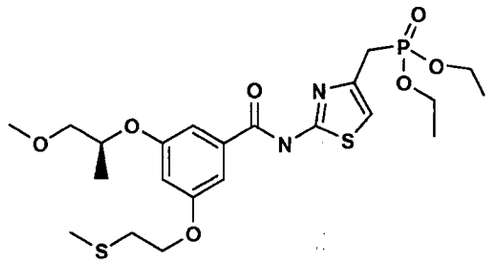
mixture was stirred at 45°C for 1 h in a sealed vial, then an additional equivalent of LiOH was added. The reaction mixture was stirred at 45°C for 16 h, then was cooled to RT. Volatiles were removed *in vacuo*, and the remaining aqueous solution was acidified with 0.5N aqueous HCl to pH <2. The aqueous layer was re-extracted with EtOAc (3x). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to give Part B compound (0.0654 g; 74%).

C.

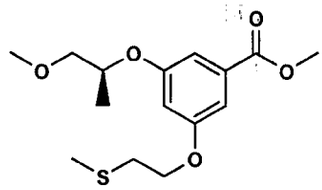


[00493] To a solution of Example 13 Part E compound (0.066 g; 0.265 mmol) in DMF (1.10 mL) were added HOAT (0.035 g; 0.254 mmol), Part B compound (0.065 g; 0.221 mmol), DIPEA (0.044 mL; 0.254 mmol), and, lastly, EDCI (0.049 g; 0.254 mmol). The reaction mixture was stirred at 25°C for 16 h. Water was added, and the mixture was extracted with EtOAc (3x). The combined organic extracts were washed with sat. aqueous NH_4Cl, sat. aqueous $NaHCO_3$, and brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by preparative HPLC (YMC reverse phase ODS-5u 30 x 100 mm column; flow rate = 40 mL/min, 25 to 100% solvent B over 12 min, where solvent A = 90:10:0.1 H_2O:CH_3CN:TFA and solvent B = 90:10:0.1 CH_3CN:H_2O:TFA) to give the title compound (50.5 mg; 43%) as a clear, colorless oil. $[M + H]^+$ = 529.1; ^1H NMR (400 MHz, $CDCl_3$): δ 1.21 - 1.33 (m, 9 H), 2.03 - 2.17 (m, 1 H), 2.17 - 2.28 (m, 1 H), 3.25 (s, 1 H), 3.31 (s, 1 H), 3.38 (s, 3 H), 3.44 - 3.53 (m, 1 H), 3.52 - 3.59 (m, 1 H), 3.68 (s, 2 H), 3.83 - 3.92 (m, 1 H), 3.93 - 4.01 (m, 2 H), 4.03 - 4.12 (m, 3 H), 4.57 - 4.67 (m, 1 H), 4.96 - 5.02 (m, *J*=2.20 Hz, 1 H), 6.67 (s, 1 H), 6.85 - 6.92 (m, *J*=3.85 Hz, 1 H), 7.13 (s, 1 H), 7.20 (s, 1 H).

EXAMPLE 134

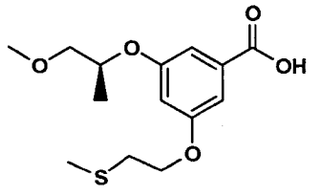


A.



[00494] To a 0°C solution of Example 124 Part C compound (0.125 g; 0.519 mmol) in THF (2.60 mL) were added 2-(methylthio)ethanol (0.105 mL; 1.14 mmol) and Ph_3P (0.30 g; 1.142 mmol), followed by the slow addition of DIAD (0.222 mL; 1.142 mmol). The reaction mixture was stirred at 25°C for 16 h under Ar, then was diluted with water and extracted with EtOAc (3x). The combined organic extracts were washed with 1N aqueous NaOH and brine, dried ($MgSO_4$), and concentrated *in vacuo*. The crude product was chromatographed (SiO_2; step gradient from 20-30-50-60% solvent B, where solvent A = hexanes and solvent B = EtOAc) to give Part A compound (61.8 mg; 38%).

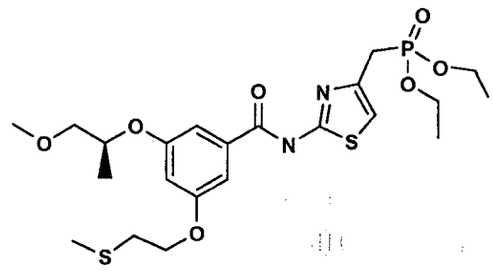
B.



[00495] To a solution of Part A compound (0.062 g; 0.197 mmol) in THF (1.63 mL) and water (0.163 mL) was added $LiOH.H_2O$ (0.016 g; 0.393 mmol). The reaction mixture was stirred at 45°C for 1 h in a sealed vial, then an additional equivalent of LiOH was added. The reaction mixture was stirred at 45°C for 16 h,

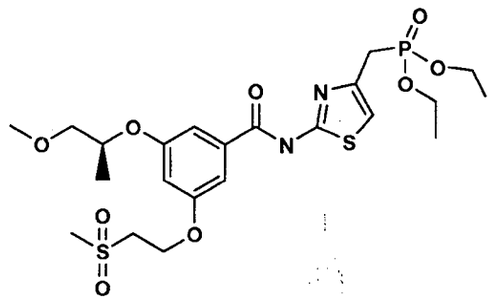
then was cooled to RT. Volatiles were removed *in vacuo*, and the remaining aqueous solution was acidified with 0.5N aqueous HCl to pH <2. The aqueous layer was re-extracted with EtOAc (3x). The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo* to give Part B compound (0.052 g; 88%).

C.



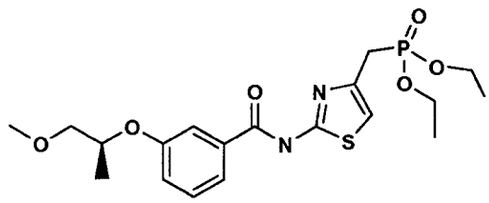
[00496] To a solution of Example 13 Part E compound (0.059 g; 0.236 mmol) in DMF (0.98 mL) were added HOAT (0.031 g; 0.226 mmol), Part B compound (0.059 g; 0.196 mmol), DIPEA (0.034 mL; 0.196 mmol), and, lastly, EDCI (0.043 g; 0.226 mmol). The reaction mixture was stirred at 25°C for 16 h. Water was added, and the mixture was extracted with EtOAc (3x). The combined organic extracts were washed with sat. aqueous NH_4Cl, sat. aqueous $NaHCO_3$, and brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by preparative HPLC (YMC reverse phase ODS-5u 30 x 100 mm column; flow rate = 40 mL/min, 25 to 100% solvent B over 12 min, where solvent A = 90:10:0.1 H_2O:CH_3CN:TFA and solvent B = 90:10:0.1 CH_3CN:H_2O:TFA) to give the title compound (62.3 mg; 60%) as a clear, colorless oil. $[M + H]^+$ = 533.4; ^1H NMR (400 MHz, $CDCl_3$): δ 1.23 - 1.31 (m, 9 H), 2.15 (s, 3 H), 3.27 (s, 1 H), 3.31 - 3.37 (m, 4 H), 3.44 - 3.56 (m, 2 H), 3.99 - 4.15 (m, 4 H), 4.19 (t, 2 H), 4.65 - 4.77 (m, 1 H), 6.69 - 6.74 (m, 1 H), 6.95 - 7.00 (m, 1 H), 7.28 - 7.33 (m, 1 H), 7.35 - 7.40 (m, 1 H).

EXAMPLE 135

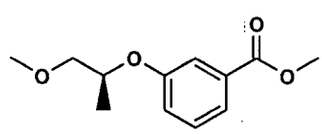


[00497] To a 0°C solution of Example 134 Part C compound (0.040 g; 0.075 mmol) in CH_2Cl_2 (0.75 mL) was added *m*CPBA (0.026 g; 0.15 mmol). The reaction mixture was stirred for 1 h at 0°C, then was warmed to RT. The reaction mixture was filtered, quenched with sat. aqueous $NaHCO_3$, and extracted with CH_2Cl_2 (3x). The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by preparative HPLC (YMC reverse phase ODS-5u 30 x 100 mm column; flow rate = 40 mL/min, 25 to 100% solvent B over 12 min, where solvent A = 90:10:0.1 H_2O:CH_3CN:TFA and solvent B = 90:10:0.1 CH_3CN:H_2O:TFA) to give the title compound (10.6 mg; 25%) as a clear, colorless oil. $[M + H]^+$ = 565.2; ^1H NMR (400 MHz, $CDCl_3$): δ 1.26 - 1.34 (m, 9 H), 3.05 (s, 3 H), 3.29 (s, 1 H), 3.34 (s, 1 H), 3.39 (s, 4 H), 3.43 (t, 3 H), 3.49 - 3.60 (m, 2 H), 4.07 - 4.18 (m, 4 H), 4.52 (t, *J*=10.44 Hz, 3 H), 4.69 - 4.79 (m, 1 H), 6.72 - 6.78 (m, 1 H), 6.99 - 7.05 (m, 1 H), 7.40 (s, 1 H), 7.45 (s, 1 H).

EXAMPLE 136

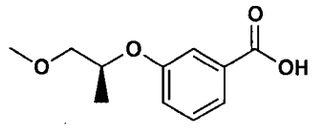


A.



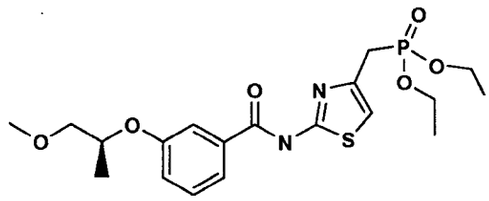
[00498] To a cold solution (0°C) of 2-hydroxy-methylbenzoate (0.20 g; 1.31 mmol) in THF (5.70 mL) were added (R)-(-)-1-methoxy-2-propanol (0.178 g; 1.97 mmol) and Ph_3P (0.517 g; 1.97 mmol), followed by the slow addition of DIAD (0.398 g; 1.97 mmol). The reaction mixture was stirred at 25°C for 16 h under Ar, then was diluted with water and extracted with EtOAc (3x). The combined organic extracts were washed with 1N aqueous NaOH and brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was chromatographed (SiO_2; stepwise gradient from 10-20-30% solvent B, where solvent A = hexanes and solvent B = EtOAc) to give Part A compound (0.219g; 74%).

B.



[00499] To a solution of Part A compound (0.219 g; 0.975 mmol) in THF (3.75 mL) and water (1.19 mL) was added $LiOH.H_2O$ (0.049 g; 1.07 mmol). The reaction mixture was stirred at 45°C for 1 h in a sealed vial, then an additional equivalent of LiOH was added. The reaction mixture was stirred at 50°C for 2 h, then cooled to RT. Volatiles were removed *in vacuo*, and the remaining aqueous solution was acidified with 0.5N aqueous HCl to pH < 2. The aqueous layer was re-extracted with EtOAc (3x). The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo* to give Part B compound (0.221 g; 100%).

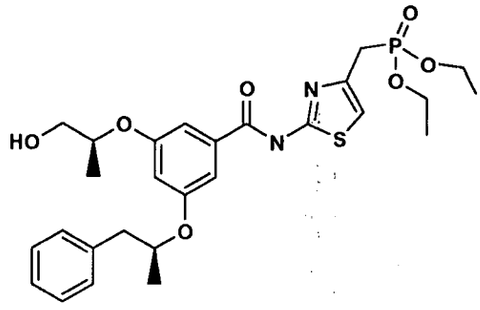
C.



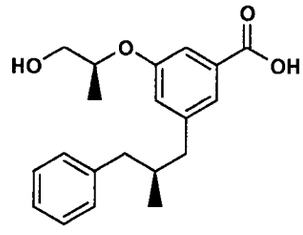
[00500] To a solution of Example 13 Part E compound (0.043 g; 0.171 mmol) in DMF (0.55 mL) were added HOAT (0.022 g; 0.164 mmol), Part B compound (0.030 g; 0.143 mmol), DIPEA (0.029 mL; 0.164 mmol), and, lastly, EDCI (0.031 g; 0.164

mmol). The reaction mixture was stirred at 25°C for 16 h. Water was added, and the mixture was extracted with EtOAc (3x). The combined organic extracts were washed with sat. aqueous NH_4Cl, sat. aqueous $NaHCO_3$, and brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by preparative HPLC (YMC reverse phase ODS-5µm, 30 x 100 mm column; flow rate = 40 mL/min, 25 to 100% solvent B over 12 min, where solvent A = 90:10:0.1 H_2O:CH_3CN:TFA and solvent B = 90:10:0.1 CH_3CN:H_2O:TFA) to give the title compound (17.3 mg; 27%) as a tacky, pale yellow oil. $[M + H]^+$ = 443.3; ^1H NMR (400 MHz, $CDCl_3$): δ 1.22 - 1.30 (m, 9 H), 3.30 (s, 1 H), 3.35 (s, 3 H), 3.35 (s, 4 H), 3.47 - 3.58 (m, 2 H), 4.01 - 4.16 (m, 4 H), 4.75 - 4.83 (m, 1 H), 6.96 - 7.00 (m, *J*=3.85 Hz, 1 H), 7.14 - 7.18 (m, *J*=8.24, 2.20 Hz, 1 H), 7.37 (t, *J*=7.97 Hz, 1 H), 7.70 (d, *J*=7.70 Hz, 2 H), 7.70 (d, *J*=7.70 Hz, 1 H).

EXAMPLE 137



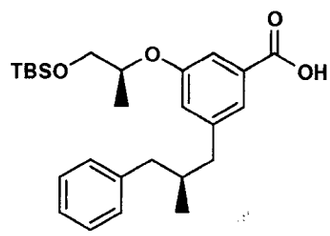
A.



[00501] To a solution of Example 33 Part A acid (0.058 g; 0.17 mmol) in Et_2O (1.30 mL) under Ar was added TMSI (0.203 g; 1.01 mmol). The reaction mixture was stirred at 25°C for 16 h, then was cooled to -40°C, cautiously quenched with water, and concentrated *in vacuo*. The residue was diluted with EtOAc and 1N aqueous HCl. The organic layer was washed with 10% (w/v) aqueous $Na_2S_2O_3$, washed with brine,

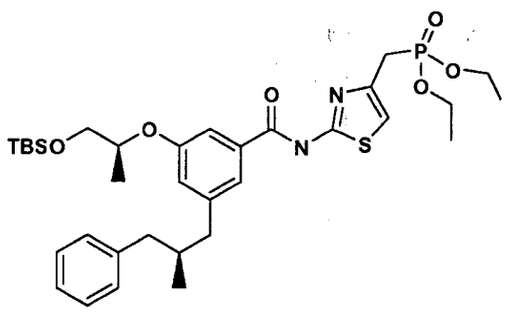
dried ($MgSO_4$), and concentrated *in vacuo* to give Part A compound (0.056 g; 99%) as a yellow oil.

B.



[00502] A solution of TBSCl (0.076 g; 0.504 mmol) in DMF (0.37 mL) was added to Part A compound (0.056 g; 0.17 mmol). Imidazole (0.069 g; 1.01 mmol) was added, and the reaction mixture was stirred for 2 h at 25°C, then was partitioned between EtOAc and sat. aqueous NH_4Cl. The organic phase was washed with sat. aqueous NH_4Cl and brine, dried ($MgSO_4$), and concentrated *in vacuo.* The residue was chromatographed (SiO_2; stepwise gradient from 20-25-30% solvent B, where solvent A = hexanes and solvent B = EtOAc) to give Part B compound (0.057 g; 76%).

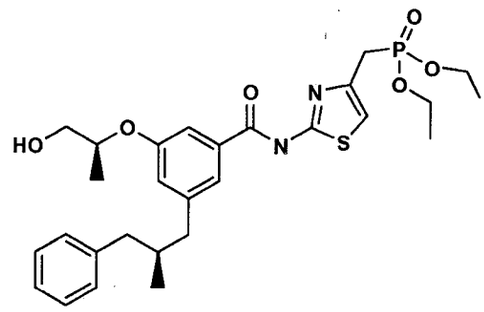
C.



[00503] To a solution of Example 13 Part E compound (0.038 g; 0.152 mmol) in DMF (0.49 mL) were added HOAT (0.020 g; 0.146 mmol), Part B compound (0.057 g; 0.127 mmol), DIPEA (0.026 mL; 0.146 mmol), and, lastly, EDCI (0.028 g; 0.146 mmol). The reaction mixture was stirred at 25°C for 16 h. Water was added, and the mixture was extracted with EtOAc (3x). The combined organic extracts were washed with sat. aqueous NH_4Cl, sat. aqueous $NaHCO_3$, and brine. The organic layer was

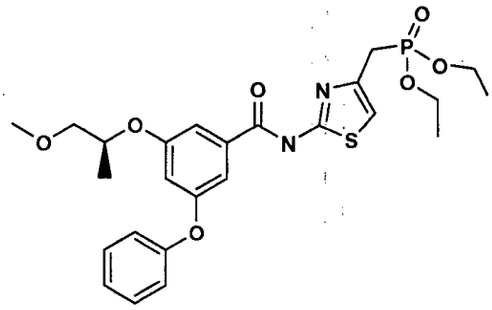
dried ($MgSO_4$), and concentrated *in vacuo* to give Part C compound (0.063 g; 74%) as a clear, gold oil .

D.

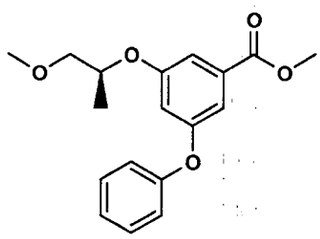


[00504] To a 0°C solution of Part C compound (0.063; 0.094 mmol) in THF (0.47 mL) was added TBAF (0.090 mL of a 1 M solution; 0.094 mmol). The reaction was stirred for 1 h at 0°C and an addition equivalent of TBAF (0.090 mL of a 1 M solution; 0.094 mmol) was added. The reaction was stirred at 0°C for another 1 h, then was concentrated *in vacuo*. The residue was partitioned between EtOAc and brine. The organic layer was washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by preparative HPLC (YMC reverse phase ODS-5μm 30 x 100 mm column; flow rate = 40 mL/min, 25 to 100% solvent B over 12 min, where solvent A = 90:10:0.1 H_2O:CH_3CN:TFA and solvent B = 90:10:0.1 CH_3CN:H_2O:TFA) to give the title compound (23.6 mg; 45%) as a clear, colorless oil. $[M + H]^+$ = 563.5; ^1H NMR (400 MHz, $CDCl_3$): δ 1.16 - 1.31 (m, *J*=11.82, 6.32 Hz, 12 H), 1.98 (s, 1 H), 2.77 - 2.87 (m, *J*=13.74 Hz, 1 H), 2.93 - 3.02 (m, *J*=13.74 Hz, 1 H), 3.27 (s, 1 H), 3.32 (s, 1 H), 3.61 - 3.69 (m, 1 H), 3.69 - 3.76 (m, 1 H), 4.01 - 4.14 (m, 4 H), 4.60 - 4.72 (m, 2 H), 6.62 - 6.66 (m, *J*=2.20, 2.20 Hz, 1 H), 6.96 (d, *J*=3.85 Hz, 1 H), 7.09 - 7.24 (m, 5 H), 7.28 (s, 1 H) 7.32 (s, 1 H).

EXAMPLE 138

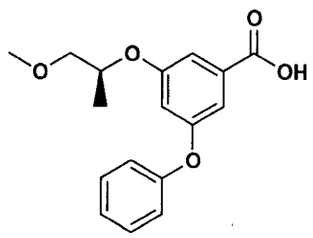


A.



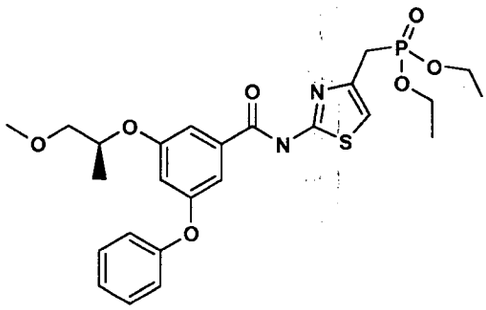
[00505] A solution of Example 124 Part C compound (0.100 g; 0.416 mmol), phenylboronic acid (0.102 g; 0.832 mmol), copper (II) acetate (0.151 g; 0.832 mmol), Et_3N (0.211 g; 2.08 mmol), and freshly activated 4Å molecular sieves (1.2 g) in CH_2Cl_2 (8.32 mL) was stirred at 25°C for 16 h. Additional solvent (8 mL), two equivalents each of boronic acid, copper (II) acetate, and Et_3N were added after 2 days. After a total of 5 days, 70% conversion was observed. The reaction mixture was filtered and washed with CH_2Cl_2. The combined filtrates were concentrated *in vacuo*, and the residue was partitioned between EtOAc and 1N aqueous HCl. The organic layer was washed with sat. aqueous $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated *in vacuo*. The crude product was chromatographed (SiO_2; step gradient from 10-20-30% solvent B, where solvent A = hexanes and solvent B = EtOAc) to give Part A compound (70.2 mg; 83% yield based on recovered starting material).

B.



[00506] To a solution of Part A compound (0.070 g; 0.222 mmol) in THF (0.85 mL) and water (0.27 mL) was added $LiOH.H_2O$ (0.010 g; 0.244 mmol). The reaction mixture was stirred at 45°C for 1 h in a sealed vial, then an additional equivalent of $LiOH.H_2O$ was added. The reaction mixture was stirred at 45°C for an additional 3 h, then was cooled to RT. Volatiles were removed *in vacuo*, and the remaining aqueous solution was acidified with 0.5N aqueous HCl to pH <2. The aqueous layer was re-extracted with EtOAc (3x). The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo* to give Part B compound (0.060 g; 90%).

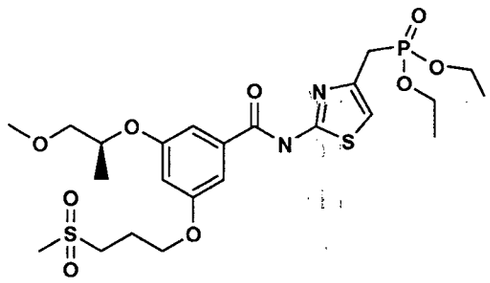
C.



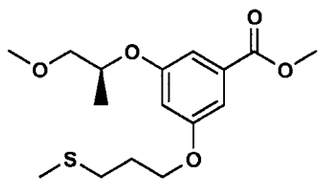
[00507] To a solution of Example 13 Part E compound (0.030 g; 0.119 mmol) in DMF (0.38 mL) were added HOAT (0.016 g; 0.114 mmol), Part B compound (0.03 g; 0.099 mmol), DIPEA (0.020 mL; 0.114 mmol), and, lastly, EDCI (0.022 g; 0.114 mmol). The reaction mixture was stirred at 25°C for 16 h. An additional equivalent of Example 13 Part E compound was added, and the reaction mixture stirred at 25°C for a further 16 h with no further conversion. Water was added, and the mixture was extracted with EtOAc (3x). The combined organic extracts were washed with sat. aqueous NH_4Cl, sat. aqueous $NaHCO_3$, and brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by preparative HPLC (YMC reverse phase ODS-

5μm 30 x 100 mm column; flow rate = 40 mL/min, 25 to 100% solvent B over 12 min, where solvent A = 90:10:0.1 H_2O:CH_3CN:TFA and solvent B = 90:10:0.1 CH_3CN:H_2O:TFA) to give the title compound (0.010 mg; 20%) as a tacky, yellow glass. $[M + H]^+$ = 535.5; ^1H NMR (400 MHz, $CDCl_3$): δ 1.21 - 1.31 (m, 9 H), 3.26 (s, 1 H), 3.29 - 3.36 (m, 4 H), 3.46 - 3.53 (m, 2 H), 4.02 - 4.15 (m, 4 H), 4.73 - 4.87 (m, 1 H), 6.74 - 6.81 (m, 1 H), 6.92 - 7.02 (m, 3 H), 7.09 (t, *J*=7.42 Hz, 1 H), 7.25 - 7.34 (m, 3 H), 7.48 (s, 1 H).

EXAMPLE 139

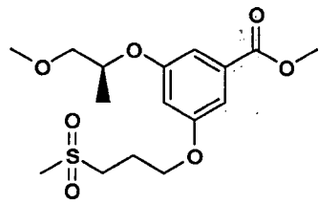


A.



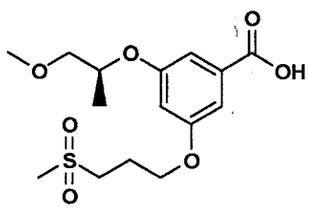
[00508] To a 0°C solution of Example 124 Part C compound (0.110 g; 0.458 mmol) in THF (2.29 mL) were added 3-(methylthio)propan-1-ol (0.107 mL; 1.01 mmol) and Ph_3P (0.265 g; 1.01 mmol), followed by the slow addition of DIAD (0.195 mL; 1.01 mmol). The reaction mixture was stirred at 25°C for 16 h under Ar, then was diluted with water and extracted with EtOAc (3x). The combined organic extracts were washed with 1N aqueous NaOH and brine, dried ($MgSO_4$), and concentrated *in vacuo*. The crude product was chromatographed (SiO_2; stepwise gradient from 10-20% solvent B , where solvent A = hexanes and solvent B = EtOAc) to give Part A compound (0.110 g; 73%).

B.



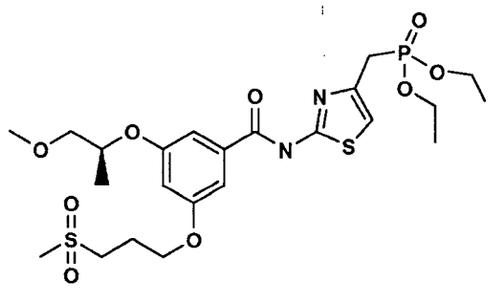
[00509] To a 0°C solution of Part A compound (0.110 g; 0.334 mmol) in CH_2Cl_2 (3.34 mL) was added *m*CPBA (0.115 g; 0.67 mmol). The reaction mixture was stirred for 1 h at 0°C, then sat. aqueous $NaHCO_3$ was added and the mixture was extracted with CH_2Cl_2 (3x). The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo* to give Part B compound (0.161 g; 88%).

C.



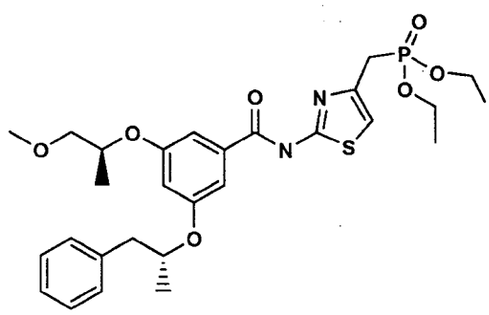
[00510] To a solution of Part C compound (0.162 g; 0.450 mmol) in THF (1.73 mL) and water (0.549 mL) was added $LiOH.H_2O$ (0.021 g; 0.495 mmol). The reaction mixture was stirred at 45°C for 1 h in a sealed vial, then an additional equivalent of LiOH was added. The reaction mixture was stirred at 45°C for 16 h, then cooled to RT. Volatiles were removed *in vacuo*, and the remaining aqueous solution was acidified with 0.5N aqueous HCl to pH <2. The aqueous layer was re-extracted with EtOAc (3x). The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo* to give Part C compound (0.147 g; 94%).

D.

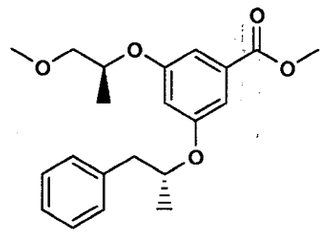


[00511] To a solution of Example 13 Part E compound (0.026 g; 0.104 mmol) in DMF (0.33 mL) were added HOAT (0.014 g; 0.100 mmol), Part C compound (0.030 g; 0.087 mmol), DIPEA (0.017 mL; 0.100 mmol), and, lastly, EDCI (0.019 g; 0.100 mmol). The reaction mixture was stirred at 25°C for 16 h. Water was added, and the mixture was extracted with EtOAc (3x). The combined organic extracts were washed with sat. aqueous NH_4Cl, sat. aqueous $NaHCO_3$, and brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by preparative HPLC (YMC reverse phase ODS-5u 30 x 100 mm column; flow rate = 40 mL/min, 25 to 100% solvent B over 12 min, where solvent A = 90:10:0.1 H_2O:CH_3CN:TFA and solvent B = 90:10:0.1 CH_3CN:H_2O:TFA) to give the title compound (8 mg, 16% yield) as a white solid lyophilate. $[M + H]^+$ = 579.4; ^1H NMR (400 MHz, $CDCl_3$): δ 1.14 - 1.28 (m, 9 H), 2.20 - 2.33 (m, 2 H), 2.89 (s, 3 H), 3.13 - 3.26 (m, 4 H), 3.33 (s, 3 H), 3.40 - 3.54 (m, 2 H), 3.92 - 4.05 (m, 4 H), 4.05 - 4.12 (m, *J*=5.77, 5.77 Hz, 2 H), 4.53 - 4.63 (m, 1 H), 6.61 - 6.65 (m, 1 H), 6.78 - 6.86 (m, *J*=3.85 Hz, 1 H), 7.14 (s, 1 H), 7.19 (s, 1 H).

EXAMPLE 140

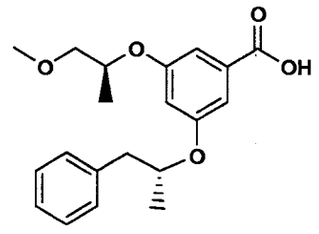


A.



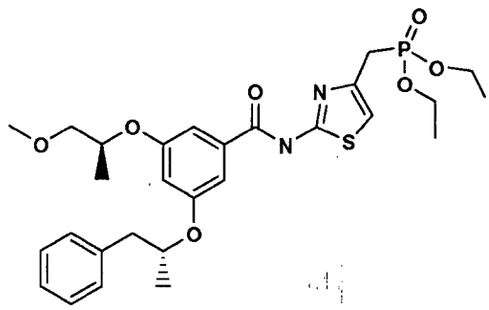
[00512] To a 0°C solution of Example 124 Part C compound (0.110 g; 0.458 mmol) in THF (2.29 mL) were added (S)-(+)-1-phenyl-2-propanol (0.138 mL; 1.01 mmol) and Ph_3P (0.265 g; 1.01 mmol), followed by the slow addition of DIAD (0.195 mL; 1.01 mmol). The reaction mixture was stirred at 25°C for 16 h under Ar, then was diluted with water and extracted with EtOAc (3x). The combined organic extracts were washed with 1N aqueous NaOH and brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was chromatographed (SiO_2; stepwise gradient from 5-10% solvent B , where solvent A = hexanes and solvent B = EtOAc) to give Part A compound (0.133 g; 81%).

B.



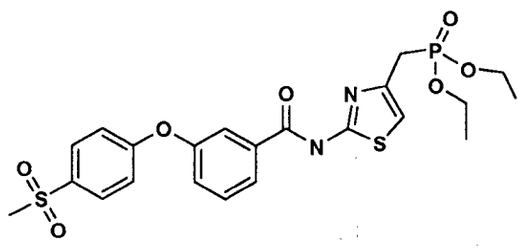
[00513] To a solution of Part A compound (0.133 g; 0.371 mmol) in THF (1.43 mL) and water (0.45 mL) was added $LiOH.H_2O$ (0.017 g; 0.408 mmol). The reaction mixture was stirred at 45°C for 1 h in a sealed vial, then an additional equivalent of LiOH was added. The reaction mixture was stirred at 45°C for 16 h, then cooled to RT. Volatiles were removed *in vacuo*, and the remaining aqueous solution was acidified with 0.5N aqueous HCl to pH <2. The aqueous layer was re-extracted with EtOAc (3x). The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo* to give Part B compound (0.123 g; 96%).

C.

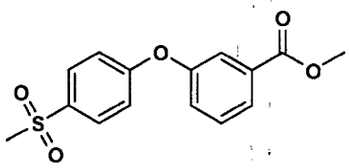


[00514] To a solution of Example 13 Part E compound (0.026 g; 0.105 mmol) in DMF (0.34 mL) were added HOAT (0.014 g; 0.100 mmol), Part B compound (0.030 g; 0.087 mmol), DIPEA (0.017 mL; 0.100 mmol), and, lastly, EDCI (0.019 g; 0.100 mmol). The reaction mixture was stirred at 25°C for 16 h. Water was added, and the mixture was extracted with EtOAc (3x). The combined organic extracts were washed with sat. aqueous NH_4Cl, sat. aqueous $NaHCO_3$, and brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by preparative HPLC (YMC reverse phase ODS-5u 30 x 100 mm column; flow rate = 40 mL/min, 25 to 100% solvent B over 12 min, where solvent A = 90:10:0.1 H_2O:CH_3CN:TFA and solvent B = 90:10:0.1 CH_3CN:H_2O:TFA) to give the title compound (16.4 mg; 33%) as a clear, colorless oil. $[M + H]^+$ = 577.4; ^1H NMR (400 MHz, $CDCl_3$): δ 1.04 - 1.32 (m, 12 H), 2.65 - 2.86 (m, *J*=13.74 Hz, 1 H), 2.88 - 3.06 (m, 1 H), 3.10 - 3.25 (m, *J*=20.89 Hz, 2 H), 3.32 (s, 3 H), 3.36 - 3.55 (m, 2 H), 3.85 - 4.05 (m, *J*=7.15 Hz, 4 H), 4.34 - 4.63 (m, 2 H), 6.41 - 6.66 (m, 1 H), 6.67 - 6.81 (m, 1 H), 6.95 - 7.07 (m, 2 H), 7.08 - 7.29 (m, 5 H), 10.44 (s, 1 H), 10.44 (s, 1 H).

EXAMPLE 141

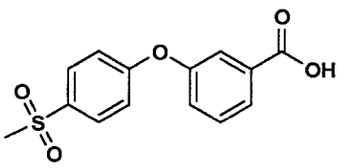


A.



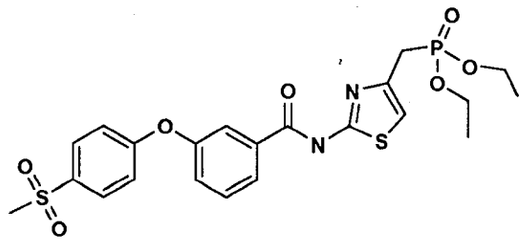
[00515] To a solution of 3-hydroxy-methylbenzoate (0.500 g; 3.29 mmol) in DMF (8.23 mL) were added K_2CO_3 (0.908 g; 6.57 mmol) and fluoro-4-(methylsulfonyl)benzene (0.573 g; 3.29 mmol). The reaction mixture was stirred at 120°C for 2 days under Ar, then cooled to RT. Volatiles were removed *in vacuo*. The residue was partitioned between sat. aqueous $NaHCO_3$ and EtOAc. The organic layer was washed with 1N aqueous HCl and brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was chromatographed (SiO_2; stepwise gradient from 20-30-40% solvent B, where solvent A = hexanes and solvent B = EtOAc) to give Part A compound (0.583 g; 58%).

B.



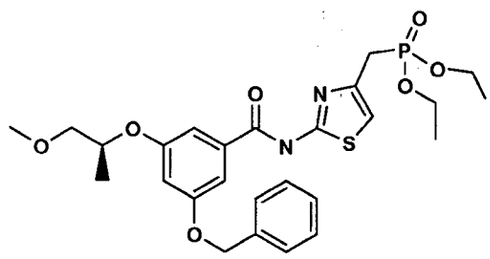
[00516] To a solution of Part A compound (0.200 g; 0.653 mmol) in THF (2.51 mL) and water (0.80 mL) was added $LiOH.H_2O$ (0.030 g; 0.718 mmol). The reaction mixture was stirred at 45°C for 1 h in a sealed vial, then an additional equivalent of LiOH was added. The reaction mixture was stirred at 50°C for 2 h, then cooled to RT. Volatiles were removed *in vacuo*, and the remaining aqueous solution was acidified with 0.5N aqueous HCl to pH < 2. The aqueous layer was re-extracted with EtOAc (3x). The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo* to give Part B compound (0.176 g; 92%).

C.

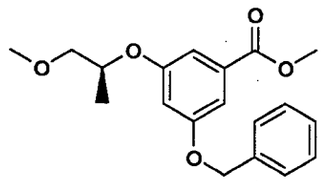


[00517] To a solution of Example 13 Part E compound (0.309 g; 0.124 mmol) in DMF (0.40 mL) were added HOAT (0.016 g; 0.118 mmol), Part B compound (0.030 g; 0.103 mmol), DIPEA (0.021 mL; 0.118 mmol), and, lastly, EDCI (0.023 g; 0.118 mmol). The reaction mixture was stirred at 25°C for 16 h. Water was added, and the mixture was extracted with EtOAc (3x). The combined organic extracts were washed with sat. aqueous NH_4Cl, sat. aqueous $NaHCO_3$, and brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by preparative HPLC (YMC reverse phase ODS-5u 30 x 100 mm column; flow rate = 40 mL/min, 25 to 100% solvent B over 12 min, where solvent A = 90:10:0.1 H_2O:CH_3CN:TFA and solvent B = 90:10:0.1 CH_3CN:H_2O:TFA) to give the title compound (14.7 mg; 27%) as a tacky, white solid. $[M + H]^+$ = 525.3; ^1H NMR (400 MHz, $CDCl_3$): δ 1.20 (t, *J*=7.15 Hz, 6 H), 2.99 (s, 3 H), 3.21 (s, 1 H), 3.26 (s, 1 H), 3.95 - 4.08 (m, 4 H), 6.85 - 6.92 (m, *J*=3.30 Hz, 1 H), 7.00 - 7.10 (m, *J*=8.79 Hz, 2 H), 7.24 - 7.32 (m, *J*=7.70 Hz, 1 H), 7.53 (t, *J*=7.97 Hz, 1 H), 7.77 (s, 1 H), 7.74 - 7.80 (m, 1 H), 7.84 (d, *J*=8.79 Hz, 2 H), 7.92 (d, *J*=7.70 Hz, 1 H).

EXAMPLE 142

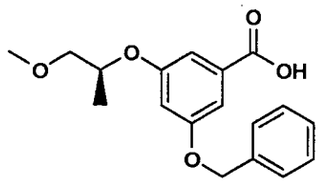


A.



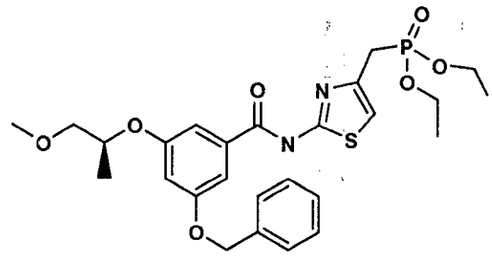
[00518] To a 0°C solution of Example 124 Part C compound (0.110 g; 0.458 mmol) in THF (2.29 mL) were added benzyl alcohol (0.109 mL; 1.01 mmol) and Ph_3P (0.265 g; 1.01 mmol), followed by the slow addition of DIAD (0.195 mL; 1.01 mmol). The reaction mixture was stirred at 25°C for 16 h under Ar, then was diluted with water and extracted with EtOAc (3x). The combined organic extracts were washed with 1N aqueous NaOH and brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was chromatographed (SiO_2; step gradient from 10-15-20% solvent B, where solvent A = hexanes and solvent B = EtOAc) to give Part A compound (0.160 g; 100%).

B.



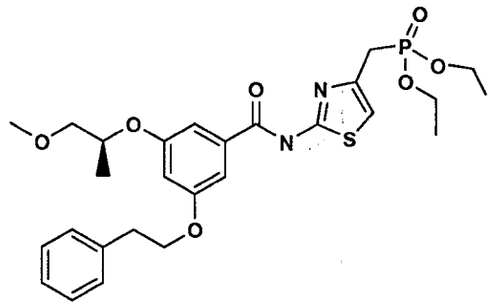
[00519] To a solution of Part A compound (0.160 g; 0.483 mmol) in THF (1.86 mL) and water (0.59 mL) was added $LiOH.H_2O$ (0.022 g; 0.532 mmol). The reaction mixture was stirred at 45°C for 2 h in a sealed vial, then an additional equivalent of LiOH was added. The reaction mixture was stirred at 45°C for 16 h, then cooled to RT. Volatiles were removed *in vacuo*, and the remaining aqueous solution was acidified with 0.5N aqueous HCl to pH < 2. The aqueous layer was re-extracted with EtOAc (3x). The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo* to give Part B compound (0.137 g; 90%).

C.

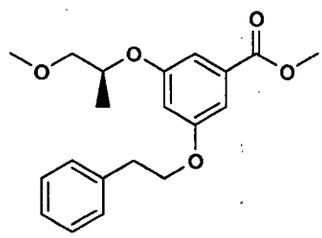


[00520] To a solution of Example 13 Part E compound (0.029 g; 0.114 mmol) in DMF (0.37 mL) were added HOAT (0.015 g; 0.109 mmol), Part B compound (0.030 g; 0.095 mmol), DIPEA (0.019 mL; 0.109 mmol), and, lastly, EDCI (0.021 g; 0.109 mmol). The reaction mixture was stirred at 25°C for 16 h. Water was added, and the mixture was extracted with EtOAc (3x). The combined organic extracts were washed with sat. aqueous NH_4Cl, sat. aqueous $NaHCO_3$, and brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by preparative HPLC (YMC reverse phase ODS-5u 30 x 100 mm column; flow rate = 40 mL/min, 25 to 100% solvent B over 12 min, where solvent A = 90:10:0.1 H_2O:CH_3CN:TFA and solvent B = 90:10:0.1 CH_3CN:H_2O:TFA) to give the title compound (18.6 mg; 36%) as a clear, colorless oil. $[M + H]^+$ = 549.2; ^1H NMR (400 MHz, $CDCl_3$): δ 1.13 - 1.29 (m, 9 H), 3.19 (s, 1 H), 3.24 (s, 2 H), 3.33 (s, 3 H), 3.39 - 3.46 (m, 1 H), 3.46 - 3.53 (m, 1 H), 3.89 - 4.04 (m, 4 H), 4.48 - 4.58 (m, *J*=3.85 Hz, 1 H), 5.01 (s, 2 H), 6.69 - 6.74 (m, 1 H), 6.75 - 6.80 (m, *J*=3.85 Hz, 1 H), 7.11 (s, 1 H), 7.23 - 7.38 (m, 5 H).

EXAMPLE 143

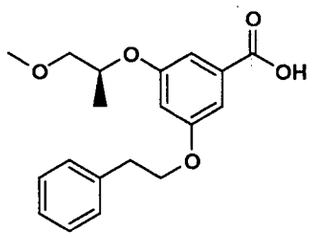


A.



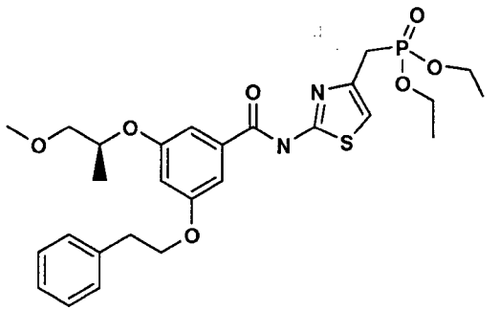
[00521] To a 0°C solution of Example 124 Part C compound (0.110 g; 0.458 mmol) in THF (2.29 mL) were added 2-phenylethanol (0.121 mL; 1.01 mmol) and Ph_3P (0.265 g; 1.01 mmol), followed by the slow addition of DIAD (0.195 mL; 1.01 mmol). The reaction mixture was stirred at 25°C for 16 h under Ar, then was diluted with water and extracted with EtOAc (3x). The combined organic extracts were washed with 1N aqueous NaOH and brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was chromatographed (SiO_2; stepwise gradient from 10-15-20% solvent B, where solvent A = hexanes and solvent B = EtOAc) to give Part A compound (0.127 g; 81%).

B.



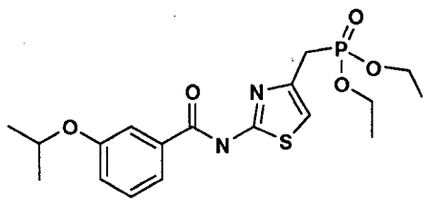
[00522] To a solution of Part A compound (0.127 g; 0.370 mmol) in THF (1.42 mL) and water (0.45 mL) was added $LiOH.H_2O$ (0.017 g; 0.407 mmol). The reaction mixture was stirred at 45°C for 2 h in a sealed vial, then an additional equivalent of LiOH was added. The reaction mixture was stirred at 45°C for 16 h, then was cooled to RT. Volatiles were removed *in vacuo*, and the remaining aqueous solution was acidified with 0.5N aqueous HCl to pH <2. The aqueous layer was re-extracted with EtOAc (3x). The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo* to give Part B compound (0.112 g; 91%).

C.



[00523] To a solution of Example 13 Part E compound (0.027 g; 0.109 mmol) in DMF (0.35 mL) were added HOAT (0.014 g; 0.104 mmol), Part B compound (0.030 g; 0.091 mmol), DIPEA (0.018 mL; 0.104 mmol), and, lastly, EDCI (0.020 g; 0.104 mmol). The reaction mixture was stirred at 25°C for 16 h. Water was added, and the mixture was extracted with EtOAc (3x). The combined organic extracts were washed with sat. aqueous NH_4Cl, sat. aqueous $NaHCO_3$, and brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by preparative HPLC (YMC reverse phase ODS-5u 30 x 100 mm column; flow rate = 40 mL/min, 25 to 100% solvent B over 12 min, where solvent A = 90:10:0.1 H_2O:CH_3CN:TFA and solvent B = 90:10:0.1 CH_3CN:H_2O:TFA) to give the title compound (24.5 mg; 48%) as a clear, colorless oil. $[M + H]^+$ = 563.2; ^1H NMR (400 MHz, $CDCl_3$): δ 1.16 - 1.28 (m, 6 H), 3.02 (t, *J*=6.60 Hz, 2 H), 3.20 (s, 1 H), 3.25 (s, 1 H), 3.33 (s, 3 H), 3.41 - 3.54 (m, 2 H), 3.96 - 4.08 (m, 4 H), 4.16 (t, *J*=6.87 Hz, 2 H), 4.57 - 4.67 (m, 1 H), 6.63 - 6.69 (m, 1 H), 6.83 - 6.89 (m, *J*=3.85 Hz, 1 H), 7.13 - 7.28 (m, 7 H).

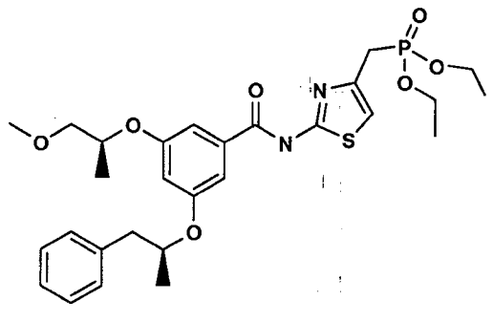
EXAMPLE 144



[00524] To a solution of Example 13 Part E compound (0.100 g; 0.400 mmol) in DMF (2.0 mL) were added HOAT (0.052 g; 0.383 mmol), 3-isopropoxybenzoic acid (0.060 g; 0.333 mmol), DIPEA (0.07 mL; 0.383 mmol), and, lastly, EDCI (0.073 g; 0.383 mmol). The reaction mixture was stirred at 25°C for 16 h. Water was added, and the mixture was extracted with EtOAc (3x). The combined organic extracts were

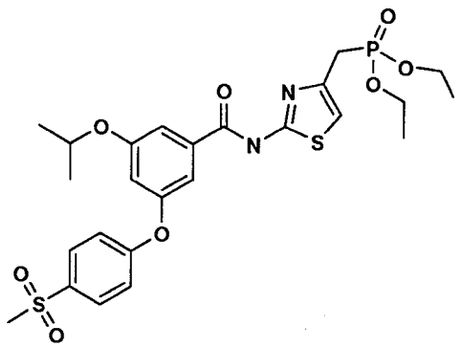
washed with 0.5N aqueous HCl and brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by preparative HPLC (YMC reverse phase ODS-5u 30 x 100 mm column; flow rate = 40 mL/min, 25 to 100% solvent B over 12 min, where solvent A = 90:10:0.1 H_2O:CH_3CN:TFA and solvent B = 90:10:0.1 CH_3CN:H_2O:TFA) to give the title compound (9.4 mg; 7%) as a clear, colorless oil. $[M + H]^+$ = 413.1; ^1H NMR (400 MHz, $CDCl_3$): δ 1.21 - 1.34 (m, *J*=7.15, 7.15 Hz, 12 H), 3.26 (s, 1 H), 3.31 (s, 1 H), 4.00 - 4.14 (m, 4 H), 4.68 - 4.80 (m, 1 H), 6.91 - 6.99 (m, 1 H), 7.04 - 7.12 (m, *J*=8.25 Hz, 1 H), 7.31 - 7.41 (m, 1 H), 7.62 - 7.72 (m, 2 H).

EXAMPLE 145

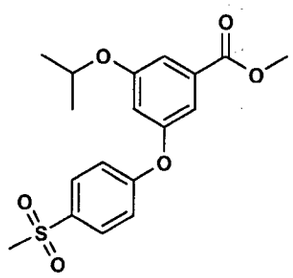


[00525] To a solution of Example 13 Part E compound (0.027 g; 0.105 mmol) in DMF (0.34 mL) were added HOAT (0.013 g; 0.093 mmol), Example 33 Part A acid (0.030 g; 0.087 mmol), DIPEA (0.016 mL; 0.093 mmol), and, lastly, EDCI (0.018 g; 0.932 mmol). The reaction mixture was stirred at 25°C for 16 h. Water was added, and the mixture was extracted with EtOAc (3x). The combined organic extracts were washed with sat. aqueous NH_4Cl, sat. aqueous $NaHCO_3$, and brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by preparative HPLC (YMC reverse phase ODS-5u 30 x 100 mm column; flow rate = 40 mL/min, 25 to 100% solvent B over 12 min, where solvent A = 90:10:0.1 H_2O:CH_3CN:TFA and solvent B = 90:10:0.1 CH_3CN:H_2O:TFA) to give the title compound (35.2 mg; 70%) as a clear, colorless oil. $[M + H]^+$ = 577.2; ^1H NMR (400 MHz, $CDCl_3$): δ 1.21 - 1.37 (m, 12 H), 2.82 - 2.93 (m, *J*=14.02, 5.22 Hz, 1 H), 2.99 - 3.09 (m, 1 H), 3.32 - 3.48 (m, 5 H), 3.51 - 3.66 (m, 2 H), 4.06 - 4.26 (m, 4 H), 4.68 - 4.84 (m, 2 H), 6.68 - 6.77 (m, 1 H), 6.96 - 7.07 (m, *J*=3.85 Hz, 1 H), 7.13 - 7.41 (m, 7 H), 10.77 (s, 1 H).

EXAMPLE 146

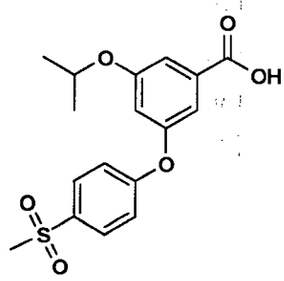


A.



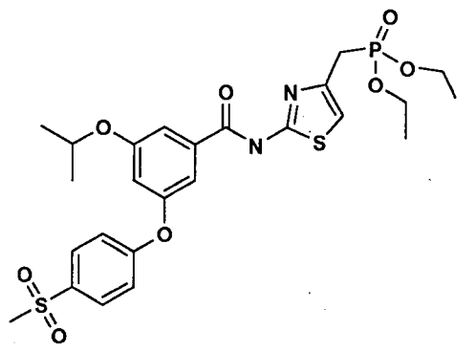
[00526] To a 0°C solution of Example 26 Part A compound (0.166 g; 0.515 mmol) in THF (2.60 mL) were added iPrOH (0.087 mL; 1.13 mmol) and Ph_3P (0.30 g; 1.13 mmol), followed by the slow addition of DIAD (0.219 mL; 1.13 mmol). The reaction mixture was stirred at 25°C for 16 h under Ar, then was diluted with water and extracted with EtOAc (3x). The combined organic extracts were washed with 1N aqueous NaOH and brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was chromatographed (SiO_2; stepwise gradient from 20-40% solvent B, where solvent A = hexanes and solvent B = EtOAc) to give Part A compound (0.258 g; >100%, contaminated with reduced DIAD).

B.



[00527] To a solution of Part A compound (0.189 g; 0.515 mmol) in THF (3.22 mL) and water (0.62 mL) was added $LiOH.H_2O$ (0.024 g; 0.567 mmol). The reaction mixture was stirred at 45°C for 1 h in a sealed vial, then an additional equivalent of LiOH was added. The reaction mixture was stirred at 45°C for 16 h, then cooled to RT. Volatiles were removed *in vacuo*, and the remaining aqueous solution was acidified with 0.5N aqueous HCl to pH < 2. The aqueous layer was re-extracted with EtOAc (3x). The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo* to give Part B compound (0.214 g; >100%, contaminated with reduced DIAD).

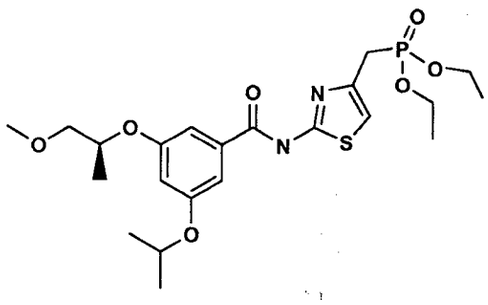
C.



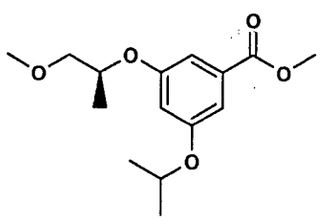
[00528] To a solution of Example 13 Part E compound (0.043 g; 0.17 mmol) in DMF (0.55 mL) were added HOAT (0.022 g; 0.164 mmol), Part B compound (0.050 g; 0.143 mmol), DIPEA (0.029 mL; 0.164 mmol), and, lastly, EDCI (0.031 g; 0.164 mmol). The reaction mixture was stirred at 25°C for 16 h. Water was added, and the mixture was extracted with EtOAc (3x). The combined organic extracts were washed with sat. aqueous NH_4Cl, sat. aqueous $NaHCO_3$, and brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by preparative HPLC (YMC reverse

phase ODS-5u 30 x 100 mm column; flow rate = 40 mL/min, 25 to 100% solvent B over 12 min, where solvent A = 90:10:0.1 H_2O:CH_3CN:TFA and solvent B = 90:10:0.1 CH_3CN:H_2O:TFA) to give the title compound (37.5 mg; 60%) as a clear, colorless oil. $[M + H]^+$ = 583.1; ^1H NMR (400 MHz, $CDCl_3$): δ 1.17 - 1.38 (m, 12 H), 3.04 (s, 3 H), 3.27 (s, 1 H), 3.32 (s, 1 H), 3.99 - 4.14 (m, 4 H), 4.64 - 4.77 (m, 1 H), 6.79 - 6.83 (m, 1 H), 6.88 - 6.96 (m, *J*=3.30 Hz, 1 H), 7.07 - 7.15 (m, *J*=8.79 Hz, 2 H), 7.30 - 7.36 (m, 1 H), 7.47 - 7.54 (m, 1 H), 7.84 - 7.92 (m, *J*=8.79 Hz, 2 H).

EXAMPLE 147

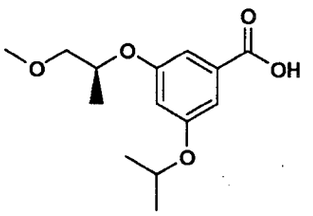


A.



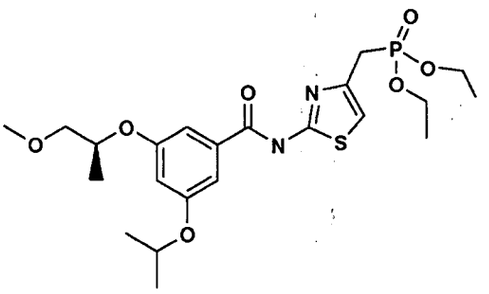
[00529] To a 0°C solution of Example 124 Part C compound (0.100 g; 0.416 mmol) in THF (2.08 mL) were added iPrOH (0.019 mL; 0.916 mmol) and Ph_3P (0.240 g; 0.916 mmol), followed by the slow addition of DIAD (0.177 mL; 0.916 mmol). The reaction mixture was stirred at 25°C for 16 h under Ar, then was diluted with water and extracted with EtOAc (3x). The combined organic extracts were washed with 1N aqueous NaOH and brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was chromatographed (SiO_2; stepwise gradient from 5-10% solvent B, where solvent A = hexanes and solvent B = EtOAc) to give Part A compound (82.2 mg; 70%).

B.



[00530] To a solution of Part A compound (0.082 g; 0.291 mmol) in THF (1.82 mL) and water (0.45 mL) was added $LiOH.H_2O$ (0.014 g; 0.32 mmol). The reaction mixture was stirred at 45°C for 3 h in a sealed vial, then an additional equivalent of LiOH. The reaction mixture was stirred at 45°C for 16 h, then was cooled to RT. Volatiles were removed *in vacuo*, and the remaining aqueous solution was acidified with 0.5N aqueous HCl to pH < 2. The aqueous layer was back extracted with EtOAc (3x). The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo* to give Part B compound (83.0 mg; 100%).

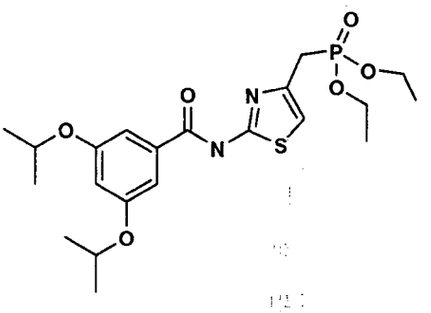
C.



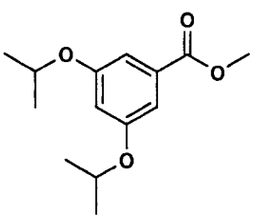
[00531] To a solution of Example 13 Part E compound (0.034 g; 0.134 mmol) in DMF (0.43 mL) were added HOAT (0.018 g; 0.129 mmol), Part B compound (0.030 g; 0.112 mmol), DIPEA (0.023 mL; 0.129 mmol), and, lastly, EDCI (0.025 g; 0.129 mmol). The reaction mixture was stirred at 25°C for 16 h. Water was added, and the mixture was extracted with EtOAc (3x). The combined organic extracts were washed with sat. aqueous NH_4Cl, sat. aqueous $NaHCO_3$, and brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by preparative HPLC (YMC reverse phase ODS-5u 30 x 100 mm column; flow rate = 40 mL/min, 25 to 100% solvent B over 12 min, where solvent A = 90:10:0.1 H_2O:CH_3CN:TFA and solvent B = 90:10:0.1 CH_3CN:H_2O:TFA) to give the title compound (28.0 mg; 50%) as a clear,

colorless oil. $[M + H]^+ = 501.0$; ^1H NMR (400 MHz, $CDCl_3$): δ 1.20 - 1.30 (m, 15 H), 3.22 (s, 1 H), 3.27 (s, 1 H), 3.34 (s, 3 H), 3.42 - 3.56 (m, 2 H), 4.00 - 4.12 (m, 4 H), 4.56 - 4.70 (m, 2 H), 6.64 - 6.69 (m, 1 H), 6.88 - 6.95 (m, *J*=3.30 Hz, 1 H), 7.21 - 7.28 (m, *J*=8.24 Hz, 2 H).

EXAMPLE 148

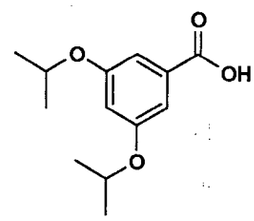


A.



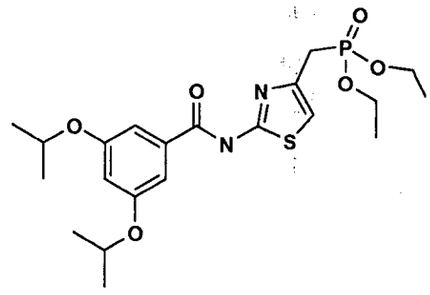
[00532] To a cold solution (0°C) of 3,5-dihydroxy-methylbenzoate (1.00 g; 5.95 mmol) in THF (29.8 mL) were added iPrOH (0.787 mL; 13.10 mmol) and Ph_3P (3.43 g; 13.10 mmol), followed by the slow addition of DIAD (2.58 mL; 13.1 mmol). The reaction mixture was stirred at 25°C for 16 h under Ar, then was diluted with water and extracted with EtOAc (3x). The combined organic extracts were washed with 1N aqueous NaOH and brine, dried ($MgSO_4$), and concentrated *in vacuo*. The crude product was chromatographed (SiO_2; stepwise gradient from 10-20-30% solvent B, where solvent A = hexanes and solvent B = EtOAc) to give Part A compound (1.27 g; 85%).

B.



[00533] To a solution of Part A compound (0.300 g; 1.19 mmol) in THF (7.44 mL) and water (1.45 mL) was added $LiOH.H_2O$ (0.055 g; 1.31 mmol). The reaction mixture was stirred at 45°C for 3 h in a sealed vial, then an additional equivalent of LiOH was added. The reaction mixture was stirred at 45°C for 16 h, then was cooled to RT. Volatiles were removed *in vacuo*, and the remaining aqueous solution was acidified with 0.5N aqueous HCl to pH < 2. The aqueous layer was re-extracted with EtOAc (3x). The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo* to give Part B compound (0.290 g; 100%).

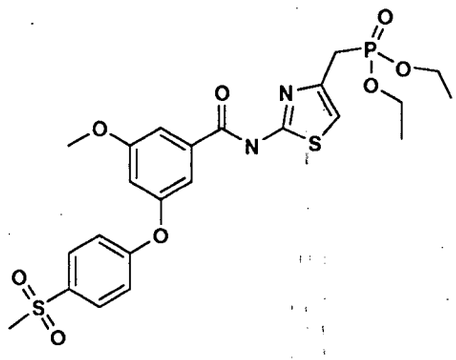
C.



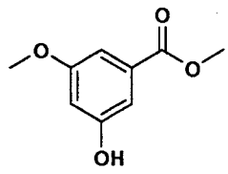
[00534] To a solution of Example 13 Part E compound (0.167 g; 0.668 mmol) in DMF (2.14 mL) were added HOAT (0.087 g; 0.641 mmol), Part B compound (0.133 g; 0.557 mmol), DIPEA (0.116 mL; 0.641 mmol), and, lastly, EDCI (0.123 g; 0.668 mmol). The reaction mixture was stirred at 25°C for 16 h. Water was added, and the mixture was extracted with EtOAc (3x). The combined organic extracts were washed with sat. aqueous NH_4Cl, sat. aqueous $NaHCO_3$, and brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by preparative HPLC (YMC reverse phase ODS-5u 30 x 100 mm column; flow rate = 40 mL/min, 25 to 100% solvent B over 12 min, where solvent A = 90:10:0.1 H_2O:CH_3CN:TFA and solvent B = 90:10:0.1 CH3CN:H_2O:TFA) to give the title compound (95.1 mg; 36%) as a white

solid. $[M + H]^+ = 471.5$; ^1H NMR (400 MHz, $CDCl_3$): δ 1.24 - 1.37 (m, 18 H), 3.27 (s, 1 H), 3.32 (s, 1 H), 4.01 - 4.19 (m, 4 H), 4.58 - 4.72 (m, 2 H), 6.65 (s, 1 H), 6.92 - 7.00 (m, *J*=3.85 Hz, 1 H), 7.21 - 7.27 (m, 2 H).

EXAMPLE 149

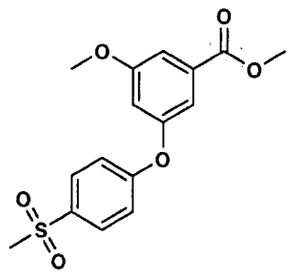


A.



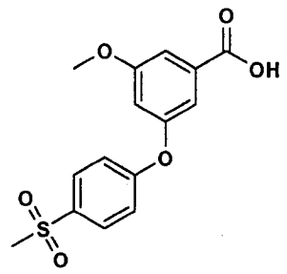
[00535] To a solution of methyl 3,5–dihydroxybenzoate (1.75 g; 10.41 mmol) in acetone (14 mL was added K_2CO_3 (2.88 g; 20.82 mmol) and nBu_4NI (384 mg; 1.04 mmol), followed by dimethyl sulfate (985 μL; 10.41 mmol). The reaction mixture was heated at reflux (~65°C) for 3 h, then was cooled to RT. The mixture was filtered, and the filtrate was concentrated *in vacuo*. The residue was chromatographed (SiO_2; continuous gradient from 0 to 45% solvent B over 40 min, where solvent A = hexanes and solvent B = EtOAc) to give Part A compound (0.74 g; 39%) as a white solid.

B.



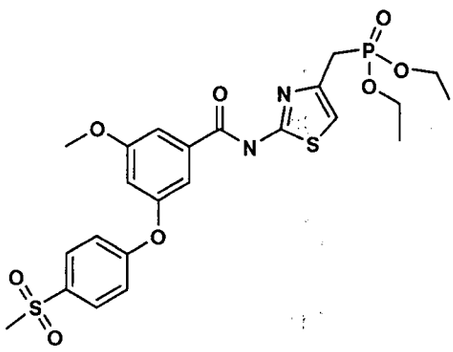
[00536] To a mixture of Part A compound (75 mg; 0.412 mmol), 4-fluorophenyl methyl sulfone (72 mg; 0.412 mmol) and K_2CO_3 (114 mg; 0.824 mmol) was added DMF (1.6 mL). The reaction mixture was heated at 120°C for 5 h, then was cooled to RT. The mixture was partitioned between EtOAc (10 mL) and H_2O (10 mL). The organic phase was washed with brine (5 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The residue was chromatographed (SiO_2; continuous gradient from 0 to 80% solvent B over 12 min, where solvent A = hexanes and solvent B = EtOAc) to give Part B compound (119 mg; 86%) as a colorless syrup.

C.



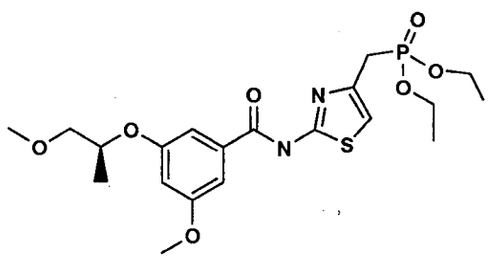
[00537] To a solution of Part B compound (118 mg; 0.351 mmol) in THF (0.47 mL), MeOH (0.47 mL), and H_2O (0.47 mL) was added $LiOH \cdot H_2O$ (44 mg; 1.053 mmol). After 1 h of stirring, the mixture was partitioned between EtOAc (6 mL) and 0.5 N aqueous HCl (6 mL). The aqueous phase was extracted with EtOAc (6 mL). The combined organic extracts were washed with brine (6 mL), dried ($MgSO_4$), and concentrated *in vacuo* to give Part C compound (94 mg; 83%) as a white solid.

D.

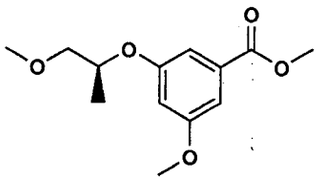


[00538] To a solution of Example 13 Part E compound (0.038 g; 0.150 mmol) in DMF (0.48 mL) were added HOAT (0.020 g; 0.144 mmol), Part C compound (0.040 g; 0.125 mmol), DIPEA (0.025 mL; 0.144 mmol), and, lastly, EDCI (0.028 g; 0.144 mmol). The reaction mixture was stirred at 25°C for 16 h. Water was added, and the mixture was extracted with EtOAc (3x). The combined organic extracts were washed with sat. aqueous NH_4Cl, sat. aqueous $NaHCO_3$, and brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by preparative HPLC (YMC reverse phase ODS-5u 30 x 100 mm column; flow rate = 40 mL/min, 25 to 100% solvent B over 12 min, where solvent A = 90:10:0.1 H_2O:CH_3CN:TFA and solvent B = 90:10:0.1 CH_3CN:H_2O:TFA) to give the title compound (27.6 mg; 40%) as a white solid. $[M + H]^+$ = 555.4; ^1H NMR (400 MHz, $CDCl_3$): δ 1.20 (t, *J*=7.15 Hz, 6 H), 3.01 (s, 3 H), 3.24 (s, 1 H), 3.30 (s, 1 H), 3.83 (s, 3 H), 3.94 - 4.09 (m, 4 H), 6.73 - 6.87 (m, 2 H), 7.08 (d, *J*=8.79 Hz, 2 H), 7.22 - 7.28 (m, 1 H), 7.36 - 7.43 (m, 1 H), 7.86 (d, *J*=8.79 Hz, 2 H).

EXAMPLE 150

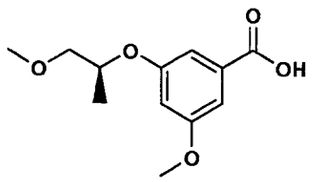


A.



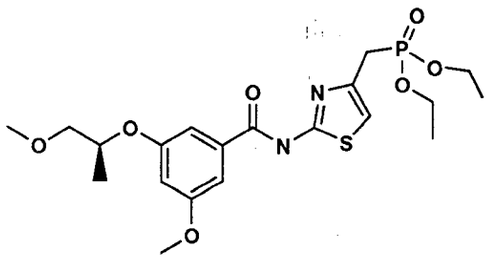
[00539] To a 0°C mixture of Example 149 Part A compound (100 mg; 0.549 mmol), R–(-) –1–methoxy–2–propanol (70 μL; 0.714 mmol), and polymer-bound PPh_3 (0.47 g; 1.43 mmol) in THF (2 mL) was added dropwise a solution of DIAD (162 μL; 0.823 mmol) in THF (0.20 mL). The reaction was stirred at RT for 18 h, then was filtered. The resin was rinsed with THF (2 x 4 mL), and the combined filtrates were concentrated *in vacuo*. The residue was chromatographed (SiO_2; continuous gradient from 0 to 45% solvent B over 20 min, where solvent A = hexanes and solvent B = EtOAc) to give Part A compound (78 mg; 56%) as a colorless oil.

B.



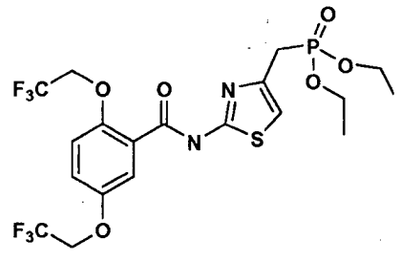
[00540] To a solution of Part A compound (74 mg; 0.291 mmol) in THF (0.39 mL), MeOH (0.39 mL), and H_2O (0.39 mL) was added $LiOH{\cdot}H_2O$ (37 mg; 0.873 mmol). The reaction was stirred for 1 h, then was partitioned between EtOAc (5 mL) and 0.5 N aqueous HCl (5 mL). The aqueous phase was extracted with EtOAc (5 mL). The combined organic extracts were washed with brine (5 mL), dried ($MgSO_4$), and concentrated *in vacuo* to give Part B compound (68 mg; 97%) as a colorless syrup

C.

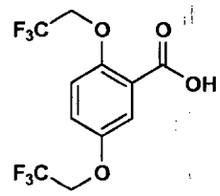


[00541] To a solution of Example 13 Part E compound (0.041 g; 0.164 mmol) in DMF (0.52 mL) were added HOAT (0.087 g; 0.641 mmol), Part B compound (0.033 g; 0.137 mmol), and DIPEA (0.028 mL; 0.158 mmol), and, lastly, EDCI (0.030 g; 0.158 mmol). The reaction mixture was stirred at 25°C for 16 h. Water was added, and the mixture was extracted with EtOAc (3x). The combined organic extracts were washed with sat. aqueous NH_4Cl, sat. aqueous $NaHCO_3$, and brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by preparative HPLC (YMC reverse phase ODS-5 μm 30 x 100 mm column; flow rate = 40 mL/min, 25 to 100% solvent B over 12 min, where solvent A = 90:10:0.1 H_2O:CH_3CN:TFA and solvent B = 90:10:0.1 CH_3CN:H_2O:TFA) to give the title compound (38.1 mg; 59%) as a clear, colorless oil. $[M + H]^+$ = 473.4; ^1H NMR (400 MHz, $CDCl_3$): δ 1.20 - 1.30 (m, 9 H), 3.23 (s, 1 H), 3.28 (s, 1 H), 3.35 (s, 3 H), 3.43 - 3.55 (m, 2 H), 3.80 (s, 3 H), 4.01 - 4.12 (m, 4 H), 4.60 - 4.72 (m, 1 H), 6.66 - 6.72 (m, 1 H), 6.89 - 6.94 (m, *J*=3.30 Hz, 1 H), 7.21 - 7.25 (m, 1 H), 7.25 - 7.29 (m, 1 H).

EXAMPLE 151

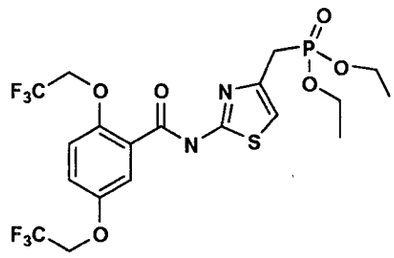


A.



[00542] To a solution of methyl 2,5-bis(2,2,2-trifluoroethoxy)benzoate (0.029 g; 1.20 mmol) in THF (2.49 mL) and water (0.25 mL) was added $LiOH.H_2O$ (0.100 g; 0.301 mmol). The reaction mixture was stirred at 45°C for 3 h in a sealed vial, then an additional equivalent of LiOH was added. The reaction mixture was stirred at 45°C for 16 h, then was cooled to RT. The solvent was removed *in vacuo*, and the remaining aqueous solution was acidified with 0.5N aqueous HCl to pH <2. The aqueous layer was re-extracted with EtOAc (3x). The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo* to give Part A compound (0.0954 g; 99%).

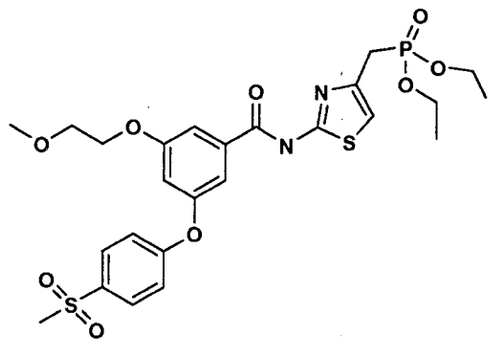
B.



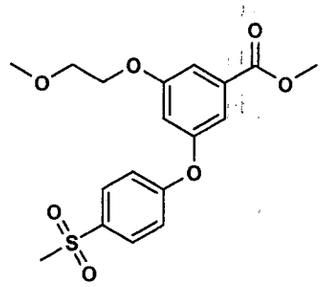
[00543] To a solution of Example 13 Part E compound (0.029 g; 0.114 mmol) in DMF (0.476 mL) were added HOAT (0.015 g; 0.11 mmol), Part A compound (0.030 g; 0.095 mmol), DIPEA (0.019 mL; 0.110 mmol), and, lastly, EDCI (0.021 g; 0.110 mmol). The reaction mixture was stirred at 25°C for 16 h. Water was added, and the mixture was extracted with EtOAc (3x). The combined organic extracts were washed with sat. aqueous NH_4Cl, sat. aqueous $NaHCO_3$, and brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by preparative HPLC (YMC reverse phase ODS-5u 30 x 100 mm column; flow rate = 40 mL/min, 0 to 100% solvent B over 12 min, where solvent A = 90:10:0.1 H_2O:CH_3CN:TFA and solvent B = 90:10:0.1 CH_3CN:H_2O:TFA) to give the title compound (13.8 mg; 26%) as a white

lyophilate. $[M + H]^+ = 551.2$; ^1H NMR (400 MHz, $CDCl_3$) δ 1.23 (t, *J*=7.15 Hz, 6 H), 3.23 (s, 1 H), 3.28 (s, 1 H), 3.94 - 4.10 (m, 4 H), 4.27 - 4.39 (m, *J*=7.88, 7.88, 7.88 Hz, 2 H), 4.46 - 4.58 (m, *J*=8.06, 8.06, 8.06 Hz, 2 H), 6.81 - 6.86 (m, *J*=3.30 Hz, 1 H), 6.93 - 6.98 (m, *J*=9.34 Hz, 1 H), 7.12 - 7.18 (m, *J*=9.34, 3.30 Hz, 1 H), 7.69 - 7.75 (m, *J*=3.30 Hz, 1 H).

EXAMPLE 152

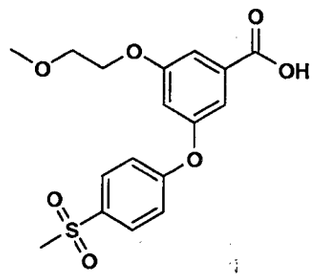


A.



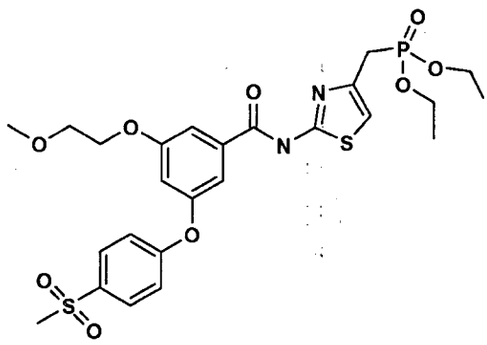
[00544] To Example 26 Part A compound (0.130 g; 0.403 mmol) were successively added 2-methoxyethanol (0.046 g; 0.605 mmol) in toluene (2.02 mL) and a suspension of Example 97 Part B compound (0.248 g; 0.605 mmol) in CH_2Cl_2 (1.1 mL). The reaction mixture was stirred for 16 h at 25°C, then was diluted with water and extracted with EtOAc (3x). The combined organic extracts were washed with 1N aqueous NaOH and brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was chromatographed (SiO_2; step gradient from 50-60% solvent B, where solvent A = hexanes and solvent B = EtOAc) to give Part A compound (0.157 g; 93%).

B.



[00545] To a solution of Part A compound (0.157 g; 0.413 mmol) in THF (3.42 mL) and water (0.342 mL) was added $LiOH.H_2O$ (0.020 g; 0.827 mmol). The reaction mixture was stirred at 45°C for 3 h in a sealed vial, then cooled to RT. Volatiles were removed *in vacuo*, and the remaining aqueous solution was acidified with 0.5N aqueous HCl to pH < 2. The aqueous layer was re-extracted with EtOAc (3x). The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo* to give Part B compound (0.166 g; 100%).

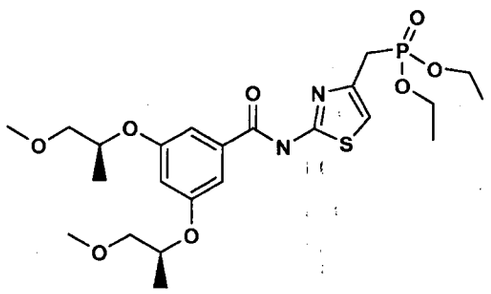
C.



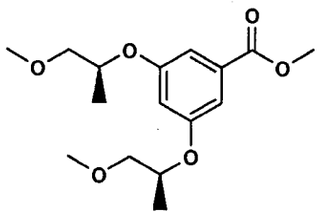
[00546] To a solution of Example 13 Part E compound (0.033 g; 0.130 mmol) in DMF (0.542 mL) were added HOAT (0.017 g; 0.125 mmol), Part B compound (0.040 g; 0.108 mmol), DIPEA (0.022 mL; 0.125 mmol), and, lastly, EDCI (0.024 g; 0.125 mmol). The reaction mixture was stirred at 25°C for 5 h. Water was added, and the mixture was extracted with EtOAc (3x). The combined organic extracts were washed with sat. aqueous NH_4Cl, sat. aqueous $NaHCO_3$, and brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by preparative HPLC (YMC reverse phase ODS-5μm 30 x 100 mm column; flow rate = 40 mL/min, 0 to 100% solvent B over 12 min, where solvent A = 90:10:0.1 H_2O:CH_3CN:TFA and solvent B =

90:10:0.1 $CH_3CN:H_2O$:TFA) to give the title compound (34.4 mg; 51%) as a white lyophilate. $[M + H]^+$ = 599.2; ^1H NMR (400 MHz, $CDCl_3$): δ 1.25 (t, *J*=6.87 Hz, 6 H), 3.00 (s, 3 H), 3.24 (s, 1 H), 3.29 (s, 1 H), 3.39 (s, 3 H), 3.67 - 3.77 (m, 2 H), 4.00 - 4.15 (m, 4 H), 4.18 - 4.28 (m, 2 H), 6.86 - 6.93 (m, 1 H), 6.94 - 7.00 (m, *J*=3.30 Hz, 1 H), 7.04 - 7.12 (m, *J*=8.79 Hz, 2 H), 7.38 - 7.45 (m, 1 H), 7.58 - 7.64 (m, 1 H), 7.81 - 7.88 (m, *J*=8.79 Hz, 2 H).

EXAMPLE 153

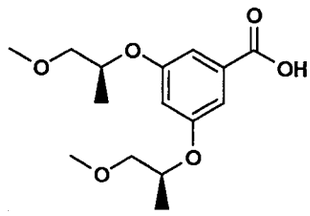


A.



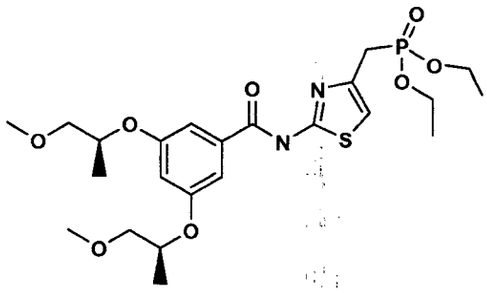
[00547] To methyl-3,5-dihydroxybenzoate (0.100 g; 0.595 mmol) were added (R)-1-methoxy- propan-2-ol (0.134 g; 1.487 mmol in toluene (2.97 mL), followed by a suspension of Example 97 Part B compound (0.610 g; 1.487 mmol) in CH_2Cl_2 (2.72 mL). The reaction mixture was stirred for 2 days at 25°C, then at 45°C for 2 days, then was cooled to RT. The reaction mixture was diluted with water and extracted with EtOAc (3x). The combined organic extracts were washed with 1N aqueous NaOH and brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was chromatographed (SiO_2; stepwise gradient from 10-20% solvent B , where solvent A = hexanes and solvent B = EtOAc) to give Part A compound (0.080 g; 40%).

B.



[00548] To a solution of Part A compound (0.080 g; 0.257 mmol) in THF (2.13 mL) and water (0.213 mL) was added $LiOH.H_2O$ (0.012 g; 0.514 mmol). The reaction mixture was stirred at 45°C for 3 h in a sealed vial, then an additional equivalent of LiOH was added. The reaction mixture was stirred at 45°C for 16 h, then was cooled to RT. Volatiles were removed *in vacuo*, and the remaining aqueous solution was acidified with 0.5N aqueous HCl to pH <2. The aqueous layer was re-extracted with EtOAc (3x). The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo* to give Part B compound (0.082g; 100%).

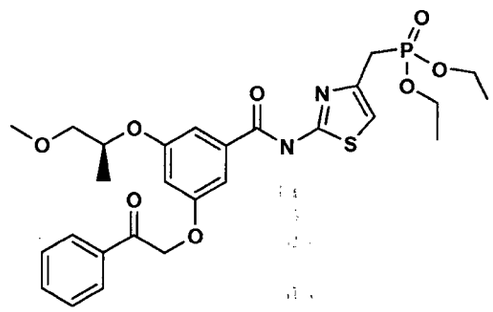
C.



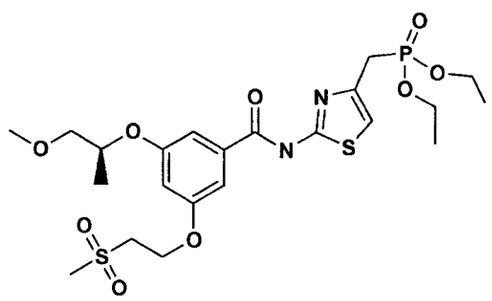
[00549] To a solution of Example 13 Part E compound (0.036 g; 0.142 mmol) in DMF (0.592 mL) were added HOAT (0.019 g; 0.136 mmol), Part B compound (0.035 g; 0.118 mmol), and DIPEA (0.024 mL; 0.136 mmol) and, lastly, EDCI (0.026 g; 0.136 mmol). The reaction mixture was stirred at 25°C for 15 h. Water was added, and the mixture was extracted with EtOAc (3x). The combined organic extracts were washed with sat. aqueous NH_4Cl, sat. aqueous $NaHCO_3$, and brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by preparative HPLC (YMC reverse phase ODS-5u 30 x 100 mm column; flow rate = 40 mL/min, 0 to 100% solvent B over 12 min, where solvent A = 90:10:0.1 H_2O:CH_3CN:TFA and solvent B = 90:10:0.1 CH_3CN:H_2O:TFA) to give the title compound (28.2 mg; 45%) as a clear, colorless oil. $[M + H]^+$ = 531.3; ^1H NMR (400 MHz, $CDCl_3$) δ 1.22 - 1.29 (m,

J=6.87, 6.87 Hz, 12 H), 3.28 (s, 1 H), 3.32 - 3.38 (m, 7 H), 3.44 - 3.56 (m, 4 H), 4.06 - 4.16 (m, 4 H), 4.64 - 4.73 (m, 2 H), 6.70 - 6.76 (m, 1 H), 6.94 - 7.00 (m, *J*=3.85 Hz, 1 H), 7.32 - 7.35 (m, *J*=2.20 Hz, 2 H).

EXAMPLE 154

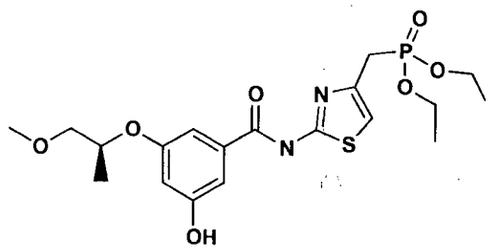


A.



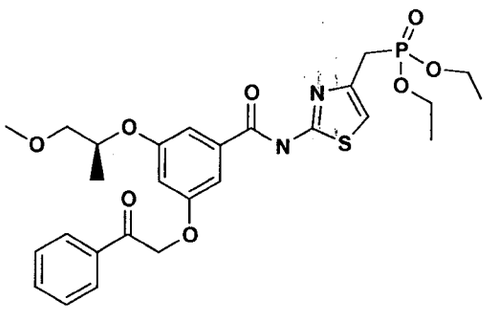
[00550] To a solution of Example 134 compound (0.298 g; 0.560 mmol) in iPrOH (12.43 mL) and water (6.22 mL) was added oxone (0.791 g; 1.287 mmol). The reaction mixture was stirred for 16 h at 25°C, then was filtered and extracted with EtOAc. The combined filtrates were washed with water and brine, dried ($MgSO_4$), and concentrated *in vacuo* to give Part A compound (0.206g; 38%).

B.



[00551] To a solution of Part A compound (0.070 g; 0.125 mmol) in THF (1.03 mL) and water (0.103 mL) was added $LiOH.H_2O$ (0.006 g; 0.249 mmol). The reaction mixture was stirred at 45°C for 1 h in a sealed vial, then two more equivalents of $LiOH.H_2O$ were added. The reaction mixture was stirred at 45°C for 20 minutes, then cooled to RT. Volatiles were removed *in vacuo*, and the remaining aqueous solution was acidified with 0.5N aqueous HCl to pH <2. The aqueous layer was re-extracted with EtOAc (3x). The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo* to give Part B compound (0.082 g; 87%).

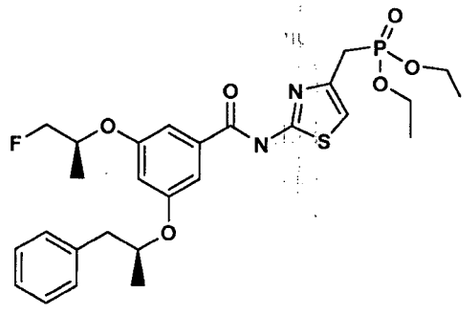
C.



[00552] To a 0°C solution of the Part B compound (0.020 g; 0.044 mmol) in NMP (0.146 mL) was added 1M LiHMDS in THF (0.087 mL; 0.087 mmol). After 15 min, 2-bromo-1-phenylethanone (0.017 g; 0.087 mmol) was added. The reaction mixture was allowed to warm to RT and stirred at RT for 15 h, then was partitioned between sat. aqueous NH_4Cl and EtOAc. The organic layer was washed with water (2x) and brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by preparative HPLC (YMC reverse phase ODS-5u 30 x 100 mm column; flow rate = 40 mL/min, 0 to 100% solvent B over 12 min, where solvent A = 90:10:0.1 H_2O:CH_3CN:TFA and solvent B = 90:10:0.1 CH_3CN:H_2O:TFA) to give the title

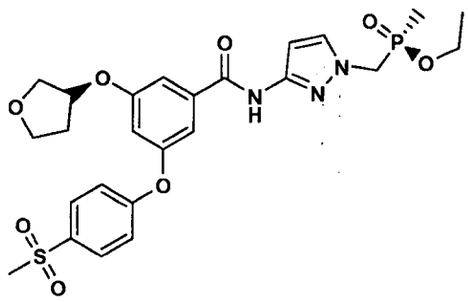
compound (6.0 mg; 24%) as a yellow oil. $[M + H]^+ = 577.3$; ^1H NMR (400 MHz, $CDCl_3$) δ 1.05 - 1.12 (m, *J*=6.05 Hz, 3 H), 1.24 (t, 6 H), 3.06 (s, 1 H), 3.11 (s, 1 H), 3.23 - 3.35 (m, 4 H), 3.36 - 3.42 (m, 1 H), 3.93 - 4.10 (m, 4 H), 4.24 - 4.35 (m, 1 H), 5.92 - 5.99 (m, *J*=4.40 Hz, 2 H), 6.41 - 6.48 (m, 1 H), 6.50 - 6.57 (m, 1 H), 7.11 (s, 1 H), 7.19 (s, 1 H), 7.44 - 7.54 (m, *J*=7.70 Hz, 2 H), 7.56 - 7.66 (m, *J*=7.15 Hz, 1 H), 7.99 - 8.08 (m, *J*=8.25 Hz, 2 H).

EXAMPLE 155

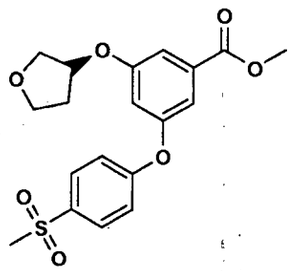


[00553] To a 0°C solution of Example 137 compound (0.021 g; 0.036 mmol) in anhydrous CH_2Cl_2 (0.369 mL) was added DAST (0.005 mL; 0.036 mmol). The reaction mixture was stirred for 2 h at 0°C, followed by careful addition of sat. aqueous $NaHCO_3$ and stirred for 5 min, then was partitioned between sat. aqueous $NaHCO_3$ and CH_2Cl_2. The aqueous layer was re-extracted with CH_2Cl_2 (3x). The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified twice by preparative HPLC (YMC reverse phase ODS-5u 30 x 100 mm column; flow rate = 40 mL/min, 20 to 100% solvent B over 12 min, where solvent A = 90:10:0.1 H_2O:CH_3CN:TFA and solvent B = 90:10:0.1 CH_3CN:H_2O:TFA) to give the title compound (6.0 mg; 29%) as a clear, colorless oil. $[M + H]^+ = 565.2$; ^1H NMR (400 MHz, $CDCl_3$) δ 1.22 - 1.32 (m, 12 H), 2.75 - 2.87 (m, *J*=13.74, 5.50 Hz, 2 H), 2.92 - 3.03 (m, *J*=13.74, 6.60 Hz, 1 H), 3.29 (s, 1 H), 3.34 (s, 1 H), 4.06 - 4.17 (m, 4 H), 4.33 - 4.45 (m, 1 H), 4.45 - 4.57 (m, 1 H), 4.63 - 4.74 (m, 1 H), 4.74 - 4.87 (m, 1 H), 6.64 - 6.69 (m, *J*=2.20, 2.20 Hz, 1 H), 6.94 - 7.00 (m, *J*=3.30 Hz, 1 H), 7.12 - 7.24 (m, 5 H), 7.30 (s, 1 H), 7.33 (s, 1 H).

EXAMPLE 156

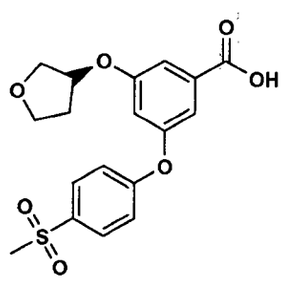


A.



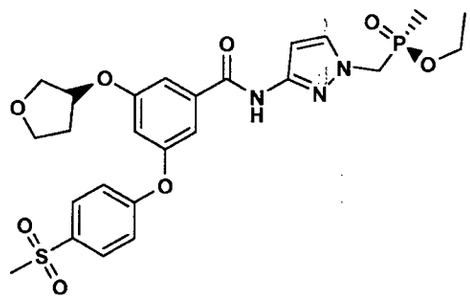
[00554] To a suspension of Example 97 Part B compound (1.4 g, 3.5 mmol) in DCM (6 mL) was added a solution of Example 26 Part A compound (141 mg, 0.44 mmol) and (R)-(-)-3-hydroxytetrahydrofuran (0.081 mL, 1.00 mmol) in toluene (2 mL). The reaction was stirred at RT for 15 h, then was diluted with EtOAc (10 mL) and washed with water and brine. The organic layer was dried ($MgSO_4$), and concentrated *in vacuo*. The residue was chromatographed (SiO_2; 40 g, 19 min continuous gradient, from 100% Hexane/0% EtOAc to 0% Hexanes/100% EtOAc) to provide Part A compound (254 mg, 148% yield, mixed with Ph_3PO) as a colorless oil.

B.



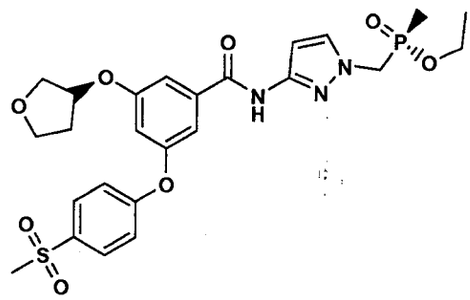
[00555] To a solution of Part A compound (254 mg, 0.65 mmol) in THF (2 mL) was added 1N aqueous NaOH (1 mL, 1.00 mmol). The reaction was stirred at RT for 15 h, then was diluted with EtOAc (6 mL) and acidified with 1N aqueous HCl (0.5 mL). The organic layer was washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by preparative HPLC (Phenomenex Luna AXIA 30 x 100 mm column; flow rate = 40 mL/min, 30 to 100% solvent B over 10 min, where solvent A = 90:10:0.1 H_2O:MeOH:TFA and solvent B = 90:10:0.1 MeOH:H_2O:TFA) to give Part B compound (90 mg, 37% yield) as a colorless oil.

C.



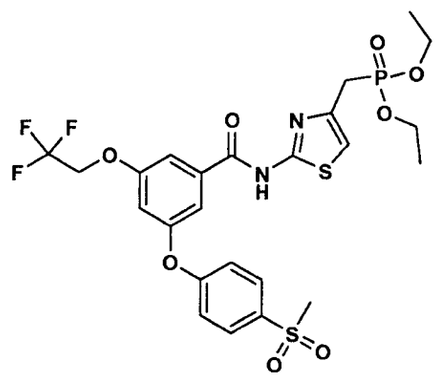
[00556] To a solution of Part B compound (25 mg, 0.066 mmol) in DMF (1 mL) were added Example 60 Part D2 amine (26.8 mg, 0.13 mmol), EDCI (25.3 mg, 0.13 mmol), HOBT (20.2 mg, 0.13 mmol), and DIPEA (0.035 mL, 0.20 mmol). The reaction was stirred at RT for 24 h. The reaction was purified directly by preparative HPLC (Phenomenex Luna AXIA 30 x 100 mm column; flow rate = 40 mL/min, 30 to 100% solvent B over 10 min, where solvent A = 90:10:0.1 H_2O:MeOH:TFA and solvent B = 90:10:0.1 MeOH:H_2O:TFA) to provide the title compound (24.6 mg, 66% yield) as a white solid. $[M + H]^+$= 564.3; ^1H NMR (500 MHz, $CDCl_3$) δ 9.63 (1 H, s), 7.92 (2 H, d, J=8.80 Hz), 7.52 (1 H, d, J=2.20 Hz), 7.33 (1 H, s), 7.27 (1 H, s), 7.09 - 7.18 (2 H, m), 7.01 (1 H, d, J=2.20 Hz), 6.71 - 6.86 (1 H, m), 5.01 - 5.14 (1 H, m), 4.37 - 4.60 (2 H, m), 4.07 - 4.22 (2 H, m), 3.96 - 4.05 (3 H, m), 3.84 - 3.96 (1 H, m), 3.07 (3 H, s), 2.05 - 2.38 (2 H, m), 1.55 (3 H, d, J=14.85 Hz), 1.34 (3 H, t, J=7.15 Hz).

EXAMPLE 157

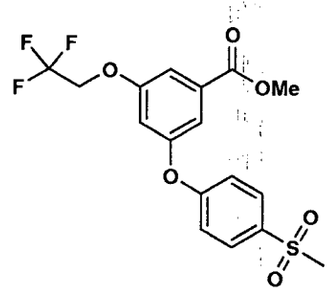


[00557] The title compound (27.4 mg, 73.6% yield; white solid) was synthesized from Example 60 Part D1 amine using the procedure employed in Example 156. [M + H]$^+$ = 564.3; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.58 (1 H, s), 7.92 (2 H, d, J=8.25 Hz), 7.52 (1 H, s), 7.31 (1 H, s), 7.26 (1 H, s), 7.14 (2 H, d, J=8.25 Hz), 7.01 (1 H, s), 6.80 (1 H, s), 5.01 - 5.13 (1 H, m), 4.41 - 4.60 (2 H, m), 4.06 - 4.21 (2 H, m), 3.96 - 4.05 (3 H, m), 3.86 - 3.96 (1 H, m), 3.07 (3 H, s), 2.09 - 2.35 (2 H, m), 1.55 (3 H, d, J=14.30 Hz), 1.27 - 1.39 (3 H, m).

EXAMPLE 158

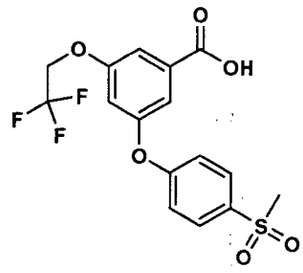


A.



[00558] To a RT solution of Example 26 Part A compound (117.8 mg, 0.365 mmol) in NMP (1.8 mL) under Ar was added Cs_2CO_3 (357 mg, 1.096 mmol), followed by dropwise addition of 2,2,2-trifluoroethyl methanesulfonate (0.075 mL, 0.640 mmol). The mixture was stirred at 60°C for 18 h, after which more 2,2,2-trifluoroethyl methanesulfonate (0.043 mL, 0.365 mmol) was added. The reaction was heated to 80°C for 29 h, then was cooled to RT. The reaction was diluted with water and stirred for 1 h, then was partitioned between EtOAc and saturated aqueous $NaHCO_3$. The organic layer was washed with water (2x), and the combined aqueous layers were back extracted with EtOAc. The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated *in vacuo*. The residue was chromatographed (12g SiO_2, eluting from 0-10% EtOAc: CH_2Cl_2, then flushing with 90% EtOAc) to give Part A compound (44 mg, 29%) as a colorless oil.

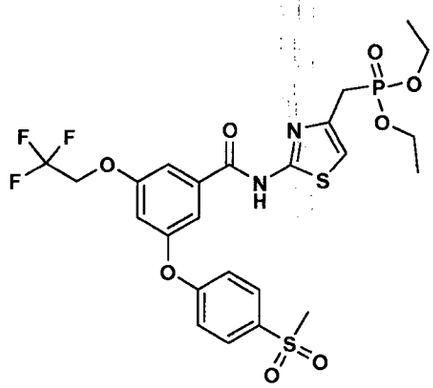
B.



[00559] To a RT solution of Part A ester (44 mg, 0.109 mmol) in THF (0.8 mL) and MeOH (0.4 mL) under Ar was added 4N aqueous $LiOH.H_2O$ (0.2 mL, 0.800 mmol). A precipitate formed immediately, and the reaction was stirred at RT for 6.5 h, then was diluted with MeOH, and volatiles were removed *in vacuo*. The residue was dissolved in water and acidified with 1N aqueous HCl. The aqueous layer was

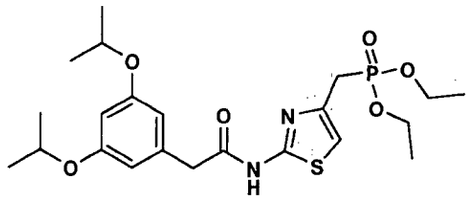
extracted with EtOAc; the organic layer was washed with brine, dried (Na_2SO_4), and concentrated *in vacuo* to give Part B acid (38.6 mg, 91%) as a colorless solid.

C.



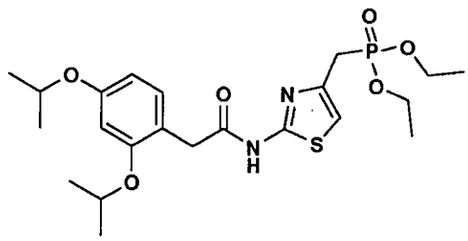
[00560] To a RT suspension of Part B acid (20 mg, 0.051 mmol) in CH_2Cl_2 (0.3 mL) under Ar were added HATU (36 mg, 0.095 mmol), and a solution of Example 13 Part E compound (18.6 mg, 0.074 mmol) in CH_2Cl_2 (0.3 mL), followed by DIPEA (0.036 mL, 0.205 mmol). The reaction was stirred at RT for 42 h, then EtOAc and sat. aqueous $NaHCO_3$ were added. The reaction was stirred for 1 h, then was partitioned between EtOAc and sat. aqueous $NaHCO_3$. The organic layer was washed with sat. aqueous $NaHCO_3$, brine, dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by preparative HPLC (Phenomenex Luna 5 μm 21.2x100mm column, detection at 220 nm; flow rate = 20 mL/min; continuous gradient from 50% A to 100% B over 10 min +2 min hold time at 100% B, where A = 90:10:0.1 H_2O:MeOH:TFA and B = 90:10:0.1 MeOH:H_2O:TFA) to give one clean fraction. The desired fraction was passed through a MeOH treated cartridge of Polymer Lab StratoSpheres TM SPE PL-HCO3 MP SPE resin (500mg), washing well with MeOH. The filtrate was concentrated *in vacuo*, then azeotroped several times with MeOH. The residue was taken up in CH_2Cl_2/MeOH; solids were filtered off, and the filtrate was concentrated *in vacuo* to give the title compound (14.8 mg, 46%) as a tan colored solid. $[M + H]^+$ = 623.2; ^1H NMR (400 MHz, $CDCl_3$) δ 1.24 (t, *J*=7.15 Hz, 6 H), 3.09 (s, 3 H), 3.46 (d, *J*=21.5 Hz, 2 H), 3.99 - 4.10 (m, 4 H), 4.48 (q, *J*=7.70 Hz, 2 H), 6.83 (d, *J*=3.30 Hz, 1 H), 6.92 (s, 1 H), 7.16 (d, *J*=8.79 Hz, 2 H), 7.46 (s, 1 H), 7.58 (s, 1 H), 7.95 (d, *J*=8.79 Hz, 2 H), ^{19}F NMR (400 MHz, $CDCl_3$): δ -73.66.

EXAMPLE 159



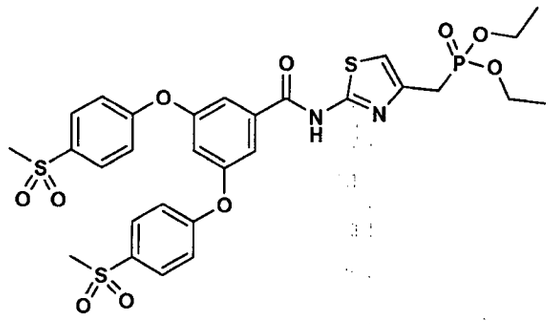
[00561] The title compound (20 mg, 51% yield, yellow oil) was prepared employing the same general sequence as described in the synthesis of Example 74. $[M + H]^+ = 485.18$; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 6.94 (1 H, d, *J*=3.95 Hz), 6.52 (2 H, d, *J*=2.20 Hz), 6.35 (1 H, t, *J*=2.20 Hz), 4.49 - 4.57 (2 H, m), 4.10 - 4.19 (4 H, m), 3.78 (2 H, s), 3.25 - 3.34 (2 H, m), 1.27 - 1.36 (18 H, m).

EXAMPLE 160

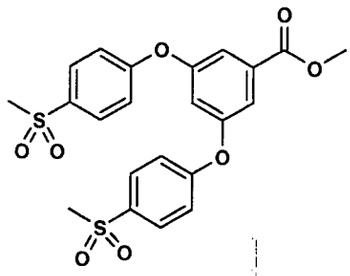


[00562] The title compound (15 mg, 45% yield, yellow oil) was prepared employing the same general sequence as described in the synthesis of Example 74. $[M + H]^+ = 485.18$; ^1H NMR (400 MHz, $CDCl_3$) δ 7.12 (1 H, d, J=8.79 Hz), 6.88 (1 H, d, J=3.95 Hz), 6.41 - 6.46 (2 H, m), 4.47 - 4.57 (1 H, m), 4.07 - 4.17 (4 H, m), 3.75 (2 H, s), 3.24 - 3.34 (2 H, m), 1.23 - 1.37 (18 H, m).

EXAMPLE 161

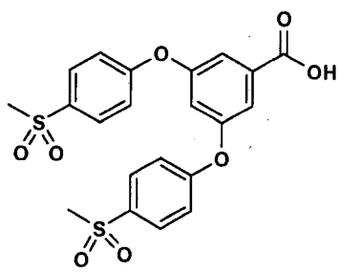


A.



[00563] A solution of methyl 3,5-dihydroxybenzoate (2.5 g, 14.9 mmol), 1-fluoro-4-(methylsulfonyl) benzene (5.18 g, 29.8 mmol), and anhydrous K_2CO_3 (8.23g, 59.6 mmol) in dry DMF (100 mL) was heated at 120°C for 10 h, then was cooled to RT and filtered. The solid was washed with CH_2Cl_2 (100 mL), and the combined filtrate was concentrated *in vacuo*. The residue was chromatographed (SiO_2; 80 g; continuous gradient from 100% hexane to 100% EtOAc over 40 min) to provide Part A compound (6.1 g, 86% yield) as a white solid. $[M + H]^+ = 477$.

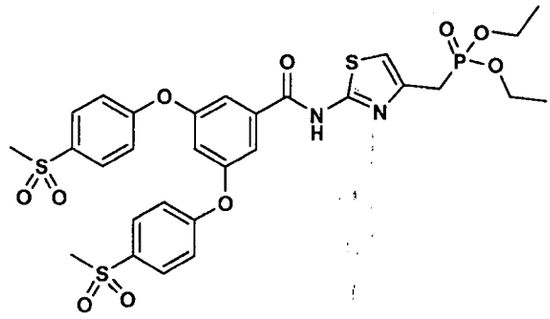
B.



[00564] A solution of Part A compound (2.3 g, 4.83 mmol), and $LiOH.H_2O$ (4.1 g, 97.5 mmol) in THF (10 mL)/H_2O (5 mL) was stirred for 2 h at RT. The reaction was

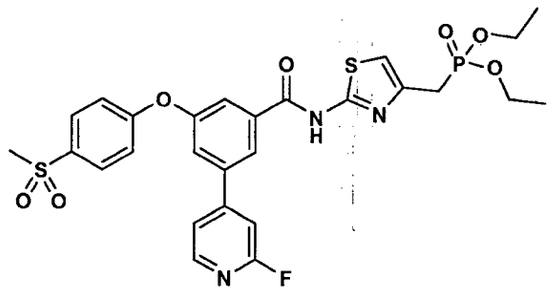
acidified to pH 1 with 1N aqueous HCl, and extracted with EtOAc (3 x 15 mL). The combined organic extracts were washed with brine (30 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give Part B compound (2.2 g, 99% yield) as a white solid. [M - H] = 461.

C.

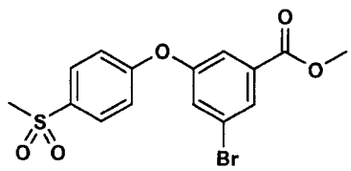


[00565] To a suspension of the Part B compound (50 mg, 0.11 mmol) in CH_2Cl_2 (3 mL) were added Example 13 Part E compound (27 mg, 0.11 mmol), Et_3N (30 μL, 0.22 mmol), and BOP (72 mg, 0.16 mmol). The reaction was stirred for 16 h, then was diluted with H_2O (1 mL), and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic extracts were washed with brine (3 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by preparative HPLC (YMC reverse phase ODS-A-5μm 30 x 250 mm column; flow rate = 25 mL/min, 20 to 100% solvent B over 30 min, hold to 40 min, where solvent A = 90:10:0.1 H_2O:MeOH:TFA and solvent B = 90:10:0.1 MeOH:H_2O:TFA) to afford the title compound (50 mg, 65% yield) as a white solid. $[M + H]^+ = 695$; ^1H NMR (500 MHz, $CDCl_3$): δ 7.95 (d, *J*=8.8 Hz, 4H), 7.65 (d, *J*=2.2 Hz, 2H), 7.20 (d, *J*=8.8 Hz, 4H), 7.09 (t, *J*=2.2 Hz, 1H), 7.01 (d, *J*=3.3 Hz, 1H), 4.11 (m, 4H), 3.28 (d, *J*=22.0 Hz, 2H), 3.06 (s, 6H), 1.28 (t, *J*=6.9 Hz, 6H).

EXAMPLE 162

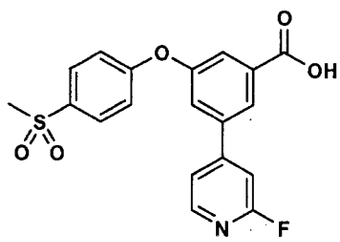


A.



[00566] A solution of methyl 3-bromo-5-hydroxybenzoate (2.13 g, 9.21 mmol), 1-fluoro-4-(methylsulfonyl)benzene (1.93 g, 11.1 mmol), and anhydrous K_2CO_3 (2.55 g, 18.42 mmol) in dry DMF (15 mL) was heated at 120°C for 20 h, then was cooled to RT and filtered. The solids were washed with CH_2Cl_2 (100 mL), and the combined filtrates were concentrated *in vacuo*. The residue was chromatographed (SiO_2; 80 g; continuous gradient from 100% hexane to 100% EtOAc over 40 min) to provide Part A compound (1.64 g, 48% yield) as a white solid. [M - H] = 370.

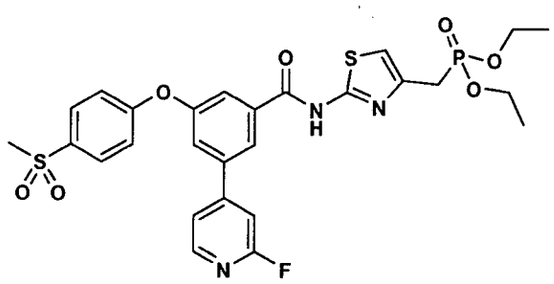
B.



[00567] A RT solution of Part A compound (124 mg, 0.322 mmol), 2-fluoropyridin-4-ylboronic acid (54.4 mg, 0.386 mmol), K_2CO_3 (89 mg, 0.644 mmol), and $(PPh_3)_4Pd$ (18.6 mg, 16 μmol) in DME (4 mL) and water (1 mL) was stirred under a stream of N_2 for 5 min. The mixture was then sealed and heated in an Emrys Optimizer® at 150°C for 30 min. The reaction was cooled to RT and was acidified to

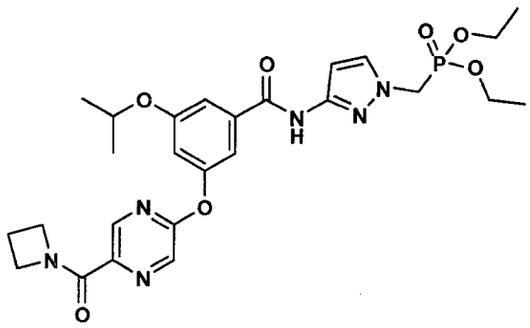
pH 2 with 1N aqueous HCl. The mixture was partitioned between EtOAc (3 mL) and water (3 mL), and was extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by preparative HPLC (YMC reverse phase ODS-A-5μm 30 x 250 mm column; flow rate = 25 mL/min, 20 to 100% solvent B over 30 min, then held for 10 min, where solvent A = 90:10:0.1 H_2O:MeOH:TFA and solvent B = 90:10:0.1 MeOH:H_2O:TFA) to afford the Part B compound (80 mg, 64%) as a white solid. [M - H] = 386.

C.

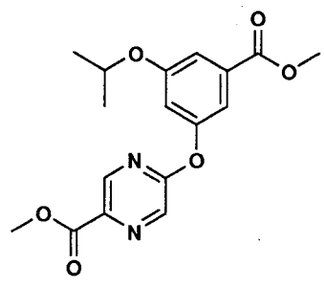


[00568] To a suspension of the Part B compound (20 mg, 0.052 mmol) in CH_2Cl_2 (2 mL) were added Example 13 Part E compound (13 mg, 0.052 mmol), Et_3N (11 μL, 0.077 mmol), and BOP (27.4 mg, 0.062 mmol). The reaction was stirred for 16 h, then was diluted with H_2O (1 mL) and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic extracts were washed with brine (3 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by preparative HPLC (YMC reverse phase ODS-A-5μm 30 x 250 mm column; flow rate = 25 mL/min, 20 to 100% solvent B over 30 min, hold to 40 min, where solvent A = 90:10:0.1 H_2O:MeOH:TFA and solvent B = 90:10:0.1 MeOH:H_2O:TFA) to afford the title compound (27 mg, 84% yield) as a white solid. $[M + H]^+ = 620$; ^1H NMR (500 MHz, CD_3OD): δ 8.32 – 8.29 (m, 2H), 8.0 (d, *J*=8.8 Hz, 2H), 7.85 – 7.82 (m, 2H), 7.72 – 7.69 (m, 1H), 7.51 (s, 1H), 7.30 (d, *J*=8.8 Hz, 2H), 7.00 (d, *J*=3.8 Hz, 1H), 4.12 – 4.05 (m, 4H), 3.37 (d, *J*=21.4 Hz, 2H), 3.13 (s, 3H), 1.28 (t, *J*=6.8 Hz, 6H).

EXAMPLE 163

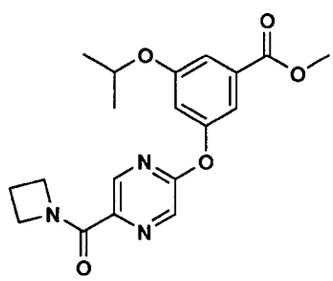


A.



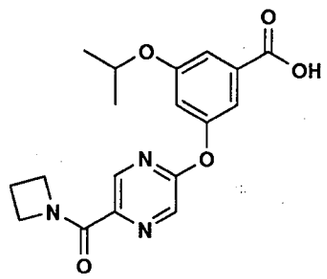
[00569] A solution of methyl 3-hydroxy-5-isopropoxybenzoate (*Bioorg. Med. Chem. Lett.* **2005**, 15:2103) (609 mg, 2.90 mmol), methyl 5-chloropyrazine-2-carboxylate (500 mg, 2.90 mmol), and K_2CO_3 (1.20 mg, 8.69 mmol) in CH_3CN (20 mL) was heated to 80°C for 2 h under Ar. The reaction was cooled to RT, diluted with CH_2Cl_2 (50 mL), filtered and the filtrate was concentrated *in vacuo*. The residue was chromatographed (SiO_2; 40 g; continuous gradient from 100% hexane to 100% EtOAc over 40 min) to provide Part A compound (1.005 g, 100% yield) as a colorless oil. $[M + H]^+ = 347$.

B.



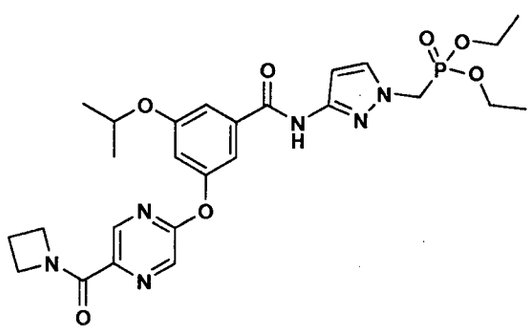
[00570] A mixture of Part B compound (1.005 g, 2.9 mmol), azetidine hydrochloride (326 mg, 3.48 mmol), Et_3N (0.485 mL, 3.48 mmol), and $MgCl_2$ (332 mg, 3.48 mmol) was stirred at RT for 5 h. More azetidine hydrochloride (326 mg, 3.48 mmol), Et_3N (0.485 mL, 3.48 mmol), and $MgCl_2$ (332 mg, 3.48 mmol) were added. The reaction was stirred at RT for 30 min, then was stored at 0°C overnight, then diluted with CH_2Cl_2 (50 mL), filtered, and the filtrate was concentrated *in vacuo*. The residue was chromatographed (SiO_2; 40 g; continuous gradient from 100% hexane to 100% EtOAc over 40 min) to provide Part B compound (267 mg, 25% yield) as a colorless oil. $[M + H]^+ = 372$.

C.



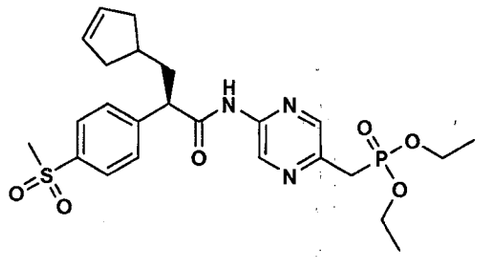
[00571] A solution of Part B compound (267 mg, 0.72 mmol) and $LiOH.H_2O$ (90 mg, 2.16 mmol) in THF (4 mL)/H_2O (4 mL) was stirred for 5 h at RT. The reaction was acidified to pH 2 with 1N aqueous HCl, then was extracted with EtOAc (3 x 10 mL). The combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give Part C compound (200 mg, 78% yield) as a white solid. $[M + H]^+ = 358$.

D.

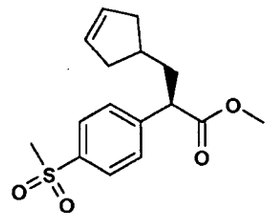


[00572] To a suspension of the Part C compound (14 mg, 0.039 mmol) in CH_2Cl_2 (1.5 mL) were added Example 32 Part A compound (9.1 mg, 0.039 mmol), Et_3N (11 μL, 0.078 mmol), and BOP (34.7 mg, 0.078 mmol). The reaction was stirred for 16 h at RT, then was diluted with H_2O (1 mL) and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic extracts were washed with brine (3 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by preparative HPLC (YMC reverse phase ODS-A-5u 30 x 250 mm column; flow rate = 25 mL/min, 20 to 100% solvent B over 30 min, hold to 40 min, where solvent A = 90:10:0.1 H_2O:MeOH:TFA and solvent B = 90:10:0.1 MeOH:H_2O:TFA) to afford the title compound (9.5 mg, 43% yield) as a white solid. $[M + H]^+ = 573$; ^1H NMR (500 MHz, $CDCl_3$): δ 9.11 (s, 1H), 8.84 (s, 1H), 8.33 (s, 1H), 7.48 (s, 1H), 7.35 (s, 1H), 7.27 (s, 1H), 6.95 (d, *J*=2.2 Hz, 1H), 6.87 (d, *J*=2.2 Hz, 1H), 4.70 – 7.62 (m, 3H), 4.44 (d, *J*=8.0 Hz, 2H), 4.26 (t, *J*=7.7 Hz, 2H), 4.15 – 4.05 (m, 4H), 2.41 – 2.34 (m, 2H), 1.35 (d, *J*=6.1 Hz, 6H), 1.29 (t, *J*=7.2 Hz, 6H).

EXAMPLE 164



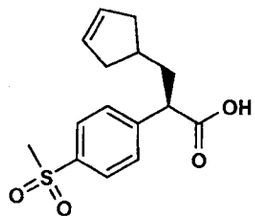
A.



[00573] To a -70°C solution of LDA (2.9 mL, 5.79 mmol, 2N in THF) and DMPU (1.75 mL, 5.79 mmoL) in THF (5.1mL) was slowly added methyl 2-(4-(methylsulfonyl)phenyl)acetate (1.27 g, 5.55 mmol) (see WO 00/58293), keeping the

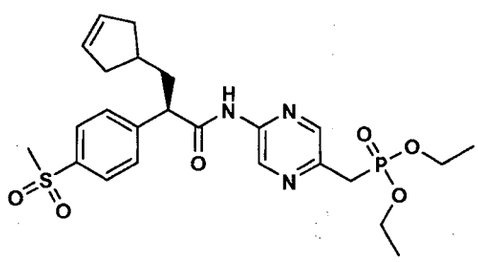
temperature below -65°C. The reaction was stirred at -70°C for 1 h and 4-(iodomethyl)cyclopent-1-ene (1.38 g, 6.58 mmol) was added, keeping the temperature below -60°C. The reaction mixture was stirred at -70°C for 30 min and then was warmed to RT and was stirred for 18 h. The reaction was cooled in an ice bath and was quenched with sat. aqueous NH_4Cl (20 mL). Volatiles were removed *in vacuo*, and the mixture was extracted with EtOAc (2x). The combined organic layer was washed with Brine, dried (MgSO4), filtered, and concentrated *in vacuo*. The residue was chromatographed (SiO_2) to give the Part A compound (880 mg, 51% yield) as a white solid.

B.



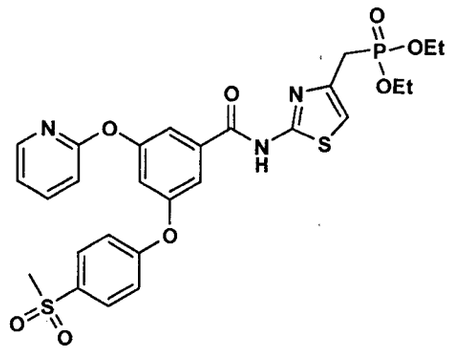
[00574] To a 0°C solution of Part A compound (880 mg, 2.85 mmol) in MeOH (8 mL) and THF (4 mL) was added 1N aqueous NaOH (6 mL). The reaction was slowly warmed to RT and was stirred at RT for 18 h. Volatiles were removed *in vacuo*, and the reaction was diluted with water, acidified with 2N aqueous HCl (5 mL), and extracted with EtOAc. The organic layer was washed with brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give the Part B compound (830 mg, 96% yield) as a white solid.

C.

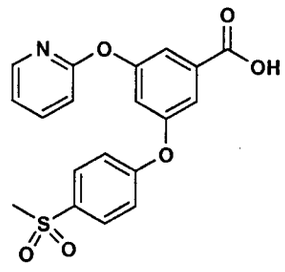


[00575] To a 0°C solution of Part B compound (29.4 mg, 0.1 mmol) in CH_2Cl_2 (0.5 mL) under Ar was added oxalyl chloride (0.065 mL, 0.13 mmol, 2M in CH_2Cl_2) and DMF (3 μL). The reaction was stirred at 0°C for 1 h and was then warmed to RT and was stirred for 2 h. Volatiles were removed *in vacuo*. To a 0°C solution of the acid chloride residue in CH_2Cl_2 (0.5 mL) under Ar was added a solution of pyridine (32.3 μL, 0.4 mmol) in CH_2Cl_2 (0.25 mL), followed by the addition of Example 7 Part B compound (27 mg, 0.11 mmol). The reaction was a stirred at RT for 18 h and was directly purified by column chromatography (SiO_2, 0-10% MeOH: CH_2Cl_2). The desired product and the Part B acid co-eluted, so the mixture was extracted with CH_2Cl_2. The organic layer was washed with 0.5 N aqueous HCl, water, sat. aqueous $NaHCO_3$, and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give the title compound (29 mg, 56% yield) as an oil. $[M+H]^+ = 522.2$.

EXAMPLE 165



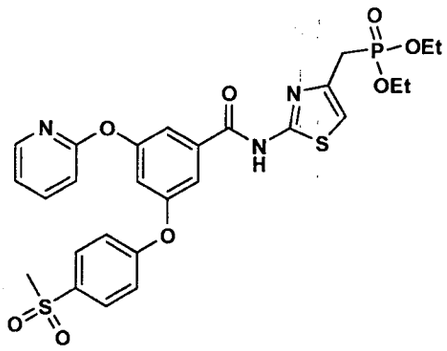
A.



[00576] To a solution of Example 26 Part A compound (80 mg, 0.248 mmol) in DMF (1 mL), were added 2-chloropyridine (0.047 mL, 0.496 mmol) and K_2CO_3 (103

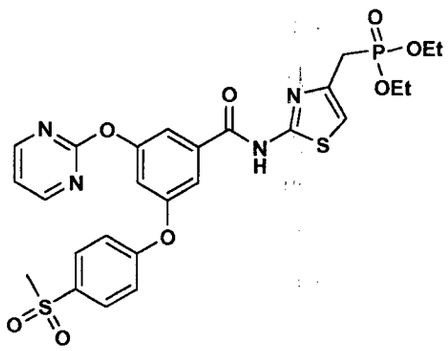
mg, 0.745 mmol). The reaction mixture was stirred at 120°C for 40 h, then was cooled to RT and filtered. The filtrate was diluted with MeOH, then was purified by preparative HPLC (Phenomenex Luna AXIA 30 x 100 mm column; detection at 220 nm; flow rate=40 mL/min.; continuous gradient from 80% A to 100% B over 10 min., where A=10% MeOH/90% H_2O/0.1% TFA and B=90% MeOH/10% H_2O/0.1% TFA) to give Part A compound (26 mg, 27%) as a white solid.

B.



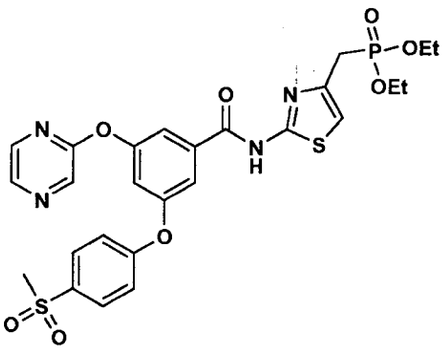
[00577] To a solution of Part A compound (26 mg, 0.067 mmol) in DMF (1 mL), was added Example 13 Part E compound (33.8 mg, 0.135 mmol), EDCI (25.9 mg, 0.135 mmol), HOBT (20.66 mg, 0.135 mmol), and DIPEA (0.035 mL, 0.202 mmol). The reaction mixture was stirred at RT for 2 days. The reaction mixture was purified directly by preparative HPLC (Phenomenex Luna AXIA 30 x 100 mm column; detection at 220 nm; flow rate=40 mL/min.; continuous gradient from 70% A to 100% B over 10 min., where A=10% MeOH/90% H_2O/0.1% TFA and B=90% MeOH/10% H_2O/0.1% TFA) to give the title compound (11 mg, 26% yield) as a yellow oil. $[M + H]^+ = 618.3$; ^1H NMR (500 MHz, $CDCl_3$): δ 8.24 (1 H, d, *J*=4.95 Hz), 7.95 (2 H, d, *J*=8.80 Hz), 7.78 - 7.84 (2 H, m), 7.71 (1 H, s), 7.20 - 7.25 (3 H, m), 7.13 (1 H, dd, *J*=6.87, 4.67 Hz), 7.07 (1 H, d, *J*=8.25 Hz), 7.04 (1 H, d, *J*=3.85 Hz), 4.10 - 4.21 (4 H, m), 3.34 (2 H, d, *J*=21.44 Hz), 3.07 (3 H, s), 1.32 (6 H, t, *J*=6.87 Hz).

EXAMPLE 166



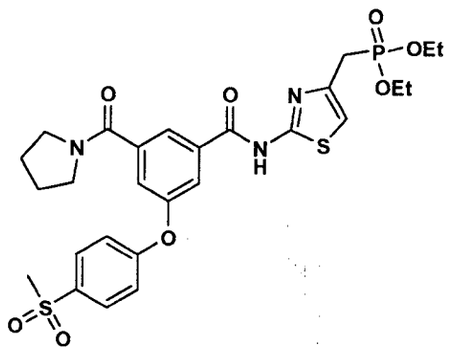
[00578] The title compound (5 mg, 24% yield, yellow oil) was prepared from 2-chloropyrimidine following the same general procedure as used for the synthesis of Example 165. $[M + H]^+ = 619.3$; ^1H NMR (500 MHz, $CDCl_3$): δ 8.63 (2 H, d, *J*=4.95 Hz), 7.88 - 7.99 (3 H, m), 7.78 (1 H, s), 7.27 - 7.28 (1 H, m), 7.24 (2 H, d, *J*=9.35 Hz), 7.15 (1 H, t, *J*=4.95 Hz), 7.05 (1 H, d, *J*=3.30 Hz), 4.11 - 4.21 (4 H, m), 3.34 (2 H, d, *J*=21.44 Hz), 3.08 (3 H, s), 1.32 (6 H, t, *J*=7.15 Hz).

EXAMPLE 167

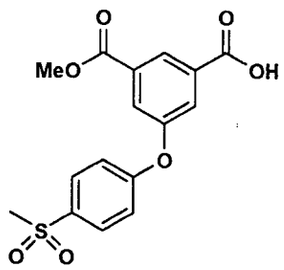


[00579] The title compound (11.5 mg, 30% yield, yellow solid) was prepared from 2-chloropyrazine following the same general procedure as used for the synthesis of Example 165. $[M + H]^+ = 619.3$; ^1H NMR (500 MHz, $CDCl_3$): δ 8.54 (1 H, s), 8.37 (1 H, d, *J*=2.75 Hz), 8.16 (1 H, s), 7.96 (2 H, d, *J*=8.80 Hz), 7.89 (1 H, s), 7.77 (1 H, s), 7.25 - 7.27 (1 H, m), 7.24 (2 H, d, *J*=8.80 Hz), 7.05 (1 H, d, *J*=3.85 Hz), 4.10 - 4.21 (4 H, m), 3.34 (2 H, d, *J*=21.44 Hz), 3.08 (3 H, s), 1.32 (6 H, t, *J*=6.87 Hz).

EXAMPLE 168

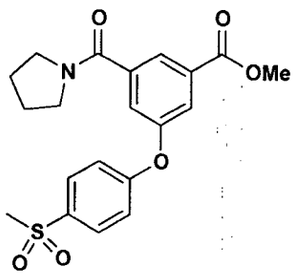


A.



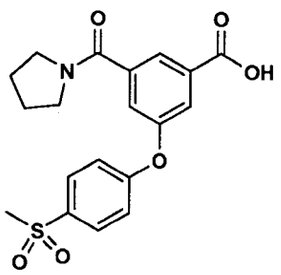
[00580] To a solution of dimethyl 5-hydroxyisophthalate (198 mg, 0.942 mmol) in DMF (2 mL), was added 1-fluoro-4-(methylsulfonyl)benzene (197 mg, 1.130 mmol) and K_2CO_3 (391 mg, 2.83 mmol). The reaction mixture was stirred at 120°C for 41 h, then was cooled to RT and filtered. The filtrate was diluted with MeOH, then was purified by preparative HPLC (Phenomenex Luna AXIA 30 x 100 mm column; detection at 220 nm; flow rate=40 mL/min.; continuous gradient from 80% A to 100% B over 10 min., where A=10% MeOH/90% H_2O/0.1% TFA and B=90% MeOH/10% H_2O/0.1% TFA) to provide Part A compound (176 mg, 53% yield) as a white solid. $[M+H]^+ = 351.2$.

B.



[00581] To a solution of Part A compound (85 mg, 0.243 mmol) in CH_2Cl_2 (1.0 ml) was added oxalyl chloride (0.243 mL, 0.485 mmol) and DMF (5.64 μL, 0.073 mmol). The mixture was stirred at RT for 1 h, then was concentrated in vacuo. The crude acid chloride was taken up in THF (1.0 mL), and pyrrolidine (0.041 mL, 0.485 mmol) and pyridine (0.059 mL, 0.728 mmol) were added. The reaction mixture was stirred at RT for 3 h, then was diluted with EtOAc (10 mL), washed with H_2O and brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by preparative HPLC (Phenomenex Luna AXIA 30 x 100 mm column; detection at 220 nm; flow rate=40 mL/min.; continuous gradient from 70% A to 100% B over 10 min., where A=10% MeOH/90% H_2O/0.1% TFA and B=90% MeOH/10% H_2O/0.1% TFA) to provide Part B compound (93 mg, 95% yield) as a colorless oil. $[M+H]^+$ = 404.3.

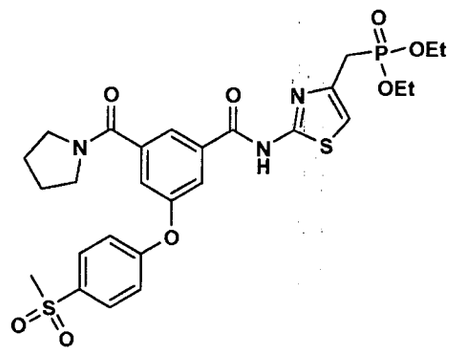
C.



[00582] To a solution of art B compound (8.5 mg, 0.021 mmol) in THF (1 mL), was added 1N aqueous NaOH (0.063 mL, 0.063 mmol). The reaction mixture was stirred at RT for 15 h and was diluted with EtOAc (6 mL), acidified with 1N aqueous HCl (0.050 mL), and separated. The organic layer was washed with brine, dried ($MgSO_4$), and concentrated *in vacuo* to give crude Part C compound (10 mg) as a

white solid, which was used in the next step without further purification. $[M+H]^+$ = 390.2.

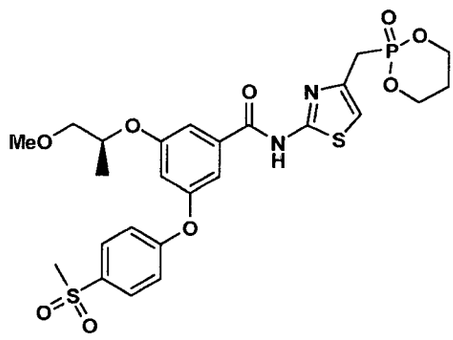
D.



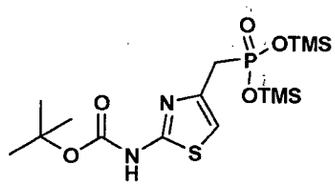
[00583] To a solution of Part C compound (10 mg, 0.026 mmol) in DMF (1 mL), was added Example 13 Part E compound (12.9 mg, 0.051 mmol), EDCI (9.9 mg, 0.051 mmol), HOBT (7.9 mg, 0.051 mmol), and DIPEA (0.013 mL, 0.077 mmol). The reaction mixture was stirred at RT for 4 days, then was purified directly by preparative HPLC (Phenomenex Luna AXIA 30 x 100 mm column; detection at 220 nm; flow rate=40 mL/min.; continuous gradient from 70% A to 100% B over 10 min., where A=10% MeOH/90% H_2O/0.1% TFA and B=90% MeOH/10% H_2O/0.1% TFA) to provide the title compound (3 mg, 23% yield over 2 steps) as a white solid. $[M+H]^+$ = 622.3 ; ^1H NMR (500 MHz, $CDCl_3$): δ 8.18 (1 H, s), 7.89 - 8.00 (3 H, m), 7.55 (1 H, s), 7.19 (2 H, d, *J*=8.80 Hz), 7.05 (1 H, d, *J*=3.30 Hz), 4.05 - 4.23 (4 H, m), 3.50 - 3.74 (4 H, m), 3.35 (2 H, d, *J*=21.44 Hz), 3.09 (3 H, s), 1.85 - 2.04 (4 H, m), 1.32 (6 H, t, *J*=7.15 Hz).

[00584]

EXAMPLE 169

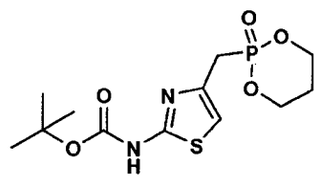


A.



[00585] To a solution of Example 13 Part A compound (377 mg, 1.08 mmol) in CH_2Cl_2 (5 mL) at RT under Ar was added TMSBr (0.307 mL, 2.37 mmol). After stirring at RT for 15 h, the reaction mixture was concentrated in vacuo under scrupulously dry conditions to provide Part A compound as a colorless oil, which was used in the next step without further purification.

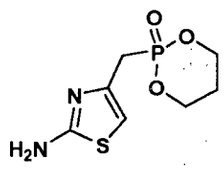
B.



[00586] To a solution of Part A compound in dry CH_2Cl_2 (5 mL; protected from the atmosphere by a $CaCl_2$-filled drying tube) was added oxalyl chloride (0.207 mL, 2.37 mmol) and DMF (8 μL, 0.1 mmol). Considerable foaming was observed, eventually resulting in the formation of a beige precipitate. After stirring at RT for 3 h, the reaction mixture was concentrated in vacuo and the residue was taken up in THF (12 mL) and cooled to -65°C under Ar. To this slurry was added a solution of

1,3-propanediol (0.086 mL, 1.18 mmol) in MeCN (6 mL) over 2 min and stirred for 5 min at -65°C. Pyridine (0.183 mL, 2.26 mmol) was then added over 1 min, and the reaction mixture was allowed to warm to RT and stirred for 16 h at RT. The mixture was partitioned between EtOAc and 5% aqueous $NaHSO_4$ (25 mL each). The organic phase was dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by preparative HPLC (Phenomenex Luna 21.2 x 100 mm column; detection at 254 nm; flow rate = 20 mL/min.; continuous gradient from 0% A to 100% B over 10 min, where A=10% MeCN/90% H_2O/0.1% TFA and B=90% MeCN /10% H_2O/0.1% TFA) to provide Part B compound (71 mg, 20% yield) as a white amorphous solid. $[M+H]^+ = 335$.

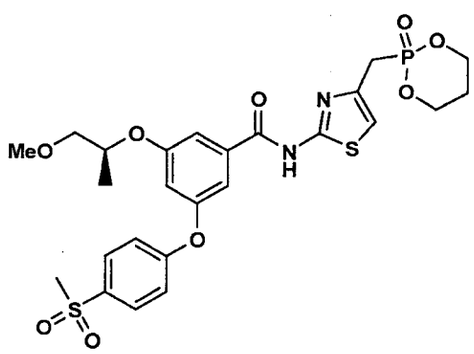
C.



[00587] To a stirred solution of Part B compound (71 mg, 0.21 mmol) in dry CH_2Cl_2 (2 mL; protected from the atmosphere by a $CaCl_2$-filled drying tube) at RT was added TFA (0.5 mL). The reaction was stirred for 4 h at RT, then was concentrated in vacuo. The residue was dissolved in MeOH and eluted through a StratoSpheres™ SPE PL-HCO_3 MP ion exchange cartridge (0.9 meq capacity) with MeOH. Concentration of the eluent in vacuo provided Part C compound as a white amorphous solid (43 mg, 86% yield). $[M+H]^+ = 235$.

[00588]

D.



[00589] To a stirred slurry of Example 26C compound (69 mg, 0.18 mmol) in CH_2Cl_2 (2 mL) at RT under Ar were successively added HOAt (25 mg, 0.18 mmol) and EDC (35 mg, 0.18 mmol). A clear solution formed within 5 min. After 30 min, this solution was added to a slurry of Part C compound in THF (2 mL) at RT under Ar, followed by iPr_2NEt (0.016 mL, 0.43 mmol) and DMAP (2.6 mg, 0.02 mmol). After stirring for 18 h at RT, analytical HPLC indicated that no product had formed. The reaction mixture was concentrated in vacuo and taken up in dry MeCN (3 mL), then was heated to reflux under Ar, whereupon a solution formed. After 2 h at reflux, analytical HPLC indicated that almost all the amine had been consumed. The reaction mixture was cooled to RT and concentrated in vacuo. The residue was partitioned between EtOAc and saturated aqueous $NaHCO_3$ (20 mL each). The organic phase was washed with brine and aqueous 10% $NaHSO_3$, dried (Na_2SO_4) and concentrated in vacuo. Purification of the oily residue by preparative HPLC (Phenomenex Luna 21.2 x 100 mm column; detection at 220 nm; flow rate=20 mL/min.; continuous gradient from 0% A to 100% B over 10 min., where A=10% MeCN/90% H_2O/0.1% TFA and B=90% MeCN/10% H_2O/0.1% TFA) provided the title compound (35 mg, 28% yield) as a white amorphous solid. $[M+H]^+ = 597$. ^1H NMR (400 MHz, $CDCl_3$): δ 7.92 (2 H, d, *J*=7.1 Hz), 7.59 (1 H, s), 7.42 (1 H, s), 7.17 (2 H, d, *J*=8.80 Hz), 6.85 (2 H, m), 4.73 (1 H, m), 4.35 (2 H, m), 4.12 (2 H, m), 3.66-3.51 (3 H, m), 3.41 (3 H, s), 3.07 (3 H, s), 1.92-1.72 (2 H, m), 1.34 (3 H, d, *J*=6.0 Hz).

ASSAYS FOR GLUCOKINASE ACTIVATION

[00590] The compounds of formula I of the invention activate glucokinase. Assays which may be used in testing the compounds of formula I of the invention in activating glucokinase are known in the art such as disclosed in U.S. Patents Nos. 6,320,050, 6,384,200 and 6,610,846 and WO 2004/052869 and in Castellano, A.L., Dong, H., Fyfe, M.C.T., Gardner, L.S., Kamikozawa, Y. et al. (2005) "Glucokinase activating ureas", *Bioorg. Med. Chem. Letters*, 15:1501-1504, and Grimsby, J., Sarabu, R., Corbett, W.L., Haynes, N-E., Bizzarro, F.T., Coffey, J.W., Guertin, K.R., Hilliard, D.W., Kester, R.F., Mahaney, P.E., Marcus, L., Qi, L., Spence, C.L., Tengi, J., Magnuson, M.A., Chu, C.A., Dvorozniak, M.T., Matschinsky, F.M., Grippo, J.F.

(2003) "Allosteric Activators of Glucokinase: Potential Role in Diabetes Therapy", *Science*, 301:370-373.

[00591] In general, compounds of the present invention, such as particular compounds disclosed in the following examples, have been identified to enhance the activity of glucokinase at concentrations equivalent to, or more potently than, 100 μM, preferably 10 μM, more preferably 1 μM, thereby demonstrating compounds of the present invention as especially effective enhancers of activity of glucokinase. Potencies can be calculated and expressed as either EC_{50} (concentration to achieve 50% of full activation) and/or the maximum percentage activation above background, and refer to activity measured employing the assay system described above.

ASSAY AND BIOLOGICAL DATA

[00592] Compounds of formula I of the invention, including compounds described in the Examples hereof, have been tested in the following assay and have shown to be activators of glucokinase.

Glucokinase Tandem Enzymatic Assay

[00593] Enzymatic activity of human glucokinase (GK) was measured by incubating GK, ATP, and glucose for discrete time periods followed by quenching with EDTA (ethylenediamine tetra-acetic acid). Relative amounts of product glucose-6-phosphate (G6P) were measured by then running a detection assay using G6P dehydrogenase and measuring the conversion of ThioNAD (thio-nicotinamide adenine dinucleotide) to ThioNADH (thio-dihydronicotinamide adenine dinucleotide) at a wavelength of 405 nm. This 'uncoupled' enzymatic reaction is denoted as the GK 'tandem' assay. Activation of GK by compounds can be assessed using this assay. The GK tandem assay protocol described below was followed using a range of activator compound concentrations from 0 to 100 μM at 5 and 12 mM of glucose. Human full-length glucokinase (GK, 15 nM) was incubated with 5 or 12 mM glucose in a 384 well black microtiter plate with a clear bottom. To initiate the GK reaction, magnesium-ATP (3 mM final concentration) was added to GK in buffer (final buffer conditions of 25 mM HEPES buffer, pH 7.1, containing 1 mM dithiothreitol and 5% DMSO). The total reaction volume was 20 μL. The reaction was allowed to proceed

for ten minutes and was then quenched with 5 μL EDTA; 45 mM final). The components of the detection reaction, ThioNAD and G6PDH (glucose-6-phosphate dehydrogenase) (final concentrations of 650 μM and 3.33 Units, respectively), were then added together in a volume of 25 μL, (to give a total volume of 50 μL). Absorbance measurements were made at 405 nm on a Spectramax Plus 384 absorbance plate reader (Molecular Devices). Absorbance was read, background glucose-6-phosphate levels were subtracted, after which activation was calculated as a percentage of control activity. Control activity was determined using GK in the presence of vehicle (DMSO), with background glucose-6-phosphate subtracted. Background glucose-6-phosphate was determined by pre-quenching GK with EDTA prior to reaction initiation with ATP.

Expression and Purification of Human GK

[00594] Full-length human hepatic GK (untagged) was expressed in BL21 STAR (DE3)pLysS cells (Invitrogen) at 25 °C as described by Mookhtiar et al. (1). The protein was purified essentially as described by Lange (2) with a slight modification. Briefly, cell pellets were lysed via three rounds of freezing and thawing, centrifuged at 15000g for clarification, and precipitated with 40-65% (NH4)2SO4. The resulting pellet was resuspended in buffer, dialyzed, and applied directly to a Q-Sepharose (Sigma) column followed by elution with a linear 100-600 mM KCl gradient. GK containing fractions were pooled, dialyzed overnight vs. 25 mM Hepes pH 7.2/1 mM MgCl2/1 mM EDTA/0.1 M KCl/1 mM DTT, then dialyzed again with same buffer with 10% glycerol added.

REFERENCES

1. Mookhtiar, K.A., Kalinowski, S.S., Brown, K.S., Tsay, Y.H., Smith-Monroy, C., and Robinson, G.W. (1996) "Heterologous expression and characterization of rat liver glucokinase regulatory protein", *Diabetes,* 45:1670-1677.

2. Lange, A.J., Xu, L.Z., Van Poelwijk, F., Lin, K., Granner, D.K., and Pilkis, S.J. (1991) "Expression and site-directed mutagenesis of hepatic glucokinase", *Biochem. J.*, 277:159-163.

[00595] Biological data for select Examples are shown in the table below.

Example No.	EC_{50} (nM) with Human Glucokinase @ 12 mM Glucose
169	9
51	15
82	18
137	21
50	22
122	23
145	24
33	26
37	34
163	38
54	49
32	65
29	98
148	178
22	402
112	428
113	437
139	467
116	469
134	476
84	492
56	534
44	564

[00596] For other Examples, the EC_{50} values could not be calculated from the activation curves, so the maximal activation data (expressed as a % of basal activation) for some select Examples are shown in the table below.

Example No.	Maximal activation (%) Human Glucokinase @ 12 mM Glucose
121	126%
65	162%
35	133%
79	133%
86	141%
123	135%
74	142%
23	150%

In Vivo Studies: Oral Glucose Tolerance Test (OGTT)

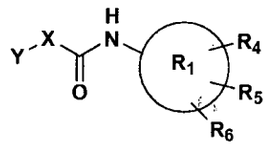
[00597] Oral glucose tolerance tests were carried out on male DIO (diet-induced obese) C57BL/6J mice fed a high fat diet (60% kcal from fat) for 26 weeks prior to experimentation. Mice were fasted overnight before use for experiments. A test compound or vehicle (either: 1) 40% PEG 400 + 10% Cremophore + 50% water or 2) 10% dimethyl acetamide + 10% ethanol + 10% Cremophore + 70% water) was given orally 60 min before oral administration of a glucose solution at a dose of 2 g/kg body weight (oral glucose tolerance test; OGTT). Blood glucose levels were measured from tail-bled samples taken at different time points before and after administration of glucose (time course of 2 hours). A time curve of the blood glucose was generated and the change from baseline area-under-the curve (ΔAUC) from 0-120 min was calculated (the time glucose administration being time zero).

[00598] The examples in the table below reduced glucose AUC levels in an OGTT test in DIO mice as described above.

Example No.	Reduction in Glucose AUC at 30 mg/kg dose
37	88%
148	60%
145	71%
54	68-82%
29	66-78%
44	62-80
32	79% @ 30 μmol/kg
82	44% @ 10 μmol/kg

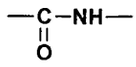
WHAT IS CLAIMED IS:

1. A compound having the structure:



I

wherein

R_1 is a heteroaryl substituted by R_4 and optionally substituted with one or two substituents R_5 and R_6, wherein said heteroaryl possesses a nitrogen atom adjacent to the atom joining said heteroaryl group to  ;

R_4 is selected from the group consisting of

$-(CH_2)_n-Z-(CH_2)_m-PO(OR_7)(OR_8)$,

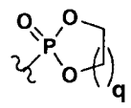
or $-(CH_2)_nZ-(CH_2)_m-PO(OR_7)R_9$,

or $-(CH_2)_n-Z-(CH_2)_m-O-PO(OR_7)R_9$,

or $-(CH_2)_nZ-(CH_2)_m-O-PO-(R_9)R_{10}$;

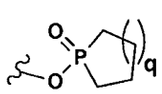
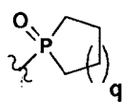
or $-(CH_2)_nZ-(CH_2)_m-PO-(R_9)R_{10}$;

R_7 and R_8 are the same or different and are independently selected from the group consisting of hydrogen and alkyl, or R_7 and R_8 can be cyclized into a ring

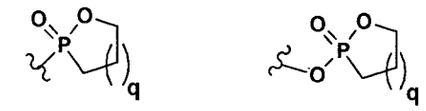
 where q = 1-3 ;

R_9 and R_{10} are the same or different and are independently selected from the group consisting of alkyl, aryl, arylalkyl, heteroaryl, and heteroarylalkyl;

or R_9 and R_{10} can be cyclized into a ring

 where q = 1-3, or  where q = 1-3 ;

or R_7 and R_9 can be cyclized into a ring



where q = 1-3 or where q = 1-3;

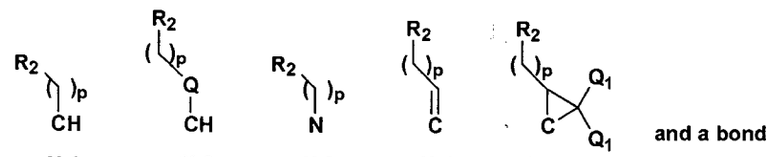
Z is selected from the group consisting of a bond, alkylene, alkenylene, O, S or SO_2;

m is 0, 1 or 2, provided that when Z is O, S or SO_2, m is 1 or 2;

n is 0, 1 or 2;

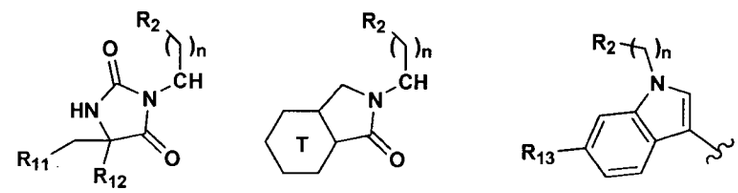
R_5 and R_6 are the same or different and are selected from the group consisting of hydrogen, alkyl, halogen and carboxy, or is absent;

X is selected from the group consisting of



X-1 , X-2 , X-3 , X-4 , X-5 , and a bond X-6 ;

and when Y is absent, X is



X-7 , X-8 and X-9 ;

R_2 is selected from the group consisting of hydrogen, alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, alkynyl, and alkenyl;

p is 0 or 1;

Q is selected from the group consisting of O, $S(O)_q$, and CO where q is 0, 1 or 2;

Q_1 is selected from the group consisting of hydrogen and fluorine;

R_{11} is selected from the group consisting of hydrogen, lower alkyl, cycloalkyl, aryl, and heteroaryl;

R_{12} is selected from the group consisting of hydrogen and lower alkyl, or R_{11} and R_{12} together with the carbon atom to which they are attached form a cycloalkyl ring of 5 to 7 carbon atoms;

R_{13} is selected from the group consisting of halo, nitro, amino, cyano, methyl, trifluoromethyl, hydroxy, methoxy, trifluoromethoxy, methylthio, methylsulfinyl, or methylsulfonyl;

T is selected from the group consisting of aryl and heteroaryl;

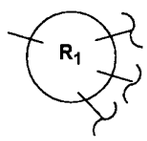
Y is R_3-$(CH_2)_s$-, or is absent;

R_3 is selected from the group consisting of aryl and heteroaryl;

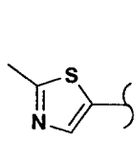
s = 0 or 1;

all stereoisomers thereof, a prodrug ester thereof or a pharmaceutically acceptable salt thereof.

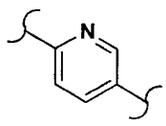
2. The compound as defined in Claim 1 wherein the moiety



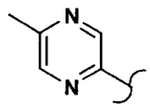
is



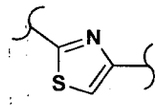
;



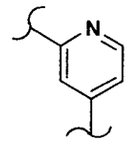
;



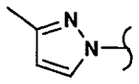
;



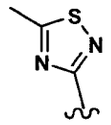
;



;



; or



.

3. The compound as defined in Claim 1 wherein Z is alkylene or alkenylene, each of which may be optionally substituted with hydroxyl, alkoxy, aminoalkyl, aminoaralkyl, aminoheteroaralkyl, aminoaryl, aminoheteroaryl, or carboxy.

4. The compound as defined in Claim 1 wherein

R_4 is $(CH_2)_n$-Z-$(CH_2)_m$-$PO(OR_7)(OR_8)$ wherein Z is alkylene or alkenylene.

5. The compound as defined in Claim 4 wherein

n is 0, m is 0 and Z is a bond, $-CH_2-$, $-CH_3-CH=CH-$, $-CH_2CH_2-$ or  ;

and

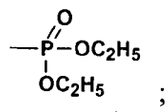
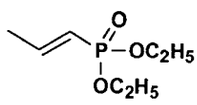
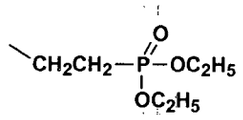
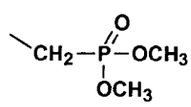
R_5 and R_6 are each H;

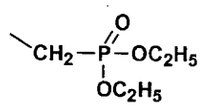
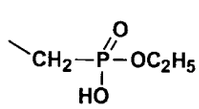
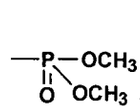
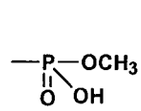
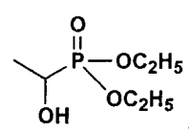
R_7 is H or alkyl; and

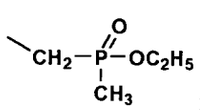
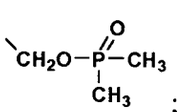
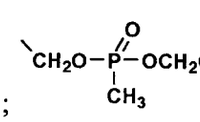
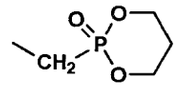
R_8 is H or alkyl.

6. The compound as defined in Claim 5 wherein

R_4 is

 ;  ;  ;  ;

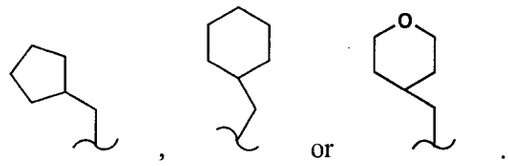
 ;  ;  ;  ;  ;

 ;  ;  or  .

7. The compound as defined in Claim 1 wherein X is  .

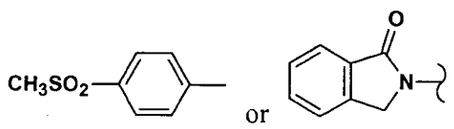
8. The compound as defined in Claim 7 wherein R_2 is cycloalkyl or cycloalkyl with an embedded oxygen, and n is 1.

9. The compound as defined in Claim 7 wherein X is



10. The compound as defined in Claim 1 wherein Y is aryl or heteroaryl or is absent.

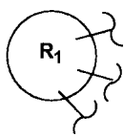
11. The compound as defined in Claim 10 wherein Y is CH_3SO_2-,



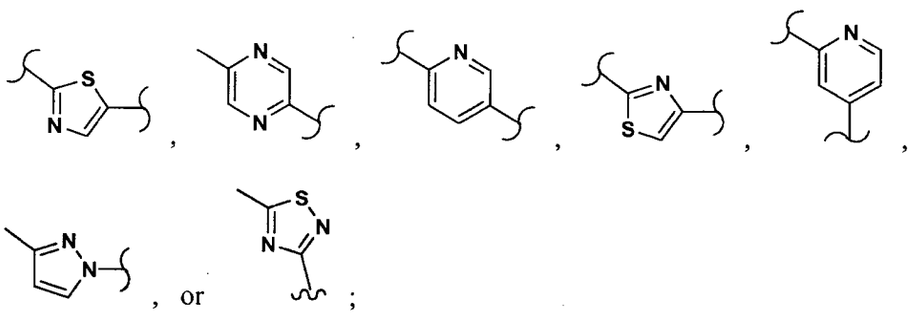
or .

12. The compound as defined in Claim 1 wherein R_5 and R_6 are each H.

13. The compound as defined in Claim 1 wherein



is



, or ;

R_4 is $(CH_2)_n$-Z-$(CH_2)_m$-$PO(OR_7)(OR_8)$, where n is 0, m is 0, Z is alkylene or alkenylene;

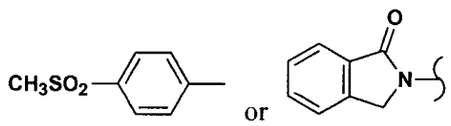
R_5 and R_6 are each H;

R_7 and R_8 are the same or different and are independently selected from H and alkyl;

X is a bond or 

where R_2 is cyclopentyl or cyclohexyl, and p is 0;

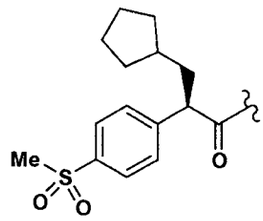
Y is



or .

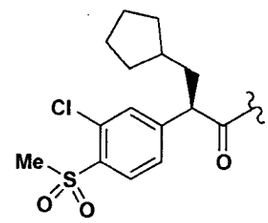
14. The compound as defined in Claim 1 include:

Y-X-CO- is



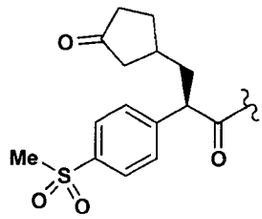
(a)

,



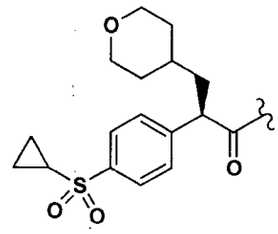
(b)

,



(c)

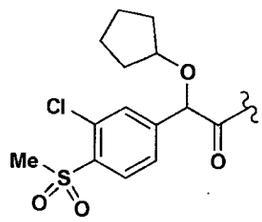
, or



(d)

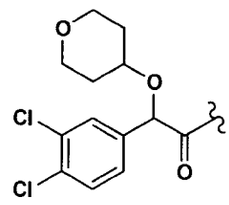
; or

Y-X-CO- is



(e)

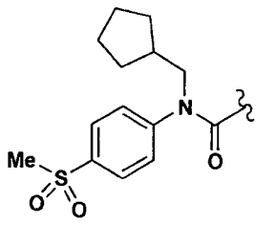
or



(f)

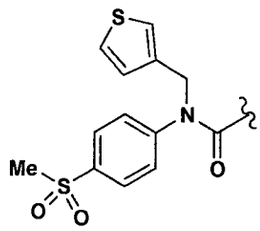
; or

Y-X-CO- is



(g)

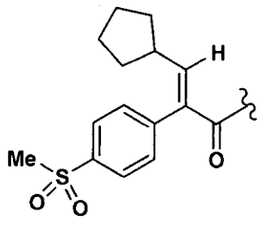
or



(h)

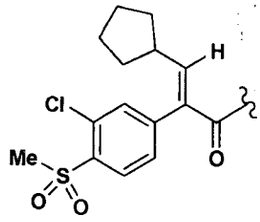
; or

Y-X-CO- is



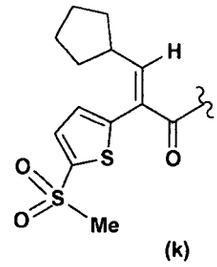
(i)

,



(j)

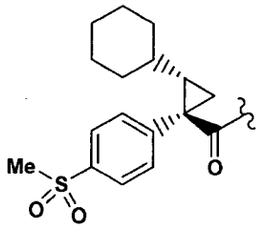
, or



(k)

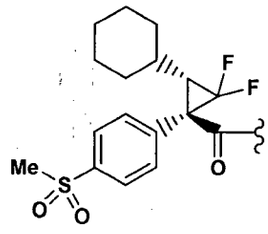
; or

Y-X-CO- is



(l)

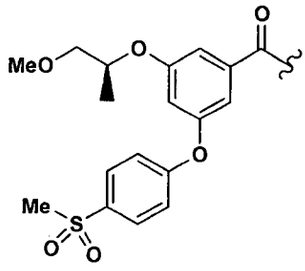
or



(m)

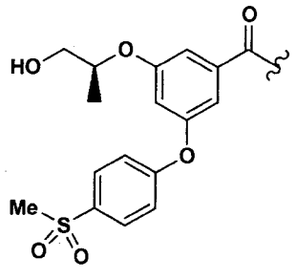
; or

Y-X-CO- is



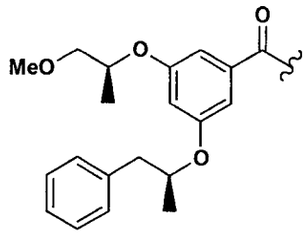
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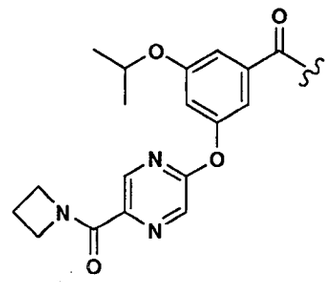


(o)

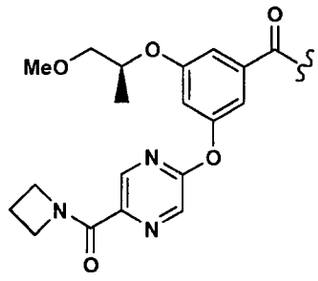
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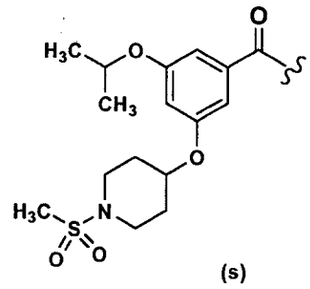
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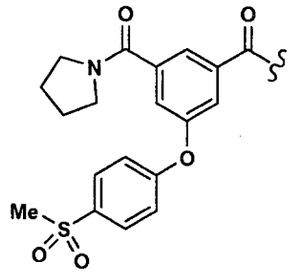
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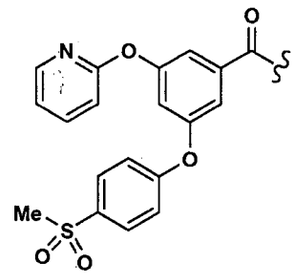
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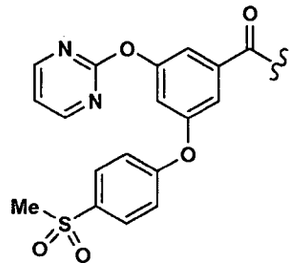
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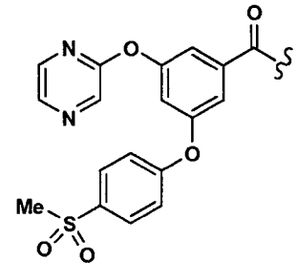
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(u) ,

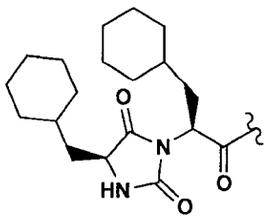


(v) ,



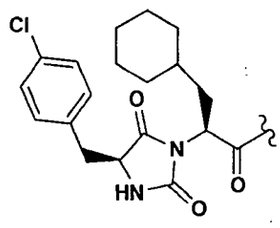
(w) ; or

Y-X-CO- is



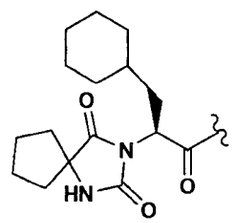
(x)

,



(y)

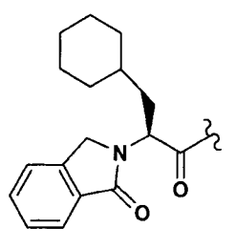
, or



(z)

; or

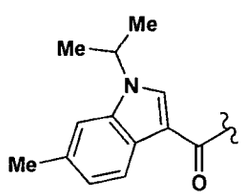
Y-X-CO- is



(aa)

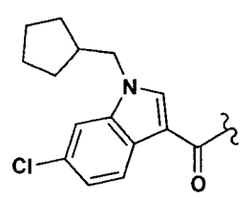
; or

Y-X-CO- is



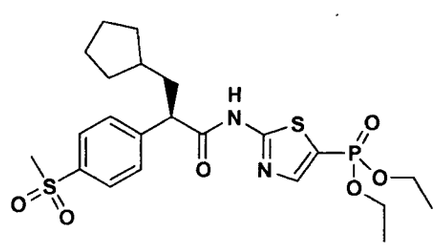
(ab)

or

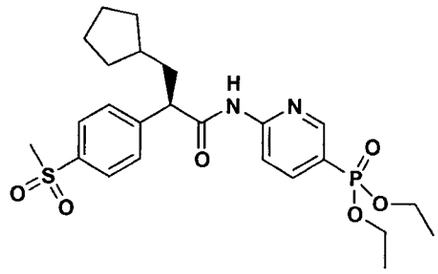


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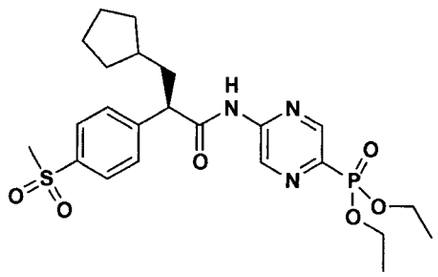
15. The compound as defined in Claim 13 wherein the compound is



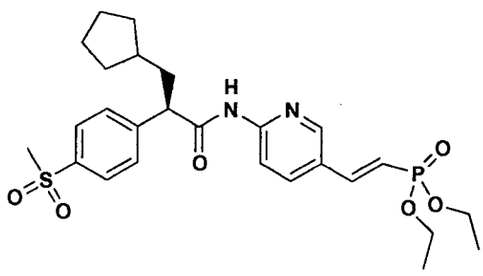
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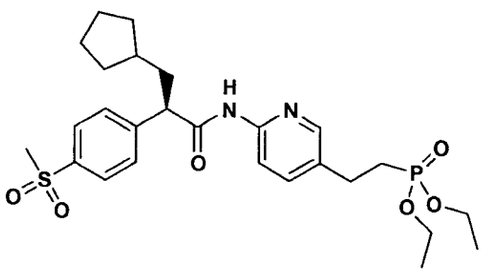
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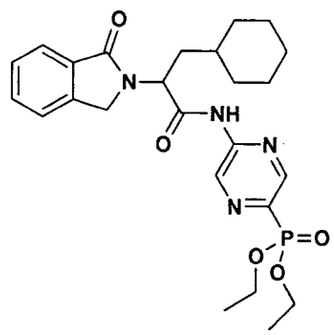
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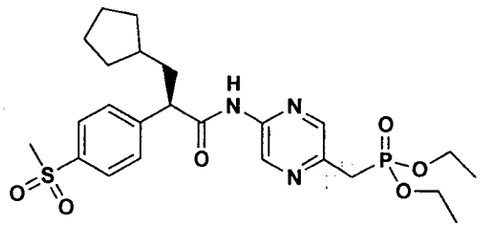
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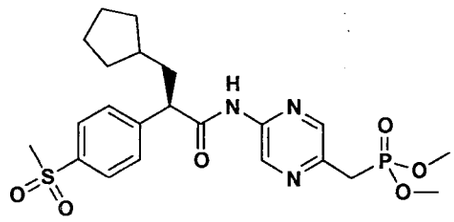
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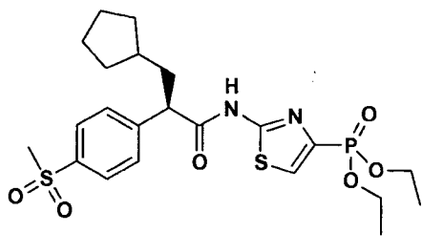
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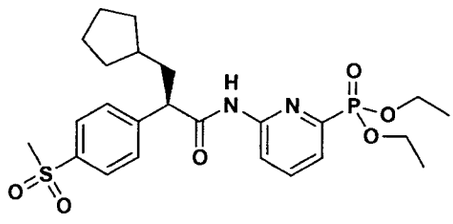
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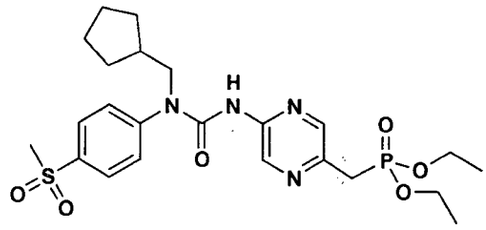
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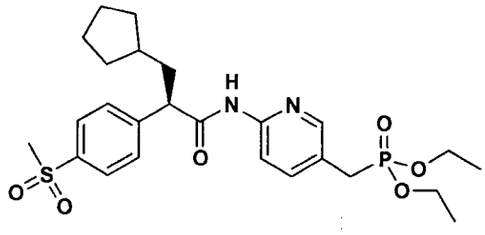
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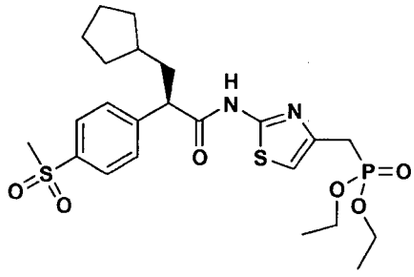
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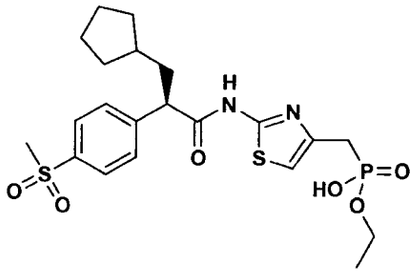
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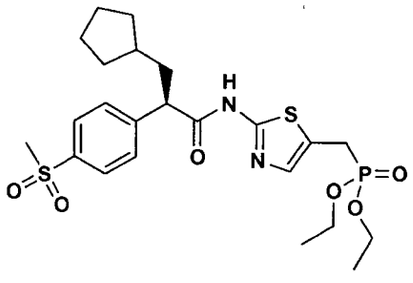
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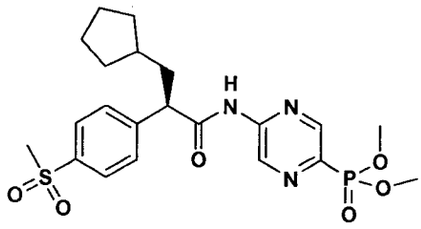
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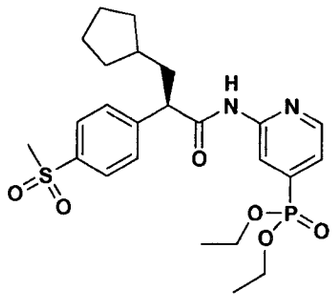
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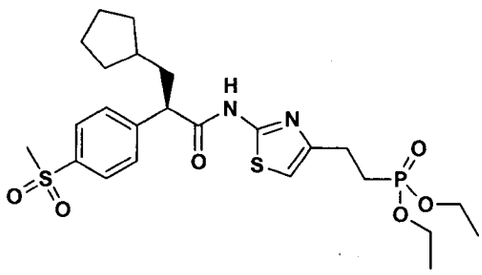
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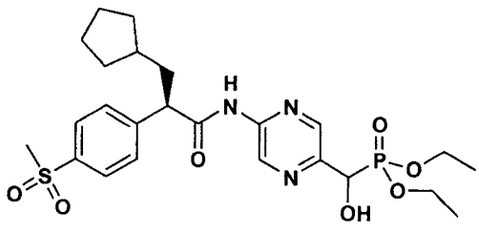
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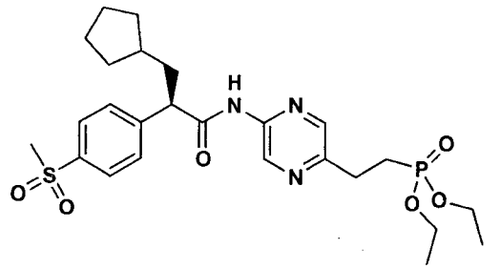
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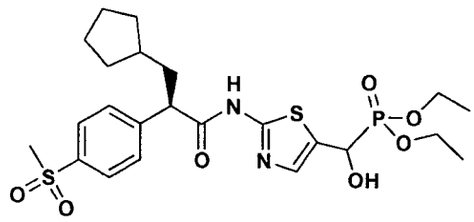
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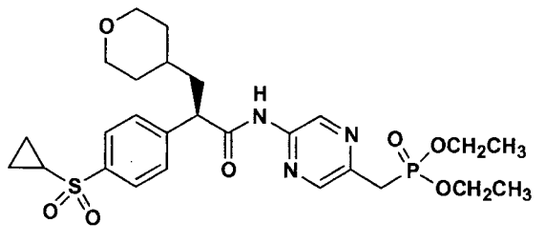
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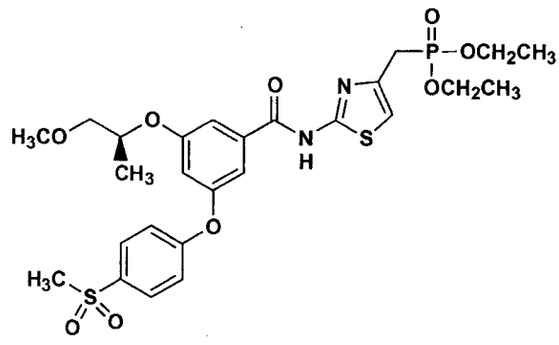
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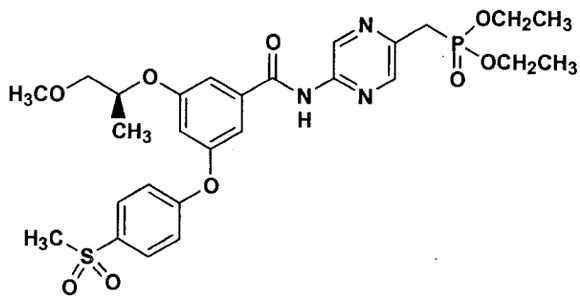
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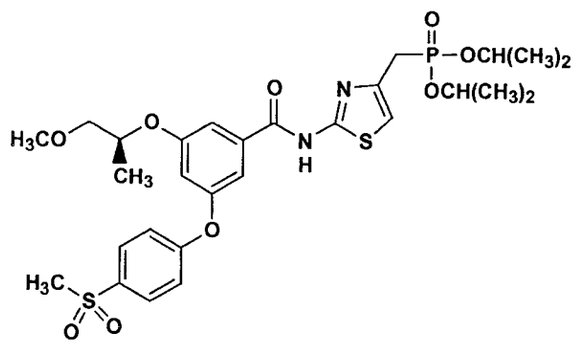


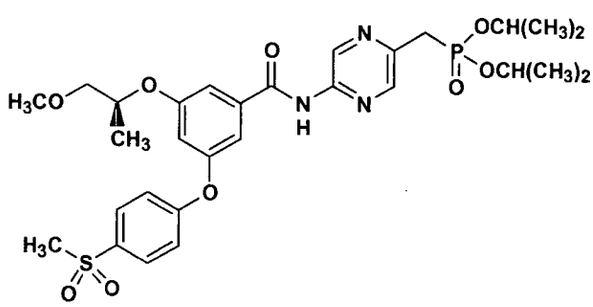
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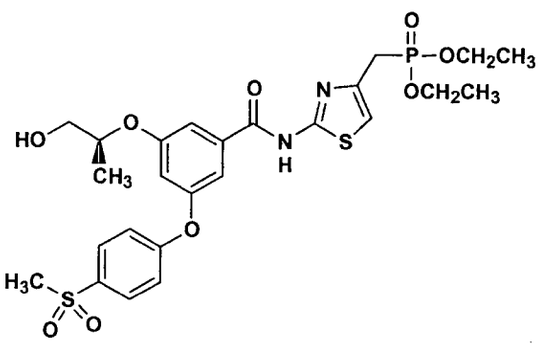


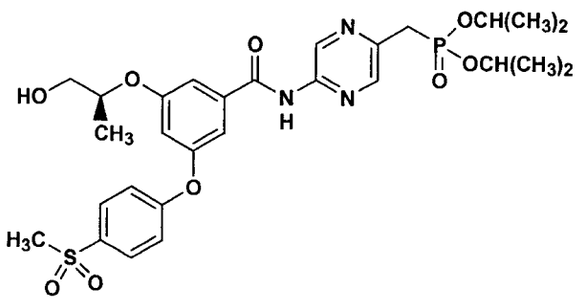
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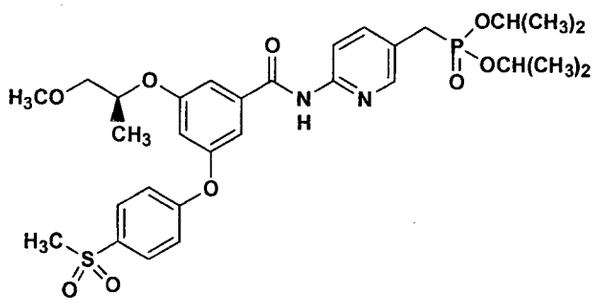


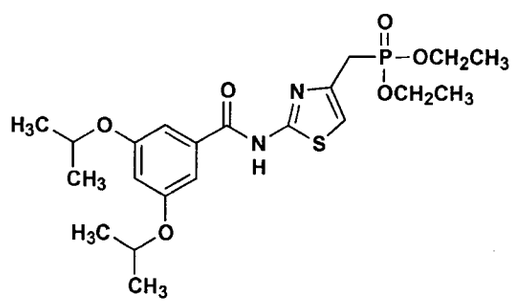


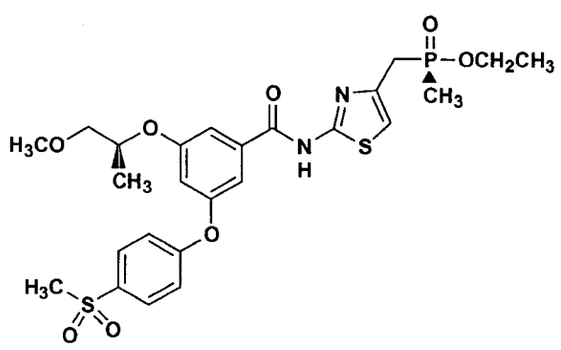


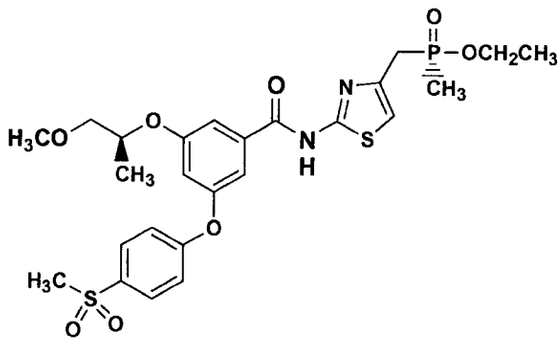




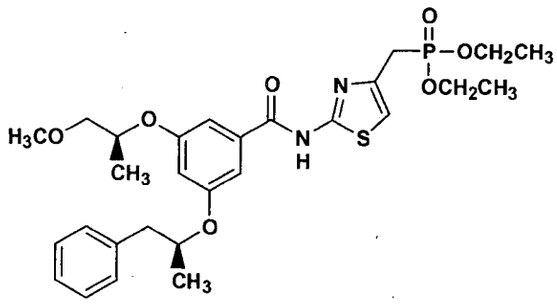




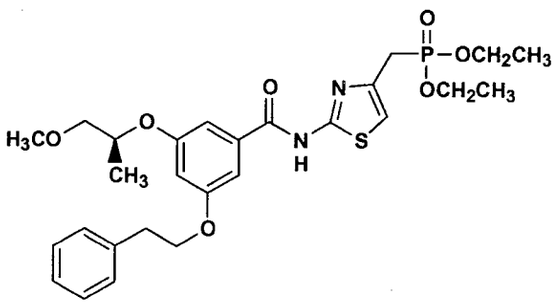




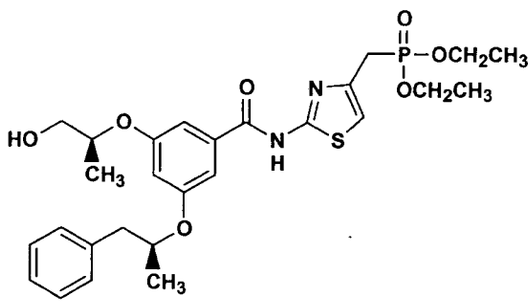
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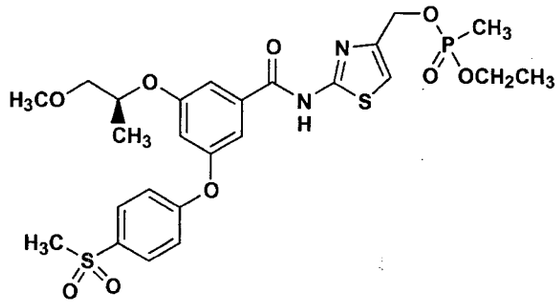
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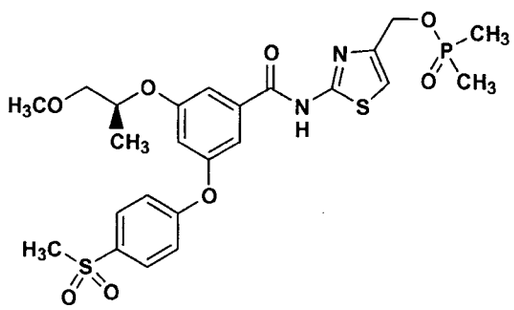
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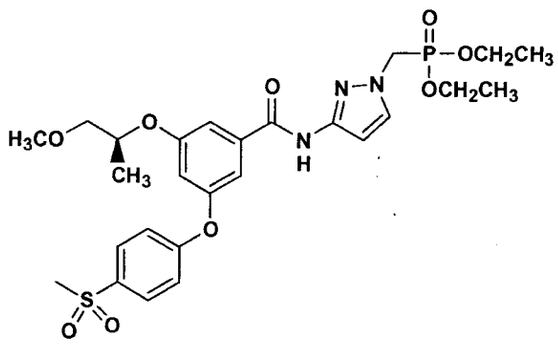
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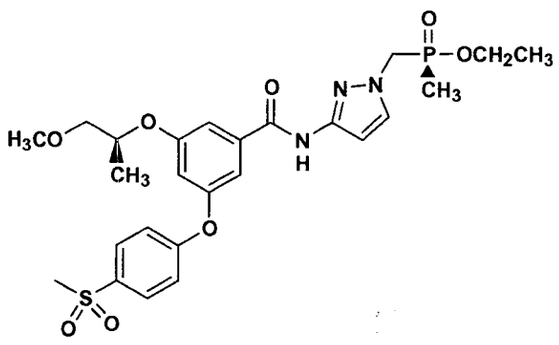
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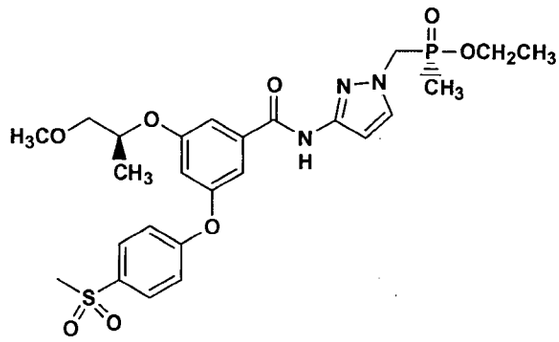
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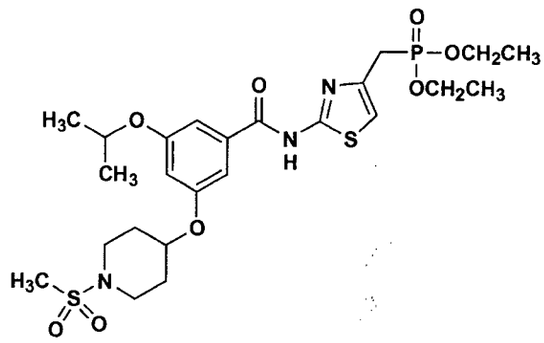
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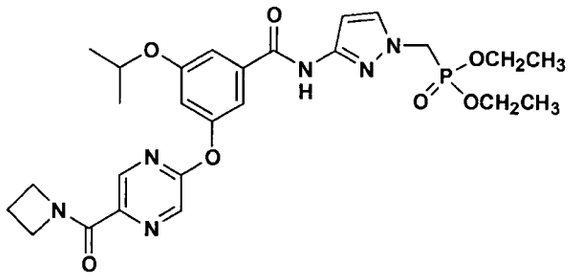
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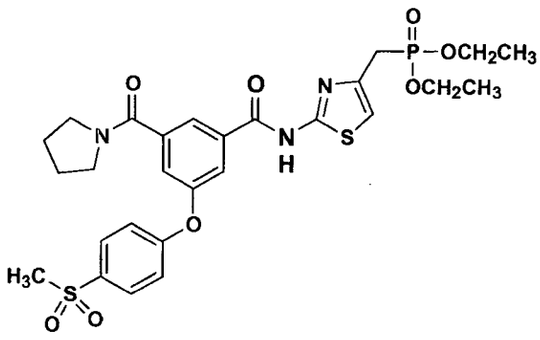
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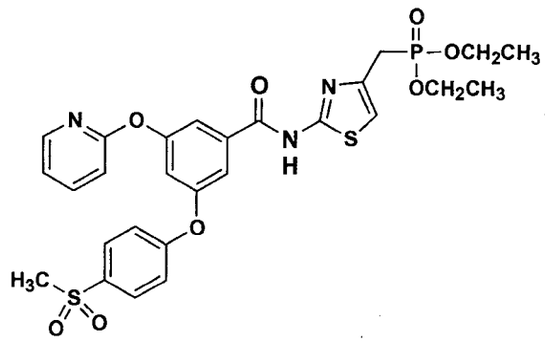
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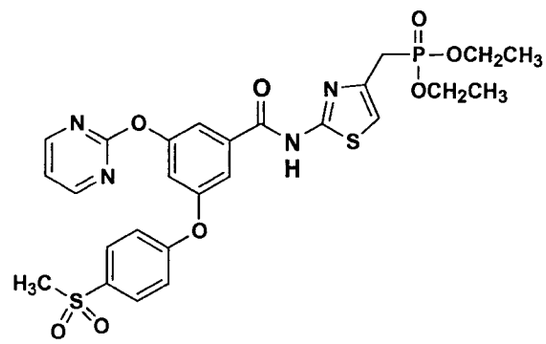
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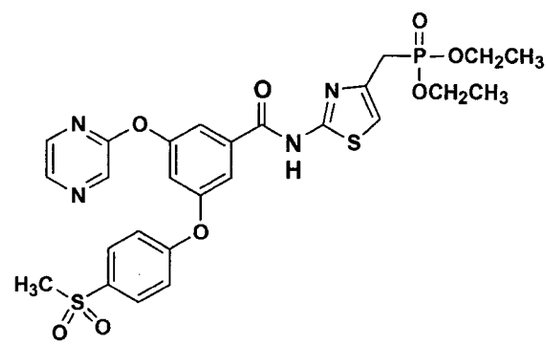
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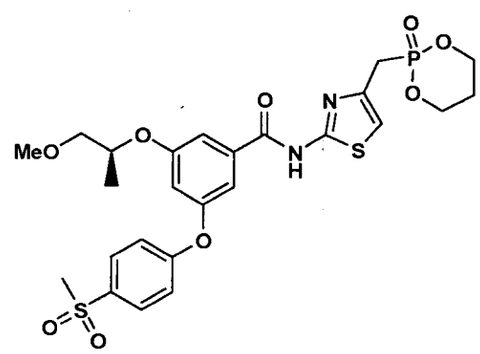
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, or



16. A pharmaceutical composition comprising a compound as defined in Claim 1 and a pharmaceutically acceptable carrier thereof.

17. A pharmaceutical composition comprising a compound as defined in Claim 1 and another therapeutic agent which is an anti-diabetic agent, anti-hyperglycemic agent, anti-hyperinsulinemic agent, anti-retinopathic agent, anti-neuropathic agent, anti-nephropathic agent, anti-atherosclerotic agent, anti-infective agent, anti-ischemic agent, anti-hypertensive agent, anti-obesity agent, anti-dyslipidemic agent, anti-hyperlipidemic agent, anti-hypertriglyceridemic agent, anti-hypercholesterolemic agent, anti-ischemic agent, anti-cancer agent, anti-cytotoxic agent, anti-restenotic agent, anti-pancreatic agent, lipid lowering agent, appetite suppressant, memory enhancing agent, or cognitive agent.

18. A method for treating, preventing, or slowing the progression of a disease requiring glucokinase activator therapy, which comprises administering to a mammalian patient in need of treatment a therapeutically effective amount of a compound of formula I as defined in Claim 1.

19. The method as defined in Claim 18 wherein the disease is diabetes, hyperglycemia, impaired glucose tolerance, insulin resistance, hyperinsulinemia, retinopathy, neuropathy, nephropathy, delayed wound healing, atherosclerosis and its sequelae, abnormal heart function, myocardial ischemia, stroke, Metabolic Syndrome, hypertension, obesity, dyslipidemia, hyperlipidemia, hypertriglyceridemia, hypercholesterolemia, low HDL, high LDL, non-cardiac ischemia, infection, cancer, vascular restenosis, pancreatitis, neurodegenerative disease, lipid disorders, cognitive impairment and dementia, bone disease, HIV protease associated lipodystrophy, and glaucoma.

20. A method of activating the enzyme glucokinase, which comprises administering to a mammalian patient in need of treatment a therapeutically effective amount of a compound of the formula I as defined in Claim 1.

21. A method of treating Type II diabetes, which comprises administering to a patient in need of treatment a compound as defined in Claim 1.

PATENT COOPERATION TREATY PCT/US2007/072708

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION CONCERNING
SUBMISSION OR TRANSMITTAL
OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

To:

RODNEY, Burton
Bristol-Myers Squibb Company
P.O. Box 4000
Princeton, New Jersey 08543-4000
ETATS-UNIS D'AMERIQUE

Date of mailing *(day/month/year)* 24 September 2007 (24.09.2007)	
Applicant's or agent's file reference 10815 PCT	**IMPORTANT NOTIFICATION**
International application No. PCT/US2007/072708	International filing date *(day/month/year)* 03 July 2007 (03.07.2007)
International publication date *(day/month/year)* **Not yet published**	Priority date *(day/month/year)* 06 July 2006 (06.07.2006)
Applicant BRISTOL-MYERS SQUIBB COMPANY et al	

1. By means of this Form, which replaces any previously issued notification concerning submission or transmittal of priority documents, the applicant is hereby notified of the date of receipt by the International Bureau of the priority document(s) relating to all earlier application(s) whose priority is claimed. Unless otherwise indicated by the letters "NR", in the right-hand column or by an asterisk appearing next to a date of receipt, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).

2. *(If applicable)* The **letters "NR"** appearing in the right-hand column denote **a priority document which, on the date of mailing of this Form, had not yet been received by the International Bureau** under Rule 17.1(a) or (b). Where, under Rule 17.1(a), the priority document must be submitted by the applicant to the receiving Office or the International Bureau, but the applicant fails to submit the priority document within the applicable time limit under that Rule, **the attention of the applicant is directed** to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

3. *(If applicable)***An asterisk (*)** appearing next to a date of receipt, in the right-hand column, denotes **a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b)** (the priority document was received after the time limit prescribed in Rule 17.1(a) or the request to prepare and transmit the priority document was submitted to the receiving Office after the applicable time limit under Rule 17.1(b)). Even though the priority document was not furnished in compliance with Rule 17.1(a) or (b), the International Bureau will nevertheless transmit a copy of the document to the designated Offices, for their consideration. In case such a copy is not accepted by the designated Office as the priority document, Rule 17.1(c) provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

Priority date	Priority application No.	Country or regional Office or PCT receiving Office	Date of receipt of priority document
06 July 2006 (06.07.2006)	60/818,912	US	08 September 2007 (08.09.2007)
28 June 2007 (28.06.2007)	11/769,964	US	08 September 2007 (08.09.2007)

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000366

ACTIVADORES NOVEDOSOS DE GLUCOCINASA Y METODOS DE USO DE LOS MISMOS

CAMPO DE LA INVENCION

La presente invención se refiere a compuestos novedosos de fosfonato y fosfinato que son activadores de la enzima glucocinasa y de esta manera son útiles en el tratamiento de diabetes, y a un método para tratar diabetes, especialmente diabetes Tipo II, usando tales compuestos.

ANTECEDENTES DE LA INVENCION

La enzima glucocinasa (GK), que se encuentra principalmente en células β pancreáticas y células parenquimales de hígado, catalizan la conversión de glucosa a glucosa-6-fosfato, que es la primera etapa en el metabolismo de glucosa. La glucocinasa es también una enzima que controla la rapidez para el metabolismo de glucosa en células β pancreáticas y células parenquimales de hígado que juegan un papel importante en la homeostasis de glucosa en todo el cuerpo.

Liag, Y. et al., (Biochem. J., 1995, 309:167-173) reportan que encuentran que la diabetes del joven Tipo II (inicio de la madurez) (MODY-2) es causada por la pérdida de mutaciones de la función en el gen de glucocinasa el cual sugiere que la glucocinasa también funciona como un sensor de glucosa en humanos. Así, los compuestos que activan glucocinasa y así aumentan la sensibilidad del sistema de

sensor de glucocinasa y de tal modo provocan un incremento en la secreción de insulina serán útiles en el tratamiento de hiperglicemia y diabetes de Tipo II.

Los activadores de glucocinasa se ha demostrado que son efectivos en potenciar: 1) el efecto de glucosa en insulina que se libera de isletas pancreáticas de humano y rata aislada, y 2) la inducción de glucosa de glucocinasa de isleta pancreática en isletas de rata cultivadas aisladas (por ejemplo. Matschinsky, F.M. et al., Diabetes, 2006, 55:1, and ("Glucokinasa and Glycemic Disease, from Basics to Novel Therapeutics", publicada por Karger, 2004; F.M. Matschinsky and M.A. Magnuson, eds., capitulo 6, pp. 360-378). En estudios de modelo animal diabético, los activadores de glucocinasa se han demostrado para estimular la liberación de insulina, potenciar la síntesis de glicógeno y reducir la producción de glucosa hepática en estudios de pinzas pancreáticas. De forma importante, los activadores de glucocinasa se han demostrado para niveles de glucosa en la sangre inferior dependientemente de dosis en modelos de animal estándar diferente de diabetes tipo 2, tales como ratones ob/ob, ratones db/db y Zucker en estudios de dosis sencilla aguda y también mejoran efectivamente la excursión de glucosa en tanto ratones ob/ob como C57/BL6J normales en pruebas de tolerancia a la glucosa oral (por ejemplo, en

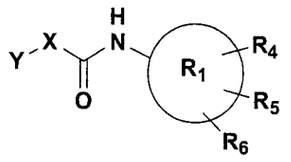
"Glucokinase and Glycemic Disease, from Basics to Novel Therapeutics", publicada por Karger, 2004; F. M. Matschinsky and M.A. Magnuson, eds., capitulo 6, pp. 360-378 así como Fyfe, M.C. et al., Diabetologia, 2007, 50:1277).

Los activadores de glucocinasa también han demostrado eficacia antidiabética en modelos de animal crónico de diabetes tipo II. Por ejemplo, en un estudio el día 9 en ratones ob/ob, un activador de glucocinasa mejora el perfil de glucosa general mostrando efectos antihiperglicémicos comparables en pruebas de tolerancia a la glucosa oral al inicio y termino del estudio (Fyfe, M.C. et al., Diabetologia, 2007, 50:1277). En otro caso, en un estudio crónico de 40 semanas, un activador de glucocinasa previene el desarrollo de hiperglicemia en ratonres obesos inducidos por dieta los cuales fueron intolerantes a la glucosa. Los ratones inducidos por dieta tratados con un activados de glucocinasa muestra mejora marcada en la excursión de glucosa en una prueba de tolerancia a la glucosa oral al termino del estudio con relación al grupo de control ("Glucokinase and Glycemic Disease, from Basics to Novel Therapeutics", publicado por Karger, 2004; F.M. Matschisky and M.A. Magnuson, eds. Capitulo 6, pp. 360-378).

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SUMARIO DE LA INVENCION

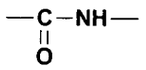
De conformidad con un aspecto de la invención, los compuestos son proporcionados que tienen la estructura I



I

en donde

R_1 es un heteroarilo sustituido por R_4 y opcionalmente sustituido con uno o dos substituyentes R_5 y/o R_6, en donde el heteroarilo posee un átomo de nitrógeno adyacente para el

átomo que une el grupo heteroarilo para  ;

R_4 es $-(CH_2)_n-Z-(CH_2)_m-PO(OR_7)(OR_8)$,

o $-(CH_2)_nZ-(CH_2)_m-PO(OR_7)R_9$,

o $-(CH_2)_n-Z-(CH_2)_m-O-PO(OR_7)R_9$,

o $-(CH_2)_nZ-(CH_2)_m-O-PO-(R_9)R_{10}$,

o $-(CH_2)_nZ-(CH_2)_m-PO(R_9)R_{10}$;

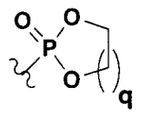
R_7 y R_8 son los mismos o diferentes y son independientemente seleccionados de hidrógeno y alquilo;

R_9 y R_{10} son los mismos o diferentes y son independientemente seleccionados de alquilo, arilo, arilalquilo, heteroarilo y heteroarilalquilo, cualquiera de los cuales pueden ser opcionalmente sustituidos;

adicionalmente, R_7 y R_8 pueden ser ciclizados en un

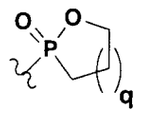
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anillo

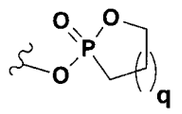


donde q = 1-3

similarmente, R_7 y R_9 pueden ser ciclizados en un anillo

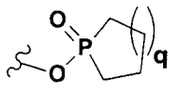


donde q = 1-3, o

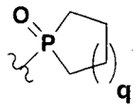


donde q = 1-3;

similarmente, R_9 y R_{10} pueden ser ciclizados en un anillo



donde q = 1-3,



donde q = 1-3,

o

Z es seleccionado de un enlace, alquileno y alquenileno, cada uno de los cuales puede ser opcionalmente sustituido (por ejemplo hdroxi, alcoxi, aminoalquilo, aminoaralquilo, aminoheteroaralquilo, aminoarilo, aminoheteroarilo o carboxi);

m es 0, 1 ó 2;

n es 0, 1 ó 2;

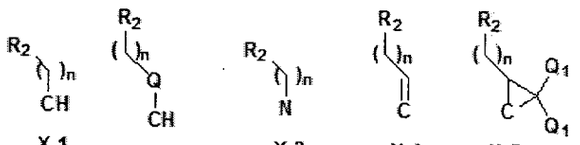
y Z puede ser O, S, SO_2 cuando

m es 1 ó 2,

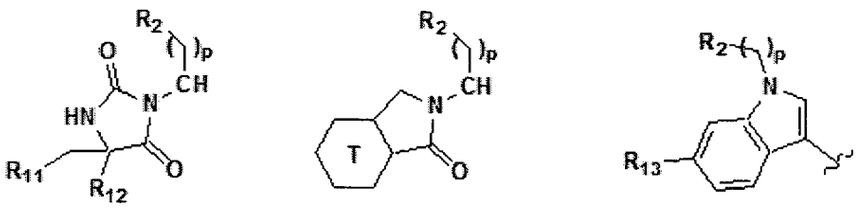
n es 0, 1, ó 2;

R_5 y R_6 son los mismos o diferentes y son independientemente seleccionados de hidrógeno, alquilo, halógeno o carboxilo, o está ausente;

X se selecciona de



y cuando Y está ausente, X se selecciona de



R_2 es seleccionado de hidrógeno, alquilo, cicloalquilo, heterociclilo, arilo, heteroarilo, alquinilo, y alquenilo (todos de los cuales pueden ser opcionalmente sustituidos);

p es 0 ó 1;

Q es seleccionado de O, $S(O)_q$ y CO, donde q es 0, 1 ó 2;

Q_1 se selecciona desde hidrógeno y flúor;

R_{11} se selecciona de hidrógeno, alquilo inferior, cicloalquilo, arilo y heteroarilo;

R_{12} se selecciona de hidrógeno, y alquilo inferior, o R_{11} y R_{12} junto con el átomo de carbono al cual se enlazan forman un anillo cicloalquilo de 5 hasta 7 átomos de carbono;

R_{13} se selecciona de halo, nitro, amino, ciano, metilo, trifluorometilo, hidroxi, metoxi, trifluorometoxi, metiltio, metilsulfinilo y metilsulfonilo;

T se selecciona de arilo y heteroarilo, cada uno de los cuales pueden ser opcionalmente sustituidos;

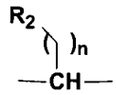
Y es $R_3-(CH_2)_s-$, o está ausente;

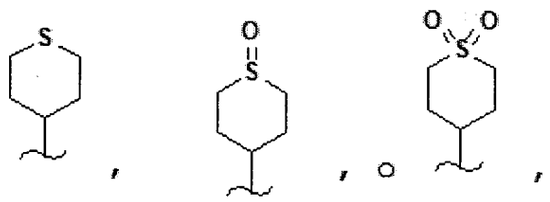
donde R_3 es arilo o heteroarilo, cada uno de los cuales pueden ser opcionalmente sustituidos;

s es 0 ó 1;

todos los estereoisómeros del mismo, un éster profarmaco del mismo o una sal farmacéuticamente aceptable del mismo.

Preferiblemente en compuestos de la fórmula I

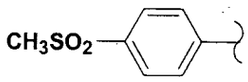
X es  donde más preferiblemente n es 1, y R_2 es un cicloalquilo, preferiblemente ciclopentilo o ciclohexilo, o R_2 es un grupo heterociclilo tal como un cicloalquilo con un heteroátomo entregado tal como un átomo de oxígeno o un átomo de sulfuro, por ejemplo tetrahidropirano, tetrahidrofurano,



preferiblemente tetrahidropirano;

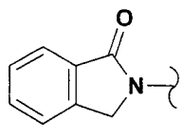
Y es arilo o heteroarilo o está ausente, todavia más preferiblemente arilo, más preferiblemente fenilo, todavia más preferiblemente

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;

o X es un enlace e Y es



;

R_4 es $(CH_2)_n$-Z-$(CH_2)_m$-$PO(OR_7)(OR_8)$ en donde Z es alquileno o alquenileno, en donde n es 0, m es 0 y Z es un enlace,



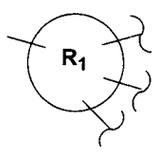
$-CH_2-$, $-CH_3-CH=CH-$, $-CH_2CH_2-$ o ; y

R_5 y R_6 son cada uno H;

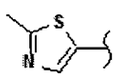
R_7 es H o alquilo; y

R_8 es H o alquilo.

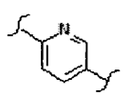
La Porción



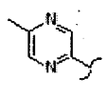
es preferiblemente



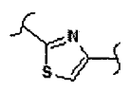
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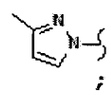
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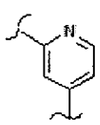
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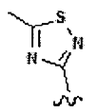
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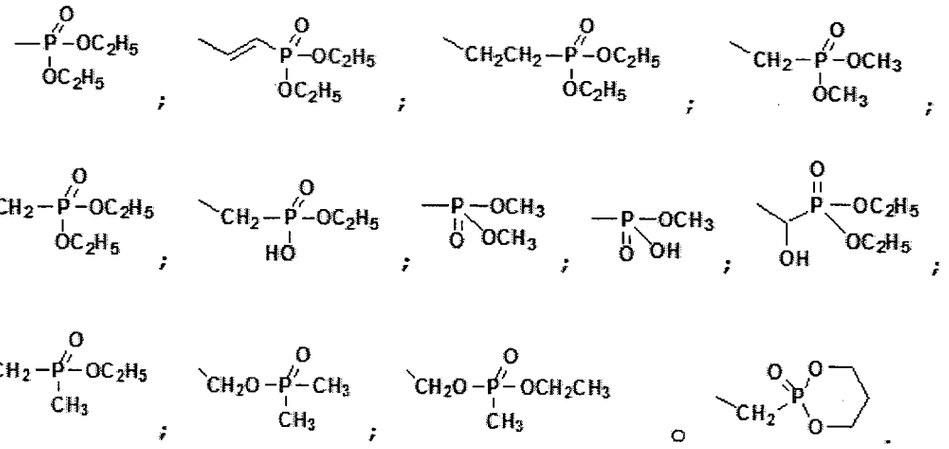
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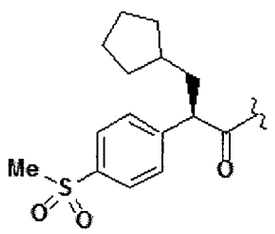
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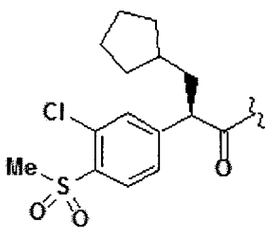
R_4 es más preferiblemente



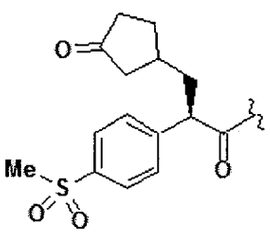
Las modalidades preferidas de Y-X-CO- en donde X es X-1 incluyen, pero no se limitan a:



(a)

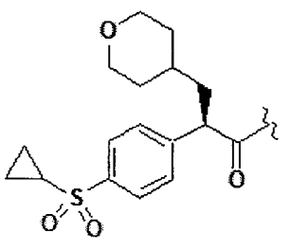


(b)



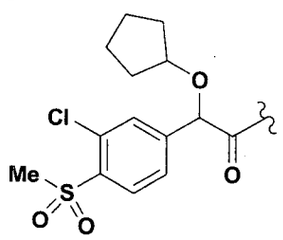
(c)

y



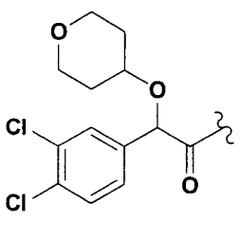
(d)

Las modalidades preferidas de Y-X-CO- en donde X = X-2 incluyen, pero no se limitan a:



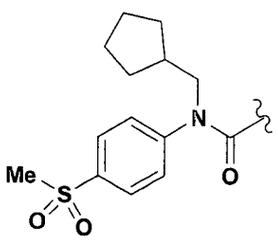
(e)

y



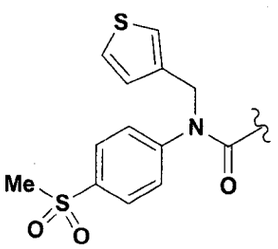
(f)

Las modalidades preferidas de Y-X-CO- en donde X = X-3 incluyen, pero no se limitan a:



(g)

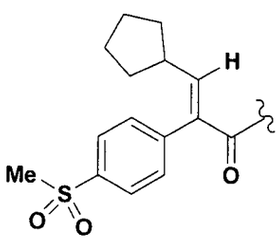
y



(h)

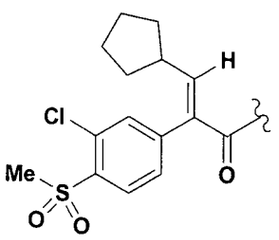
.

Las modalidades preferidas de Y-X-CO- en donde X = X-4 incluyen, pero no se limitan a:



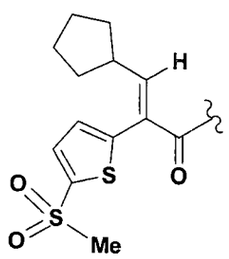
(i)

,



(j)

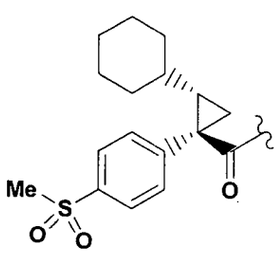
y



(k)

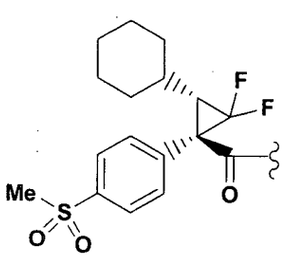
.

Las modalidades preferidas de Y-X-CO- en donde X = X-5 incluyen, pero no se limitan a:



(l)

y

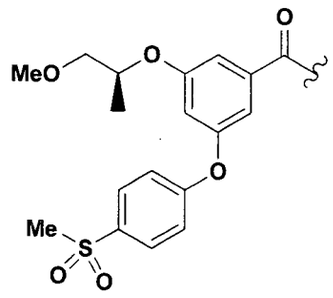


(m)

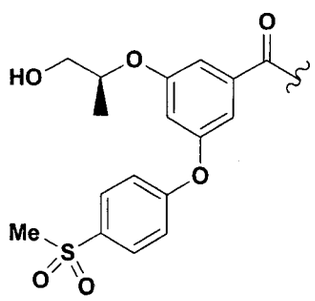
.

Las modalidades preferidas de Y-X-CO- en donde X =

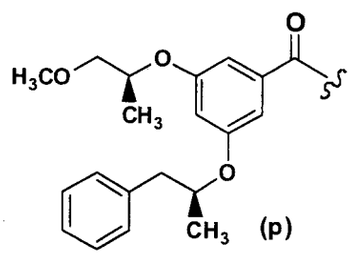
X-6 (en donde X es un enlace) incluyen, pero no se limitan a:



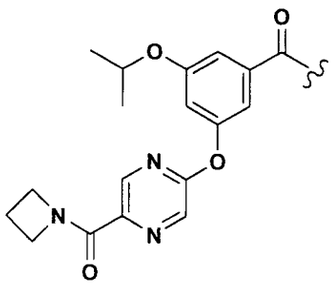
(n)



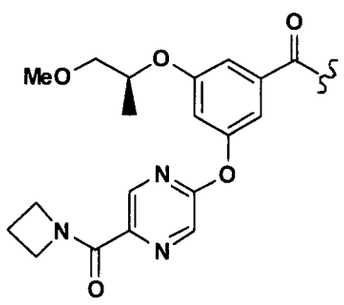
(o)



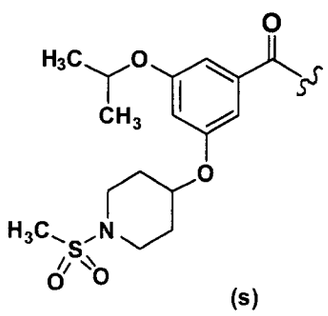
(p)



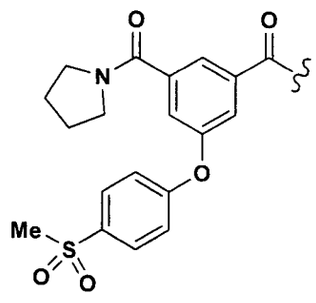
(q)



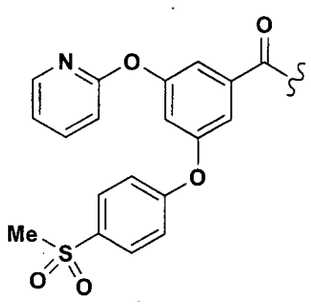
(r)



(s)

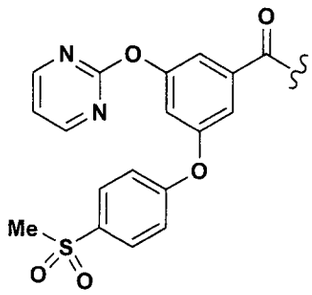


(t)

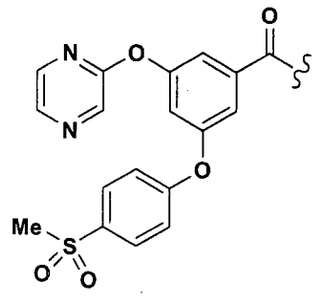


(u)

377



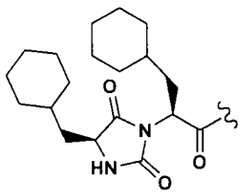
(v)



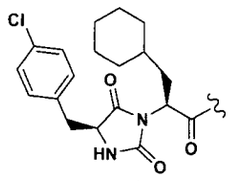
(w)

, y .

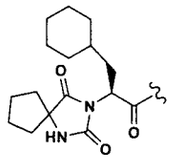
Las modalidades preferidas de Y-X-CO- en donde X = X-7 incluyen, pero no se limitan a:



(x)



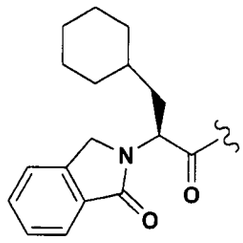
(y)



(z)

, , y .

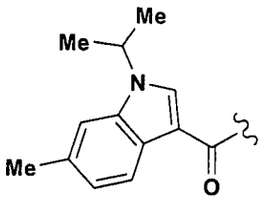
Las modalidades preferidas de Y-X-CO- en donde X = X-8 incluyen, pero no se limitan a:



(aa)

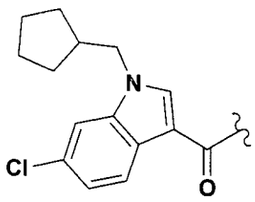
Las modalidades preferidas de Y-X-CO- en donde X = X-9 incluyen, pero no se limitan a:

050378



(ab)

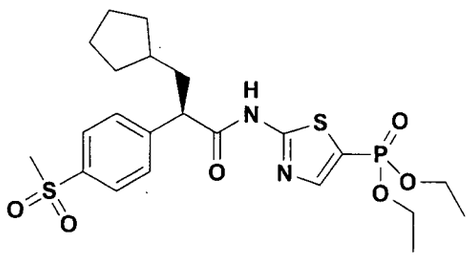
y

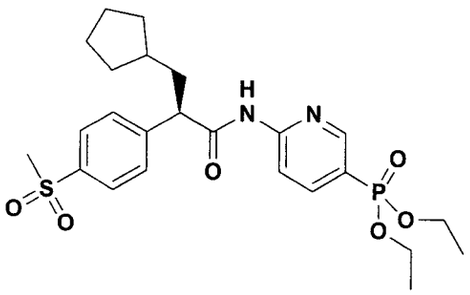


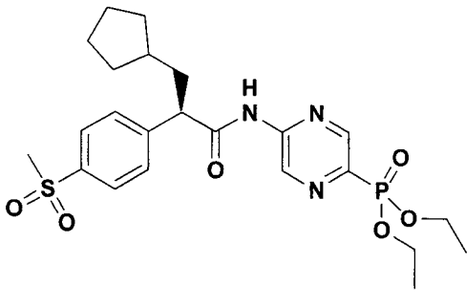
(ac)

.

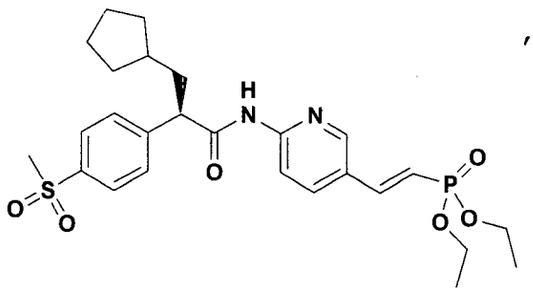
Los ejemplos de los compuestos preferidos de conformidad con la presente invención incluyen, pero no se limitan a, lo siguiente:





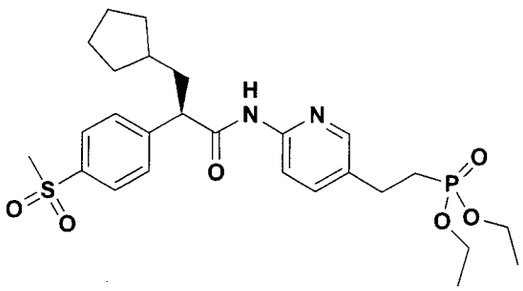


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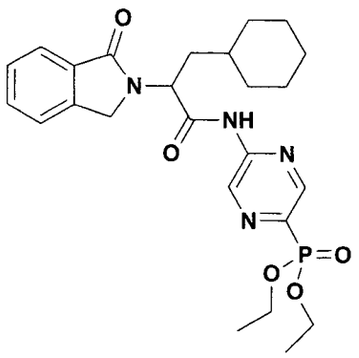


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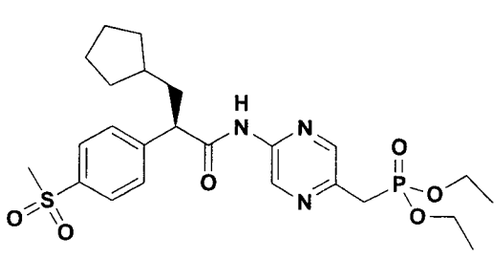
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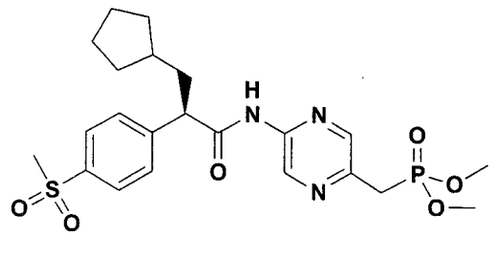
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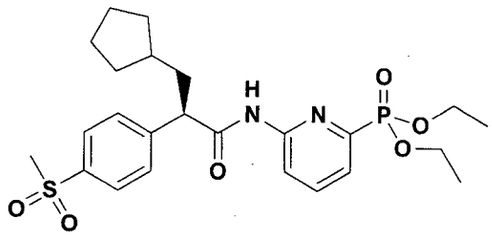
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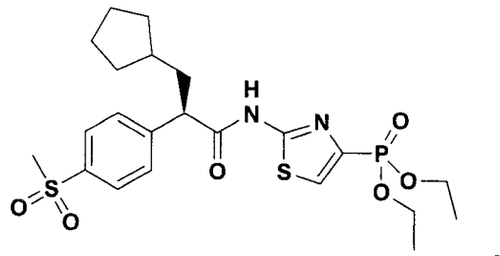
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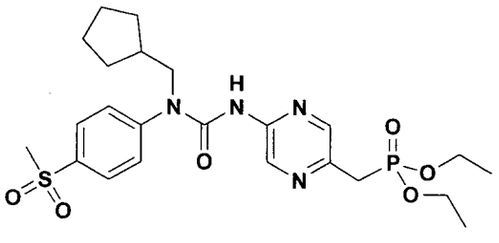
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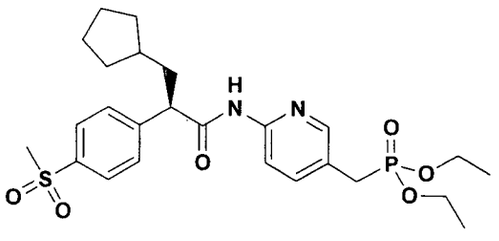
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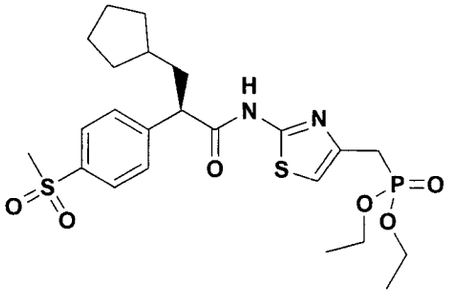
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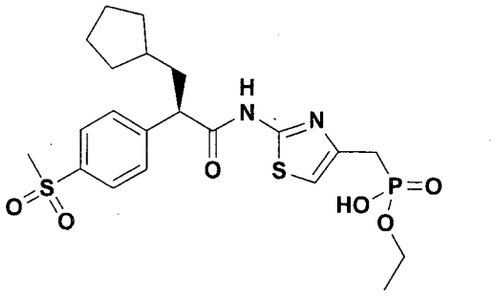
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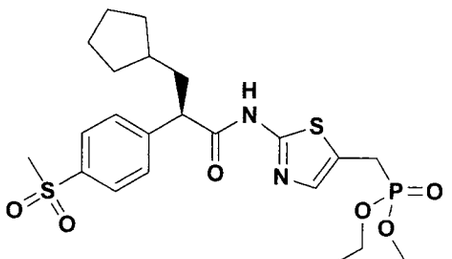
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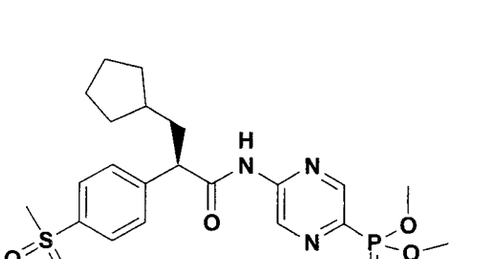
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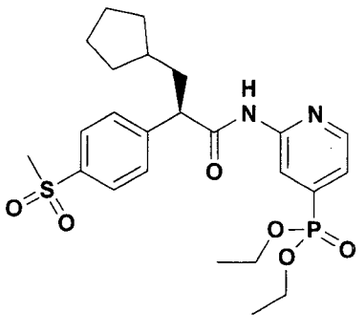


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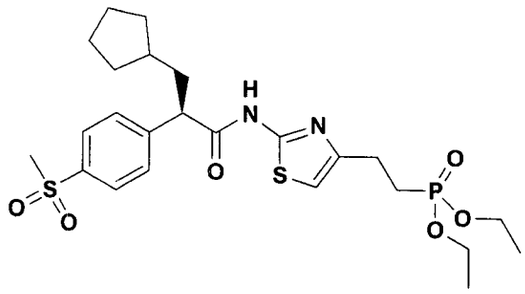
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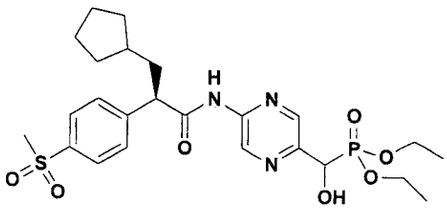
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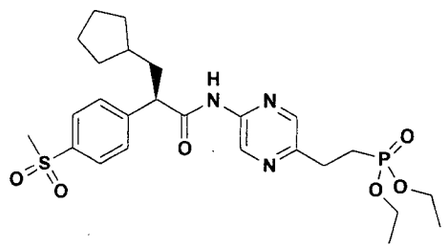
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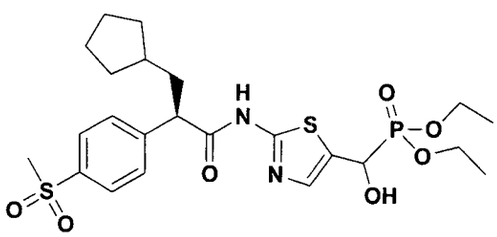
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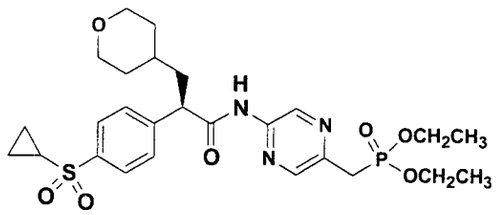
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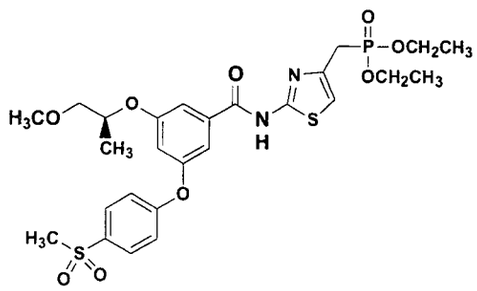
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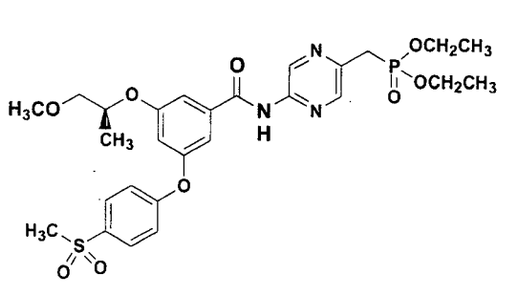
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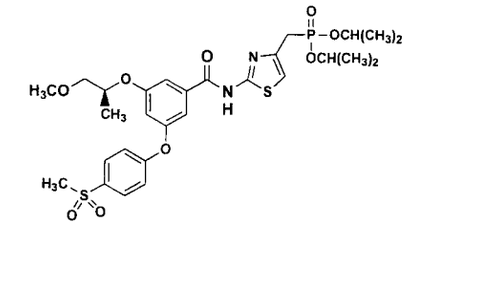
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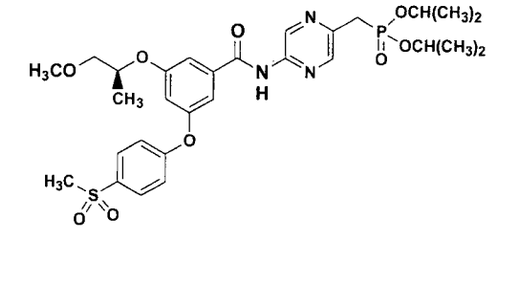
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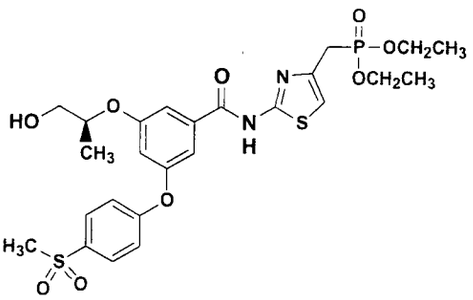


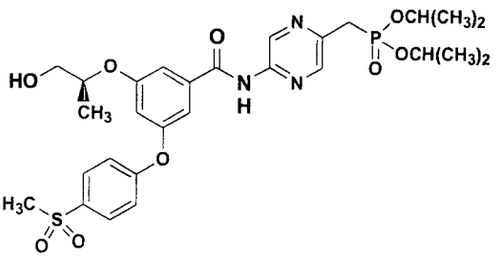
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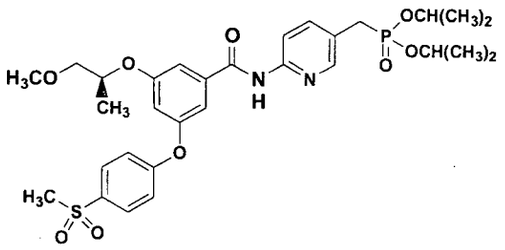
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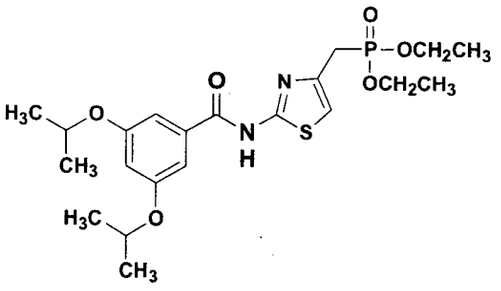


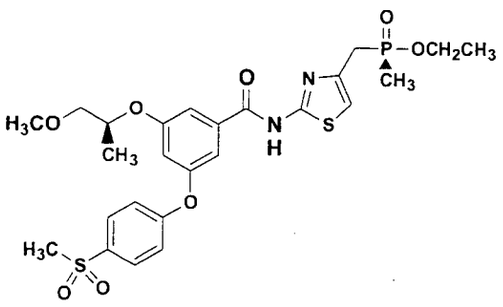
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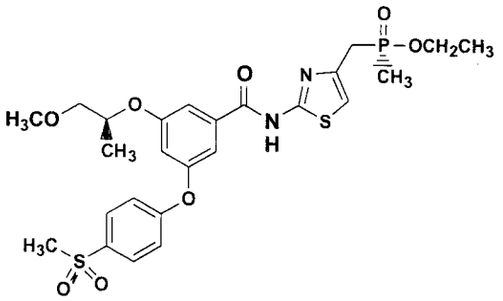


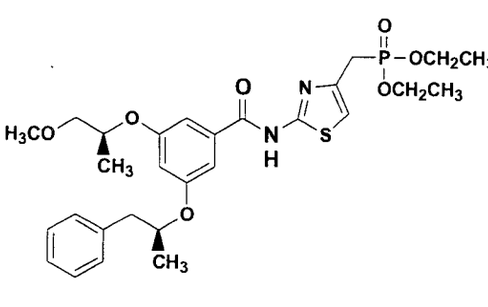


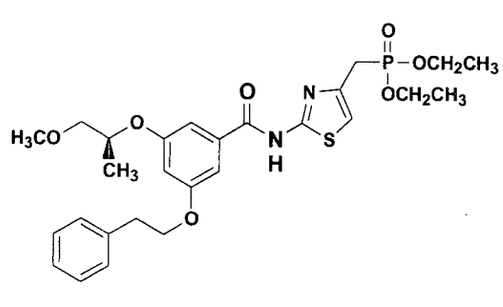


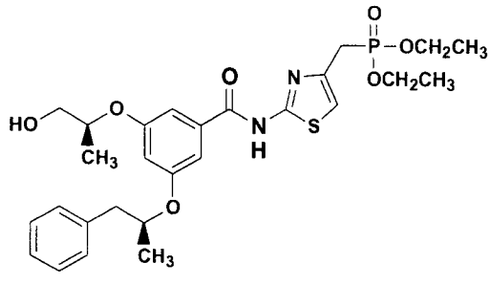


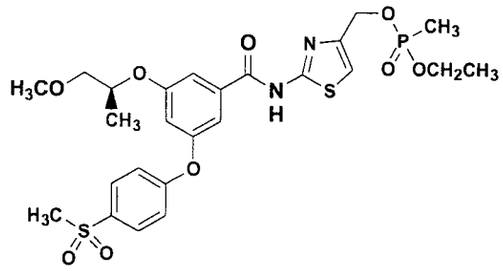


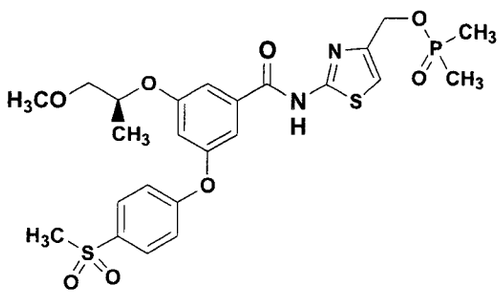


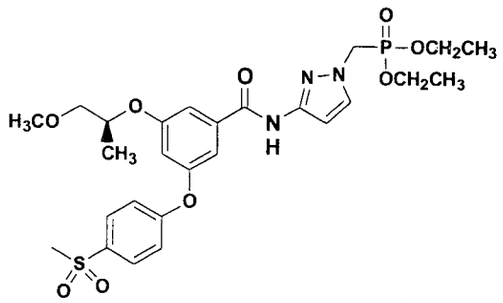


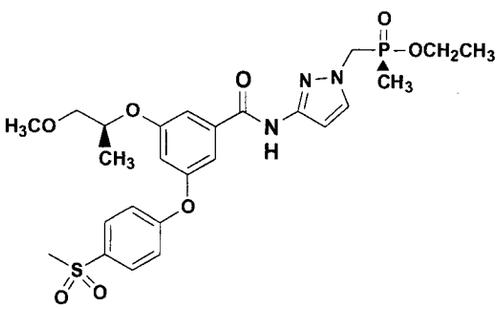


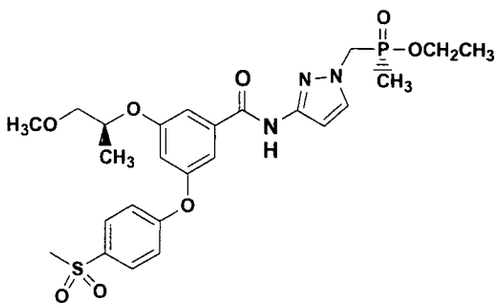


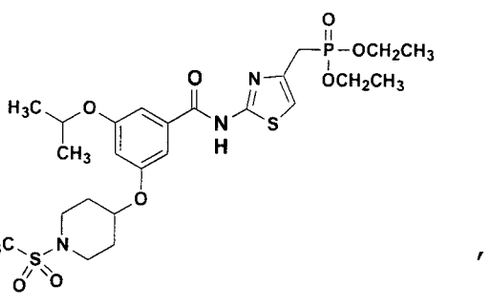


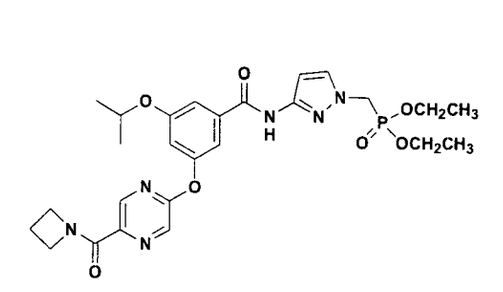


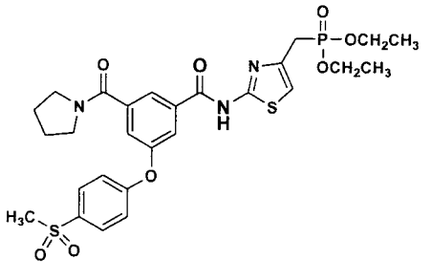


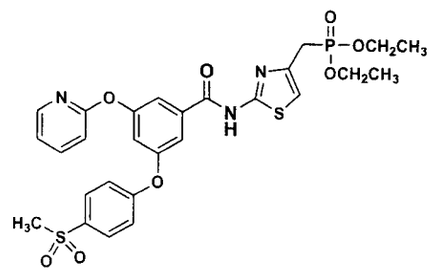


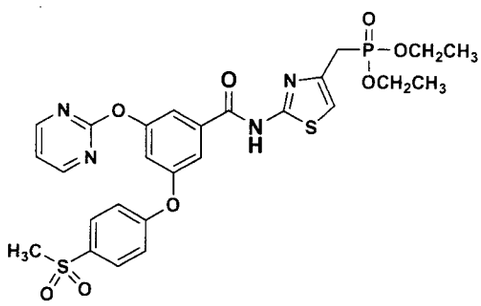


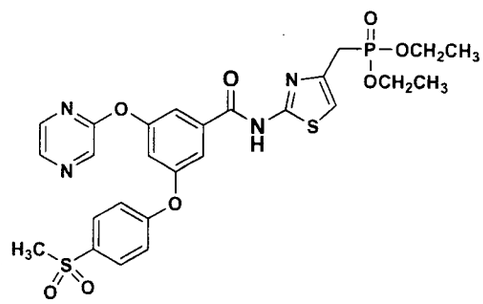


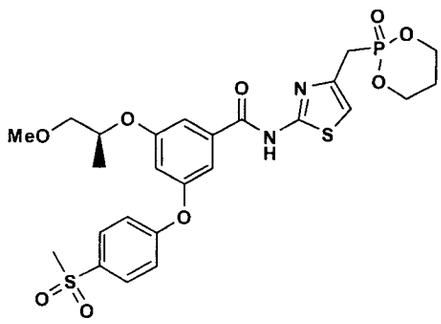












Los compuestos de la presente invención activan o aumentan la actividad de la enzima glucocinasa. Consecuentemente, los compuestos de la presente invención se pueden usar en el tratamiento de múltiples enfermedades o trastornos asociados con un déficit de glucocinasa, tal como diabetes y condiciones relacionadas, complicaciones microvasculares asociadas con diabetes, las complicaciones

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macrovasculares asociadas con diabetes, enfermedades cardiovasculares, Síndrome Metabólico y sus condiciones del componente, y otros males. Ejemplos de enfermedades o trastornos asociados con déficit en la actividad de la enzima glucocinasa que se puede prevenir, inhibir, o tratar de conformidad con la presente invención incluyen, pero no se limitan a, diabetes, hiperglicemia, deterioro de la tolerancia a la glucosa, resistencia a la insulina, hiperinsulinemia, retinopatía, neuropatía, nefropatía, cicatrización retrasada de herida, ateroesclerosis y sus secuelas, función cardiaca anormal, isquemia miocardial, apoplejía, Sindrome metabólico, hipertensión, obesidad, dislipidemia, hiperlipidemia, hipertrigliceridemia, hipercolesterolemia, HDL bajo, LDL alto, isquemia no cardiaca, infección, cáncer, restenosis vascular, pancreatitis, enfermedad neurodegenerativa, trastornos de lípido, insuficiencia cognitiva y demencia, enfermedad del hueso, lipodistrofia asociada con la proteasa de VIH, y glaucoma.

La presente invención proporciona compuestos de la fórmula I, composiciones farmacéuticas que emplean tales compuestos, y métodos que usan tales compuestos. En particular, la presente invención proporciona una composición farmacéutica que contiene una cantidad terapéuticamente efectiva de un compuesto de la fórmula I, solo o en

combinación con un portador farmacéuticamente aceptable.

Además, de conformidad con la presente invención, un método se proporciona para prevenir, inhibir, o tratar la progresión o el inicio de enfermedades o trastornos asociados con déficit en la actividad de la enzima glucocinasa, tal como se define arriba y más abajo, en donde una cantidad terapéuticamente efectiva de un compuesto de la fórmula I se administra a un paciente mamífero, esto es, humano, que necesita del tratamiento.

Los compuestos de la invención se pueden usar solos, en combinación con otros compuestos de la presente invención, o en combinación con uno o más de otros agentes terapéuticos.

Además, la presente invención proporciona un método para prevenir, inhibir, o tratar las enfermedades como se definen anteriormente y más abajo, en donde una cantidad terapéuticamente efectiva de una combinación de un compuesto de la fórmula I y otro compuesto de la fórmula I y/o al menos uno de otro tipo de agente terapéutico, se administra a un mamífero, esto es, un paciente humano, que necesita del tratamiento.

En otra modalidad, los compuestos de la presente invención se seleccionan de los compuestos ejemplificados en los ejemplos.

En otra modalidad, la presente invención se refiere a composiciones farmacéuticas que incluyen de una cantidad

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terapéuticamente efectiva de un compuesto de la presente invención, solo u, opcionalmente, en combinación con un portador farmacéuticamente aceptable y/o uno o más de otros agentes.

En otra modalidad, la presente invención se refiere a métodos que aumentan la actividad de la enzima glucocinasa que incluye la etapa de administrar a un paciente mamífero, por ejemplo, un paciente humano, que necesita del mismo una cantidad terapéuticamente efectiva de un compuesto de la presente invención, solo, u opcionalmente, en combinación con otro compuesto de la presente invención y/o al menos uno de otro tipo de agente terapéutico.

En otra modalidad, la presente invención se refiere a un método para prevenir, inhibir, o tratar la progresión o el inicio de enfermedades o trastornos asociados con déficit en la actividad de la enzima glucocinasa que incluye la etapa de administrar a un paciente mamífero, por ejemplo, un paciente humano, que necesita de prevención, inhibición, o tratamiento con una cantidad terapéuticamente efectiva de un compuesto de la presente invención, solo, u, opcionalmente, en combinación con otro compuesto de la presente invención y/o al menos uno de otro tipo de agente terapéutico.

Ejemplos de enfermedades o trastornos asociados con el déficit en la actividad de la enzima glucocinasa que se pueden prevenir, inhibir, o tratar de conformidad con la

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presente invención incluyen, pero no se limitan a, son aquellas enfermedades o trastornos mencionados arriba.

En otra modalidad, la presente invención se refiere a un método para prevenir, inhibir, o tratar la progresión o el inicio de diabetes, hiperglicemia, obesidad, dislipidemia, hipertensión, e insuficiencia cognitiva que incluye la etapa de administrar a un paciente mamífero, por ejemplo, un paciente humano, que necesita de prevención, inhibición, o tratamiento una cantidad terapéuticamente efectiva de un compuesto de la presente invención, solo, u, opcionalmente, en combinación con otro compuesto de la presente invención y/o al menos uno de otro tipo de agente terapéutico.

En todavía otra modalidad, la presente invención se refiere a un método para prevenir, inhibir, o tratar la progresión o el inicio de diabetes, que incluye la etapa de administrar a un paciente mamífero, por ejemplo, un paciente humano, que necesita de prevención, inhibición, o tratamiento una cantidad terapéuticamente efectiva de un compuesto de la presente invención, solo, u, opcionalmente, en combinación con otro compuesto de la presente invención y/o al menos uno de otro tipo de agente terapéutico.

En todavía otra modalidad, la presente invención se refiere a un método para prevenir, inhibir, o tratar la progresión o el inicio de hiperglicemia que incluye la etapa de administrar a un paciente mamífero, por ejemplo, un

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paciente humano, que necesita de prevención, inhibición, o tratamiento una cantidad terapéuticamente efectiva de un compuesto de la presente invención, solo, u, opcionalmente, en combinación con otro compuesto de la presente invención y/o al menos uno de otro tipo de agente terapéutico.

En otra modalidad, la presente invención se refiere a un método para prevenir, inhibir, o tratar la progresión o el inicio de obesidad que incluye la etapa de administrar a un paciente mamífero, por ejemplo, un paciente humano, que necesita de prevención, inhibición, o tratamiento con una cantidad terapéuticamente efectiva de un compuesto de la presente invención, solo, u, opcionalmente, en combinación con otro compuesto de la presente invención y/o al menos uno de otro tipo de agente terapéutico.

En una modalidad, la presente invención se refiere a un método para prevenir, inhibir, o tratar la progresión o el inicio de dislipidemia, que incluye la etapa de administrar a un paciente mamífero, por ejemplo, un paciente humano, que necesita de prevención, inhibición, o tratamiento con una cantidad terapéuticamente efectiva de un compuesto de la presente invención, solo, u, opcionalmente, en combinación con otro compuesto de la presente invención y/o al menos uno de otro tipo de agente terapéutico.

DESCRIPCION DETALLADA DE LA INVENCION

Los compuestos descritos en la presente pueden tener

centros asimétricos. Los compuestos de la presente invención que contienen un átomo asimétricamente substituido se pueden aislar en formas ópticamente activas o racémicas. Es bien conocido en la técnica cómo preparar formas ópticamente activas, tal como por resolución de formas racémicas o por síntesis de materiales de partida ópticamente activos. Muchos isómeros geométricos de olefinas, enlaces dobles C=N, y similares se pueden también presentar en los compuestos descritos en la presente, y todos los isómeros estables se contemplan en la presente invención. Los isómeros geométricos cis y trans de los compuestos de la presente invención se describen y se pueden aislar como una mezcla de isómeros o como formas isoméricas separadas. Todas las formas quirales, diaestereoméricas, racémicas, y todas las formas geométricas isoméricas de una estructura se pretenden, a menos que la estereoquímica específica o forma isomérica se indique específicamente.

El término "substituido," como se usa en la presente, significa que cualesquiera de uno o más hidrógenos en el átomo designado o anillo se reemplazan con una selección del grupo indicado, con la condición de que la valencia normal del átomo designado no se exceda, y que la substitución resulte en un compuesto estable. Cuando un substituyente es ceto (esto es, =O), entonces 2 hidrógenos en el átomo se reemplazan.

Cuando cualquier variable (por ejemplo, R^a) se presenta más de una vez en cualquier constituyente o fórmula para un compuesto, su definición cada que se presenta es independiente de su definición cada otra vez que se presenta. Así, por ejemplo, si un grupo se muestra para ser substituido con 0-2 R^a, entonces el grupo puede opcionalmente substituirse con hasta dos grupos R^a y R^a cada que se presenta se selecciona independientemente de la definición de R^a. También, las combinaciones de substituyentes y/o variables se permiten solo si tales combinaciones resultan en compuestos estables.

Cuando un enlace a un substituyente se muestra a través de un enlace que conecta dos átomos en un anillo, entonces tal substituyente puede enlazarse a cualquier átomo en el anillo. Cuando un substituyente se enlista sin indicar el átomo por medio del cual tal substituyente se enlaza al resto del compuesto de una fórmula dada, entonces tal substituyente puede enlazarse por medio de cualquier átomo en tal substituyente. Las combinaciones de substituyentes y/o variables se permiten solamente si tales combinaciones resultan en compuestos estables.

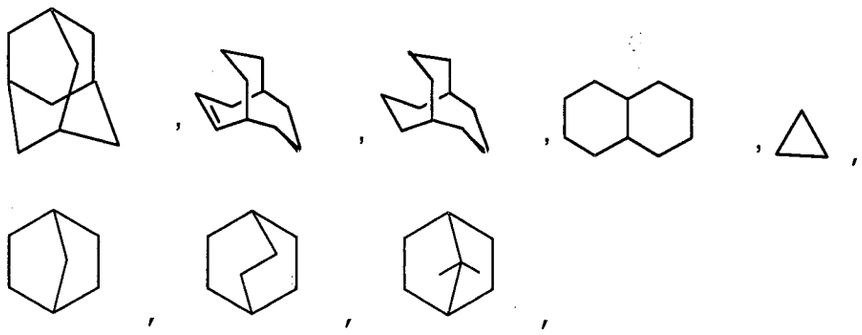
A menos que se indique de otra manera, el término "alquilo inferior," "alquilo," o "alq" como se emplea en la presente solo o como parte de otro grupo incluye ambos hidrocarburos de cadena recta y ramificada, que contiene 1

hasta 20 carbonos, preferiblemente 1 hasta 10 carbonos, más preferiblemente 1 hasta 8 carbonos, en la cadena normal, tal como metilo, etilo, propilo, isopropilo, butilo, t-butilo, isobutilo, pentilo, hexilo, isohexilo, heptilo, 4,4-dimetilpentilo, octilo, 2,2,4-trimetil-pentilo, nonilo, decilo, undecilo, dodecilo, los diversos isómeros de cadena ramificada del mismo, y los similares así como tales grupos pueden opcionalmente incluir 1 hasta 4 substituyentes tal como halo, por ejemplo F, Br, Cl, o I, o CF_3, alquilo, alcoxi, arilo, ariloxi, arilo(arilo) o diarilo, arilalquilo, arilalquiloxi, alquenilo, cicloalquilo, cicloalquilalquilo, cicloalquilalquiloxi, amino, hidroxi, hidroxialquilo, acilo, heteroarilo, heteroariloxi, heteroarilalquilo, heteroarilalcoxi, ariloxialquilo, alquiltio, arilalquiltio, ariloxiarilo, alquilamido, alcanoilamino, arilcarbonilamino, nitro, ciano, tiol, haloalquilo, trihaloalquilo, y/o alquiltio así como (=O), OR_a, SR_a, (=S), $-NR_aR_b$, $-N(alquil)_3^+$, $-NR_aSO_2$, $-NR_aSO_2R_c$, $-SO_2R_c-SO_2NR_aR_b$, $-SO_2NR_aC(=O)R_b$, SO_3H, $-PO(OH)_2$, $-C(=O)R_a$, $-CO_2R_a$, $-C(=O)NR_aR_b$, $-C(=O)(alquileno\ C_{1-4})NR_aR_b$, $-C(=O)NR_a(SO_2)R_b$, $-CO_2(alquileno\ C_{1-4})NR_aR_b$, $-NR_aC(=O)R_b$, $-NR_aCO_2R_b$, $-NR_a(alquileno\ C_{1-4})CO_2R_b$, =N-OH, =N-O-alquilo, en donde R_a y R_b son iguales o diferentes y se seleccionan independientemente de hidrógeno, alquilo, alquenilo, CO_2H, $CO_2(alquilo)$, cicloalquilo C_{3-7}, fenilo, bencilo, feniletilo, naftilo, un heterociclo de cuatro a siete miembros, o un

heteroarilo de cinco a seis miembros, o cuando se enlazan al mismo átomo de nitrógeno pueden unirse para formar un heterociclo o heteroarilo, y R_c se selecciona de los mismos grupos como R_a y R_b pero no es hidrógeno. Cada grupo R_a y R_b cuando es diferente a hidrógeno, y cada grupo R_c tiene opcionalmente hasta tres substituyentes adicionales enlazados a cualquier átomo de carbono o nitrógeno disponible de R_a, R_b, y/o R_c, los substituyentes son los mismos o diferentes y se seleccionan independientemente del grupo que consiste de alquilo (C_{1-6}), alquenilo(C_{2-6}), hidroxi, halógeno, ciano, nitro, CF_3, O(alquilo C_{1-6}), OCF_3, C(=O)H, C(=O)(alquilo C_{1-6}), CO_2H, CO_2(alquilo C_{1-6}), $NHCO_2$(alquilo C_{1-6}), -S(alquilo C_{1-6}), -NH_2, NH(alquilo C_{1-6}), N(alquilo $C_{1-6})_2$, $N(CH_3)_3^+$, SO_2(alquilo C_{1-6}), C(=O)(alquileno C_{1-4})NH_2, C(=O)(alquileno C_{1-4})NH(alquilo), C(=O)(alquileno C_{1-4})N(alquilo $C_{1-4})_2$, cicloalquilo C_{3-7}, fenilo, bencilo, feniletilo, feniloxi, benciloxi, naftilo, un heterociclo de cuatro a siete miembros, o un heteroarilo de cinco a seis miembros. Cuando un alquilo substituido está substituido con un grupo arilo, heterociclo, cicloalquilo, o heteroarilo, los sistemas anillados son como se define a continuación y así pueden tener cero, uno, dos, o tres substituyentes, también como se define a continuación.

A menos que se indique de otra manera, el término "cicloalquilo" como se emplea en la presente solo o como parte de otro grupo incluye grupos hidrocarburos cíclicos

saturados o parcialmente insaturados (que contienen 1 ó 2 enlaces dobles) que contienen 1 hasta 3 anillos, incluyendo alquilo monocíclico, alquilo bicíclico (o bicicloalquilo), y alquilo tricíclico, que contiene un total de 3 hasta 20 carbonos formando el anillo, preferiblemente 3 hasta 10 carbonos, formando el anillo y que se puede fusionar hasta 1 ó 2 anillos aromáticos como se describe por arilo, que incluye ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, cicloheptilo, ciclooctilo, ciclodecilo y ciclododecilo, ciclohexenilo,



cualquiera de los cuales los grupos pueden ser substituidos opcionalmente con 1 hasta 4 substituyentes tal como halógeno, alquilo, alcoxi, hidroxi, arilo, ariloxi, arilalquilo, cicloalquilo, alquilamido, alcanoilamino, oxo, acilo, arilcarbonilamino, amino, nitro, ciano, tiol, y/o alquiltio, y/o cualquiera de los substituyentes para alquilo.

A menos que se indique de otra manera, el término "alquenilo inferior" o "alquenilo" como se usa en la presente por sí mismo o como parte de otro grupo se refiere a

radicales de cadena recta o ramificada de 2 hasta 20 carbonos, preferiblemente 2 hasta 12 carbonos, y más preferiblemente 1 hasta 8 carbonos en la cadena normal, que incluye uno hasta seis enlaces dobles en la cadena normal, tal como vinilo, 2-propenilo, 3-butenilo, 2-butenilo, 4-pentenilo, 3-pentenilo, 2-hexenilo, 3-hexenilo, 2-heptenilo, 3-heptenilo, 4-heptenilo, 3-octenilo, 3-nonenilo, 4-decenilo, 3-undecenilo, 4-dodecenilo, 4,8,12-tetradecatrienilo, y similares, y que pueden ser substituidos opcionalmente con 1 hasta 4 substituyentes, en particular, halógeno, haloalquilo, alquilo, alcoxi, alquenilo, alquinilo, arilo, arilalquilo, cicloalquilo, amino, hidroxi, heteroarilo, cicloheteroalquilo, alcanoilamino, alquilamido, arilcarbonil-amino, nitro, ciano, tiol, alquiltio, y/o cualquiera de los substituyentes alquilo antes mencionado.

A menos que se indique de otra manera, el término "alquinilo inferior" o "alquinilo" como se usa en la presente por sí mismo o como parte de otro grupo se refiere a radicales de cadena recta o ramificada de 2 hasta 20 carbonos, preferiblemente 2 hasta 12 carbonos y más preferiblemente 2 hasta 8 carbonos en la cadena normal, que incluye un enlace triple en la cadena normal, tal como 2-propinilo, 3-butinilo, 2-butinilo, 4-pentinilo, 3-pentinilo, 2-hexinilo, 3-hexinilo, 2-heptinilo, 3-heptinilo, 4-heptinilo, 3-octinilo, 3-noninilo, 4-decinilo, 3-undecinilo,

4-dodecinilo, y similares, y que pueden ser substituidos opcionalmente con 1 hasta 4 substituyentes, en particular, halógeno, haloalquilo, alquilo, alcoxi, alquenilo, alquinilo, arilo, arilalquilo, cicloalquilo, amino, heteroarilo, cicloheteroalquilo, hidroxi, alcanoilamino, alquilamido, arilcarbonilamino, nitro, ciano, tiol, y/o alquiltio, y/o cualquiera de los substituyentes alquilo citados en la presente.

Donde los grupos alquilo como se definen anteriormente tienen enlaces sencillos para enlazar a otros grupos en dos diferentes átomos de carbono, se llaman grupos "alquileno" y se pueden opcionalmente substituir como se define arriba para "alquilo".

Donde grupos alquenilo como se define arriba y grupos alquinilo como se define arriba, respectivamente, tienen enlaces sencillos para enlazarse en dos diferentes átomos de carbono, se llaman "grupos alquenileno" y "grupos alquinileno", respectivamente, y se pueden opcionalmente substituir como se define arriba por "alquenilo" y "alquinilo".

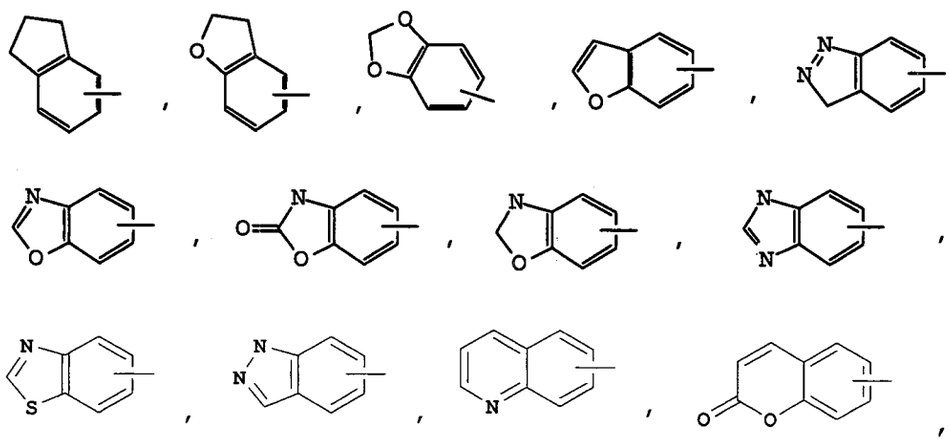
El término "halógeno" o "halo" como se usa en la presente solo o como parte de otro grupo se refiere a cloro, bromo, fluoro, y yodo así como CF_3, con cloro o fluoro siendo preferido.

A menos que se indique de otra manera, el término

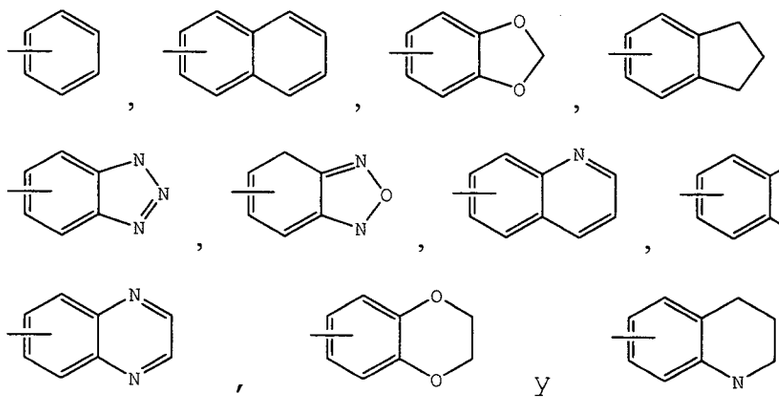
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"arilo" como se emplea en la presente solo o como parte de otro grupo se refiere a grupos aromáticos monocíclicos y bicíclicos que contienen 6 hasta 10 carbonos en la porción de anillo (tal como fenilo, bifenilo o naftilo, incluyendo 1-naftilo y 2-naftilo) y pueden opcionalmente incluir 1 hasta 3 anillos adicionales fusionados a un anillo carbocíclico o un anillo heterocíclico (tal como anillos arilo, cicloalquilo, heteroarilo, o cicloheteroalquilo)

por ejemplo



y



El grupo arilo puede ser substituido opcionalmente a través de átomos de carbono disponibles con 1, 2, ó 3 substituyentes, por ejemplo, hidrógeno, halo, haloalquilo, alquilo, haloalquilo, alcoxi, haloalcoxi, alquenilo, trifluorometilo, trifluorometoxi, alquinilo, cicloalquil-alquilo, cicloalquilo, cicloheteroalquilo, cicloheteroalquilalquilo, arilo, heteroarilo, arilalquilo, ariloxi, ariloxialquilo, arilalcoxi, ariltio, arilazo, heteroarilalquilo, heteroarilalquenilo, heteroarilheteroarilo, heteroariloxi, hidroxi, nitro, ciano, amino, amino substituido en donde el amino incluye 1 ó 2 substituyentes (que son alquilo, arilo, o cualquiera de los otros compuestos arilo mencionados en las definiciones), tiol, alquiltio, ariltio, heteroariltio, ariltioalquilo, alcoxiariltio, alquilcarbonilo, arilcarbonilo, alquil-aminocarbonilo, arilaminocarbonilo, alcoxicarbonilo, aminocarbonilo, alquilcarboniloxi, arilcarboniloxi, alquilcarbonilamino, arilcarbonilamino, arilsulfinilo, arilsulfinilalquilo, arilsulfonilamino, o arilsulfon-aminocarbonilo, OR_a, SR_a, (=S), $-NR_aR_b$, $-N(alquil)_3^+$, $-NR_aSO_2$, $-NR_aSO_2R_c$, $-SO_2R_c$ $-SO_2NR_aR_b$, $-SO_2NR_aC(=O)R_b$, SO_3H, $-PO(OH)_2$, $-C(=O)R_a$, $-CO_2R_a$, $-C(=O)NR_aR_b$, $-C(=O)$(alquileno C_{1-4})NR_aR_b, $-C(=O)NR_a(SO_2)R_b$, $-CO_2$(alquileno C_{1-4})NR_aR_b, $-NR_aC(=O)R_b$, $-NR_aCO_2R_b$, o $-NR_a$(alquileno C_{1-4})CO_2R_b, en donde R_a, R_b y R_c son como se define arriba por grupos alquilo substituido, y son

también a su vez substituidos opcionalmente como se cita anteriormente. Adicionalmente, dos substituyentes enlazados a un arilo, particularmente un grupo fenilo, pueden unirse para formar un anillo adicional tal como un anillo fusionado o espiro, por ejemplo, ciclopentilo o ciclohexilo, o heterociclo fusionado o heteroarilo. Cuando un arilo está substituido con un anillo adicional (o tiene un segundo anillo fusionado a ello), el anillo a su vez está substituido opcionalmente con uno hasta dos de alquilo(C_{1-4}), alquenilo(C_{2-4}), halógeno, hidroxi, ciano, nitro, CF_3, O(alquilo C_{1-4}), OCF_3, C(=O)H, C(=O)(alquilo C_{1-4}), CO_2H, CO_2(alquilo C_{1-4}), $NHCO_2$(alquilo C_{1-4}), -S(alquilo C_{1-4}), $-NH_2$, NH(alquilo C_{1-4}), N(alquilo C_{1-4})$_2$, N(alquilo C_{1-4})$_3^+$, SO_2(alquilo C_{1-4}), C(=O)(alquileno C_{1-4})NH_2, C(=O)(alquileno C_{1-4})NH(alquilo), y/o C(=O)(alquileno C_{1-4})N(alquilo C_{1-4})$_2$ y/o cualquiera de los substituyentes alquilo citados en la presente.

A menos que se indique de otra manera, el término "alcoxi inferior", "alcoxi", "ariloxi" o "aralcoxi" como se emplea en la presente solo o como parte de otro grupo incluye cualquiera de los grupos alquilo, aralquilo, o arilo anteriores ligados a un átomo de oxígeno.

A menos que se indique de otra manera, el término "amino" como se emplea en la presente solo o como parte de otro grupo se refiere a amino que puede ser substituido con uno o dos substituyentes, que pueden ser el mismo o

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diferente, tal como alquilo, arilo, arilalquilo, heteroarilo, heteroarilalquilo, cicloheteroalquilo, cicloheteroalquilalquilo, cicloalquilo, cicloalquilalquilo, haloalquilo, hidroxialquilo, alcoxialquilo, o tioalquilo. Estos substituyentes pueden ser además substituidos con un ácido carboxílico y/o cualquiera de los grupos R_3 o substituyentes para R_3 como se cita anteriormente. Además, los substituyentes amino pueden ser tomados junto con el átomo de nitrógeno al cual se enlazan para formar 1-pirrolidinilo, 1-piperidinilo, 1-azepinilo, 4-morfolinilo, 4-tiamorfolinilo, 1-piperazinilo, 4-alquil-1-piperazinilo, 4-arilalquil-1-piperazinilo, 4-diarilalquil-1-piperazinilo, 1-pirrolidinilo, 1-piperidinilo, o 1-azepinilo, substituido opcionalmente con alquilo, alcoxi, alquiltio, halo, trifluorometilo, o hidroxi.

A menos que se indique de otra manera, el término "alquiltio inferior," "alquiltio," "ariltio," o "aralquiltio" como se emplea en la presente solo o como parte de otro grupo incluye cualquiera de los grupos alquilo, aralquilo, o arilo anteriores ligados a un átomo de azufre.

A menos que se indique de otra manera, el término "alquilamino inferior," "alquilamino," "arilamino," o "arilalquilamino" como se emplea en la presente solo o como parte de otro grupo incluye cualquiera de los grupos alquilo, arilo, o arilalquilo anteriores ligados a un átomo de

nitrógeno.

El término "acilo" solo o como parte de otro grupo se refiere a un grupo carbonilo ligado a un radical orgánico, más particularmente, el grupo $C(=O)R_e$, así como los grupos bivalentes $-C(=O)-$ o $-C(=O)R_e-$, los cuales se ligan a radicales orgánicos. El grupo R_e se puede seleccionar de alquilo, alquenilo, alquinilo, aminoalquilo, alquilo substituido, alquenilo substituido, o alquinilo substituido, como se define en la presente, o cuando es apropiado, el grupo bivalente correspondiente, por ejemplo, alquileno, alquenileno, y similares.

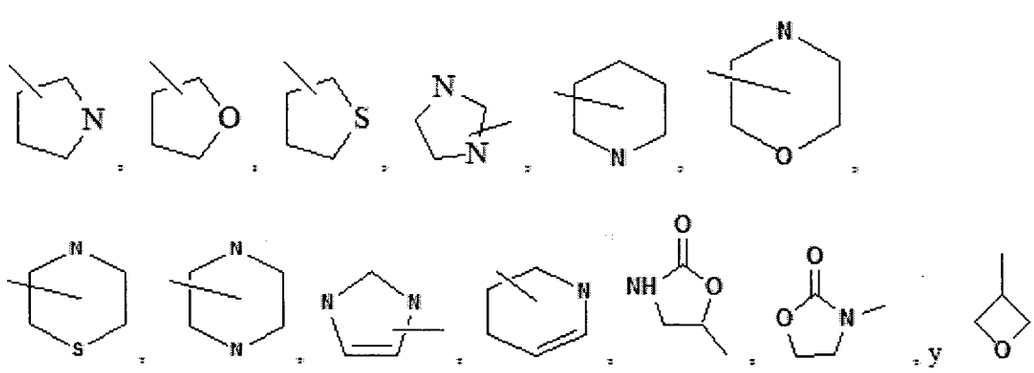
El término "heterociclo" o "heterocíclico" o "heterociclilo" o "cicloheteroalquilo" se refiere a grupos monocíclicos de 3 hasta 7 miembros no aromáticos substituidos y no substituidos, grupos bicíclicos de 7 hasta 11 miembros, y grupos tricíclicos de 10 hasta 15 miembros, en los cuales al menos uno de los anillos tiene al menos un heteroátomo (O, S, ó N) (también se refiere como cicloheteroalquilo o heterocicloalquilo). Cada anillo del grupo heterociclo que contiene un heteroátomo puede contener uno o dos átomos de oxígeno o azufre y/o desde uno hasta cuatro átomos de nitrógeno con la condición de que el número total de heteroátomos en cada anillo es cuatro o menos, y además con la condición de que el anillo contiene al menos un átomo de carbono. Los anillos fusionados que completan los grupos

bicíclicos y tricíclicos pueden contener solamente átomos de carbono y pueden ser saturados, parcialmente saturados, o insaturados. Los átomos de nitrógeno y azufre se pueden opcionalmente oxidizar y los átomos de nitrógeno se pueden opcionalmente cuaternizar. El grupo heterociclo puede ser enlazado a cualquier átomo de nitrógeno o carbono disponible. El anillo heterociclo puede contener cero, uno, dos, o tres substituyentes seleccionados del grupo que consiste de halógeno, trifluorometilo, trifluorometoxi, alquilo, alquilo substituido, alquenilo, alquenilo substituido, alquinilo, nitro, ciano, oxo (=O), OR_a, SR_a, (=S), $-NR_aR_b$, $-N(alquil)_3^+$, $-NR_aSO_2$, $-NR_aSO_2R_c$, $-SO_2R_c$ $-SO_2NR_aR_b$, $-SO_2NR_aC(=O)R_b$, SO_3H, $-PO(OH)_2$, $-C(=O)R_a$, $-CO_2R_a$, $-C(=O)NR_aR_b$, $-C(=O)$(alquileno C_{1-4})NR_aR_b, $-C(=O)NR_a(SO_2)R_b$, $-CO_2$(alquileno C_{1-4})NR_aR_b, $-NR_aC(=O)R_b$, $-NR_aCO_2R_b$, $-NR_a$(alquileno C_{1-4})CO_2R_b, =N-OH, =N-O-alquilo, arilo, cicloalquilo, heterociclo, y/o heteroarilo, en donde R_a, R_b, y R_c son como se definen anteriormente por grupos alquilo substituidos, y son también a su vez substituidos opcionalmente como se cita anteriormente. Cuando un heterociclo está substituido con un anillo adicional, el anillo a su vez está substituido opcionalmente con uno hasta dos de alquilo (C_{1-4}), alquenilo(C_{2-4}), halógeno, hidroxi, ciano, nitro, CF_3, O(alquilo C_{1-4}), OCF_3, C(=O)H, C(=O)(alquilo C_{1-4}), CO_2H, CO_2(alquilo C_{1-4}), $NHCO_2$(alquilo C_{1-4}), -S(alquilo C_{1-4}), $-NH_2$, NH(alquilo C_{1-4}), N(alquilo C_{1-4})$_2$, N(alquilo C_{1-}

$_4)_3^+$, SO_2(alquilo C_{1-4}), C(=O)(alquileno C_{1-4})NH_2, C(=O)(alquileno C_{1-4})NH(alquilo), y/o C(=O)(alquileno C_{1-4})N(alquilo $C_{1-4})_2$.

Los grupos monocíclicos ejemplares incluyen azetidinilo, pirrolidinilo, oxetanilo, imidazolinilo, oxazolidinilo, isoxazolinilo, tiazolidinilo, isotiazolidinilo, tetrahidrofuranilo, piperidilo, piperazinilo, 2-oxopiperazinilo, 2-oxopiperidilo, 2-oxopirrolodinilo, 2-oxoazepinilo, azepinilo, 4-piperidonilo, tetrahidropiranilo, morfolinilo, tiamorfolinilo, sulfóxido tiamorfolinilo, sulfona tiamorfolinilo, 1,3-dioxolano, y tetrahidro-1,1-dioxotienilo, y similares. Los grupos bicíclicos heterociclos ejemplares incluyen quinuclidinilo.

Los grupos heterociclo preferidos en compuestos de la fórmula (I) incluyen



que opcionalmente pueden ser substituidos.

El término "heteroarilo" solo o como parte de otro grupo se refiere a grupos monocíclicos substituidos y no

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substituidos aromáticos de 5 ó 6 miembros, grupos bicíclicos de 9 ó 10 miembros, y grupos tricíclicos de 11 hasta 14 miembros que tienen al menos un heteroátomo (O, S ó N) en al menos uno de los anillos. Cada anillo del grupo heteroarilo contiene un heteroátomo que puede contener uno o dos átomos de oxígeno o azufre y/o de uno hasta cuatro átomos de nitrógeno con la condición de que el número total de heteroátomos en cada anillo es cuatro o menos y cada anillo tiene al menos un átomo de carbono. Los anillos fusionados al terminar los grupos bicíclicos y tricíclicos pueden contener solamente átomos de carbono y pueden ser saturados, parcialmente saturados, o no saturados, y pueden incluir arilo, cicloalquilo, heteroarilo o cicloheteroarilo. Los átomos de nitrógeno y azufre se pueden opcionalmente oxidizar y los átomos de nitrógeno se pueden opcionalmente cuaternizar. Los grupos heteroarilo que son bicíclicos o tricíclicos deben incluir al menos un anillo completamente aromático pero el otro anillo fusionado o anillos pueden ser aromáticos o no aromáticos. El grupo heteroarilo se puede enlazar a cualquier átomo de nitrógeno o carbono disponible de cualquier anillo. El sistema de anillo heteroarilo puede contener cero, uno, dos o tres substituyentes que pueden ser cualquiera de los substituyentes mencionados para alquilo y se pueden seleccionar del grupo que consiste de halógeno, trifluorometilo, trifluorometoxi, alquilo, alquilo

substituido, alquenilo, alquenilo substituido, alquinilo, nitro, ciano, OR_a, SR_a, (=S), $-NR_aR_b$, $-N(alquilo)_3^+$, $-NR_aSO_2$, $-NR_aSO_2R_c$, $-SO_2R_c$ $-SO_2NR_aR_b$, $-SO_2NR_aC(=O)R_b$, SO_3H, $-PO(OH)_2$, $-C(=O)R_a$, $-CO_2R_a$, $-C(=O)NR_aR_b$, $-C(=O)$(alquileno C_{1-4})NR_aR_b, $-C(=O)NR_a(SO_2)R_b$, $-CO_2$(alquileno C_{1-4})NR_aR_b, $-NR_aC(=O)R_b$, $-NR_aCO_2R_b$, $-NR_a$(alquileno C_{1-4})CO_2R_b, arilo, cicloalquilo, heterociclo, y/o heteroarilo, en donde R_a, R_b y R_c son como se define arriba por grupos alquilo substituidos, y son también a su vez substituidos opcionalmente como se cita anteriormente. Cuando un heteroarilo está substituido con un anillo adicional, el anillo a su vez está substituido opcionalmente con uno hasta dos de alquilo (C_{1-4}), alquenilo(C_{2-4}), halógeno, hidroxi, ciano, nitro, CF_3, O(alquilo C_{1-4}), OCF_3, C(=O)H, C(=O)(alquilo C_{1-4}), CO_2H, CO_2(alquilo C_{1-4}), $NHCO_2$(alquilo C_{1-4}), -S(alquilo C_{1-4}), $-NH_2$, NH(alquilo C_{1-4}), N(alquilo C_{1-4})$_2$, N(alquilo C_{1-4})$_3^+$, SO_2(alquilo C_{1-4}), C(=O)(alquileno C_{1-4})NH_2, C(=O)(alquileno C_{1-4})NH(alquilo), y/o C(=O)(alquileno C_{1-4})N(alquilo C_{1-4})$_2$.

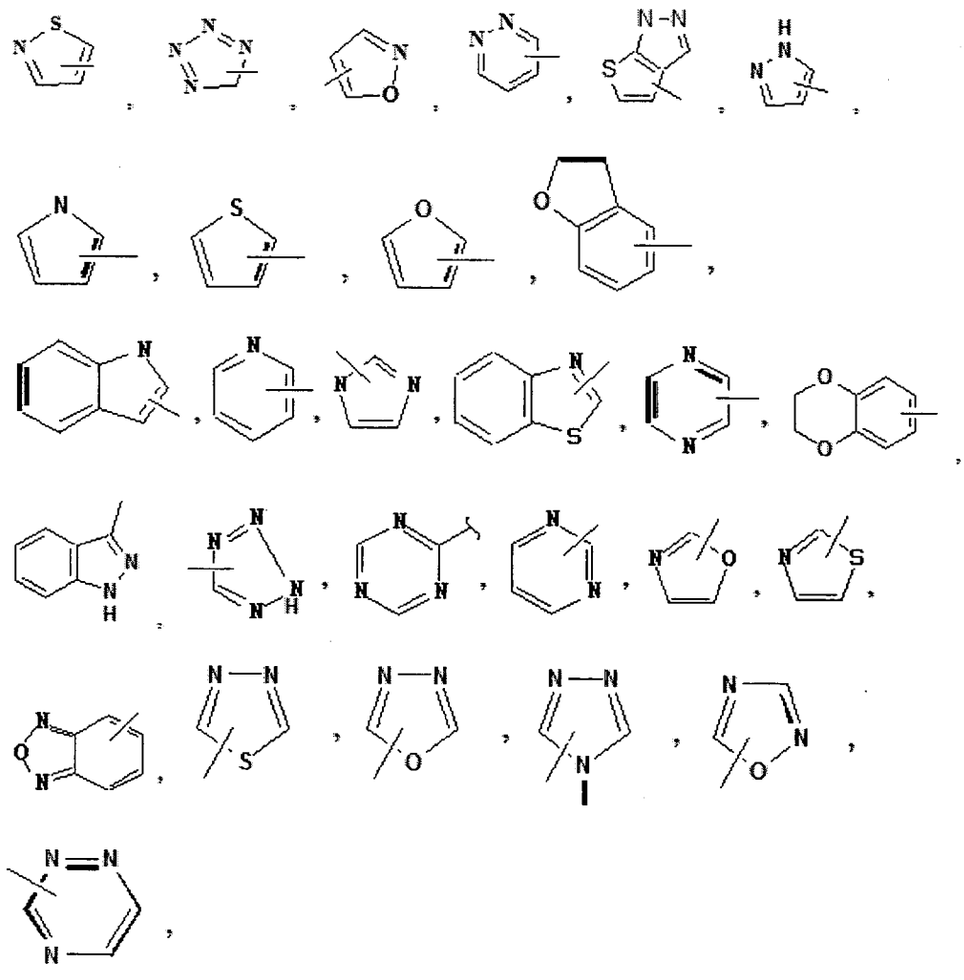
Los grupos heteroarilo monocíclicos ejemplares incluyen pirrolilo, pirazolilo, pirazolinilo, imidazolilo, oxazolilo, isoxazolilo, tiazolilo, tiadiazolilo, isotiazolilo, furanilo, tienilo, oxadiazolilo, piridilo, pirazinilo, pirimidinilo, piridazinilo, triazinilo y similares.

Los grupos heteroarilo bicíclicos ejemplares incluyen indolilo, benzotiazolilo, benzodioxolilo, benzoxazolilo, benzotienilo,

quinolinilo, tetrahidroisoquinolinilo, isoquinolinilo, benzimidazolilo, benzopiranilo, indolizinilo, benzofuranilo, cromonilo, coumarinilo, benzopiranilo, cinolinilo, quinoxalinilo, indazolilo, pirrolopiridilo, furopiridilo, dihidroisoindolilo, tetrahidroquinolinilo y similares.

Los grupos heteroarilo tricíclicos ejemplares incluyen carbazolilo, benzidolilo, fenantrolinilo, acridinilo, fenantridinilo, xantenilo y similares.

En compuestos de la fórmula (I), grupos heteroarilo preferidos incluyen



y similares.

El término "heterociclilalquilo" o "heterocicloalquilo" o "cicloheteroalquilalquilo" como se usa en la presente solo o como parte de otro grupo se refiere a grupos heterociclilo como se define arriba ligados a través de un átomo C o heteroátomo a una cadena alquilo.

El término "heteroarilalquilo" o "heteroarilalquenilo" como se usa en la presente solo o como parte de otro grupo se refiere a un grupo heteroarilo como se define arriba ligado a través de un átomo C o heteroátomo a una cadena alquilo, alquileno, o alquenileno como se define arriba.

El término "ciano" como se usa en la presente, se refiere a un grupo -CN.

El término "nitro" como se usa en la presente, se refiere a un grupo $-NO_2$.

El término "hidroxi" como se usa en la presente, se refiere a un grupo -OH.

A menos que se indique de otra manera, cuando la referencia se hace a un arilo nombrado especificamente (por ejemplo, fenilo), cicloalquilo (por ejemplo, ciclohexilo), heterociclo (por ejemplo, pirrolidinilo) o heteroarilo (por ejemplo, imidazolilo), a menos que se indique específicamente de otra manera la referencia se pretende que incluya anillos que tienen 0 hasta 3, preferiblemente 0-2, substituyentes seleccionados de aquellos citados arriba para los grupos

arilo, cicloalquilo, heterociclo y/o heteroarilo, como es apropiado.

El término "heteroátomos" incluirá oxígeno, azufre y nitrógeno.

El término "carbocíclico" significa un anillo saturado o no saturado monocíclico o bicíclico en el cual todos los átomos de todos los anillos son carbono. Así, el término incluye anillos cicloalquilo y arilo. El anillo carbocíclico puede ser substituido en este caso los substituyentes se seleccionan de aquellos citados arriba para grupos cicloalquilo y arilo.

Cuando el término "no saturado" se usa en la presente para referirse a un anillo o grupo, el anillo o grupo puede ser completamente no saturado o parcialmente no saturado.

A través de la especificación, los grupos y substituyentes del mismo pueden ser elegidos por un experto en la técnica para proporcionar porciones y compuestos estables y compuestos útiles . como compuestos farmacéuticamente aceptables y/o compuestos intermediarios útiles en la fabricación de compuestos farmacéuticamente aceptables.

La frase "farmacéuticamente aceptable" se emplea en la presente para referirse a aquellos compuestos, materiales, composiciones, y/o formas de dosis que están, dentro del alcance del juicio médico sólido, apropiado para el uso en

contacto con los tejidos de seres humanos y animales sin excesiva toxicidad, irritación, respuesta alérgica, u otro problema o complicación, en proporción con una razonable relación beneficio/riesgo.

Como se usa en la presente, "sales farmacéuticamente aceptable" se refieren a derivados de los compuestos descritos en donde el compuesto precursor se modifica al hacer sales ácidas o de base del mismo.

Los términos "sal" y "sales" farmacéuticamente aceptable se pueden referir a sales básicas formadas con bases inorgánicas y orgánicas. Tales sales incluyen sales de amonio; sales de metal alcalino, tal como sales de litio, sodio, y potasio (que son preferidas); sales de metal alcalino terreo, tal como sales de calcio y magnesio; sales con bases orgánicas, tal como sales tipo amina (por ejemplo, sal diciclohexilamina, benzatina, N-metil-D-glucamina, y sales hidrabamina); y sales con aminoácidos tipo arginina, lisina, y similares; y zwitteriones, las llamadas "sales internas". Las sales farmacéuticamente aceptables, no tóxicas, son preferidas, aunque otras sales son también útiles, por ejemplo, en aislar o purificar el producto.

El término "sal" y "sales" farmacéuticamente aceptable también incluye sales de adición ácida. Se forman estos, por ejemplo, con ácidos inorgánicos fuertes, tal como ácidos minerales, por ejemplo ácido sulfúrico, ácido fosfórico, o un

ácido hidrohalico tal como HCl o HBr, con ácidos carboxílicos orgánicos fuertes, tal como ácidos alcanocarboxílicos de 1 hasta 4 átomos de carbono que son no substituidos o substituidos, por ejemplo, por halógeno, por ejemplo ácido acético, tal como ácidos dicarboxílicos saturados o no saturados, por ejemplo ácido oxálico, malónico, succínico, maléico, fumárico, ftálico, o tereftálico, tal como ácidos hidroxicarboxílicos, por ejemplo ácido ascórbico, glicólico, láctico, málico, tartárico, o cítrico, tal como aminoácidos, (por ejemplo ácido aspártico o glutámico o lisina o arginina), o ácido benzoico, o con ácidos orgánicos sulfónicos, tal como alquilo (C_1-C_4) o ácidos arilsulfónicos, que son no substituidos o substituidos, por ejemplo por halógeno, por ejemplo ácido metansulfónico o ácido p-toluensulfónico.

Las sales farmacéuticamente aceptables de la presente invención se pueden sintetizar a partir del compuesto precursor que contiene una porción básica o ácida por métodos químicos convencionales. Generalmente, tales sales se pueden preparar al reaccionar las formas de ácido o base libre de estos compuestos con una cantidad estequiométrica de la base o ácido apropiado en agua o en un solvente orgánico, o en una mezcla de los dos; generalmente, medios no acuosos tipo éter, acetato de etilo, etanol, isopropanol, o acetonitrilo son preferidos. Las listas de sales apropiadas se encuentran en

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Remington's Pharmaceutical Sciences, 17th ed., Mack Publishing Company, Easton, PA, 1985, p. 1418, la descripción de la cual se incorpora en la presente como referencia.

A través de la especificación, grupos y substituyentes del mismo pueden ser elegidos por un experto en la técnica para proporcionar porciones y compuestos estables y compuestos útiles como compuestos farmacéuticamente aceptables y/o compuestos intermediarios útiles en la fabricación de compuestos farmacéuticamente aceptables.

Cualquier compuesto que se puede convertir *in vivo* para proporcionar el agente bioactivo (esto es, el compuesto de la fórmula I) es un profármaco dentro del alcance y espíritu de la invención.

El término "profármaco" significa un compuesto que, durante la administración a un sujeto, experimenta conversión química por procesos metabólicos o químicos hasta producir un compuesto de la fórmula, y/o una sal y/o solvato del mismo. Por ejemplo, compuestos que contienen un grupo carboxi pueden formar ésteres fisiológicamente hidrolizables que sirven como profármacos al hidrolizarse en el cuerpo hasta producir compuestos de fórmula per se. Tales profármacos son preferiblemente administrados oralmente desde hidrólisis en muchas instancias se presentan principalmente bajo la influencia de las enzimas digestivas. La administración parenteral puede ser usada donde el éster per se está activo,

o en esos casos donde la hidrólisis se presenta en la sangre.

El término "profármacos" como se emplea en la presente incluye ésteres y carbonatos formados al reaccionar uno o más hidroxilos de los compuestos de la fórmula I con agentes de acilación substituidos alquilo, alcoxi, o arilo empleando procedimientos conocidos por aquellos expertos en la técnica para generar acetatos, pivalatos, metilcarbonatos, benzoatos, y similares.

Diversas formas de profármacos son bien conocidas en la técnica y se describen en:

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

b) Design of Prodrugs, editado por H. Bundgaard (Elsevier, 1985);

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

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

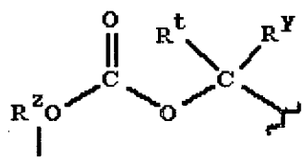
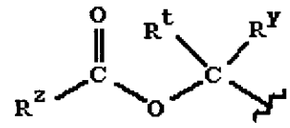
Las referencias se incorporan en la presente como referencia.

Ejemplos de ésteres fisiológicamente hidrolizables de los compuestos de la fórmula (I) incluyen alquilbencilo C_{1-6}, 4-metoxibencilo, indanilo, ftalilo, metoximetilo, alcanoiloxi C_{1-6}-alquilo C_{1-6}, por ejemplo, acetoximetilo, pivaloiloximetilo, o

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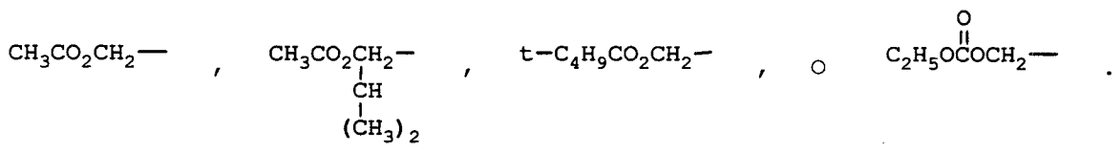
propioniloximetilo, alcoxicarboniloxi C_{1-6}-alquilo C_{1-6}, por ejemplo, metoxicarbonil-oximetilo o etoxicarboniloximetilo, gliciloximetilo, fenilgliciloximetilo, (5-metil-2-oxo-1,3-dioxolen-4-il)-metilo, y otros bien conocidos ésteres fisiológicamente hidrolizables usados, por ejemplo, en las técnicas de penicilina y cefalosporina. Tales ésteres se pueden preparar por técnicas convencionales conocidas en la técnica.

Los ejemplos de éster de profármaco incluyen los siguientes grupos: (1-alcanoiloxi)alquilo tal como,

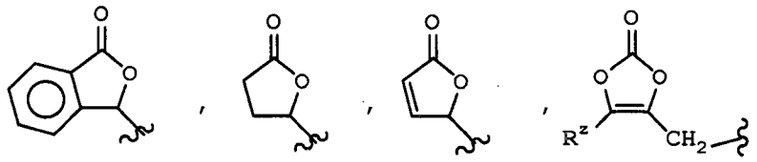

o


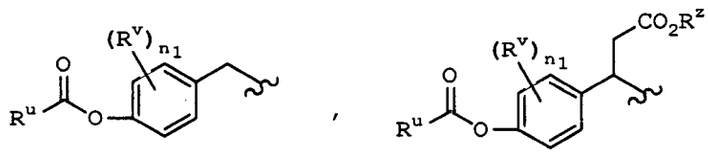
en donde R^z, R^t, y R^y son H, alquilo, arilo, o arilalquilo; sin embargo, R^zO no puede ser HO.

Ejemplos de tales ésteres de profármacos incluyen



Otros ejemplos de ésteres de profármacos adecuados incluyen





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en donde R^z puede ser H, alquilo (tal como metilo o t-butilo), arilalquilo (tal como bencilo) o arilo (tal como fenilo); R^v es H, alquilo, halógeno o alcoxi, R^u es alquilo, arilo, arilalquilo, o alcoxilo, y n_1 es 0, 1, ó 2.

El término "tautómero" se refiere a compuestos de la fórmula I y sales del mismo que pueden existir en su forma tautomérica, en la cual los átomos de hidrógeno se transportan a otras partes de las moléculas y los enlaces químicos entre los átomos de las moléculas se disponen por lo tanto. Se entenderá que todas las formas tautoméricas, de manera que pueden existir, se incluyen dentro de la invención.

Además, compuestos de la fórmula I son, posterior a su preparación, preferiblemente aislados y purificados para obtener una composición que contiene una cantidad en peso igual a o mayor que 99% de compuesto de fórmula I (compuesto I "substancialmente puro"), que se usa luego o se formula como se describe en la presente. Tales compuestos "substancialmente puros" de la fórmula I se contemplan también en la presente como parte de la presente invención.

Todos los estereoisómeros de los compuestos de la actual invención se contemplan, ya sea en mezcla o en forma pura o substancialmente pura. Los compuestos de la presente invención pueden tener centros asimétricos en cualquiera de los átomos de carbono incluyendo cualesquiera de los

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substituyentes R y/o mostrar polimorfismo. En consecuencia, los compuestos de la fórmula I pueden existir en formas enantioméricas, o diaestereoméricas, o en mezclas de los mismos. Los procesos para la preparación pueden utilizar racematos, enantiómeros, o diaestereómeros como materiales de partida. Cuando los productos diaestereoméricos o enantioméricos se preparan, se puede separar por métodos convencionales por ejemplo, cristalización cromatográfica o fraccional.

"Compuesto estable" y "estructura estable" significan para indicar un compuesto que es suficientemente robusto para sobrevivir al aislado hasta un grado útil de pureza a partir de una mezcla de reacción, y formulación dentro de un agente terapéutico eficaz. La presente invención se pretende que abarque compuestos estables.

"Cantidad terapéuticamente efectiva" se pretende que incluya una cantidad de un compuesto de la presente invención solo o una cantidad de la combinación de compuestos reivindicados o una cantidad de un compuesto de la presente invención en combinación con otros ingredientes activos efectivos para tratar o prevenir diabetes y/u obesidad.

Como se usa en la presente, "tratar" o "tratamiento" cubre el tratamiento de un estado de enfermedad en un mamífero, particularmente en un humano, e incluye: (a) prevenir el estado de enfermedad a partir que se presenta en un mamífero, en particular, cuando tal mamífero se

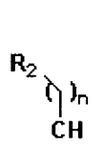
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predispone al estado de enfermedad pero no se le ha diagnosticado como que lo tiene; (b) inhibir el estado de enfermedad, esto es, frenar este desarrollo; y/o (c) aliviar el estado de enfermedad, esto es, causando regresión del estado de enfermedad.

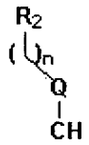
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Los compuestos de las fórmulas I y Ia se pueden preparar como se muestra en los siguientes esquemas de reacción y la descripción de los mismos, así como los procedimientos relevantes de la literatura que pueden ser utilizados por una persona experta en la técnica. Reactivos ejemplares y procedimientos y los procedimientos para estas reacciones aparecen mas abajo y en los ejemplos trabajados. La protección y desprotección en los esquemas de reacción de abajo puede ser realizado por procedimientos generalmente conocidos en la técnica (ver, por ejemplo, Greene, T.W. and Wuts, P.G.M., Protecting Groups in Organic Synthesis, 3rd Edición, 1999 [Wiley]).

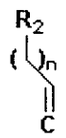
La síntesis de compuestos de amida de la fórmula I en donde X =



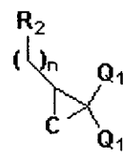
X-1



X-2



X-4

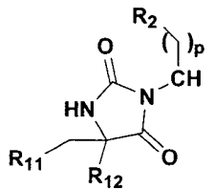


X-5

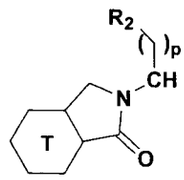
o enlace,

X-6

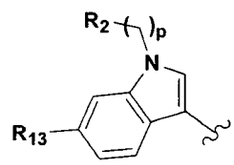
y cuando Y está ausente,



X-7



X-8

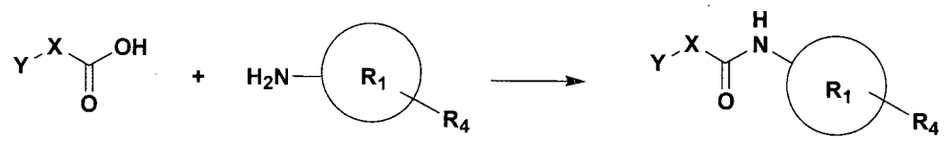


X-9

- 000416

se describen en el esquema de reacción 1. El ácido carboxílico 1 se acopla con la amina 2 seguido por condiciones de literatura estándar, tales como: (1) el uso de cloruro oxalil con DMF catalítico para formar el intermediario de cloruro ácido seguido por reacción subsecuente con amina 2 en la presencia de una base amina; o (2) el tratamiento de una mezcla de 1 y 2 con un reactivo acoplado tal como DEPBT (Li et al., *Org. Lett.*, **1999**, 1:91). Donde el anillo heteroaromático R_1 se representa en el esquema de reacción 1 y en todos los esquemas de reacción descritos abajo, los substituyentes del anillo opcional R_5 y R_6 se pueden presentar.

ESQUEMA DE REACCION 1

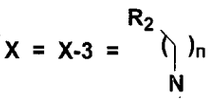


1 2 I

Los procedimientos para la síntesis de ejemplos pertinentes de ácido carboxílico 1 se pueden encontrar en la literatura (las referencias incluyen, pero no se limitan a, las siguientes solicitudes internacionales PCT: para X-1, WO 2000/058293, WO 2001/083465, WO 2001/085706, WO 2001/085707, WO 2002/046173, WO 2003/095438, WO 2004/052869, WO 2004/072031, WO 2004/063194, WO 2004/072066, WO 2005/103021, WO 2006/016194, WO 2006/016174, WO 2006/016178; para X-2, WO 2002/008209, WO 2004/063194; para X-4, WO 2001/044216, WO 2004/072031, WO 2004/072066, WO 2004/063194, WO 2002/014312, WO 2005/103021, WO 2006/016194; para X-5, WO 2004/063179; para X-6, WO 2003/000262, WO 2003/000267, WO 2003/080585, WO 2003/015774, WO

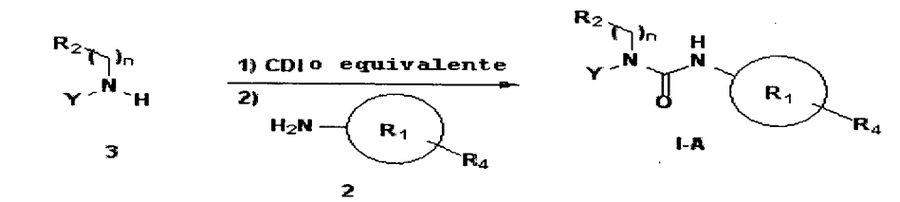
2004/045614, WO 2004/046139, WO 2004/076420, WO 2005/121110; WO 2006/040528, WO 2006/040529, WO 2006/125972, WO 2007/007040, WO 2007/007041, WO 2007/007042, WO 2007/0017649; para X-7, WO 2001/083478; para X-8, WO 2002/048106; para X-9, WO 2004/031179.

La síntesis de compuestos de urea de la fórmula I en donde

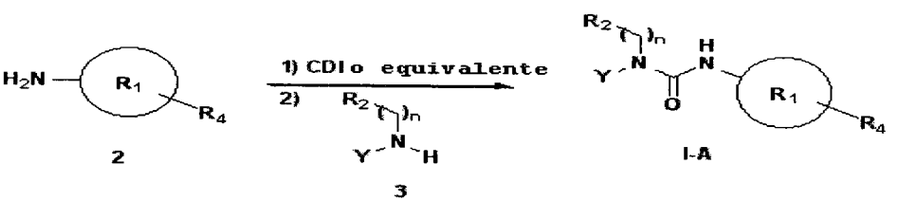


se describe en el esquema de reacción 2. La amina 3 se puede tratar con un reactivo tal como carbonildiimidazol, 4-nitrofenilcloroformato, fosgeno, o un derivativo del fosgeno tal como difosgeno o trifosgeno, seguido por la adición de la amina 2 para proporcionar el producto de urea deseado de la fórmula I. Alternativamente, la amina 2 puede ser primero tratada con un reactivo tal como carbonildiimidazol (u otro reactivo similar como se describe anteriormente), seguido por adición de la amina 3 para proveer ureas de la fórmula I-A.

ESQUEMA DE REACCION 2



alternativamente



Los procedimientos para la síntesis de ejemplos pertinentes de la amina 3 están disponibles en la literatura (las referencias incluyen solicitudes Internacionales PCT WO2003/055482 y WO2004/002481; y Castellano et al., *Bioorg. Med. Chem. Lett.* **2005**, 15:1501).

El esquema de reacción 3 describe un acercamiento general para la síntesis de la amina 2A en donde

$R_4 = -(CH_2)_n-Z-(CH_2)_m-PO(OR_7)(OR_8)$

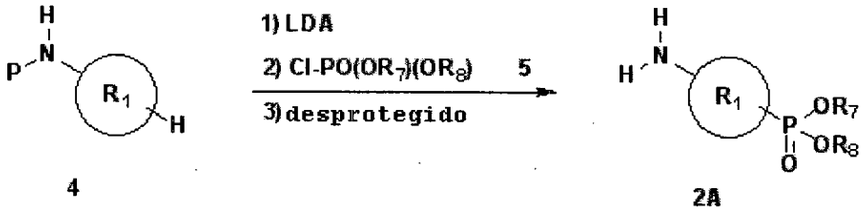
Z = enlace

m y n = 0

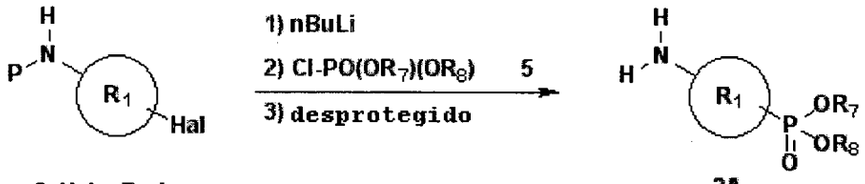
esto es, donde el grupo de fosfonato resultante es directamente enlazado al anillo heteroaromático, R_1. Un heteroaril substituido del amino protegido 4 con a substituto de hidrógeno convenientemente activado se desprotona con una base fuerte tal como LDA o n-butillitio. El anion resultante reacciona con un dialquiloclorofosfato 5 resultante en enlace directo del grupo fosfonato para R_1. El retiro de los grupos de protección proporciona la amina 2A. Alternativamente, el heteroaril del halo substituido 6 puede también ser convertido al mismo intermediario aniónico por medio de intercambio de halógeno-metal por reacción con una base tal como n-butillitio. Este acercamiento puede también ser extendido a la síntesis de ácidos fosfinicos por el uso de un reacctivo tal como N,N-dietilclorometilfosfonamida para reaccionar con el intermediario anion (Rumthao et al., *Bioorg. Med. Chem. Lett.*, **2004**, 14:5165-5170). Como un ejemplo, la amina de tiazola protegida 7 puede ser desprotonada como se muestra en el esquema de reacción 3

usando una base tal como LDA o n-BuLi y fosfonilada según lo descrito para dar, después de la desprotección, la amina tiazol 5-fosfonato-substituido 2B (South et al., *J. Het. Chem.*, **1991**, 28:1017).

ESQUEMA DE REACCION 3

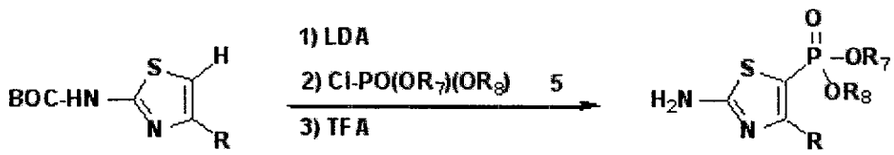


4 2A



6, Hal = Br, I 2A

- por ejemplo,



7 2B

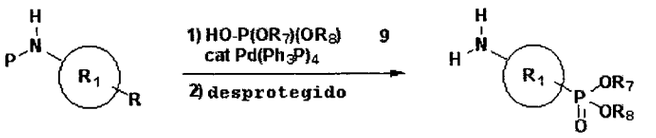
Las reacciones descritas anteriormente en el esquema de reacción 3 y esquemas de reacción 4, 5, 6, 7 y 8 abajo puede también ser conducida en compuestos en donde el grupo Y-X-CO- a sido ya acilado para la amina 2 y donde la química se permite por estructura compatible en Y-X-CO- y/o el uso de grupos protegidos apropiados.

El esquema de reacción 4 describe otro enfoque para la síntesis

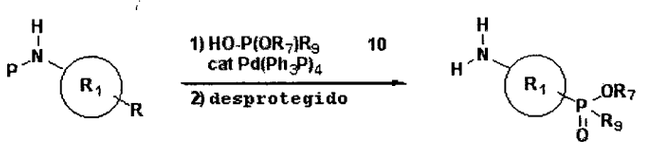
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de la amina 2A. La amina heteroaril protegida 8 que contiene un substituyente tal como bromo, yodo o triflato es acoplado al dialquilofosfito 9 en la presencia de una cantidad catalitica de catalizador de paladio(0), tal como tetraquis-trifenilfosfina de paladio(0) para proporcionar, después de la desprotección, la amina heteroaril substituida de fosfonato 2A (Hirao et al., Sintesis, **1981**, 56-57). El uso del reactivo 10 en esta reacción proporciona el fosfinato correspondiente 2C (Rumthao et al., *Bioorg. Med. Chem. Lett.*, **2004**, 14:5165-5170). Como un ejemplo, la reacción entre la piridina de bromo 11 y el dialquilofosfito 9 catalizado por $Pd(Ph_3P)_4$ proporciona el compuesto piridino fosfonilado I-B. El compuesto 11 se obtiene por acoplamiento del ácido 1 al 5-bromo-2-aminopirazina de una manera descrita en el esquema de reacción 1.

ESQUEMA DE REACCION 4

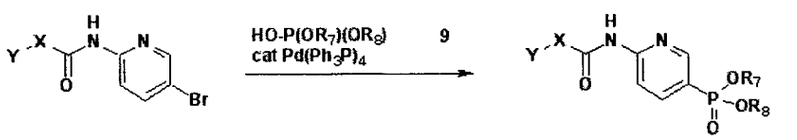


8, R = Br, I, OTf — 2A



8, R = Br, I, OTf — 2C

-por ejemplo,



11 — I-B

El Esquema de reacción 5 describe la síntesis de compuestos de la fórmula I en la cual

$R_4 = -(CH_2)_n-Z-(CH_2)_m-PO(OR_7)(OR_8)$

Z = alqueno o etileno

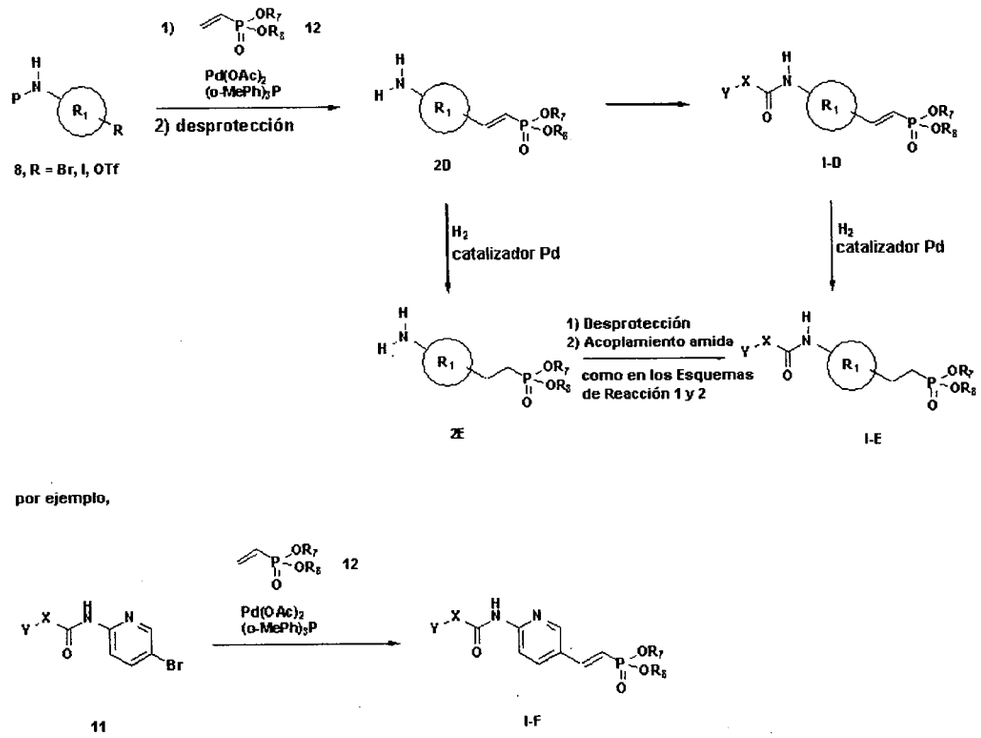
m y n = 0

así conectado el grupo fosfonato al anillo heteroaromático con un ligador de dos carbonos. Una amina 8 de heteroarilo protegida apropiadamente se acopla al fosfonato de vinilo 12 en la presencia de cantidaes catalíticas de un catalizador Pd(II) tal como $Pd(OAc)_2$ y ligando de fosfina tal como tri-o-tolilfosfina para dar un producto intermediario de fosfonato de vinilo protegido (Xu et al., Synthesis, 1983, 556-558). La eliminación de grupos protectores proporciona la amina de fosfonato de vinilo 2D que se convierte a I-D, el compuesto correspondiente de la fórmula I en donde Z = alqueno (vinilo) por la forma descrita en los Esquemas de reacción 1 y 2. La hidrogenación en la presencia de Pd(0) catalítico de 2D y 1D proporciona el etileno correspondiente (dos carbonos) ligado a compuestos de fosfonato, 2E y 1-E. Como se mencionó anteriormente, estas transformaciones se pueden conducir en un intermediario completamente elaborado tal como describe la conversión de amida de aminopirazina 11 a la pirazina substituida con producto de fosfonato de

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vinilo I-F.

ESQUEMA DE REACCION 5

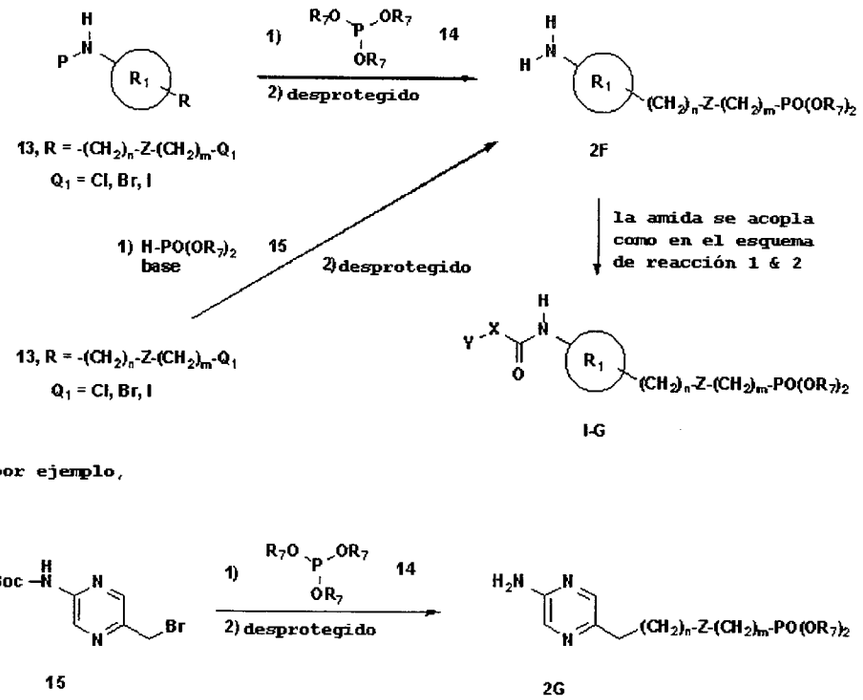


El Esquema de reacción 6 describe la síntesis de compuestos de la fórmula I en la cual los grupos fosfonato o fosfinato en R_4 se incorporan usando las reacciones Arbusov (Engel, R., Handbook of Organophosphorus Chemistry, 1992 [Marcel Dekker]) o Michaelis-Becker (Engel, R., Handbook of Organophosphorus Chemistry, 1992 [Marcel Dekker]). En la reacción Arbusov, el haluro de alquilo 13 se calienta con el trialquilfosfito 14 para producir, después de la eliminación de grupos protectores, amina 2F. La amina 2F se convierte a compuestos de la fórmula IG por medios descritos en los Esquemas de reacción 1 y 2. Cuando se lleva a cabo usando

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$R_9P(OR_7)_2$ en lugar del trialquilfosfito 14, el producto de éster fosfínico correspondiente se obtiene (esto es, donde R_4 = $-(CH_2)_n-Z-(CH_2)_m-PO-(R_9)(OR_7)$ (Kapustin et al., Org. Lett., 2003, 5, 3053-3057). En la reacción Michaelis-Becker, el compuesto 13 reacciona con dialquilfosfito 15 en la presencia de base para producir, después de la eliminación de grupos protectores, amina 2F. La amina 2F se puede convertir a los compuestos de la fórmula I-G por medios descritos en Esquemas de reacción 1 y 2. Como un ejemplo, la 5-bromometilpirazina protegida por Boc puede calentarse con trialquilfosfito 14 para dar, después de la eliminación del grupo Boc, la amina 2G pirazina substituido con fosfonometil, que se puede convertir a compuestos de la fórmula I como se describe anteriormente.

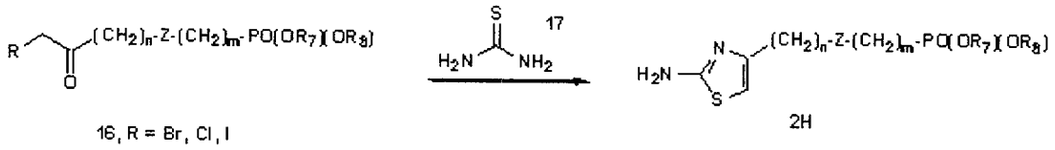
ESQUEMA DE REACCION 6



El Esquema de reacción 7 describe los compuestos

de síntesis de la fórmula I en la cual el anillo heteroaromático R_1 es un tiazol. En este esquema de reacción, el grupo fosfonato o fosfinato incorporado en un precursor acíclico a la formación del anillo heteroaromático. En una síntesis de tiazol Hantzsch estándar, halocetona 16 se reacciona con tiourea 17 para formar el 4-substituido, 2-aminotiazol 2H. Como un ejemplo, ácido acetilfosfónico 18 se trata con bromo para formar la α-halocetona 19. La reacción de 19 con tiourea 17 proporciona el 5-fosfono-2-aminotiazol 2I (Ohler et al., Chem. Ber., 1984, 117, 3034-3047). Los aminotiazoles 2H y 2I se pueden convertir a compuestos de la fórmula I por medios descritos en el Esquema de reacción 1 y 2.

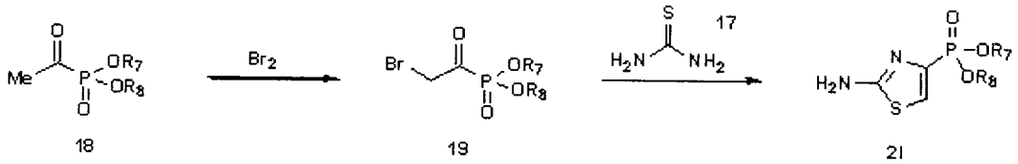
ESQUEMA DE REACCION 7



16, R = Br, Cl, I

2H

por ejmplo



18 19 2I

El Esquema de reacción 8 describe compuestos de la fórmula I en la cual

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$R_4 = -(CH_2)_n-Z-(CH_2)_m-PO(OR_7)(OR_8)$

Z = CH(OH)

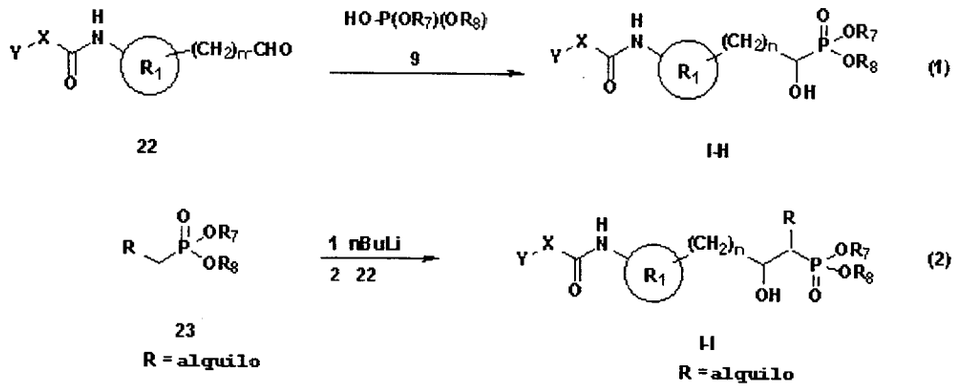
m = 0, 1

n = 0, 1, 2

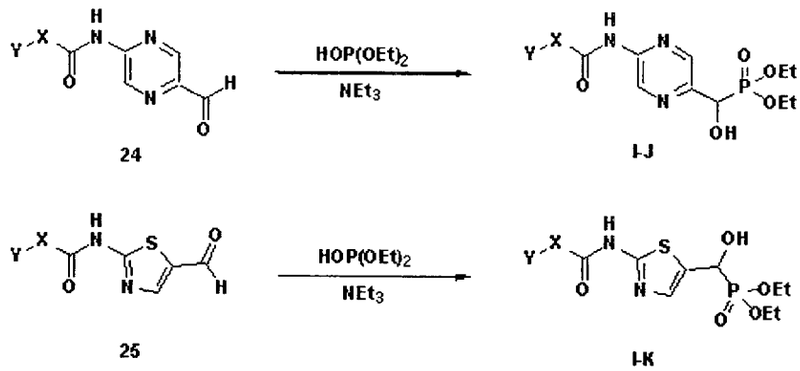
esto es, compuestos en los cuales R_4 contiene un metileno substituido con hidroxi [Z = CH(OH)] colocado entre el anillo heteroaromático R_1 y el grupo fosfonato. En la ecuación (1), la reacción de dialquilfosfito 9 con aldehído 22 en la presencia de una base tal como trietilamina o DBN dando el producto hidroxifosfonato I-H (Caplan et al., J. Chem. Soc. Perkin I, 2000, 3, 421-437), representando un compuesto de la fórmula I en el cual Z = CH(OH), n = 0, 1, 2 y m = 0. En la ecuación (2), fosfonato de alquilo 23 se trata con una base tal como n-BuLi, seguido por adición de aldehído 22 dando el producto hidroxifosfonato I-I (Mikolajczyk et al., Synthesis, 1984, 691-694), que representa un compuesto de la fórmula I en la cual Z = CH(OH), n = 0, 1, 2 y m = 1. Como ejemplos, la pirazina 24 y tiazol 25 se convierten como se muestra en la hidroxifosfonatos correspondientes, I-J y I-K.

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ESQUEMA DE REACCION 8



por ejemplo,



El Esquema de reacción 9 describe compuestos de la fórmula I en la cual

$R_4 = -(CH_2)_n-Z-(CH_2)_m-PO(OR_7)(OR_8)$

$Z = CH(OR_9)$

$m = 0$

$n = 0, 1, 2$

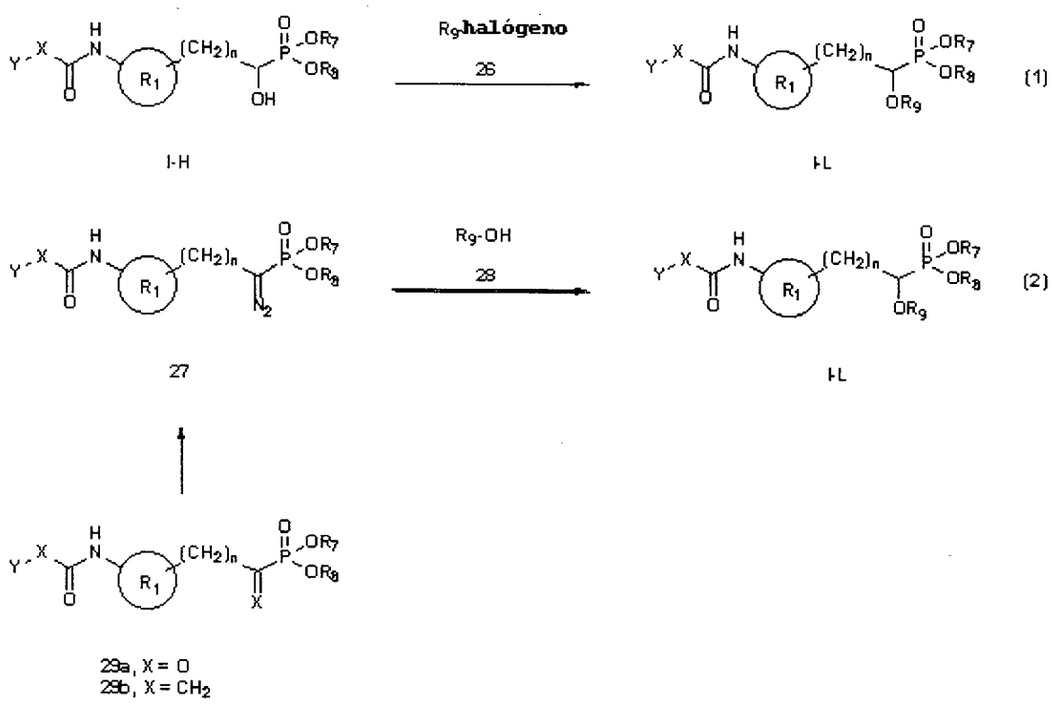
esto es, compuestos en los cuales R_4 contiene un metileno substituido con alcoxi [$Z = CH(OR_9)$] colocado entre el anillo heteroaromático R_1 y el grupo fosfonato. En la ecuación (1), los productos de fosfonato de hidroxilo del

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Esquema de reacción 8 se pueden alquilar con haluros de alquilo activo adecuados 26 para dar los fosfonatos alfa-alcoxi I-L (Wrobleski et al., Tetrahedron Asymmetry, 2002, 13, 845-850). Alternativamente, la ecuación (2) describe la reacción de inserción catalizada por rodio de alcoholes 28 con fosfonatos alfa-diazo 27 que también proporcionan compuestos I-L (Cox, G. et al., Tetrahedron, 1994, 50, 3195-3212; Moody, C. et al., Tetrahedron Asymmetry, 2001, 12, 1657-1661). La preparación de fosfonatos alfa-diazo 28 se ha descrito por transferencia diazo directa a la cetona correspondiente 29a (Regitz, M., Tetrahedron Lett., 1968, 9, 3171-3174). Alternativamente, los fosfonatos diazo 28 se pueden obtener por medio de descomposición catalizada por base de las alfa-toluensulfonilhidrazidas derivadas a partir de los fosfonatos ceto correspondientes 29b (Marmor, R. et al., J. Org. Chem., 1971, 36, 128-136). Los fosfonatos alfa-ceto 29a se pueden sintetizar directamente a partir de fosfonatos alfa-hidroxi (I-H) por oxidación usando un reactivo tal como CrO_3 (Kaboudin, B. et al., Tetrahedron Lett., 2000, 41, 3169-2171). Alternativamente, la reacción Arbusov entre un cloruro ácido y trialquilfosfito proporciona el fosfonato alfa-ceto correspondiente (Marmor, R., et al., J. Org. Chem., 1971, 36, 128-136). Los

métodos para la síntesis de fosfonatos tal como 29a se han descrito arriba.

ESQUEMA DE REACCION 9



El Esquema de reacción 10 describe compuestos de la fórmula I en la cual

$R_4 = -(CH_2)_n-Z-(CH_2)_m-PO(OR_7)(OR_8)$

$Z = CH(NHR_9)$

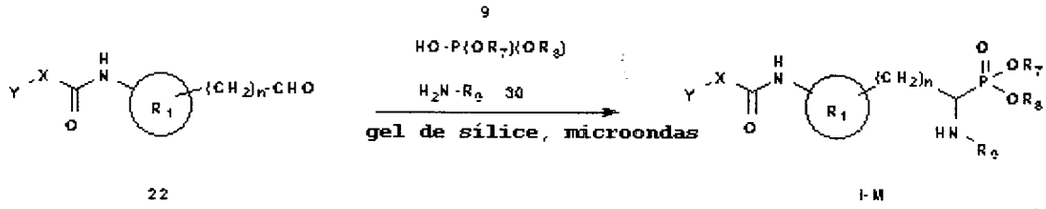
$m = 0$

$n = 0, 1, 2$

esto es, compuestos en los cuales R_4 contiene un metileno substituido con amino [$Z = CH(NHR_9)$] colocado entre el anillo heteroaromático R_1 y el grupo fosfonato. En el Esquema de reacción 10, aldehído 22 se puede hacer reaccionar

con un dialquilfosfito 9 y amina 30 para dar el fosfonato substituido alfa-amino I-M al conducir la reacción en la presencia de gel de sílice e irradiación de microondas (Zhan et al., Chem. Lett., 2005, 34, 1042-1043). Otros métodos implican la preformación de la imina correspondiente que resulta de la condensación del aldehído 22 y amina 30, que se sigue por la reacción con el dialquilfosfito 9 en la presencia de diversos catalizadores tal como ácidos Lewis (Laschat and Kunz, Synthesis, 1992, 90). Además, otros catalizadores se pueden usar por la síntesis en un recipiente descrita en el Esquema 10 (por ejemplo, uso de SmI_2 se describe en Xu et al., Eur. J. Org. Chem., 2003, 4728).

ESQUEMA DE REACCION 10



El esquema de reacción 11 describe la síntesis de compuestos de la fórmula I en la cual

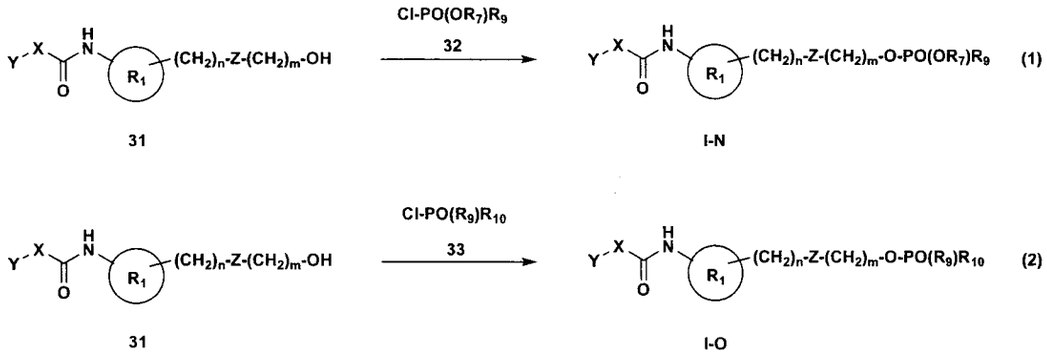
$R_4 = -(CH_2)_n-Z-(CH_2)_m-O-PO(OR_7)R_9$

y $-(CH_2)_nZ-(CH_2)_m-O-PO-R_9R_{10}$.

La reacción del alcohol precursor 31 con el cloruro de fosfonilo 32 o cloruro de fosfinilo 33 en la presencia de una base tal como piridina o rendimientos de trietilamina del compuesto fosfonato

I-N (ecuación 1) o el compuesto fosfinato I-O (ecuación 2). Además la reacción se muestra para la síntesis de fosfonatos I-N, otros métodos que incluyen la esterificación directa de un ácido fosfónico o el uso de la reacción Mitsunobu (Saady et al., Tetrahedron Lett., 1995, 36, 2239-2242). La preparación de ésteres fosfínicos de ácido dimetilfosfínico (I-O en donde R_9 y R_{10} = Me) se ha descrito usando cloruro de dimetilfosfinilo y tetrazol en la presencia de piridina para producir un tetrazoluro de fosfinilo intermediario (Solicitud PCT Intl. WO2000/078763).

ESQUEMA DE REACCION 11



El Esquema de reacción 12 describe compuestos de la fórmula I en la cual

$R_4 = -(CH_2)_n-Z-(CH_2)_m-O-PO(OR_7)R_9$

y $-(CH_2)_nZ-(CH_2)_m-O-PO-R_9$,

y Z = S o SO_2,

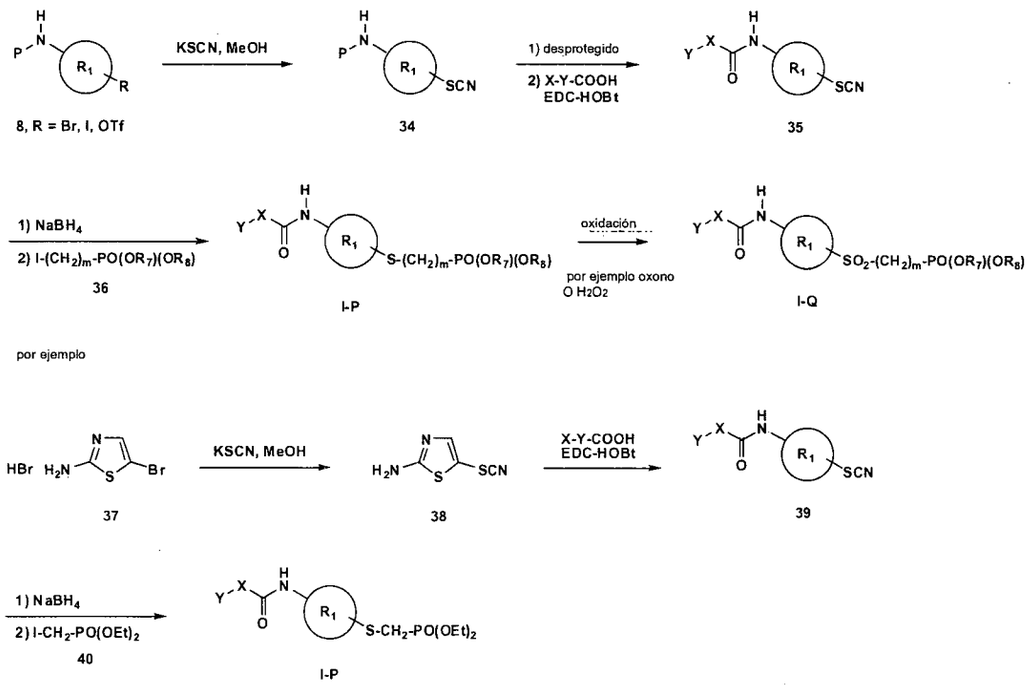
y m = 1 ó 2,

y n = 0, 1 ó 2.

La reacción de un intermediario 8 heteroaromático substituido con halógeno activado adecuadamente con tiocianato de potasio dio el intermediario de tiocianato 34. En este punto, los grupos protectores se pueden remover y el compuesto heteroaromático amino resultante se acopla con ácido 1 usando medios estándares tal como EDC-HOBt para dar el intermediario 35. El tratamiento de tiocianato 35 con $NaBH_4$ proporcionó el intermediario tiol correspondiente que se alquila con el haluro substituido 36 para dar compuestos de la fórmula I en donde Z = S (I-P). El tratamiento del producto I-P con agentes de oxidación tal como peróxido de hidrógeno o oxona dio compuestos de la fórmula I en donde Z = SO_2 (I-Q). Como un ejemplo, el tratamiento de la sal HBr de 2-amino-5-bromotiazol (37) con tiocianato de potasio en metanol proporciona tiocianato 38. El producto se acila con ácido 1 usando medios estándares para dar el intermediario 39. La reducción del grupo tiocianato en 39 con $NaBH_4$, seguido por la alquilación del tiol libre resultante con fosfonato de yodometilo 40 dio compuestos de fosfonato de la fórmula I donde Z = S, m = 1 y n = 0

(I-P).

ESQUEMA DE REACCION 12



El Esquema de reacción 13 describe la síntesis de los compuestos de la fórmula I en la cual

$R_4 = -(CH_2)_n-Z-(CH_2)_m-O-PO(OR_7)R_9$

y $-(CH_2)_nZ-(CH_2)_m-O-PO-(R_9)R_{10}$,

y Z = O,

y m = 1 ó 2,

y n = 0, 1 ó 2.

La reacción de un intermediario 41 heteroaromático substituido con halógeno activado adecuadamente con el intermediario 42 de fosfonato substituido con hidroxi en la presencia de óxido de plata proporcionó I-R, el compuesto de fosfonato de la fórmula I en el cual Z = O, m = 1 ó 2, y n =

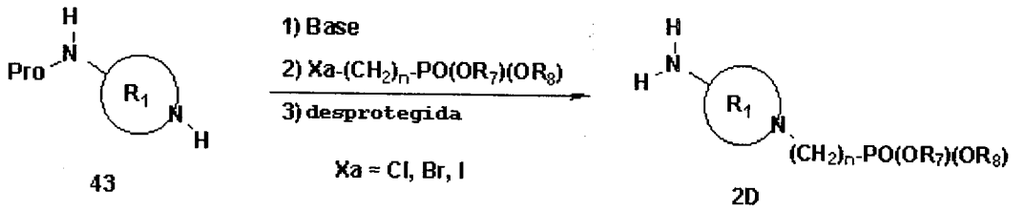
0, 1 ó 2 (Flor et al., J. Med. Chem., 1999, 42, 2633-2640).

ESQUEMA DE REACCION 13



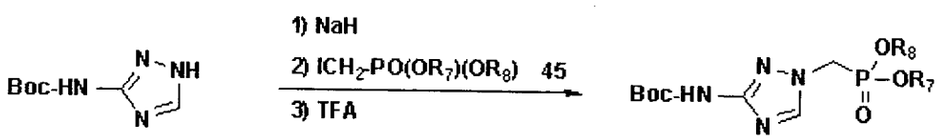
El esquema de reacción 14 describe una síntesis general de amina 2D, donde la porción de fosfato o fosfinato (aquí ilustrada por un fosfanato) se liga al heterociclo R1 por un átomo de nitrógeno en vez de un átomo de carbono. Un heterociclo (Pro)amino protegido tal como 43 se puede desprotonar con una base seguido por aquilación con un haluro apropiado que contiene la porción de fosfanato/fosfinato seguido por la desprotección para dar la amina 2D. Esto se ilustra por el ejemplo de la triazola protegida N-Boc 44, la cual se desprotona con una base (por ejemplo, NaH), luego se alquila con un fosfonato de yodometilo 46. La desprotección del grupo N-Boc proporciona entonces el fosfonato aminotriazol 46. Por otro lado, en ciertos casos, el heterociclo-amino no necesita ser protegido, como se ilustra en el caso de pirazol 47, el cual se puede desprotonar con una base tal como KOtBu y alquilar preferentemente en el nitrógeno en el anillo con electrófilos tales como un fosfonato de yodometilo 45 para formar el producto 48.

ESQUEMA DE REACCION 14

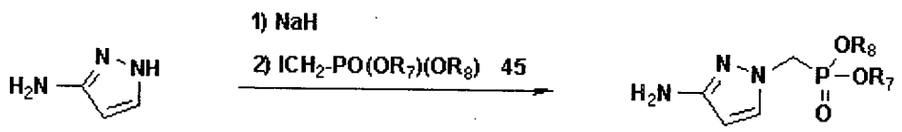


43 2D

-por ejemplo,



44 46



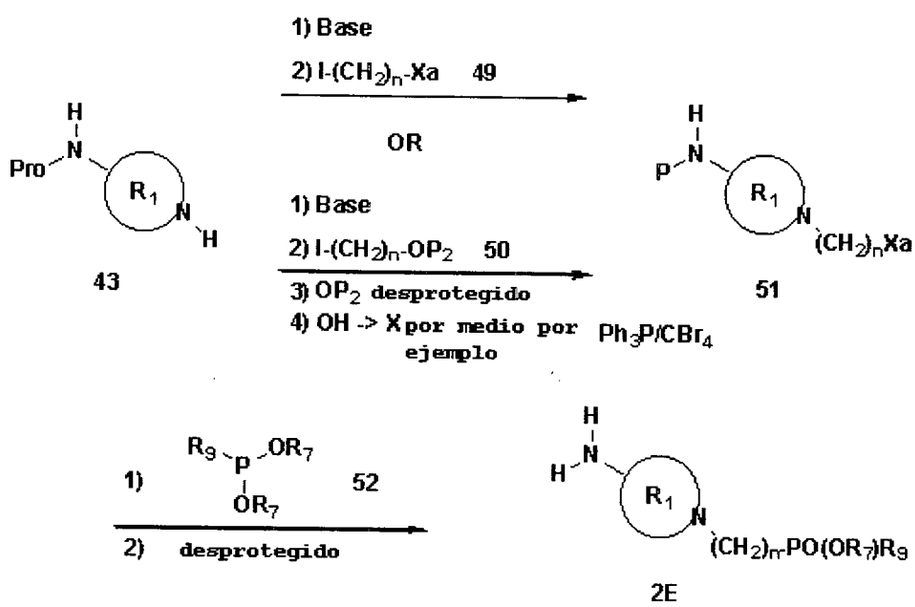
47 48

Un enfoque representativo alternativo para fosfonatos/fosfinatos N-alquilados se muestra en el Esquema de reacción 15. La amina 43 se puede desprotonarse con una base apropiada y hacerse reaccionar con un yoduro tal como 49 (que contiene un grupo funcional Xa, por ejemplo Cl, Br, Ots) para dar el heterociclo N-alquilado 51. Alternativamente, la amina puede hacerse reaccionar con un yoduro tal como 50 (que contiene por ejemplo, un grupo hidroxilo protegido OP_2, que puede posteriormente desprotegerse y convertirse a un haluro por medio de métodos conocidos, por ejemplo Ph_3P/CBr_4) para

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proporcionar el heterociclo N-alquilatado 51. Este intermediario luego se puede hacer reaccionar con ya sea un fosfato de trialquilo (reacción Arbusov) como se describe en el Esquema 6 para proporcionar un fosfonato, o, como se muestra aquí. Cuando el haluro 51 se hace reaccionar con el fosfonito 52, el producto es el correspondiente éster fosfínico 2E (referencia: Kapustin et al., Org Lett., **2003**, 5:3053-3057).

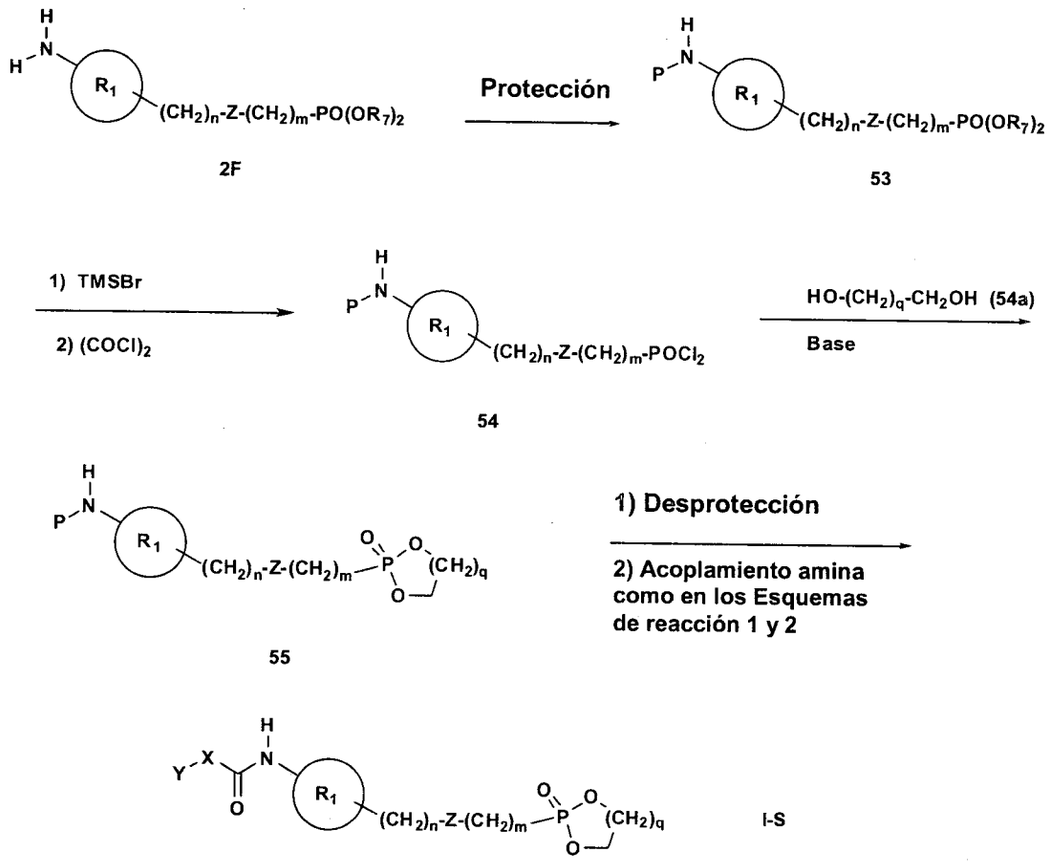
ESQUEMA DE REACCION 15



El Esquema de reacción 16 describe la síntesis de los compuestos de la fórmula I-S los cuales contienen ésteres de fosfonato cíclicos. El diéster de fosfonato de la amina intermediaria 2F se protege (por ejemplo como un carbamato de tert-butilo o como un carbamato de bencilo) para dar el fosfonato 53, el cual se desalquila con un agente tal como

bromotrimetilsilano. El éster del ácido fosfonico de bis-trimetilsililo resultante se hace reaccionar directamente con cloruro de oxalilo para dar el dicloruro de fosforilo 54. El intermediario 54 se convierte al fosfonato cíclico deseado 55 por reacción con un diol 54a apropiado en la presencia de una base (referencia: Notter et al., Bioorg. Med. Chem. Lett., **2007,** 17:113-117). La desprotección de 55 dio la amina correspondiente, la cual luego fácilmente se convierte al compuesto de la fórmula I-S por los métodos previamente descritos en los Esquemas de reacción 1 y 2.

ESQUEMA DE REACCION 16

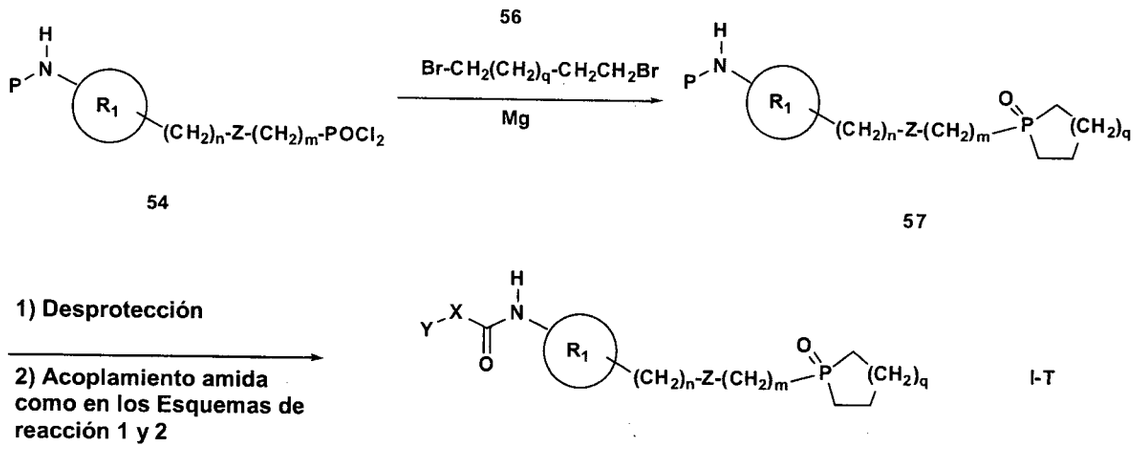


2F 53 54 55 I-S

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Similarmente, el Esquema de reacción 17 describe la síntesis del compuesto de la fórmula I-T que contiene óxidos de fosfina cíclicos. El dicloruro de fosforilo 54 puede hacerse reaccionar con un reactivo Grignard formado de un dibromo 56 y magnesio para proporcionar el óxido de fosfino cíclico 57 (referencia: R. Polniaszek et. al., J. Org. Chem., **1991**, 56:3137-3146). La desprotección de 57 dio la amina correspondiente, la cual es luego convertida a los compuestos de la fórmula I-T por los métodos previamente descritos en los Esquemas de reacción 1 y 2.

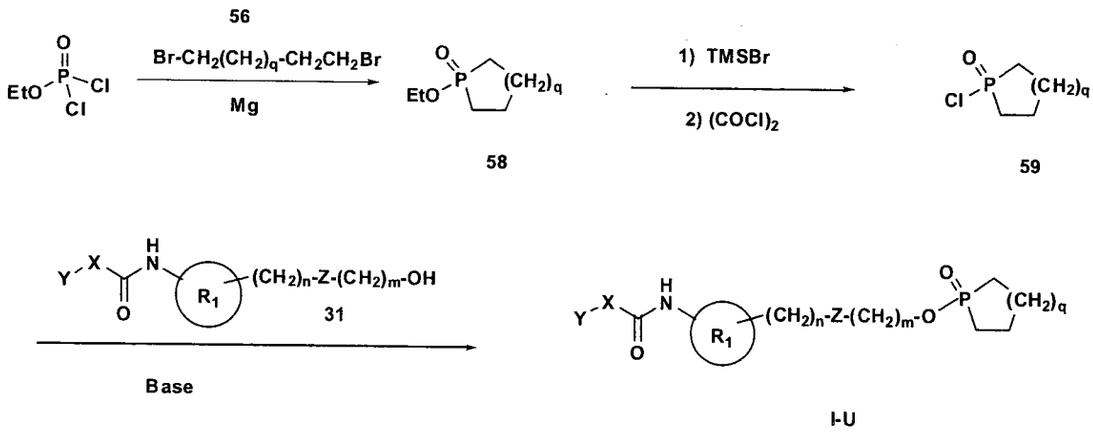
ESQUEMA DE REACCION 17



El Esquema de reacción 18 describe la síntesis de los compuestos de la fórmula I-U los cuales contienen fosfinatos cíclicos. El etil diclorofosfato se hace reaccionar con un reactivo Grignard formado de un dibromo 56 y magnesio para dar el éster de fosfinato cíclico 58 (referencia: R. Polniaszek et. al., J. Org. Chem., **1991**, 56:3137-3146). El

éster 58 se desalquila (por ejemplo con bromotrimetilsilano). El éster del ácido trimetilsilil fosfónico resultante se hace reaccionar directamente con un agente clorante (por ejemplo cloruro de oxalilo) para dar el cloruro de fosforilo 59, el cual luego se hace reaccionar con alcohol 31 en la presencia de una base para dar los compuestos de la fórmula I-U.

ESQUEMA DE REACCION 18



UTILIDADES Y COMBINACIONES

A. Utilidades

Los compuestos de la presente invención poseen actividad como potenciadores de actividad de la enzima glucocinasa, y, por lo tanto, puede usarse en el tratamiento de enfermedades asociadas con la actividad de glucocinasa.

En consecuencia, los compuestos de la presente invención pueden administrarse a mamíferos, preferiblemente humanos, para el tratamiento de una variedad de condiciones y trastornos, que incluyen, pero no se limitan a, tratar,

prevenir, o disminuir la progresión de diabetes y condiciones relacionadas, complicaciones microvasculares asociadas con diabetes, complicaciones macrovasculares asociadas con diabetes, enfermedades cardiovasculares, síndrome metabólico y sus condiciones de componente, y otros males. En consecuencia, se cree que los compuestos de la presente invención pueden usarse al prevenir, inhibir o tratar la diabetes, hiperglicemia, mejora de la tolerancia de glucosa, resistencia a la insulina, hiperinsulinemia, retinopatía, neuropatía, nefropatia, cicatrización de heridas desarrolladas, ateroesclerosis y sus secuelas, función cardiaca anormal, isquemia miocardial, apoplejía, síndrome metabólico, hipertensión, obesidad, dislipidemia, hiperlipidemia, hipertrigliceridemia, hipercolesterolemia, HDL bajo, LDL alto, isquemia no cardiaca, infección, cáncer, restinosis vascular, pancreatitis, enfermedad neurodegenerativa, trastornos de lípido, insuficiencia cognitiva y demencia, enfermedad del hueso, lipodistrofia asociada con la proteasa del VIH, y glaucoma.

Síndrome metabólico o "Síndrome X", se describe en el Ford, et al., J. Am. Med. Assoc. **2002**, 287, 356-359 y Arbeeny, et al., Curr. Med. Chem. - Imm.; Endoc. & Metab. Agents **2001**, 1, 1-24.

B. Combinaciones

La presente invención incluye dentro de su alcance

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composiciones farmacéuticas que comprenden, como un ingrediente activo, una cantidad terapéuticamente efectiva de al menos uno de los compuestos de la fórmula I, solo o en combinación con un portador o diluyente farmacéutico. Opcionalmente, los compuestos de la presente invención pueden usarse solos, en combinación con otros compuestos de la invención, o en combinación con uno o más agentes terapéuticos, por ejemplo, un agente antidiabético u otro material farmacéuticamente activo.

Los compuestos de la presente invención pueden emplearse en combinación con otros potenciadores de actividad de glucocinasa o uno o más de otros agents terapéuticos adecuados útiles en el tratamiento de los trastornos antes mencionados incluyendo: agentes anti-diabéticos, agentes anti-hiperglicémicos, agentes anti-hiperinsulinémicos, agentes anti-retinopáticos, agentes anti-neuropáticos, agentes anti-nefropáticos, agentes anti-ateroescleróticos, agentes anti-infecciosos, agentes anti-isquémicos, agentes anti-hipertensivos, agentes anti-obesidad, agentes anti-dislipidémico, agentes anti-hiperlipidémicos, agentes anti-hipertrigliceridémicos, agentes anti-hipercolesterolémicos, agentes anti-isquémicos, agentes anti-cáncer, agentes anti-citotóxicos, agentes anti-restenóticos, agentes anti-pancreáticos, agentes que disminuyen el lípido, supresores del apetito, agentes potenciadores de la memoria, y agentes

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cognitivos.

Los ejemplos de agentes anti-diabéticos adecuados para uso en combinación con los compuestos de la presente invención incluyen insulina y análogos de insulina: insulina LysPro, formulaciones inhaladas que comprenden insulina; péptidos tipo glucagon; sulfonilureas y análogos: clorpropamida, glibenclamida, tolbutamida, tolazamida, acetohexamida, glipizida, gliburida, glimepirida, repaglinida, meglitinida; biguanidas: metformina, fenformina, buformina; antagonistas alfa2 e imidazolinas: midaglizol, isaglidol, deriglidol, idazoxan, efaroxan, fluparoxan; otros secretagogos de insulina: linoglirida, insulinotropina, exendin-4, BTS-67582, A-4166; tiazolidindionas (agonistas PPARgamma): ciglitazona, pioglitazona, troglitazona, rosiglitazona; agonista PPAR-gamma de no tiazolidindiona; moduladores de PPARgamma selectivos (SPPARMs; por ejemplo metaglidasen de Metabolex); agonista PPAR-alfa; agonistas duales PPAR alfa/gamma; agonistas PPAR delta, agonistas PPAR alfa/gamma/delta pan; inhibidores SGLT2; inhibidores de dipeptidil peptidasa-IV (DPP4); inhibidores de aldosa reductasa; agonistas RXR: JTT-501, MX-6054, DRF2593, LG100268; inhibidores de oxidación de ácido graso: clomoxir, etomoxir; inhibidores de α-glucosidasa: precosa, acarbosa, miglitol, emiglitato, voglibosa, MDL-25,637, camiglibosa, MDL-73,945; agonistas beta: BRL 35135, BRL 37344, Ro 16-8714,

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ICI D7114, CL 316, 243, TAK-667, AZ40140; inhibidores de fosfodiesterasa, tanto tipo cAMP como cGMP: sildenafil, L686398: L-386,398; antagonistas de amilina: pramlintida, AC-137; inhibidores de lipoxigenasa: masoprocal; análogos de somatostatina: BM-23014, seglitida, octreotida; antagonistas de glucagon: BAY 276-9955; agonistas de señalización de insulina, miméticos de insulina, inhibidores de PTP1B: L-783281, TER17411, TER17529; inhibidores de gluconeogenesis: GP3034; análogos y antagonistas de somatoestatina; agentes anti-lipolíticos: ácido nicotínico, acipimox, WAG 994; agentes que estimulan el transporte de glucosa: BM-130795; inhibidores de glucosa sintasa cinasa: cloruro de litio, CT98014, CT98023; y agonistas del receptor de galanina.

Otras tiazolidindionas adecuadas incluyen MCC-555 de Mitsubishi (descrita en la Patente de EUA No. 5,594,016), farglitazar de Glaxo-Wellcome (GI-262570), englitazona (CP-68722, Pfizer), o darglitazona (CP-86325, Pfizer), isaglitazona (MIT/J&J), JTT-501 (JPNT/P&U), L-895645 (Merck), R-119702 (Sankyo/WL), NN-2344 o balaglitazona (Dr. Reddy/NN), o YM-440 (Yamanouchi).

Los agonistas duales PPAR alfa/gamma adecuados incluyen muraglitazar (Bristol-Myers Squibb), tesaglitazar (Astra/Zeneca), naveglitazar (Lilly/Ligand); AVE-0847 (Sanofi-Aventis); TAK-654 (Takeda), así como aquellos descritos por Murakami et al, "A Novel Insulin Sensitizer

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Acts As a Coligand for Peroxisome Proliferation - Activated Receptor Alpha (PPAR alpha) and PP AR gamma; Effect of PPAR alpha Activation on Abnormal Lipid Metabolism in Liver of Zucker Fatty Rats", Diabetes 47, 1841-1847 (1998), WO 01/21602 y US-6414002, la descripción de la cual se incorpora en la presente para referencia, empleando dosis como se establece en la presente, cuyos compuestos designados como preferidos son preferidos para uso en la presente. Los agonistas PPARdelta adecuados incluyen, por ejemplo, GW-501516 (Glaxo). Agonistas PPAR alfa/gamma/delta pan adecuados incluyen, por ejemplo, GW-677954 (Glaxo).

Los antagonistas alfa2 adecuados también incluyen aquellos descritos en WO 00/59506, empleandos dosis como se establece en la presente.

Los inhibidores SGLT2 adecuados incluyen T-1095, florizina, WAY-123783, y aquellos descritos en WO 01/27128.

Los inhibidores DPP4 adecuados incluyen saxagliptina (Bristol-Myers Squibb), vildagliptina (Novartis) y sitagliptina (Merck) así como aquellos descritos en WO99/38501, WO99/46272, WO99/67279 (PROBIODRUG), WO99/67278 (PROBIODRUG), WO99/61431 (PROBIODRUG), NVP-DPP728A (1-[[[2-[(5-cianopiridin-2-il)amino]etil]amino]acetil]-2-ciano-(S)-pirrolidina) (Novartis) como se describe por Hughes et al, Biochemistry, 38 (36), 11597-11603, 1999, TSL-225 (ácido triptofil-1,2,3,4-tetrahidroisoquinolin-3-carboxílico) como

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se describe por Yamada et al., Bioorg. & Med. Chem. Lett. 8 (1998) 1537-1540, 2-cianopirrolididas y 4-cianopirrolididas, como se describe por Ashworth et al., Bioorg. & Med. Chem. Lett., Vol. 6, No. 22, pp 1163-1166 y 2745-2748 (1996), empleando dosis como se establece en las referencias arriba.

Los inhibidores de aldosa reductasa adecuados incluyen aquellos descritos en WO 99/26659.

Las meglitinidas adecuadas incluyen nateglinida (Novartis) o KAD1229 (PF/Kissei).

Los ejemplos de péptido 1 tipo glucagón (GLP-1) incluye GLP-1 (1-36) amida, GLP-1 (7-36) amida, GLP-1 (7-37) (como se describe en la Patente de EUA No. 5,614,492 para Habener), así como AC2993 (Amylin), y LY-315902 (Lilly).

Otros agentes anti-diabéticos que pueden usarse en combinación con compuestos de la invención incluyen ergoset y D-quiroinositol.

Los agentes anti-isquémicos adecuados incluyen, pero no se limitan a, aquellos descritos en la Physicians Desk Reference e inhibidores NHE, incluyendo aquellos descritos en WO 99/43663.

Los ejemplos de agentes anti-infecciosos adecuados son agentes antibióticos, incluyen, pero no se limitan a, aquellos descritos en la Physicians Desk Reference.

Los ejemplos de agentes que disminuyen el lípido adecuados para uso en combinación con los compuestos de la

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presente invención incluyen uno o más inhibidores MTP, inhibidores de HMG CoA reductasa, inhibidores de escualeno sintetasa, derivados de ácido fíbrico, inhibidores ACAT, inhibidores de lipoxigenasa, inhibidores de la absorción de colesterol, inhibidores cotransportadores del ácido ileal Na^+/biliar, subreguladores de la actividad del receptor LDL, secuestrantes del ácido biliar, inhibidores de proteína de transferencia de éster de colesterol (por ejemplo, torcetrapib (Pfizer)), y/o ácido nicotínico y derivados de los mismos.

Inhibidores MTP los cuales pueden emplearse como se describe anteriormente incluyendo aquellos descritos en Patente de EUA No. 5,595,872, Patente de EUA No. 5,739,135, Patente de EUA No. 5,712,279, Patente de EUA No. 5,760,246, Patente de EU No. 5,827,875, Patente de EUA No. 5,885,983, y Patente de EUA No. 5,962,440.

Los inhibidores de HMG CoA reductasa los cuales pueden emplearse en combinación con uno o más compuestos de la fórmula I incluyen mevastatina y compuestos relacionados, como se describe en la Patente de EUA No. 3,983,140, lovastatina, (mevinolina) y compuestos relacionados, como se describe en la Patente de EUA No. 4,231,938, pravastatina, y compuestos relacionados, tales como descritos en la Patente de EUA No. 4,346,227, simvastatina, y compuestos relacionados, como se describe en la Patente de EUA Nos.

4,448,784 y 4,450,171. Otros inhibidores de HMG CoA reductasa los cuales pueden emplearse en la presente que incluyen, pero no se limitan a, fluvastatina, descrito en la Patente de EUA No. 5,354,772; cerivastatina, como se describe en la Patente de EUA Nos. 5,006,530 y 5,177,080; atorvastatina, como se describe en la Patente de EUA Nos. 4,681,893, 5,273,995, 5,385,929 y 5,686,104; atavastatina (Nissan/Sankyo nisvastatina (NK-104)), como se describe en la Patente de EUA No. 5,011,930; visastatina (Shionogi-Astra/Zeneca (ZD-4522)) como se describe en la Patente de EUA No. 5,260,440; y compuestos de estatina relacionados descritos en la Patente de EUA No. 5,753,675; análogos de pirazol de derivados de mevalonolactona, como se describe en la Patente de EUA No. 4,613,610; análogos de indeno de derivados de mevalonolactona, como se describe en la Solicitud de PCT WO 86/03488; 6-[2-(substituido-pirrol-1-il)alquil)piran-2-onas y derivados de los mismos, como se describe en la Patente de EUA No. 4,647,576; Searle SC-45355 (un derivado ácido pentandioico 3-substituido) dicloroacetato; análogos de imidazol de mevalonolactona, como se describe en la solicitud de PCT WO 86/07054; derivados de ácido 3-carboxi-2-hidroxi-propan-fosfónico, como se describe en la Patente Francesa No. 2,596,393; pirrol 2,3-disubstituido, derivados de furano y tiofeno, como se describe en la Solicitud de patente Europea No. 0221025; análogos de naftilo de mevalonolactona, como se

describe en la Patente de EUA No. 4,686,237; octahidronaftalenos, tales como se describen en la Patente de EUA No. 4,499,289; análogos ceto de mevinolina (lovastatina), como se describe en la Solicitud de Patente Europea No.0142146 A2; y derivados de quinolina y piridina, como se describe en la Patente de EUA Nos. 5,506,219 y 5,691,322.

Los agentes hipolipidémicos preferidos son pravastatina, lovastatina, simvastatina, atorvastatina, fluvastatina, cerivastatina, atavastatina, y ZD-4522.

Además, los compuestos de ácido fosfínico útiles en la inhibición de HMG CoA reductasa, tales como aquellos descritos en GB 2205837, son adecuados para uso en combinación con los compuestos de la presente invención.

Los inhibidores de escualeno sintetasa adecuados para uso en la presente incluyen, pero no se limitan a, α-fosfono-sulfonatos descritos en la Patente de EUA No. 5,712,396, aquellos descritos por Biller et al., J. Med. Chem., 1988, Vol. 31, No. 10, pp 1869-1871, incluyendo isoprenoide (fosfinil-metil)fosfonatos, así como otros inhibidores de escualeno sintetasa conocidos, por ejemplo, como se describe en la Patente de EUA No. 4,871,721 y 4,924,024 y en Biller, S.A., Neuenschwander, K., Ponpipom, M.M., and Poulter, CD., Current Pharmaceutical Design, 2, 1-40 (1996).

Además, otros inhibidores de escualeno sintetasa adecuados para uso en la presente incluyen los pirofosfatos

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de terpenoide descritos por P. Ortiz de Montellano et al., J. Med. Chem., 1977,20,243-249, el análogo de difosfato de famesilo A y análogos de prescualeno pirofosfato (PSQ-PP) como se describe por Corey and Volante, J. Am. Chem. Soc., 1976, 98:1291-1293, fosfinilfosfonatos reportados por McClard, R.W. et al., J.A.C.S., 1987, 109:5544 y ciclopropanos reportados por Capson, T.L., Ph.D. dissertation, Junio, 1987, Dept. Med. Chem. U of Utah, resumen, Tabla de contenidos, pp. 16, 17, 40-43, 48-51, resumen.

Los derivados de ácido fíbrico los cuales pueden emplearse en combinación con uno o más compuestos de la fórmula I incluye fenofibrato, gemfibrozil, clofibrato, bezafibrato, ciprofibrato, clinofibrato, y los similares, probucol, y compuestos relacionados, como se describe en la Patente de EUA No. 3,674,836, probucol y gemfibrozil son preferidos, secuestrantes de ácido biliar, tales como colestiramina, colestipol y DEAE-Sephadex (Secholex®, Policexide®), así como lipostabil (Rhone-Poulenc), Eisai E-5050 (un derivado de etanolamina substituido por N), imanixilo (HOE-402), tetrahidrolipestatina (THL), istigmastanilfosforilcolina (SPC, Roche), aminociclodextrina (Tanabe Seiyoku), Ajinomoto AJ-814 (derivado de azuleno), melinamida (Sumitomo), Sandoz 58-035, American Cyanamid CL-277,082 y CL-283,546 (derivados de urea disubstituido), ácido

nicotínico, acipimox, acifran, neomicina, ácido p-aminosalicílico, aspirina, derivados poli(dialilmetilamina), tales como se describen en la Patente de EUA No. 4,759,923, amina cuaternaria poli(cloruro de dialildimetilamonio) e ionenos, tales como se describen en la Patente de EUA No. 4,027,009, y otros agentes que disminuyen el suero de colesterol conocidos.

El inhibidor ACAT el cual puede emplearse en combinación con uno o más compuestos de la fórmula I incluyen aquellos descritos en Drugs of the Future 24, 9-15 (1999), (Avasimibe); "The ACAT inhibitor, C1-1011 is effective in the prevention and regression of aortic fatty streak area in hamsters", Nicolosi et al, Atherosclerosis (Shannon, Irel). (1998), 137(1), 77-85; "The pharmacological profile of FCE 27677: a novel ACAT inhibitor with potent hypolipidemic activity mediated by selective suppression of the hepatic secretion of ApoB 100-containing lipoprotein", Ghiselli, Giancarlo, Cardiovasc. Drug Rev. (1998), 16(1), 16-30; "RP 73163: a bioavailable alkylsulfinyl-diphenylimidazole ACAT inhibitor", Smith, C., et al, Bioorg. Med. Chem. Lett. (1996), 6(1), 47-50; "ACAT inhibitors: physiologic mechanisms for hypolipidemic and anti-atherosclerotic activities in experimental animals", Krause et al, Editor(s): Ruffolo, Robert R., Jr.; Hollinger, Mannfred A., Inflammation: Mediators Pathways (1995), 173-98, Publisher: CRC, Boca

Raton, Fla.; "ACAT inhibitors: potential anti-atherosclerotic agents", Sliskovic et al, Curr. Med. Chem. (1994), 1(3), 204-25; "Inhibitors of acyl-CoA:cholesterol O-acyl transferase (ACAT) as hypocholesterolemic agents. 6. The first agua-soluble ACAT inhibitor with lipid-regulating activity. Inhibitors of acyl-CoA:cholesterol acyltransferase (ACAT). 7. Development of a series of substituted N-phenyl-N'-[(1-phenylciclopentil)methyl]ureas with enhanced hypocholesterolemic activity", Stout et al, Chemtracts: Org. Chem. (1995), 8(6), 359-62, or TS-962 (Taisho Pharmaceutical Co. Ltd.).

El agente hipolipidémico puede ser un sobreregulador de la actividad del receptor LD2, tales como MD-700 (Taisho Pharmaceutical Co. Ltd) y LY295427 (Eli Lilly).

Los ejemplos de inhibidores de absorción de colesterol adecuados para uso en combinación con los compuestos de la invención incluyen SCH48461 (Schering-Plough), así como aquellos descritos en Atherosclerosis 115:45-63 (1995) and J. Med. Chem. 41:973 (1998).

Los ejemplos de inhibidores cotransportadores de ácido ileal Na^+/biliár adecuados para uso en combinación con los compuestos de la invención incluyen compuestos como se describen en Drugs of the Future, 24, 425-430 (1999).

Los inhibidores de lipoxigenasa los cuales pueden emplearse en combinación con uno o más compuestos de la

fórmula I inlcuyen inhibidores de 15-lipoxigenasa (15-LO), tales como derivados de benzimidazol, como se describen en WO 97/12615, inhibidores 15-LO, como se describen en WO 97/12613, isotiazolonas, como se describen en WO 96/38144, e inhibidores 15-LO, como se describen por Sendobry et al "Attenuation of diet-induced atherosclerosis in rabbits with a highly selective 15-lipoxygenase inhibitor lacking significant antioxidant properties", Brit. J. Pharmacology (1997) 120, 1199-1206, and Cornicelli et al, "15-Lipoxygenase and its Inhibition: A Novel Therapeutic Target for Vascular Disease", Current Phaceutical Design, 1999, 5, 11-20.

Los ejemplos de agentes anti-hipertensivos adecuados para uso en combinación con los compuestos de la presente invención incluyen bloqueadores beta adrenérgicos, bloqueadores del canal de calcio (tipo L y tipo T; por ejemplo diltiazem, verapamil, nifedipina, amlodipina y mibefradil), diuréticos (por ejemplo, clorotiazida, hidroclorotiazida, flumetiazida, hidroflumetiazida, bendroflumetiazida, metilclorotiazida, triclorometiazida, politiazida, benztiazida, tricrinafen de ácido etacrínico, clortalidona, furosemida, musolimina, bumetanida, triamtrenena, amilorida, espironolactona), inhibidores de renina, inhibidores de ACE (por ejemplo, captopril, zofenopril, fosinopril, enalapril, ceranopril, cilazopril, delapril, pentopril, quinapril, ramipril, lisinopril),

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antagonistas del receptor AT-1 (por ejemplo, losartan, irbesartan, valsartan), antagonistas del receptor ET (por ejemplo, sitaxsentan, atrsentan, y compuestos descritos en la Patente de EUA Nos. 5,612,359 y 6,043,265), antagonistas duales ET/AII (por ejemplo, compuestos descritos en WO 00/01389), inhibidores de endopeptidasa neutrales (NEP); inhibidores de vasopepsidasa (inhibidores duales NEP-ACE) (por ejemplo, omapatrilat y gemopatrilat), y nitratos.

Los ejemplos de agentes anti-obesidad adecuados para uso en combinación con los compuestos de la presente invención incluyen un antagonista 1 del receptor canabinoide o agonista inverso, un agonista adrenérgico a beta 3, un inhibidor de lipasa, un inhibidor de la reabsorción de serotonina (y dopamina), un fármaco beta del receptor de tiroide, y/o un agente anoréxico.

Agonistas inversos y antagonistas del receptor 1 cannabinoide los cuales pueden ser opcionalmente empleados en combinación con los compuestos de la presente invención incluye rimonabant, SLV 319, y aquellos descritos en D. L. Hertzog, Expert Opin. Ther. Patents 2004, 14, 1435-1452.

Los agonistas adrenérgicos de beta 3 los cuales pueden ser opcionalmente empleados en combinación con compuestos de la presente invención incluye AJ9677 (Takeda/Dainippon), L750355 (Merck), o CP331648 (Pfizer,) u otros agonistas de beta 3 conocidos, como se describen en la Patente de EUA Nos.

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5,541,204, 5,770,615, 5,491,134, 5,776,983, y 5,488,064, con AJ9677, L750,355, y CP331648 son preferidos.

Los ejemplos de inhibidores de lipasa los cuales pueden ser opcionalmente empleados en combinación con compuestos de la presente invención incluyen orlistat o ATL-962 (Alizyme), con orlistat son preferidos.

El inhibidor de reabsorción de serotonina (y dopoamina) el cual puede ser opcionalmente empleado en combinación con un compuesto de la fórmula I puede ser sibutramina, topiramato (Johnson & Johnson), o axokina (Regeneron), con sibutramina y topiramato son preferidos.

Los ejemplos de compuestos beta del receptor de tiroide los cuales pueden ser opcionalmente empleados en combinación con compuestos de la presente invención incluyen ligandos del receptor de tiroide, tales como aquellos descritos en WO97/21993 (U. Cal SF), WO99/00353 (KaroBio), y WO00/039077 (KaroBio), con compuestos de las solicitudes KaroBio son preferidos.

El agente anoréxico el cual puede ser opcionalmente empleado en combinación con compuestos de la presente invención incluyen dexamfetamina, fentermina, fenilpropanolamina, o mazindol, con dexamfetamina son preferidos.

Otros compuestos que pueden usarse en combinación con los compuestos de la presente invención incluyen agonistas

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del receptor CCK (por ejemplo, SR-27895B); antagonistas del receptor de galaniri; antagonistas MCR-4 (por ejemplo, HP-228); leptina o miméticos; inhibidores tipo 1 de deshidrogenasa 11-beta-hidroxiesteroide; miméticos de urocortina, antagonistas CRF, y proteínas que enlazan CRF (por ejemplo, RU-486, urocortina).

Además, los compuestos de la presente invención pueden usarse en combinación con agentes citotóxicos y anti-cáncer, que incluyen pero no se limitan a agentes alquilantes tales como mostazas de nitrógeno, sulfonatos de alquilo, nitrosoureas, etileniminas, y triazenos; antimetabolitos tales como antagonistas de folato, análogos de purina, y análogos de pirimidina; antibióticos tales como antraciclinas, bleomicinas, mitomicina, dactinomicina, y plicamicina; enzimas tales como L-asparaginasa; inhibidores de transferasa de proteína de famesilo; inhibidores de reductasa de 5α; inhibidores de tipo 3 de deshidrogenasa de esteroide 17β-hidroxi; agentes hormonales tales como glucocorticoides, estrógenos/antiestrógenos, andrógenos/antiandrógenos, progestinas, y antagonistas de hormona que liberan hormona luteinizada, acetato de octreotido; agentes disruptores de microtúbulos, tales como ecteinascidinas o sus análogos y derivados; agentes estabilizantes de microtúbulo tales como taxanos, por ejemplo, paclitaxel (Taxol®), docetaxel (Taxotere®), y sus

análogos, y epotilonas, tales como epotilonas A-F y sus análogos; productos derivados de planta, tales como alcaloides vinca, epipodofilotoxinas, taxanos; e inhibidores de topiosomerasa; inhibidores de transferasa de proteína prenilo; y agentes misceláneos tales como hidroxiurea, procarbazina, mitotano, hexametilmelamina, complejos de coordinación de platino tales como cisplatina y carboplatina; y otros agentes usados como agentes anti-cáncer y citotóxicos tales como modificadores de respuesta biológica, factores de crecimiento; moduladores inmunes; y anticuerpos monoclonales. Los agentes anti-cáncer adicionales se describen en EP 1177791. Los compuestos de la invención también pueden usarse en conjunto con terapia de radiación.

Los ejemplos de agentes potenciadores de la memoria adecuados, agentes anti-demencia, o agentes cognitivos para uso en combinación con los compuestos de la presente invención incluyen, pero no se limitan a, donepezil, rivastigmina, galantamina, memantina, tacrina, metrifonato, muscarino, xanomelina, deprenilo, y fisostigmina.

Las patentes antes mencionadas y solicitudes de patentes se incorporan en la presente para referencia.

Los otros agentes terapéuticos anteriores, cuando se emplean en combinación con los compuestos de la presente invención pueden usarse, por ejemplo, en aquellas cantidades indicadas en la Physician's Desk Reference, como en las

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patentes establecidas arriba, o como se determine de otra manera por alguien de experiencia ordinaria en la técnica.

Los compuestos de la fórmula I pueden administrarse para cualesquiera de los usos descritos en la presente por cualquier medio adecuado, por ejemplo, oralmente, tales como en forma de tabletas, cápsulas, granulos, o polvos; sublingualmente; bucalmente; parenteralmente, tales como por inyección subcutánea, intravenosa, intramuscular, o intrasternal, o técnicas de infusión (por ejemplo, como soluciones o suspensiones acuosas o no acuosos inyectables estériles); nasalmente, incluyendo administración a las membranas nasales, tales como por inhalación de rocío; topicamente, tales como en la forma de una crema o ungüento; o rectalmente tales como en la forma de supositorios; en formulaciones de dosis unitaria que contienen vehículos o diluyentes farmacéuticamente aceptables no tóxicos.

Al llevar a cabo el método de la invención para tratar diabetes y enfermedades relacionadas, una composición farmacéutica se empleará que contienen los compuestos de la fórmula I, con o sin otros agentes antidiabéticos y/o agentes antihiperlipidémicos y/u otro tipo de agentes terapéuticos en asociación con un vehículo o diluyen farmacéutico. La composición farmacéutica puede formularse empleando vehículos o diluyentes sólidos o líquidos convencionales y aditivos farmacéuticos de un tipo apropiado al modo de administración

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deseada, tales como portadores, excipientes, aglutinantes farmacéuticamente aceptables y los similares. Los compuestos pueden administrarse a un paciente mamífero, incluyendo humanos, changos, perros, etc., por una ruta oral, por ejemplo, en la forma de tabletas, cápsulas, perlas, gránulos, o polvos. La dosis para adultos es entre 0.25 y 2,000 mg por día, preferiblemente entre 1 y 500 mg, la cual puede administrarse en una dosis sencilla o en la forma de dosis inviduales de 1-4 veces por día.

Una cápsula típica para administración oral contiene compuestos de la estructura I (250 mg), lactosa (75 mg), y estearato de magnesio (15 mg). La mezcla se pasa a través de un tamiz de malla 60 y se empaca en una cápsula de gelatina No.1.

Una preparación inyectable típica se produce por colocación asépticamente 250 mg de compuestos de la estructura I en un vial, secado asépticamente por congelación y sellado. Para uso, los contenidos del vial se mezclan con 2 mL de solución salina fisiológica, para producir una preparación inyectable.

ABREVIATURAS

Las siguientes abreviaturas se emplean en los ejemplos y se adjuntan en la presente:

Ph = fenilo

Bn = bencilo

t-Bu = butilo terciario

i-Bu = iso-butilo

Me = metilo

Et = etilo

Pr = propilo

iPr = isopropilo

Bu = butilo

AIBN = 2,2'-Azobisisobutironitrilo

TMS = trimetilsilil

$TMSCHN_2$ = (trimetilsilil)diazometano

$TMSN_3$ = trimetilsilil azida

TBS = tert-butildimetilsililo

FMOC = fluorenilmetoxicarbonilo

Boc o BOC = tert-butoxicarbonilo

Cbz = carbobenciloxi o carbobenzoxi o benciloxicarbonilo

THF = tetrahidrofurano

Et_2O = éter de dietilo

hex = hexanos

EtOAc = acetato de etilo

DMF = N,N-dimetilformamida

MeOH = metanol

EtOH = etanol

DCM = diclorometano

i-PrOH = isopropanol

DMSO = dimetilsulfóxido

DME = 1,2-dimetoxietano

DMA = N,N-dimetilacetilamida

DCE = 1,2-dicloroetano

HMPA = triamida de hexametil fosfórico

HOAc o AcOH = ácido acético

TFA = ácido trifluoroacético

DIEA o DIPEA o i-Pr_2Net o Base Huning = diisopropiletilamina

TEA o Et_3N = trietilamina

NMM = N-metil morfolina

NBS = N-Bromosuccinimida

NCS = N-clorosuccinimida

DMAP = 4-dimetilaminopiridina

DEPBT = 3-(dietoxifosforiloxi)-1,2,3-benzotriazin-4[3H]-ona

mCPBA = ácido 3-cloroperoxibenzoico

$NaBH_4$ = borohidruro de sodio

$NaBH(OAc)_3$ = triacetoxiborohidruro de sodio

NaN_3 = azida de sodio

DIBALH = hidruro de diisobutil aluminio

$LiAlH_4$ = hidruro de litio aluminio

n-BuLi = n-butillitio

Oxone® = Monopersulfato

Pd/C = paladio en carbono

$PXPd_2$ = dímero de dicloro(clorodi-tert-

butilfosfoina)paladio (II) o $[PdCl_2(t\text{-}Bu)_2PCl]_2$.

PtO_2 = óxido de platino

KOH = hidróxido de potasio

NaOH = hidróxido de sodio

LiOH = hidróxido de litio

$LiOH.H_2O$ = monohidrato de hidróxido de litio

HCl = ácido clorhídrico

H_2SO_4 = ácido sulfúrico

H_2O_2 = peróxido de hidrógeno

Al_2O_3 = óxido de aluminio

K_2CO_3 = carbonato de potasio

Cs_2CO_3 = carbonato de cesio

$NaHCO_3$ = bicarbonato de sodio

$ZnBr_2$ = bromuro de zinc

$MgSO_4$ = sulfato de magnesio

Na_2SO_4 = sulfato de sodio

KSCN = tiocianato de potasio

NH_4Cl = cloruro de amonio

DBU = 1,8-diazabiciclo[5.4.0]undec-7-eno

EDC (o EDC.HCl) o EDCl (o EDCl.HCl) o EDAC = clorohidrato de 3-etil-3'-(dimetilamino)propil-carbodiimida (o clorohidrato de 1-(3-dimetilaminopropil)-3-etilcarbodiimida)

HOBT o $HOBT.H_2O$ = hidrato 1-hidroxibenzotriazol

HOAT = 1-hidroxi-7-azabenzotriazol

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Reactivo PyBOP o reactivo BOP = benzotriazol-1-iloxi-tris (dimetilamino)fosfonio hexafluorofosfato

$NaN(TMS)_2$ = hexametildisilazida de sodio o bis(trimetilsilil)amida de sodio

Ph_3P = trifenilfosfina

$Pd(OAc)_2$ = acetato de paladio

$(Ph_3P)_4Pd^\circ$ = tetraquis trifenilfosfina paladio

$Pd_2(dba)_3$ = tris(dibencilacetona)paladio

DPPF = 1,1'-bis(difenilfosfino)ferroceno

HATU = hexafluorofosfato 2-(7-aza-1H-benzotriazol-1-il)-1,1,3,3-tetrametiluronio, hexafluorofosfato 2-(3H-[1,2,3]triazolo[4,5-b]piridin-3-il)-1,1,3,3-tetrametilisouronio (V)

DEAD = azodicarboxilato de dietilo

DIAD = azodicarboxilato de diisopropilo

Cbz-Cl = cloroformiato de bencilo

CAN = nitrato de amonio cerico

SAX = Intercambiador de anión grande

SCX = Intercambiador de catión grande

H_2 = hidrógeno

Ar = argón

N_2 = nitrógeno

equiv = equivalente(s)

min = minuto(s)

h o hr = hora(s)

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L = litro

mL = mililitro

μL = microlitro

g = gramo(s)

mg = miligramo(s)

mol = mole(s)

mmol = milimole(s)

meq = miliequivalente

TA o T.A. = temperatura ambiente

sat o sat'd = saturado

ac. = acuoso

CCD = cromatografía de capa delgada

HPLC = cromatografía líquida de alta resolución

HPLC Tr = tiempo de retención HPLC

CL/EM = cromatografía líquida de alta resolución/espectrometría de masa

EM o Esp Mas = Espectrometría de masa

RMN = resonancia magnética nuclear

Datos de espectro RMN: s = singlete; d = doblete; m = multiplete; br = amplio; t = triplete

pf = punto de fusión

EJEMPLOS

Los siguientes ejemplos de trabajo sirven para ilustrar mejor, pero no limitan, algunas de las modalidades preferidas de la presente invención.

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GENERAL

El término HPLC se refiere a una cromatografía líquida de alta resolución Shimadzu con uno de los siguientes métodos:

Método A: Columna YMC o Phenomenex C18 5 micron 4.6 X 50mm usando un gradiente de 4 minutos de 0-100% solvente B [MeOH 90%: H_2O 10%: H_3PO_4 0.2%] y 100-0% solvente A [MeOH 10%: H_2O 90%: H_3PO_4 0.2%] con 4 mL/min relación de flujo y una espera de 1 min., un detector (uv) ultra violeta colocado a 220 nm.

Método B: Columna Phenomenex S5 ODS 4.6 x 30 mm, elución de gradiente 0-100% B/A durante 2 min (solvente A = MeOH 10%/H_2O que contiene TFA 0.1%, solvente B = MeOH 90%/H_2O que contiene TFA 0.1%), relación de flujo 5 mL/min, detección UV a 220 nm.

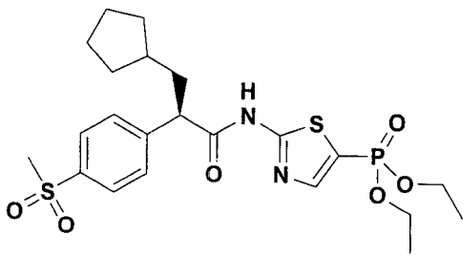
Método C: Columna YMC S7 ODS 3.0 x 50 mm, elución de gradiente 0-100% B/A durante 2 min (solvente A = MeOH 10%/H_2O que contiene TFA 0.1%, solvente B = MeOH 90%/H_2O que contiene TFA 0.1%), relación de flujo 5 mL/min, detección UV a 220 nm.

El término HPLC prep se refiere a un sistema HPLC Shimadzu automático usando una mezcla de solvente A (MeOH 10%/H_2O 90%/TFA 0.2%) y solvente B (MeOH 90%/H_2O 10%/TFA 0.2%). Las columnas preparativas se empacan con resina YMC o Phenomenex ODS C18 5 micron o equivalente.

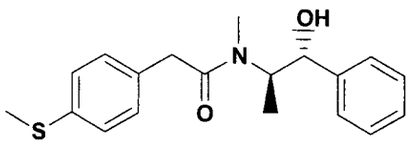
Los siguientes Ejemplos se ilustran de compuestos

preferidos de la invención.

EJEMPLO 1



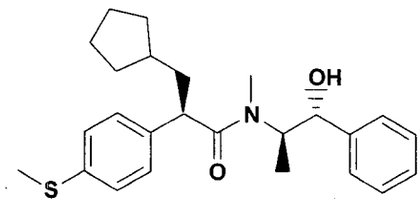
A.



Cloruro de trimetilacetilo (3.83 mL; 31.1 mmol) se agregó gota a gota a una mezcla -10°C de ácido 4-metiltio-fenilacético (5.40 g; 29.6 mmol) y K_2CO_3 (12.3 g; 88.8 mmol) en acetona (40 mL), mientras se mantiene la temperatura a <-10°C. Después de 10 minutos a -10°C, la reacción se calentó a 0°C. Después de 10 minutos a 0°C, la reacción se enfrió a -10°C. (1R,2R)-(-)-pseudoefredina (7.34 g; 44.4 mmol) se agregó. Después de 10 minutos a -10°C, la mezcla de reacción se permitió calentar a temperatura ambiente. Después de 4 h, la reacción se dividió entre EtOAc (60 mL) y H_2O (30 mL). La fase acuosa se extrajo con EtOAc (30 mL). Todas las fases orgánicas se combinaron, se lavaron con salmuera (30 mL), se secaron ($MgSO_4$) y se concentraron in vacuo. El producto crudo se recristalizó a partir de EtOAc caliente/hexanos para

proporcionar la parte A del compuesto (7.3 g; 75%) como un sólido cristalino.

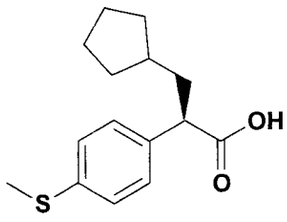
B.



Una solución de la parte A del compuesto (7.0 g; 21.27 mmol) en THF (51 mL) se agregó durante 45 minutos a -70°C de una solución de $LiN(TMS)_2$ (44.7 mL de una solución 1.0 M en THF; 44.7 mmol) mientras se mantiene la temperatura interna debajo de -65°C. Después de la adición la mezcla de reacción se agitó a -70°C durante 15 minutos y luego se permitió calentar a 0°C. Después de 20 min a 0°C la reacción se reenfrió a -70°C. Una solución de yoduro de ciclopentilmetilo (6.70 g; 31.91 mmol) en DMPU (5.4 mL; 44.68 mmol) se agregó. La reacción se agitó a -70°C durante 30 minutos y luego se permitió calentar a temperatura ambiente. Después de 20 h la mezcla de reacción se apagó por la adición de NH_4Cl acuoso saturado (20 mL). La solución se extrajo con EtOAc (175 mL). La fase orgánica se aisló, se lavó NH_4Cl saturado (50 mL) y salmuera (50 mL), se secó ($MgSO_4$) y se concentró. El producto crudo se purificó por cromatografía instantánea (SiO_2; gradiente continuo de 0 hasta 90% solvente B durante 75 minutos, en donde el solvente A = hexanos y solvente B =

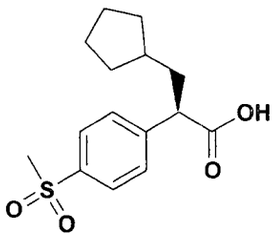
EtOAc) para dar la parte B del compuesto (6.94 g; 79%).

C.



Una solución de la parte B del compuesto (5.44 g; 13.22 mmol) en 1,4 dioxano (24 mL) se trató con H_2SO_4 acuoso 9N (15 mL). La mezcla de reacción luego se calentó a 105°C. Después de 20 h el calentamiento se detuvo y la solución se enfrió a temperatura ambiente. H_2O (100 mL) se agregó al producto precipitado. El sólido se aisló por filtración y se secó in vacuo para dar la parte C del compuesto (3.40 g; 97%).

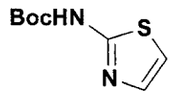
D.



Oxona (17.64 g; 28.70 mmol) se agregó a una mezcla de la parte C del compuesto (3.30 g; 12.48 mmol) en 2-propanol (90 mL) y H_2O (45 mL). Después de 20 h a temperatura ambiente el 2-propanol se removió in vacuo. La solución acuosa se extrajo con EtOAc (175 mL). La fase orgánica se lavó con H_2O (50 mL) y salmuera (50 mL), se secó ($MgSO_4$) y se concentró in vacuo para dar la parte D del compuesto (3.60 g; 97%) como un

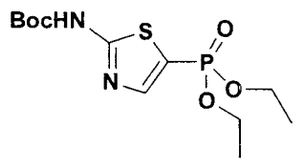
sólido blanco. (La parte D del compuesto se preparó por una modificación ligera del procedimiento encontrado en la patente WO 02/46173).

E.



Bicarbonato de di-tert-butilo (2.40 g; 11.00 mmol) se agregó a una solución de 2-aminotiazol (1.00 g; 9.99 mmol) en THF (5 mL). TEA (1.67 mL; 11.98 mmol) se agregó seguido por una cantidad catalítica de 4-DMAP (2.0 mg). Después de 4 h la mezcla de reacción se concentró in vacuo. El residuo se dividió entre EtOAc (20 mL) y HCl acuoso 0.1N (15 mL). La fase orgánica se lavó salmuera (15 mL), se secó ($MgSO_4$) y se concentró in vacuo. El producto crudo se procesó por cromatografía (SiO_2; gradiente continuo de 0 hasta 100% solvente B durante 25 min; espera a 100% solvente B durante 5 min, en donde el solvente A = hexanos y solvente B = EtOAc) para dar la parte E del compuesto (0.77 g; 39%) como un sólido blanco.

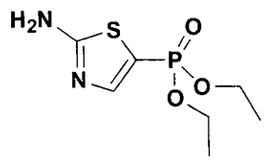
F.



A -78°C una solución de LDA (1.44 mL de una solución 2.0 M en THF/heptano/etilbenceno; 2.88 mmol) se pasó por una

cánula a -78°C una solución de la parte A del compuesto (0.25 g; 1.25 mmol) en THF (4 mL). Después de 30 minutos una solución de $ClPO_3Et_2$ (270 µL; 1.87 mmol) en THF (0.5 mL) se agregó lentamente. La mezcla de reacción se permitió calentar lentamente a temperatura ambiente durante la noche. Después de 16 h la reacción se apagó por la adición de H_2O (0.5 mL). La solución se dividió entre EtOAc (5 mL) y salmuera (5 mL). La fase orgánica se secó ($MgSO_4$) y se concentró in vacuo. El producto crudo se procesó por cromatografía (SiO_2; gradiente continuo de 0 hasta 100% solvente B durante 10 min, espera a 100% solvente B durante 10 min, en donde el solvente A = hexanos y solvente B = EtOAc) para dar la parte F del compuesto (0.12 g; 29%).

G.

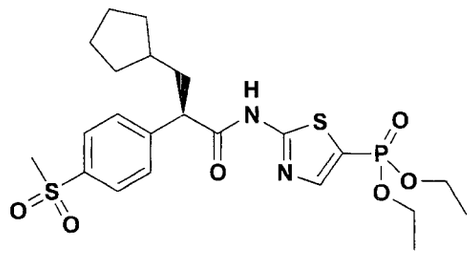


TFA (0.40 mL) se agregó a 0°C a una solución de la parte B del compuesto (0.12 g; 0.37 mmol) en DCM (0.80 mL). Después de que la adición se completó la mezcla de reacción se permitió calentar a temperatura ambiente y se agitó a temperatura ambiente durante 4 h. Los volátiles se removieron in vacuo, y el residuo se disolvió en EtOAc (3 mL). La solución EtOAc se lavó con $NaHCO_3$ acuoso saturado (3 mL). La capa acuosa se extrajo con EtOAc (2 mL). Los extractos

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orgánicos combinados se secaron ($MgSO_4$) y se concentraron in vacuo para dar la parte G del compuesto (83.0 mg; 96%).

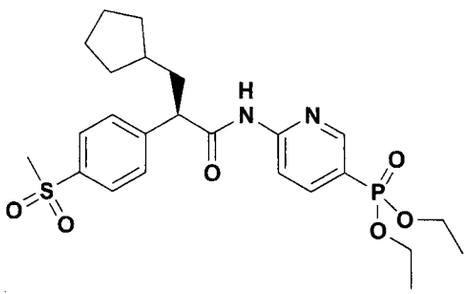
H.



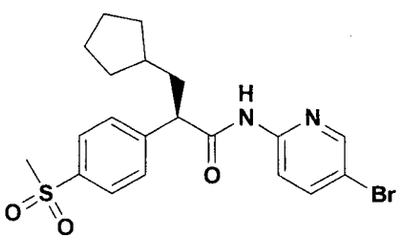
DEPBT (47.8 mg; 0.16 mmol) se agregó a una solución de la parte D del compuesto (23.7 mg; 0.08 mmol) y la parte G del compuesto (20.8 mg; 0.09 mmol) en THF (0.40 mL). DIPEA (27.0 uL; 0.16 mmol) se agregó. Después de 24 h a temperatura ambiente la mezcla de reacción se concentró in vacuo. El residuo se disolvió en EtOAc (3 mL). La capa EtOAc se lavó HCl acuoso 1N (2 mL), H_2O (2 mL), $NaHCO_3$ acuoso saturado (2 x 2 mL) y salmuera (2 mL), se secó ($MgSO_4$) y se concentró in vacuo. El producto crudo se disolvió en DCM (3 mL). La solución se agitó con resina de poliestierno aminometilada (40 mg; para remover el éster activado sin reacción) durante 20 minutos y luego se filtró. El filtrado se concentró in vacuo. El residuo se purificó por HPLC preparativa (columna YMC de fase inversa ODS-A-5u 30 x 100 mm; relación de flujo = 40 mL/min, 10 hasta 100% solvente B durante 12 min, mantenido a 16 min, en donde el solvente A = 90:10:0.1 H_2O:MeOH:TFA y solvente B = 90:10:0.1 MeOH:H_2O:TFA) para dar el compuesto

del título (15 mg; 37%) como un sólido incoloro. $[M + H]^+$ = 515.2 ^1H RMN (400 MHz, CD_3OD): δ 1.19 (m, 2H), 1.33 (m, 6H), (1.50 (m, 2H), 1.64 (m, 3H), 1.80 (m, 2H), 1.89 (m, 1H), 2.23 (m, 1H), 3.10 (s, 3H), 4.00 (t, 1H), 4.12 (m, 4H), 7.69 (d, 2H), 7.89 (d, J = 4.8 Hz, 1H), 7.93 (d, 2H).

EJEMPLO 2



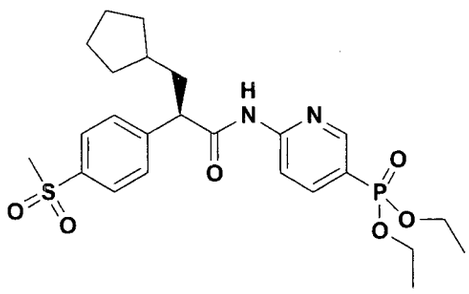
A.



Cloruro de oxalilo (2.0 M en DCM) (0.68 mL; 1.35 mmol) se agregó a una mezcla del ejemplo 1 parte D del compuesto (200 mg; 0.68 mmol) en DCM (1 mL). DMF (5 µL) se agregó. La evolución del gas se presentó. Después de 2 h a temperatura ambiente la mezcla de reacción se concentró in vacuo. El residuo se despojó del $CHCl_3$ (2 X 2 mL), luego se disolvió en DCM (2.5 mL). La solución se enfrió a 0°C y 2-amino-5-bromopiridina (175 mg; 1.01 mmol) se agregó seguido por

piridina (82 uL; 1.01 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 16 h, luego se concentró in vacuo. El residuo se dividió entre EtOAc (5 mL) y HCl acuoso 0.1N (4 mL). La fase orgánica se lavó salmuera (4 mL), se secó ($MgSO_4$), y se concentró in vacuo. El producto crudo se procesó por cromatografía (SiO_2; gradiente continuo desde 0 hasta 80% solvente B durante 18 min, en donde el solvente A = hexanos y solvente B = EtOAc) para dar la parte A del compuesto (250 mg; 82%).

B.

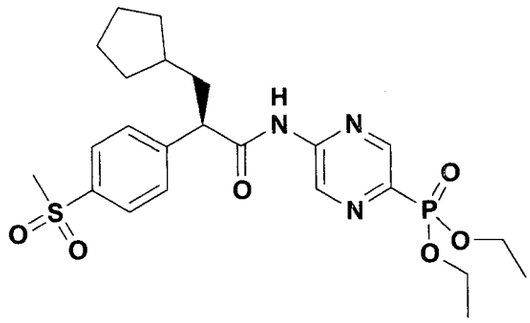


THF (desgasificado) (0.50 mL) se agregó a la parte A del compuesto (28.9 mg; 0.064 mmol) y $(Ph_3P)_4Pd^\circ$ (14.8 mg; 0.013 mmol). $H(O)P(OEt)_2$ (10.3 µL; 0.079 mmol) se agregó seguido por TEA (13.7 µL; 0.098 mmol). El recipiente se tapó y la mezcla de reacción se calentó a 75°C durante 9 h, luego se enfrió a temperatura ambiente y se concentró in vacuo. El producto crudo se purificó por HPLC preparativa (columna YMC de fase inversa ODS-A-5u 30 x 100 mm; relación de flujo = 40 mL/min, 20 hasta 100% solvente B durante 12 min, espera a 100% solvente B durante 17 min, en donde el solvente A = 90:10:0.1 H_2O:MeOH:TFA y el solvente B = 90:10:0.1 MeOH:H_2O:TFA) para dar el compuesto del título

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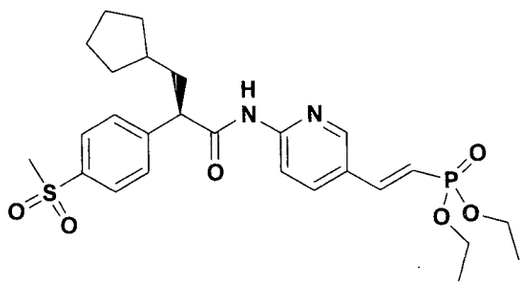
(18 mg; 55%) como un sólido amorfo. $[M + H]^+$ = 509.2 ^1H RMN (400 MHz, CD_3OD): δ 1.19 (m, 2H), 1.32 (t, 6H), 1.51 (m, 2H), 1.64 (m, 3H), 1.84 (m, 3H), 2.22 (m, 1H), 3.09 (s, 3H), 4.02 (t, 1H), 4.12 (m, 4H), 7.70 (d, 2H), 7.92 (d, 2H), 8.08 (ddd, 1H), 8.26 (dd, 1H), 8.60 (dd, 1H).

EJEMPLO 3



El compuesto del título (14.3 mg; 44%; sólido amorfo amarillo) se sintetizó de 5-bromo-2-pirazinamina empleando el procedimiento descrito en el Ejemplo 2. $[M + H]^+$ = 510.2 ^1H RMN (400 MHz, CD_3OD): δ 1.19 (m, 2H), 1.33 (t, 6H), 1.51 (m, 2H), 1.64 (m, 3H), 1.84 (m, 3H), 2.22 (m, 1H), 3.09 (s, 3H), 4.03 (t, 1H), 4.21 (m, 4H), 7.71 (d, 2H), 7.92 (d, 2H), 8.71 (s, 1H), 9.59 (s, 1H).

EJEMPLO 4

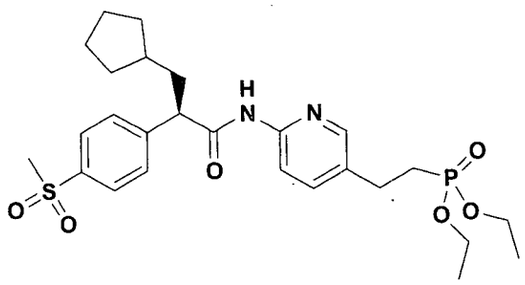


CH_3CN (150 µL) se agregó a una mezcla del ejemplo 2 de

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la parte A del compuesto (30 mg; 0.066 mmol), $Pd(OAc)_2$ (0.30 mg; 0.0013 mmol) y tri-o-tolilfosfina (0.80 mg; 0.0026 mmol). Vinilfosfato de dietilo (10.7 uL; 0.083 mmol) se agregó seguido por TEA (27.7 uL; 0.199 mmol). La mezcla de reacción se calentó a 95°C durante 4 h, luego se enfrió a temperatura ambiente. La solución se dividió entre EtOAc (3 mL) y salmuera (2 mL). La fase orgánica se secó ($MgSO_4$) y se concentró in vacuo. El residuo se procesó por cromatografía (SiO_2; gradiente continuo de 0 hasta 100% solvente B durante 12 min, espera a 100% durante 8 min, en donde el solvente A = hexanos y el solvente B = EtOAc) para dar el compuesto del título (24 mg; 68%) como un sólido amorfo. $[M + H]^+$ = 535.3 ^1H RMN (400 MHz, $CDCl_3$): δ 1.15 (m, 2H), 1.36 (t, 6H), 1.48 (m, 2H), 1.61 (m, 3H), 1.74 (m, 2H), 1.92 (m, 1H), 2.23 (m, 1H), 3.05 (s, 3H), 3.68 (t, 1H), 4.14 (m, 4H), 6.25 (t,1H), 7.42 (d, J = 22.4 Hz, 2H), 7.59 (d, 2H), 7.85 (dd, 1H), 7.92 (d, 2H), 8.23 (s, 1H), 8.24 (d, 2H), 8.31 (d, 1H).

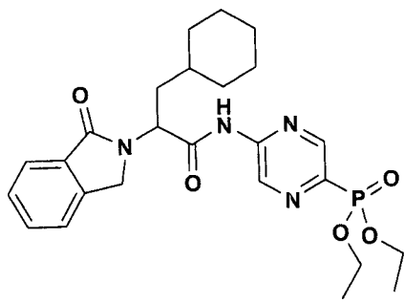
EJEMPLO 5



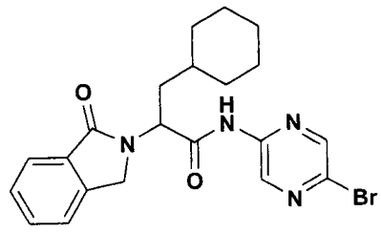
Pd/C al 10% (5 mg) se agregó a una solución del compuesto del ejemplo 4 (20 mg; 0.037 mmol) en MeOH (0.30

mL). Una atmósfera H_2 se introdujo por medio de un globo. Después de 8 h la mezcla de reacción se filtró. El catalizador se enjuagó con MeOH (1.5 mL) y los filtrados combinados se concentraron in vacuo. El producto crudo se procesó por cromatografía (SiO_2; gradiente continuo de 0 hasta 100% solvente B durante 6 min, espera a 100% solvente B durante 15 min, en donde el solvente A = hexanos y el solvente B = EtOAc) para dar el compuesto del título (14.5 mg; 73%) como un sólido incoloro. $[M + H]^+$ = 537.2 ^1H RMN (400 MHz, $CDCl_3$): δ 1.13 (m, 2H), 1.31 (t, 6H), 1.47 (m, 2H), 1.61 (m, 2H), 1.74 (m, 3H), 1.90 (m, 1H), 2.00 (m, 2H), 2.21 (m, 1H), 2.87 (m, 2H), 3.05 (s, 3H), 3.65 (t, 1H), 4.10 (m, 4H), 7.56 (dd, 1H), 7.58 (d, 2H), 7.90 (d, 2H), 8.08 (d, 1H), 8.13 (d, 1H), 8.20 (s, 1H).

EJEMPLO 6



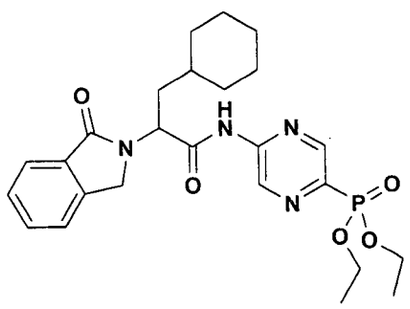
A.



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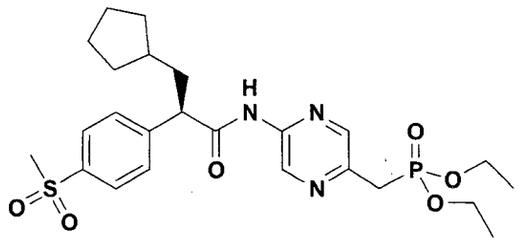
A 0°C una solución del ácido (S)-3-Ciclohexil-2-(1-oxo-1,3-dihidroisoindol-2-il)-propiónico (144 mg, 0.5 mmol, preparada como se describe en WO 2002/048106) y cloruro de oxalilo (0.38 mL de una solución 2M en DCM; 0.75 mmol) en DCM (1 mL) bajo Ar se agregó DMF (1 gota). Después de 30 minutos, la reacción se permitió calentar a temperatura ambiente y se agitó a temperatura ambiente durante 4 h. Los volátiles se removieron in vacuo; el cloruro ácido crudo se redisolvió en DCM (3 mL). La 5-Bromo-2-aminopirazina (130 mg, 0.75 mmol) y piridina (0.061 mL, 0.75 mmol) se agregaron a la solución de cloruro ácido fría en un baño de hielo bajo Ar. La mezcla de reacción se permitió calentar a temperatura ambiente durante la noche, luego se diluyó con DCM (6 mL) y se enjuagó con HCl acuoso 0.5 N (1 mL, 2x), agua (1 mL), $NaHCO_3$ acuoso saturado (1 mL), salmuera (1 mL), luego se secó ($MgSO_4$) y se concentró in vacuo. El residuo se procesó por cromatografía (40 g SiO_2, 0-50% gradiente de EtOAc-hexano) da 188 mg (84%) de la parte A del compuesto racémico.

B.



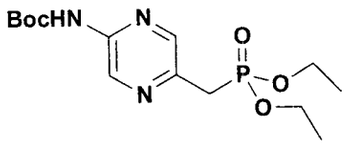
THF (desgasificado) (0.40 mL) se agregó a un matraz de reacción que contiene la parte A del compuesto (25.0 mg; 0.056 mmol) y $(Ph_3P)_4Pd(O)$ (12.9 mg; 0.011 mmol). Fosfito de dietilo (8.72 uL; 0.068 mmol) se agregó seguido por TEA (10.9 uL; 0.078 mmol). El recipiente de reacción se tapó y la mezcla de reacción se calentó a 85°C durante 6 h, luego se enfrió a temperatura ambiente y se concentró in vacuo. El residuo se dividió entre EtOAc (2 mL) y salmuera (1.5 mL). La fase orgánica se aisló, se secó ($MgSO_4$), se concentró in vacuo. El producto crudo se purificó por HPLC preparativa (columna YMC de fase inversa ODS-A-5u 30 x 100 mm; relación de flujo = 40 mL/min., 45 hasta 100% solvente B durante 12 min, mantenido a 16 min, en donde el solvente A = 90:10:0.1 H_2O:MeOH:TFA y el solvente B = 90:10:0.1 MeOH:H_2O:TFA) para dar el compuesto del título (8 mg; 29%; sólido incoloro) como una mezcla racémica. $[M + H]^+$ = 501.3; ^1H RMN (400 MHz, $CDCl_3$): δ 1.00 (m, 2H), 1.20 (m, 4H), 1.35 (m, 6H), 1.65 (m, 3H), 1.85 (m, 3H), 2.05 (m, 1H), 4.22 (m, 4H), 4.54 (q, 2H), 5.23 (t, 1H), 7.50 (m, 3H), 7.60 (dd, 1H), 7.92 (d, 1H), 8.75 (s, 1H), 9.52 (s, 1H), 9.62 (s, 1H).

EJEMPLO 7



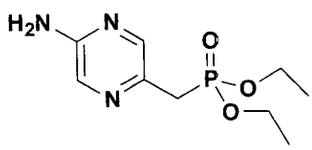
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A.



$(EtO)_3P$ (0.60 mL; 3.47 mmol) se agregó a un matraz de reacción que contiene una solución de 5-(bromometil)pirazin-2-ilcarbamato de tert-butilo (Bioorg. Med. Chem. Lett., 2002, 12, 1203-1208) (125 mg; 0.434 mmol) en THF (1.0 mL). El recipiente de reacción se tapó y la mezcla de reacción se calentó a 80°C durante 16 h, luego se enfrió a temperatura ambiente y se concentró in vacuo. El producto crudo se procesó por cromatografía (SiO_2; gradiente continuo de 0 hasta 100% solvente B durante 8 min, espera a 100% solvente B durante 8 min, en donde el solvente A = hexanos y el solvente B = EtOAc) para dar la parte A del compuesto (145 mg; 96%).

B.

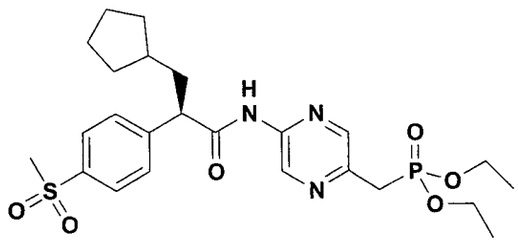


TFA (0.30 mL) se agregó una solución fría (0°C) de la parte A del compuesto (144 mg; 0.417 mmol) en DCM (1.2 mL). La mezcla de reacción luego se agitó a temperatura ambiente durante 16 h, luego se concentró in vacuo. El residuo se dividió entre EtOAc (4 mL) y $NaHCO_3$ acuoso saturado (3 mL). La fase orgánica se aisló, se lavó salmuera (3 mL), se secó

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($MgSO_4$), y se concentró in vacuo para dar la parte B del compuesto (51 mg; 50%).

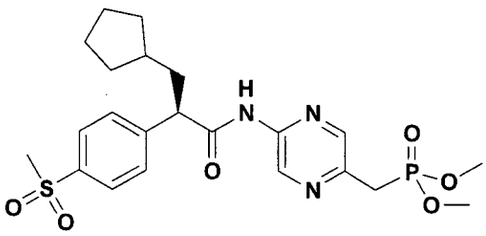
C.



Cloruro de oxalilo (0.84 uL de una solución 2.0 M en DCM; 0.168 mmol) se agregó a una mezcla del ejemplo 1 de la parte D del compuesto (25 mg; 0.084 mmol) en DCM (0.15 mL). DMF (5 μL) se agregó. La evolución del gas se presentó. Después de 1.5 h a temperatura ambiente la mezcla de reacción se concentró in vacuo. El residuo se despojó del $CHCl_3$ (2 X 0.8 mL). El cloruro ácido crudo luego se disolvió en DCM (0.25 mL). La parte B del compuesto (24.8 mg; 0.101 mmol) se agregó seguido por piridina (10.2 uL; 0.126 mmol). Después de agitarse durante 16 h a temperatura ambiente la reacción se concentró in vacuo. El residuo se dividió entre EtOAc (4 mL) y salmuera (2 mL). La fase orgánica se secó ($MgSO_4$) y se concentró in vacuo. El producto crudo se purificó por HPLC preparativa (columna YMC de fase inversa ODS-A-5u 30 x 100 mm; relación de flujo = 40 mL/min, 10 hasta 100% solvente B durante 12 min, mantenido a 16 min, en donde el solvente A = 90:10:0.1 H_2O:MeOH:TFA y el solvente B = 90:10:0.1 MeOH:H_2O:TFA) para dar el compuesto del título (18 mg; 41%)

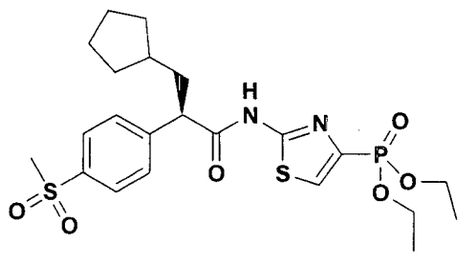
como un sólido amorfo. $[M + H]^+$ = 524.4; ^1H RMN (400 MHz, CD_3OD): δ 1.18 (m, 2H), 1.27 (t, 6H), 1.51 (m, 2H), 1.64 (m, 2H), 1.72 (m, 1H), 1.83 (m, 3H), 2.22 (m, 1H), 3.09 (s, 3H), 3.46 (d, 2H), 4.00 (t, 1H), 4.09 (m, 4H), 7.70 (d, 2H), 7.92 (d, 2H), 8.32 (s, 1H), 9.30 (s, 1H).

EJEMPLO 8

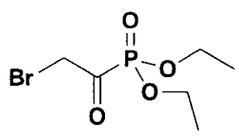


El compuesto del título (11 mg; 19%; sólido incoloro) se sintetizó de trimetilfosfito empleando la secuencia descrita para la síntesis del ejemplo 7. $[M + H]^+$ = 496.3; ^1H RMN (400 MHz, CD_3OD): δ 1.19 (m, 2H), 1.51 (m, 2H), 1.64 (m, 2H), 1.72 (m, 1H), 1.84 (m, 3H), 2.23 (m, 1H), 3.09 (s, 3H), 3.50 (d, 2H), 3.73 (s, 3H), 3.76 (s, 3H), 4.00 (t, 1H), 7.69 (d, 2H), 7.91 (d, 2H), 8.31 (s, 1H), 9.29 (s, 1H).

EJEMPLO 9

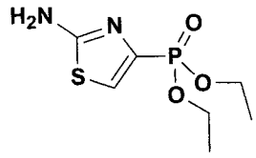


A.



Una solución de bromo (145 uL; 2.82 mmol) en CCl_4 (5 mL) se agregó gota a gota a 0°C una solución de éster de di-etilo del ácido acetil-fosfónico (0.508 g; 2.82 mmol) en CCl_4 (5 mL). La mezcla de reacción luego se agitó a temperatura ambiente durante 2 h, luego se concentró in vacuo. El residuo se procesó por cromatografía (SiO_2; gradiente continuo de 0 hasta 100% solvente B durante 10 min, mantenido al 100% solvente B durante 10 min, en donde el solvente A = hexanos y el solvente B = EtOAc) para dar la parte A del compuesto (250 mg; 34%).

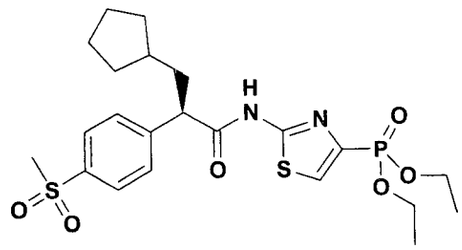
B.



Tiourea (43.9 mg; 0.577 mmol) se agregó a una solución de la parte A del compuesto (135 mg 0.52 mmol) en EtOH (1.0 mL). La mezcla de reacción se agitó a temperatura ambiente durante 48 h, luego se concentró in vacuo. El residuo se dividió entre EtOAc (5 mL) y con $NaHCO_3$ acuoso saturado (3 mL). La fase orgánica se aisló, se lavó con salmuera (3 mL), se secó ($MgSO_4$) y se concentró in vacuo. El residuo se procesó por cromatografía (SiO_2; gradiente continuo desde 0 hasta 100% solvente B durante 2 min, mantenido al 100% solvente B durante 10 min, en donde el solvente A = hexanos y el solvente B = EtOAc) para dar la parte B del compuesto (22

mg; 18%).

C.

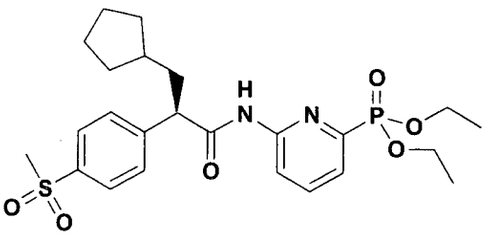


DEPBT (50 mg; 0.168 mmol) se agregó a una solución agitada del ejemplo 1 de la parte D del compuesto (25 mg; 0.084 mmol) y la parte B del compuesto (21.9 mg; 0.093 mmol) en THF (0.40 mL). DIPEA (28.4 uL; 0.168 mmol) se agregó. Después de 96 horas a temperatura ambiente la mezcla de reacción se concentró in vacuo. El residuo se disolvió en EtOAc (3 mL). La solución EtOAc se lavó salmuera (2 mL), se secó ($MgSO_4$), se filtró y se concentró in vacuo. El producto crudo se purificó por HPLC preparativa (columna YMC de fase inversa ODS-A-5u 30 x 100 mm; relación de flujo = 40 mL/min, 20 hasta 100% solvente B durante 12 min, mantenido a 15 min, en donde el solvente A = 90:10:0.1 H_2O:MeOH:TFA y el solvente B = 90:10:0.1 MeOH:H_2O:TFA) para dar el compuesto del título (13 mg; 30%) como un sólido blanco. $[M + H]^+$ = 515.2; ^1H RMN (400 MHz, CD_3OD): δ 1.18 (m, 2H), 1.31 (m, 6H), 1.51 (, 2H), 1.64 (m, 3H), 1.81 (m, 2H), 1.88 (m, 1H), 2.23 (m, 1H), 3.10 (s, 3H), 3.96 (t, 1H), 4.14 (m, 4H), 7.68 (d, 2H),

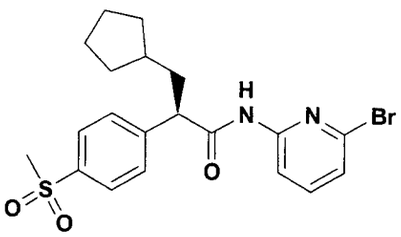
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7.86 (d, J = 4.95 Hz, 1H),7.93 (d, 2H).

EJEMPLO 10



A.

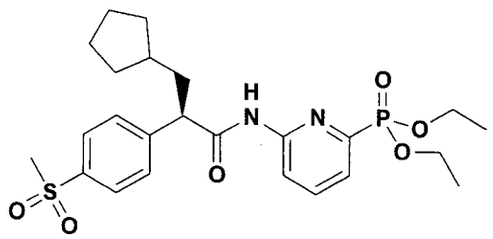


DEPBT (162 mg; 0.540 mmol) se agregó a una solución agitada del ejemplo 1 de la parte D del compuesto (80 mg; 0.270 mmol) y 2-amino-6-bromopiridina (51.4 mg; 0.297 mmol) en THF (1.0 mL). DIPEA (91.0 uL; 0.540 mmol) se agregó. Después de 48 h a temperatura ambiente más 2-amino-6-bromopiridina (93.0 mg; 0.537 mmol) se agregó. Después de 48 horas adicionales la mezcla de reacción se concentró in vacuo. El residuo se dividió entre EtOAc (6 mL) y HCl acuoso 0.1 N (3 mL). La fase orgánica se lavó con salmuera (3 mL), se secó ($MgSO_4$) y se concentró in vacuo. El producto crudo se purificó por HPLC preparativa (columna YMC de fase inversa ODS-A-5u 30 x 100 mm; relación de flujo = 40 mL/min, 35 hasta 100% solvente B durante 10 min, mantenido a 13 min, en donde el solvente A = 90:10:0.1 H_2O:MeOH:TFA y el solvente B =

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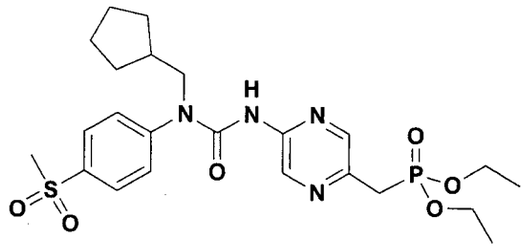
90:10:0.1 MeOH:H_2O:TFA) para dar la parte A del compuesto (16 mg; 13%).

B.

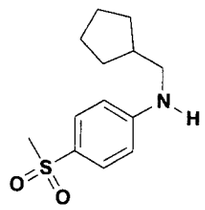


THF (desgasificado) (0.50 mL) se agregó a un matraz de reacción que contiene la parte A del compuesto (14.0 mg; 0.031 mmol) y $(Ph_3P)_4Pd(0)$(7.2 mg; 0.006 mmol). Fosfito de dietilo (4.8 uL; 0.037 mmol) se agregó seguido por Et_3N (6.0 µL; 0.043 mmol). El recipiente de reacción se tapó y la mezcla de reacción se calentó a 75°C durante 12 h, luego se enfrió a temperatura ambiente. La mezcla de reacción se concentró in vacuo. El producto crudo se purificó por HPLC preparativa (columna YMC de fase inversa ODS-A-5u 20 x 100 mm; relación de flujo = 40 mL/min., 20 hasta 100% solvente B durante 12 min, mantenido a 15 min, en donde el solvente A = 90:10:0.1 H_2O:MeOH:TFA y el solvente B = 90:10:0.1 MeOH:H_2O:TFA) para dar el compuesto del título (3.6 mg; 23%) como un sólido incoloro. $[M + H]^+$ = 509.3 ^1H RMN (400 MHz, CD_3OD): δ 1.20 (m, 2H), 1.33 (m, 6H), 1.53 (m, 2H), 1.65 (m, 2H),1.72 (m, 1H), 1.83 (m, 3H), 2.22 (m, 1H), 3.09 (s, 3H), 4.01 (t, 1H), 4.19 (m, 4H), 7.61 (t, 1H), 7.71 (d, 2H), 7.91 (m, 3H), 8.32 (d, 1H).

EJEMPLO 11

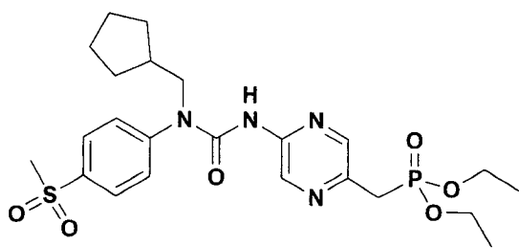


A.



A una mezcla a 0°C de 4-metilsulfonilanilina, clorohidrato (1.06 g, 5.10 mmol), carboxaldehído de ciclopentano (0.5 g, 5.10 mmol) y Et_3N (1 mL, 7.14 mmol) en 20 mL de dicloroetano se agregó $NaBH(OAc)_3$ (1.51 g, 7.14 mmol). La reacción se permitió calentar a temperatura ambiente y se agitó a temperatura ambiente durante dos días, luego se trató con exceso de $NaHCO_3$ acuoso saturado. La capa acuosa se extrajo con EtOAc. El extracto orgánico se enjuagó con salmuera, se secó ($MgSO_4$) y se concentró in vacuo. La purificación por cromatografía instantánea (120 g gel de sílice, gradiente continuo de 0-100% EtOAc-hexanos) da la parte A del compuesto (904 mg, 70% de rendimiento).

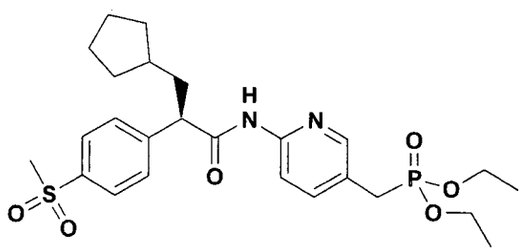
B.



Parte 1: 4-Nitrofenilcloroformiato (49.3 mg; 0.245 mmol) se agregó una solución fría (0°C) del ejemplo 7 de la parte B del compuesto (60 mg; 0.245 mmol). Piridina 20.8 µL; 0.257 mmol) se agregó. La mezcla de reacción se agitó a temperatura ambiente durante 1 h, luego se concentró in vacuo para dar el carbamato crudo.

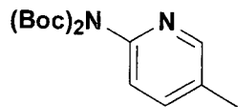
Parte 2: El carbamato crudo se disolvió en CH_3CN (1.0 mL). La parte A del compuesto (62 mg; 0.245 mmol) se agregó. La mezcla de reacción se calentó a 40°C durante 2 h, luego se enfrió a temperatura ambiente y se concentró in vacuo. El producto crudo se procesó por cromatografía (SiO_2; gradiente continuo de 0 hasta 100% solvente B durante 4 min, cambia al solvente C, espera a 100% solvente C durante 8 min, en donde el solvente A = hexanos, solvente B = EtOAc y solvente C = 10% MeOH en EtOAc) para dar el compuesto del título (30 mg; 23% - dos etapas) como un sólido amorfo. $[M + H]^+$ = 525.3 ^1H RMN (400 MHz, CD_3OD): δ 1.28 (t, 8H), 1.54 (m, 2H), 1.67 (m, 4H), 2.10 (m, 1H), 3.17 (s, 3H), 3.45 (d, 2H), 3.83 (d, 2H), 4.09 (m, 4H), 7.65 (d, 2H), 8.05 (d, 2H), 8.19 (s, 1H), 9.12 (s, 1H).

EJEMPLO 12



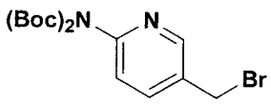
004466

A.



DIPEA (8.05 mL; 46.24 mmol) se agregó una solución fría (0°C) de 2-amino-5-picolina (2.50 g; 23.12 mmol) en DCM (30 mL). Una solución de bicarbonato de di-tert-butilo (12.61 g; 57.80 mmol) en DCM (17 mL) se agregó seguido por 4-DMAP (2.82 g; 23.12 mmol). La mezcla de reacción luego se agitó a temperatura ambiente durante 16 h, luego se concentró in vacuo hasta la mitad del volumen. La solución se diluyó con EtOAc (125 mL). La solución orgánica se lavó con NH_4Cl acuoso saturado (3 x 45 mL), salmuera (45 mL), con $NaHCO_3$ acuoso saturado (2 x 45 mL) y salmuera (45 mL). La solución luego se secó ($MgSO_4$) y se concentró in vacuo. El producto crudo se procesó por cromatografía (SiO_2; gradiente continuo de 15 hasta 20% EtOAc en hexanos) para dar la parte A del compuesto (2.70 g; 38%).

B.

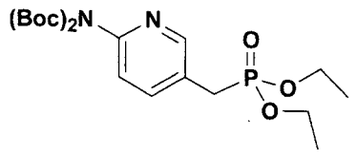


N-bromosuccinimida (1.56 g; 8.76 mmol) se agregó a una solución de la parte A del compuesto (2.70 g; 8.76 mmol) en CCl_4 (40 mL). Peróxido de benzoilo (0.21 g; 0.88 mmol) se

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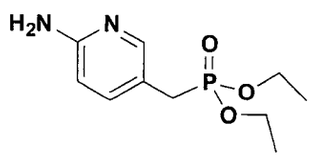
agregó. La mezcla de reacción se calentó a reflujo (80°C) durante 7 h, luego se enfrió a temperatura ambiente. La mezcla de reacción se filtró y el filtrado se concentró in vacuo. El producto crudo se procesó por cromatografía (SiO_2; 5 % EtOAc en DCM) para dar la parte B del compuesto (1.48 g; 44%). (Bioorg. Med. Chem. Lett, 2004, 14, 2227-2231).

C.



Trietilfosfito (1.2 mL; 6.97 mmol) se agregó a una solución de la parte B del compuesto (0.45 g; 1.16 mmol) en THF (2.5 mL). El recipiente de reacción se tapó y la mezcla de reacción se calentó a 80°C durante 16 h, luego se enfrió a temperatura ambiente, la solución se concentró in vacuo. El producto crudo se procesó por cromatografía (SiO_2; gradiente continuo de 0 hasta 100% solvente B durante 8 min, espera a 100% solvente B durante 6 min, en donde el solvente A = hexanos y el solvente B = EtOAc) para dar la parte C del compuesto (0.52 g; 100%).

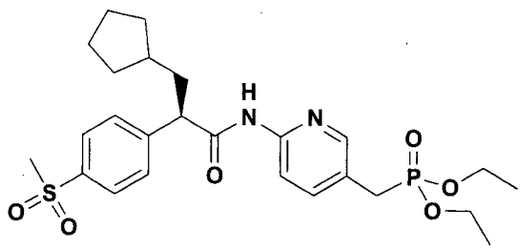
D.



TFA (1.5 mL) se agregó a una solución fría (0°C) de la

parte C del compuesto (0.52 g; 1.17 mmol) en DCM (3 mL). La mezcla de reacción luego se agitó a temperatura ambiente durante 3 h, luego se concentró in vacuo. El residuo se dividió entre $CHCl_3$ (10 mL) y con $NaHCO_3$ acuoso saturado (8 mL). La fase acuosa se extrajo con $CHCl_3$ (8 mL). Los extractos orgánicos combinados se secaron ($MgSO_4$) y se concentraron in vacuo para dar la parte D del compuesto (0.25 g; 88%).

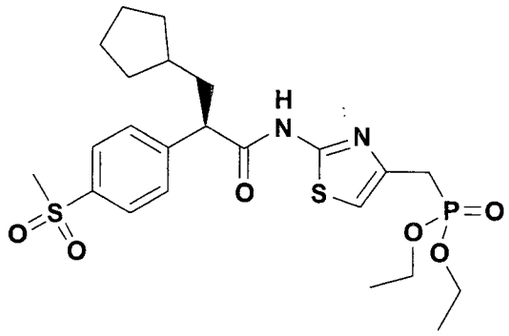
E.



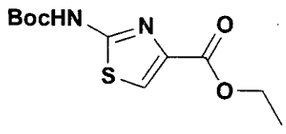
Cloruro de oxalilo (2.0 M en DCM) (104 µL; 0.208 mmol) se agregó a 0°C a una solución del ejemplo 1 de la parte D del compuesto (30.9 mg; 0.104 mmol) en DCM (0.3 mL). DMF (5 µL) se agregó. La evolución del gas se presentó. Después de 1 h a temperatura ambiente la mezcla de reacción se concentró in vacuo. El residuo se despojó del $CHCl_3$ (2 x 1 mL). El cloruro ácido crudo se disolvió en DCM (0.42 mL). La parte D del compuesto (25.5 mg; 0.104 mmol) se agregó seguido por piridina (12.6 uL; 0.156 mmol). Después de agitarse durante 16 horas la reacción se concentró in vacuo. El residuo se dividió entre EtOAc (5 mL) y salmuera (4 mL). La fase orgánica se secó ($MgSO_4$) y se concentró in vacuo. El producto

crudo se purificó por HPLC preparativa (columna YMC de fase inversa ODS-A-5u 30 x 100 mm; relación de flujo = 40 mL/min, 20 hasta 100% solvente B durante 15 min, mantenido a 20 min, en donde el solvente A = 90:10:0.1 H_2O:MeOH:TFA y el solvente B = 90:10:0.1 MeOH:H_2O:TFA) para dar el compuesto del título (19 mg; 34%) como un sólido amorfo. $[M + H]^+$ = 523.4; ^1H RMN (400 MHz, CD_3OD): δ 1.20 (m, 2H), 1.27 (t, 6H), 1.51 (m, 2H), 1.65 (m, 2H), 1.71 (m, 1H), 1.85 (m, 3H), 2.21 (m, 1H), 3.10 (s, 3H), 3.30 (d, 2H), 3.98 (t, 1H), 4.07 (m, 4H), 7.70 (d, 2H), 7.92 (m, 4H), 8.23 (s, 1H).

EJEMPLO 13



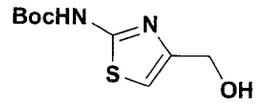
A.



Una solución de bicarbonato de di-tert-butilo (11.3 g; 51.83 mmol) en THF (50 mL) se agregó una solución fría (0°C) de 2-aminotiazol-4-carboxilato de etilo (8.59 g; 49.36 mmol) en THF (150 mL). TEA (7.57 mL; 54.30 mmol) se agregó seguido por una cantidad catalítica de 4-DMAP (30 mg). La mezcla de

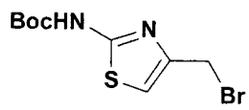
reacción se agitó a temperatura ambiente durante 16 h, luego se concentró in vacuo. El residuo se dividió entre EtOAc (300 mL) y HCl acuoso 0.5N (250 mL). La fase orgánica se lavó salmuera (150 mL), se secó ($MgSO_4$) y se concentró in vacuo para dar la parte A del compuesto (12.38 g; proporcionado dado a continuación en la parte B). El producto crudo se usó en la siguiente etapa sin purificación adicional.

B.



Una solución de $LiAlH_4$ (1.0 M en THF) (48.0 mL; 48.0 mmol) se agregó a una solución fría (0°C) de la parte A del compuesto (12.38 g; 45.3 mmol) en THF (130 mL). Después de 3 horas a 0°C la reacción se apagó cuidadosamente por la adición gota a gota de H_2O (5 mL). Después de 10 min, NaOH acuoso 5N (2.5 mL) se agregó. Después de otros 10 min, la solución se concentró in vacuo. El residuo se dividió entre EtOAc (300 mL) y H_2O (200 mL). La fase acuosa se extrajo con EtOAc (100 mL). Las fases orgánicas combinadas se secaron ($MgSO_4$) y se concentraron in vacuo. El producto crudo se procesó por cromatografía (SiO_2; gradiente continuo de 0 hasta 100% solvente B durante 16 min, espera a 100% solvente B durante 5 min, en donde el solvente A = hexanos y el solvente B = EtOAc) para dar la parte B del compuesto (8.67 g; 67% - dos etapas).

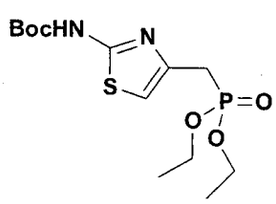
C.



Método 1: Una solución de cloruro de metansulfonilo (318 µL; 4.10 mmol) en DCM (3 mL) se agregó lentamente a 0°C a una solución de la parte B del compuesto (900 mg; 3.91 mmol) y TEA (600 µL; 4.30 mmol) en DCM (10 mL). Después de 25 minutos de agitación la mezcla de reacción se diluyó con acetona (13 mL). LiBr (2.03 g; 23.46 mmol) se agregó. La reacción se agitó a temperatura ambiente durante 1 h, luego se diluyó con NH_4Cl acuoso saturado (20 mL) y se extrajo con Et_2O (2 x 40 mL). Los extractos orgánicos combinados se lavaron con NH_4Cl acuoso saturado (2 x 20 mL) y salmuera (20 mL). La solución se secó ($MgSO_4$) y se concentró in vacuo para dar la parte C del compuesto (1.03 g; 89%). El producto crudo se tomó sin purificación adicional.

Método 2: N.Boc tiourea (428 mg; 2.427 mmol) se agregó a una solución de 1,3-dibromoacetona (524 mg; 2.427 mmol) en acetona (9.7 mL). Después de 24 h a temperatura ambiente la mezcla de reacción se concentró in vacuo para dar la parte C del compuesto (0.78 g; cuant.) como una espuma café. El producto crudo se tomó sin purificación adicional.

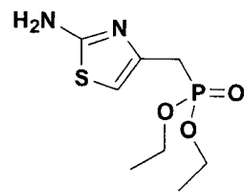
D.



Fosfito de trietilo (3.6 mL; 20.96 mmol) se agregó a una

solución de la parte C del compuesto (878 mg; 2.99 mmol) en THF (6 mL). El recipiente de reacción se tapó y la mezcla de reacción se calentó a 80°C durante 16 h, luego se enfrió a temperatura ambiente. La solución se concentró in vacuo. El producto crudo se procesó por cromatografía (SiO_2; gradiente continuo de 0 hasta 100% solvente B durante 8 min, espera a 100% solvente B durante 10 min, en donde el solvente A = hexanos y el solvente B = EtOAc) para dar la parte D del compuesto (0.86 g; 82%).

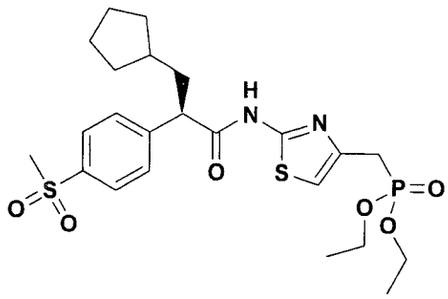
E.



TFA (3.0 mL) se agregó a 0°C a una solución de la parte D del compuesto (0.86 g; 2.45 mmol) en DCM (7 mL). La mezcla de reacción se agitó a temperatura ambiente durante 2.5 h, luego se concentró in vacuo. El residuo se dividió entre EtOAc (15 mL) y con $NaHCO_3$ acuoso saturado (10 mL). La fase acuosa se extrajo con EtOAc (10 mL). Los extractos orgánicos combinados se secaron ($MgSO_4$) y se concentraron in vacuo para dar la parte E del compuesto (488 mg; 80%). ^1H RMN (400 MHz, $CDCl_3$) δ 6.17 (1H, d, J=3.95 Hz), 5.85 (2 H, br. s.), 3.92-4.05 (4 H, m), 3.08 (2 H, d, J=21.09 Hz), 1.18 (6 H, t, J=7.03 Hz).

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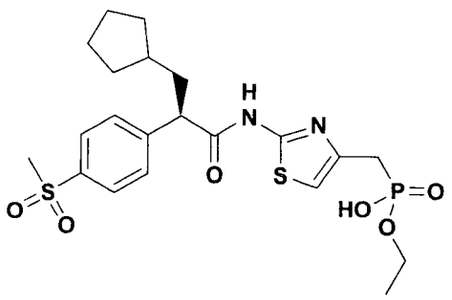
F.



Cloruro de oxalilo (2.0 M en DCM) (0.63 mL; 1.26 mmol) se agregó a 0°C a una mezcla del ejemplo 1 de la parte D del compuesto (250 mg; 0.844 mmol) en DCM (2.5 mL). DMF (10 uL) se agregó. La evolución del gas se presentó. Después de 1.5 h a temperatura ambiente la mezcla de reacción se concentró in vacuo. El residuo se despojó del $CHCl_3$ (2 x 3 mL). El cloruro ácido crudo se disolvió en DCM (3.0 mL). La parte E del compuesto (253 mg; 1.013 mmol) se agregó seguido por piridina (205 uL; 2.532 mmol). Después de 2 h a temperatura ambiente la reacción se concentró in vacuo. El residuo se dividió entre EtOAc (15 mL) y HCl acuoso 0.5N (10 mL). La fase orgánica se lavó con HCl acuoso 0.5N (10 mL) y salmuera (10 mL). La solución se secó ($MgSO_4$), y se concentró in vacuo. El producto crudo se procesó por cromatografía (SiO_2; gradiente continuo de 0 hasta 100% solvente B durante 3 min, espera a 100% solvente B durante 14 min, en donde el solvente A = hexanos y el solvente B = EtOAc) para dar el compuesto del título (0.40 g; 89%) como un sólido amorfo. $[M + H]^+ = 529.2$; ^1H RMN (400 MHz, CD_3OD): δ 1.18 (m, 2H), 1.26 (t, 6H), 1.51

(m, 2H), 1.64 (m, 3H), 1.83 (m, 3H), 2.22 (m, 1H), 3.09 (s, 3H), 3.31 (d, 2H), 3.95 (t, 1H), 4.07 (m, 4H), 6.89 (d, J = 4.03Hz, 1H), 7.67 (d, 2H), 7.92 (d, 2H).

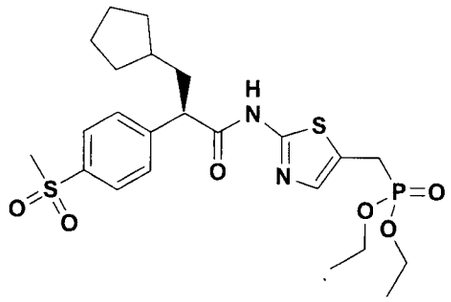
EJEMPLO 14



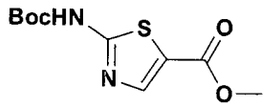
NaOH acuoso 1N (136 uL; 0.136 mmol) se agregó a una solución del ejemplo 13 la parte F del compuesto (50.5 mg; 0.096 mmol) en EtOH (100 µL). La mezcla de reacción se calentó a 80°C durante 48 h, luego se enfrió a temperatura ambiente y se concentró in vacuo. El producto crudo se purificó por HPLC preparativa (columna YMC de fase inversa ODS-A-5u 30 x 100 mm; relación de flujo = 40 mL/min, 10 hasta 100% solvente B durante 16 min, mantenido a 20 min, en donde el solvente A = 90:10:0.1 H_2O:MeOH:TFA y el solvente B = 90:10:0.1 MeOH:H_2O:TFA) para dar el compuesto del título (12.5 mg; 26%) como un sólido amorfo. $[M + H]^+$ = 501.1 ^1H RMN (400 MHz, $CDCl_3$): δ 1.13 (m, 2H), 1.30 (t, 3H), 1.48 (m, 2H), 1.60 (m, 3H), 1.78 (m, 2H), 1.90 (m, 1H), 2.23 (m, 1H), 3.04 (s, 3H), 3.28 (d, 2H), 4.05 (m, 3H), 6.68 (d, 1H),

7.68 (d, 2H), 7.88 (d, 2H).

EJEMPLO 15

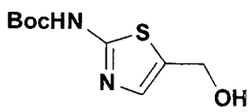


A.



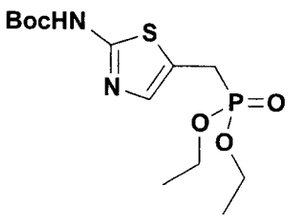
Una solución de bicarbonato de di-tert-butilo (1.66 g; 7.59 mmol) en THF (10 mL) se agregó a 0°C a una solución de 2-aminotiazol-5-carboxilato de metilo (1.20 g; 7.59 mmol) en THF (20 mL). TEA (1.11 mL; 7.97 mmol) se agregó seguido por una cantidad catalítica de 4-DMAP (10 mg). La mezcla de reacción luego se agitó a temperatura ambiente durante 20 h, luego se concentró in vacuo. El residuo se dividió entre EtOAc (80 mL) y HCl acuoso 0.2 N (40 mL). La fase orgánica se lavó con salmuera (40 mL), se secó ($MgSO_4$) y se concentró in vacuo para dar la parte A del compuesto (1.70 g; proporcionado dado a continuación en la parte B). El producto crudo se tomó sin purificación adicional.

B.



Una solución de $LiAlH_4$ (7.60 mL de una solución 1.0 M en THF); 7.60 mmol) se agregó a 0°C a una solución de la parte A del compuesto (1.70 g; 6.58 mmol) en THF (30 mL). La mezcla de reacción se agitó a temperatura ambiente durante 1 h, luego se enfrió a 0°C y se apagó cuidadosamente por la adición gota a gota de H_2O (0.76 mL). Después de 10 min, NaOH acuoso 5N (0.38 mL) se agregó. Después de otros 10 min, la solución se filtró a través de una almohadilla de celite y el filtrado se concentró in vacuo. El producto crudo se procesó por cromatografía (SiO_2; gradiente continuo de 0 hasta 100% solvente B durante 13 min, espera a 100% solvente B durante 6 min, en donde el solvente A = hexanos y el solvente B = EtOAc) para dar la parte B del compuesto (0.80 g; 46% - dos etapas).

C.

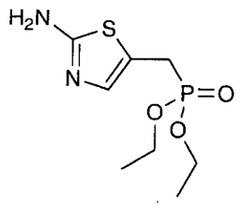


Parte 1: Cloruro de tionilo (253 µL; 3.47 mmol) se agregó a 0°C a una mezcla de la parte B del compuesto (200 mg; 0.869 mmol) en DCM (0.40 mL). La mezcla de reacción se agitó a 0°C durante 2 h luego se concentró al vacío para dar el cloruro crudo.

Parte 2: El cloruro crudo se disolvió en THF (3.0 mL). $(EtO)_3P$ (1.20 mL; 6.95 mmol) se agregó. La mezcla de reacción se calentó a 80°C

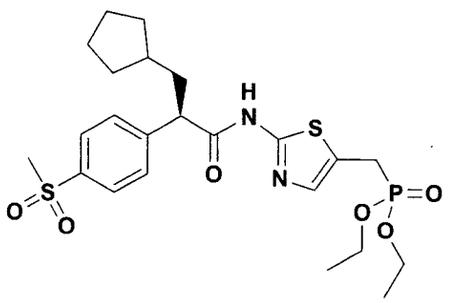
durante 16 h, luego se enfrió a temperatura ambiente y se concentró in vacuo. El producto crudo se procesó por cromatografía (SiO_2; gradiente continuo de 0 hasta 100% solvente B durante 8 min, cambia al solvente C, espera a 100% solvente C durante 7 min, en donde el solvente A = hexanos, solvente B = EtOAc y solvente C = 3% MeOH en EtOAc) para dar la parte C del compuesto (270 mg; 89% - dos etapas).

D.



TFA (0.80 mL) se agregó a 0°C a una solución de la parte C del compuesto (0.31 g; 0.885 mmol) en DCM (2.4 mL). La mezcla de reacción se agitó a temperatura ambiente durante 3 h luego se concentró in vacuo. El residuo se dividió entre $CHCl_3$ (10 mL) y $NaHCO_3$ acuoso saturado (10 mL). La fase acuosa se extrajo con $CHCl_3$ (10 mL). Los extractos orgánicos combinados se secaron ($MgSO_4$) y se concentraron in vacuo para dar la parte D del compuesto (198 mg; 89%).

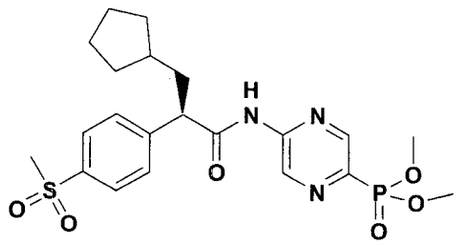
E.



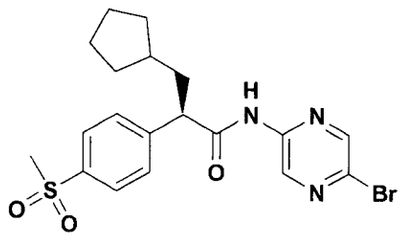
Cloruro de oxalilo (2.0 M en DCM) (101 uL; 0.202 mmol)

se agregó a 0°C a una mezcla del ejemplo 1 de la parte D del compuesto (40 mg; 0.135 mmol) en DCM (0.35 mL). DMF (6 uL) se agregó. La evolución del gas se presentó. La mezcla de reacción luego se agitó a temperatura ambiente durante 1.5 h luego se concentró in vacuo. El residuo se despojó del $CHCl_3$ (2 X 1 mL). El cloruro ácido crudo se disolvió en DCM (0.45 mL). La parte D del compuesto (47.3 mg; 0.189 mmol) se agregó seguido por piridina (33.0 uL; 0.405 mmol). Después de 4 h a temperatura ambiente la reacción se concentró in vacuo. El residuo se dividió entre EtOAc (6 mL) y salmuera (4 mL). La fase orgánica se secó ($MgSO_4$) y se concentró in vacuo. El producto crudo se purificó por HPLC preparativa (columna YMC de fase inversa ODS-A-5u 30 x 100 mm; relación de flujo = 40 mL/min, 15 hasta 100% solvente B durante 10 min, espera a 15 min, en donde el solvente A = 90:10:0.1 H_2O:MeOH:TFA y el solvente B = 90:10:0.1 MeOH:H_2O:TFA) para dar el compuesto del título (46 mg; 65%) como un sólido blanco. $[M + H]^+$ = 529.1; ^1H RMN (400 MHz, CD_3OD): δ 1.18 (m, 2H), 1.29 (t, 6H), 1.49 (m, 2H), 1.63 (m, 3H), 1.80 (m, 3H), 2.22 (m, 1H), 3.09 (s, 3H), 3.43 (d, 2H), 3.96 (t, 1H), 4.09 (m, 4H), 7.26 (d, J = 4.4Hz, 1H), 7.67 (d, 2H), 7.92 (d, 2H).

EJEMPLO 16

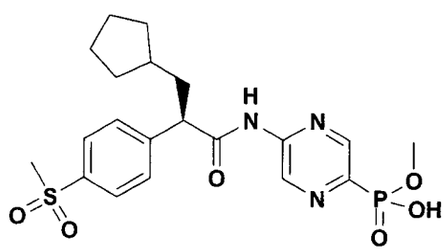


A.



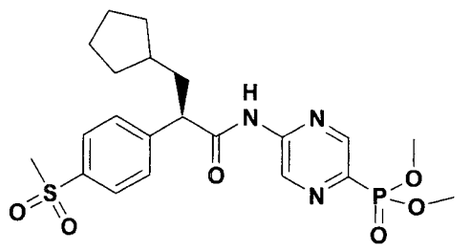
Cloruro de oxalilo (169 µL de una solución 2M en DCM; 0.338 mmol) se agregó a una mezcla del Ejemplo 1 de la parte D del compuesto (50 mg; 0.169 mmol) en DCM (0.35 mL). La solución se enfrió a 0°C. DMF (5 uL) se agregó. La evolución del gas se presentó. Después de 2 h a temperatura ambiente la mezcla de reacción se concentró in vacuo. El residuo se despojó del $CHCl_3$ (2 X 1 mL). El cloruro ácido crudo se disolvió en DCM (0.5 mL). 5-bromo-2-pirazinamina (44 mg; 0.253 mmol) se agregó seguido por piridina (20.5 uL; 0.253 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 3 h, luego se concentró in vacuo. El residuo se dividió entre EtOAc (6 mL) y salmuera (4 mL). La fase orgánica se secó ($MgSO_4$) y se concentró in vacuo. El producto crudo se procesó por cromatografía (SiO_2; gradiente continuo de 0 hasta 30% solvente B durante 30 min, luego 30% hasta 65% solvente B durante 5 min, luego espera a 65% solvente B durante 5 min, en donde el solvente A = hexanos y el solvente B = EtOAc) para dar la parte A del compuesto (64 mg; 84%).

B.



Una solución de la parte A del compuesto (44 mg; 0.097 mmol) en THF (desgasificado) (0.50 mL) se agregó a un matraz de reacción que contiene $(Ph_3P)_4Pd(0)$ (22.4 mg; 0.019 mmol). $(MeO)_3P$ (11.6 mL; 0.126 mmol) se agregó seguido por TEA (21.6 µL; 0.155 mmol). El recipiente de reacción se tapó y la mezcla de reacción se calentó a 75°C durante 6 h, luego se enfrió a temperatura ambiente y se concentró in vacuo. El producto crudo se purificó por HPLC preparativa (columna YMC de fase inversa ODS-A-5u 30 x 100 mm; relación de flujo = 40 mL/min, 15 hasta 100% solvente B durante 10 min, espera a 13 min, en donde el solvente A = 90:10:0.1 H_2O:MeOH:TFA y el solvente B = 90:10:0.1 MeOH:H_2O:TFA) para dar la parte B del compuesto (17 mg; 38%).

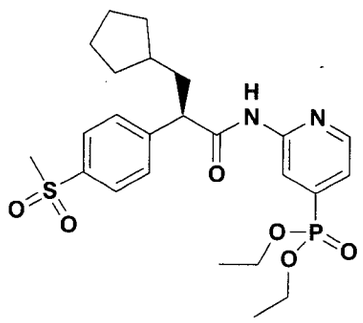
C.



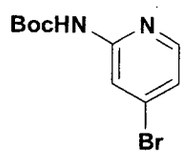
$TMSCHN_2$ (2.0 M en hexano) (73 µL; 0.145 mmol) se agregó a una mezcla de la parte B del compuesto (17 mg; 0.036 mmol) en Et_2O (75 µL) y THF (250 µL). Después de agitarse a temperatura ambiente durante 1 h la mezcla de reacción se concentró in vacuo. El producto crudo se purificó por HPLC preparativa (columna YMC de fase inversa ODS-A-5u 20 x 100 mm; relación de flujo = 20 mL/min., 20 hasta 100% solvente B

durante 10 min, espera a 15 min, en donde el solvente A = 90:10:0.1 H_2O:MeOH:TFA y el solvente B = 90:10:0.1 MeOH:H_2O:TFA) para dar el compuesto del título (9 mg; 51%) como un sólido incoloro. $[M + H]^+$ = 482.2; ^1H RMN (400 MHz, CD_3OD): δ 1.19 (m, 2H), 1.51 (m, 2H), 1.64 (m, 3H), 1.83 (m, 3H), 2.22 (m, 1H), 3.09 (s, 3H), 3.83 (d, 3H), 3.86 (d, 3H), 4.04 (t, 1H), 7.70 (d, 2H), 7.92 (d, 2H), 8.71 (s, 1H), 9.59 (s, 1H).

EJEMPLO 17



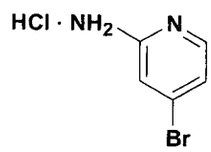
A.



TEA (311 uL; 2.23 mmol) se agregó a una mezcla de ácido 4-bromo-picolínico (450 mg; 2.23 mmol) en tolueno (6.7 mL). Azida de difenilfosforilo (480 uL; 2.23 mmol) se agregó y la reacción se agitó durante 30 min a temperatura ambiente, después de lo cual tert-butanol (427 uL; 4.46 mmol) se agregó. La mezcla de reacción se calentó a 90°C durante 2 h, luego se enfrió a temperatura ambiente. La solución se diluyó

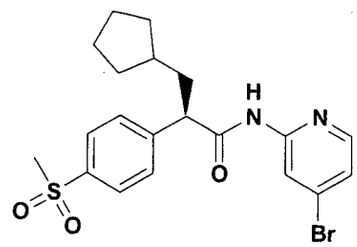
con EtOAc (15 mL), se lavó 10% Na_2CO_3 acuoso (3 x 3 mL) y salmuera (10 mL), se secó ($MgSO_4$) y se concentró in vacuo. El producto crudo se procesó por cromatografía (SiO_2; gradiente continuo de 0 hasta 75% solvente B durante 15 min, en donde el solvente A = hexanos y el solvente B = EtOAc) para dar la parte A del compuesto (0.39 g; 65%).

B.



HCl (1 mL de una solución 4.0M en 1,4 dioxano) se agregó a un recipiente de reacción que contiene la parte A del compuesto (106.5 mg; 0.390 mmol). Después de agitarse a temperatura ambiente durante 20 h la mezcla de reacción se concentró in vacuo. El producto crudo se agitó con hexanos (3 mL). La sal HCl de la parte B del compuesto (81 mg; 100%) se aisló por filtración.

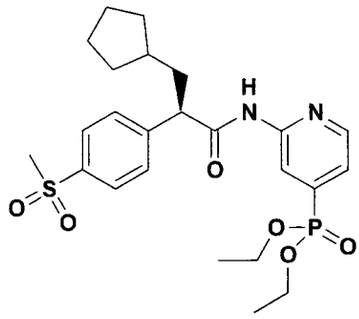
C.



Cloruro de oxalilo (152 µL de una solución 2M en DCM; 0.304 mmol) se agregó a una mezcla del ejemplo 1 de la parte D del compuesto (60 mg; 0.202 mmol) en DCM (0.4 mL). La

solución se enfrió a 0°C. DMF (7 µL) se agregó. La evolución del gas se presentó. Después de 2 h a temperatura ambiente la mezcla de reacción se concentró in vacuo. El residuo se despojó del $CHCl_3$ (2 X 1 mL). El cloruro ácido crudo luego se disolvió en DCM (0.5 mL). La parte B del compuesto (53 mg; 0.253 mmol) se agregó seguido por piridina (49 uL; 0.606 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 2 h luego se concentró in vacuo. El residuo se dividió entre EtOAc (8 mL) y salmuera (4 mL). La fase orgánica se secó ($MgSO_4$) y se concentró in vacuo. El producto crudo se procesó por cromatografía (SiO_2; gradiente continuo de 0 hasta 100% solvente B durante 10 min, en donde el solvente A = hexanos y el solvente B = EtOAc) para dar la parte C del compuesto (72 mg; 79%).

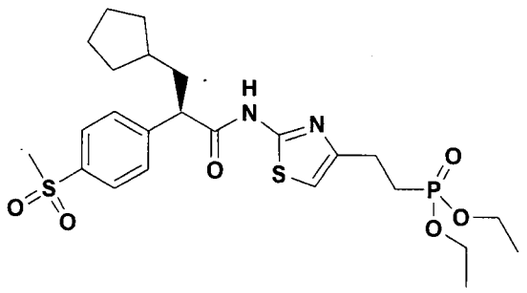
D.



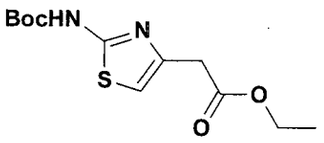
Una solución de la parte C del compuesto (66 mg; 0.146 mmol) en THF (desgasificado) (0.38 mL) se agregó a un matraz de reacción que contiene $(Ph_3P)_4Pd(0)$(34 mg; 0.029 mmol). $H(O)P(OEt)_2$ (21 µL; 0.161 mmol) se agregó seguido por TEA (24.4 µL; 0.175 mmol). El recipiente de reacción se tapó y la

mezcla de reacción se calentó a 75°C durante 16 h, luego se enfrió a temperatura ambiente y se concentró in vacuo. El producto crudo se purificó por HPLC preparativa (columna YMC de fase inversa ODS-A-5u 30 x 100 mm; relación de flujo = 40 mL/min, 35 hasta 100% solvente B durante 12 min, espera a 14 min, en donde el solvente A = 90:10:0.1 H_2O:MeOH:TFA y el solvente B = 90:10:0.1 MeOH:H_2O:TFA) para dar el compuesto del título (49 mg; 66%) como un sólido blanco. $[M + H]^+$ = 509.1; ^1H RMN (400 MHz, CD_3OD): δ 1.19 (m, 2H), 1.34 (m, 6H), 1.52 (m, 2H), 1.65 (m, 3H), 1.84 (m, 3H), 2.23 (m, 1H), 3.09 (s, 3H), 4.01 (t, 1H), 4.16 (m, 4H), 7.38 (dd, 1H), 7.71 (d, 2H), 7.92 (d, 2H), 8.47 (m, 2H).

EJEMPLO 18



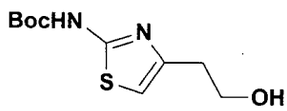
A.



Una solución de bicarbonato de di-tert-butilo (1.03 g; 4.73 mmol) en tolueno (15 mL) se agregó a un recipiente de reacción que contiene (2-(2-aminotiazol-4-il)acetato de etilo

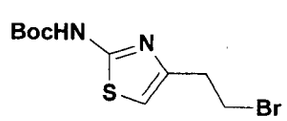
(0.80 g; 4.30 mmol). La mezcla de reacción se calentó a 85°C durante 24 h, luego se enfrió a temperatura ambiente y se concentró in vacuo para dar la parte A del compuesto (1.14 g; rendimiento cuantitativo). El compuesto crudo se llevó a cabo sin purificación adicional.

B.



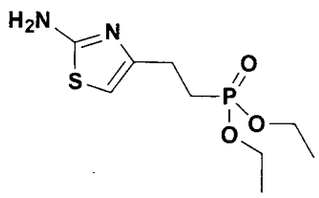
Una solución de $LiAlH_4$ (4.30 mL de una solución 1M en THF; 4.40 mmol) se agregó a 0°C a una solución de cruda de la parte A del compuesto (1.14 g; 3.98 mmol) en THF (13 mL). La mezcla de reacción se agitó a 0°C durante 2 h, luego se apagó cuidadosamente por la adición gota a gota de NH_4Cl acuoso saturado (0.6 mL). La solución se dividió entre EtOAc (20 mL) y salmuera (10 mL). La fase orgánica se lavó con salmuera (10 mL), se secó ($MgSO_4$) y se concentró in vacuo. El producto crudo se procesó por cromatografía (SiO_2; gradiente continuo de 0 hasta 100% solvente B durante 8 min, espera a 100% solvente B durante 8 min, en donde el solvente A = hexanos y el solvente B = EtOAc) para dar la parte B del compuesto (0.42 g; 43%).

C.



Una solución de CH_3SO_2Cl (140 µL; 1.81 mmol) en DCM (1.7 mL) se agregó a 0°C a una solución de la parte B del compuesto (0.42 g; 1.72 mmol) y TEA (264 uL; 1.89 mmol) en DCM (4.0 mL). Después de 30 minutos a 0°C la mezcla de reacción se diluyó con acetona (5.7 mL). LiBr (896 mg; 10.32 mmol) se agregó. La reacción se agitó a temperatura ambiente durante 1 h, luego se dividió entre Et_2O (10 mL) y NH_4Cl acuoso saturado (10 mL). La fase orgánica se lavó NH_4Cl acuoso saturado (10 mL) y salmuera (10 mL), se secó ($MgSO_4$) y se concentró in vacuo para dar la parte C del compuesto (0.50 g; 94%).

D.

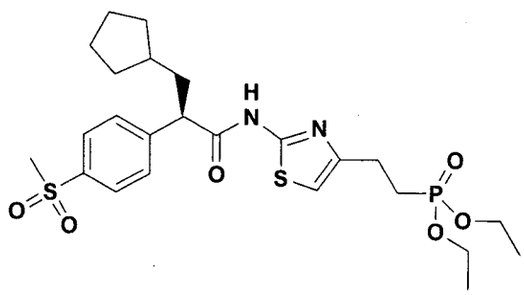


Parte 1: La parte C del compuesto (0.50 g; 1.63 mmol) se disolvió en $(EtO)_3P$ puro (1.0 mL). La mezcla de reacción se calentó a 130°C durante 2 h; a este punto el HPLC analítico mostró picos múltiples. La reacción se enfrió a temperatura ambiente y se concentró in vacuo. El producto crudo se procesó por cromatografía (SiO_2; gradiente continuo de 0 hasta 100% solvente B durante 7 min, cambia al solvente C, espera a 100% solvente C durante 7 min, en donde el solvente A = hexanos, solvente B = EtOAc y solvente C = 3% MeOH en EtOAc). El compuesto no fue puro en este punto (65% de

pureza).

Parte 2: A 0°C una solución del intermediario impuro de la parte 1 en DCM (0.8 mL) se agregó TFA (0.4 mL). La reacción se permitió calentar a temperatura ambiente y se agitó a temperatura ambiente durante 2 h, luego se concentró in vacuo. El residuo se dividió entre EtOAc (10 mL) y $NaHCO_3$ acuoso saturado (10 mL). La fase orgánica se secó ($MgSO_4$) y se concentró in vacuo para dar la parte D del compuesto (73 mg; 17% - dos etapas). (65% de pureza).

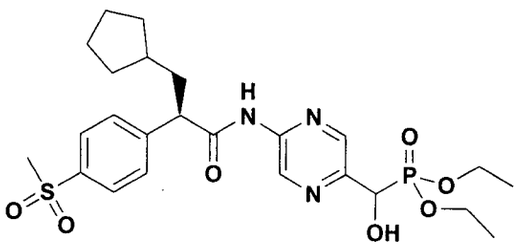
E.



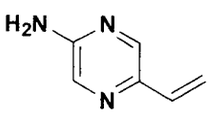
Cloruro de oxalilo (2.0 M en DCM) (78 µL; 0.155 mmol) se agregó a una mezcla del ejemplo 1 de la parte D del compuesto (33 mg; 0.111 mmol) en DCM (0.25 mL). La solución se enfrió a 0°C. DMF (7 µL) se agregó. La evolución del gas se presentó. Después de 1.5 h a temperatura ambiente la mezcla de reacción se concentró in vacuo. El residuo se despojó de $CHCl_3$ (2 X 0.8 mL). El cloruro ácido crudo se disolvió en DCM (0.25 mL). La parte D del compuesto (38 mg; 0.144 mmol) se agregó seguido por piridina (27 uL; 0.333 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 2 h, luego

se concentró in vacuo. El residuo se dividió entre EtOAc (8 mL) y HCl acuoso 0.5N (4 mL). La fase orgánica se lavó con salmuera (4 mL), se secó ($MgSO_4$), y se concentró in vacuo. El producto crudo se purificó por HPLC preparativa (columna YMC de fase inversa ODS-A-5u 30 x 100 mm; relación de flujo = 40 mL/min, 20 hasta 100% solvente B durante 10 min, mantenido a 14 min, en donde el solvente A = 90:10:0.1 H_2O:MeOH:TFA y el solvente B = 90:10:0.1 MeOH:H_2O:TFA) para dar el compuesto del título (29 mg; 48%) como un sólido amorfo. $[M + H]^+$ = 543.0; ^1H RMN (400 MHz, CD_3OD): δ 1.19 (m, 2H), 1.27 (t, 6H), 1.50 (m, 2H), 1.63 (m, 3H), 1.81 (m, 3H), 2.20 (m, 3H), 2.87 (m, 2H), 3.09 (s, 3H), 3.95 (t, 1H), 4.06 (m, 4H), 6.77 (s, 1H), 7.67 (d, 2H), 7.92 (d, 2H).

EJEMPLO 19



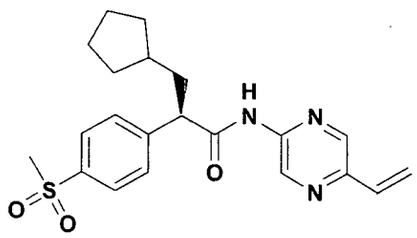
A.



DMF (20 mL) se agregó a un matraz de reacción que contiene 5-bromo-2-pirazinamina (1.00 g; 5.75 mmol), $(Ph_3P)_4Pd(0)$ (199 mg; 0.173 mmol) y LiCl (853 mg; 20.13 mmol). DIPEA (2.50 mL; 14.38 mmol) se agregó seguido por tributil

(vinil)estaño (2.52 mL; 8.62 mmol). La mezcla de reacción se calentó a 120°C durante 4 h, luego se enfrió a temperatura ambiente. Una solución de KF acuoso saturado (20 mL) se agregó. Después de agitarse durante 16 h la mezcla se diluyó con EtOAc (80 mL) y se filtró a través de Celite. El filtrado se lavó con H_2O (80 mL), se secó ($MgSO_4$) y se concentró in vacuo. El producto crudo se procesó por cromatografía (SiO_2; gradiente continuo de 0 hasta 100% solvente B durante 13 min, espera a 100% durante 4 min, en donde el solvente A = hexanos y solvente B = EtOAc) para dar la parte A del compuesto (0.41 g; 59%).

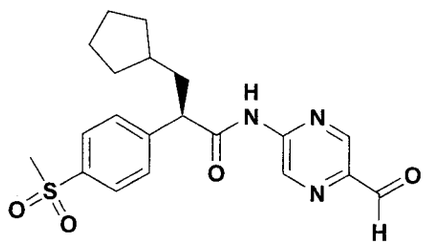
B.



Cloruro de oxalilo (127 µL de una solución 2M en DCM; 0.253 mmol) se agregó a una mezcla del ejemplo 1 de la parte D del compuesto (50 mg; 0.169 mmol) en DCM (0.5 mL). La solución se enfrió a 0°C. DMF (7 mL) se agregó. La evolución del gas se presentó. Después de 1.5 h a temperatura ambiente la mezcla de reacción se concentró in vacuo. El residuo se despojó del $CHCl_3$ (2 X 1 mL). El cloruro ácido crudo luego se disolvió en DCM (0.6 mL). La parte A del compuesto (24.5 mg; 0.202 mmol) se agregó seguido por piridina (41 uL; 0.507

mmol). La mezcla de reacción se agitó a temperatura ambiente durante 1.5 h, luego se concentró in vacuo. El producto crudo se procesó por cromatografía (SiO_2; gradiente continuo de 0 hasta 100% solvente B durante 12 min, espera a 100% solvente B durante 3 min, en donde el solvente A = hexanos y el solvente B = EtOAc) para dar la parte B del compuesto (70 mg; 100%).

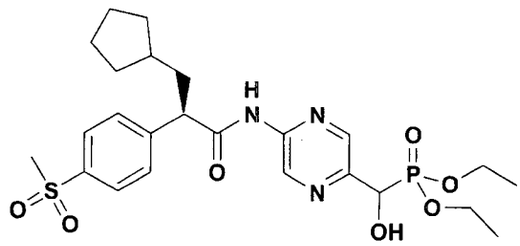
C.



Ácido acético (15 µL) se agregó a una solución de la parte B del compuesto (70 mg; 0.175 mmol) en DCM (0.50 mL). La solución se enfrió a -78°C (enfriado en hielo/acetona). Ozono se burbujeó a través de la solución hasta que se volvió ligeramente azul (~4 min). El baño enfriado en hielo/acetona se removió y la reacción se permitió calentar a temperatura ambiente. Después de 5 min de agitación a temperatura ambiente la solución se diluyó con DCM (3 mL). $NaHCO_3$ acuoso saturado (3 mL) se agregó (emulsión formada). La mezcla se concentró in vacuo para remover el DCM. La solución acuosa luego se extrajo con EtOAc (4 mL). La fase orgánica se secó ($MgSO_4$) y se concentró in vacuo para dar la parte C del compuesto (55 mg; 78%).

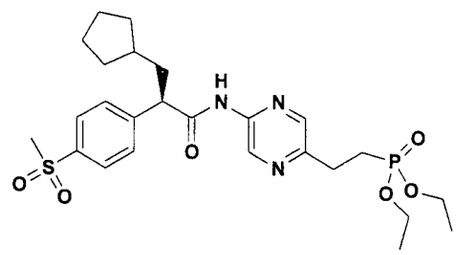
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D.

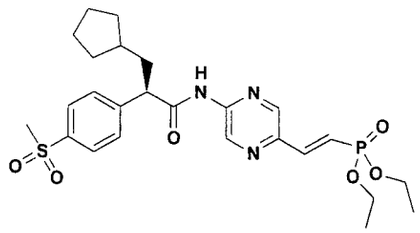


Fosfito de dietilo (8.0 µL; 0.062 mmol) se agregó a una solución de la parte C del compuesto (25 mg; 0.062 mmol) en THF (0.30 mL). TEA (8.68 uL; 0.062 mmol) luego se agregó. Después de 8 horas a temperatura ambiente la solución se concentró in vacuo. El producto crudo se purificó por HPLC preparativa (columna YMC de fase inversa ODS-A-5u 30 x 100 mm; relación de flujo = 40 mL/min, 15 hasta 100% solvente B durante 15 min, espera a 20 min, en donde el solvente A = 90:10:0.1 H_2O:MeOH:TFA y el solvente B = 90:10:0.1 MeOH:H_2O:TFA) para dar el compuesto del título (15 mg; 45%; sólido amorfo) como una mezcla 1:1 de diastereómeros. $[M + H]^+$ = 540.2; ^1H RMN (400 MHz, $CDCl_3$): δ 1.15 (m, 2H), 1.31 (m, 6H), 1.48 (m, 2H), 1.62 (m, 3H), 1.78 (m, 2H), 1.93 (m, 1H), 2.22 (m, 1H), 3.88 (m, 1H), 4.20 (m, 4H), 5.13 (dd, 1H), 7.63 (d, 2H), 7.89 (d, 2H), 8.34 (d, 1H), 9.11 (d, 1H), 9.43 (s, 1H).

EJEMPLO 20

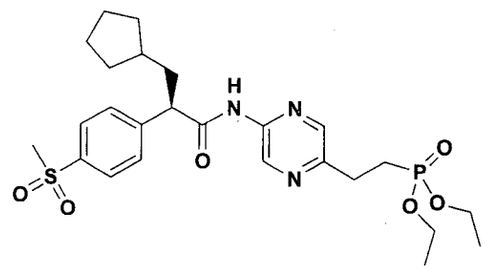


A.



Una solución del ejemplo 19 de la parte C del compuesto (26 mg; 0.065 mmol) en DCM (150 uL) se agregó a una solución de $CH_2(PO_3Et_2)_2$ (16.2 µL; 0.065 mmol) en NaOH acuoso 5N (150 µL). Después de 1 h a temperatura ambiente la mezcla de reacción se dividió entre DCM (3 mL) y H_2O (2 mL). La fase orgánica se secó ($MgSO_4$) y se concentró in vacuo para dar la parte A del compuesto (35 mg; 100%).

B.

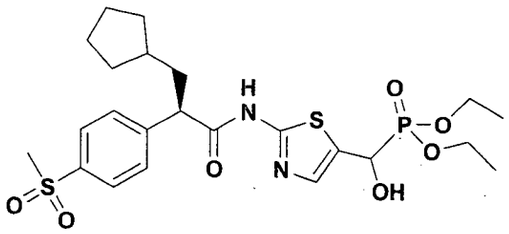


Pd/C al 10% (3 mg) se agregó a una solución de la parte A del compuesto (35 mg; 0.065 mmol) en MeOH (0.30 mL). Una atmósfera H_2 se introdujo por medio de un globo. Después de 6 h la mezcla de reacción se filtró y el filtrado se concentró in vacuo. El producto crudo se purificó por HPLC preparativa (columna YMC de fase inversa ODS-A-5u 30 x 100 mm; relación de flujo = 40 mL/min, 20 hasta 100% solvente B durante 11 min, espera a 15 min, en donde el solvente A = 90:10:0.1

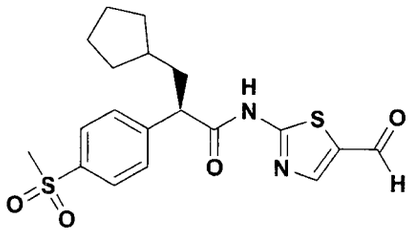
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H_2O:MeOH:TFA y el solvente B = 90:10:0.1 MeOH:H_2O:TFA) para dar el compuesto del título (11 mg; 31%) como un sólido amorfo. $[M + H]^+$ = 538.2; ^1H RMN (400 MHz, $CDCl_3$): δ 1.15 (m, 2H), 1.30 (m, 8H), 1.48 (m, 2H), 1.61 (m, 3H), 1.76 (m, 2H), 1.93 (m, 1H), 2.22 (m, 3H), 3.05 (s, 3H), 3.74 (m, 1H), 4.09 (m, 4H), 7.61 (d, 2H), 7.92 (d, 2H), 8.08 (s, 1H), 8.29 (s, 1H), 9.44 (s, 1H).

EJEMPLO 21



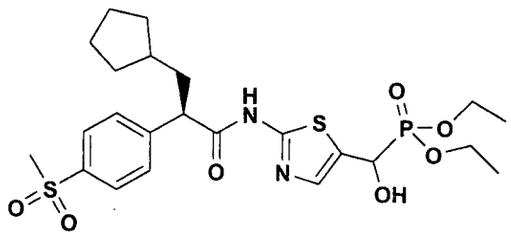
A.



Cloruro de oxalilo (203 µL de una solución 2M en DCM; 0.406 mmol) se agregó a 0°C a una mezcla del ejemplo 1 de la parte D del compuesto (80 mg; 0.270 mmol) en DCM (0.70 mL). DMF (10 uL) se agregó. La evolución del gas se presentó. La mezcla de reacción se agitó a temperatura ambiente durante 1.5 h, luego se concentró in vacuo. El residuo se despojó de $CHCl_3$ (2 x 2 mL). El cloruro ácido crudo se disolvió en DCM (0.90 mL). 2-amino-5-formiltiazol (45.0 mg; 0.351 mmol) se

agregó seguido por piridina (66.0 uL; 0.810 mmol). Después de 16 h a temperatura ambiente la reacción se concentró in vacuo. El producto crudo se procesó por cromatografía (SiO_2; gradiente continuo de 0 hasta 100% solvente B durante 6 min, espera a 100% solvente B durante 8 min, en donde el solvente A = hexanos y solvente B = EtOAc) para dar la parte A del compuesto (27 mg; 25%).

B.



$H(O)P(OEt)_2$ (8.9 mL; 0.069 mmol) se agregó a una solución de la parte A del compuesto (27 mg; 0.066 mmol) en THF (0.30 mL). TEA (9.6 mL; 0.069 mmol) se agregó. La mezcla de reacción se agitó a temperatura ambiente durante 20 h, después de lo cual más $H(O)P(OEt)_2$ (8.89 uL; 0.069 mmol) y TEA (9.62 uL; 0.069 mmol) se agregaron junto con THF (0.10 mL). Después de 20 h la reacción se calentó a 45°C durante 16 h, luego se enfrió a temperatura ambiente. Después de dos semanas a temperatura ambiente el residuo el cual se formó se purificó por HPLC preparativa (coluna YMC de fase inversa ODS-A-5u 30 x 100 mm; relación de flujo = 40 mL/min, 15 hasta 100% solvente B durante 20 min, en donde el solvente A = 90:10:0.1 H_2O:MeOH:TFA y el solvente B = 90:10:0.1

PATENTE DE INVENCION

Organizacion y
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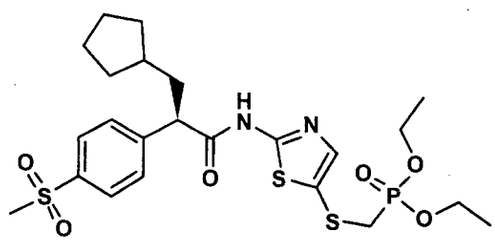
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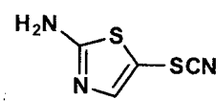
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MeOH:H_2O:TFA) para dar el compuesto del título (27 mg; 75%; sólido amorfo) como una mezcla 1:1 de diastereómeros. [M + H]$^+$ = 540.2 ^{1}H RMN (400 MHz, $CDCl_3$): δ 1.16 (m, 2H), 1.32 (m, 6H), 1.49 (m, 2H), 1.62 (m, 3H), 1.78 (m, 2H), 1.95 (m, 1H), 2.24 (m, 1H), 3.04 (s, 3H), 4.01 (t, 1H), 4.21 (m, 4H), 5.18 (d, 1H), 7.37 (s, 1H), 7.65 (d, 2H), 7.91 (d, 2H).

EJEMPLO 22



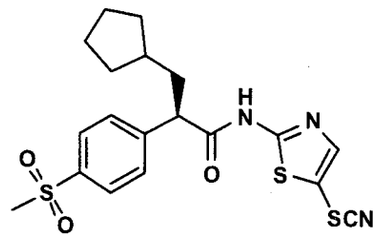
A.



A una solución de bromohidrato de 2-amino-5-bromotiazol (10.0 g, 38.4 mmol) en MeOH (50 mL) se agregó KSCN (15.0 g, 160 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 18 h, luego se concentró in vacuo, y H_2O (40 mL) se agregó al residuo. La mezcla se ajustó hasta pH 12 con NaOH acuoso 1N. Un precipitado se formó, el cual se recolectó por filtración de succión, y se lava con H_2O (3 x) y Et_2O (3 x). El sólido se secó in vacuo durante 18 h para dar La parte A del compuesto como un sólido café (2.8 g, 47%).

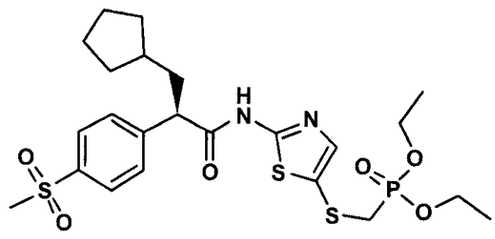
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B.



A una solución de la parte A del tiocianato (800 mg, 5.09 mmol) y el Ejemplo 1D (1.51 g, 5.09 mmol) en THF (20 mL) se agregó DEPBT (3.05 g, 10.18 mmol) y iPr_2NEt (1.8 mL, 10.18 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 18 h, luego se concentró in vacuo. El residuo se tomó en EtOAc y salmuera, y se extrae con EtOAc (3x). Los extractos orgánicos combinados se lavaron con HCl acuoso 1N, H_2O, $NaHCO_3$ acuoso al 5%, H_2O, y salmuera, se secan ($MgSO_4$), y se concentran in vacuo. El residuo se procesó por cromatografía (SiO_2; gradiente continuo 10% EtOAc/Hex hasta 100% EtOAc/Hexano) para dar la parte B del compuesto (927 mg, 42%) como un sólido anaranjado.

C.

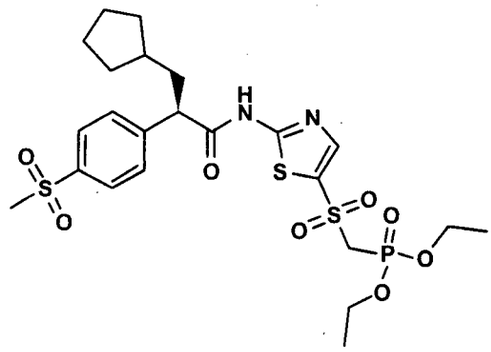


A 0°C una solución de tiocianato B (50 mg, 0.11 mmol) en EtOH absoluto (2 mL) se agregó $NaBH_4$ (7 mg, 0.22 mmol). La mezcla se agitó a 0°C durante 1 h, después de lo cual el

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exceso de $NaBH_4$ se apagó cuidadosamente con acetona (0.5 mL). La mezcla se calentó hasta temperatura ambiente, y se agregó a un matraz cargado con $ICH_2PO_3Et_2$ (41 mg, 0.15 mmol). La reacción se agitó a temperatura ambiente durante 18 h, luego se concentró in vacuo. El residuo se purificó por HPLC preparativa (Columna Phenomenex Luna 5u C18 21.2 x 100 mm; detección a 220 nm; relación de flujo = 20 mL/min; gradiente continuo desde 70% A hasta 100% B durante 8 min + 7 min tiempo de espera a 100% B, donde A = 90:10:0.1 H_2O:MeOH:TFA y B = 90:10:0.1 MeOH:H_2O:TFA) para proporcionar el compuesto del título (25.1 mg, 39% de rendimiento) como un liofilado blanco opaco. $[M + H]^+$ = 561.1; ^1H RMN (400 MHz, DMSO-D_6): δ 7.83 (d, J=8.4, 2H), 7.58 (d, J=8.3, 2H), 7.51 (s, 1H), 3.92 (m, 5H), 3.15 (s, 2H), 3.12 (s, 3H), 2.09-1.36 (m, 11H), 1.12 (m, 6H).

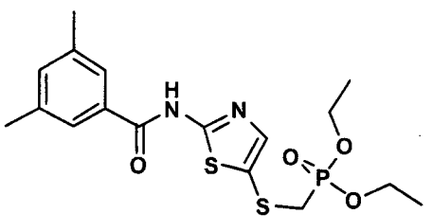
EJEMPLO 23



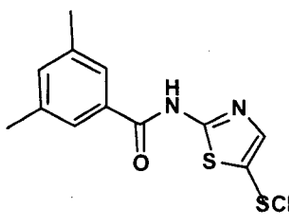
A una solución del compuesto del Ejemplo 22 (20 mg, 0.04 mmol) en MeOH (1 mL) y THF (1 mL) se agregó p-toluensulfonil imidazol (24 mg, 0.11 mmol), H_2O_2 acuoso al 30% (0.02 mL, 0.14

mmol), y NaOH acuoso 1N (1.0 mL). La reacción se agitó a temperatura ambiente durante 3 h, luego se concentró in vacuo. El residuo se purificó por HPLC preparativa (Columna Phenomenex Luna 5u C18 21.2 x 100 mm; detección a 220 nm; relación de flujo = 20 mL/min; gradiente continuo desde 70% A hasta 100% B durante 8 min + 7 min tiempo de espera a 100% B, donde A = 90:10:0.1 H_2O:MeOH:TFA y B = 90:10:0.1 MeOH:H_2O:TFA) para proporcionar el compuesto del título (12 mg, 57% de rendimiento) como un liofilato blanco. $[M + H]^+$ = 593.2; ^1H RMN (400 MHz, DMSO-D_6): δ 8.00 (s, 1H), 7.84 (d, J=8.4, 2H), 7.59 (d, J=8.4, 2H), 4.08-3.94 (m, 5H), 3.13 (s, 2H), 3.10 (s, 3H), 2.02-1.10 (m, 11H), 1.10-1.06 (m, 6H).

EJEMPLO 24



A.

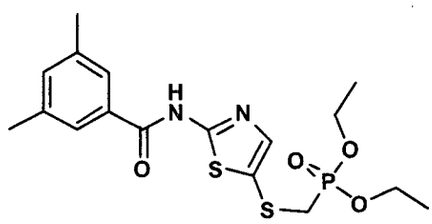


A una solución de ácido 3,5-dimetilbenzoico (800 mg, 5.3 mmol) en CH_2Cl_2 (20 mL) se agregó cloruro de oxalilo (0.51 mL, 5.8 mmol) y DMF (0.1 mL). La mezcla de reacción se agitó a temperatura ambiente durante 2 h, luego se concentró in

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vacuo. El residuo se tomó en THF (20 mL), y del Ejemplo 22 Parte A de la amina (922 mg, 5.8 mmol) y piridina (0.86 mL, 10.6 mmol) se agregaron. La mezcla se agitó a temperatura ambiente durante 18 h, luego se diluyó con EtOAc (60 mL), se lava con H_2O y salmuera, y se extrae con EtOAc (2x). Los extractos orgánicos combinados se secaron ($MgSO_4$) y se concentran in vacuo. El residuo se procesó por cromatografía (10% EtOAc/Hex hasta 100% EtOAc/Hexano) para dar la parte A del compuesto (770 mg, 51% de rendimiento) como un sólido café.

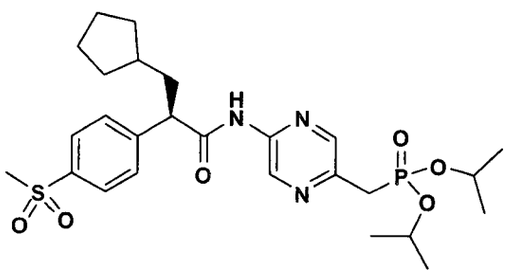
B.



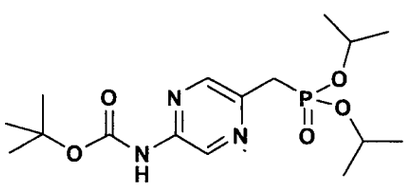
A 0°C una solución of la parte A del compuesto (50 mg, 0.17 mmol) en EtOH absoluto (2 mL) se agregó $NaBH_4$ (13 mg, 0.35 mmol), y la mezcla se agitó durante 1 h a 0°C. El exceso de $NaBH_4$ se apagó con acetona (0.5 mL), y la mezcla se calentó hasta temperatura ambiente. La mezcla se agregó a un matraz cargado con $ICH_2PO_3Et_2$ (62 mg, 0.22 mmol). La reacción se agitó a temperatura ambiente durante 18 h, luego se concentró in vacuo. El residuo se purificó por HPLC preparativa (Columna Phenomenex Luna 5mm C18 21.2 x 100 mm; detección a 220 nm; relación de flujo = 20 mL/min; gradiente

continuo desde 70% A hasta 100% B durante 8 min + 7 min tiempo de espera a 100% B, donde A = 90:10:0.1 H_2O:MeOH:TFA y B = 90:10:0.1 MeOH:H_2O:TFA) para proporcionar el compuesto del título (22.4 mg, 32% de rendimiento) como un sólido blanco. $[M + H]^+$ = 415.1; ^1H RMN (400 MHz, DMSO-D_6): δ 7.71 (s, 1H), 7.66 (s, 2H), 7.27 (s, 1H), 4.02 (m, 4H), 3.27 (s, 2H), 2.34 (s, 6H), 1.21 (m, 6H).

EJEMPLO 25



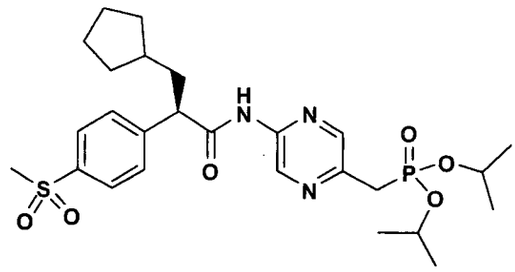
A.



Una mezcla de 5-(bromometil)pirazin-2-ilcarbamato de tert-butilo(399 mg, 1.23 mmol) y $(iPrO)_3P$ (2 mL) se calentó a 100°C durante la noche. La mezcla de reacción se enfrió hasta temperatura ambiente, luego se procesó por cromatografía (120 g SiO_2; gradiente continuo desde 0-50% EtOAc en DCM, seguido por un gradiente continuo desde 0-10% MeOH en DCM) para dar 399 mg (86% de rendimiento) de la parte A del compuesto como un sólido amarillo ligero (88% de pureza por HPLC). $[M + H]^+$

= 374.3; ^{1}H-RMN (400 MHz, $CDCl_3$): δ 9.18 (s, 1H), 8.24 (s, 1H), 7.32 (s, 1H), 4.67 (m, 2H), 3.33 (d, 2H), 1.54 (s, 9H), 1.25 -1.30 (m, 12H).

B.



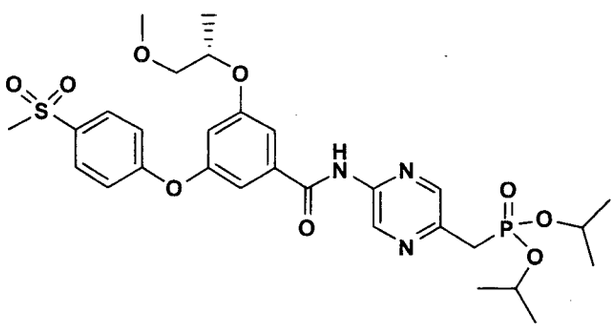
A 0°C una solución de la parte A del compuesto (200 mg, 0.535 mmol) en DCM (1 mL) se trató con 1 mL de HCl acuoso 4N en dioxano bajo Ar. La mezcla de reacción se permitió calentar hasta temperatura ambiente durante la noche, luego se concentró in vacuo. El residuo se disolvió en agua (5 mL) y se extrae con Et_2O para remover una impureza. La solución acuosa se hizo básica con NaOH acuoso 1N y se extrae con DCM (3 x 2 mL). Los extractos orgánicos combinados se enjuagaron con salmuera, se secan ($MgSO_4$), y se concentran in vacuo para proporcionar 103 mg (71% de rendimiento) de diisopropilo (5-aminopirazin-2-il)metilfosfonato como un sólido ceroso, amarillo. $[M + H]^+$ = 274.3. Este material se usó directamente en la siguiente etapa sin purificación adicional.

El ácido del ejemplo 1D se convirtió al cloruro ácido correspondiente usando cloruro de oxalilo (como se describe en el Ejemplo 2 Parte A). El cloruro ácido se transfirió con

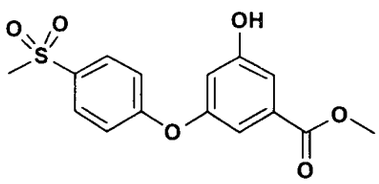
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dos porciones 0.3 mL de DCM en una mezcla a 0°C de la amina anterior (45 mg, 0.165 mmol) y piridina (53.4 µL, 0.66 mmol) en DCM (0.7 mL) bajo Ar. La reacción se permitió calentar hasta temperatura ambiente durante la noche, luego se extrajo con DCM (5 mL). El extracto orgánico se lavó con 2 mL cada uno de HCl acuoso 0.1N, agua, y salmuera, se secó ($MgSO_4$), y se concentra in vacuo para proporcionar 142 mg de producto crudo. El material crudo se procesó por cromatografía (40 g SiO_2; gradiente continuo desde 10-100% EtOAc en DCM) para dar el compuesto del título (25.6 mg, 28% de rendimiento) como un aceite incoloro. $[M + H]^+$ = 552.4; ^{1}H-RMN (400 MHz, $CDCl_3$): δ 9.40 (s, 1H), 8.24 (s, 2H), 7.93 (d, 2H), 7.61 (d, 2H), 4.68 (m, 2H), 3.74 (m, 1H), 3.34 (d, 2H), 3.05 (s, 3H), 2.22 (m, 1H), 1.95 (m, 1H), 1.10 - 2.83 (m, 9H), 1.25 - 1.29 (m, 12H).

EJEMPLO 26



A.



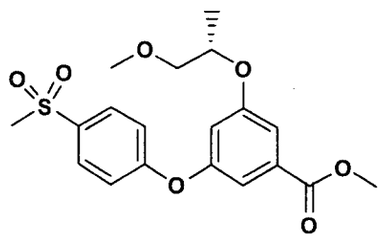
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A una mezcla agitada rápidamente de 3,5-dihidroxibenzoato de metilo (38 g, 0.226 mol) y K_2CO_3 (47.7 g, 0.345 mol) en DMF (150 mL) se calienta a 120°C bajo Ar se agregó una solución de 1-fluoro-4-(metilsulfonil)benceno (20 g, 0.115 mol) en DMF (50 mL) durante 3 h. Después se calienta a 120°C durante la noche, la mezcla de reacción se enfrió hasta temperatura ambiente, se diluye con DMF (300 mL), y luego se trata con Celite® como un auxiliar de filtrado. La mezcla de reacción heterogénea se filtró, y la torta filtro se enjuagó completamente con más DMF. Los filtrados combinados se concentraron in vacuo, y el residuo se dividió entre HCl acuoso 1N (200 mL) y EtOAc (250 mL). Unos 100 mL adicionales de agua se agregó. La capa acuosa se extrajo con EtOAc (200 mL), y los extractos orgánicos combinados se enjuagaron con agua y salmuera (250 mL cada uno), y se secan ($MgSO_4$). Los volátiles se removieron in vacuo. El residuo se procesó por cromatografía en 3 porciones. Cada porción se absorbió en SiO_2 (~20 g) y se procesa por cromatografía (330 g SiO_2; elución con un gradiente continuo de 0-20% EtOAc en CH_2Cl_2 seguido por EtOAc 20% isocrático: CH_2Cl_2) para dar la parte A del compuesto (14.77 g; rendimiento combinado de 40%) como un sólido blanco. $[M + H]^+ = 323.0$; ^1H-RMN (400 MHz, $CDCl_3$): δ 7.89 (d, 2H), 7.33 (s, 1H), 7.22 (s, 1H), 7.11 (dd, 2H), 6.89 (d, 1H), 3.89 (s, 3H), 3.07

000524

(s, 3H).

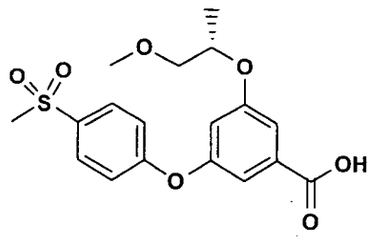
B.



A 5°C una mezcla de la parte A del compuesto (5 g, 15.5 mmol), (R)-(-)-1-metoxi-2-propanol (2 mL, 20.4 mmol) y Ph_3P soportada con polímero (13.4 g de 3 mmol/g, 40.2 mmol) en THF (175 mL) se agregó gota a gota una solución de DIAD (4.5 mL, 23.2 mmol) en THF (25 mL) durante 25 min bajo Ar (temperatura interna mantenida a $\leq$ 5°C). La mezcla de reacción se permitió calentar hasta temperatura ambiente durante la noche, y luego se filtró. Los sólidos se lavaron completamente con THF y CH_2Cl_2. Los filtrados combinados se concentraron in vacuo, se redisolvieron en CH_2Cl_2 y se dividen en 2 porciones iguales. La primera porción se procesó por cromatografía (330 g SiO_2; elución con un gradiente continuo de 0-10% EtOAc en CH_2Cl_2 durante 40 min) para dar 2.53 g de la Parte B del compuesto puro como un aceite incoloro. Las fracciones del producto impuro de esta columna se combinaron con el resto del producto crudo y esta mezcla se procesó por cromatografía como arriba en 330 g SiO_2, pero con un gradiente continuo desde 0-8% EtOAc en CH_2Cl_2 para dar la parte B del compuesto (3.02 g) como un aceite incoloro. El rendimiento combinado de

la Parte B del compuesto fue 5.55 g (90%). $[M + H]^+$ = 395.0; ^{1}H-RMN (400 MHz, $CDCl_3$): δ 7.90 (d, 2H), 7.48 (s, 1H), 7.30 (s, 1H), 7.11 (dd, 2H), 6.86 (d, 1H), 4.61 (m, 1H), 3.90 (s, 3H), 3.49-3.62 (m, 2H), 3.40 (s, 3H), 3.07 (s, 3H), 1.32 (d, 3H).

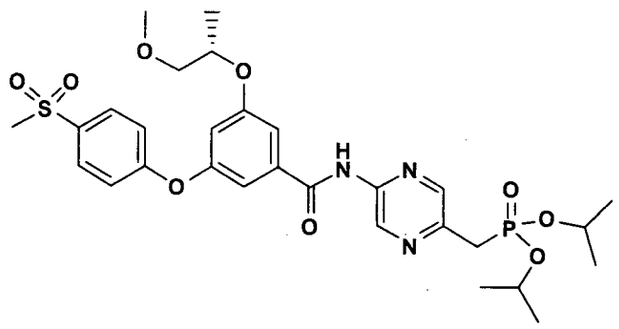
C.



A 0°C una solución de la Parte B del compuesto (4.24 g, 10.75 mmol) en THF (50 mL) y agua (15 mL) se agregó $LiOH.H_2O$ (1.287 g, 53.7 mmol). La mezcla de reacción se permitió calentar hasta temperatura ambiente durante la noche (reacción completa por CL/EM). La mezcla de reacción se concentró in vacuo y 50 mL de H_2O se agregó; la solución se hizo ácida con HCl acuoso 5N. La mezcla se extrajo con EtOAc (2 x 100 mL). Los extractos EtOAc combinados se lavaron con salmuera (50 mL), se secan ($MgSO_4$) y se concentran in vacuo para proporcionar la Parte C del compuesto (3.95 g, 96.5% de rendimiento) como un vidrio incoloro. $[M + H]^+$ = 381.1; ^{1}H-RMN (400 MHz, $CDCl_3$): δ 7.91 (d, 2H), 7.52 (s, 1H), 7.35 (s, 1H), 7.13 (dd, 2H), 6.90 (s, 1H), 4.61 (m, 1H), 3.52-3.64 (m, 2H),

3.42 (s, 3H), 3.07 (s, 3H), 1.33 (d, 3H).

D.

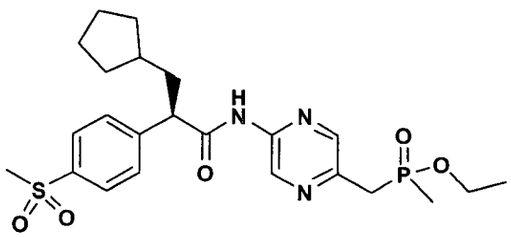


A 0°C una solución del Ejemplo 25A del compuesto (199 mg, 0.533 mmol) en DCM (1 mL) se agregó TFA (1 mL) bajo Ar. La mezcla de reacción se permitió calentar hasta temperatura ambiente. Después de 5.5 h, la mezcla de reacción se concentró in vacuo y se divide entre HCl acuoso 0.5N y Et_2O (4 mL cada uno). La capa acuosa se hizo básica con K_2CO_3 sólido, luego se extrae con DCM (3x). Los extractos orgánicos combinados se lavaron con salmuera, se secan ($MgSO_4$), y se concentran in vacuo para proporcionar 108 mg (74%) de diisopropilo (5-aminopirazin-2-il)metilfosfonato aislado como un sólido amarillo. $[M + H]^+ = 274.3$.

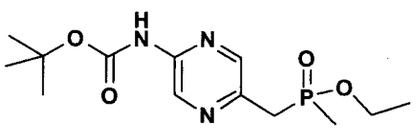
La parte C del ácido (32 mg, 0.0841 mmol) se convirtió al cloruro ácido correspondiente usando cloruro de oxalilo (como se describe en el Ejemplo 2 Parte A). El cloruro ácido crudo se transfirió con dos porciones (0.2 mL cada uno) de DCM a una mezcla de diisopropilo (5-aminopirazin-2-il)metilfosfonato (25.3 mg, 0.0926 mmol) y piridina (27.2 mL, 0.370 mmol) en DCM (0.4 mL) se enfría hasta 0°C bajo Ar. La

reacción se permitió calentar hasta temperatura ambiente durante la noche. La mezcla de reacción luego se extrajo con DCM (4 mL), se lava con 2 mL cada uno de HCl acuoso 0.5N, agua, $NaHCO_3$ acuoso saturado y salmuera, se seca ($MgSO_4$) y se concentra in vacuo. El producto crudo (47 mg) se procesó por cromatografía (12 g SiO_2; elución con un gradiente continuo desde 15 hasta 100% EtOAc en DCM) para proporcionar 17.6 mg (30%) del compuesto del título como un aceite incoloro. $[M + H]^+$ = 636.3; ^{1}H-RMN (400 MHz, $CDCl_3$): δ 9.57 (s, 1H), 8.46 (s, 1H), 8.34 (s, 1H), 7.93 (d, 2H), 7.36 (s, 1H), 7.18 (s,1H), 7.17 (d, 2H), 6.87 (s, 1H), 4.60 - 4.75 (m, 3H), 3.52 - 3.63 (m, 2H), 3.41 (s, 3H), 3.39 (d, 2H), 3.08 (s, 3H), 1.25 - 1.36 (m, 15H).

EJEMPLO 27 (Isómero A) y EJEMPLO 28 (Isómero B)



A.

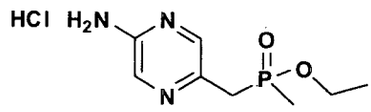


Una mezcla de 5-(bromometil)pirazin-2-ilcarbamato de tert-butilo (300 mg, 1.04 mmol) y metilfosfonito de dietilo

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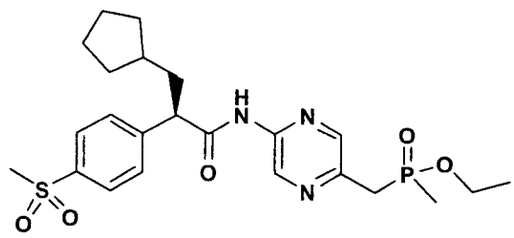
(0.2 mL) en THF (0.2 mL) se calentó durante la noche a 100°C, luego se enfría a temperatura ambiente y se disuelve en EtOAc (15 mL). La solución se lavó con agua (3 x 5 mL) y salmuera (5 mL), se secó (MgSO4), y se concentra in vacuo. El producto crudo (279 mg) se procesó por cromatografía (SiO_2; 80 g; elución con un gradiente continuo desde 0 - 100% EtOAc en DCM) para dar la parte A del compuesto (114 mg) como un sólido blanco ceroso, el cual todavía contiene el mismo sub-producto del reactivo de metilfosfonito de dimetilo. $[M + H]^+$ = 316.3.

B.



Una solución a 0°C de la parte A del compuesto (114 mg, 0.361 mmol) en DCM (1 mL) se trató con 4N HCl en dioxano (1 mL). La reacción se permitió calentar hasta temperatura ambiente durante la noche, luego se diluyó con Et_2O hasta que completamente el precipitado de la sal de HCl del producto deseado y se decanta. Este proceso se repitió varias veces para proporcionar la Parte B del compuesto (82 mg; 90%) como un sólido blanco. CL/EM muestra el correcto $[M + H]^+$ = 216.3 para la amina libre.

C.



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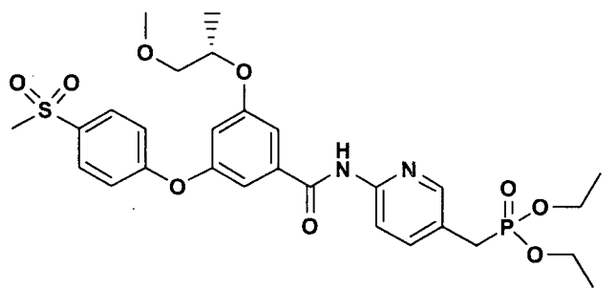
El ejemplo 1 Parte D del compuesto (91.9 mg, 0.310 mmol) se convirtió al cloruro ácido correspondiente usando cloruro de oxalilo (como se describe en el Ejemplo 2 Parte A). El cloruro ácido crudo se disolvió en un volumen mínimo de DCM y se agrega a una mezcla a 0°C de la Parte B del compuesto (52 mg, 0.242 mmol) y piridina (78.2 µL, 0.968 mmol) en DCM (1 mL) bajo Ar. La reacción se permitió calentar hasta temperatura ambiente durante la noche, luego se diluyó con DCM (7 mL) y se lava con dos porciones 2 mL de HCl acuoso 0.5N, agua, $NaHCO_3$ acuoso saturado y salmuera, se seca ($MgSO_4$) y se concentra in vacuo. El material crudo (150 mg) se procesó por cromatografía (40 g SiO_2; elución con un gradiente continuo desde 0 hasta 100% EtOAc en DCM, seguido por un gradiente continuo desde 0-10% MeOH en DCM) para dar el producto de diastereómeros (43 mg) como una mezcla. La HPLC de fase inversa preparativa en una YMC ODS-A 5µ 30x100 mm (elución con un gradiente continuo 40-100% desde 90:10:0.1 hasta 10:90:0.1, agua:MeOH:TFA) da 17.9 mg de un isómero A eluido más rápido y 18.3 mg del isómero B eluido más lento. Cada una de las muestras anteriores se disolvió en 6 mL de DCM y se enjuaga con 2 mL de $NaHCO_3$ acuoso saturado para remover TFA. Las soluciones DCM se enjuagaron con salmuera, se secan ($MgSO_4$) y se concentran in vacuo para dar los isómeros A y B deseados.

El isómero A (Ejemplo 27) se obtuvo como 16.8 mg de un

vidrio incoloro. $[M + H]^+$ = 494.4; ^{1}H-RMN (400 MHz, CD_3OD): δ 9.31 (s, 1H), 8.31 (s, 1H), 7.92 (m, 2H), 7.72 (m, 2H), 3.96 - 4.12 (m, 3H), 3.44 (d, 2H), 3.30 (s, 3H), 2.18 - 2.26 (m, 1H), 1.13 - 1.89 (m, 9H), 1.56 (d, 3H), 1.27 (m, 3H).

El isómero B (Ejemplo 28) se obtuvo como 15.6 mg de un vidrio incoloro: $[M + H]^+$ = 494.4; ^{1}H-RMN (400 MHz, CD_3OD): δ 9.31 (s, 1H), 8.31 (s, 1H), 7.91 (m, 2H), 7.70 (m, 2H), 3.97 - 4.12 (m, 3H), 3.44 (d, 2H), 3.30 (s, 3H), 2.16 - 2.26 (m, 1H), 1.13 - 1.88 (m, 9H), 1.54 (d, 3H), 1.28 (m, 3H).

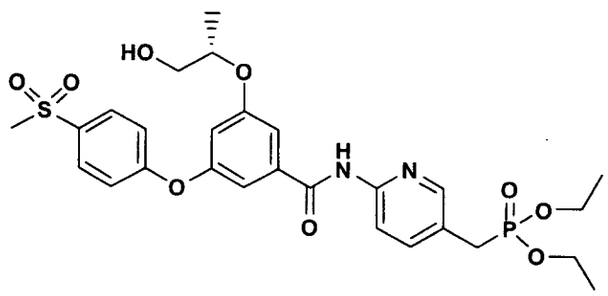
EJEMPLO 29



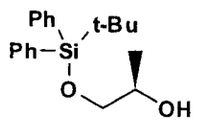
EDC (19.7 mg, 0.100 mmol) se agregó a 0°C una mezcla del Ejemplo 26C del ácido (34.6 mg, 0.091 mmol), HOAT (14.8 mg, 0.109 mmol), (6-aminopiridin-3-il)metilfosfonato de dietilo (24.4 mg, 0.100 mmol) y Et_3N (12.6 µL, 0.091 mmol) en 0.7 mL de DCM bajo Ar. La mezcla de reacción se permitió calentar hasta temperatura ambiente durante la noche. 12 mg adicionales de amina se agregó y se continuo agitando durante 4 días. La reacción se extrajo con 3 mL de DCM y se lava con 1 mL cada uno de HCl acuoso 0.5N, agua, $NaHCO_3$ acuoso saturado y salmuera, se seca ($MgSO_4$) y se concentra in vacuo.

El producto crudo (34 mg) se purificó por HPLC de fase inversa preparativa en una columna 30 x 100 mm Phenomenex Axia Luna 5μ C18 (gradiente continuo desde 30-100% 90:10:0.1 hasta 10:90:0.1, agua:CH_3CN: TFA) para proporcionar 29 mg de producto deseado. Este material se disolvió en 3 mL de DCM y se lava con dos porciones 1 mL de $NaHCO_3$ acuoso saturado, salmuera y se seca ($MgSO_4$). La concentración in vacuo proporcionar 20.8 mg (38% de rendimiento) del compuesto del título como un aceite incoloro. $[M + H]^+$ = 607.3; ^{1}H-RMN (400 MHz, $CDCl_3$): δ 8.54 (s, 1H), 8.30 (d, 1H), 8.20 (s, 1H), 7.91 (d, 2H), 7.72 (d, 1H), 7.34 (s, 1H), 7.12 - 7.17 (m, 3H), 6.85 (s, 1H), 4.62 (m, 1H), 4.06 (m, 4H), 3.50 - 3.62 (m, 2H), 3.41 (s, 3H), 3.11 (d, 2H), 3.08 (s, 3H), 1.23 - 1.35 (m, 9H).

EJEMPLO 30



A.

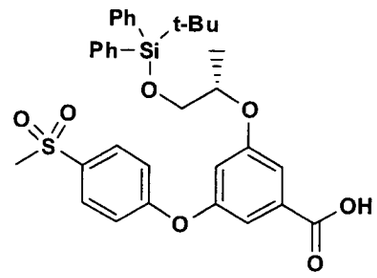


El imidazol (1.86 g, 27.4 mmol) se agregó a una mezcla

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de (R)-propano-1,2-diol (1 mL, 13.7 mmol) y TBSCl (4.1 mL, 16.44 mmol) en DMF (13 mL) a temperatura ambiente. La reacción se agitó a temperatura ambiente durante la noche, luego se concentró in vacuo. El residuo se extrajo con DCM (25 mL) y se lava con agua (20 mL). La capa acuosa se vuelve a extraer con DCM (25 mL), y los extractos orgánicos combinados se lavaron con salmuera (20 mL), se secan ($MgSO_4$) y se concentran in vacuo. El producto aceitoso crudo (6 g) se procesó por cromatografía (120 g SiO_2; gradiente continuo desde 0-20%, EtOAc en Hexano) para proporcionar la parte A del compuesto (3.69 g, 86% de rendimiento) como un aceite incoloro. $[M + H]^+$ no se observó en CL/EM. ^{1}H-RMN (400 MHz, $CDCl_3$): δ 7.67 (m, 4H), 7.41 (m, 6H), 3.91 (m, 1H), 3.61 (dd, 1H), 3.45 (dd, 1H), 2.58 (d, 1H), 1.10 (d, 3H), 1.07 (s, 9H).

B.



Una solución de DIAD (0.216 mL, 1.12 mmol) en THF (0.5 mL) se agregó gota a gota durante 3 min a una mezcla a 0°C de la parte A del compuesto (304 mg, 0.967 mmol), 3-hidroxi-5-(4-(metilsulfonil)fenoxi)benzoato de metilo (240 mg, 0.744 mmol) y Ph_3P soportada con polímero (1.6 mmol/g carga, 1.2 g,

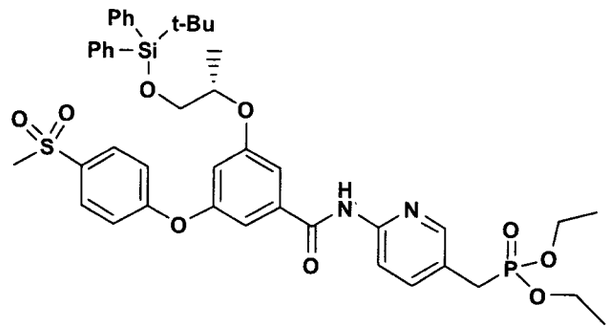
000533

1.92 mmol) en 10 mL de THF bajo Ar. La reacción se permitió calentar hasta temperatura ambiente. Después de 3 horas a temperatura ambiente, la reacción se filtró y la resina completamente se enjuaga con THF y DCM. Los filtrados combinados se concentraron in vacuo. El residuo se procesó por cromatografía (SiO_2; 40 g; gradiente continuo desde 0-40% EtOAc en Hexano) para dar el producto parcialmente purificado (contiene algo de DIAD reducido por ^{1}H-RMN) el cual se usó en la siguiente etapa sin purificación adicional.

LiOH.H_2O (93 mg, 2.22 mmol) se agregó a 0°C una mezcla del éster de metilo de arriba (nominalmente 0.744 mmol) en 4 mL de THF y 1 mL de agua. La reacción se permitió calentar hasta temperatura ambiente durante la noche. HPLC analítica indica que ~16% del material de partida restante, más LiOH.H_2O (31 mg) se agregó. Después de 4.5 h adicionales, la mezcla de reacción se concentró in vacuo, luego se dividió entre agua y EtOAc (15 mL cada uno). La capa acuosa se extrajo con 15 mL de EtOAc. Los extractos orgánicos combinados se lavaron con $KHSO_4$ acuoso al 10% (10 mL), 10 mL cada uno de agua y salmuera, se secan ($MgSO_4$) y se concentran in vacuo para dar la parte B del compuesto (402 mg, 90% de rendimiento), el cual todavía contiene algo de DIAD reducido. ^{1}H RMN (400 MHz, $CDCl_3$) asignaturas parciales: δ 7.90 (d, 2H), 7.63 (d, 4H), 7.46 (s, 1H), 7.30 - 7.43 (m, 7H), 7.10 (d, 2H), 6.82 (s, 1H), 4.58 (m, 1H), 3.77 (dd, 2H), 3.06 (s, 3H),

1.01 (s, 9H).

C.

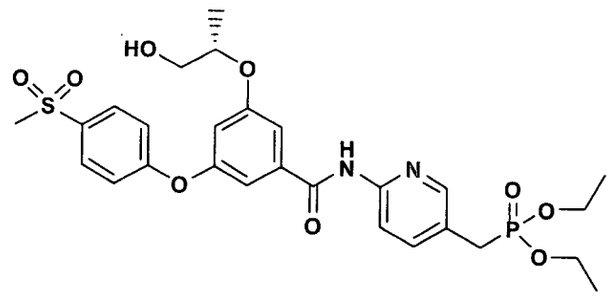


EDC (26.1 mg, 0.136 mmol) se agregó a 0°C una mezcla de la Parte B del compuesto (75 mg, 0.124 mmol), HOAT (20.2 mg, 0.149 mmol), (6-aminopiridin-3-il)metilfosfonato de dietilo (39.3 mg, 0.161 mmol) y Et_3N (19 µL, 0.136 mmol) en 1.5 mL de DCM bajo Ar. Después de 5 días, el análisis CL/EM muestra una relación ca. 62:9 de producto deseado al éster de HOAT de la parte B del ácido. Después de otras 24 h, la mezcla de reacción se diluyó con 7 mL de DCM y se lava con 2 mL cada uno de HCl acuoso 0.5N, agua, $NaHCO_3$ acuoso saturado y salmuera, se seca ($MgSO_4$) y se concentra in vacuo. El producto crudo (85 mg) se procesó por cromatografía (12 g SiO_2; elución con un gradiente continuo desde 0-5% MeOH hasta DCM) para proporcionar la Parte C del compuesto (46 mg; 45%) como un aceite incoloro. $[M + H]^+$ = 831.4; ^{1}H-RMN (400 MHz, $CDCl_3$): δ 8.57 (s,1H), 8.31 (d, 1H), 8.21 (s, 1H), 7.90 (d, 2H), 7.74 (d, 1H), 7.63 (m, 4H), 7.32 - 7.43 (m, 6H), 7.28 (s, 1H), 7.07 - 7.14 (m, 3H), 6.79 (s, 1H), 4.59 (m, 1H), 4.08 (m, 4H), 3.78 (dd, 2H), 3.12 (d, 2H), 3.07 (s, 3H), 1.33

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(d, 3H), 1.25 - 1.30 (m, 6H), 1.02 (s, 9H).

D.

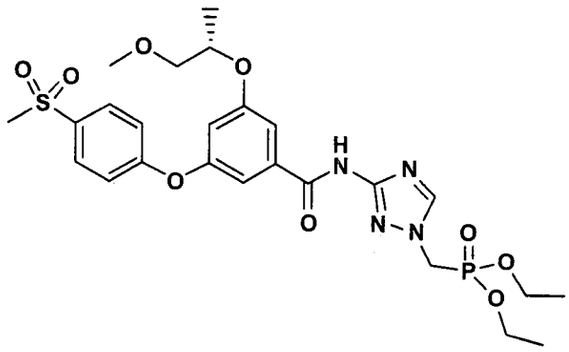


A 0°C una solución de la Parte C del compuesto (46 mg, 0.0553 mmol) en 1.5 mL de THF bajo Ar se agregó Bu_4NF (0.11 mL de una solución 1M en THF, 0.11 mmol). La reacción se permitió calentar hasta temperatura ambiente. Después de 4 hr, la mezcla de reacción se concentró in vacuo y se divide entre 6 mL de EtOAc y 2 mL de agua. El extracto orgánico se lavó con 2 mL cada uno de agua y salmuera, se seca ($MgSO_4$) y se concentra in vacuo. El residuo (44 mg) se purificó por HPLC de fase inversa preparativa en una columna 30x100 mm Phenomenex Axia Luna 5μ C18 (gradiente lineal 20-100% desde 90:10:0.1 hasta 10:90:0.1, agua:CH_3CN:TFA). El material purificado se disolvió en DCM (6 mL) y se lava con 2 mL cada uno de $NaHCO_3$ acuoso saturado y salmuera, se seca ($MgSO_4$) y se concentra in vacuo para proporcionar el compuesto del título (25 mg; 76%) como un aceite incoloro. $[M + H]^+$ = 593.2; ^1H-RMN (400 MHz, $CDCl_3$): δ 8.85 (s,1H), 8.31 (d, 1H), 8.17 (s, 1H), 7.92 (d, 2H), 7.72 (d, 1H), 7.34 (s, 1H), 7.16 (s, 1H), 7.12 (d, 2H), 6.81 (s, 1H), 4.58 (m, 1H), 4.07 (m, 4H), 3.77 (m,

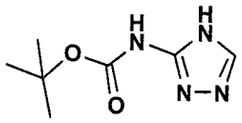
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2H), 3.08 (s, 3H), 1.27 (m, 6H).

EJEMPLO 31



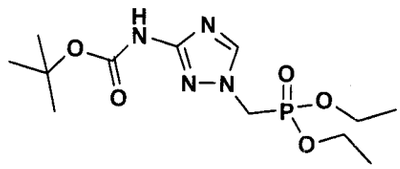
A.



A temperatura ambiente una mezcla espesa de 3-amino-1,2,4-triazol (1.0 g, 11.9 mmol) en Hexanos (20 mL) se agregó TMEDA (0.07 g, 0.6 mmol) y bicarbonato de di-tert-butilo (3.89 g, 17.8 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 24 h, se vacía en $NaHCO_3$ acuoso saturado (150 mL) y el producto se extrajo con EtOAc (2 x 25 mL). Los extractos orgánicos se combinaron, se secaron ($MgSO_4$) y se concentran in vacuo. El residuo se procesó por cromatografía (SiO_2: gradiente continuo desde 0% EtOAc/Hexano hasta 100% EtOAc/Hex) para dar la parte A del compuesto deseado (1.33 g, 61% de rendimiento) como un sólido blanco. $[M + H]^+$ = 185.0; ^1H RMN (400 MHz, $CDCl_3$): δ 7.48 (s, 1H), 1.66 (s, 9H)

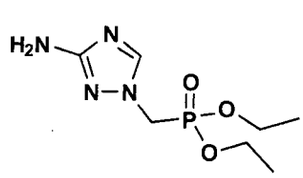
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B.



A 0°C una solución de la parte A del compuesto (0.500g, 2.71 mmol) en DMF (5 mL) se agregó 60% NaH en aceite (0.119 g, 2.99 mmol), en 1 porción, y la mezcla espesa resultante se agitó a 0°C durante 1 h. $ICH_2PO_3Et_2$ (0.830 g, 2.99 mmol) se agregó, y la mezcla de reacción se agitó durante la noche a temperatura ambiente. La mezcla de reacción se vació en salmuera (35 mL); y se extrae con EtOAc (4 x 25 mL); los extractos orgánicos combinados se secaron ($MgSO_4$) y se concentran in vacuo. El residuo se purificó por HPLC preparativa (columna Phenomenex Luna AXIA 30 x 100 mm; detección a 220 nm; relación de flujo =40 mL/min.; gradiente continuo desde 100% A hasta 100% B durante 15 min. + 2 min. espera a 100% B, donde A=90:10 H_2O:MeOH y B=90:10 MeOH: H_2O) para proporcionar la Parte B del compuesto (0.059 g, 6.5% de rendimiento) como un sólido blanco. [M + H]=335.1; ^1H RMN (400 MHz, DMSO-d_6): δ 9.59 (s, 1H), 8.24 (d, J=1.76 Hz, 1H), 4.75 (d, J=11.87 Hz, 2H), 4.10-4.00 (m, 4H), 1.42 (s, 9H) 1.21 (t, J=7.03 Hz, 6H).

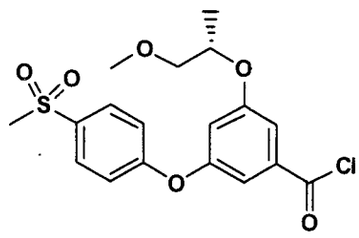
C.



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A temperatura ambiente una solución de la Parte B del compuesto (0.059 g, 0.177 mmol) en CH_2Cl_2 (1 mL) se agregó TFA (2.04 mL, 3.13 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 2 h, luego se concentró in vacuo. El residuo se purificó por HPLC preparativa (columna Phenomenex Luna 21.2 x 100 mm; detección a 220 nm; relación de flujo = 20 mL/min.; gradiente continuo desde 100% A hasta 100% B durante 15 min. + 2 min. espera a 100% B, donde A=90:10:0.1 H_2O:MeOH:TFA y B=90:10:0.1 MeOH: H_2O:TFA) para proporcionar la Parte C del compuesto (0.050 g, 81% de rendimiento) como un aceite claro. ^1H RMN (400 MHz, $CDCl_3$) δ 7.27 (s, 1H), 6.78 (s, 2H), 4.43 (d, J=13.62 Hz, 2H), 4.24-4.15 (m, 4H), 1.32-1.38 (m, 6H).

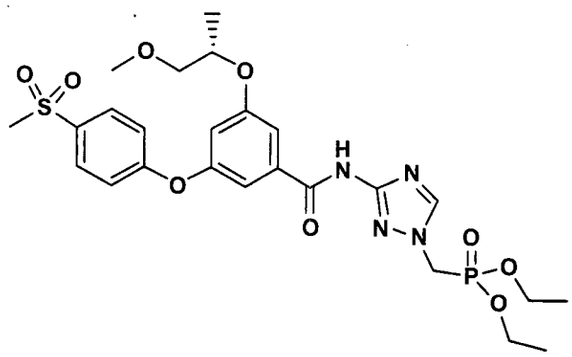
D.



A temperatura ambiente una solución del Ejemplo 26 Parte C del compuesto (0.023 g, 0.060 mmol) en CH_2Cl_2 (1 mL) se agregaron cloruro de oxalilo (10.6 μL, 0.121 mmol) y DMF (0.9 μL, 0.012 mmol) y la mezcla de reacción se agitó a temperatura ambiente durante 1 h. Los volátiles se removieron in vacuo para proporcionar la Parte D del compuesto crudo (0.060 g) como un aceite amarillo.

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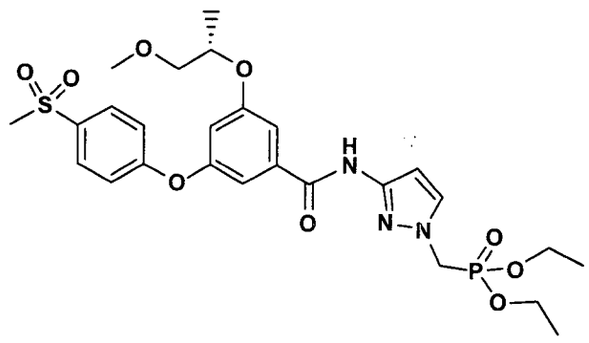
E.



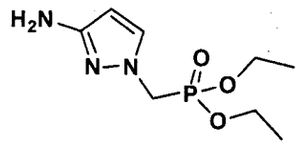
A temperatura ambiente una solución de la parte D del compuesto crudo (0.060 g, 0.24 mmol) en CH_2Cl_2 (1 mL) se agregaron una solución de la Parte C del compuesto (0.031 g, 0.090 mmol) y piridina (0.019 mL, 0.241 mmol) en CH_2Cl_2 (1 mL). La mezcla de reacción se agitó a temperatura ambiente durante la noche, luego se dividió entre $NaHCO_3$ acuoso saturado (1 mL) y EtOAc (2 mL); la fase orgánica se lavó con $NaHCO_3$ acuoso saturado (1 mL), se seca ($MgSO_4$) y se concentra in vacuo. El residuo se purificó por HPLC preparativa (Columna Phenomenex Luna AXIA 21.2 x 100 mm; detección a 220 nm; relación de flujo = 40 mL/min.; gradiente continuo desde 100% A hasta 100% B durante 15 min. + 2 min. espera a 100% B, donde A=90:10 H_2O:MeOH y B=90:10 MeOH: H_2O) para proporcionar el compuesto del título (0.007 g, 19.0% de rendimiento) como un sólido blanco. $[M + H]^+$ = 597.3; ^1H RMN (400 MHz, $CDCl_3$): δ 9.65 (s, 1H), 8.42 (d, J=1.76 Hz 1H), 7.92 (t, J=1.76 Hz, 1H), 7.90 (t, J=1.76 Hz, 7.45 (t, J=1.75 Hz, 1H), 7.32 (t, J=1.76 Hz 1H), 7.15 (t, J=1.76 1H), 7.14 (t, J=1.76 Hz), 6.88

(t, J=2.19 Hz 1H), 4.80-4.75 (m, 1H), 4.70 (d, J=13.18 Hz, 2H), 4.29-4.19 (m, 4H), 3.64-3.54 (m, 2H), 3.42 (s, 3H), 3.07 (s, 3H), 1.35 (t, J=7.03, 9H).

EJEMPLO 32



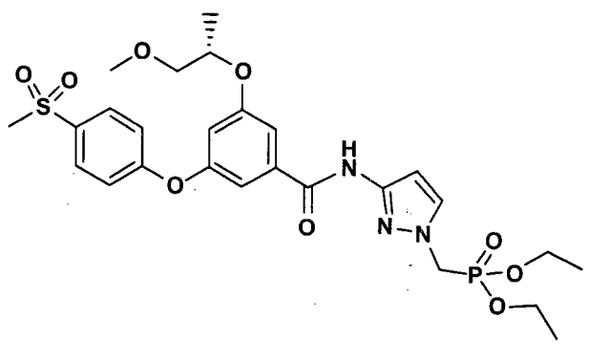
A.



A 0°C una solución of 1H-pirazol-3-amina (1.00g, 12.03 mmol) en DMF (25 mL) se agregó tert-butóxido de potasio (2.70 g, 24.07 mmol) y la mezcla de reacción se agitó a 0°C durante 1 h. $ICH_2PO_3Et_2$ (3.35 g, 12.03 mmol) se agregó, y la mezcla de reacción se agitó a 0°C durante 1.5 h, luego se permitió calentar hasta temperatura ambiente y se agita a temperatura ambiente durante la noche. Los volátiles se removieron in vacuo, y el residuo se dividió entre salmuera (30 mL) y EtOAc (30 mL). El producto se extrajo con EtOAc (5 x 30 mL); los extractos orgánicos combinados se secaron ($MgSO_4$), y se concentran in vacuo. El residuo se purificó por HPLC

preparativa (columna Phenomenex Luna AXIA 5 mm C18 30 x 100 mm; detección a 220 nm; relación de flujo =40 mL/min.; gradiente continuo desde 100% A hasta 20% B durante 25 min. + 2 min. espera a 20% B, donde A=90:10 H_2O:MeCN y B=90:10 MeCN: H_2O) para proporcionar la parte A del compuesto (0.470 g, 16.8% de rendimiento) como un sólido amarillo pálido. $[M + H]^+$ = 233.9; ^1H RMN (400 MHz, $CDCl_3$): δ 7.29 (s, 1H), 5.66 (d,J=2.20 Hz, 1H), 4.36 (d, J=11.55 Hz, 2H), 4.10 (m, 4H), 3.76 (s, 2H) 1.29 (t, J=7.15 Hz, 6H).

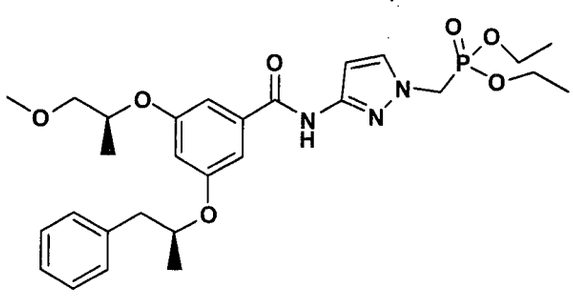
B.



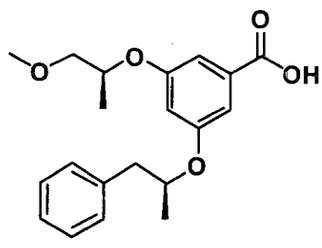
A temperatura ambiente una solución del Ejemplo 26 Parte C del compuesto (0.16 g, 0.421 mmol) en DMF (8 mL) se agregaron EDAC (0.161 g, 0.841 mmol), HOAT (0.114 g, 0.841 mmol), y iPr_2NEt (0.185 mL, 1.05 mmol), y la mezcla de reacción se agitó a temperatura ambiente durante 30 min. Una solución de la parte A del compuesto (0.123 g, 0.526 mmol) en DMF (2 mL) se agregó y la mezcla de reacción se agitó a temperatura ambiente durante la noche, luego se vacía en H_2O (40 mL). La mezcla se extrajo con EtOAc (2 x 15 mL); los extractos orgánicos combinados se secaron ($MgSO_4$) y se concentran in vacuo. El

residuo se purificó por HPLC preparativa (columna Phenomenex Luna 5 μ C18 30 x 100 mm; detección a 220 nm; relación de flujo =40 mL/min.; gradiente continuo desde 100% A hasta 1000% B durante 25 min. + 10 min. espera a 100% B, donde A=90:10 H_2O:MeCN y B=90:10 MeCN: H_2O) para proporcionar el compuesto del título (0.149 g, 59.4% de rendimiento) como un sólido blanco. $[M + H]^+$ = 596.3; ^1H RMN (400 MHz, $CDCl_3$): δ 8.98 (s, 1H), 7.92 (t, J=1.65 Hz, J=3.3 Hz 1H), 7.90 (t, J=2.70 Hz, j=2.2 Hz, 1H) 7.47 (d, J=2.2 Hz, 1H), 7.35 (t, J=1.65 Hz, 1H), 7.20 (t, J=2.2 Hz,1H), 7.14 (t, J=2.75 Hz, J=2.2 Hz, 1H),7.12 (t, J=2.75 Hz, J=2.20 Hz, 6.90 (d, J=2.20 Hz, 1H), 6.82 (t, J=2.20 Hz, 1H), 4.67-4.59 (m, 1H), 4.51 (d, J=12.09 Hz, 2H), 4.13-4.03 (m, 4H), 3.58 (dd, J= 10.44 Hz, J= 6.05 Hz, 1H), 3.51 (dd, J=10.44 Hz, J=3.85 Hz, 1H), 3.40 (s, 3H), 3.08 (s, 3H), 1.33 (d, J=6.05 Hz, 3H), 1.27 (t, J=7.14 Hz, 6H).

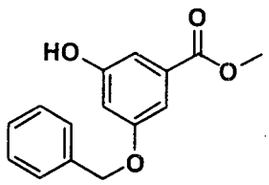
EJEMPLO 33



A.

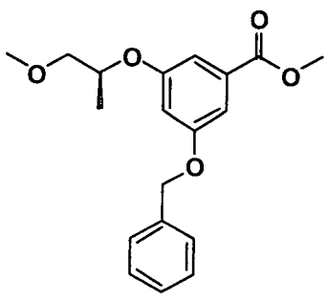


i.



A una solución de 3,5-dihidroxibenzoato de metilo (10.0 g, 59.5 mmol) en DMF (60.0 mL) bajo Ar se agregó K_2CO_3 (12.4 g, 89.7 mmol) a temperatura ambiente. Bromuro de bencilo (10.0 mL, 84.2 mmol; se filtra a través de Al_2O_3 básico previo al uso) se agregó lentamente durante 10 min. La mezcla de reacción se agitó durante 12 h a temperatura ambiente y luego se apaga cuidadosamente con NH_4Cl acuosos saturado (50 mL), seguido por H_2O (350 mL). La suspension acuosa se extrajo con CH_2Cl_2 (1x30 mL, 2x50 mL). Los extractos orgánicos combinados se lavaron con H_2O (100 mL) y salmuera, se secan [$MgSO_4$] y se concentran in vacuo para dar el producto crudo (27.0 g) como un aceite color dorado. El material crudo se procesó por cromatografía (producto eluido durante la porción de EtOAc/Hexano al 30% de un gradiente en etapas (10-50% EtOAc/Hexano) para proporcionar la Parte A(i) del compuesto (4.6 g, 30%) como un polvo color crema.

ii.

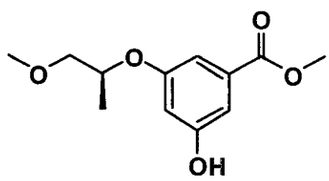


A 0°C una solución de la Parte A(i) del compuesto (1.0

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g, 3.9 mmol) en THF (16.8 mL) se agregaron sucesivamente (R)-(-)-1-metoxi-2-propanol (0.5 g, 5.8 mmol) y Ph_3P (1.5 g, 5.8 mmol), seguido por la adición lenta de DIAD (1.1 mL, 5.8 mmol). La mezcla de reacción se calentó hasta temperatura ambiente y se agita a temperatura ambiente durante 2 días. La mezcla de reacción se diluyó con H_2O y se extrae con Et_2O. La capa orgánica se secó [$MgSO_4$] y se concentra in vacuo para dar un aceite amarillo, pálido, espeso. Este material crudo se procesó por cromatografía (producto eluido durante la porción de EtOAc/Hexano al 20% de un gradiente en etapas de 10-30% EtOAc/Hexano) para dar la Parte A(ii) del compuesto (1.1 g, 85% de rendimiento) como un aceite incoloro.

iii.

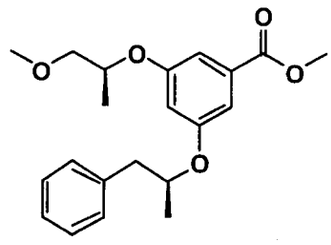


Un matraz que contiene la Parte A(ii) del compuesto (1.2 g, 3.6 mmol) en MeOH (45.4 mL) se evacuaron y se mojan con Ar. En una porción, 10% Pd/C (0.38 g, 0.36 mmol) se agregó. La mezcla se agitó bajo una atmosfera de H_2 durante 12 h a temperatura ambiente, luego se filtró a través de Celite®, el cual se lavó con EtOAc. Los filtrados combinados se concentraron in vacuo para dar la Parte A(iii) del compuesto (0.81 g, 93% de rendimiento) como un aceite

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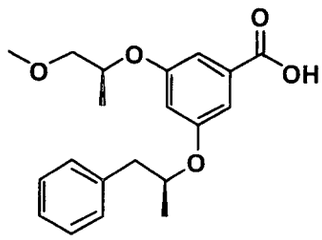
amarillo.

iv.



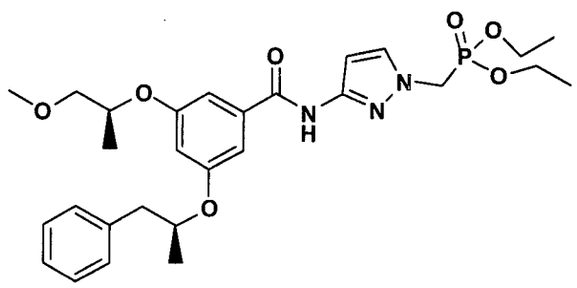
A 0°C una solución de la Parte A(iii) del compuesto (0.14 g, 0.59 mmol) en THF (2.9 mL) se agregaron Ph_3P (0.4 g, 1.3 mmol) y (R)-1-fenilpropan-2-ol (0.2 g, 1.3 mmol) bajo Ar. La mezcla de reacción se agitó durante 5 min a 0°C, luego DIAD (0.3 mL, 1.3 mmol) se agregó gota a gota. La mezcla de reacción se agitó a temperatura ambiente durante 12 h, luego se diluyó con H_2O y se extrae con EtOAc (2x). Los extractos orgánicos combinados se lavaron con NaOH acuoso 1N y salmuera, se secan [$MgSO_4$] y se concentran in vacuo para dar un aceite amarillo pálido (1.0 g). Este material crudo se procesó por cromatografía (producto eluido durante la porción de EtOAc/Hexano al 20% de un gradiente en etapas desde 5-20% EtOAc/Hexano) para dar la Parte A(iv) del compuesto (0.17 g, 81% de rendimiento) como un aceite incoloro puro.

v.



A una solución de la Parte A(iv) del compuesto (0.17g, 0.5 mmol) en THF (1.8 mL) y H_2O (0.6 mL) se agregó $LiOH.H_2O$ (0.02 g, 0.52 mmol) a temperatura ambiente. La mezcla de reacción se agitó a 45°C durante 1 h; una porción adicional de $LiOH.H_2O$ se agregó, y se continuó agitando a 45°C. El material de partida se consumió después de 6 h, y la reacción se enfrió hasta temperatura ambiente. Los volátiles se removieron in vacuo, y la capa acuosa restante se hizo ácida hasta pH 2 con HCl acuoso 0.5 N, luego se extrajo con EtOAc (3x). Los extractos orgánicos combinados se lavaron con salmuera, se secan [$MgSO_4$] y se concentran in vacuo para dar la parte A(v) del compuesto crudo (0.16 g, 86%) como un aceite amarillo pálido.

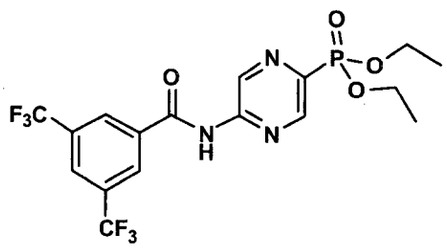
B.



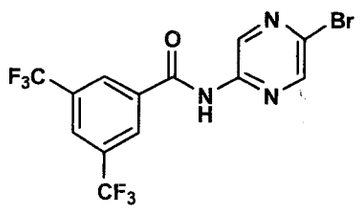
A temperatura ambiente una solución de la Parte A(v) del compuesto (0.030 g, 0.087 mmol) en DMF (1.5 mL) se agregó EDAC (0.033 g, 0.174 mmol), HOAt (0.024 g, 0.174 mmol), y DIEA (0.038 mL, 0.218 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 30 min, después del cual una solución del Ejemplo 32 de la parte A del compuesto (0.025 g, 0.109 mmol) en DMF (0.5 mL) se agregó. La mezcla de

reacción se agitó a temperatura ambiente durante la noche, luego se vació en agua (7 mL); la mezcla se extrajo con EtOAC (2 x 10 mL). Los extractos orgánicos combinados se secaron ($MgSO_4$) y se concentran in vacuo. El residuo se purificó por HPLC preparativa (columna Phenomenex Luna AXIA 100A 5 m C18; detección a 220 nm; relación de flujo =40 mL/min.; gradiente continuo desde 100% A hasta 100% B durante 25 min. + 2 min. espera a 100% B, donde A=90:10 H_2O:MeCN y B=90:10 MeCN: H_2O) para proporcionar el compuesto del título (0.027 g, 56.3% de rendimiento) como un aceite claro. $[M + H]^+$ = 560.4; ^1H RMN (400 MHz, $CDCl_3$): δ 8.59 (s, 1H), 7.44-7.46 (m, 1H), 7.32-7.19 (m, 5H), 7.00 (t, J=1.65 Hz, 1H), 6.97 (t, J=2.2 Hz, 1H), 6.91 (d, J=2.2 Hz, 1H), 6.63 (t, J=2.2 Hz, 1H), 4.65-4.53 (m, 2H), 4.44 (d, J=11.54 Hz, 2H), 4.14-4.04 (m, 4H), 3.56 (dd, J=9.9 Hz, J=5.5 Hz,1H), 3.49 (dd,J=9.89 Hz, J=3.84 Hz, 1H), 3.41 (s, 3H), 3.06 (dd, J=13.74 Hz, J=6.04 Hz, 1H), 2.85 (dd, J=13.74 Hz, J=6.04 Hz, 1H), 1.26 (m, 12H).

EJEMPLO 34

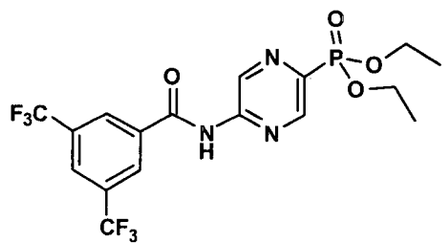


A.



A 0°C una solución del ácido 3,5-bis(trifluorometil)benzoico (129 mg, 0.50 mmol) en CH_2Cl_2 (1 mL) se agregó cloruro de oxalilo (0.375 mL, 0.75 mmol, 2M en CH_2Cl_2) y DMF (1 gota). La reacción se agitó a 0°C durante 30 min y luego se calienta a temperatura ambiente y se agitó durante 4 h. La mezcla se concentró in vacuo. A una solución del residuo de cloruro ácido en CH_2Cl_2 (3 mL) se agregó 5-bromopirazin-2-amina (130 mg, 0.75 mmol) y piridina (0.061 mL, 0.75 mmol). La reacción se agitó a temperatura ambiente durante 18 h y se diluyó con CH_2Cl_2 (6 mL), y se lavó con HCl acuoso 0.5 N (1 mL, 2x), agua (1 mL), $NaHCO_3$ acuoso saturado (1 mL), y salmuera. La capa orgánica se secó ($MgSO_4$), se filtró, y se concentra in vacuo. El residuo se procesó por cromatografía (SiO_2) para proporcionar la parte A del compuesto (40 mg, 19% de rendimiento) como un sólido blanco.

B.

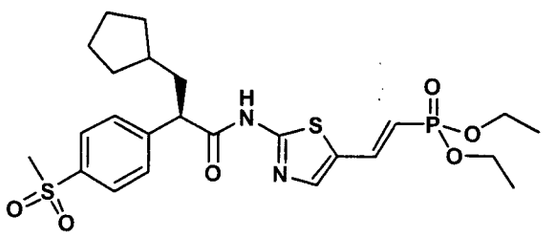


THF (desgasificado)(0.40 mL) se agregó a la parte A del compuesto (25.0 mg; 0.060 mmol) y $(Ph_3P)_4Pd°$ (13.9 mg; 0.012 mmol). $H(O)P(OEt)_2$ (9.33 µL; 0.072 mmol) se agregó seguido por TEA (11.7 mL; 0.084 mmol). La mezcla de reacción se calentó a 85°C durante 5 h, luego se enfrió hasta temperatura

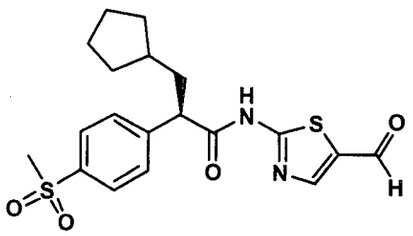
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ambiente y se divide entre EtOAc (3 mL) y salmuera (3 mL). La fase orgánica se secó ($MgSO_4$) y se concentra in vacuo. El producto crudo se purificó por HPLC preparativa (columna YMC de fase inversa ODS-A-5mm 30 x 100 mm; relación de flujo = 40 mL/min, 45 hasta 100% solvente B durante 12 min, espera a 15 min, donde solvente A = 90:10:0.1 H_2O:MeOH:TFA y solvent B = 90:10:0.1 MeOH:H_2O:TFA) para dar el compuesto del título (11.6 mg; 41%) como un sólido amarillo ligero. $[M + H]^+$ = 472.2; ^1H RMN (400 MHz, $CDCl_3$): δ 1.37 (t, 6H), 4.27 (m, 4H), 8.12 (s, 1H), 8.53 (s, 2H), 8.82 (s, 1H), 9.53 (s, 1H), 9.80 (s, 1H).

EJEMPLO 35



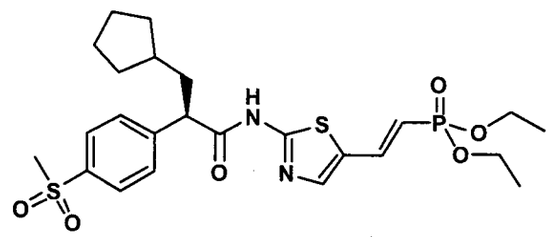
A.



DIPEA (66 µL; 0.378 mmol) se agregó a una solución agitada del Ejemplo 1 de la Parte D del compuesto (80 mg; 0.270 mmol), 2-amino-5-formiltiazol (43.3 mg; 0.338 mmol) y HOAt (44.0 mg; 0.324 mmol) en DMF (1.0 mL). EDAC (62.0 mg;

0.324 mmol) se agregó. Después de 3 h a temperatura ambiente, la mezcla de reacción se dividió entre EtOAc (8 mL) y H_2O (8 mL). La fase orgánica se lavó con HCl acuoso 1N (5 mL), $NaHCO_3$ acuoso saturado (5 mL) y salmuera (5 mL), se seca ($MgSO_4$) y se concentra in vacuo. El producto crudo se procesó por cromatografía (SiO_2; gradiente continuo desde 0 hasta 100% EtOAc in Hexanos over 11 min, espera a 100% EtOAc for 4 min) para dar la parte A del compuesto (81 mg; 74%) como una espuma.

B.

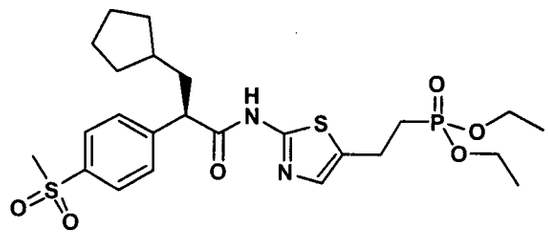


$CH_2(PO_3Et)_2$ (59.4 µL; 0.239 mmol) se agregó a una mezcla de LiCl pulverizado (10.13 mg; 0.239 mmol) en CH_3CN (1.0 mL). DBU (35.7 µL; 0.239 mmol) se agregó seguido por una solución de la parte A del compuesto (81.0 mg; 0.199 mmol) en CH_3CN (1.0 mL). Después de 24 h a temperatura ambiente más $CH_2(PO_3Et)_2$ (9.92 µL; 0.040 mmol), DBU (5.96 µL; 0.040 mmol) y LiCl (1.7 mg; 0.040 mmol) se agregaron. Después de 72 h la mezcla de reacción se concentró in vacuo. El residuo se dividió entre EtOAc (8 mL) y HCl acuoso 0.2 N (8 mL). La fase orgánica se lavó con salmuera (6 mL), se seca ($MgSO_4$) y se concentra in vacuo. El producto crudo se procesó por

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cromatografía (SiO_2; gradiente continuo desde 0% hasta 100% EtOAc en Hexanos durante 6 min, cambiado a MeOH al 2% en EtOAC y mantenido durante 8 min) para dar el compuesto del título (67 mg; 62%) como un sólido incoloro. $[M + H]^+$ = 541.1; ^1H RMN (400 MHz, $CDCl_3$)(19:1, E/Z): δ 1.15 (m, 2H), 1.37 (m, 6H), 1.48 (m, 2H), 1.66 (m, 3H), 1.78 (m, 2H), 1.92 (m, 1H), 2.27 (m, 1H), 3.03 (s, 3H), 4.12 (m, 5H), 5.88 (dd, J = 17.3 Hz, 1H), 7.58 (s, 1H), 7.66 (d, 2H), 7.89 (d, 2H), 8.14 (dd, J = 17.1 Hz, 1H).

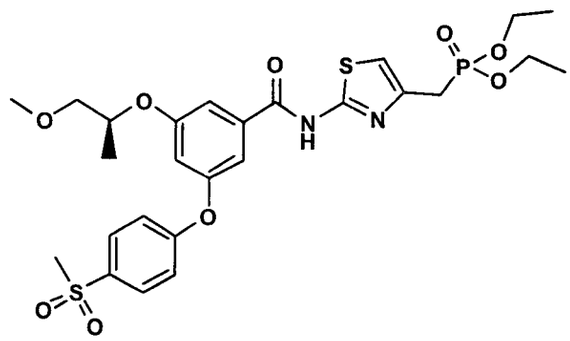
EJEMPLO 36



$Pd(OH)_2$ al 20% (16 mg) se agregó a una solución del Ejemplo 35 del compuesto (35 mg; 0.065 mmol) en MeOH (0.40 mL). Una atmosfera H_2 (g) se introdujo por medio de globo. Después de 48 h de agitar, la mezcla de reacción se filtró. El catalizador se enjuagó con MeOH (1.5 mL), EtOAc (1.5 mL) y $CHCl_3$ (1.5 mL) y los filtrados combinados se concentraron in vacuo. El producto crudo se purificó por HPLC preparativa (columna YMC de fase inversa ODS-A-5u 20 x 100 mm; relación de flujo = 20 mL/min, 15 hasta 100% solvente B durante 10 min, espera a 12 min, donde el solvente A = 90:10:0.1 H_2O:MeOH:TFA y solvente B = 90:10:0.1 MeOH:H_2O:TFA) para

proporcionar el compuesto del título (18 mg; 51%). $[M + H]^+$ = 543.2; ^1H RMN (400 MHz, CD_3OD): δ 1.19 (m, 2H), 1.29 (t, 6H), 1.51 (m, 2H), 1.64 (m, 3H), 1.80 (m, 3H), 2.17 (m, 3H), 3.05 (m, 2H), 3.09 (s, 3H), 3.96 (t, 1H), 4.07 (m, 4H), 7.20 (s, 1H), 7.67 (d, 2H), 7.92 (d, 2H).

EJEMPLO 37

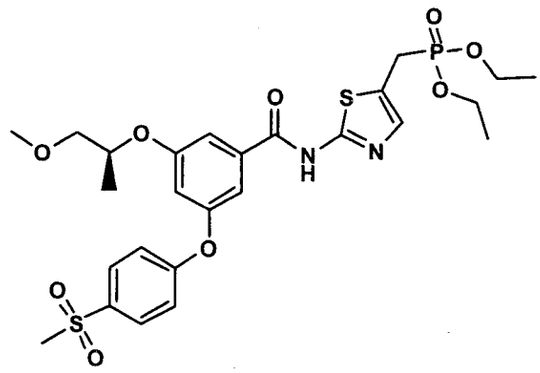


DIPEA (387 μL; 2.22 mmol) se agregó a una solución fría (0°C) del Ejemplo 26 Parte C del compuesto (704 mg; 1.85 mmol), Ejemplo 13 Parte E del compuesto (556 mg; 2.22 mmol) y HOAt (302 mg; 2.22 mmol) en DMF (7.4 mL). EDAC (426 mg; 2.22 mmol) se agregó. Después de 24 h a temperatura ambiente, la mezcla de reacción se dividió entre EtOAc (100 mL) y H_2O (75 mL). La fase orgánica se lavó con HCl acuoso 0.5 N (50 mL), $NaHCO_3$ acuoso saturado (50 mL) y salmuera (50 mL), se seca ($MgSO_4$) y se concentra in vacuo. El producto crudo se purificó por HPLC preparativa (Columna YMC de fase inversa ODS-A-5u 30 x 250 mm; relación de flujo = 30 mL/min, 15 hasta 100% solvente B durante 25 min, espera a 30 min, donde el solvente A = 90:10:0.1 H_2O:CH_3CN:TFA y solvente B = 90:10:0.1 CH_3CN:H_2O:TFA). El producto se purificó por HPLC preparativa una segunda vez usando las

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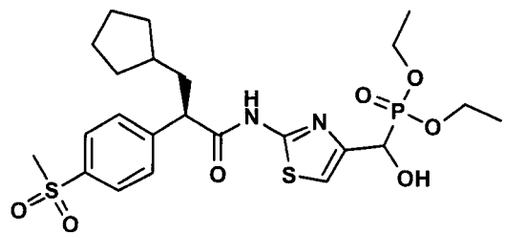
mismas condiciones pero usando MeOH en lugar de CH_3CN para dar el compuesto del título (778 mg; 69%) como una espuma blanca. $[M + H]^+$ = 613.2; ^1H RMN (400 MHz, $CDCl_3$): δ 1.26 (t, 6H), 1.35 (d, 3H), 3.08 (s, 3H), 3.34 (d, 2H), 3.41 (s, 3H), 3.55 (m, 2H), 4.08 (m, 4H), 4.69 (m, 1H), 6.88 (s, 2H), 7.14 (d, 2H), 7.30 (s, 1H), 7.48 (s, 1H), 7.92 (d, 2H).

EJEMPLO 38

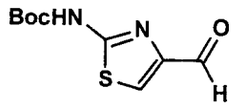


El compuesto del título (39 mg; 78%; sólido amarillo) se sintetizó del Ejemplo 15 Parte D del compuesto empleando el procedimiento descrito para el Ejemplo 37. $[M + H]^+$ = 613.3; ^1H RMN (400 MHz, $CDCl_3$): δ 1.34 (m, 9H), 3.08 (s, 3H), 3.28 (d, 2H), 3.41 (s, 3H), 3.59 (m, 2H), 4.15 (m, 4H), 4.84 (m, 1H), 6.93 (s, 1H), 7.15 (d, 2H), 7.34 (d, 1H), 7.40 (s, 1H), 7.63 (s, 1H), 7.92 (d, 2H).

EJEMPLO 39

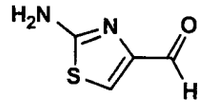


A.



Una solución del Ejemplo 13 Parte B del compuesto (0.94 g; 4.08 mmol) en DCM (8 mL) se agregó gota a gota a 0°C una solución de peryodinano Dess-Martin (1.82 g; 4.28 mmol) en DCM (8 mL). Después de 20 h a temperatura ambiente, la reacción se diluyó con DCM (4 mL) y NaOH acuoso 1.0 N (6 mL). Después de agitar durante 10 min, la mezcla se filtró a través de Celite®. La fase orgánica se lavó con salmuera (10 mL), se seca ($MgSO_4$) y se concentra in vacuo. El residuo se procesó por cromatografía (SiO_2; gradiente continuo desde 0 hasta 50% EtOAc en Hexanos durante 12 min, espera a 50% EtOAc en Hexanos durante 8 min) para dar la parte A del compuesto (0.65 g; 70%) como un sólido blanco.

B.

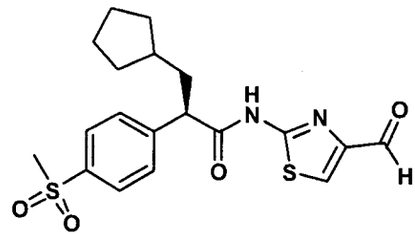


TFA (2.0 mL) se agregó a 0°C una solución de la parte A del compuesto (0.64 g; 2.80 mmol) en DCM (4.0 mL). Después de 20 h a temperatura ambiente la mezcla de reacción se concentró in vacuo. El residuo se dividió entre EtOAc (10 mL) y $NaHCO_3$ acuoso saturado (8 mL). La fase acuosa se aisló y se extrae con EtOAc (5 x 8 mL). Los extractos orgánicos combinados se secaron ($MgSO_4$) y se concentran in vacuo para

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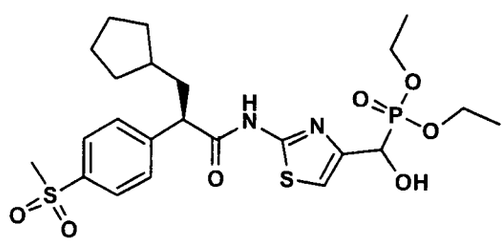
dar la parte B del compuesto (0.30 g; 83%) como un sólido amarillo.

C.



DIPEA (88.7 µL; 0.509 mmol) se agregó a una solución agitada del Ejemplo 1 Parte D del compuesto (130 mg; 0.439 mmol), Parte B del compuesto (67.4 mg; 0.526 mmol) y HOAt (69.3 mg; 0.509 mmol) en DMF (1.5 mL). EDAC (97.6 mg; 0.509 mmol) se agregó. Después de 20 h agitando a temperatura ambiente la mezcla de reacción se dividió entre EtOAc (12 mL) y H_2O (12 mL). La fase orgánica se lavó con HCl acuoso 0.5 N (8 mL), $NaHCO_3$ acuoso saturado (8 mL) y salmuera (8 mL), se seca ($MgSO_4$) y se concentra in vacuo. El producto crudo se procesó por cromatografía (SiO_2; gradiente continuo desde 0 hasta 80% EtOAc en Hexanos durante 13 min, espera a 80% EtOAC en Hexanos durante 3 min) para dar la Parte C del compuesto (100 mg; 56%) com una espuma amarilla.

D.

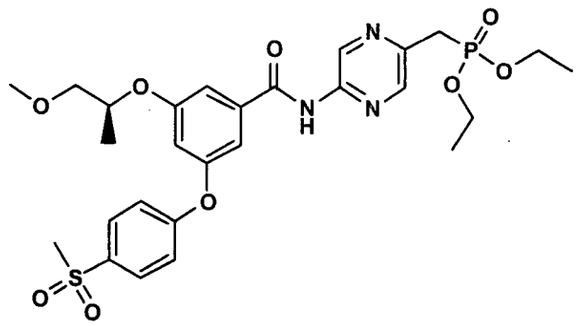


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$H(O)P(OEt)_2$ (10.0 µL; 0.078 mmol) se agregó a la Parte C del compuesto (30.0 mg; 0.074 mmol) seguido por piridina (6.6 µL; 0.081 mmol). La mezcla de reacción se calentó a 70°C durante 5 h, luego se enfría hasta temperatura ambiente. Después de 48 h más $H(O)P(OEt)_2$ (10.0 µL; 0.078 mmol) y piridina (10.0 µL; 0.123 mmol) se agregaron y se continua calentando a 70°C. Después de 7 h la reacción se enfrió hasta temperatura ambiente y se diluye con EtOAc (3 mL), se lava con HCl acuoso 1.0 N (1.5 mL) y salmuera (1.5 mL), se seca ($MgSO_4$) y se concentra in vacuo. El producto crudo se procesó por cromatografía (SiO_2; gradiente continuo desde 0 hasta 100% EtOAc en Hexanos durante 3 min, cambiado a MeOH al 3% en EtOAc y se mantiene durante 8 min). El producto luego se purificó por HPLC preparativa (columna YMC de fase inversa ODS-A-5u 20 x 100 mm; relación de flujo = 20 mL/min, 10 hasta 100% solvente B durante 10 min, espera a 12 min, donde el solvente A = 90:10:0.1 H_2O:MeOH:TFA y solvente B = 90:10:0.1 MeOH:H_2O:TFA) para dar el compuesto del título (14 mg; 35%) como un sólido amarillo ligero (mezcla diastereomérica). $[M + H]^+$ = 545.2; ^1H RMN (400 MHz, $CDCl_3$): δ 1.13 (m, 2H), 1.28 (m, 6H), 1.49 (m, 2H), 1.60 (m, 3H), 1.76 (m, 2H), 1.96 (m, 1H), 2.23 (m, 1H), 3.04 (s, 3H), 4.01 (t, 1H), 4.16 (m, 4H), 5.18 (dd, 1H), 7.03 (d, 1H),

7.65 (d, 2H), 7.90 (d, 2H).

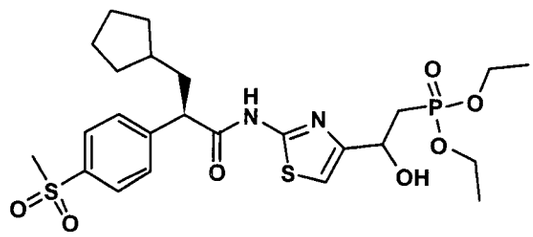
EJEMPLO 40



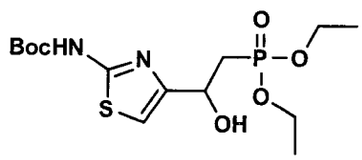
Cloruro de oxalilo (2.0 M en DCM) (45.0 µL; 0.091 mmol) se agregó a una solución de cloruro de oxalilo (2.0 M en DCM) (45.0 µL; 0.091 mmol) se agregó a una solución del Ejemplo 26 Parte C del compuesto (23.0 mg; 0.060 mmol) en DCM (0.20 mL). DMF (5 µL) se agregó. La evolución del gas se presentó. La mezcla de reacción se agitó a temperatura ambiente durante 1 h, luego se concentró in vacuo. El residuo se destiló de DCM (2 X 1 mL). El cloruro ácido crudo se disolvió en DCM (0.25 mL). El ejemplo 7 Parte B del compuesto (16.2 mg; 0.066 mmol) se agregó seguido por piridina (14.6 µL; 0.180 mmol). Después de 20 h a temperatura ambiente la reacción se concentró in vacuo. El residuo se dividió entre EtOAc (4 mL) y 0.5 N HCl acuoso (3 mL). La fase orgánica se lavó con $NaHCO_3$ acuoso saturado (3 mL) y salmuera (3 mL), se seca (MgSO4) y se concentra in vacuo. El producto crudo se purificó por HPLC preparativa (columna YMC de fase inversa ODS-A-5u 30 x 100 mm; relación de flujo = 40 mL/min, 15 hasta 100% solvente B durante 12 min, espera a 14 min, donde el solvente A =

90:10:0.1 H_2O:MeOH:TFA y solvente B = 90:10:0.1 MeOH:H_2O:TFA) para dar el compuesto del título (13 mg; 36%) como un sólido blanco. $[M + H]^+$ = 608.2; ^1H RMN (400 MHz, CDCl3): δ 1.32 (m, 9H), 3.07 (s, 3H), 3.40 (s, 3H), 3.44 (d, 2H), 3.57 (q, 2H), 4.13 (m, 4H), 4.63 (m, 1H), 6.88 (s, 1H), 7.16 (d, 2H), 7.19 (s, 1H), 7.35 (s, 1H), 7.93 (d, 2H), 8.32 (s, 1H), 8.53 (s, 1H), 9.59 (s, 1H).

EJEMPLO 41



A.

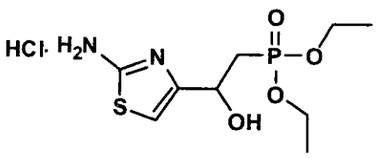


nBuLi (575 µL de una solución 1.6 M en Hexanos; 0.920 mmol) se agregó gota a gota a una solución fría (-78°C) de Me(O)P(OEt)$_2$ (134 µL; 0.920 mmol) en THF (0.30 mL). Después de 20 min una solución del Ejemplo 39 parte A del compuesto (100 mg; 0.438 mmol) en THF (0.70 mL) se agregó gota a gota. Después de 1 h a -78°C, la reacción se apagó por la adición de AcOH (63 µL; 1.10 mmol). La reacción se calentó hasta temperatura ambiente y se concentra usando una corriente de

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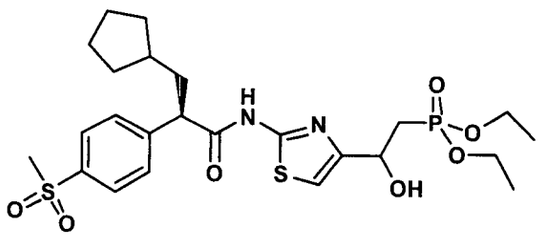
Ar. El residuo se dividió entre EtOAc (5 mL) y salmuera (4 mL). La fase orgánica se secó ($MgSO_4$) y se concentra in vacuo. El producto crudo se procesó por cromatografía (SiO_2; gradiente continuo desde 0 hasta 100% EtOAc en Hexanos durante 8 min, cambiado a MeOH al 4% en EtOAc y mantenido durante 6 min) para dar la parte A del compuesto (104 mg; 62%) como un jarabe.

B.



HCl (100 µL de una solución 4.0 N en 1,4 dioxano) se agregó a la parte A del compuesto (104 mg; 0.273 mmol). Después de 20 h, la mezcla de reacción se concentró in vacuo para dar la parte B del compuesto (64 mg; 75%) como un aceite, el cual se usó en la siguiente etapa sin purificación adicional.

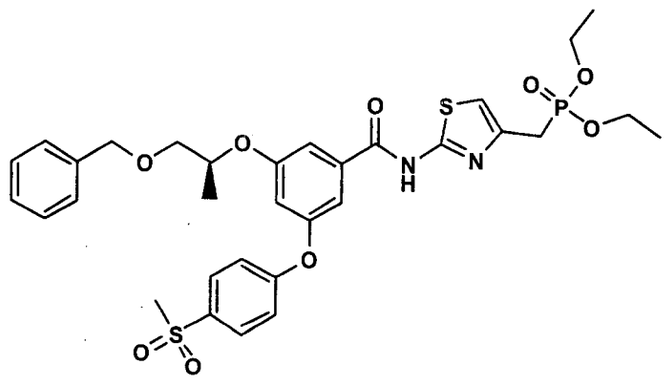
C.



DIPEA (56.0 µL; 0.324 mmol) se agregó a una solución agitada del Ejemplo 1 Parte D del compuesto (32.0 mg; 0.108

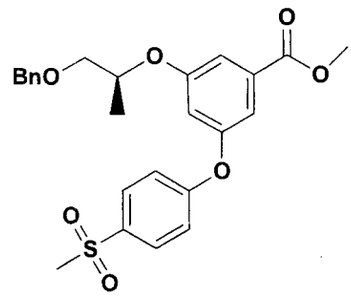
mmol), Parte B del compuesto (48.0 mg; 0.151 mmol) y HOAt (16.9 mg; 0.124 mmol) en DMF (0.42 mL). EDAC (23.8 mg; 0.124 mmol) se agregó. Después de 2 h a temperatura ambiente la mezcla de reacción se dividió entre EtOAc (4 mL) y HCl acuoso 0.5 N (3 mL). La fase orgánica se lavó con $NaHCO_3$ acuoso saturado (3 mL) y salmuera (3 mL), se seca ($MgSO_4$) y se concentra in vacuo. El producto crudo se purificó por HPLC preparativa (columna YMC de fase inversa ODS-A-5u 20 x 100 mm; relación de flujo = 20 mL/min, 15 hasta 100% solvente B durante 12 min, espera a 14 min, donde el solvente A = 90:10:0.1 H_2O:MeOH:TFA y solvente B = 90:10:0.1 MeOH:H_2O:TFA) para dar el compuesto del título (27 mg; 45%) como un sólido blanco. $[M + H]^+$ = 559.3; ^1H RMN (400 MHz, $CDCl_3$): δ 1.15 (m, 2H), 1.27 (m, 3H), 1.35 (t, 3H), 1.49 (m, 2H), 1.62 (m, 3H), 1.78 (m, 2H), 1.95 (m, 1H), 2.25 (m, 1H), 2.41 (m, 2H), 3.04 (s, 3H), 4.03 (t, 1H), 4.16 (m, 4H), 5.19 (t, 1H), 6.93 (s, 1H), 7.65 (d, 2H), 7.90 (d, 2H).

EJEMPLO 42



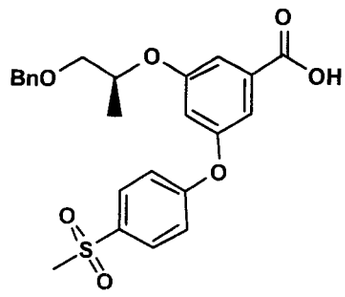
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A.



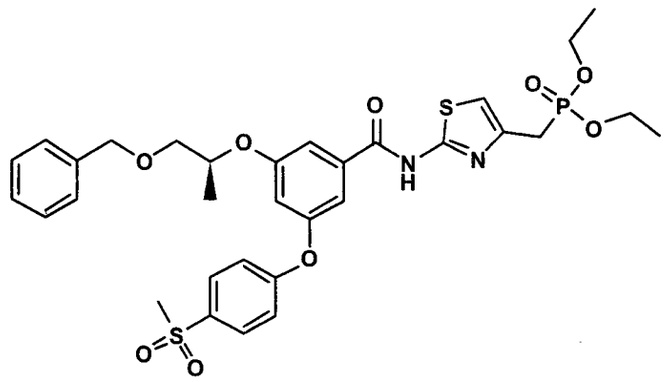
A una solución fría (temperatura interna mantenida a ≤ 5°C) del Ejemplo 26A (3.7 g, 11.5 mmol), (R)-(-)-1-benciloxi-2-propanol (2.5 g, 15 mmol), y Ph_3P soportada con polímero (30 g de 1 mmol/g, 30 mmol) en THF (150 mL) bajo N_2 (g) se agregó gota a gota durante 15 min una solución de DIAD (3.4 mL, 17.3 mmol). La mezcla de reacción se calentó hasta temperatura ambiente y se agitó durante 18 h, luego se filtra. Los sólidos se lavaron completamente con THF y CH_2Cl_2. Los filtrados combinados se concentraron in vacuo. La mezcla se procesó por cromatografía (SiO_2; EtOAc/Hexano 1:1) para dar la parte A del compuesto (6.0 g, 110%) como un aceite incoloro. [M + H]=471.2; ^1H RMN (400 MHz, $CDCl_3$) δ 7.90 (2 H, d, J=8.79 Hz), 7.48 (1 H, s), 7.27 - 7.37 (6 H, m), 7.09 (2 H, d, J=8.79 Hz), 6.83 - 6.89 (1 H, m), 4.60 - 4.69 (1 H, m), 4.58 (2 H, s), 3.90 (3 H, s), 3.54 - 3.70 (2 H, m), 3.06 (3 H, s), 1.34 (3 H, d, J=6.15 Hz).

B.



Una solución de la Parte A (6 g, 13 mmol), LiOH (1.6 g, 39 mmol), y H_2O (50 mL) en THF (20 mL) se agitó a temperatura ambiente durante 3 h, luego se concentró in vacuo. La solución acuosa se lavó con Et_2O (15 mL x 4), se hace ácida pasta pH 4 con HCl concentrado, y se extrajo con EtOAc (50 mL). La capa orgánica se lavó con H_2O, se seca ($MgSO_4$), se filtra, y se concentra in vacuo para dar la parte B del compuesto (5 g, 95%) como un sólido blanco. [M + H]=457.2; ^1H RMN (400 MHz, $CDCl_3$) δ 7.91 (2 H, d, J=8.79 Hz), 7.52 (1 H, s), 7.27 - 7.38 (6 H, m), 7.11 (2 H, d, J=8.79 Hz), 6.90 (1 H, t, J=2.20 Hz), 4.61 - 4.70 (1 H, m), 4.59 (2 H, s), 3.56 - 3.70 (2 H, m), 3.07 (3 H, s), 1.35 (3 H, d, J=6.59 Hz).

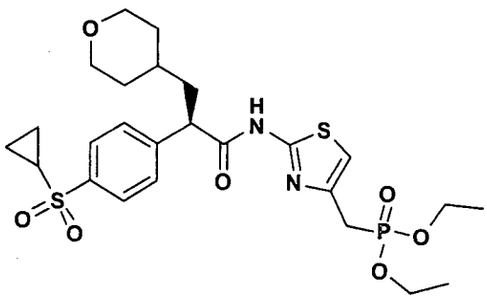
C.



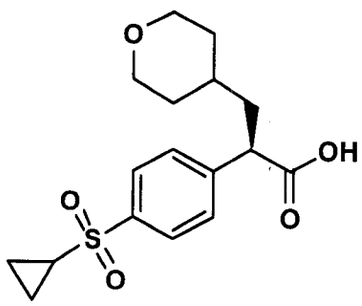
DIPEA (22.0 µL; 0.127 mmol) se agregó a 0°C una solución de la Parte C del compuesto (50 mg; 0.110 mmol), Ejemplo 13 Parte E del compuesto (33.0 mg; 0.131 mmol) y HOAt (17.0 mg; 0.127 mmol) en DMF (0.44 mL), seguido por EDAC (24.0 mg; 0.127 mmol). Después de 24 h a temperatura ambiente la mezcla de reacción se dividió entre EtOAc (7 mL) y HCl acuoso 0.5 N

(5 mL). La fase orgánica se lavó con $NaHCO_3$ acuoso saturado (5 mL) y salmuera (5 mL), se seca ($MgSO_4$) y se concentra in vacuo. El producto crudo se procesó por cromatografía (SiO_2; gradiente continuo desde 0 hasta 100% EtOAc en Hexanos durante 12 min, espera a 100% EtOAc durante 4 min). El producto se purificó además al disolver en MeOH (1 mL) y se carga en una columna SAX 0.5g (intercambio de anion fuerte). La columna se eluyó con MeOH (4 mL). El filtrado se concentró para dar el compuesto del título (50 mg; 67%) como un residuo amarillo ligero. $[M + H]^+$ = 689.3; ^1H RMN (400 MHz, $CDCl_3$): δ 1.26 (t, 6H), 1.34 (m, 3H), 3.08 (s, 3H), 3.34 (d, 2H), 3.62 (m, 2H), 4.06 (m, 4H), 4.58 (s, 2H), 4.68 (m, 1H), 6.85 (s, 1H), 6.88 (s, 1H), 7.14 (d, 2H), 7.20 (s, 1H), 7.27 (m, 5H), 7.39 (s, 1H), 7.92 (d, 2H).

EJEMPLO 43

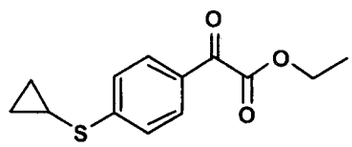


A.



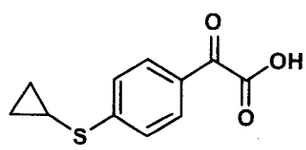
Nota: El siguiente procedimiento se adaptó de WO 2006/016178 y WO 2006/016174.

i.



A 0°C una suspension de NH_4Cl (8.44 g, 63.3 mmol) en DCM (40 mL) se agregó 2-cloro-2-oxoacetato de etilo (5.53 mL, 49.7 mmol) durante 10 min. La reacción se agitó a 0°C durante 30 min. Sulfuro de ciclopropil fenilo (6.5 mL, 45.2 mmol) luego se agregó durante un periodo de 45 min, manteniendo la temperatura a 0°C. [Nota: cuando el sulfuro se agregó, la reacción inmediatamente se volvió morado oscuro/rojo en su color]. La reacción se permitió calentar hasta temperatura ambiente y se agitó a temperatura ambiente durante 18 h. El agua con hielo (100 mL) se agregó lentamente a la mezcla a 0°C. La fase orgánica se lavó con H_2O (2x), $NaHCO_3$ acuoso saturado (2x), y nuevamente con H_2O. La capa orgánica se secó [$MgSO_4$] y se concentra in vacuo para dar la Parte A(i) del compuesto crudo (6.1 g, 54%) como un aceite amarillo.

ii.

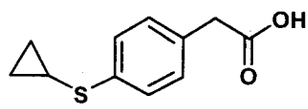


Una solución de la Parte A(i) del compuesto (6.1 g,

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24.37 mmol) en tolueno (50 mL) se calentó hasta 50°C con agitación. NaOH acuoso 3N (9.75 mL, 29.2 mmol) se agregó gota a gota mientras se mantiene la temperatura a $\leq$60°C. Después de que se completó, la reacción se agitó a 50°C durante 4 h, luego se enfrió hasta temperatura ambiente y se neutraliza por la adición cuidadosa de HCl concentrado (0.821 mL, 26.8 mmol). La reacción se agitó a temperatura ambiente durante 18 h. La fase orgánica se concentró in vacuo para dar la Parte A(ii) del compuesto crudo (6.0g, 111%) como un sólido amarillo.

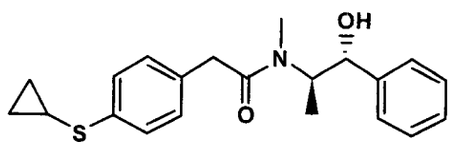
iii.



A $NH_2NH_2.H_2O$ (5.89 mL, 121 mmol) a -78°C se agregó la Parte A(ii) del compuesto (5.4 g, 24.30 mmol) en una porción, y la reacción se calentó hasta 80°C con agitación, luego se enfrió hasta temperatura ambiente. KOH (0.818 g, 14.58 mmol) se agregó; la reacción se agitó a temperatura ambiente durante varios minutos, y luego una segunda porción de KOH (0.818 g, 14.58 mmol) se agregó. La reacción se agitó a temperatura ambiente durante varios minutos, y luego una tercera porción de KOH (0.818 g, 14.58 mmol) se agregó. La reacción nuevamente se agitó a temperatura ambiente durante varios minutos, y una cuarta porción de KOH (0.818 g, 14.58

mmol) se agregó. La reacción luego se calentó a 100°C con agitación durante 18 h. La reacción se enfrió hasta temperatura ambiente y se diluye con H_2O. La mezcla de reacción se dividió entre Et_2O y H_2O. Las capas se separaron, y la capa acuosa se transfirió a un matraz de fondo redondo. La capa orgánica se lavó con H_2O, y las capas acuosas combinadas se trataron con heptano (~50 mL), y la mezcla se agitó vigorosamente. La solución agitada se trató gota a gota con HCl cncentrado (11.66 mL, 384 mmol) durante 30 min a 0°C. La suspensión se calentó hasta temperatura ambiente y se agitó a temperatura ambiente durante varias horas. Un precipitado amarillo se forma y se filtró completamente; este material se lavó con HCl acuoso 1N y heptano, luego se secó in vacuo durante 48 h. La Parte A (iii) del compuesto (3.7g, 73% de rendimiento) de esta manera se aisló como un sólido amarillo pálido.

iv.

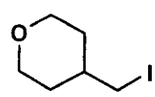


La Parte A (iii) del compuesto se destiló de tolueno (2x). A -10°C una mezcla de la Parte A(iii) del compuesto (3.7 g, 17.76 mmol) y K_2CO_3 (7.37 g, 53.3 mmol) en acetona anhidra (50 mL) se agregó gota a gota cloruro de trimetilacetilo (2.297 mL, 18.65 mmol) mientras se mantiene

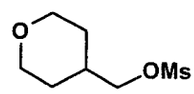
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la temperatura a ≤-10°C. La reacción se agitó a -10°C durante 30 min, luego se calienta hasta 0°C durante 1 h y finalmente se calienta hasta temperatura ambiente durante 30 min. La mezcla se volvió a enfriar hasta -10°C y se trató con (1R, 2R)-(-)-pseudoefedrina (4.40 g, 26.6 mmol). La reacción se agitó a -10°C durante 1h, luego se calentó hasta 25°C y se agita durante 18 h a 25°C. La reacción se apagó con H_2O (25 mL) y se extrae con EtOAc. La fase orgánica se lavó con HCl acuoso 1N, se seca ($MgSO_4$) y se concentra in vacuo para dar la Parte D del compuesto crudo. La parte D del compuesto crudo se disolvió en CH_2Cl_2 y se procesó por cromatografía (SiO_2; 120g; gradiente desde 30% EtOAc/Hexano hasta 100% EtOAc). Las fracciones combinadas se concentraron in vacuo para dar la parte A(iv) del compuesto (1.16g, 18.4% de rendimiento) como un sólido blanco.

v.



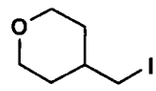
a.



A una solución de tetrahidropirano-4-MeOH (5.0 g, 43 mmol) en CH_2Cl_2 (30 mL) se agregó Et_3N (7.2 mL, 51.6 mmol). La mezcla se enfrió hasta 0°C, y cloruro de metanosulfonilo (4.0 mL, 51.6 mmol) se agregó. La mezcla se agitó a 0°C durante

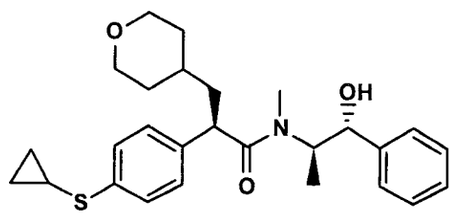
varias horas, luego se calentó lentamente a temperatura ambiente. La reacción se agitó a temperatura ambiente durante 18 h, luego se concentró in vacuo. El residuo se tomó en EtOAc y se lavó con $NaHCO_3$. La capa orgánica se secó [$MgSO_4$] y se concentra in vacuo para dar el mesilato de la Parte A(v)(a) del compuesto (8.3 g, rendimiento cuantitativo) como un sólido tipo agujas, blanco.

b.



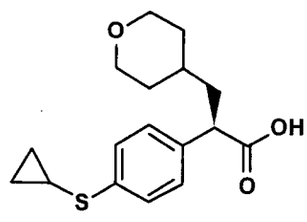
Una mezcla del mesilato de la Parte A(v)(a) del compuesto (8.3 g, 43.0 mmol) y NaI (12.8 g, 85.5 mmol) se puso a reflujo a 65°C en acetona (100 mL) durante 18 h, luego se enfrió hasta temperatura ambiente y se filtra. La torta filtra se lavó con acetona. Los filtrados combinados se concentraron in vacuo, y el residuo se dividió entre Et_2O y agua. La capa acuosa se extrajo con Et_2O (3x). Los extractos orgánicos combinados se lavaron con $Na_2S_2O_3$ acuosoa al 10% y agua, se seca [$MgSO_4$] y se concentra in vacuo para dar la parte A(v)(b) del compuesto (7.1 g, 74% de rendimiento) como un aceite amarillo.

vi.



Todos los materiales de partida se evaporaron con tolueno varias veces y todo el recipiente de vidrio se secó en un horno durante la noche. A -78°C una solución de LiHMDS (5.91 mL, 5.91 mmol) en THF (15 mL) se agregó gota a gota una solución de la Parte A(iv) del compuesto (1.0 g, 2.81 mmol) en THF (15 mL) durante 15 min. La reacción se agitó a -78°C durante 15 min, luego se calentó hasta 0°C durante 45 min y se vuelve a enfriar hasta -78°C. DMPU destilado (0.714 mL, 5.91 mmol) se agregó y la reacción se agitó a -78°C durante ~15 min, después de los cual la Parte A(v) del yoduro (0.954 g, 4.22 mmol) se agregó. La reacción se agitó a -78°C durante 1h, luego se calentó lentamente hasta temperatura ambiente y se agita durante 18 h. La reacción se apagó con NH_4Cl acuoso saturado (~10 mL) y se diluye con EtOAc. La mezcla se lavó con H_2O. La capa acuosa se extrajo con EtOAc, y los extractos orgánicos combinados se lavaron con salmuera, se secan [$MgSO_4$] y se concentran in vacuo para dar la parte A(vi) del compuesto (1.3 g, 100%) como un aceite amarillo.

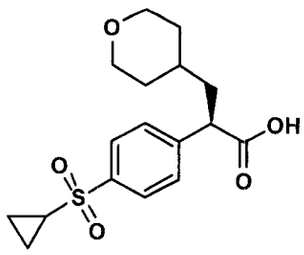
vii.



Una solución de la parte A(vi) del compuesto (1.3 g, 2.87 mmol) y H_2SO_4 concentrado 9N (10.4 mL, 94 mmol) en

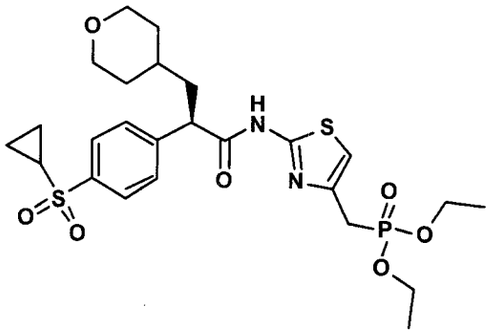
dioxano (20 mL) se puso a reflujo a 110°C durante 18 h, luego se enfrió hasta temperatura ambiente. La solución se diluyó con EtOAc (50 mL) y se lava con H_2O (40 mL x 2) y salmuera (20 mL). La capa orgánica se secó [$MgSO_4$] y se concentra in vacuo para dar la parte A(vii) del compuesto (1.17 g, 133% de rendimiento) como una aceite pegajoso, amarillo.

viii.



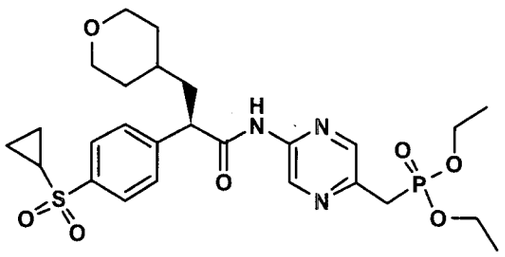
A una solución de la parte A(vii) del compuesto (0.9 g, 2.94 mmol) en isopropanol (20 mL) y agua (10 mL) se agregó oxona (4.15 g, 6.76 mmol). La reacción se agitó a temperatura ambiente durante 18 h, luego se filtró, y el filtrado se concentró in vacuo. El residuo se tomó en EtOAc y se lavó con H_2O y salmuera. La capa orgánica se secó [$MgSO_4$] y se concentra in vacuo para dar la Parte A(viii) del compuesto (0.9 g, 91% de rendimiento) como una espuma amarillo pálido.

B.



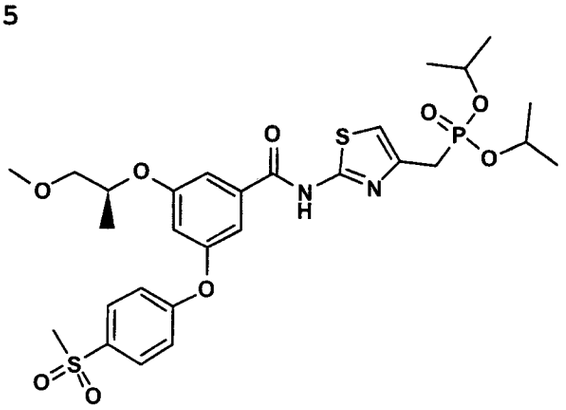
Cloruro de oxalilo (58.0 μL de una solución 2.0 M en DCM; 0.116 mmol) se agregó a una solución de la parte A del compuesto (26.0 mg; 0.077 mmol) en DCM (0.25 mL). DMF (5 μL) se agregó. La evolución del gas se presentó. La mezcla de reacción se agitó a temperatura ambiente durante 1 h, luego se concentró in vacuo. El residuo se destiló de DCM (2 X 1 mL). El cloruro ácido crudo se disolvió en DCM (0.32 mL). El ejemplo 13 parte E del compuesto (23.0 mg; 0.092 mmol) se agregó seguido por piridina (18.7 μL; 0.231 mmol). Después de 20 h a temperatura ambiente la reacción se concentró in vacuo. El residuo se dividió entre EtOAc (4 mL) y HCl acuoso 0.5 N (3 mL). La fase orgánica se lavó con $NaHCO_3$ acuoso saturado (3 mL) y salmuera (3 mL), se seca ($MgSO_4$) y se concentra in vacuo. El producto crudo se purificó por HPLC preparativa (columna YMC de fase inversa ODS-A-5mm 30 x 100 mm; relación de flujo = 40 mL/min, 15 hasta 100% solvente B durante 16 min, espera a 20 min, donde el solvente A = 90:10:0.1 H_2O:MeOH:TFA y solvente B = 90:10:0.1 MeOH:H_2O:TFA) para dar el compuesto del título (17 mg; 39%) como un sólido amarillo ligero. $[M + H]^+$ = 571.4; ^1H RMN (400 MHz, $CDCl_3$): δ 1.04 (m, 2H), 1.33 (m, 11H), 1.63 (m, 2H), 1.87 (m, 1H), 2.21 (m, 1H), 2.46 (m, 1H), 3.28 (m, 4H), 3.92 (m, 2H), 4.02 (t, 1H), 4.11 (m, 4H), 6.88 (d, 1H), 7.61 (d, 2H), 7.88 (d, 2H).

EJEMPLO 44

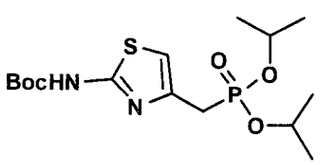


El compuesto del título (22 mg; 51%; sólido Amarillo ligero) se sintetizó del Ejemplo 7 Parte B del compuesto y Ejemplo 43 Parte A(viii) del compuesto empleando el procedimiento para la síntesis del Ejemplo 43 del compuesto. $[M + H]^+ = 566.4$; ^1H RMN (400 MHz, $CDCl_3$): δ 1.05 (m, 2H), 1.34 (m, 10H), 1.48 (m, 1H), 1.67 (m, 2H), 1.79 (m, 1H), 2.22 (m, 1H), 2.46 (m, 1H), 3.35 (m, 4H), 3.92 (d, 2H), 4.04 (t, 1H), 4.14 (m, 4H), 7.62 (d, 2H), 7.85 (d, 2H), 8.20 (s, 1H), 9.34 (s, 1H), 9.36 (s, 1H).

EJEMPLO 45

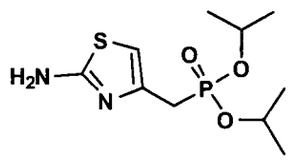


A.



$(iPrO)_3P$ (2.02 mL; 8.20 mmol) se agregó a un recipiente que contiene el Ejemplo 13 Parte C del compuesto (600 mg; 2.05 mmol). El recipiente de reacción se tapó y la mezcla se calentó a 85°C durante 16 h, luego se enfría hasta temperatura ambiente. La solución se procesó por cromatografía directamente (SiO_2; gradiente continuo desde 0 hasta 100% EtOAc en Hexanos durante 7 min, se cambia a MeOH al 4% en EtOAc y se mantiene durante 12 min) para dar la parte A del compuesto (607 mg; 78%) como un sólido viscoso.

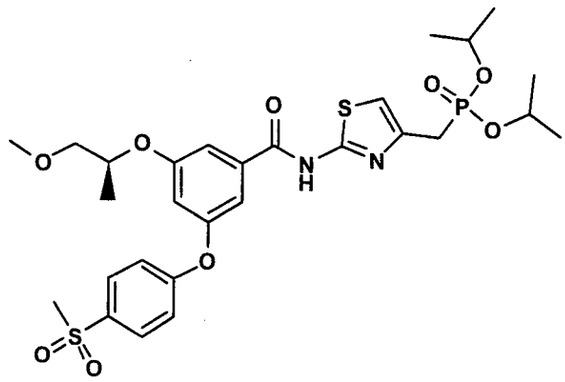
B.



TFA (2.0 mL) se agregó a 0°C una solución de la parte A del compuesto (559 mg; 1.48 mmol) en DCM (4 mL). La mezcla de reacción se permitió calentar hasta temperatura ambiente y se agita a temperatura ambiente durante 2 h, luego se concentró in vacuo. El residuo se dividió entre EtOAc (15 mL) y $NaHCO_3$ acuoso saturado (10 mL). La fase acuosa se extrajo con EtOAc (10 mL). Los extractos orgánicos combinados se lavaron con salmuera (10 mL), se secan ($MgSO_4$) y se concentran in vacuo para dar la parte B del compuesto

(0.41 g; 100%) como un sólido amarillo.

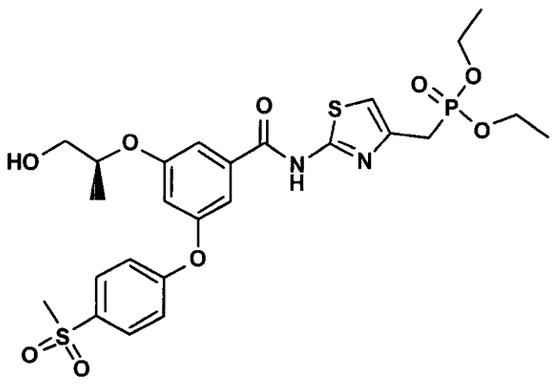
C.



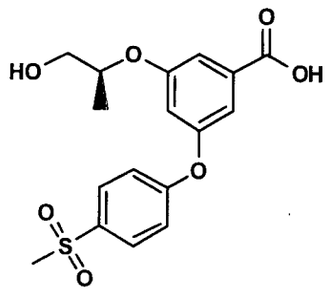
DIPEA (81.3 µL; 0.467 mmol) se agregó a una solución de la parte B del compuesto (135.6 mg; 0.487 mmol), Ejemplo 26 Parte C del compuesto (154.5 mg; 0.406 mmol) y HOAt (63.6 mg; 0.467 mmol)en DMF (1.5 mL). EDAC (89.5 mg; 0.467 mmol) se agrega. Después de 48 h a temperatura ambiente la mezcla de reacción se dividió entre EtOAc (15 mL) y H_2O (12 mL). La fase orgánica se lavó con HCl acuoso 0.5 N (10 mL), $NaHCO_3$ acuoso saturado (10 mL) y salmuera (10 mL), se seca ($MgSO_4$) y se concentra in vacuo. El producto crudo se purificó por HPLC preparativa (Columna YMC de fase inversa ODS-A-5u 30 x 250 mm; relación de flujo = 30 mL/min, 20 hasta 100% solvente B durante 18 min, mantenido a 25 min, donde el solvente A = 90:10:0.1 H_2O:MeOH:TFA y solvente B = 90:10:0.1 MeOH:H_2O:TFA) para dar el compuesto del título (0.24 g; 92%) como un sólido amarillo ligero. $[M + H]^+$ = 641.3; ^1H RMN (400 MHz,

$CDCl_3$): δ1.25 (m, 6H), 1.31 (m, 9H), 3.08 (s, 3H), 3.27 (d, 2H), 3.41 (s, 3H), 3.58 (m, 2H), 4.71 (m, 2H), 4.80 (m, 1H), 6.92 (s, 1H), 6.99 (s, 1H), 7.15 (d, 2H), 7.37 (s, 1H), 7.58 (s, 1H), 7.92 (d, 2H).

EJEMPLO 46

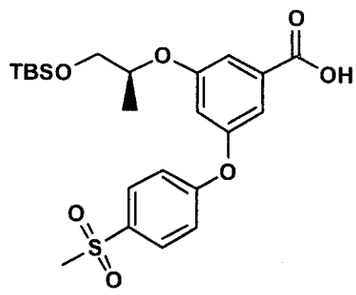


A.



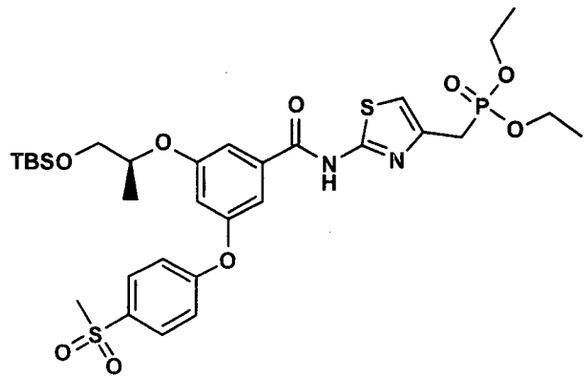
Una mezcla de Pd/C al 10% (100 mg) y Ejemplo 42 Parte B del compuesto (1.03 g; 2.26 mmol) en EtOAc (6 mL) se agitó bajo una atmósfera de H_2 durante 8 h, después de la cual la mezcla de reacción se filtró. El catalizados se enjuagó con MeOH (10 mL) y los filtrados combinados se concentraron in vacuo para dar la parte A del compuesto (0.82 g; 99%).

B.



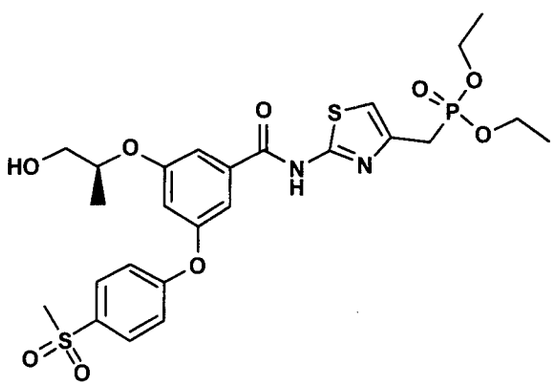
Una solución de TBSCl (1.01 g; 6.71 mmol) en DMF (6 mL) se agregó a la parte A del compuesto (0.82 g; 2.24 mmol), seguido por imidazol (0.91 g; 13.43 mmol). Después de 20 h la mezcla de reacción se dividió entre EtOAc (50 mL) y NH_4Cl acuoso saturado (50 mL). La fase orgánica se lavó con NH_4Cl acuosos saturado (25 mL) y salmuera (25 mL), se seca ($MgSO_4$) y se concentra in vacuo. El producto crudo se procesó por cromatografía (SiO_2; gradiente continuo desde 0 hasta 100% EtOAc en Hexanos durante 14 min, espera a 100% EtOAc durante 4 min) para dar la parte B del compuesto (725 mg; 68%) como una espuma blanca.

C.



DIPEA (14.5 µL; 0.083 mmol) se agregó a una solución a temperatura ambiente de la Parte B del compuesto (30.8 mg; 0.064 mmol), Ejemplo 13 Parte E compuesto (21.6 mg; 0.086 mmol) y HOAt (10.9 mg; 0.080 mmol) en DMF (0.33 mL). EDAC (15.3 mg; 0.080 mmol) luego se agregó. Después de 48 h a temperatura ambiente la mezcla de reacción se dividió entre EtOAc (3 mL) y H_2O (3 mL). La fase orgánica se lavó con salmuera (30 mL), se seca ($MgSO_4$) y se concentra in vacuo para dar la parte C del compuesto (53 mg; 100%) como un jarabe. El producto crudo se usó en la siguiente etapa sin purificación adicional.

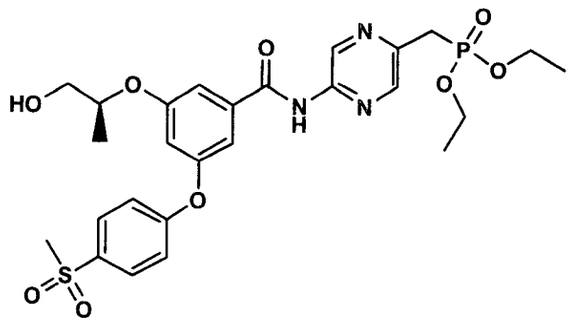
D.



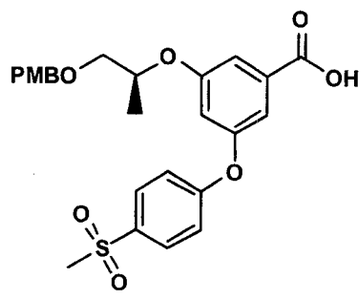
TBAF (1.0 M en THF) (152 µL; 0.152 mmol) se agregó a 0°C una solución de la parte C del compuesto (54 mg; 0.76 mmol) en THF (0.22 mL). La reacción se permitió calentar hasta temperatura ambiente y se agita durante 2 h a temperatura ambiente, luego se concentró in vacuo. El residuo se dividió entre EtOAc (2.5 mL) y salmuera (2.5 mL). La fase orgánica se secó ($MgSO_4$) y se concentra in vacuo. El producto crudo se

purificó por HPLC preparativa (Columna YMC de fase inversa ODS-A-5u 30 x 100 mm; relación de flujo = 40 mL/min, 10 hasta 100% solvente B durante 10 min, espera a 13 min, donde el solvente A = 90:10:0.1 H_2O:MeOH:TFA y solvente B = 90:10:0.1 MeOH:H_2O:TFA) para dar el compuesto del título (23 mg; 51%) como un jarabe incoloro. $[M + H]^+$ = 599.3; ^1H RMN (400 MHz, $CDCl_3$): δ 1.33 (m, 9H), 3.07 (s, 3H), 3.33 (d, 2H),3.79 (q, 2H), 4.15 (m, 4H), 4.82 (m, 1H), 6.93 (s, 1H), 7.05 (d, 1H), 7.15 (d, 2H), 7.44 (s, 1H), 7.70 (s, 1H), 7.92 (d, 1H).

EJEMPLO 47



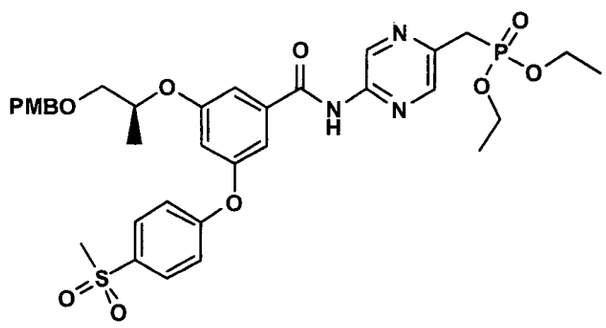
A.



KOH en polvo (141 mg; 2.51 mmol) se agregó a una solución del Ejemplo 46 Parte B del compuesto (0.41 g; 1.12 mmol) en DMSO-D6 (2.5 mL). Una solución de bromuro de 4-

metoxibencilo (0.47 g; 2.35 mmol) en DMSO-D6 (1 mL) se agregó. Después de 2 h H_2O (0.5 mL) se agregó. Después de 30 min la solución se dividió entre EtOAc (20 mL) y H_2O (20 mL). La fase orgánica se secó ($MgSO_4$) y se concentra in vacuo. El producto crudo se procesó por cromatografía (SiO_2; gradiente continuo desde 0 hasta 70% EtOAc en Hexanos durante 13 min, mantenido al 70% de EtOAc durante 4 min) para dar la parte A del compuesto (195 mg; 33%).

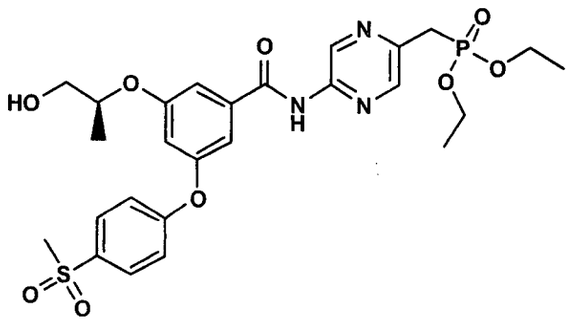
B.



Cloruro de oxalilo (2.0 M en DCM) (72 µL; 0.144 mmol) se agregó a 0°C una solución de la parte A del compuesto (43.9 mg; 0.096 mmol) en DCM (0.33 mL). DMF (5 µL) se agregó. La evolución del gas se presentó. Después de agitar durante 1.5 h a temperatura ambiente la solución se concentró in vacuo. El residuo se destiló de $CHCl_3$ (2 mL). El cloruro ácido crudo se disolvió en DCM (0.40 mL). El ejemplo 7 Parte B del compuesto (29.4 mg; 0.120 mmol) se agregó seguido por piridina (23.3 uL; 0.288 mmol). Después de 14 h a temperatura ambiente la reacción se concentró in vacuo. El residuo se

dividió entre EtOAc (3 mL) y HCl acuoso 0.5 N (2 mL). La fase orgánica se lavó con $NaHCO_3$ acuoso saturado (2 mL) y salmuera (2 mL), se seca ($MgSO_4$) y se concentra in vacuo. El producto crudo se procesó por cromatografía (SiO_2; gradiente continuo desde 0 hasta 100% EtOAc en Hexanos durante 13 min, se cambia a 3% MeOH en EtOAc y se mantiene durante 7 min) para dar la parte B del compuesto (28 mg; 40%).

C.

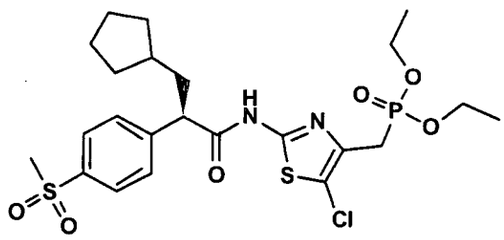


DDQ (9.4 mg; 0.041 mmol) se agregó a una solución de la parte B del compuesto (28 mg; 0.039 mmol) en DCM (400 µL) y H_2O (25 µL). Después de agitar durante 1 h a temperatura ambiente la mezcla se concentró in vacuo. El residuo se dividió entre EtOAc (3 mL) y $NaHCO_3$ acuoso saturado (2 mL). La fase orgánica se lavó con $NaHCO_3$ acuoso saturado (2 mL) y salmuera (2 mL), se seca ($MgSO_4$) y se concentra in vacuo. El producto crudo se purificó por HPLC preparativa (Columna YMC de fase inversa ODS-A-5u 30 x 100 mm; relación de flujo = 40 mL/min, 10 hasta 100% solvente B durante 10 min, espera a 14 min, donde el solvente A = 90:10:0.1 H_2O:ACN:TFA y solvente B

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= 90:10:0.1 ACN:H_2O:TFA) para dar 20 mg de un jarabe. El material se procesó además por cromatografía para remover el contaminante de aldehído (SiO_2; eluido con 100% EtOAc para remover el aldehído, luego se cambia a 5% MeOH en EtOAc para eluir el producto) para dar el compuesto del título (12 mg; 52%) como un jarabe incoloro. $[M + H]^+$ = 594.3; ^1H RMN (400 MHz, $CDCl_3$): δ 1.29 (m, 9H), 2.29 (s, 1H), 3.08 (s, 3H), 3.42 (d, 2H), 3.77 (m, 2H), 4.11 (m, 4H), 4.59 (m, 1H), 6.86 (s, 1H), 7.14 (d, 2H), 7.19 (s, 1H), 7.37 (s, 1H), 7.93 (d, 2H), 8.30 (s, 1H), 8.68 (s, 1H), 9.57 (s, 1H).

EJEMPLO 48

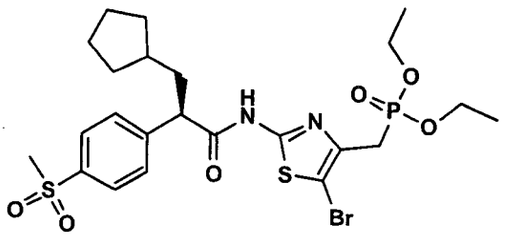


NCS (13.1 mg; 0.098 mmol) se agregó a una solución del Ejemplo 13 del compuesto (52.0 mg; 0.098 mmol) en MeOH (0.5 mL) a temperatura ambiente y se agita a temperatura ambiente durante 48 h. Los volátiles se removieron in vacuo. El residuo se purificó por HPLC preparativa (Columna YMC de fase inversa ODS-A-5u 30 x 100 mm; relación de flujo = 40 mL/min, 20 hasta 100% solvente B durante 12 min, espera a 18 min, donde el solvente A = 90:10:0.1 H_2O:MeOH:TFA y solvente B = 90:10:0.1 MeOH:H_2O:TFA) para dar el compuesto del título (42 mg; 76%) como un sólido blanco. $[M + H]^+$ = 563.3; ^1H RMN (400

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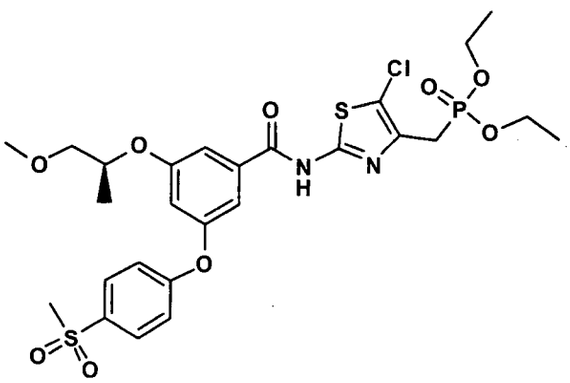
MHz, $CDCl_3$): δ1.13 (m, 2H), 1.29 (m, 6H), 1.48 (m, 2H), 1.60 (m, 3H), 1.74 (m, 2H), 1.92 (m, 1H), 2.20 (m, 1H), 3.06 (s, 3H), 3.33 (d, 2H), 3.84 (t, 1H), 4.11 (m, 4H), 7.59 (d, 2H), 7.89 (d, 2H).

EJEMPLO 49



El compuesto del título (23 mg; 69%; sólido blanco) se sintetizó empleando el mismo procedimiento como para la síntesis del Ejemplo 48, excepto que NBS se usó en lugar de NCS. La reacción de bromación se completó dentro de 1 h. $[M + H]^+$ = 607.3; ^1H RMN (400 MHz, $CDCl_3$): δ 1.13 (m, 2H), 1.28 (m, 6H), 1.48 (m, 2H), 1.59 (m, 3H), 1.76 (m, 2H), 1.92 (m, 1H), 2.20 (m, 1H), 3.06 (s, 3H), 3.31 (d, 2H), 3.83 (t, 1H), 4.09 (m, 4H), 7.59 (d, 2H), 7.89 (d, 2H).

EJEMPLO 50

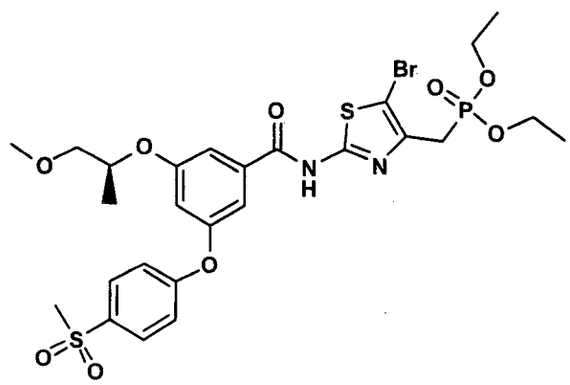


NCS (8.55 mg; 0.064 mmol) se agregó a una solución del

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Ejemplo 37 del compuesto (39.0 mg; 0.064 mmol) en MeOH (0.4 mL). Después de 48 h a temperatura ambiente la mezcla de reacción se concentró in vacuo. El producto crudo se purificó por HPLC preparativa (Columna YMC de fase inversa ODS-A-5u 30 x 100 mm; relación de flujo = 40 mL/min, 25 hasta 100% solvente B durante 10 min, espera a 13 min, donde el solvente A = 90:10:0.1 H_2O:MeOH:TFA y solvente B = 90:10:0.1 MeOH:H_2O:TFA) para dar el compuesto del título (27 mg; 66%) como un sólido blanco. $[M + H]^+$ = 647.2; ^1H RMN (400 MHz, $CDCl_3$): δ 1.29 (t, 6H), 1.35 (d, 3H), 3.09 (s, 3H), 3.29 (d, 2H), 3.41 (s, 3H), 3.56 (q, 2H), 4.10 (m, 4H), 4.65 (m, 1H), 6.89 (s, 1H), 7.15 (d, 2H), 7.19 (s, 1H), 7.36 (s, 1H), 7.94 (d, 2H).

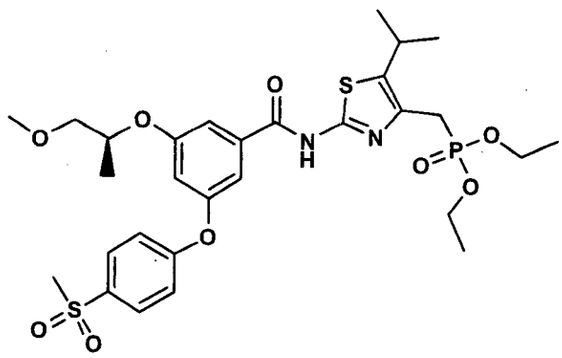
EJEMPLO 51



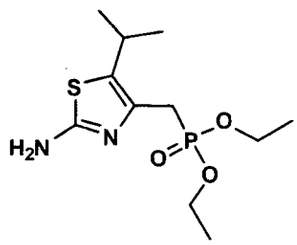
El compuesto del título (32 mg; 78%; sólido blanco) se sintetizó empleando el mismo procedimiento como se describe para la síntesis del Ejemplo 50, excepto que NBS se usó en lugar de NCS. La reacción de bromación se completó dentro de 1 h. $[M + H]^+$ = 691.3; ^1H RMN (400 MHz, $CDCl_3$): δ 1.29 (t,

6H), 1.34 (d, 3H), 3.09 (s, 3H), 3.33 (d, 2H), 3.41 (s, 3H), 3.55 (q, 2H), 4.09 (m, 4H), 4.65 (m, 1H), 6.89 (s, 1H), 7.14 (d, 2H), 7.21 (s, 1H), 7.38 (s, 1H), 7.94 (d, 2H).

EJEMPLO 52

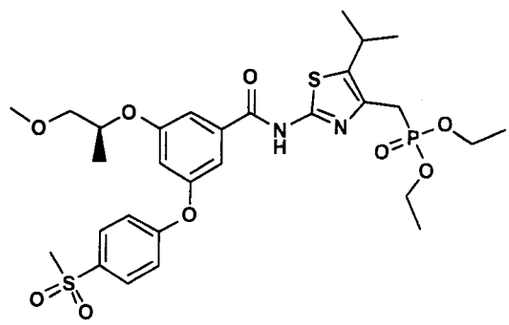


A.



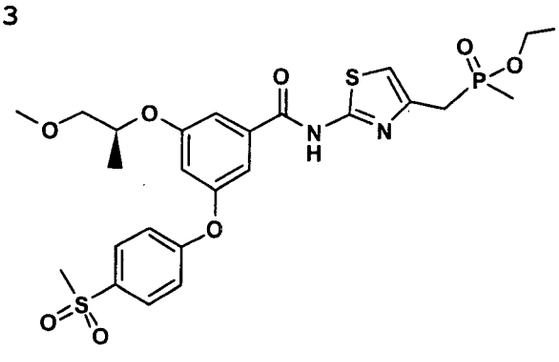
El compuesto A (120 mg; 16% durante 5 etapas; sólido blanco suave) se sintetizó de 2-amino-5-isopropil-1,3-tiazol-4-carboxilato de metilo empleando el mismo procedimiento usado para preparar el Ejemplo 13 Parte E del compuesto.

B.

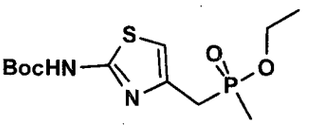


DIPEA (19.2 µL; 0.110 mmol) se agregó a una solución de la parte A del compuesto (33.6 mg; 0.115 mmol), Ejemplo 26 Parte C del compuesto (36.4 mg; 0.096 mmol) y HOAt (15.0 mg; 0.110 mmol)en DMF (0.35 mL), seguido por EDAC (21.1 mg; 0.110 mmol). Después de 24 h a temperatura ambiente la mezcla de reacción se dividió entre EtOAc (15 mL) y HCl acuoso 0.5 N (10 mL). La fase orgánica se lavó con $NaHCO_3$ acuoso saturado (10 mL) y salmuera (10 mL), se seca ($MgSO_4$) y se concentra in vacuo. El producto crudo se purificó por HPLC preparativa (Columna YMC de fase inversa ODS-A-5u 30 x 100 mm; relación de flujo = 40 mL/min, 15 hasta 100% solvente B durante 10 min, espera a 12 min, donde el solvente A = 90:10:0.1 H_2O:ACN:TFA y solvente B = 90:10:0.1 ACN:H_2O:TFA) para dar el compuesto del título (49 mg; 75%) como un residuo incoloro. $[M + H]^+$ = 655.3; ^1H RMN (400 MHz, $CDCl_3$): δ 1.29 (t, 6H), 1.35 (m, 9H), 3.07 (s, 3H), 3.28 (d, 2H), 3.31 (m, 1H), 3.41 (s, 3H), 3.57 (m, 2H), 4.13 (m, 4H), 4.84 (m, 1H), 6.92 (s, 1H), 7.15 (d, 2H), 7.38 (s, 1H), 7.62 (s, 1H), 7.92 (d, 2H).

EJEMPLO 53

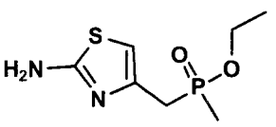


A.



Metilfosfonito de dietilo (690 mg; 5.07 mmol) se agregó a una solución del Ejemplo 13 Parte C del compuesto (496 mg; 1.69 mmol) en THF (0.5 mL). La mezcla de reacción se calentó a 75°C durante 16 h, luego se enfrió hasta temperatura ambiente. La solución se cargo directamente en una columna SiO_2 de 12 g y el producto crudo se procesó por cromatografía (gradiente continuo desde 0 hasta 100% EtOAc en Hexanos durante 4 min, se cambia a 5% MeOH en EtOAc y se mantiene durante 10 min) para dar la parte A del compuesto (493 mg; 91%) como un sólido amarillo ligero.

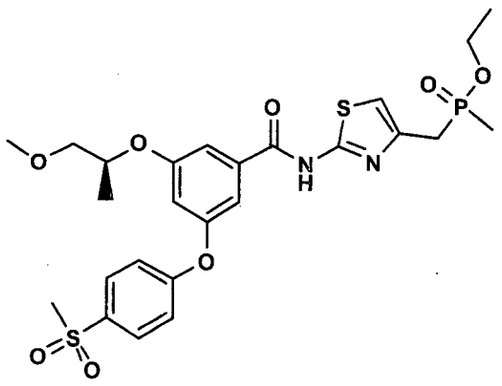
B.



TFA (2.0 mL) se agregó a 0°C una solución de la parte A del compuesto (768 mg; 2.40 mmol) en DCM (6 mL). La mezcla de reacción se agitó a temperatura ambiente durante 3 h, luego se concentró in vacuo. El residuo se dividió entre EtOAc (15 mL) y $NaHCO_3$ acuoso saturado (10 mL). La fase acuosa se extrajo con EtOAc (2 x 10 mL). Los extractos orgánicos combinados se secaron ($MgSO_4$) y se concentran in vacuo para dar la parte B del compuesto (203 mg; 38%).

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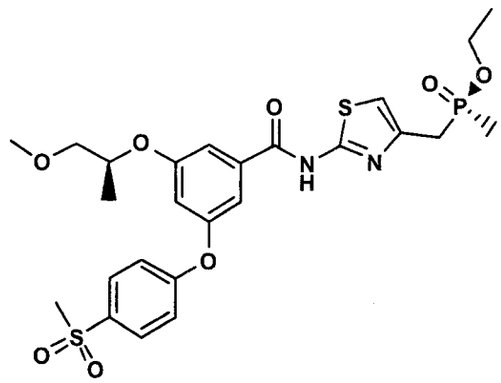
c.



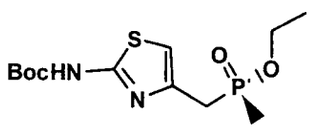
DIPEA (228 µL; 1.31 mmol) se agregó a una solución de la parte B del compuesto (369 mg; 1.67 mmol), Ejemplo 26 Parte C del compuesto (415 mg; 1.09 mmol) y HOAt (178 mg; 1.31 mmol) en DMF (4.0 mL). EDAC (251 mg; 1.31 mmol) se agregó. Después de 48 h a temperatura ambiente la mezcla de reacción se dividió entre EtOAc (15 mL) y H_2O (12 mL). La fase orgánica se lavó con HCl acuoso 0.5 N (10 mL), $NaHCO_3$ acuoso saturado (10 mL) y salmuera (10 mL), se seca ($MgSO_4$) y se concentra in vacuo. El producto crudo se procesó por cromatografía (SiO_2; gradiente continuo desde 0 hasta 100% EtOAc en Hexanos durante 6 min, se cambia a 1% MeOH en EtOAc y se mantiene durante 4 min, luego se cambia a 4% MeOH en EtOAc y se mantiene durante 10 min) para dar el compuesto del título (354 mg; 56%) como un sólido blanco (mezcla diastereomérica). $[M + H]^+$ = 583.3; ^1H RMN (400 MHz, $CDCl_3$): δ 1.34 (m, 6H), 1.50 (d, 3H), 3.08 (s, 3H), 3.32 (m, 1H), 3.41 (s, 3H), 3.57 (m, 3H), 4.06 (m, 2H), 4.76 (m, 1H), 6.89 (s, 2H), 7.15 (d, 2H), 7.44 (s, 1H), 7.61 (s, 1H), 7.92 (d, 2H).

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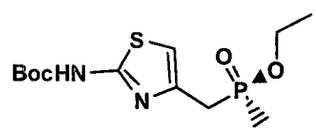
EJEMPLO 54



A.



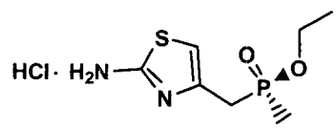
Isómero 1



Isómero 2

Los dos isómeros del Ejemplo 53 Parte A del compuesto (2.6 g; 8.12 mmol) se separaron por HPLC preparativa quiral (columna ChiralPak AD, 5 x 50 cm, 20μ, isocrática a 15% de 50/50 MeOH:EtOH; 85% heptano, 50 mL/min durante 2 h). El material se purificó en tres corridas. El isómero 1 tiene un tiempo de retención de 38 min y el siómero 2 tiene un tiempo de retención de 52 min. Las fracciones que contienen el isómero 1 se concentraron in vacuo para dar 1.07 g (82%) de un sólido vidrioso. Las fracciones que contienen el isómero 2 se concentraron in vacuo para dar 1.09 g (84%) de un sólido vidrioso.

B.

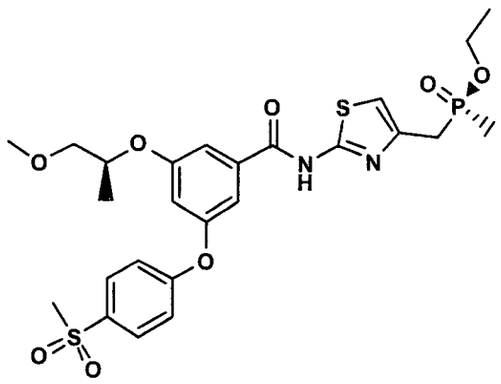


Isómero 2

HCl (6.0 mL de una solución 4.0 N en 1,4 dioxane) se

agregó a la parte A del compuesto del isomero 2 (1.05 g; 3.28 mmol). Después de agitar a temperatura ambiente durante 5 h, la mezcla de reacción se concentró in vacuo. El residuo se disolvió en H_2O (20 mL), se congeal y liofiliza. El liofilato se disolvió en MeOH (25 mL) y se concentra in vacuo para dar la parte B del compuesto (0.85 g; 100%) como una espuma blanca.

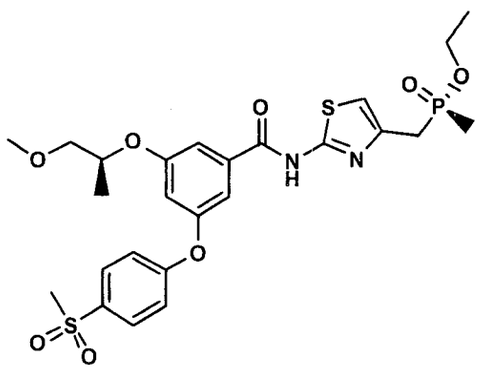
C.



DIPEA (1.45 mL; 8.28 mmol) se agregó a una solución de la parte B del compuesto (0.85 g; 3.31 mmol), Ejemplo 26 Parte C del compuesto (1.05 g; 2.76 mmol) y HOAt (526 mg; 3.86 mmol) en DMF (10.0 mL). EDAC (741 mg; 3.86 mmol) se agregó. Después de 72 h a temperatura ambiente la mezcla de reacción se dividió entre EtOAc (140 mL) y H_2O (120 mL). La fase orgánica se lavó con HCl acuoso 0.5 N (100 mL), $NaHCO_3$ acuoso saturado (100 mL) y salmuera (80 mL), se seca ($MgSO_4$) y se concentra in vacuo. El producto crudo se dividió en 4 porciones y se purifica por HPLC preparativa (Columna YMC de fase inversa ODS-A-5u 30 x 250 mm; relación de flujo = 30

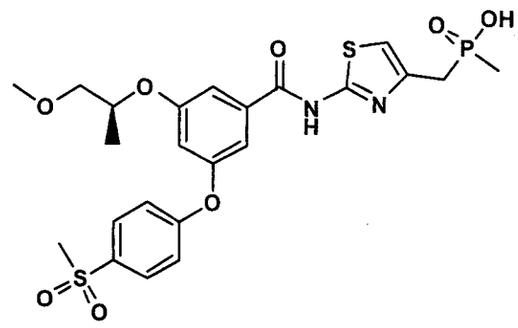
mL/min, 20 hasta 100% solvente B durante 20 min, espera a 25 min, donde el solvente A = 90:10:0.1 H_2O:MeOH:TFA y solvente B = 90:10:0.1 MeOH:H_2O:TFA). El producto se purificó por HPLC preparativa una segunda vez usando las mismas condiciones pero usando CH_3CN en lugar de MeOH para dar el compuesto del título (920 mg; 57%) como un sólido blanco. $[M + H]^+$ = 583.0; ^1H RMN (400 MHz, $CDCl_3$): δ 1.33 (m, 6H), 1.45 (d, 3H), 3.07 (s, 3H), 3.34 (m, 1H), 3.40 (s, 3H), 3.55 (q, 2H), 3.86 (m, 1H), 4.05 (m, 2H), 4.70 (m, 1H), 6.77 (d, 1H), 6.86 (s, 1H), 7.14 (d, 2H), 7.49 (s, 1H), 7.62 (s, 1H), 7.91 (d, 2H).

EJEMPLO 55



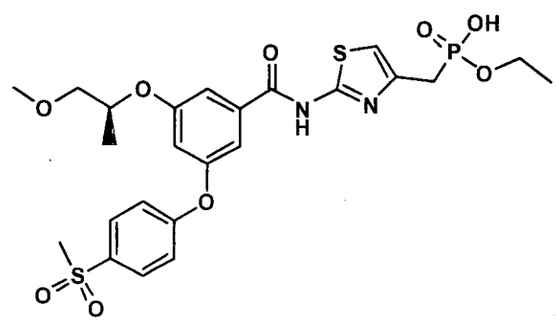
El compuesto del título (133 mg, 44% de rendimiento crudo, sólido blanco) se preparó del Ejemplo 54 Parte A isómero 1 empleando el procedimiento establecido en el Ejemplo 54. $[M + H]^+$ = 583.2; ^1H RMN (400 MHz, $CDCl_3$): δ 1.33 (m, 6H), 1.45 (d, 3H), 3.07 (s, 3H), 3.32 (m, 1H), 3.40 (s, 3H), 3.55 (q, 2H), 3.77 (m, 1H), 4.06 (m, 2H), 4.70 (m, 1H), 6.77 (d, 1H), 6.86 (s, 1H), 7.14 (d, 2H), 7.47 (s, 1H), 7.59 (s, 1H), 7.91 (d, 2H).

EJEMPLO 56



NaOH acuoso 2.0 N (81 µL; 0.162 mmol) se agregó a una mezcla del Ejemplo 55 del compuesto (31.5 mg; 0.054 mmol) en EtOH (70 µL) y THF (70 µL). Después de 16 h la mezcla se dividió entre EtOAc (2 mL) y HCl acuoso 0.5 N (1 mL). La fase orgánica se lavó con salmuera (1 mL), se seca ($MgSO_4$) y se concentra in vacuo para dar el compuesto del título (27.4 mg; 91%) como un sólido blanco. $[M + H]^+$ = 555.0; ^1H RMN (400 MHz, $CDCl_3$): δ 1.28 (d, 3H), 1.37 (d, 3H), 3.10 (s, 3H), 3.21 (d, 2H), 3.43 (s, 3H), 3.59 (q, 2H), 4.77 (m, 1H), 6.74 (s, 1H), 6.92 (s, 1H), 7.20 (d, 2H), 7.70 (s, 1H), 7.77 (s, 1H), 7.93 (d, 2H).

EJEMPLO 57

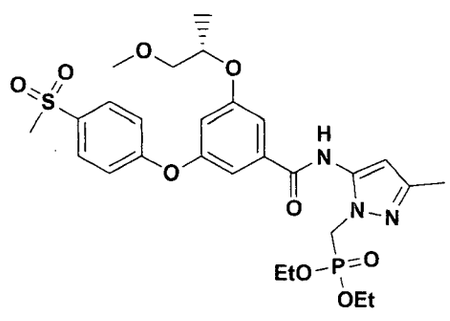


NaOH acuoso 2.5 N (131 µL; 0.328 mmol) se agregó a una solución del Ejemplo 37 del compuesto (67 mg; 0.109 mmol) en

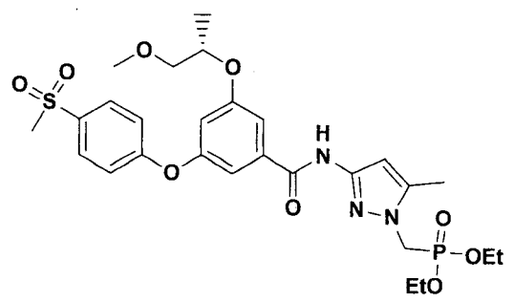
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MeOH (130 µL) y THF (130 µL). La solución se calentó a 50°C durante 20 h, luego se enfrió hasta temperatura ambiente y se divide entre EtOAc (4 mL) y HCl acuoso 1.0 N (2 mL). La fase orgánica se lavó con salmuera (2 mL), se seca ($MgSO_4$) y se concentra in vacuo. El producto crudo se purificó por HPLC preparativa (columna YMC de fase inversa ODS-A-5mm 30 x 100 mm; relación de flujo = 40 mL/min, 15 hasta 100% solvente B durante 10 min, espera a 12 min, donde el solvente A = 90:10:0.1 H_2O:ACN:TFA y solvente B = 90:10:0.1 ACN:H_2O:TFA) para dar a sólido blanco. El material se purificó por HPLC preparativa una segunda vez (mismas condiciones como arriba pero usando MeOH en lugar de ACN) para dar el compuesto del título (30 mg; 47%) como un sólido blanco. $[M + H]^+$ = 585.0; ^1H RMN (400 MHz, CD_3OD): δ 1.30 (m, 6H), 3.12 (s, 3H), 3.28 (d, 2H), 3.37 (s, 3H), 3.56 (m, 2H), 4.05 (m, 2H), 4.71 (m, 1H), 6.96 (m, 2H), 7.24 (d, 2H), 7.31 (s, 1H), 7.48 (s, 1H), 7.97 (d, 2H).

EJEMPLOS 58 Y 59



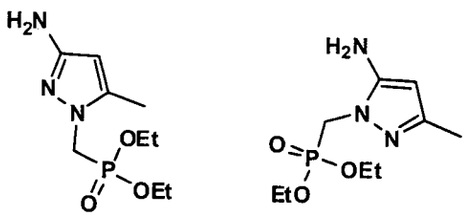
58



59

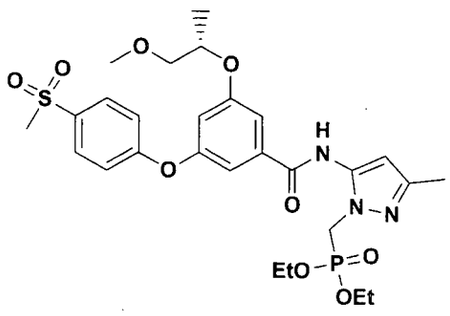
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A.

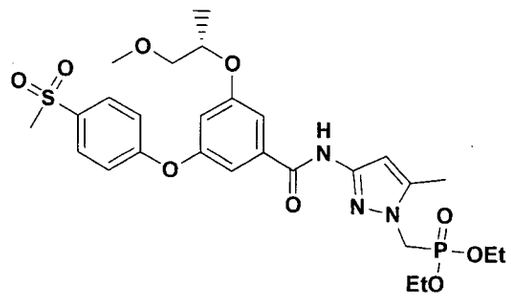


A 0°C una solución de 5-metil-1H-pirazol-3-amina (260 mg, 2.68 mmol) en DMF (4 mL) se agregó KOtBu (601 mg, 5.35 mmol). La reacción se agitó a 0°C durante 30 min, y luego $ICH_2PO_3Et_2$ (1116 mg, 4.02 mmol) se agregó gota a gota. La reacción se agitó a 0°C durante 1 h, luego se calentó hasta temperatura ambiente y se agita a temperatura ambiente durante 18 h. Los volátiles se removieron in vacuo a 50°C. El residuo se dividió entre EtOAc y salmuera. La capa acuosa se extrajo con EtOAc (4x), y los extractos orgánicos combinados se secaron ($MgSO_4$) y se concentran in vacuo para dar un aceite café. El residuo crudo se purificó por HPLC preparativa (columna Luna 5u 21.2 x 100 mm; relación de flujo = 20 mL/min, 0 hasta 100% solvente B durante 12 min, espera a 15 min, donde el solvente A = 90:10:0.1 H_2O:MeOH:TFA y solvente B = 90:10:0.1 MeOH:H_2O:TFA) para proporcionar la parte A de los compuestos (mezcla 1:1, 80 mg, 12%) como un sólido blanco.

B.



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A temperatura ambiente una solución del Ejemplo 26C del ácido (0.110 g, 0.288 mmol) en DMF (4.5 mL), se agregó EDC (0.110 g, 0.576 mmol), HOAT (0.078 g, 0.576 mmol), y DIEA (0.088 mL, 0.5004 mmol). La solución amarilla homogénea se agitó a 25°C durante 30 min. Una solución de la parte A del compuesto (0.100g, 288 mmol) en DIEA (0.088 mL, 0.5004 mmol) y DMF (1.5 mL) se agregó, y la mezcla de reacción amarilla homogénea se agitó a 25°C durante 2 h, luego se vació en agua (15 mL). La mezcla se extrajo con EtOAc (10 mL); la fase orgánica se secó ($MgSO_4$) y se concentra in vacuo. El residuo se purificó por HPLC preparativa (columna Phenomenex Luna 5 μ C18 30 x 250 mm; detección a 220 nm; relación de flujo =20 mL/min.; gradiente continuo desde 100% A hasta 100% B durante 30 min. + 7 min. espera a 100% B, donde A=90:10 H_2O:MeOH y B=90:10 MeOH: H_2O) para proporcionar una espuma amarilla (una mezcla de los dos regioisómeros).

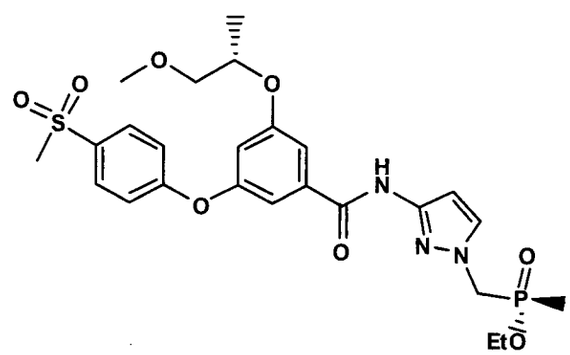
Los regioisómeros se separaron por HPLC preparativa quiral (columna 5 cm x 50 cm AD, detección a 220 nm, isocrática 50:50 fase móvil EtOH:MeOH, 50 mL/min. flujo) para proporcionar el compuesto del título 58 (27 mg, 15.2 % de rendimiento) como un sólido canela y el compuesto del título 59 (64mg, 36.3 % de rendimiento) como un sólido blanco opaco.

Ejemplo 58: $[M + H]^+$ = 610.4; ^1H RMN (400 MHz, $CDCl_3$) δ 10.56 (s, 1H), 7.91 (d, J=8.79 Hz, 2H), 7.52 (t, J=1.75, 1.76 Hz, 1H), 7.37 (t, J=1.75,1.32 Hz, 1H), 7.15 (d, J=8.79 Hz,

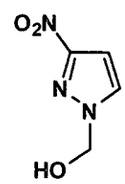
2H), 6.83 (t, J=2.20 Hz, 1H), 6.44 (s, 1H), 4.64-4.74 (m, 1H), 4.50 (d, J=10.55 Hz, 2H), 3.97-4.17 (m, 4H), 3.49-3.64 (m, 2H), 3.42 (s, 3H), 3.07 (s, 3H), 2.26 (s, 3H), 1.36 (d, J=6.15 Hz, 3H), 1.27 (t, J=7.03 Hz, 6H).

Ejemplo 59: $[M + H]^+$ = 610.4; ^1H RMN (400 MHz, $CDCl_3$) δ 8.6 (s, 1H), 7.92 (d, J=8.79 Hz, 2H), 7.31 (t, J=1.76 Hz, 1H), 7.12-7.17 (m, 3H), 6.83 (t, J=2.19, 1.76 Hz, 1H), 6.66 (s, 1H), 4.57-4.69 (m, 1H), 4.37 (d, J=11.42 Hz, 2H), 4.01-4.15 (m, 4H), 3.48-3.63 (m, 2H), 3.42 (s, 3H), 3.09 (s, 3H), 2.34 (s, 3H), 1.34 (d, J=6.59 Hz, 3H), 1.29 (t, J=7.03 Hz, 6H).

EJEMPLO 60



A.

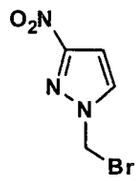


A una suspension de 3-nitro-1H-pirazol (1.00 g, 8.84 mmol) en agua (31 mL) se agregó formaldehído (37% p en agua, 1.317 mL, 17.69 mmol). La mezcla de reacción se agitó a

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temperatura ambiente durante 48 h (después de 2 h la mezcla de reacción se volvió una solución amarilla pálida homogénea). La mezcla de reacción se diluyó con $NaHCO_3$ acuoso saturado (20 mL) y se extrae con CH_2Cl_2 (4 x 40 mL) y EtOAc (3 x 50 mL). Los extractos orgánicos combinados se secaron ($MgSO_4$) y se concentra in vacuo para proporcionar la parte A del compuesto (1.26 g, 99% de rendimiento) como un sólido blanco. ^1H RMN (400 MHz, CD_3OD) δ 7.69 (d, J=2.20 Hz, 1H),. 6.95 (d, J=2.75 Hz, 1H), 5.62 (d, J=7.70 Hz, 2H), 4.40 (t, J=7.70, 7.69 Hz, 1H).

B.

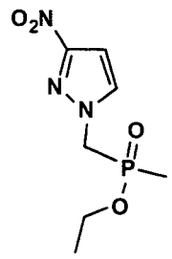


A 75°C una solución de la parte A del compuesto (1.809 g, 12.64 mmol) en MeCN (54 mL) se agregó PBr_3 (1.788 mL, 18.96 mmol) gota a gota durante 10 min. La mezcla de reacción se agitó a 75°C durante 15 min, luego se enfrió hasta temperatura ambiente y se filtra. La torta filtro se lavó con CH_3CN (2 x 2 mL), y los filtrados combinados se concentraron in vacuo. El residuo se dividió entre EtOAc (50 mL) y $NaHCO_3$ acuoso saturado (30 mL). La fase orgánica se lavó con salmuera (20 mL), se seca ($MgSO_4$), y se concentra in-vacuo. El residuo se procesó por cromatografía (SiO_2: gradiente continuo 0% EtOAc/Hexano hasta 70% EtOAc/Hex) para

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proporcionar la parte B del compuesto (1.693 g, 65% de rendimiento) como un sólido amarillo pálido. ^{1}H RMN (400 MHz, $CDCl_3$) δ 7.80 (d, J=2.20 Hz, 1H), 7.01 (d, J=2.75 Hz, 1H), 5.98 (s, 2H).

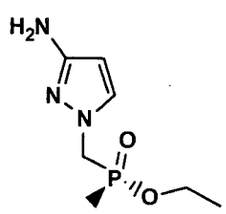
C.



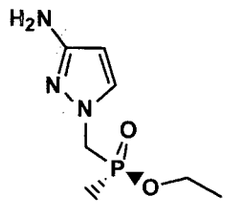
A una solución de la parte B del compuesto (1.7366 g, 8.43 mmol) en THF (4 mL) se agregó $CH_3P(OEt)_2$ (1.377 g, 10.12 mmol). La mezcla de reacción se agitó a 75°C durante 15 h. $CH_3P(OEt)_2$ adicional (0.53 g, 3.89 mmol) se agregó, y la mezcla de reacción se agitó a 75°C durante 24 h, luego se enfrió hasta temperatura ambiente. Los volátiles se removieron in vacuo, y el residuo se procesó por cromatografía (SiO_2: gradiente continuo desde 0% MeOH/CH_2Cl_2 hasta 15% MeOH/CH_2Cl_2) para proporcionar la parte C del compuesto (1.56 g, 80% de rendimiento) como un aceite anaranajado. $[M + H]^+$ = 234.1; ^{1}H RMN (400 MHz, $CDCl_3$) δ 7.71 (d, J=3.30 Hz, 1H), 6.96 (d, J=2.75 Hz, 1H), 4.63 (d, J=9.34 Hz, 2H), 4.03-4.20 (m, 4H), 1.57 (d, J=14.85 Hz, 3H), 1.30-1.37 (m, 6H).

598

D.



D1



D2

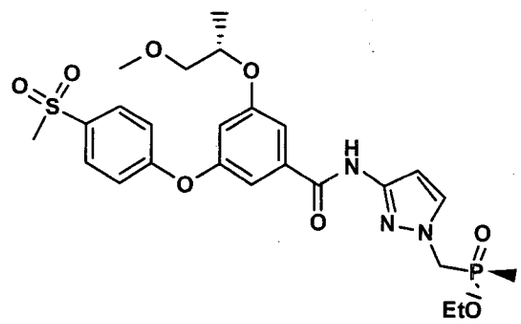
A una solución de la Parte C del compuesto (1.60 g, 6.86 mmol) en MeOH (190 mL) se agregó 10% Pd/C (0.730 g, 0.686 mmol). La mezcla de reacción se agitó bajo una atmósfera de H_2(g) durante 3 h. La mezcla de reacción se filtró a través de Celite®, y el filtrado se concentró in vacuo. Los estereoisómeros individuales se separaron en una columna Chiralcel OJ (5 cm x 50 cm, condiciones isocráticas: 40% IPA en heptano, detección a 220 nm, 50 mL/min. flujo) para proporcionar el isómero D1 (0.59 g, 42.3% de rendimiento) como un sólido blanco opaco e isómero D2 (0.56 g, 40% de rendimiento) como un sólido canela.

Isómero D1: $[M + H]^+$ = 204.1; ^1H RMN (400 MHz, $CDCl_3$) δ 7.24 (d, J=2.19 Hz, 1H), 5.66 (d, J=2.20 Hz, 1H), 4.32 (d, J=8.79 Hz, 2H), 4.02-4.17 (m, 2H), 3.59-3.81 (s, 2H), 1.48 (d, J=14.50 Hz, 3H), 1.33 (t, J=7.03 Hz, 3H), rotación específica =48.5°.

Isómero D2: $[M + H]^+$ = 204.1; ^1H RMN (400 MHz, $CDCl_3$) δ 7.21-7.27 (m, 1H), 5.62-5.70 (m, 1H), 4.32 (d, J=8.79 Hz, 2H), 4.01-4.19 (m, 2H), 3.55-3.81 (s, 2H), 1.48 (d, J=14.50

Hz, 3H), 1.33 (t, J=7.03 Hz, 3H), rotación específica =-49.6°.

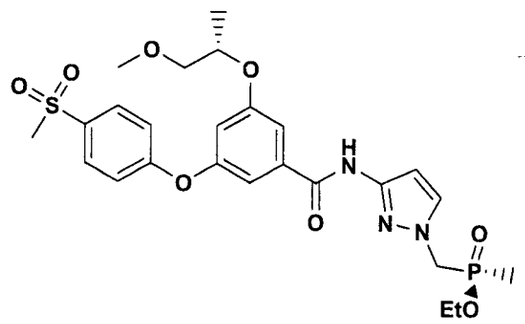
E.



A temperatura ambiente una solución del Ejemplo 26 Parte C del compuesto (0.120 g, 0.315 mmol) en DMF (6 mL) se agregó EDAC (0.121 g, 0.631 mmol), HOAT (0.086 g, 0.631 mmol), y DIEA (0.165 mL, 0.946 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 30 min y Parte D1 del compuesto (0.064 g, 0.315 mmol) se agregó. La mezcla de reacción se agitó a temperatura ambiente durante 18 h. La mezcla de reacción se vació en agua (40 mL) y la mezcla se extrajo con EtOAc (3 x 15 mL). Los extractos orgánicos combinados se concentraron in vacuo. El residuo se purificó por HPLC preparativa (columna Phenomenex Luna 5 µm C18 30 x 100 mm; detección a 220 nm; relación de flujo =40 mL/min; gradiente continuo desde 100% A hasta 100% B durante 20 min. + 2 min. espera a 100% B, donde A=90:10:0.1 H_2O:MeOH:TFA y B=90:10:0.1 MeOH: H_2O:TFA) para proporcionar el compuesto del título (0.121 g, 68.1% de rendimiento) como un sólido blanco. $[M + H]^+$ = 566.3; ^1H RMN (400 MHz, $CDCl_3$): δ 9.24 (s, 1H), 7.91 (d,

J=8.78 Hz 2H), 7.46 (d, J=1.76 Hz, 1H), 7.38 (t, J=1.76 Hz, 1H), 7.23 (t, J=1.76 Hz,1H), 7.13 (d, J=8.79 Hz, 2H), 6.96 (d, J=2.19 Hz, 1H), 6.84 (t, J=2.20 Hz, 1H), 4.73-4.63 (m, 1H), 4.56 (dd, J=16.25, 8.35 Hz, 1H), 4.46 (dd, J=15.82, 8.35, 9.67 Hz, 1H), 4.20-4.05 (m, 2H), 3.63-3.50 (m, 2H), 3.42 (s, 3H), 3.08 (s, 3H), 1.51 (d, J=14.5 Hz, 3H), 1.39-1.29 (m, 6H).

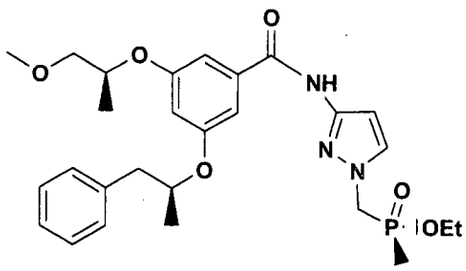
EJEMPLO 61



A una solución a temperatura ambiente del Ejemplo 26C el ácido (0.120 g, 0.315 mmol) en DMF (6 mL) se agregó EDAC (0.121 g, 0.631 mmol), HOAT (0.086 g, 0.631 mmol), y DIEA (0.165 mL, 0.946 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 30 min y Compuesto del ejemplo 60 parte D2 (0.064 g, 0.315 mmol) se agregó. La mezcla de reacción se agitó a temperatura ambiente durante 18 h, luego se vació en agua (40 mL). La mezcla se extrajo con EtOAc (3 x 15 mL); los extractos orgánicos combinados se concentraron *in vacuo*. El residuo se purificó por HPLC preparativa (columna Phenomenex Luna 5 µm C18 30 x 100 mm; detección a 220 nm;

relación de flujo =40 mL/min.; gradiente continuo de 100% A hasta 100% B durante 20 minutos. + 2 min. mantenido a 100% B, donde A=90:10:0.1 H_2O:MeOH:TFA y B=90:10:0.1 MeOH: H_2O:TFA) para proporcionar el compuesto del título (0.117 g, 65.4% de rendimiento) como un sólido blanco. $[M + H]^+$ = 566.3; ^1H RMN (400 MHz, $CDCl_3$): δ 9.19 (s, 1H), 7.92 (d, *J*=9.22 Hz 2H), 7.46 (d, *J*=1.76 Hz, 1H), 7.37 (t, *J*=1.76 Hz, 1H), 7.22 (t, *J*=1.76 Hz,1H), 7.13 (d, *J*=8.78 Hz, 2H), 6.96 (d, *J*=2.63 Hz, 1H), 6.85 (t, *J*=2.20 Hz, 1H), 4.72-4.62 (m, 1H), 4.56 (dd, *J*=16.25, 8.35 Hz, 1H), 4.46 (dd, *J*=15.82, 8.35, 9.67 Hz, 1H), 4.19-4.05 (m, 2H), 3.63-3.50 (m, 2H), 3.42 (s, 3H), 3.08 (s, 3H), 1.51 (d, J=14.5 Hz, 3H), 1.38-1.29 (m, 6H).

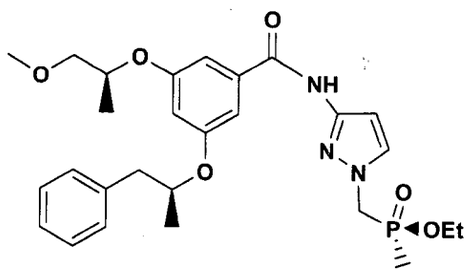
EJEMPLO 62



A una solución a temperatura ambiente del Ejemplo 33 Parte A el ácido ((0.030 g, 0.087 mmol) en DMF (2.0 mL) se agregó EDAC (0.033 g, 0.174 mmol), HOAt (0.024 g, 0.174 mmol) y DIEA (0.046 mL, 0.261 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 30 min, después de lo cual el compuesto del ejemplo 60 parte D1 (0.018 g, 0.087 mmol) se agregó. La mezcla de reacción se agitó a temperatura ambiente

durante 18 h, luego se vació en agua (20 mL). La mezcla se extrajo con EtOAc (2 x 10 mL); los extractos orgánicos combinados se secaron ($MgSO_4$) y se concentraron *in vacuo*. El residuo se purificó por HPLC preparativa (columna Phenomenex Luna 5 µ C18 21.2 x 100 mm; detección a 220 nm; relación de flujo=40 mL/min.; gradiente continuo de 100% A hasta 100% B durante 15 min. + 2 min. mantenido a 100% B, donde A=90:10:0.1 H_2O:MeOH:TFA y B=90:10:0.1 MeOH: H_2O:TFA) para proporcionar el compuesto del título (0.034 g, g, 74.8% de rendimiento) como un sólido blanco opaco viscoso. $[M + H]^+$ = 530.4; ^1H RMN (400 MHz, $CDCl_3$): δ 9.16 (s, 1H), 7.45 (d, *J*=1.65 Hz, 1H), 7.32-7.18 (m, 5H), 7.06 (t, *J*=1.65 Hz, 1H), 7.03 (t, *J*=1.65 Hz, 1H), 6.98 (d, *J*=2.19 Hz, 1H), 6.64 (t, *J*=2.2 Hz, 1H), 4.69-4.56 (m, 2H), 4.55- 4.40 (m, 2H), 4.18-4.04 (m, 2H), 3.57 (dd, *J*=10.45 Hz, *J*=6.04 Hz, 1H), 3.50 (dd, *J*=9.89 Hz, *J*=3.85 Hz, 1H), 3.41 (s, 3H), 3.06 (dd, *J*=13.74 Hz, *J*=6.04 Hz, 1H), 2.86 (dd, *J*=13.75 Hz, *J*=6.05 Hz, 1H), 1.53 (d, *J*=14.84 Hz, 3H), 1.35-1.27 (m, 9H).

EJEMPLO 63

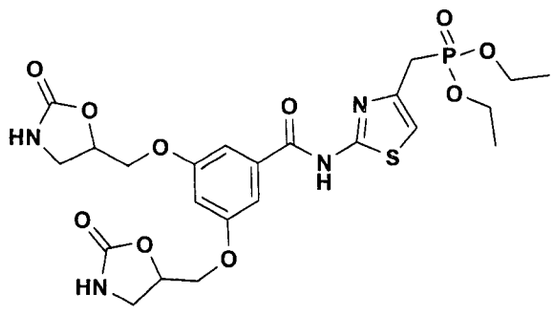


A una solución a temperatura ambiente del Ejemplo 33

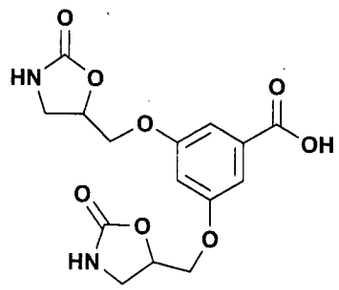
Parte A el ácido ((0.030 g, 0.087 mmol) en DMF (2.0 mL) se agregó EDAC (0.033 g, 0.174 mmol), HOAt (0.024 g, 0.174 mmol) y DIEA (0.046 mL, 0.261 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 30 min, después de lo cual Compuesto del ejemplo 60 parte D2 (0.018 g, 0.087 mmol) se agregó. La reacción se agitó a temperatura ambiente durante 18 h, luego se vació en agua (20 mL). La mezcla se extrajo con EtOAc (2 x 10 mL) y los extractos orgánicos combinados se secaron ($MgSO_4$) y se concentraron *in vacuo*. El residuo se purificó por HPLC preparativa (columna Phenomenex Luna 5 µ C18 21.2 x 100 mm; detección a 220 nm; relación de flujo=40 mL/min.; gradiente continuo de 100% A hasta 100% B durante 15 min. + 2 min. mantenido a 100% B, donde A=90:10:0.1 H_2O:MeOH:TFA y B=90:10:0.1 MeOH: H_2O:TFA) para proporcionar el compuesto del título (0.03626 g, 79% de rendimiento) como un sólido blanco viscoso. $[M + H]^+$ = 530.4; ^1H RMN (400 MHz, $CDCl_3$): δ 9.17 (s, 1H), 7.45 (d, *J*=2.20 Hz, 1H), 7.32-7.17 (m, 5H), 7.06 (t, *J*=2.2 Hz, 1H), 7.03 (t, *J*=2.2 Hz, 1H), 6.98 (d, *J*=2.19 Hz, 1H), 6.64 (t, *J*=2.2 Hz, 1H), 4.70-4.57 (m, 2H), 4.54- 4.40 (m, 2H), 4.17-4.03 (m, 2H), 3.57 (dd, *J*=9.90 Hz, *J*=6.04 Hz, 1H), 3.50 (dd, *J*=10.44 Hz, *J*=3.38 Hz, 1H), 3.41 (s, 3H), 3.06 (dd, *J*=13.74 Hz, *J*=6.59 Hz, 1H), 2.85 (dd, *J*=13.75 Hz,

J=6.05 Hz, 1H), 1.52 (d, *J*=14.29 Hz, 3H), 1.36-1.26 (m, 9H).

EJEMPLO 64



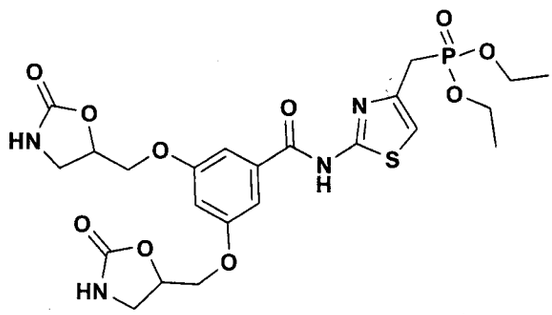
A.



Una mezcla de 3,5-dihidroxibenzoato de metilo (350 mg, 2.082 mmol), 5-(clorometil)oxazolidin-2-ona (1.0 g, 7.38 mmol), y K_2CO_3 (5.75 g, 41.6 mmol) en DMF (10 mL) se agitó a 80°C durante 18 h, luego se enfrió a temperatura ambiente y se filtró. La torta filtro se lavó con EtOAc, y los filtrados combinados se concentraron *in vacuo* para dar un aceite café. El benzoato bis-alquilado de metilo crudo se disolvió en THF (1 mL), y NaOH 1N acuoso (1 mL, 1.00 mmol) se agregó. La mezcla se agitó a temperatura ambiente durante 18 h, luego se concentró *in vacuo*. El residuo se acidificó con TFA y luego se purificó por HPLC preparativa (columna Phenomenex AXIA 5u

C18 30 x 100 mm; detección a 220 nm; relación de flujo = 40 mL/min; gradiente continuo de 30% A hasta 100% B durante 10 min + 1 min tiempo de espera a 100% B, donde A = 90:10:0.1 H_2O:MeOH:TFA y B = 90:10:0.1 MeOH:H_2O:TFA) para dar el compuesto parte A (83 mg, 9% de rendimiento) como un sólido rojo. $[M + H]^+$ = 353.1; ^1H RMN (400 MHz, MEOH-d_4) δ 3.56 (dd, J=8.79, 6.60 Hz, 2 H) 3.75 (t, J=9.07 Hz, 2 H) 4.10 - 4.30 (m, 4 H) 4.96 - 5.07 (m, 2 H) 6.77 - 6.85 (m, 0 H) 7.22 (d, J=2.75 Hz, 2 H).

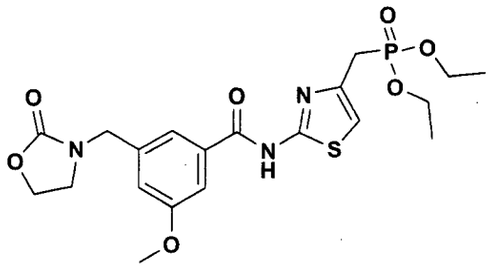
B.



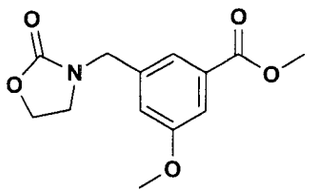
Una mezcla del compuesto parte A (13 mg, 0.037 mmol), Compuesto del ejemplo 13 parte E (23 mg, 0.037 mmol), HOAt (10 mg, 0.072 mmol), EDCI (20 mg, 0.500 mmol) y DIPEA (0.2 mL, 1.148 mmol) en DMF (0.5 mL) se agitó a 21°C durante 18 h. La mezcla de reacción se diluyó con EtOAc (1 mL) y se lavó con HCl acuoso 1N (1mL). La capa orgánica se secó ($MgSO_4$) y se concentró *in vacuo*. El residuo se purificó por HPLC preparativa (columna Phenomenex AXIA 5u C18 30 x 100 mm; detección a 220 nm; relación de flujo = 40 mL/min; gradiente continuo de 30% A hasta 100% B durante 10 min + 1 min tiempo

de espera a 100% B, donde A = 90:10:0.1 H_2O:MeOH:TFA y B = 90:10:0.1 MeOH:H_2O:TFA) para dar el compuesto del título (12.5 mg, 58.0 % de rendimiento) como un sólido blanco. $[M + H]^+$ = 585.3; ^1H RMN (400 MHz, $CDCl_3$) δ 1.33 (t, J=7.15 Hz, 6 H) 3.35 (d, J=21.44 Hz, 2 H) 3.63 (dd, J=8.25, 6.60 Hz, 2 H) 3.79 (t, J=8.79 Hz, 2 H) 4.11 - 4.20 (m, 4 H) 4.21 - 4.37 (m, 4 H) 4.96 - 5.04 (m, 2 H) 5.76 (br. s., 2 H) 6.80 (br. s., 1 H) 7.04 (d, J=3.85 Hz, 1 H) 7.44 (s, 2 H).

EJEMPLO 65



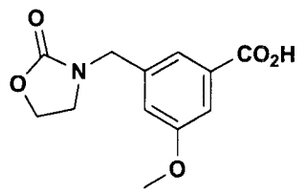
A.



Una suspensión de NaH (70 mg de una suspensión 60% en aceite, 1.750 mmol) en THF (3 mL) se agitó a 0°C bajo N_2 (g) durante 15 min. La reacción se enfrió a -30°C y oxazolidin-2-ona (125 mg, 1.436 mmol) se agregó. La mezcla se agitó a -30°C durante 30 min, luego se calentó a temperatura ambiente y se agitó durante 30 min. La mezcla se enfrió a -30°C

nuevamente y una solución de 3-(bromometil)-5-metoxibenzoato de metilo (200 mg, 0.772 mmol) en THF (2 mL) se agregó. La mezcla se agitó a temperatura ambiente durante 5 días, luego se enfrió a -30°C y NH_4Cl acuoso saturado (1 mL) se agregó. La capa acuosa se volvió a extraer con EtOAc (2 x 5mL), y los extractos orgánicos combinados se secaron (Na_2SO_4) y se concentraron *in vacuo*. El residuo se procesó por cromatografía [SiO_2; EtOAc/Hexano (1:1)] para dar el compuesto parte A 184 mg, 90% de rendimiento) como un aceite claro. $[M + H]^+$ = 266.01; ^1H RMN (500 MHz, $CDCl_3$) δ 3.46 (t, J=7.70 Hz, 2 H) 3.85 (s, 3 H) 3.92 (s, 3 H) 4.33 (t, J=7.70 Hz, 2 H) 4.44 (s, 2 H) 7.05 (s, 1 H) 7.50 (s, 1 H) 7.54 (s, 1 H).

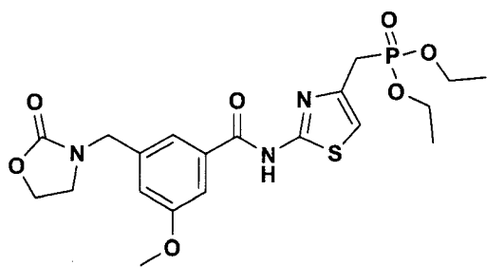
B.



Una mezcla del compuesto parte A (50 mg, 0.188 mmol), y NaOH (1 mL, 1.00 mmol) en THF (2 mL) se agitó a temperatura ambiente durante 2h, luego se acidificó con HCl acuoso 1N (0.5 mL). La mezcla se filtró y se concentró *in vacuo*; el residuo se purificó por HPLC preparativa (columna Phenomenex AXIA 5u C18 30 x 100 mm; detección a 220 nm; relación de flujo = 40 mL/min; gradiente continuo de 30% A hasta 100% B

durante 10 min + 1 min tiempo de espera a 100% B, donde A = 90:10:0.1 H_2O:MeOH:TFA y B = 90:10:0.1 MeOH:H_2O:TFA) para dar el compuesto parte B como un sólido blanco (42 mg, 0.167 mmol, 89 %). $[M + H]^+$ = 251.98; ^1H RMN (400 MHz, CD_3OD) δ 3.53 (t, J=8.24 Hz, 2 H), 3.84 (s, 3 H), 4.34 (t, J=8.24 Hz, 2 H), 4.44 (s, 2 H), 7.09 (t, J=1.65 Hz, 1 H), 7.49 (dd, J=2.75, 1.10 Hz, 1 H), 7.55 (s, 1 H).

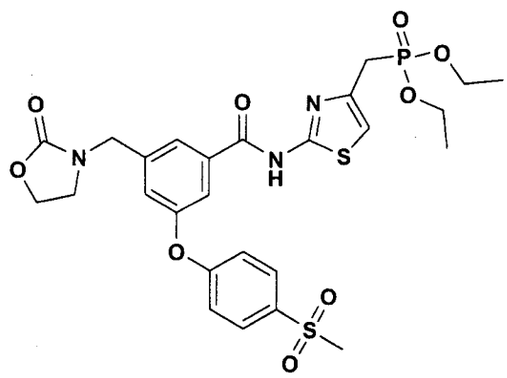
C.



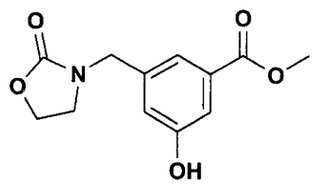
Una mezcla del compuesto parte B (12 mg, 0.048 mmol), Compuesto del ejemplo 13 parte E (11.95 mg, 0.048 mmol), HOAt (10 mg, 0.072 mmol), DIPEA (0.2 mL, 1.148 mmol) y EDCI (20 mg, 0.500 mmol) en DMF (0.5 mL) se agitó a temperatura ambiente durante 18 h, luego se diluyó con EtOAc (1 mL) y se lavó con HCl acuoso 1N (1 mL). Los volátiles se removieron *in vacuo*. El residuo crudo se purificó por HPLC preparativa (columna Phenomenex AXIA 5u C18 30 x 100 mm; detección a 220 nm; relación de flujo = 40 mL/min; gradiente continuo de 30% A hasta 100% B durante 10 min + 1 min tiempo de espera a 100% B, donde A = 90:10:0.1 H_2O:MeOH:TFA y B = 90:10:0.1 MeOH:H_2O:TFA) para dar el compuesto del título como un aceite

claro (20 mg, 87 % de rendimiento). $[M + H]^+$ = 483.99; ^1H RMN (400 MHz, $CDCl_3$) δ 1.33 (t, J=7.15 Hz, 6 H), 3.36 (d, J=21.44 Hz, 2 H), 3.52 (s, J=8.24, 8.24 Hz, 2 H), 3.91 (s, 3 H), 4.12 - 4.22 (m, J=7.35, 7.35, 7.28, 7.15 Hz, 4 H) 4.33 (t, J=8.25 Hz, 2 H), 4.46 (s, 2 H), 7.05 (d, J=3.30 Hz, 1 H), 7.17 (s, 1 H), 7.66 (s, 1 H), 7.68 (d, J=2.20 Hz, 1 H).

EJEMPLO 66



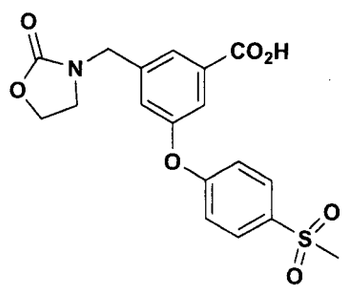
A.



A una solución a 0°C del compuesto del ejemplo 64 parte B (177 mg, 0.667 mmol) en DCM (1 mL) se agregó BBr_3 (1 mL, 1.000 mmol). La reacción se agitó a 0°C durante 24 h, después de lo cual los volátiles se removieron *in vacuo*. El residuo se disolvió en MeOH (3 mL), y el pH se ajustó hasta pH~4 con $NaHCO_3$ acuoso saturado. Los sólidos se removieron por filtración, y el filtrado se concentró *in vacuo*. El residuo se purificó por HPLC preparativa (columna Phenomenex AXIA 5u

C18 30 x 100 mm; detección a 220 nm; relación de flujo = 40 mL/min; gradiente continuo de 30% A hasta 100% B durante 10 min + 1 min tiempo de espera a 100% B, donde A = 90:10:0.1 H_2O:MeOH:TFA y B = 90:10:0.1 MeOH:H_2O:TFA) para dar el compuesto parte A (67 mg, 40% de rendimiento) como un sólido blanco. $[M + H]^+$ = 252.19; ^1H RMN (400 MHz, CD_3OD) δ 3.52 (t, J=8.24 Hz, 2 H), 3.88 (s, 3 H), 4.34 (t, J=8.24 Hz, 2 H), 4.40 (s, 2 H), 6.97 (s, 1 H), 7.36 (s, 1 H), 7.42 (s, 1 H).

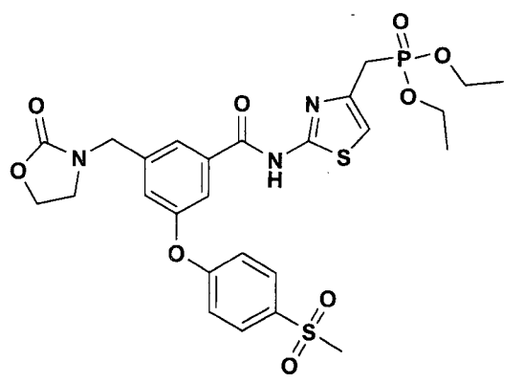
B.



Una solución del compuesto parte A (67 mg, 0.267 mmol), 1-fluoro-4-(metilsulfonil)benceno (50 mg, 0.287 mmol), y K_2CO_3 (300 mg, 2.171 mmol) en DMF (3 mL) se agitó a 100°C en un tubo sellado durante 18 h, luego se enfrió a temperatura ambiente. Los sólidos se filtraron completamente, y el filtrado se concentró *in vacuo*. El residuo se acidificó con TFA y luego se purificó por HPLC preparativa (columna Phenomenex AXIA 5µm C18 30 x 100 mm; detección a 220 nm; relación de flujo = 40 mL/min; gradiente continuo de 30% A hasta 100% B durante 10 min + 1 min tiempo de espera a 100% B, donde A = 90:10:0.1 H_2O:MeOH:TFA y B = 90:10:0.1

MeOH:H_2O:TFA) para dar el compuesto parte B (73mg, 69.9% de rendimiento) como un sólido blanco. $[M + H]^+$ = 392.01; ^1H RMN (400 MHz, CD_3OD) δ 3.12 (s, 3 H), 3.57 (t, J=8.24 Hz, 2 H), 4.36 (t, J=8.24 Hz, 2 H), 4.50 (s, 2 H), 7.20 (d, J=8.79 Hz, 2 H), 7.32 (s, 1 H), 7.63 (s, 1 H), 7.84 (s, 1 H), 7.96 (d, J=8.79 Hz, 2 H).

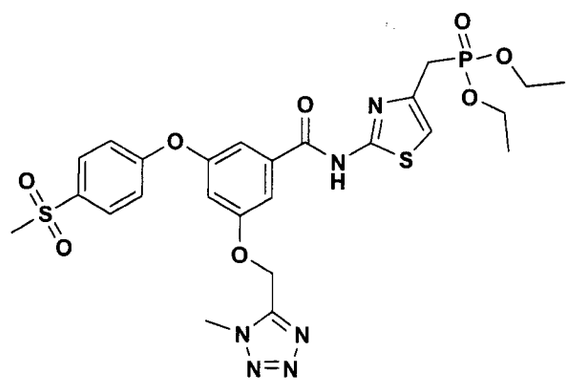
C.



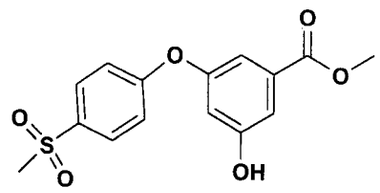
Una mezcla del compuesto parte B (15 mg, 0.038 mmol), Compuesto del ejemplo 13 parte E (9.59 mg, 0.038 mmol), HOAt (10 mg, 0.072 mmol), EDCI (20 mg, 0.500 mmol), y DIPEA (0.2 mL, 1.148 mmol) en DMF (0.5 mL) se agitó a 25°C durante 18 h. La mezcla se diluyó con EtOAc (1 mL) y se lavó con HCl acuoso 1N (1 mL). La fase orgánica se secó ($MgSO_4$) y se concentró *in vacuo*. El residuo se purificó por HPLC preparativa (Columna Phenomenex AXIA 5u C18 30 x 100 mm; detección a 220 nm; relación de flujo = 40 mL/min; gradiente continuo de 30% A hasta 100% B durante 10 min + 1 min tiempo de espera a 100% B, donde A = 90:10:0.1 H_2O:MeOH:TFA y B = 90:10:0.1 MeOH:H_2O:TFA) para dar el compuesto del título (17mg, 70% de

rendimiento) como un sólido blanco. $[M + H]^+$ = 624.2; ^1H RMN (400 MHz, $CDCl_3$) (1.32 (t, J=7.15 Hz, 6 H), 3.07 (s, 3 H), 3.33 (d, J=21.44 Hz, 2 H), 3.64 (t, J=7.70 Hz, 2 H), 4.15 (dd, J=8.25, 7.15 Hz, 4 H), 4.35 (t, J=8.24 Hz, 2 H), 4.51 (s, 2 H), 7.05 (d, J=3.85 Hz, 1 H), 7.14 (d, J=8.79 Hz, 2 H), 7.40 (s, 1 H), 7.76 (t, J=1.65 Hz, 1 H), 7.89 - 7.96 (m, 3 H).

EJEMPLO 67



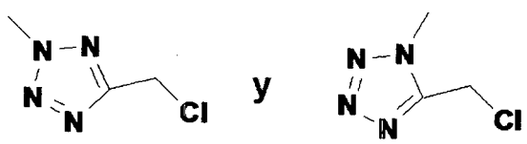
A.



Una mezcla de 3,5-dihidroxibenzoato de metilo (10 g, 59.5 mmol) y K_2CO_3 (13 g, 94 mmol) en DMF (50 mL) se agitó a 120°C durante 2 h. Una solución de 1-fluoro-4-(metilsulfonil) benceno (5 g, 28.7 mmol) en DMF (10 mL) se agregó, y la reacción se agitó a 120°C durante otras 24 h. La mezcla de reacción se filtró, y la torta filtro resultante se enjuagó

con DMF (50 mL). Los filtrados combinados se concentraron *in vacuo*. El residuo se dividió entre EtOAc (100 mL) y HCl acuoso 1N (100 mL). La capa acuosa se extrajo con EtOAc (50 mL x 3), y los extractos orgánicos combinados se lavaron con agua, se secaron (Na_2SO_4), se filtraron, y se concentraron *in vacuo*. El residuo crudo se procesó por cromatografía (SiO_2; EtOAc/Hexano 1:3) para dar el compuesto parte A (4 g, 43% de rendimiento) como un sólido amarillo. $[M + H]^+$ = 323.0; ^1H RMN (400 MHz, $CDCl_3$) δ 3.08 (s, 3 H), 3.91 (s, 3 H), 6.13 (s, 1 H), 6.80 (t, J=2.20 Hz, 1 H), 7.11 (d, J=8.79 Hz, 2 H), 7.27 - 7.28 (m, 1 H), 7.41 - 7.44 (m, 1 H), 7.91 (d, J=8.79 Hz, 2 H).

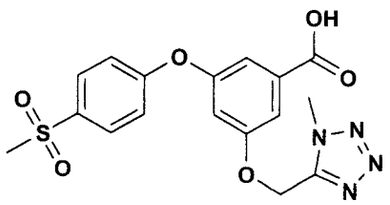
B.



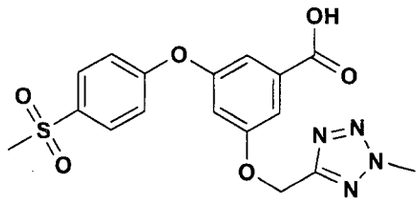
A una solución agitada de 5-(clorometil)-2H-tetrazol (0.5 g, 4.22 mmol) en Et_2O (5 mL) se agregó gota a gota una solución de CH_2N_2 en Et_2O (5 mL) preparada a partir de 1-metil-3-nitro-1-nitrosoguanidina (700 mg, 4.76 mmol) y 40% KOH acuoso (4 g, 28.5 mmol, 10 mL agua) a 0°C. La solución de reacción se mantuvo a 0°C durante la adición, y la reacción se agitó a temperatura ambiente durante 1 h y luego se concentró usando una corriente de aire. El residuo del solvente se removió *in vacuo* para dar los compuestos

isómericos parte B como aceites amarillos (400 mg, 71.5 % de rendimiento).

C.



C1



C2

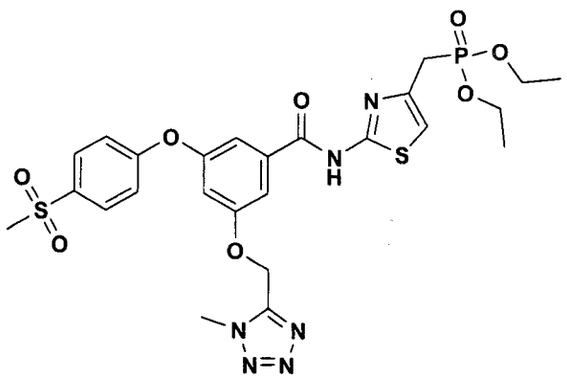
Una mezcla del compuesto parte A (100 mg, 0.310 mmol), el compuesto parte B (41.1 mg, 0.310 mmol), y K_2CO_3 (300 mg, 2.17 mmol) se agitó a 100°C en un tubo sellado durante 18 h, luego se enfrió a temperatura ambiente. La mezcla de reacción se diluyó con EtOAc (5 mL) y se lavó con H_2O (5 mL x 2); la capa orgánica se secó (Na_2SO_4) y se concentró *in vacuo* para dar un aceite amarillo. Este éster de metilo crudo se agitó en NaOH acuoso 1N (0.5 mL, 0.500 mmol) y THF (1 mL) durante 2 h. La reacción se concentró *in vacuo* y se acidificó con TFA. Los dos isómeros se separaron por HPLC preparativa (Columna Phenomenex AXIA 5u C18 30 x 100 mm; detección a 220 nm; relación de flujo = 40 mL/min; gradiente continuo de 30% A hasta 100% B durante 10 min + 1 min tiempo de espera a 100% B, donde A = 90:10:0.1 H_2O:MeOH:TFA y B = 90:10:0.1 MeOH:H_2O:TFA) para dar el compuesto parte C (40 mg, 31% de rendimiento) como un sólido blanco y el compuesto parte C2 (72 mg, 57% de rendimiento) como un sólido blanco.

Compuesto parte C1: $[M + H]^+$ = 405.1; ^1H RMN (400 MHz,

DMSO-d6) δ 3.22 (s, 3 H), 4.13 (s, 3 H), 5.63 (s, 2 H), 7.20 - 7.28 (m, 4 H), 7.49 (s, 1 H), 7.95 (d, J=8.79 Hz, 2 H), 13.35 (s, 1 H).

Compuesto parte C2: $[M + H]^+$ = 405.1; ^1H RMN (400 MHz, DMSO-d6) δ 3.21 (s, 3 H), 4.38 (s, 3 H), 5.47 (s, 2 H), 7.18 (d, J=5.50 Hz, 2 H), 7.24 (d, J=8.79 Hz, 2 H), 7.44 (s, 1 H), 7.94 (d, J=8.79 Hz, 2 H), 13.30 (s, 1 H).

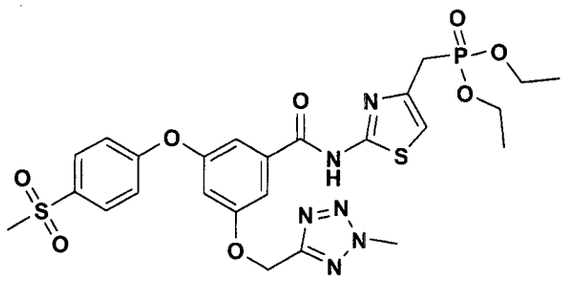
D.



Una mezcla del compuesto parte C (12 mg, 0.030 mmol), Compuesto del ejemplo 13 parte E (7.43 mg, 0.030 mmol), HOAt (10 mg, 0.072 mmol), EDCI (20 mg, 0.500 mmol), y DIPEA (0.2 mL, 1.148 mmol) en DMF (0.5 mL) se agitó a 25°C durante 18 h. La mezcla de reacción se diluyó con EtOAc (1 mL) y se lavó con HCl acuoso 1N (1 mL). La capa orgánica se secó (Na_2SO_4) y se concentró *in vacuo*. El residuo se purificó por HPLC preparativa (columna Phenomenex AXIA 5µm C18 30 x 100 mm; detección a 220 nm; relación de flujo = 40 mL/min; gradiente continuo de 30% A hasta 100% B durante 10 min + 1 min tiempo de espera a 100% B, donde A = 90:10:0.1 H_2O:MeOH:TFA y B =

90:10:0.1 MeOH:H_2O:TFA) para dar el compuesto del título (12 mg, 64% de rendimiento) como un sólido blanco. $[M + H]^+$ = 636.99; ^1H RMN (400 MHz, $CDCl_3$) δ 1.30 (t, J=6.87 Hz, 6 H), 3.08 (s, 3 H), 3.29 (d, J=21.44 Hz, 2 H), 4.08 - 4.17 (m, J=7.56, 7.56, 7.42, 7.15 Hz, 4 H), 4.18 (s, 3 H), 5.56 (s, 2 H), 6.98 (s, 1 H), 7.03 (d, J=3.30 Hz, 1 H), 7.15 (d, J=8.79 Hz, 2 H), 7.50 (s, 1 H), 7.80 (s, 1 H), 7.94 (d, J=8.79 Hz, 2 H).

EJEMPLO 68

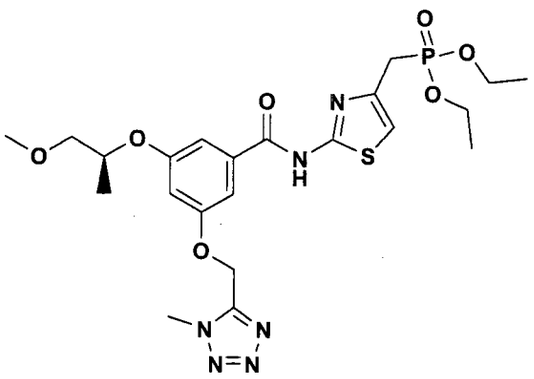


Una mezcla del Compuesto del ejemplo 67 parte C2 (12 mg, 0.030 mmol), Compuesto del ejemplo 13 parte E (7.43 mg, 0.030 mmol), HOAt (10 mg, 0.072 mmol), DIPEA (0.2 mL, 1.148 mmol), y EDCI (0.500 mL, 0.500 mmol) en DMF (0.5 mL) se agitó a 25°C durante 18 h. La mezcla de reacción se diluyó con EtOAc (1 mL) y se lavó con HCl acuoso 1N (1 mL). La capa orgánica se secó (Na_2SO_4) y se concentró *in vacuo*. El residuo se purificó por HPLC preparativa (columna Phenomenex AXIA 5µm C18 30 x 100 mm; detección a 220 nm; relación de flujo = 40 mL/min; gradiente continuo de 30% A hasta 100% B durante 10 min + 1 min tiempo de espera a 100% B, donde A = 90:10:0.1

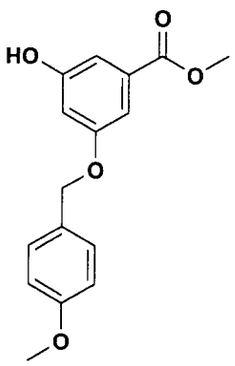
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H_2O:MeOH:TFA y B = 90:10:0.1 MeOH:H_2O:TFA) para dar el compuesto del título (10 mg, 53% de rendimiento) como un sólido blanco. $[M + H]^+$ = 637.00; ^1H RMN (400 MHz, $CDCl_3$) δ 1.30 (t, J=7.15 Hz, 6 H), 3.07 (s, 3 H), 3.32 (d, J=21.44 Hz, 2 H), 4.07 - 4.17 (m, J=7.35, 7.35, 7.28, 7.15 Hz, 4 H), 4.39 (s, 3 H), 5.48 (s, 2 H), 6.97 - 7.02 (m, 2 H), 7.15 (d, J=8.79 Hz, 2 H), 7.49 (s, 1 H), 7.78 (s, 1 H), 7.93 (d, J=8.79 Hz, 2 H).

EJEMPLO 69



A.

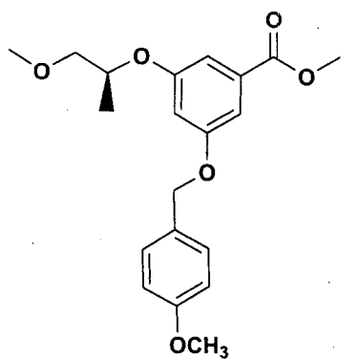


Una mezcla de 1-(bromometil)-4-metoxibenceno (2.151 mL, 14.92 mmol), 3,5-dihidroxibenzoato de metilo (5 g, 29.7

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mmol), y K_2CO_3 (12.33 g, 89 mmol) en MeCN (100 mL) se agitó a 80°C durante 3 días. La reacción se diluyó con agua (50 mL), se acidificó con 12N HCl (30 mL) hasta pH~2, y se extrajo con EtOAc (20 mL x 3). Los extractos orgánicos combinados se lavaron con agua, se secaron (Na_2SO_4) y se concentraron *in vacuo*. El residuo se procesó por cromatografía (SiO_2: EtOAc/Hexano 1:3) para dar el compuesto parte A (3.0 g, 35% de rendimiento) como un sólido blanco. ^1H RMN (400 MHz, $CDCl_3$) δ 3.82 (s, 3 H), 3.90 (s, 3 H), 5.00 (s, 2 H), 5.14 (s, 1 H), 6.66 (t, J=2.20 Hz, 1 H), 6.92 (d, J=8.35 Hz, 2 H), 7.10 - 7.16 (m, 1 H), 7.22 - 7.29 (m, 1 H), 7.35 (d, J=8.35 Hz, 2 H).

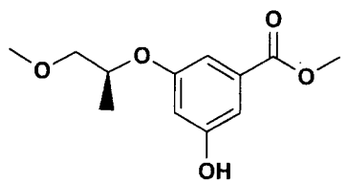
B.



A una solución a 0°C de Ph_3P (1.820 g, 6.94 mmol), el compuesto parte A (1 g, 3.47 mmol), y (R)-1-metoxipropan-2-ol (0.365 mL, 4.16 mmol) en THF seco (5 mL) se agregó DIAD (1.012 mL, 5.20 mmol). La reacción se agitó a temperatura ambiente durante 18 h. Los volátiles se removieron *in vacuo*, y el residuo se procesó por cromatografía (SiO_2;

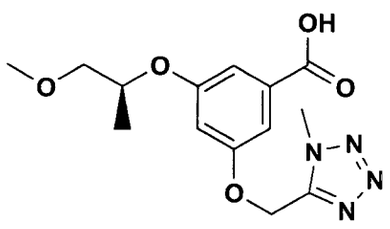
EtOAc/Hexano, 1:5) para dar el compuesto crudo parte B (1.7 g, 136%), el cual se usó en la siguiente etapa sin purificación adicional.

C.

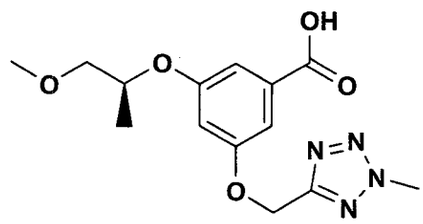


Una solución del compuesto crudo parte B (1.75 g, 4.86 mmol) y TFA (3 mL, 38.9 mmol) en DCM seco (5 mL) se agitó a temperatura ambiente durante 2 h. Los volátiles se removieron *in vacuo*, y el residuo se procesó por cromatografía (SiO_2; EtOAc/Hexano 1:5) para dar el compuesto parte C (407 mg, 35%) como un aceite claro. $[M + H]^+$ = 241.27; ^1H RMN (400 MHz, $CDCl_3$) δ 1.29 (d, J=6.05 Hz, 3 H), 3.41 (s, 3 H), 3.47 - 3.62 (m, 2 H), 3.88 (s, 3 H), 4.51 - 4.62 (m, 1 H), 4.95 (br. s., 1 H), 6.65 (s, 1 H), 7.13 (dd, J=5.22, 1.37 Hz, 2 H).

D.



D1



D2

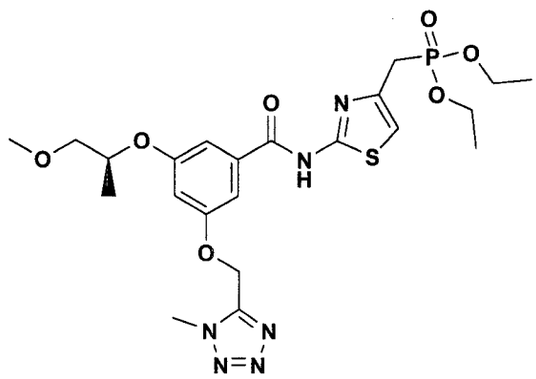
Una mezcla del compuesto parte C (300 mg, 1.249 mmol), Compuesto del ejemplo 67 parte B (166 mg, 1.249 mmol), y K_2CO_3 (300 mg, 2.171 mmol) en DMF (3 mL) se agitó a 100°C en un

tubo sellado durante 18 h, luego se enfrió a temperatura ambiente. Los sólidos se filtraron completamente, y el filtrado se concentró *in vacuo*. El residuo se acidificó con TFA y los dos isómeros se separaron por HPLC preparativa (Columna Phenomenex AXIA 5u C18 30 x 100 mm; detección a 220 nm; relación de flujo = 40 mL/min; gradiente continuo de 30% A hasta 100% B durante 10 min + 1 min tiempo de espera a 100% B, donde A = 90:10:0.1 H_2O:MeOH:TFA y B = 90:10:0.1 MeOH:H_2O:TFA) para dar el compuesto parte D1 (160 mg, 40% de rendimiento) como un sólido blanco y el compuesto parte D2 (33 mg, 8.2% de rendimiento) como un sólido blanco.

El compuesto parte D1: $[M + H]^+$ = 323.15; ^1H RMN (400 MHz, $CDCl_3$) δ 1.31 (d, J=6.05 Hz, 3 H), 3.43 (s, 3 H), 3.50 - 3.64 (m, 2 H), 4.18 (s, 3 H), 4.57 - 4.67 (m, 1 H), 5.47 (s, 2 H), 6.82 (t, J=2.47 Hz, 1 H), 7.30 (dd, J=2.20, 1.10 Hz, 1 H), 7.35 (s, 1 H).

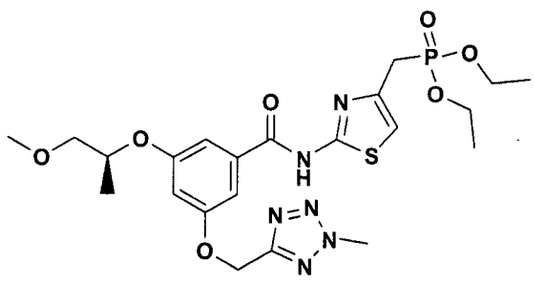
El compuesto parte D2: $[M + H]^+$ = 323.18; ^1H RMN (400 MHz, $CDCl_3$) δ 1.32 (d, J=6.05 Hz, 3 H), 3.42 (s, 3 H), 3.48 - 3.62 (m, 2 H), 4.39 (s, 3 H), 4.55 - 4.64 (m, 1 H), 5.35 (s, 2 H), 6.86 (t, J=2.47 Hz, 1 H), 7.34 (s, 1 H), 7.37 (dd, J=2.20, 1.10 Hz, 1 H).

E.



Una mezcla del compuesto parte D1 (15 mg, 0.047 mmol), Compuesto del ejemplo 13 parte E (11.65 mg, 0.047 mmol), HOAt (10 mg, 0.072 mmol), EDCI (20 mg, 0.500 mmol), y DIPEA (0.2 mL, 1.148 mmol) en DMF (0.5 mL) se agitó a 25°C durante 18 h. La mezcla de reacción se diluyó con EtOAc (1 mL) y se lavó con HCl acuoso 1N (1 mL). La fase orgánica se secó (Na_2SO_4) y se concentró *in vacuo*. El residuo se purificó por HPLC preparativa (Columna Phenomenex AXIA 5u C18 30 x 100 mm; detección a 220 nm; relación de flujo = 40 mL/min; gradiente continuo de 30% A hasta 100% B durante 10 min + 1 min tiempo de espera a 100% B, donde A = 90:10:0.1 H_2O:MeOH:TFA y B = 90:10:0.1 MeOH:H_2O:TFA) para dar el compuesto del título (13 mg, 50% de rendimiento) como un sólido blanco. $[M + H]^+$ = 555.3; ^1H RMN (400 MHz, $CDCl_3$) δ 1.28 - 1.35 (m, 9 H), 3.29 - 3.36 (m, 2 H), 3.40 (s, 3 H), 3.49 - 3.61 (m, 2 H), 4.09 - 4.19 (m, 7 H), 4.74 (td, J=6.19, 3.79 Hz, 1 H), 5.49 (s, 2 H), 6.84 (t, J=2.15 Hz, 1 H), 7.03 (d, J=3.54 Hz, 1 H), 7.47 (t, J=1.77 Hz, 1 H), 7.49 (dd, J=2.02, 1.52 Hz, 1 H).

EJEMPLO 70

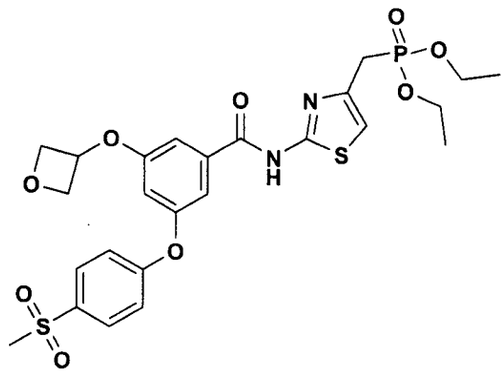


El compuesto del título (10 mg; 58% de rendimiento;

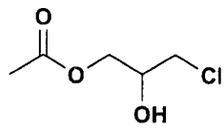
...0622

aceite incoloro) se sintetizó empleando el procedimiento descrito en el ejemplo 69 Parte E, excepto que el ejemplo 69 Parte D2 se usó en la secuencia en lugar del Ejemplo 69 Parte D1. $[M + H]^+$ = 555.3; ^1H RMN (400 MHz, $CDCl_3$) δ 1.25 - 1.37 (m, 9 H), 3.26 - 3.37 (m, 2 H), 3.40 (s, 3 H), 3.47 - 3.62 (m, 2 H), 4.06 - 4.19 (m, 4 H), 4.38 (s, 3 H), 4.71 (td, J=6.19, 4.04 Hz, 1 H), 5.40 (s, 2 H), 6.86 (t, J=2.27 Hz, 1 H), 6.98 (d, J=3.54 Hz, 1 H), 7.40 (d, J=1.52 Hz, 1 H), 7.45 (d, J=1.52 Hz, 1 H).

EJEMPLO 71



A.

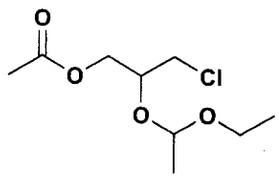


A una solución de $FeCl_3$ (100mg, 0.62 mmol) en HOAc (68.8 mL, 1202 mmol) se agregó 2-(clorometil)oxirano (111.2 g, 1202 mmol) con agitación durante un periodo de 10 minutos. La mezcla se calentó a 70°C con agitación durante 24 h, luego se enfrió a temperatura ambiente y se filtró para dar el

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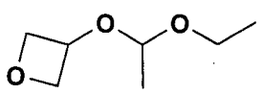
compuesto parte A (183 g, 100% de rendimiento) como un aceite amarillo. ^{1}H RMN (400 MHz, $CDCl_3$) (2.11 (s, 3 H), 3.57 - 3.66 (m, 2 H), 4.05 - 4.12 (m, 1 H), 4.21 (t, J=4.83 Hz, 2 H).

B.



Al compuesto crudo parte A (183 g, 1202 mmol) se agregó pTsOH (1 g, 5.26 mmol), seguido por la adición gota a gota de éter de etil vinilo (118 mL, 1232 mmol) durante un periodo de 2 h. El matraz se enfrió para mantener una temperatura de reacción de 35-37°C. Después de que la adición se completó, la mezcla se calentó a 40-45°C durante 18 h, luego se enfrió a temperatura ambiente para dar el compuesto crudo parte B (270 g, 100 %) como un líquido rojo.

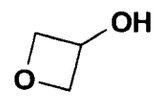
C.



A una solución 110°C de NaOH (110 g, 2750 mmol) en agua (110 mL) se agregó el compuesto parte B (270 g, 1202 mmol) durante un periodo de 1.5 h. La mezcla de reacción se puso a reflujo durante otras 4 h, luego se enfrió a temperatura ambiente y se lavó con agua (110 mL). La capa acuosa se extrajo con DCM (110 mL), y los extractos orgánicos combinados se concentraron *in vacuo* para dar un aceite café.

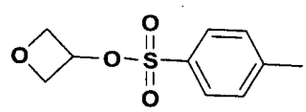
La destilación (bp = 45-50°C @ 0.5 mm Hg) dio el compuesto parte C (15 g, 8.5%) como un aceite claro. ^{1}H RMN (400 MHz, $CDCl_3$) δ 1.15 (t, J=7.15 Hz, 3 H), 1.25 (d, J=5.50 Hz, 3 H), 3.44 (dd, J=9.34, 7.15 Hz, 1 H), 3.56 (q, J=7.15 Hz, 1 H), 4.55 - 4.84 (m, 4 H).

D.



Una solución del compuesto parte C (15 g, 103 mmol) en MeOH (5.26 mL, 125 mmol) se enfrió a 15-18°C, y p-TsOH (100 mg, 0.581 mmol) se agregó con agitación. La mezcla de reacción se agitó durante 45 min, después de lo cual $NaHCO_3$ (50 mg, 0.595 mmol) se agregó. La destilación a 35-40°C (0.1 mmHg) dio el compuesto crudo parte D (7.0 g, 95%) como un aceite claro.

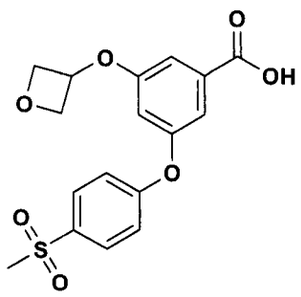
E.



A una solución a 50°C bien agitada del compuesto parte D (7 g, 94 mmol) y p-TsCl (12.8 g, 67.1 mmol) en agua (15 mL) se agregó gota a gota una solución de NaOH (2.69 g, 67.1 mmol) en agua (15 mL). La reacción se calentó durante 1 h a 50°C, luego se enfrió a temperatura ambiente y tolueno (10 mL) se agregó. La capa acuosa se extrajo con tolueno (5 mL x 2). Los extractos orgánicos combinados se lavaron con NH_4OH

concentrado (3x) y agua (2x), luego se concentró *in vacuo*. El hexano (50 mL) se agregó al residuo y un sólido se formó, el cual se colectó por filtración y luego se secó *in vacuo* durante 1 h para dar el compuesto parte E (10 g, 65% de rendimiento) como un sólido blanco. $[M + H]^+$ = 229.1; ^1H RMN (400 MHz, $CDCl_3$) δ ppm 2.46 (s, 3 H), 4.64 - 4.75 (m, 4 H), 5.27 - 5.34 (m, 1 H), 7.37 (d, J=8.25 Hz, 2 H), 7.78 (d, J=8.25 Hz, 2 H).

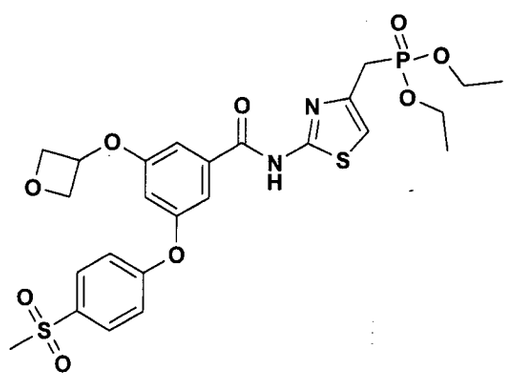
F.



Una mezcla del compuesto del ejemplo 67 parte A (450 mg, 1.396 mmol), el compuesto parte E (500 mg, 2.190 mmol), y K_2CO_3 (2.7 g, 19.54 mmol) en DMF (5 mL) se agitó en un tubo sellado a 110°C durante 18 h, luego se enfrió a temperatura ambiente. La reacción se filtró, los sólidos se lavaron con DMF, y los filtrados combinados se concentraron *in vacuo*. El residuo se neutralizó con TFA y se purificó por HPLC preparativa (Columna Phenomenex AXIA 5u C18 30 x 100 mm; detección a 220 nm; relación de flujo = 40 mL/min; gradiente continuo de 30% A hasta 100% B durante 10 min + 1 min tiempo de espera a 100% B, donde A = 90:10:0.1 H_2O:MeOH:TFA y B =

90:10:0.1 MeOH:H_2O:TFA) para dar el compuesto parte F (220 mg, 42% de rendimiento) como un sólido blanco. $[M + H]^+$ = 365.2; ^1H RMN (400 MHz, $CDCl_3$) δ 3.08 (s, 3 H), 4.78 (dd, J=7.15, 4.95 Hz, 2 H), 5.02 (t, J=6.87 Hz, 2 H), 5.23 - 5.31 (m, 1 H), 6.75 (t, J=1.92 Hz, 1 H), 7.13 (d, J=8.79 Hz, 2 H), 7.18 (s, 1 H), 7.39 (s, 1 H), 7.93 (d, J=8.24 Hz, 2 H).

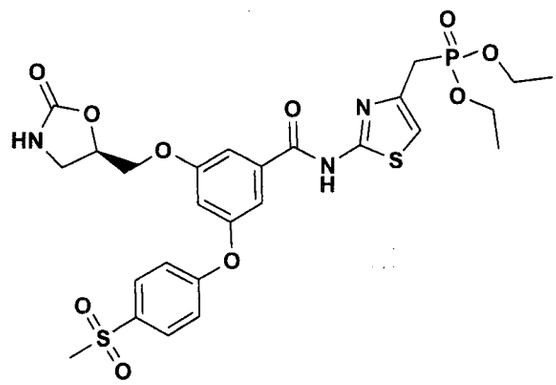
G.



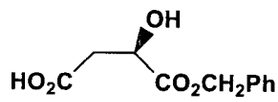
Una mezcla del compuesto parte F (14 mg, 0.038 mmol), Compuesto del ejemplo 13 parte E (9.62 mg, 0.038 mmol), HOAt (10 mg, 0.072 mmol), EDCI (20 mg, 0.500 mmol) y DIPEA (0.2 mL, 1.148 mmol) en DMF (0.5 mL) se agitó a 40°C durante 18h, luego se enfrió a temperatura ambiente. La mezcla de reacción se dividió entre EtOAc (1mL) y HCl acuoso 1N (1 mL). La capa orgánica se secó (Na_2SO_4) y se concentró *in vacuo*. El residuo se purificó por HPLC preparativa (columna Phenomenex AXIA 5µm C18 30 x 100 mm; detección a 220 nm; relación de flujo = 40 mL/min; gradiente continuo de 30% A hasta 100% B durante 10 min + 1 min tiempo de espera a 100% B, donde A = 90:10:0.1 H_2O:MeOH:TFA y B = 90:10:0.1 MeOH:H_2O:TFA) para dar el

compuesto del título (13 mg, 55.6% de rendimiento) como un sólido blanco. $[M + H]^+$ = 597.2; ^1H RMN (400 MHz, $CDCl_3$) δ 1.28 (t, J=7.03 Hz, 6 H), 3.08 (s, 3 H), 3.34 (d, J=21.09 Hz, 2 H), 4.04 - 4.16 (m, 4 H), 4.75 (dd, J=7.47, 4.83 Hz, 2 H), 5.05 (t, J=6.81 Hz, 2 H), 5.36 - 5.45 (m, J=5.49, 5.38, 5.33, 5.33 Hz, 1 H), 6.82 (t, J=2.20 Hz, 1 H), 6.96 (d, J=3.52 Hz, 1 H), 7.15 (d, J=8.79 Hz, 2 H), 7.24 (s, 1 H), 7.42 (s, J=1.76, 1.76 Hz, 1 H), 7.94 (d, J=9.23 Hz, 2 H).

EJEMPLO 72



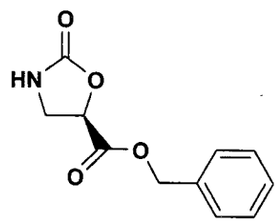
A.



El TFAA pre-enfriado (25 mL, 177 mmol) a 0°C se agregó al Ácido D-málico (5 g, 37.3 mmol) con agitación. La suspensión se agitó durante 2 h a temperatura ambiente, luego se concentró *in vacuo*. El alcohol de bencilo seco (25 mL, 240 mmol) se agregó y la solución se agitó durante la noche a

temperatura ambiente. Los volátiles (alcohol de bencilo y TFAA) se removieron *in vacuo*. El residuo se procesó por cromatografía [SiO_2; EtOAc/Hexano (1:1 + 0.5%TFA)] para dar el compuesto parte A (7.9 g, 94% de rendimiento) como un aceite incoloro. ^1H RMN (400 MHz, $CDCl_3$) δ 2.80 - 2.96 (m, 2 H), 4.55 (dd, J=6.19, 4.42 Hz, 1 H), 5.24 (s, 2 H), 7.30 - 7.38 (m, 5 H); [a]=+12.19 @ 1.4% p/v en DMF a 589 nm.

B.

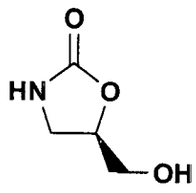


A una solución del compuesto parte A (7.9 g, 35.2 mmol) y Et_3N (5.6 mL, 40.2 mmol) en tolueno (120 mL) se agregó lentamente Ph_2PON_3 (8.64 mL, 40.0 mmol) durante ~30 min. La mezcla de reacción se puso a reflujo durante 2 h, se agitó a 70°C durante 2 h, luego se enfrió a temperatura ambiente y se agitó a temperatura ambiente durante 3 días. Los volátiles se removieron *in vacuo*; el residuo se disolvió en agua y se extrajo con EtOAc (20 mL x 3). Los extractos orgánicos combinados se lavaron con $NaHCO_3$ acuoso saturado, se secaron (Na_2SO_4) y se concentraron *in vacuo*. El residuo se procesó por cromatografía [SiO_2; EtOAc/Hexano (1:1)] para dar el compuesto parte B (2.28 g, 27.5 % de rendimiento) como un sólido pálido. $[M + H]^+$ = 222.16; ^1H RMN (400 MHz, $CDCl_3$) δ

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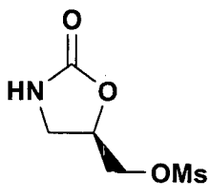
3.58 - 3.73 (m, 1 H), 3.86 (t, J=9.35 Hz, 1 H), 5.02 (dd, J=9.60, 5.56 Hz, 1 H), 5.24 (d, J=1.77 Hz, 2 H), 6.40 (br. s., 1 H), 7.36 (s, 5 H); [a]=-4.56 @ 1.2% w/v en DMF a 589 nm.

C.



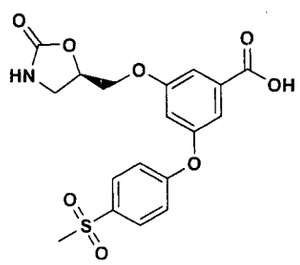
A una suspensión a 0°C del compuesto parte B (2.28 g, 10.31 mmol) en EtOH (50 mL) se agregó lentamente $NaBH_4$ (0.390 g, 10.31 mmol). La mezcla se agitó durante 3 h a 0°C, luego se calentó a temperatura ambiente y NH_4Cl acuoso saturado (2 mL) se agregó. La reacción se agitó durante 30 min, luego los sólidos se filtraron completamente, y el filtrado se concentró *in vacuo*. El residuo se procesó por cromatografía (SiO_2; EtOAc/MeOH, 5:1) para dar el compuesto parte C (0.966 g, 80 % de rendimiento) como un sólido blanco. ^1H RMN (400 MHz, DMSO-d6) δ 3.20 (t, J=7.70 Hz, 1 H), 3.41 - 3.57 (m, 3 H), 4.52 (dt, J=15.39, 4.67 Hz, 1 H), 5.06 (t, J=5.77 Hz, 1 H), 7.39 (br. s., 1 H); [a] = -33.11 @ 1.1% p/v en EtOH a 589 nm.

D.



A una solución a -5°C del compuesto parte C (966 mg, 8.25 mmol) y piridina (10 mL, 124 mmol) en DCM (15 mL) se agregó lentamente MsCl (0.8 mL, 10.27 mmol) durante 1 h. Después de 3 h, los volátiles se removieron *in vacuo* a una temperatura mínima. El residuo se procesó por cromatografía (SiO_2; CH_2Cl_2/MeOH 95:5 v/v) para dar el compuesto parte D (1.5 g, 93 % de rendimiento) como un sólido incoloro. ^1H RMN (400 MHz, DMSO-d6) δ 3.21 - 3.27 (m, 4 H), 3.58 (t, J=9.34 Hz, 1 H), 4.28 - 4.35 (m, 1 H), 4.36 - 4.43 (m, 1 H), 4.80 - 4.88 (m, 1 H), 7.63 (br. s., 1 H); [a]= -33.93 @ 0.55% p/v en EtOH a 589 nm.

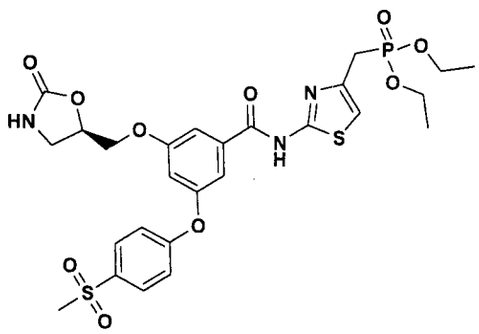
E.



Una mezcla del compuesto del ejemplo 26 parte A (400 mg, 1.241 mmol), Compuesto parte D (242 mg, 1.241 mmol), y K_2CO_3 (2.7 g, 19.54 mmol) en DMF (5 mL) se agitó en un tubo sellado a 110°C durante 18 h, luego se enfrió a temperatura ambiente y se filtró. El filtrado se concentró *in vacuo*. El residuo se neutralizó con TFA y luego se purificó por HPLC preparativa (Columna Phenomenex AXIA 5u C18 30 x 100 mm; detección a 220 nm; relación de flujo = 40 mL/min; gradiente continuo de 30% A hasta 100% B durante 10 min + 1 min tiempo de espera a 100%

B, donde A = 90:10:0.1 H_2O:MeOH:TFA y B = 90:10:0.1 MeOH:H_2O:TFA) para dar el compuesto parte E (260 mg, 51.4 % de rendimiento) como un sólido blanco. $[M + H]^+$ = 408.1; ^1H RMN (400 MHz, CD_3OD) δ 3.12 (s, 3 H), 3.55 (dd, J=9.01, 6.37 Hz, 1 H), 3.75 (t, J=9.23 Hz, 1 H), 4.17 - 4.24 (m, 1 H), 4.26 - 4.33 (m, 1 H), 4.97 - 5.05 (m, 1 H), 6.98 (t, J=2.20 Hz, 1 H), 7.19 (d, J=8.79 Hz, 2 H), 7.30 (s, 1 H), 7.47 (s, 1 H), 7.95 (d, J=9.23 Hz, 2 H); [a]= -23.97 @ 1.4% p/v en MeOH a 589 nm.

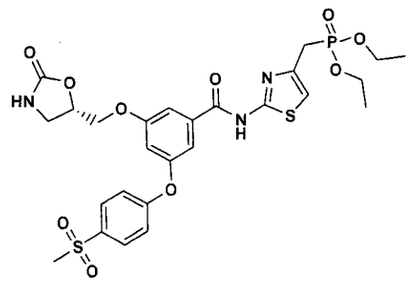
F.



Una mezcla del compuesto parte E (20 mg, 0.049 mmol), compuesto del ejemplo 13 parte E (12.29 mg, 0.049 mmol), HOAt (10 mg, 0.072 mmol), EDCI (20 mg, 0.500 mmol), y DIPEA (0.2 mL, 1.148 mmol) en DMF (0.5 mL) se agitó a 25°C durante 18 h. Los volátiles se removieron *in vacuo* y el residuo se purificó por HPLC preparativa (columna Phenomenex AXIA 5µm C18 30 x 100 mm; detección a 220 nm; relación de flujo = 40 mL/min; gradiente continuo de 30% A hasta 100% B durante 10 min + 1 min tiempo de espera a 100% B, donde A = 90:10:0.1 H_2O:MeOH:TFA y B = 90:10:0.1 MeOH:H_2O:TFA) para dar el

compuesto del título (17 mg, 51.4 % de rendimiento) como un sólido blanco. $[M + H]^+$ = 640.3; ^1H RMN (400 MHz, $CDCl_3$) δ 1.31 (td, J=7.07, 5.05 Hz, 6 H), 3.07 (s, 3 H), 3.32 (d, J=21.22 Hz, 2 H), 3.64 (dd, J=8.84, 6.32 Hz, 1 H), 3.82 (t, J=8.97 Hz, 1 H), 4.07 - 4.18 (m, 4 H), 4.38 (d, J=4.55 Hz, 2 H), 4.96 - 5.06 (m, 1 H), 6.12 (br. s., 1 H), 6.93 (t, J=2.27 Hz, 1 H), 6.99 (d, J=3.79 Hz, 1 H), 7.15 (d, J=8.84 Hz, 2 H), 7.50 (dd, J=2.15, 1.39 Hz, 1 H), 7.71 (t, J=1.77 Hz, 1 H), 7.92 (d, J=8.84 Hz, 2H); e.e.=98.2% (Chiralpak AS, 250 X 4.6 mm ID; 10 µm, temperatura ambiente, 60% (50/50 MeOH-EtOH): 40% Heptano, 1 mL/min).

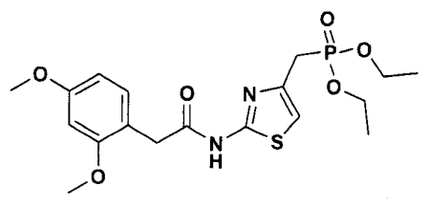
EJEMPLO 73



El compuesto del título (22 mg; 58% de rendimiento; sólido blanco) se sintetizó a partir del ácido L-málico empleando el mismo procedimiento como se describe en el ejemplo 72. $[M + H]^+$ = 640.3; ^1H RMN (400 MHz, $CDCl_3$) δ 1.33 (t, J=7.07 Hz, 6 H), 3.07 (s, 3 H), 3.38 (d, J=21.47 Hz, 2 H), 3.64 (dd, J=8.84, 6.57 Hz, 1 H), 3.81 (t, J=8.97 Hz, 1 H), 4.17 (dd, J=8.21, 7.20 Hz, 3 H), 4.29 - 4.37 (m, 1 H), 4.40 - 4.48 (m, 1 H), 4.99 - 5.08 (m, 1 H), 5.91 (br. s., 1

H), 6.96 (t, J=2.15 Hz, 1 H), 7.06 (d, J=3.79 Hz, 1 H), 7.15 (dq, J=8.84, 4.80 Hz, 1 H), 7.51 (dd, 1 H), 7.71 (t, J=1.52 Hz, 1 H), 7.93 (dq, J=8.84, 4.80 Hz, 1 H); e.e.=99.9% (Chiralpak AS, 250 X 4.6 mm ID; 10 µm, temperatura ambiente, 60% (50/50 MeOH-EtOH): 40% Heptano, 1 mL/min).

EJEMPLO 74

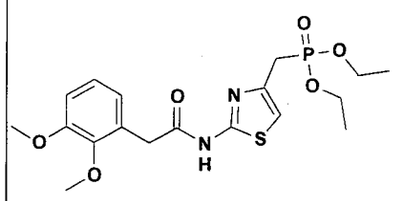
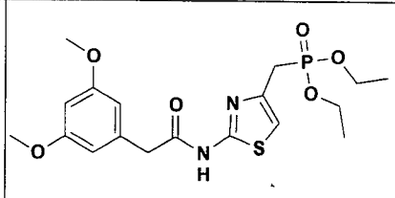
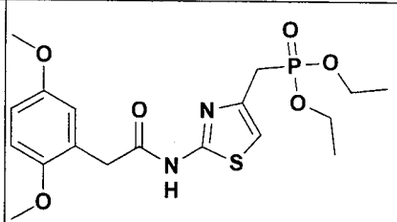


Una mezcla de ácido 2-(2,4-dimetoxifenil)acético (20 mg, 0.12 mmol), Compuesto del ejemplo 13 parte E (25 mg, 0.1 mmol), HOAt (20 mg, 0.015 mmol), EDCI (25 mg, 0.500 mmol), y DIPEA (0.2 mL, 1.148 mmol) en DMF (0.5 mL) se agitó a 25°C durante 18 h. La mezcla de reacción se concentró *in vacuo*, y el residuo se purificó por HPLC preparativa (columna Phenomenex AXIA 5µm C18 30 x 100 mm; detección a 220 nm; relación de flujo = 40 mL/min; gradiente continuo de 30% A hasta 100% B durante 10 min + 1 min tiempo de espera a 100% B, donde A = 90:10:0.1 H_2O:MeOH:TFA y B = 90:10:0.1 MeOH:H_2O:TFA) para dar el compuesto del título (2.6 mg, 6 % de rendimiento) como un aceite amarillo. $[M + H]^+$ = 429.4; ^1H RMN (400 MHz, $CDCl_3$) δ 1.31 (t, J=7.03 Hz, 6 H), 3.25 - 3.34 (d, J=21.53 Hz, 2 H), 3.79 (s, 3 H), 3.80 (s, 3 H), 3.83 (s, 2 H), 4.09 - 4.18 (m, 4 H), 6.46 - 6.50 (m, 2 H), 6.91 (d,

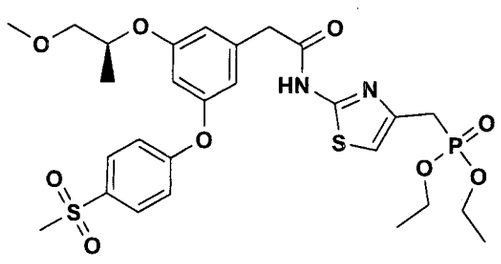
J=3.52 Hz, 1 H), 7.15 (d, 1 H);

EJEMPLOS 75 HASTA 77

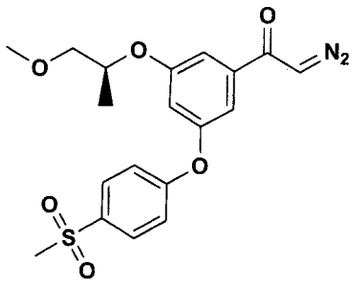
Los siguientes ejemplos se prepararon en la misma manera como en el ejemplo 74:

Ejemplo #	Estructura	$[M+H]^+$	1HRMN (400 MHz, $CDCl_3$)	Rendimiento y descripción
75		429.4	δ 1.29 (t, *J*=7.03 Hz, 6 H), 3.27 (d, *J*=21.09 Hz, 2 H), 3.83 - 3.91 (m, 8 H), 4.04 - 4.17 (m, 4 H), 6.83 - 6.93 (m, 3 H), 7.01 - 7.08 (m, 1 H)	8.3 mg (19% de rendimiento); aceite amarillo
76		429.4	(1.27 (t, J=7.03 Hz, 6 H), 3.25 (d, J=21.09 Hz, 2 H), 3.75 - 3.78 (m, 2 H), 3.79 (s, 6 H), 4.02 - 4.12 (m, 4 H), 6.40 - 6.43 (m, 1 H), 6.47 (d, J=2.20 Hz, 2 H), 6.82 (ninguno, 1H)	8.6 mg (20% de rendimiento); aceite amarillo
77		429.4	δ 1.29 (t, *J*=7.03 Hz, 6 H), 3.23 - 3.31 (m, 2 H), 3.77 (s, 3 H), 3.82 (s, 5 H), 4.06 - 4.14 (m, 4 H), 6.82 - 6.87 (m, 4 H)	8.3 mg (19% de rendimiento); aceite amarillo

EJEMPLO 78

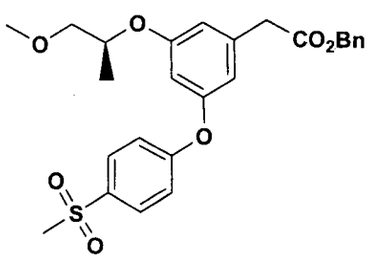


A.



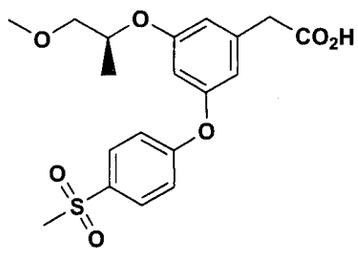
Una solución del ácido ejemplo 26C (146mg, 0.384 mmol) y $(COCl)_2$ (2 mL de una solución 2M en DCM, 4 mmol) en DCM (2 mL) se agitó a temperatura ambiente durante 18 h, luego se concentró *in vacuo*. El cloruro ácido crudo se tomó en Et_2O (5 mL) y se agregó gota a gota a una solución a 0°C de CH_2N_2 en Et_2O (5 mL) preparada a partir de 1-metil-3-nitro-1-nitrosoguanidina (735 mg, 5 mmol) y 40% KOH acuoso (0.8 g, 15 mmol, 2 mL agua) a 0°C. La mezcla de reacción se agitó a temperatura ambiente durante 1 h y se concentró bajo una corriente de aire; el residuo del solvente se removió *in vacuo*. El residuo se procesó por cromatografía (SiO_2; EtOAc/Hexano 5:1) para dar el compuesto parte A (130 mg, 84 % de rendimiento) como un aceite amarillo. $[M + H]^+$ = 405.2; ^1H RMN (400 MHz, $CDCl_3$) δ 1.28 (d, J=6.15 Hz, 3 H), 3.03 (s, 3 H), 3.36 (s, 3 H), 3.43 - 3.57 (m, 2 H), 4.51 - 4.62 (m, 1 H), 5.86 (s, 1 H), 6.79 (t, J=2.20 Hz, 1 H), 6.99 (s, 1 H), 7.08 (d, J=8.79 Hz, 2 H), 7.15 (s, 1 H), 7.87 (d, 2 H).

B.



A una solución a -25°C del compuesto parte A (130 mg, 0.321 mmol) y BnOH (0.5 mL, 5 mmol) en THF seco (2 mL) se agregó durante 15 min una solución de $PhCO_2Ag$ (206.1mg, 0.9 mmol) en Et_3N (1.67 mL, 12 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 5 h en la oscuridad. La reacción se filtró a través de Celite®; el filtrado se concentró *in vacuo*, y el residuo se procesó por cromatografía [SiO_2; EtOAc/Hexano(2:1)] para dar el compuesto parte B (130mg, 83.6%) como un aceite claro. $[M + H]^+$ = 485.2; ^1H RMN (400 MHz, $CDCl_3$) δ 1.28 (d, *J*=6.15 Hz, 3 H), 3.05 (s, 3 H), 3.39 (s, 3 H), 3.44 - 3.50 (m, 1 H), 3.52 - 3.58 (m, 1 H), 3.62 (s, 2 H), 4.45 - 4.54 (m, 1 H), 5.14 (s, 2 H), 6.56 (t, *J*=2.20 Hz, 1 H), 6.59 (t, *J*=1.76 Hz, 1 H), 6.73 (d, *J*=1.76 Hz, 1 H), 7.08 (d, *J*=9.23 Hz, 2 H), 7.28 - 7.38 (m, 5 H), 7.86 (d, *J*=8.79 Hz, 2 H).

C.

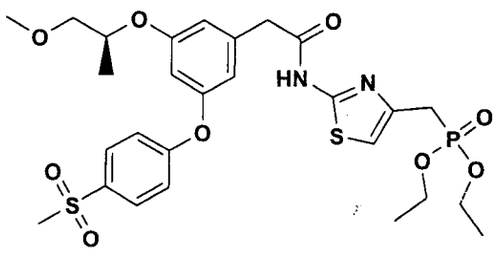


Una solución del compuesto parte B (130 mg, 0.268 mmol) y 10% Pd-C (20 mg) en EtOAc (10 mL) se agitó bajo H_2 (g; 60 psi (4.218 kg/cm^2)) durante 18 h. El catalizador se removió

020637

por filtración y el filtrado se concentró *in vacuo* para dar el compuesto parte C (86 mg, 81.4%) como un aceite claro. [M + H]$^+$ = 395.1; ^{1}H RMN (400 MHz, $CDCl_3$) δ 1.28 (d, *J*=6.15 Hz, 3 H), 3.05 (s, 3 H), 3.38 (s, 3 H), 3.44 - 3.51 (m, 1 H), 3.51 - 3.57 (m, 1 H), 3.58 (s, 2 H), 4.46 - 4.56 (m, 1 H), 6.55 (t, *J*=2.20 Hz, 1 H), 6.58 (s, 1 H), 6.72 (s, 1 H), 7.09 (d, *J*=8.79 Hz, 2 H), 7.87 (d, 2 H).

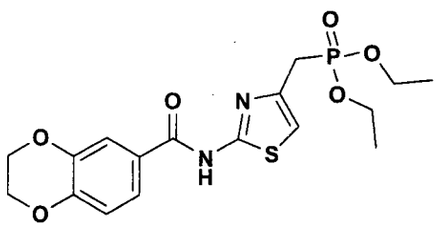
D.



Una solución del compuesto parte C (43 mg, 0.109 mmol) y $(COCl)_2$ (3.0 mL de una solución 2M en DCM, 6 mmol) en DCM (3 mL) se agitó a temperatura ambiente durante 18 h, luego se concentró *in vacuo*. El cloruro ácido crudo se tomó en DCM (2 mL) y se agregó durante 15 min a una solución a 0°C del Compuesto del ejemplo 13 parte E (37 mg, 0.148 mmol) y piridina (0.2 mL, 2.5 mmol) en DCM (3 mL). La reacción se agitó a 0°C durante 30 min, luego se concentró *in vacuo*. El residuo se purificó por HPLC preparativa (columna Phenomenex AXIA 5µm C18 30 x 100 mm; detección a 220 nm; relación de flujo = 40 mL/min; gradiente continuo de 30% A hasta 100% B durante 10 min + 1 min tiempo de espera a 100% B, donde A =

90:10:0.1 H_2O:MeOH:TFA y B = 90:10:0.1 MeOH:H_2O:TFA) para dar el compuesto del título (20 mg, 29% de rendimiento) como un aceite amarillo. $[M + H]^+$ = 627.3; ^1H RMN (400 MHz, $CDCl_3$) δ 1.21 - 1.34 (m, 6 H), 3.06 (s, 3 H), 3.23 - 3.34 (m, 2 H), 3.38 (s, 3 H), 3.44 - 3.51 (m, 1 H), 3.51 - 3.59 (m, 1 H), 3.77 (s, 2 H), 4.03 - 4.15 (m, 4 H), 4.46 - 4.58 (m, 1 H), 6.58 (t, *J*=2.20 Hz, 1 H), 6.64 (s, 1 H), 6.79 (s, 1 H), 6.85 (d, *J*=3.52 Hz, 1 H), 7.11 (d, *J*=8.79 Hz, 2 H), 7.88 (d, 2 H).

EJEMPLO 79

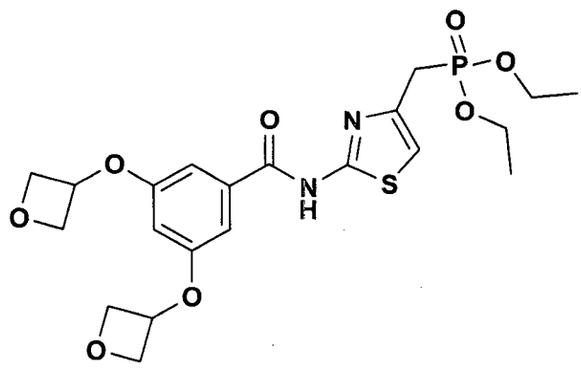


Una solución de ácido 2,3-dihidrobenzo[b][1,4]dioxina-6-carboxílico (20 mg, 0.11 mmol), compuesto del ejemplo 13 parte E (20 mg, 0.083 mmol), HOAt (20 mg, 0.147 mmol), EDCI (40 mg, 0.21 mmol), y DIPEA (40mg, 0.31 mmol) en DMF (1 mL) se agitó a 25°C durante 18 h. La mezcla de reacción se concentró *in vacuo*, y el residuo se purificó por HPLC preparativa (Columna Phenomenex AXIA 5u C18 30 x 100 mm; detección a 220 nm; relación de flujo = 40 mL/min; gradiente continuo de 30% A hasta 100% B durante 10 min + 1 min tiempo de espera a 100% B, donde A = 90:10:0.1 H_2O:MeOH:TFA y B = 90:10:0.1 MeOH:H_2O:TFA) para dar el compuesto del título (8.2 mg, 24 % de rendimiento) como un sólido blanco. $[M + H]^+$ =

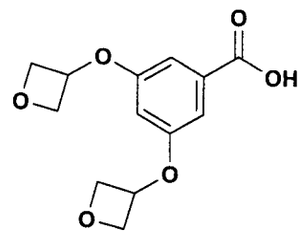
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413.3; ^{1}H RMN (400 MHz, $CDCl_3$) δ 1.29 (t, J=7.03 Hz, 6 H), 3.27 - 3.36 (d, J=21.09 Hz, 2 H), 4.06 - 4.16 (m, 4 H), 4.28 - 4.37 (m, 4 H), 6.94 (d, J=3.52 Hz, 1 H), 6.99 (d, J=8.35 Hz, 1 H), 7.64 - 7.71 (m, 2 H).

EJEMPLO 80



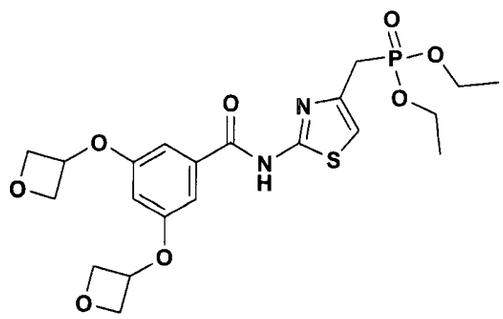
A.



Una mezcla de 3,5-dihidroxibenzoato de metilo (200 mg, 1.189 mmol), compuesto del ejemplo 71 parte E (600 mg, 2.63 mmol), y K_2CO_3 (2 g, 14.47 mmol) en DMF (10 mL) se agitó en un tubo sellado a 115°C durante 18 h, luego se enfrió a temperatura ambiente. Los sólidos se removieron por filtración y se lavaron con DMF. Los filtrados combinados se concentraron *in vacuo*. El residuo se neutralizó con TFA y se purificó por HPLC preparativa (Columna Phenomenex AXIA 5u C18

30 x 100 mm; detección a 220 nm; relación de flujo = 40 mL/min; gradiente continuo de 30% A hasta 100% B durante 10 min + 1 min tiempo de espera a 100% B, donde A = 90:10:0.1 H_2O:MeOH:TFA y B = 90:10:0.1 MeOH:H_2O:TFA) para dar el compuesto parte A (60 mg, 19.0 %) como un sólido blanco. $[M + H]^+$ = 267.2; ^1H RMN (400 MHz, CD_3OD) δ 4.68 (dd, J=7.15, 4.95 Hz, 4 H), 5.02 (t, J=6.60 Hz, 4 H), 5.26 - 5.35 (m, 2 H), 6.46 (t, J=2.20 Hz, 1 H), 6.98 (d, J=2.20 Hz, 2 H).

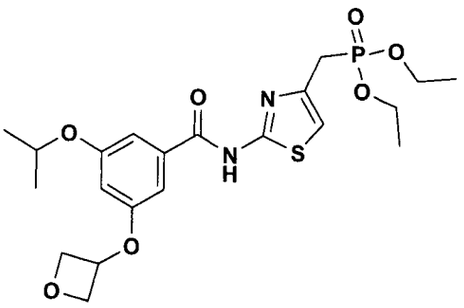
B.



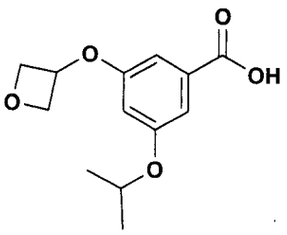
Una mezcla del compuesto parte A (21 mg, 0.079 mmol), Compuesto del ejemplo 13 parte E (19.74 mg, 0.079 mmol), HOAt (20 mg, 0.145 mmol), EDCI (20 mg, 0.500 mmol), y DIPEA (0.2 mL, 1.148 mmol) en DMF (0.5 mL) se agitó a 25°C durante 18 h, luego se concentró *in vacuo*. El residuo se purificó por HPLC preparativa (Columna Phenomenex AXIA 5u C18 30 x 100 mm; detección a 220 nm; relación de flujo = 40 mL/min; gradiente continuo de 30% A hasta 100% B durante 10 min + 1 min tiempo de espera a 100% B, donde A = 90:10:0.1 H_2O:MeOH:TFA y B = 90:10:0.1 MeOH:H_2O:TFA) para dar el compuesto del título (25 mg, 63.6 % de rendimiento) como un sólido blanco. $[M + H]^+$ =

499.3; ^{1}H RMN (400 MHz, $CDCl_3$) (7.09 (2 H, d), 7.03 (1 H, d, J=3.30 Hz), 6.54 (1 H, t, J=2.20 Hz), 5.31 - 5.39 (2 H, m), 5.04 (4 H, t, J=6.60 Hz), 4.74 (4 H, dd, J=7.70, 4.95 Hz), 4.10 - 4.19 (4 H, m), 3.36 (1 H, s), 3.31 (1 H, s), 1.32 (6 H, t, J=6.87 Hz).

EJEMPLO 81



A.

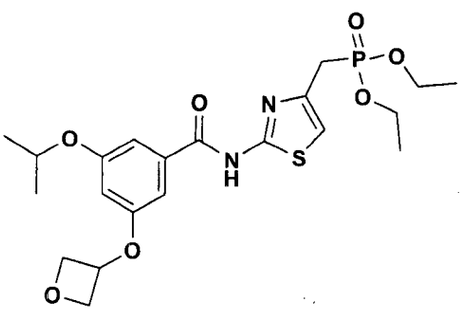


Una mezcla de 3-hidroxi-5-isopropoxibenzoato de metilo (100 mg, 0.476 mmol), Compuesto del ejemplo 71 parte E (180 mg, 0.789 mmol), y K_2CO_3 (1 g, 7.24 mmol) en DMF (5 mL) se agitó en un tubo sellado a 115°C durante 18 h, luego se enfrió a temperatura ambiente. Los sólidos se filtraron completamente y se lavaron con DMF. Los filtrados combinados se concentraron *in vacuo*. El residuo se neutralizó con TFA y se purificó por HPLC preparativa (columna Phenomenex AXIA 5µm

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C18 30 x 100 mm; detección a 220 nm; relación de flujo = 40 mL/min; gradiente continuo de 30% A hasta 100% B durante 10 min + 1 min tiempo de espera a 100% B, donde A = 90:10:0.1 H_2O:MeOH:TFA y B = 90:10:0.1 MeOH:H_2O:TFA) para dar el compuesto parte A (100 mg, 83 % de rendimiento) como un sólido blanco. ^1H RMN (400 MHz, $CDCl_3$) δ 1.35 (d, J=6.05 Hz, 6 H), 4.59 (dt, J=12.09, 6.05 Hz, 1 H), 4.77 (dd, J=7.42, 5.22 Hz, 2 H), 5.01 (t, J=6.60 Hz, 2 H), 5.19 - 5.27 (m, 1 H), 6.52 (t, J=2.47 Hz, 1 H), 6.94 (s, 1 H), 7.27 (s, 1 H).

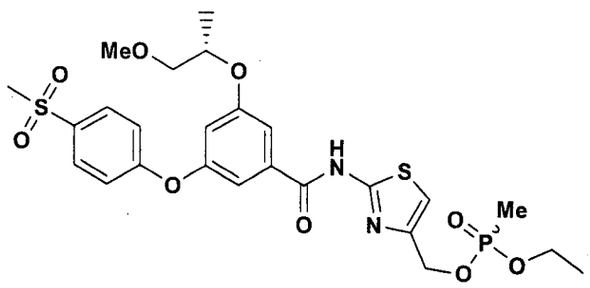
B.



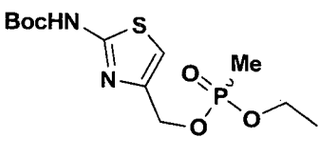
Una mezcla del compuesto parte A (21 mg, 0.083 mmol), Compuesto del ejemplo 13 parte E (20.83 mg, 0.083 mmol), HOAt (20 mg, 0.145 mmol), EDCI (20 mg, 0.500 mmol), y DIPEA (0.2 mL, 1.148 mmol) en DMF (0.5 mL) se agitó a 25°C durante 18 h, luego se concentró *in vacuo*. El residuo se neutralizó con TFA y se purificó por HPLC preparativa (columna Phenomenex AXIA 5µm C18 30 x 100 mm; detección a 220 nm; relación de flujo = 40 mL/min; gradiente continuo de 30% A hasta 100% B durante 10 min + 1 min tiempo de espera a 100% B, donde A = 90:10:0.1 H_2O:MeOH:TFA y B = 90:10:0.1 MeOH:H_2O:TFA) para dar el

compuesto del título (28 mg, 0.058 mmol, 69.4 % de rendimiento) como una cera transparente. $[M + H]^+$ = 485.3; ^1H RMN (400 MHz, $CDCl_3$) δ 7.31 (1 H, t, J=1.52 Hz), 6.96 - 7.01 (2 H, m), 6.56 (1 H, t, J=2.27 Hz), 5.28 - 5.35 (1 H, m, J=5.53, 5.53, 5.49, 5.43 Hz), 5.03 (2 H, t, J=6.95 Hz), 4.64 - 4.78 (3 H, m), 4.13 (4 H, dd, J=8.21, 7.20 Hz), 3.36 (1 H, s), 3.30 (1 H, s), 1.35 (6 H, d, J=6.06 Hz), 1.30 (6 H, t, J=7.07 Hz).

EJEMPLO 82



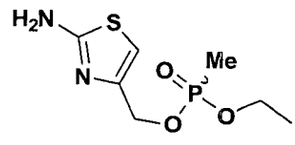
A.



A una solución de 4-(clorometil)tiazol-2-ilcarbamato de tert-butilo (249 mg, 1.00 mmol) y $CH_3P(OEt)_2$ (124.2 mg, 1.00 mmol) en MeCN (4.0 mL) bajo Ar a temperatura ambiente se agregó 18-corona-6 (52.9 mg, 0.2 mmol), K_2CO_3 (138.2 mg, 1.00 mmol), y $(n\text{-}Bu)_4NI$ (74.0 mg, 0.20 mmol). La mezcla de reacción se calentó a 55°C durante 2 h, luego se enfrió a temperatura ambiente y se apagó con $NaHCO_3$ acuoso saturado.

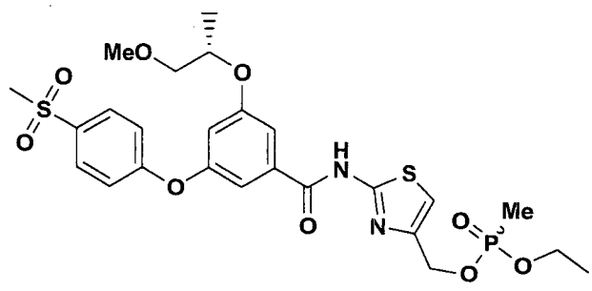
La mezcla se extrajo con EtOAc (2x). Los extractos orgánicos combinados se lavaron con salmuera, se secaron ($MgSO_4$) y se concentraron *in vacuo*. El residuo de aceite se procesó por cromatografía (SiO_2; gradiente continuo de 0% EtOAc/Hexano hasta 100% EtOAc/Hexano) para proporcionar el compuesto parte A (171 mg, 51% balance de material, 90% purificado por HPLC) como un aceite incoloro.

B.



A una solución a temperatura ambiente del Compuesto del ejemplo 82 parte A (171 mg, ~0.51 mmol) en CH_2Cl_2 (1.5 mL) [Nota: el matraz se equipó con un tubo seco lleno con $CaCl_2$ para protegerse de la humedad atmósferica] se agregó TFA (0.5 mL). La reacción se agitó a temperatura ambiente durante 14 h, luego se concentró *in vacuo* y luego se depuró de CH_2Cl_2. El residuo aceitoso se usó sin purificación adicional o caracterización de la parte C.

C.



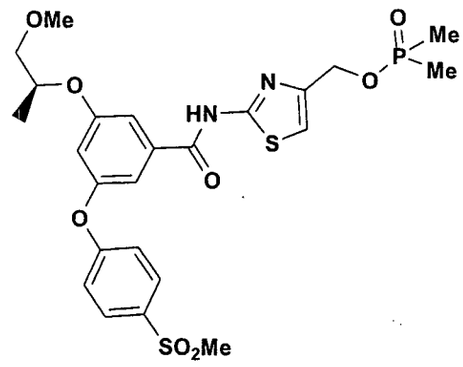
Una solución a temperatura del ácido ejemplo 26 Parte C

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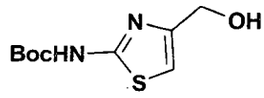
(193.4 mg, 0.51 mmol) en CH_2Cl_2 (2.0 mL) [Nota: el matraz se equipó con un tubo seco llebo con $CaCl_2$ para protegerse de la humedad atmósferica] se trató con cloruro de oxalilo (0.305 mL de una solución 2M en CH_2Cl_2, 0.61 mmol) y DMF (0.020 mL). La mezcla de reacción se agitó a temperatura ambiente durante 2 h, luego se concentró *in vacuo*, y se re-disolvió en CH_2Cl_2 (2 mL). A esta solución a temperatura ambiente bajo Ar se agregó una solución del compuesto parte B en CH_2Cl_2 (2 mL), seguido por Et_3N (0.213 mL, 1.53 mmol). Después de 15 h a temperatura ambiente, la mezcla de reacción se diluyó con CH_2Cl_2 y se lavó con $NaHCO_3$ acuoso saturado. El extracto orgánico se secó (Na_2SO_4) y se concentró *in vacuo*. El residuo se purificó por HPLC preparativa (columna Phenomenex Luna 5u C18 30 x 250 mm; detección a 220 nm; relación de flujo = 30 mL/min; gradiente continuo de 20% B hasta 100% B durante 20 minutos + 5 min tiempo de espera a 100% B, donde A = 90:10:0.1 H_2O: CH_3CN:TFA y B = 10:90:0.1 H_2O:CH_3CN:TFA) para proporcionar el compuesto del título (33 mg, 11%) como un aceite espeso incoloro. $[M + H]^+$ = 599.2; ^1H RMN (400 MHz, $CDCl_3$): δ 11.23 (br s, 1H), 7.92 (d, J=8.8 Hz, 2H), 7.57 (t, J=1.6 Hz, 1H), 7.47 (t, J=1.6 Hz, 1H), 7.13 (d, J=8.8 Hz, 2H), 6.95 (s, 1H), 6.87 (t, J=2.2 Hz, 1H), 5.22 (m, 2H), 4.68 (m, 1H), 4.05 (m, 2H), 3.56 (ddd, J=6.6, 10.5, 30.3 Hz, 2H), 3.39 (s, 1H), 3.09 (s, 1H), 1.51 (dd, J=13.7, 17.6 Hz, 3H), 1.34 (d, J=6.6 Hz, 3H), 1.27 (dt, J=2.2, 7.2 Hz, 3H).

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EJEMPLO 83



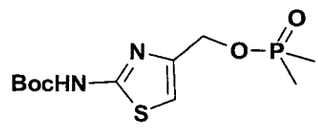
A.



A una solución agitada de tiazol-4-carboxilato de etil 2-(tert-butoxicarbonilamino) (2.24 g, 8.23 mmol) en CH_2Cl_2 (25 mL) bajo Ar a -78°C se agregó una solución de DiBALH (25.5 mL, 1.0 M en CH_2Cl_2, 25.5 mmol) tal como unrango que mantiene la temperature ≤-65°C. La reacción se agitó durante 20 min a -65°C, luego se permitió calentar a -30°C. Después de 30 min, la mezcla de reacción se apagó con una solución de tartrato de potasio de sodio 1M (30 mL), se calentó a temperatura ambiente y se agitó durante 2 h a temperatura ambiente. La mezcla se filtró a través de Celite®, la cual se lavó con CH_2Cl_2. Los filtrados combinados se secaron (Na_2SO_4), y se concentraron *in vacuo*. El aceite resultante se procesó por cromatografía (SiO_2; gradiente continuo de 0% EtOAc/Hexano hasta 100% EtOAc/Hexano) para proporcionar el compuesto parte

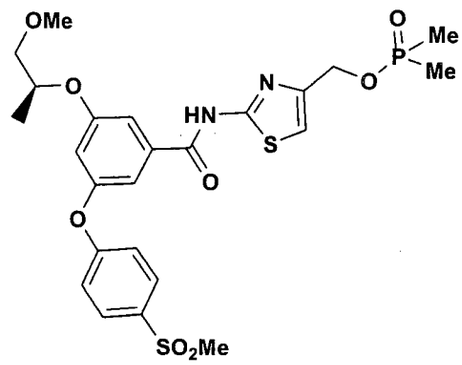
A (1.66 g, 88% de rendimiento) como un sólido blanco amorfo.

B.



A una solución a 0°C del compuesto parte A (310 mg, 1.35 mmol) en CH_2Cl_2 (5 mL) bajo Ar se agregó cloruro de dimetilfosfínico (182 mg, 1.62 mmol), y luego Et_3N (0.244 mL, 1.75 mmol) durante 2 min. La reacción se permitió calentar a temperatura ambiente y se agitó a temperatura ambiente durante 14 h, luego se diluyó con EtOAc. La mezcla se lavó con 1% HCl acuoso y salmuera. La fase orgánica se secó ($MgSO_4$) y se concentró *in vacuo* para dar el compuesto parte B como un aceite incoloro (413 mg, 100% crudo). Este material se usó en la siguiente etapa sin purificación adicional.

C.



C1: A una solución agitada del compuesto parte B (410 mg, 1.34 mmol) en CH_2Cl_2 (3 mL) a temperatura ambiente [Nota: el matraz se equipó con un tubo seco lleno con $CaCl_2$ para

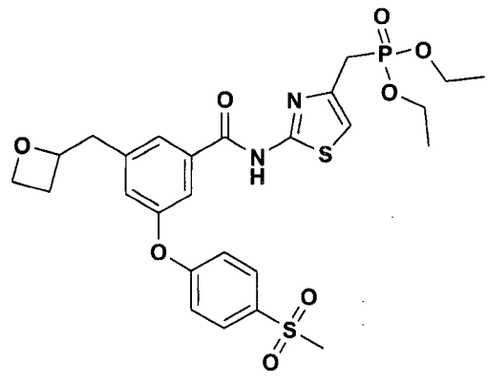
protegerse de la humedad atmósferica] se agregó TFA (1 mL). La reacción se agitó durante 14 h a temperatura ambiente, y la mezcla de reacción se concentró *in vacuo* y se re-disolvió en MeOH (5 mL). La solución se pasó a través de 2 cartuchos StratroSpheres™ PL-HCO_3 MP SPE (0.9 meq capacidad), y el eluyente se evaporó *in vacuo* para proporcionar el compuesto parte C. El aceite incoloro resultante (225 mg) se re-disolvió en CH_2Cl_2 (2 mL). La mitad (en peso) de esta solución se usó sin purificación adicional por la parte C2.

C2: A una mezcla espesa agitada del Compuesto del ejemplo 26 parte C (152 mg, 0.40 mmol) y HOAt (54.5 mg, 0.40 mmol) en CH_2Cl_2 (2.4 mL) a temperatura ambiente bajo Ar se agregó EDC (76.3 mg, 0.40 mmol). Una solución transparente tan pronto como se forma. Después de 30 min, la solución del compuesto parte C en CH_2Cl_2 del C1 se agregó, seguido por iPr_2NEt (0.028 mL, 0.20 mmol) y DMAP (5 mg, 0.04 mmol). La reacción se agitó durante 16 h a temperatura ambiente, luego se apagó con NH_4Cl acuoso saturado y se extrajo dos veces con EtOAc. Los extractos orgánicos combinados se secaron (Na_2SO_4) y se evaporaron *in vacuo* para dar un aceite anaranjado. El residuo se purificó por HPLC preparativa (columna Phenomenex AXIA Luna 5u 30 x 75 mm; detección a 220 nm; relación de flujo = 40 mL/min; gradiente continuo de 0% B hasta 100% B durante 10 min + 10 min tiempo de espera a 60% B, donde A = 90:10:0.1 H_2O: CH_3CN:TFA y B = 10:90:0.1 H_2O:CH_3CN:TFA) para

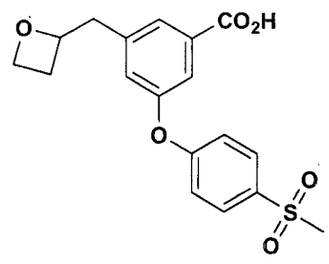
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proporcionar el compuesto del título (28.9 mg, 13% de rendimiento) como un sólido blanco ceroso. $[M + H]^+$ = 569.0; ^1H RMN(400 MHz, $CDCl_3$) δ 11.75 (br s, 1H), 7.92 (d, *J*=8.8 Hz, 2H), 7.63 (t, *J*=2.2 Hz, 1H), 7.49 (t, *J*=1.9 Hz, 1H), 7.14 (d, *J*=8.8 Hz, 2H), 6.94 (s, 1H), 6.87 (t, *J*= 2.2 Hz, 1H), 5.20 (d, *J*=7.7 Hz, 2H), 4.70 (m, 1H), 3.55 (ddd, *J*=6.0, 9.9, 30.2 Hz, 2H), 3.40 (s, 1H), 3.08 (s, 1H), 1.53 (dd, *J*=2.8, 14.3 Hz, 6H), 1.33 (d, *J*=6.6 Hz, 3H).

EJEMPLO 84



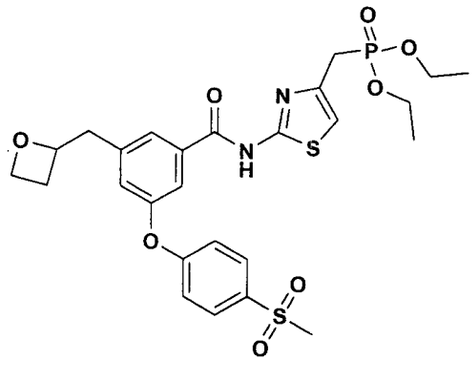
A.



A una solución a 0°C del Compuesto del ejemplo 26 parte A (100 mg, 0.310 mmol), Ph_3P (150 mg, 0.572 mmol), y oxetan-2-ilmetanol (40 mg, 0.454 mmol) en THF (5 mL) se agregó DIAD (0.2 mL, 1.029 mmol). La reacción se agitó a temperatura

ambiente durante 18h, y los volátiles se removieron *in vacuo*. El residuo se procesó por cromatografía (EtOAc/Hexano, 1:1) para dar el éster de metilo crudo. A una solución de este material en MeOH (1 mL) se agregó NaOH acuoso 1N (1 mL). La reacción se agitó a temperatura ambiente durante 2 h y luego se acidificó con TFA y se concentró *in vacuo*. El residuo se purificó por HPLC preparativa (Columna Phenomenex AXIA 5u C18 30 x 100 mm; detección a 220 nm; relación de flujo = 40 mL/min; gradiente continuo de 30% A hasta 100% B durante 10 min + 1 min tiempo de espera a 100% B, donde A = 90:10:0.1 H_2O:MeOH:TFA y B = 90:10:0.1 MeOH:H_2O:TFA) para dar el compuesto parte A (40 mg, 34.1 % de rendimiento) como un sólido blanco. $[M + H]^+$ = 377.2; ^1H RMN (400 MHz, $CDCl_3$) δ 2.66 - 2.88 (m, 2 H), 3.08 (s, 3 H), 4.20 (d, J=3.85 Hz, 2 H), 4.66 - 4.81 (m, 2 H), 5.16 - 5.25 (m, 1 H), 6.92 (t, J=2.47 Hz, 1 H), 7.11 (d, J=8.79 Hz, 2 H), 7.36 (d, J=2.20 Hz, 1 H), 7.52 (dd, J=2.20, 1.10 Hz, 1 H), 7.92 (d, J=8.79 Hz, 2 H).

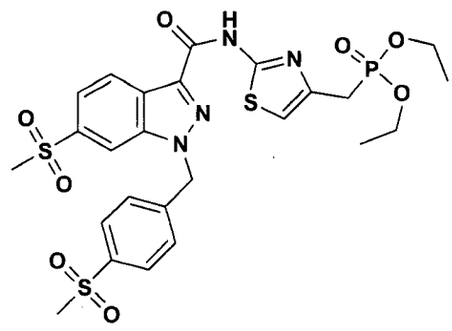
B.



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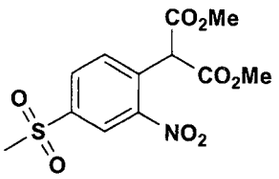
Una mezcla del compuesto parte A (15 mg, 0.040 mmol), Compuesto del ejemplo 13 parte E (20 mg, 0.080 mmol), HOAt (20 mg, 0.145 mmol), EDCI (40 mg, 1.000 mmol) y DIPEA (0.2 mL, 1.148 mmol) en DMF (0.5 mL) se agitó a 25°C durante 18 h. La mezcla de reacción se concentró *in vacuo*, y el residuo crudo se purificó por HPLC preparativa (Columna Phenomenex AXIA 5u C18 30 x 100 mm; detección a 220 nm; relación de flujo = 40 mL/min; gradiente continuo de 30% A hasta 100% B durante 10 min + 1 min tiempo de espera a 100% B, donde A = 90:10:0.1 H_2O:MeOH:TFA y B = 90:10:0.1 MeOH:H_2O:TFA) para proporcionar el compuesto del título (9.8 mg, 0.016 mmol, 39.7 % de rendimiento) como un sólido blanco. $[M + H]^+$ = 611.3; ^1H RMN (400 MHz, $CDCl_3$) δ 7.93 (2 H, d, *J*=8.79 Hz), 7.59 (1 H, s), 7.39 (1 H, s), 7.15 (2 H, d, *J*=8.79 Hz), 6.94 - 6.98 (2 H, m), 5.12 - 5.20 (1 H, m), 4.62 - 4.78 (2 H, m), 4.22 - 4.32 (2 H, m), 4.06 - 4.17 (4 H, m, *J*=7.35, 7.35, 7.28, 7.15 Hz), 3.32 (2 H, d, *J*=20.89 Hz), 3.08 (3 H, s), 2.64 - 2.86 (2 H, m), 1.30 (6 H, t, *J*=6.87 Hz).

EJEMPLO 85



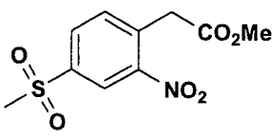
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A.



A una solución de KOtBu (17.1 mL, 17.1 mmol) en t-BuOH (10 mL) se agregó gota a gota malonato de dimetilo (2.0 mL, 17.1 mmol). A la mezcla resultante se agregó una solución caliente de 1-cloro-4-(metilsulfonil) 2-nitrobenceno (2.0 g, 8.6 mmol) en t-BuOH (10 mL). La mezcla de reacción se calentó a reflujo durante 15 h, luego se enfrió a temperatura ambiente y se diluyó con EtOAc (50 mL), se lavó con agua y salmuera (30 mL cada uno), se secó ($MgSO_4$) y se concentró *in vacuo* para proporcionar el compuesto parte A (2.8 g, 100%).

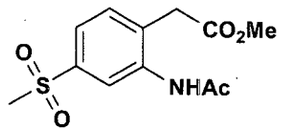
B.



A una solución del compuesto parte A (2.8 g, 8.6 mmol) en DMSO (10 mL) se agregó NaCl (1.0 g, 17.1 mmol) y agua (2 mL, 111 mmol). La mezcla se calentó a 120°C durante 5 h, luego se enfrió a temperatura ambiente y se diluyó con EtOAc (50 mL). La capa orgánica se lavó con agua y salmuera (35 mL cada uno), se secó ($MgSO_4$) y se concentró *in vacuo*. El residuo se procesó por cromatografía (SiO_2; 30 min gradiente de 100% hasta 0% hexano/EtOAc) para proporcionar el compuesto parte B (863 mg, 37% de rendimiento durante 2 etapas).

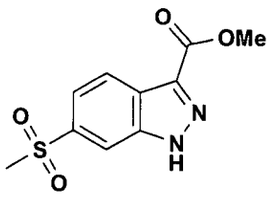
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C.



A una solución del compuesto parte B (830 mg, 3.0 mmol) y Ac_2O (2.0 mL, 21.6 mmol) en tolueno (10 mL) se agregó lentamente 10% Pd/C (200 mg, 1.7 mmol). La reacción se agitó bajo una atmósfera de H_2 (g) (1 atm) a temperatura ambiente durante 4 h. El catalizador se filtró completamente y se lavó con tolueno (2x). Los filtrados combinados se concentraron *in vacuo* para proporcionar el compuesto crudo parte C (398 mg, 46%).

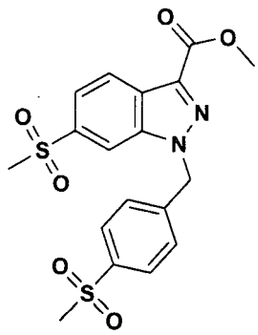
D.



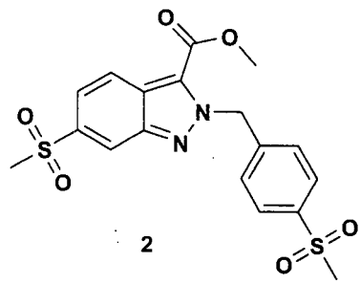
A una solución a 90-95°C del compuesto parte C (398 mg, 1.4mmol) en AcOH (6 mL) se agregó gota a gota t-butil nitrito (0.18 mL, 1.5 mmol). La reacción se agitó a 95°C durante 30 min. La reacción se enfrió a temperatura ambiente y se diluyó con EtOAc (30 mL). La capa orgánica se lavó con agua (15 mL) y salmuera (15 mL), se secó ($MgSO_4$), y se concentró *in vacuo* hasta un precipitado sólido. Este precipitado sólido se colectó por filtración y se lavó con tolueno para dar el Compuesto parte D (280 mg, 79% de rendimiento), el cual se usó en la siguiente etapa sin purificación adicional.

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E.



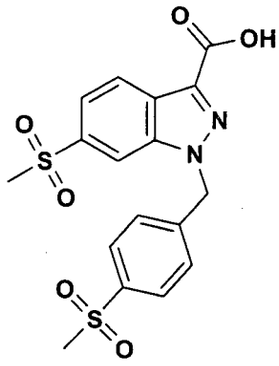
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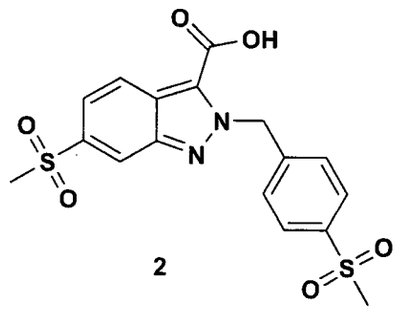
2

A una solución del Compuesto parte D (30 mg, 0.12 mmol) en CH_3CN (1.5 mL) se agregó 1-(clorometil)-4-(metilsulfonil) benceno (72.4 mg, 0.35 mmol), K_2CO_3 (48.9 mg, 0.35 mmol), y $(n\text{-}Bu)_4NI$ (3.5 mg, 9.4 µmol). La reacción se agitó a 80°C durante 3 h, luego se enfrió a temperatura ambiente. Los sólidos se filtraron completamente y se lavaron con acetona. Los filtrados combinados se concentraron *in vacuo* para proporcionar una mezcla de los compuestos parte E.

F.



1



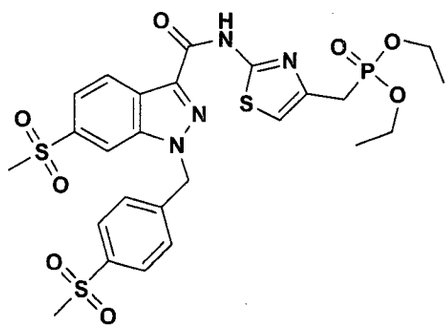
2

A una solución de los compuestos parte E (0.12 mmol rendimiento teorético) en THF (1 mL) se agregó NaOH acuoso 1N (0.4 mL, 0.40 mmol). La reacción se agitó a temperatura ambiente durante 15 h., luego se diluyó con EtOAc (4 mL) y se acidificó con HCl acuoso 1N (0.45 mL). La

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capa orgánica se lavó con salmuera, se secó ($MgSO_4$) y se concentró *in vacuo*. La mezcla cruda se purificó por HPLC preparativa (columna Phenomenex Luna AXIA 30x100 mm; detección a 220 nm; relación de flujo = 25 mL/min; gradiente continuo de 60% A hasta 100% B durante 10 min, donde A = 90:10:0.1 H_2O:MeOH:TFA y B = 90:10:0.1 MeOH:H_2O:TFA) para proporcionar el compuesto parte F1 (15.2 mg, 32% de rendimiento durante 2 etapas) y compuesto parte F2 (9.0 mg, 19% de rendimiento durante 2 etapas).

G.



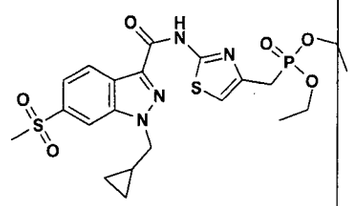
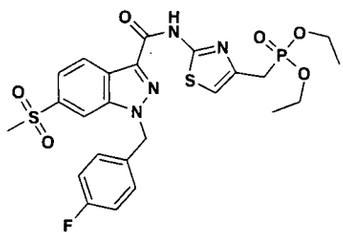
A una solución del compuesto parte F1 (7 mg, 0.02 mmol) en CH_2Cl_2 (0.8 mL) se agregó cloruro de oxalilo (0.03 mL de una solución 2M en DCM, 0.05 mmol) y DMF (1.3 µL, 0.02 mmol). La reacción se agitó a temperatura ambiente durante 1 h, luego se concentró *in vacuo*. El residuo se tomó en THF (0.4 mL) y se agregó a una solución del Compuesto del ejemplo 13 parte E (17.2 mg, 0.07 mmol) y $NaHCO_3$ (7.2 mg, 0.09 mmol) en THF/H_2O (1:1, 0.8 mL). La reacción se agitó a temperatura ambiente durante 2 h, luego se diluyó con EtOAc (4 mL) y agua (1 mL). La capa orgánica se concentró *in vacuo*. El residuo se purificó por HPLC preparativa (columna Phenomenex Luna AXIA 30x100 mm; detección a 220 nm; relación de flujo = 40 mL/min; gradiente continuo de 70% A hasta 100% B durante 10 min, donde A = 90:10:0.1 H_2O:MeOH:TFA y B = 90:10:0.1

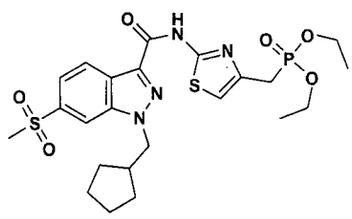
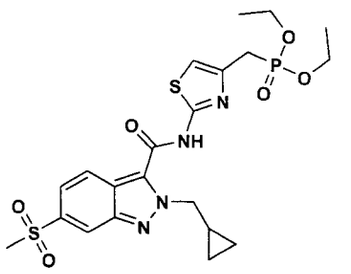
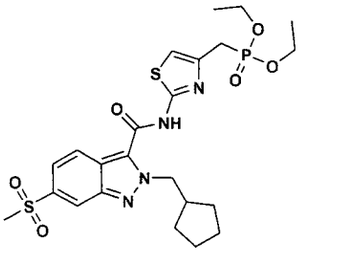
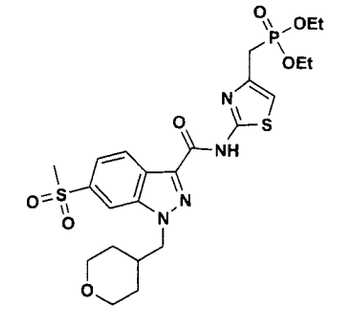
676

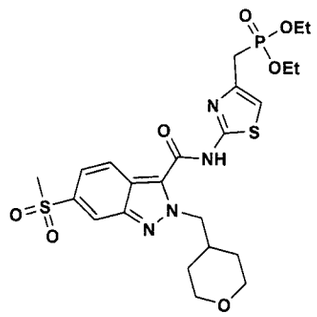
MeOH:H_2O:TFA) para proporcionar el compuesto del título (0.63 mg, 5.7% de rendimiento) como un sólido blanco. $[M + H]^+$ = 641.2; ^1H RMN (400 MHz, $CDCl_3$) δ 8.63 (1 H, d, *J*=8.35 Hz), 8.21 (1 H, s), 7.96 (2 H, d, *J*=8.35 Hz), 7.90 (1 H, d, *J*=8.35 Hz), 7.63 (2 H, d, *J*=8.35 Hz), 6.94 - 7.04 (1 H, m), 5.81 (2 H, s), 4.05 - 4.21 (4 H, m), 3.35 (2 H, d, *J*=21.09 Hz), 3.16 (3 H, s), 3.05 (3 H, s), 1.33 (6 H, t, *J*=7.03 Hz).

EJEMPLOS 86 HASTA 92

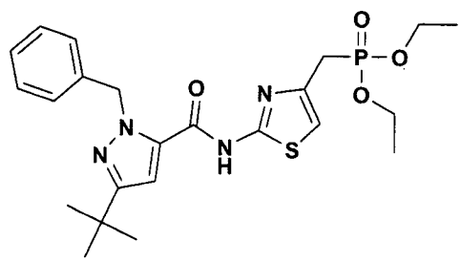
Los siguientes ejemplos se sintetizaron del Compuesto ejemplo 85 parte D por emplear las rutas sintéticas generales descritas para la preparación del Compuesto ejemplo 85 del Compuesto ejemplo 85 parte D.

Ejemplo #	Estructura	$[M+H]^+$	^{1}HRMN	Rendimiento y descripción
86		527.0	(400 MHz, $CDCl_3$) δ 8.62 (1 H, d, *J*=8.79 Hz), 8.24 (1 H, s), 7.86 (1 H, d, *J*=8.35 Hz), 6.94 (1 H, d, *J*=3.95 Hz), 4.41 (2 H, d, *J*=7.03 Hz), 4.04 - 4.21 (4 H, m), 3.35 (2 H, d, *J*=21.09 Hz), 3.16 (3 H, s), 1.41 - 1.52 (1 H, m), 1.32 (6 H, t, *J*=7.03 Hz), 0.66 - 0.75 (2 H, m), 0.50 - 0.58 (2 H, m)	4.0 mg (24% de rendimiento), sólido blanco
87		581.1	(400 MHz, $CDCl_3$) δ 8.62 (1 H, d, *J*=7.91 Hz), 8.18 (1 H, s), 7.79 - 7.89 (1 H, m), 7.34 (2 H, dd, *J*=8.57, 5.05 Hz), 7.06 (2 H, t, *J*=8.57 Hz), 6.92 (1 H, d, *J*=3.52 Hz), 5.67 (2 H, s), 4.02 - 4.20 (4 H, m), 3.34 (2 H, d, *J*=21.09 Hz), 3.13 (3 H, s), 1.31 (6 H, t, *J*=7.03 Hz)	8.5 mg (37% de rendimiento), sólido gris

Ejemplo #	Estructura	$[M+H]^+$	^{1}HRMN	Rendimiento y descripción
88		555.1	(500 MHz, $CDCl_3$) δ 8.60 (1 H, d, *J*=7.70 Hz), 8.22 (1 H, s), 7.85 (1 H, d, *J*=7.15 Hz), 6.96 (1 H, d, *J*=3.85 Hz), 4.46 (2 H, d, *J*=7.15 Hz), 4.06 - 4.21 (4 H, m), 3.35 (2 H, d, *J*=20.89 Hz), 3.17 (3 H, s), 2.62 - 2.75 (1 H, m), 1.68 - 1.81 (4 H, m), 1.57 - 1.68 (2 H, m), 1.34 - 1.43 (2 H, m), 1.32 (6 H, t, *J*=7.15 Hz)	8.5 mg (40% de rendimiento), sólido blanco
89		527.0	(500 MHz, $CDCl_3$) δ ppm 8.56 (1 H, s), 8.05 (1 H, d, *J*=8.80 Hz), 7.75 (1 H, d, *J*=9.35 Hz), 7.07 (1 H, d, *J*=3.30 Hz), 4.77 (2 H, d, *J*=7.15 Hz), 4.08 - 4.24 (4 H, m), 3.38 (2 H, d, *J*=21.44 Hz), 3.12 (3 H, s), 1.46 - 1.63 (1 H, m), 1.26 - 1.37 (6 H, m), 0.51 - 0.65 (4 H, m)	3.0 mg (21% de rendimiento), aceite
90		555.1	(500 MHz, $CDCl_3$) δ 8.54 (1 H, s), 8.06 (1 H, d, *J*=8.80 Hz), 7.74 (1 H, d, *J*=9.35 Hz), 7.05 (1 H, d, *J*=3.30 Hz), 4.87 (2 H, d, *J*=7.70 Hz), 4.09 - 4.21 (4 H, m), 3.36 (2 H, d, *J*=21.44 Hz), 3.12 (3 H, s), 2.56 - 2.71 (1 H, m), 1.64 - 1.76 (4 H, m), 1.51 - 1.63 (2 H, m), 1.35 - 1.43 (2 H, m), 1.32 (6 H, t, *J*=7.15 Hz)	3.5 mg (29% de rendimiento), aceite
91		571.3	(500 MHz, $CDCl_3$) δ 8.57 (1 H, d, *J*=8.25 Hz), 8.22 (1 H, s), 7.88 (1 H, d, *J*=9.90 Hz), 7.04 (1 H, d, *J*=3.85 Hz), 4.43 (2 H, d, *J*=7.15 Hz), 4.12 - 4.24 (4 H, m), 4.01 (2 H, dd, *J*=11.55, 2.75 Hz), 3.43 - 3.49 (2 H, m), 3.40 (2 H, d, *J*=21.44 Hz), 3.18 (3 H, s), 2.51 - 2.68 (1 H, m), 1.43 - 1.64 (4 H, m), 1.34 (6 H, t, *J*=7.15 Hz)	10.5 mg (37% de rendimiento), sólido gris

Ejemplo#	Estructura	$[M+H]^+$	^{1}HRMN	Rendimiento y descripción
92		571.3	(500 MHz, $CDCl_3$) δ 8.55 (1 H, s), 8.04 (1 H, d, *J*=8.80 Hz), 7.76 (1 H, d, *J*=10.45 Hz), 7.12 (1 H, d, *J*=3.85 Hz), 4.81 (2 H, d, *J*=7.15 Hz), 4.13 - 4.28 (4 H, m), 3.99 - 4.08 (2 H, m), 3.33 - 3.48 (4 H, m), 3.13 (3 H, s), 2.32 - 2.53 (1 H, m), 1.48 - 1.65 (4 H, m), 1.36 (6 H, t, *J*=6.87 Hz)	4.8 mg (24 % de rendimiento), aceite amarillo

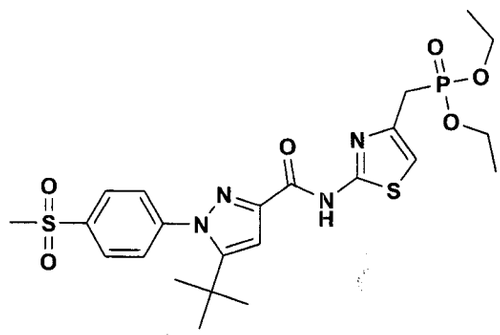
EJEMPLO 93



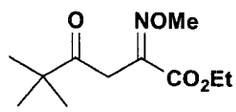
A una solución del Compuesto del ejemplo 13 parte E (50 mg, 0.20 mmol) en DCM (1 mL) se agregó cloruro de 1-bencil-3-tert-butil-1H-pirazol-5-carbonilo (71.9 mg, 0.26 mmol) y piridina (0.02 mL, 0.26 mmol). La reacción se agitó a temperatura ambiente durante 16 h, luego se concentró *in vacuo*. El residuo se purificó por HPLC preparativa (columna Phenomenex Luna AXIA 30x100 mm; detección a 220 nm; relación de flujo = 40 mL/min; gradiente continuo de 50% A hasta 100% B durante 10 min, donde A = 90:10:0.1 H_2O:MeOH:TFA y B = 90:10:0.1 MeOH:H_2O:TFA) para dar el compuesto del título (64 mg, 65% de rendimiento) como un aceite. $[M + H]^+$ = 491.1; ^{1}H RMN (400 MHz, $CDCl_3$) δ 7.31 (1 H, s), 7.17 - 7.30 (5 H, m),

6.96 (1 H, d, *J*=3.52 Hz), 5.81 (2 H, s), 4.05 - 4.19 (4 H, m), 3.31 (2 H, d, *J*=21.09 Hz), 1.36 (9 H, s), 1.29 (6 H, t, *J*=7.03 Hz).

EJEMPLO 94

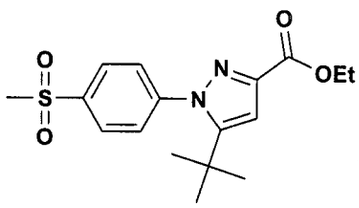


A.

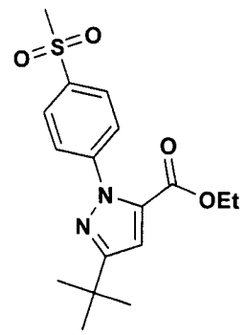


A una solución de trimetilacetopiruvato de etilo (205 mg, 1.02 mmol) en EtOH seco (1 mL) se agregó clorohidrato de O-metilhidroxilamina (90 mg, 1.07 mmol) y 3A tamiz molecular. La reacción se agitó a temperatura ambiente durante 15 h, luego se filtró y se lavó con EtOH. El filtrado se concentró *in vacuo*, y el residuo se dividió entre Et_2O y $NaHCO_3$ acuoso saturado. La capa Et_2O se lavó con agua y salmuera, se secó ($MgSO_4$) y se concentró *in vacuo* para dar el compuesto parte A (176 mg, 75%) como un aceite rojo-anaranjado.

B.



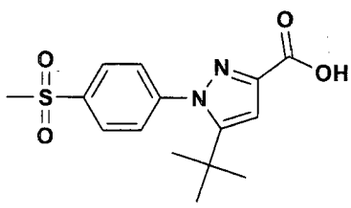
1



2

A una solución del compuesto parte A (176 mg, 0.77 mmol) en AcOH:EtOH (1.5 mL) se agregó (4-(metilsulfonil)fenil)hidrazina (286 mg, 1.54 mmol). La reacción se agitó a 90°C durante 10 h, luego se enfrió a temperatura ambiente. La mezcla de reacción se concentró *in vacuo*, y el residuo se dividió entre EtOAc y HCl acuoso 0.2 N. La capa orgánica se lavó con agua y salmuera, se secó ($MgSO_4$) y se concentró *in vacuo*. El residuo se procesó por cromatografía (SiO_2; 15 min gradiente de 0% EtOAc/Hexanos hasta 100% EtOAc/Hexanos) para proporcionar El compuesto parte B2 (214 mg, 80%) y Compuesto parte B2 (20 mg, 7%).

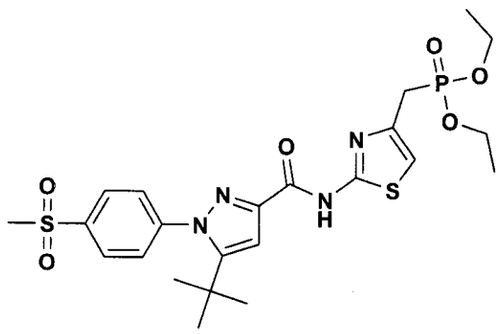
C.



A una solución del compuesto parte B2 (23 mg, 0.07 mmol) en THF (1 mL) se agregó NaOH acuoso 1N. La mezcla se agitó a temperatura ambiente durante 15 h, luego se diluyó con EtOAc

(4 mL) y se acidificó con HCl acuoso 1N (0.5 mL). La capa orgánica se lavó con salmuera, se secó ($MgSO_4$) y se concentró *in vacuo* para dar el compuesto crudo parte C (23 mg, 109% recuperación).

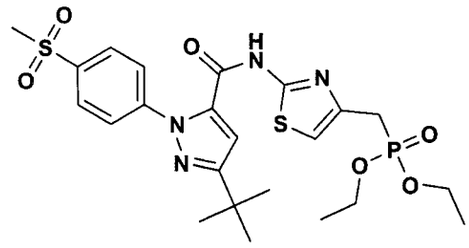
D.



A una solución del compuesto parte C (21.3 mg, 0.07 mmol) en DMF (1 mL) se agregó el compuesto del ejemplo 13 parte E (33.0 mg, 0.13mmol), EDCI (25.3 mg, 0.13 mmol), HOBT (20.2 mg, 0.13 mmol), y Base hunig (0.034 mL, 0.20 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 4 días y se purificó directamente por HPLC preparativa (columna Phenomenex Luna AXIA 30x100 mm; detección a 220 nm; relación de flujo = 40 mL/min; gradiente continuo de 50% A hasta 100% B durante 10 min, donde A = 90:10:0.1 H_2O:MeOH:TFA y B = 90:10:0.1 MeOH:H_2O:TFA) para proporcionar el compuesto del título (14 mg, 38% de rendimiento) como un aceite amarillo. $[M + H]^+$ = 555.1; ^1H RMN (500 MHz, $CDCl_3$) δ 8.11 (2 H, d), 7.71 (2 H, d, J=8.25 Hz), 6.99 (1 H, s), 6.98 (1 H, d, J=3.85 Hz), 4.10 - 4.18 (4 H, m), 3.98 (1 H, s), 3.35 (2 H, d, J=21.44 Hz), 3.13 (3 H, s), 1.30 (6 H, t, J=7.15 Hz), 1.27 (9

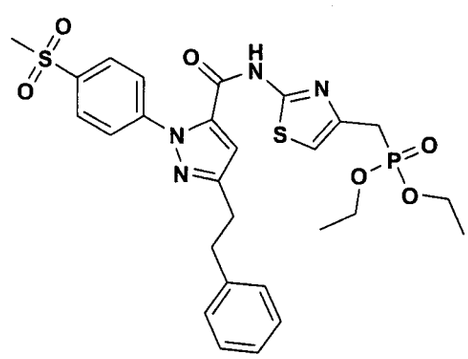
H, s).

EJEMPLO 95

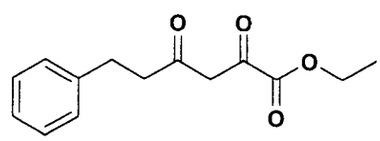


El compuesto del título (10 mg, 32% de rendimiento, sólido café) se sintetizó a partir del Compuesto del ejemplo 94 parte B2 usando el procedimiento empleado en el ejemplo 94. $[M + H]^+$ = 555.1; ^1H RMN (500 MHz, $CDCl_3$) δ 8.04 (2 H, d, J=8.80 Hz), 7.68 (2 H, d, J=8.80 Hz), 7.49 (1 H, s), 7.01 (1 H, d, J=3.85 Hz), 4.15 - 4.22 (4 H, m), 3.37 (2 H, d, J=21.44 Hz), 3.11 (3 H, s), 1.40 (9 H, s), 1.34 (6 H, t, J=6.87 Hz).

EJEMPLO 96



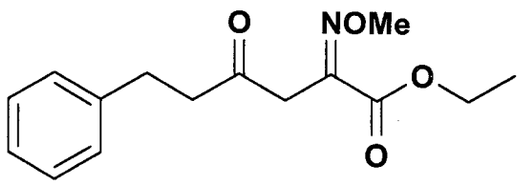
A.



A una solución a 0°C de bencilacetona (0.54 mL, 3.6

mmol) y oxalato de dietilo (0.53 mL, 3.9 mmol) en EtOH seco (6 mL) se agregó NaOEt (0.31 mL, 3.9 mmol). La reacción se calentó lentamente a temperatura ambiente y se agitó durante 15 h a temperatura ambiente, luego se diluyó con EtOAc (20 mL) y se lavó con salmuera. La capa orgánica se secó ($MgSO_4$) y se concentró *in vacuo* para proporcionar el compuesto parte A (0.65 g, 73% de rendimiento) como un aceite amarillo.

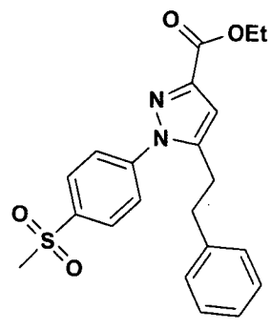
B.



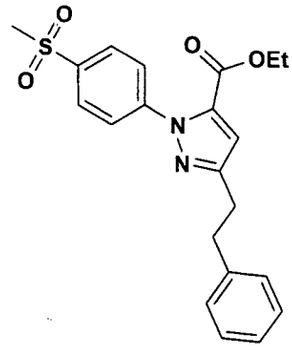
A una solución del compuesto parte A (0.65 g, 2.6 mmol) en EtOH seco (5 mL) se agregó clorohidrato de O-metilhidroxilamina (0.31 g, 3.7 mmol) y 3A tamiz molecular (2 g). La reacción se agitó a temperatura ambiente durante 15 h, luego se filtró y se lavó con EtOH. Los filtrados combinados se concentraron *in vacuo*, y el residuo se dividió entre Et_2O y $NaHCO_3$ acuoso saturado. La capa Et_2O se lavó con agua y salmuera, se secó ($MgSO_4$) y se concentró *in vacuo*. El residuo se procesó por cromatografía (SiO_2; 16 min gradiente de 0% EtOAc/Hexanos hasta 100% EtOAc/Hexanos) para proporcionar el compuesto parte B (117 mg, 16%).

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C.



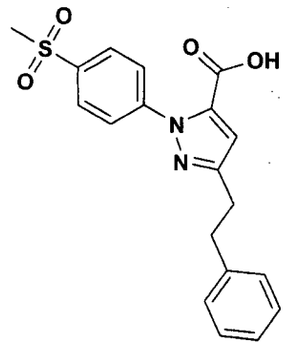
1



2

A una solución del compuesto parte B (117 mg, 0.42 mmol) en AcOH:EtOH (1.5 mL) se agregó (4-(metilsulfonil)fenil)hidrazina (157 mg, 0.84 mmol). La reacción se agitó a 100°C durante 10 h, luego se enfrió a temperatura ambiente y se concentraron *in vacuo*. El residuo se dividió entre EtOAc y 0.2N HCl acuoso. La capa orgánica se lavó con agua y salmuera, se secó ($MgSO_4$), se filtró, y se concentró *in vacuo*. El residuo se procesó por cromatografía (SiO_2; 22 min gradiente continuo de 0% EtOAc/Hexanos hasta 100% EtOAc/Hexanos) para dar el compuesto parte C (20 mg, 12%) y el compuesto parte C2 (95 mg, 57%).

D.

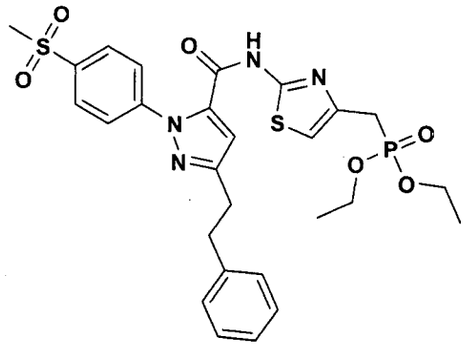


A una solución del compuesto parte C2 (28 mg, 0.07 mmol)

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en THF (1 mL) se agregó NaOH acuoso (0.3 mL de una solución 1M, 0.30 mmol). La reacción se agitó a temperatura ambiente durante 15 h, luego se diluyó con EtOAc (4 mL) y se acidificó con HCl acuoso 1N (0.5 mL). La capa orgánica se lavó con salmuera, se secó ($MgSO_4$) y se concentró *in vacuo* para dar el compuesto parte D (29 mg, 111% crudo).

E.

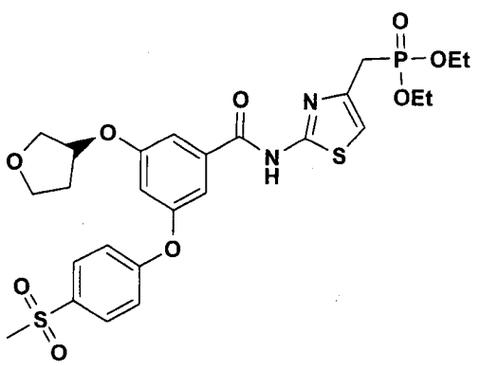


A una solución del Compuesto parte D (25.9 mg, 0.07 mmol) en DMF (1 mL) se agregó el compuesto del ejemplo 13 parte E (35.0 mg, 0.14 mmol), EDCI (26.8 mg, 0.14 mmol), HOBT (21.4 mg, 0.14 mmol) y base Hunig (0.037 mL, 0.21 mmol). La reacción se agitó a temperatura ambiente durante 2 días, luego se concentró *in vacuo*. El residuo se purificó directamente por HPLC preparativa (columna Phenomenex Luna AXIA 30x100 mm; detección a 220 nm; relación de flujo = 40 mL/min; gradiente continuo de 50% A hasta 100% B durante 10 min, donde A = 90:10:0.1 H_2O:MeOH:TFA y B = 90:10:0.1 MeOH:H_2O:TFA) para proporcionar el compuesto del título (7 mg, 17% de rendimiento) como un sólido gris. $[M + H]^+$ =

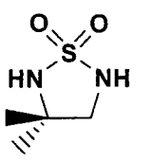
666

603.0; ^{1}H RMN (500 MHz, $CDCl_3$) δ 8.04 (2 H, d, *J*=8.80 Hz), 7.67 (2 H, d, *J*=8.25 Hz), 7.18 - 7.36 (5 H, m), 7.14 (1 H, br. s.), 6.90 (1 H, s), 4.01 - 4.17 (4 H, m), 3.32 (2 H, d, *J*=21.44 Hz), 3.00 - 3.15 (7 H, m), 1.22 - 1.35 (6 H, m).

EJEMPLO 97



A.

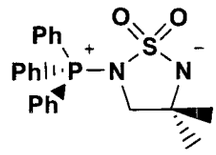


A una solución a reflujo de sulfamida (6.09 mL; 102.0 mmol) en piridina anhidra (109.0 mL) se agregó gota a gota 2-metilpropano-1,2-diamina (10.7 mL; 102.0 mmol) durante 30 min por medio de una bomba de jeringa. La mezcla de reacción se puso a reflujo durante 16 h, luego se enfrió a temperatura ambiente y se concentró *in vacuo*. El residuo se trituró con hexanos hasta que el filtrado se volvió casi incoloro. El sólido resultante se secó *in vacuo* para dar el compuesto parte A (14.89 g, 97%) como un

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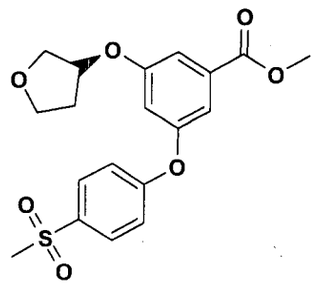
sólido beige.

B.



A una solución agitada de Ph_3P (26.0 g; 99.0 mmol) y el compuesto parte A (14.89 g; 99.0 mmol) en THF anhidro (300 mL) se agregó DIAD (19.3 mL; 99.0 mmol) gota a gota durante 5 min bajo Ar. La mezcla de reacción se agitó a temperatura ambiente durante 16 h. El sólido blanco opaco resultante se filtró completamente, se lavó con THF anhidro y Et_2O anhidro, luego se secó *in vacuo* para dar el compuesto parte B (36.68 g, 90%) como un sólido blanco opaco.

C.

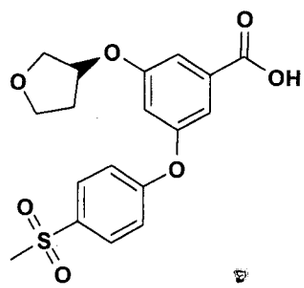


A una suspensión del compuesto parte B (1.4 g, 3.5 mmol) en DCM (6 mL) se agregó una solución del compuesto del ejemplo 26A (141 mg, 0.44 mmol) y (R)-(-)-3-hidroxitetrahidrofurano (0.08 mL, 1.0 mmol) en tolueno (2 mL). La reacción se agitó a temperatura ambiente durante 15 h, luego se diluyó con EtOAc, y se lavó con agua y salmuera.

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La capa orgánica se secó ($MgSO_4$), se filtró, y se concentró *in vacuo*. El residuo se procesó por cromatografía (SiO_2; 19 min gradiente de 0% EtOAc/Hexanos hasta 100% EtOAc/0% Hexanos) para proporcionar el compuesto parte C (254 mg, 148 % de rendimiento).

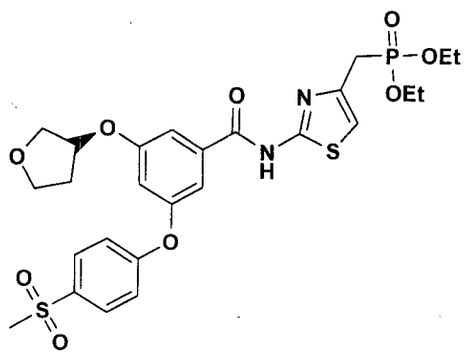
D.



A una mezcla del compuesto parte C (254 mg, 0.65 mmol) en THF (2 mL) se agregó NaOH acuoso 1N (1 mL, 1.0 mmol). La reacción se agitó a temperatura ambiente durante 15 h, luego se diluyó con EtOAc (6 mL) y se acidificó con HCl acuoso 1N (0.5 mL). La capa orgánica se lavó con salmuera, se secó ($MgSO_4$) y se concentró *in vacuo*. El residuo se purificó por HPLC preparativa (columna Phenomenex Luna AXIA 30x100 mm; detección a 220 nm; relación de flujo = 40 mL/min; gradiente continuo de 70% A hasta 100% B durante 10 min, donde A = 90:10:0.1 H_2O:MeOH:TFA y B = 90:10:0.1 MeOH:H_2O:TFA) para dar el compuesto parte D (90 mg, 54% de rendimiento durante 2 etapas) como un aceite incoloro.

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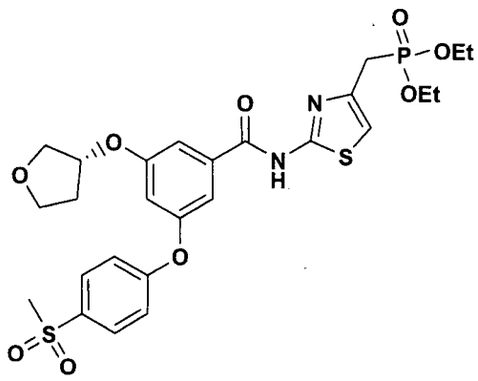
E.



A una solución del Compuesto parte D (43.0 mg, 0.11 mmol) en DMF (1 mL) se agregó el Compuesto del ejemplo 13 parte E (56.9 mg, 0.23 mmol), EDCI (43.6 mg, 0.23 mmol), HOBT (34.8 mg, 0.23 mmol), y Base hunig (0.059 mL, 0.34 mmol). La reacción se agitó a temperatura ambiente durante 24 h y se purificó directamente por HPLC preparativa (columna Phenomenex Luna AXIA 30x100 mm; detección a 220 nm; relación de flujo = 40 mL/min; gradiente continuo de 70% A hasta 100% B durante 10 min, donde A = 90:10:0.1 H_2O:MeOH:TFA y B = 90:10:0.1 MeOH:H_2O:TFA) para proporcionar el compuesto del título (36 mg, 52% de rendimiento) como un sólido blanco. $[M + H]^+$ = 611.3; ^1H RMN (500 MHz, $CDCl_3$) δ 7.94 (2 H, d, *J*=8.80 Hz), 7.63 (1 H, s), 7.49 (1 H, s), 7.16 (2 H, d, *J*=8.80 Hz), 7.07 (1 H, d, *J*=3.85 Hz), 6.91 (1 H, s), 5.22 - 5.33 (1 H, m), 4.12 - 4.24 (4 H, m), 3.85 - 4.08 (4 H, m), 3.37 (2 H, d, *J*=20.89 Hz), 3.08 (3 H, s), 2.08

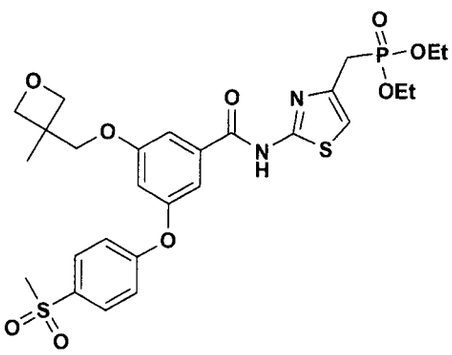
- 2.41 (2 H, m), 1.34 (6 H, t, *J*=7.15 Hz).

EJEMPLO 98



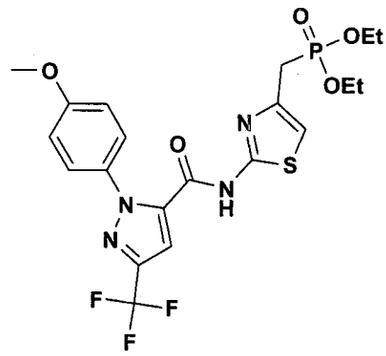
El compuesto del título (10 mg, 16% de rendimiento, sólido blanco) se preparó a partir de (S)-(+)-3-hidroxitetrahidrofurano empleando el mismo procedimiento como se describe para la síntesis del Compuesto del ejemplo 97. $[M + H]^+$ = 611.3; ^{1}H RMN (500 MHz, $CDCl_3$) δ 7.94 (2 H, d, *J*=8.80 Hz), 7.57 (1 H, s), 7.44 (1 H, s), 7.16 (2 H, d, *J*=8.80 Hz), 7.00 (1 H, d, *J*=3.30 Hz), 6.89 (1 H, s), 5.15 - 5.26 (1 H, m), 4.06 - 4.19 (4 H, m), 3.86 - 4.06 (4 H, m), 3.32 (2 H, d, *J*=20.89 Hz), 3.08 (3 H, s), 2.06 - 2.39 (2 H, m), 1.30 (6 H, t, *J*=7.15 Hz).

EJEMPLO 99



El compuesto del título (24 mg, 42% de rendimiento, sólido blanco) se preparó a partir de 3-Metil-3-Oxetano-metanol empleando el mismo procedimiento como se describe para la síntesis del Compuesto del ejemplo 97. $[M + H]^+$ = 625.3; ^1H RMN (500 MHz, $CDCl_3$) δ 7.94 (2 H, d, *J*=8.80 Hz), 7.70 (1 H, s), 7.51 (1 H, s), 7.13 - 7.20 (2 H, m), 7.07 (1 H, d, *J*=3.30 Hz), 6.97 (1 H, s), 4.70 (2 H, d, *J*=6.05 Hz), 4.51 (2 H, d, *J*=6.05 Hz), 4.13 - 4.26 (6 H, m), 3.98 (1 H, s), 3.38 (2 H, d, *J*=21.44 Hz), 3.08 (3 H, s), 1.47 (3 H, s), 1.34 (6 H, t, *J*=7.15 Hz).

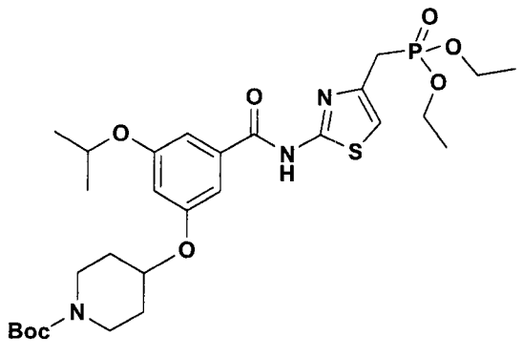
EJEMPLO 100



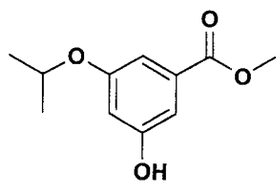
A una solución del ácido 1-(4-metoxifenil)-3-(trifluorometil)-1H-pirazol-5-carboxílico (61 mg, 0.213 mmol) [ver WO 1998/57937] en DMF (1 ml), se agregó el Compuesto del ejemplo 13 parte E (107 mg, 0.426 mmol), EDC (82 mg, 0.426 mmol), HOBT (65.3 mg, 0.426 mmol), y DIPEA (0.111 ml, 0.639 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 4 días. La mezcla de reacción se purificó directamente por HPLC preparativa (columna Phenomenex Luna

AXIA 30x100 mm; detección a 220 nm; relación de flujo = 40 mL/min; gradiente continuo de 50% B hasta 100% B durante 10 min, donde A = 90:10:0.1 H_2O:MeOH:TFA y B = 90:10:0.1 MeOH:H_2O:TFA) para proporcionar el compuesto del título (13 mg, 12% de rendimiento) como un sólido gris. $[M + H]^+$ = 519.0; ^1H RMN (400 MHz, $CDCl_3$) δ 7.59 (1 H, s), 7.33 - 7.46 (2 H, m), 6.91 - 7.02 (2 H, m), 6.80 (1 H, d, *J*=3.52 Hz), 3.99 - 4.15 (4 H, m), 3.86 (3 H, s), 3.51 (2 H, d, *J*=21.53 Hz), 1.26 (6 H, t, *J*=7.03 Hz).

EJEMPLO 101



A.

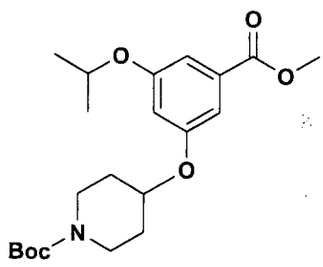


A una solución de 3,5-dihidroxibenzoato de metilo (2.7 g, 16.06 mmol) en CH_3CN (35 mL) se agregó K_2CO_3 (2.70 g, 19.54 mmol), seguido por la adición lenta de 2-bromopropano (1.975 g, 16.06 mmol). La mezcla de reacción se calentó a 80°C durante 3 días. La mezcla de reacción se diluyó con agua y se

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extrajo con EtOAc (3x). La capa orgánica combinada se lavó H_2O y salmuera, se secó ($MgSO_4$), se filtró, y se concentró *in vacuo*. El residuo se purificó por cromatografía de columna (SiO_2; gradiente continuo 15% EtOAc/Hex hasta 60% EtOAc/Hexano) para dar el compuesto parte A (1.22 g, 36% de rendimiento) como un sólido amarillo. $[M + H]^+ = 211.0$; ^1H RMN (400 MHz, $CDCl_3$) δ 1.33 (d, J=6.15 Hz, 6 H), 3.89 (s, 3 H), 4.51 - 4.62 (m, 1 H), 5.21 (s, 1 H), 6.59 (t, J=2.42 Hz, 1 H), 7.08 - 7.12 (m, 1 H), 7.13 - 7.17 (m, 1 H).

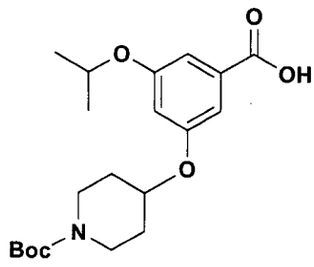
B.



A una solución del compuesto parte A (300 mg, 1.427 mmol) y 4-hidroxipiperidina-1-carboxilato de tert-butilo (1.15 g, 5.7 mmol) en tolueno (2 mL) se agregó una suspensión de Compuesto ejemplo 97B (2.34g, 5.7mmol) en DCM (2 mL). La mezcla de reacción se agitó a temperatura ambiente durante 3 h, luego se concentró *in vacuo*. El residuo se procesó por cromatografía (SiO_2; gradiente continuo de 10% EtOAc/Hex hasta 60% EtOAc/Hexano) para dar el compuesto parte B (490 mg, 87%) como un sólido amarillo ligero. $[M + H]^+ = 294.0$; ^1H RMN (500 MHz, $CDCl_3$) δ 1.32 (d, *J*=6.05 Hz, 6 H), 1.45 (s, 9 H), 1.66 - 1.78 (m, 2 H), 1.85 - 1.96 (m, 2 H), 3.26 - 3.38

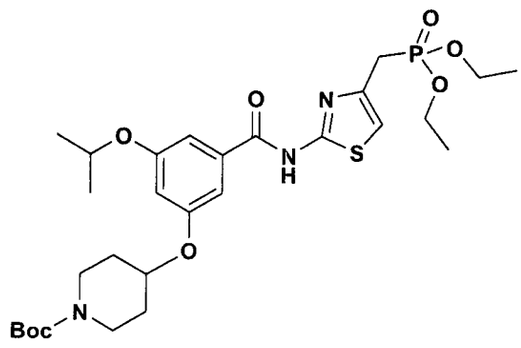
(m, 3 H), 3.62 - 3.72 (m, 3 H), 3.86 - 3.90 (m, 3 H), 4.44 - 4.51 (m, 1 H), 4.52 - 4.62 (m, 1 H), 6.61 (t, *J*=2.20 Hz, 1 H), 7.10 - 7.19 (m, 2 H).

C.



A una solución a 0°C del compuesto parte B (490mg, 1.245 mmol) en THF/agua (1/1, 4 mL) se agregó $LiOH.H_2O$ (209 mg, 4.98 mmol). La mezcla se agitó a temperatura ambiente durante 18 h, luego se diluyó con EtOAc y se acidificó con HCl acuoso 1N hasta pH~4-5. La capa acuosa se extrajo con EtOAc (2x). Los extractos orgánicos combinados se lavaron con HCl acuoso 1N, H_2O, y salmuera, se secaron ($MgSO_4$) y se concentraron *in vacuo* para proporcionar el compuesto parte C (440 mg, 93% de rendimiento) como un sólido blanco. $[M + H]^+ = 561.1$.

D.

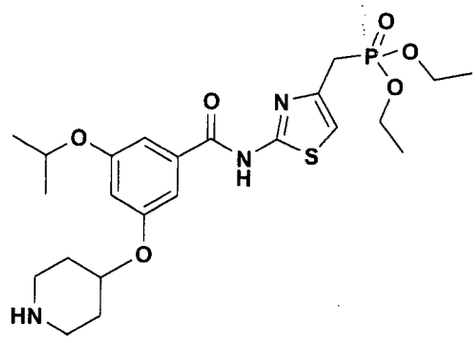


A una solución del compuesto parte C (200mg, 0.527 mmol)

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y el compuesto del ejemplo 13 parte E (132 mg, 0.527 mmol) (amortiguado con DIEA) en DCM/DMF (1/1) se agregó sucesivamente HOAT (201 mg, 1.476 mmol), EDCI (202 mg, 1.054 mmol), y DIEA (641 µL, 3.69 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 18 h, luego se diluyó con DCM. La capa orgánica se lavó con agua (2x) y salmuera, se secó ($MgSO_4$) y se concentró *in vacuo*. El residuo se procesó por cromatografía (SiO_2; gradiente continuo 0% DCM/MeOH hasta 5% DCM/MeOH) para dar el compuesto del título (140 mg, 43% de rendimiento) como un sólido blanco. $[M + H]^+$ = 612; ^1H RMN (500 MHz, $CDCl_3$) δ 1.26 (t, *J*=7.15 Hz, 6 H), 1.33 (d, *J*=6.05 Hz, 6 H), 1.45 (s, 9 H), 1.63 (s, 2 H), 1.67 - 1.80 (m, 2 H), 1.92 (dd, *J*=12.65, 3.85 Hz, 2 H), 3.21 - 3.39 (m, 4 H), 3.63 - 3.76 (m, 2 H), 4.00 - 4.14 (m, 4 H), 4.44 - 4.53 (m, 1 H), 4.53 - 4.62 (m, 1 H), 6.63 (t, *J*=2.20 Hz, 1 H), 6.84 (d, *J*=3.85 Hz, 1 H), 8.00 (s, 1 H).

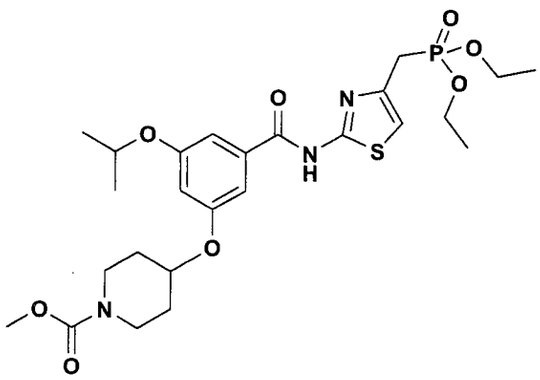
EJEMPLO 102



A una solución del Compuesto del ejemplo 101 (15mg, 0.025mmol) en DCM (0.5 mL) se agregó TFA (0.15 mL). La mezcla

de reacción se agitó a temperatura ambiente durante 2 h, luego se concentró *in vacúo*. El residuo se purificó por HPLC preparativa (Columna Phenomenex AXIA 5u C18 30 x 100 mm; detección a 220 nm; relación de flujo = 40 mL/min; gradiente continuo de 35% B hasta 100% B durante 10 min, donde A = 90:10:0.1 H_2O:MeOH:TFA y B = 90:10:0.1 MeOH:H_2O:TFA) dio el compuesto del título (11 mg, 85% de rendimiento) como un sólido blanco. $[M + H]^+$ = 512; ^1H RMN (500 MHz, $CDCl_3$) δ 1.29 (t, *J*=7.15 Hz, 6 H), 1.33 (d, *J*=5.50 Hz, 6 H), 2.08 - 2.16 (m, 2 H), 2.16 - 2.26 (m, 2 H), 3.22 (d, *J*=9.90 Hz, 2 H), 3.30 (d, *J*=21.44 Hz, 2 H), 3.35 (d, *J*=7.70 Hz, 2 H), 4.02 - 4.17 (m, 4 H), 4.60 - 4.73 (m, 1 H), 4.82 (s, 1 H), 6.69 (t, *J*=2.20 Hz, 1 H), 6.96 (d, *J*=3.30 Hz, 1 H), 7.36 (d, *J*=8.80 Hz, 2 H), 9.37 (s, 1 H), 9.47 (s, 1 H).

EJEMPLO 103

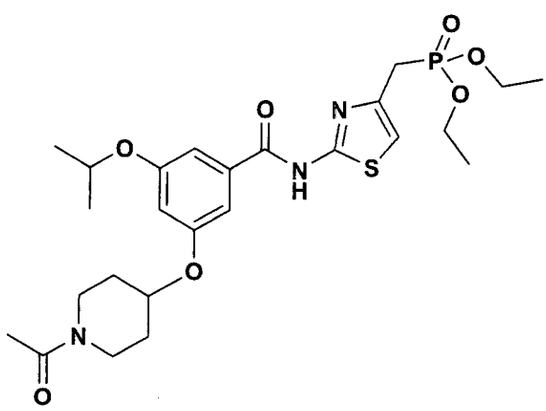


A una solución del Compuesto del ejemplo 102 (30 mg, 0.059 mmol) en THF (1 mL) y $NaHCO_3$ acuoso saturado (1 mL) se agregó cloroformiato de metilo (6.77 µL, 0.088 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 18

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h, luego se diluyó con EtOAc. La capa acuosa se extrajo con EtOAc (2x), y los extractos orgánicos combinados se concentraron *in vacuo*. El residuo se purificó por HPLC preparativa (Columna Phenomenex AXIA 5u C18 30 x 100 mm; detección a 220 nm; relación de flujo = 40 mL/min; gradiente continuo de 35% B hasta 100% B durante 10 min, donde A = 90:10:0.1 H_2O:MeOH:TFA y B = 90:10:0.1 MeOH:H_2O:TFA) para dar el compuesto del título (16mg, 48% de rendimiento) como un sólido blanco. $[M + H]^+$ = 570.3; ^1H RMN (500 MHz, $CDCl_3$) δ 1.30 (t, *J*=7.15 Hz, 6 H), 1.33 (d, *J*=6.05 Hz, 6 H), 1.76 (s, 2 H), 1.91 (s, 2 H), 3.31 (d, *J*=20.89 Hz, 2 H), 3.31 (d, *J*=20.89 Hz, 2 H), 3.44 (s, 2 H), 3.66 (d, *J*=5.50 Hz, 2 H), 3.69 (s, 3 H), 4.10 - 4.17 (m, 4 H), 4.64 - 4.75 (m, 2 H), 6.69 (t, *J*=2.20 Hz, 1 H), 7.01 (d, *J*=3.30 Hz, 1 H), 7.33 (dd, *J*=4.67, 1.92 Hz, 2 H).

EJEMPLO 104

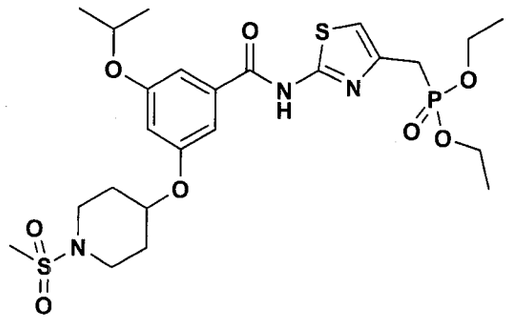


A una solución del Compuesto del ejemplo 102 (30 mg, 0.059 mmol) en DCM (1 mL) se agregó piridina (0.1 mL) y

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cloruro de acetilo (6.90 mg, 0.088 mmol). La reacción se agitó a temperatura ambiente durante 18 h, luego se diluyó con EtOAc. La capa acuosa se extrajo con EtOAc (2x), y los extractos orgánicos combinados se concentraron *in vacuo*. El residuo se purificó por HPLC preparativa (Columna Phenomenex AXIA 5u C18 30 x 100 mm; detección a 220 nm; relación de flujo = 40 mL/min; gradiente continuo de 35% B hasta 100% B durante 10 min, donde A = 90:10:0.1 H_2O:MeOH:TFA y B = 90:10:0.1 MeOH:H_2O:TFA) para dar el compuesto del título (22 mg, 68% de rendimiento) como un sólido blanco. $[M + H]^+$ = 554.4; ^1H RMN (500 MHz, $CDCl_3$) δ 1.34 (t, *J*=7.15 Hz, 6 H), 1.36 (d, *J*=6.05 Hz, 6 H), 1.79 - 2.04 (m, 4 H), 2.17 (s, 3 H), 3.36 (d, *J*=21.44 Hz, 2 H), 3.43 - 3.54 (m, 1 H), 3.63 - 3.86 (m, 3 H), 4.12 - 4.24 (m, 4 H), 4.68 - 4.86 (m, 2 H), 6.73 (s, 1 H), 7.06 (d, *J*=3.30 Hz, 2 H), 7.39 (s, 2 H).

EJEMPLO 105

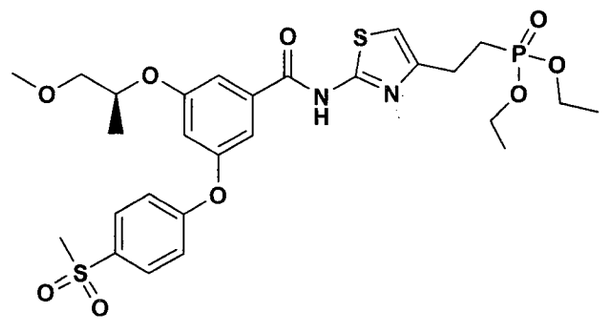


Una solución del Compuesto del ejemplo 102 (50 mg, 0.098 mmol) y Et_3N (10 mg, 0.098 mmol) en DCM (0.5 mL) se agregó a una solución de cloruro de metansulfonilo (11.20 mg, 0.098

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mmol) en DCM (0.5mL). La reacción se agitó a temperatura ambiente durante 18 h, luego se diluyó con EtOAc. La capa acuosa se extrajo con EtOAc (2x), y los extractos orgánicos combinados se concentraron *in vacuo*. El residuo se purificó por HPLC preparativa (columna Phenomenex AXIA 5µm C18 30 x 100 mm; detección a 220 nm; relación de flujo = 40 mL/min; gradiente continuo de 35% B hasta 100% B durante 10 min, donde A = 90:10:0.1 H_2O:MeOH:TFA y B = 90:10:0.1 MeOH:H_2O:TFA) para dar el compuesto del título (19.5 mg, 34% de rendimiento) como un aceite incoloro. $[M + H]^+$ = 590.3; ^1H RMN (500 MHz, $CDCl_3$) δ 1.28-1.38 (m,12H), 1.93-2.10 (m, 4 H), 2.97(s, 3H), 3.29-3.40 (m, 6 H), 4.12 - 4.22(m, 4 H), 4.68 - 4.75 (m, 2 H), 6.70 (t, *J*=2.20 Hz, 1 H), 7.03(d, *J*=3.85 Hz, 1 H), 7.337 (d, 1.10 Hz, 2 H).

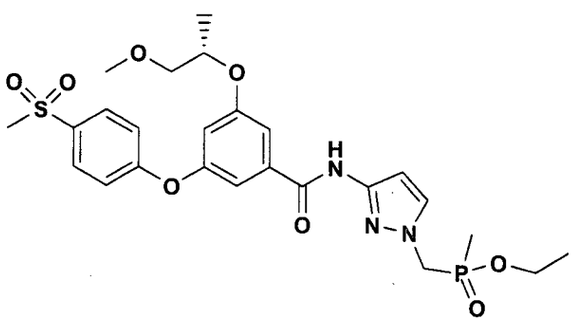
EJEMPLO 106



A una solución del Compuesto del ejemplo 26 parte C (25.0 mg; 0.066 mmol), Compuesto del ejemplo 18 parte D (20.9 mg; 0.079 mmol), y HOAt (10.3 mg; 0.076 mmol) en DMF (0.25 mL) se agregó sucesivamente DIPEA (13.2 µL; 0.076 mmol) y

EDAC (14.6 mg; 0.076 mmol). La reacción se agitó a temperatura ambiente durante 20 h, luego se dividió entre EtOAc (4 mL) y H_2O (3 mL). La capa orgánica se lavó con 0.5 N HCl acuoso (3 mL), $NaHCO_3$ acuoso saturado (3 mL), y salmuera (3 mL), se secó ($MgSO_4$) y se concentró *in vacuo*. El residuo se purificó por HPLC preparativa (columna YMC fase inversa ODS-A-5µm 20 x 100 mm; relación de flujo = 20 mL/min, hasta 100% solvente B durante 10 min, mantenido a 14 min, donde solvente A = 90:10:0.1 H_2O:MeOH:TFA y solvente B = 90:10:0.1 MeOH:H_2O:TFA) para dar el compuesto del título (22.0 mg; 54%) como un sólido amarillo ligero. $[M + H]^+$ = 627.1; ^1H RMN (400 MHz, $CDCl_3$): δ 1.34 (m, 9H), 2.19 (m, 2H), 3.07 (m, 5H), 3.41 (s, 3H), 3.57 (m, 2H), 4.12 (m, 4H), 4.89 (m, 1H), 6.81 (s, 1H), 6.94 (s, 1H), 7.15 (d, 2H), 7.44 (s, 1H), 7.69 (s, 1H), 7.92 (d, 2H).

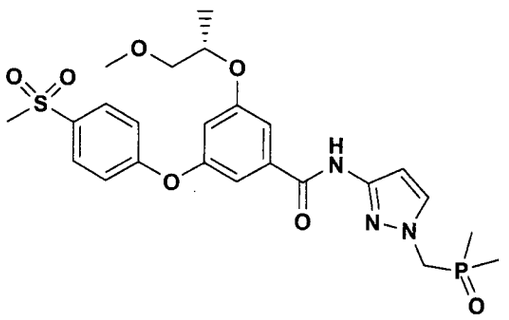
EJEMPLO 107



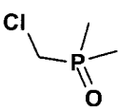
El compuesto del título (20 mg, 65% de rendimiento, sólido blanco) se preparó a partir de (3-amino-1H-pirazol-1-il)metil(metil)fosfinato de etilo racémico empleando la misma secuencia general usada para preparar el ejemplo 58. $[M + H]^+$

= 566.3; ^{1}H RMN (400 MHz, CD_3OD): δ 1.33 (d, J = 6.6 Hz, 3H), 1.34 (t, J = 6.6 Hz, 3H), 1.57 (d, J = 14.3 Hz, 3H), 3.01 (s, 3H), 3.42 (s, 3H), 3.53-3.63 (m, 2H), 4.08-4.21 (m, 2H), 4.52 (dd, J = 2.4, 6.0 Hz, 2H), 4.71 (m, 1H), 6.86 (d, J = 2.2 Hz, 1H), 7.03 (s, 1H), 7.14 (d, J = 8.8 Hz, 2H), 7.24 (s, 1H), 7.39 (s, 1H), 7.52 (d, J = 2.2 Hz, 1H), 7.91 (d, J = 8.8 Hz, 2H).

EJEMPLO 108



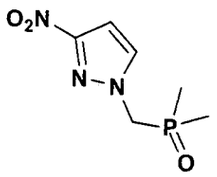
A.



A una solución agitada a 10°C de cloruro de clorometil(metil)fosfínico (2 g, 13.61 mmol) en Et_2O (10 mL) se agregó gota a gota MeMgBr (4.54 mL de una solución 3M en Et_2O, 13.61 mmol). La reacción se volvió turbia y gomosa, luego se calentó lentamente a temperatura ambiente durante 1 h. Los volátiles se removieron *in vacuo* y el residuo se apagó cuidadosamente con $NaHCO_3$ acuoso saturado y se extrajo con $CHCl_3$ (4×). Los extractos orgánicos combinados se secaron ($MgSO_4$) y se concentraron *in vacuo*. El aceite transparente

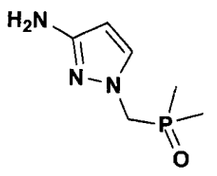
resultante se agregó en hexanos (50 mL); una forma de precipitado blanco. El precipitado se filtró para colectar el sólido blanco (agujas cristalinas, finas) como el compuesto parte A (360 mg, 21%).

B.



A una solución agitada de 3-nitro-1H-pirazol (45 mg, 0.398 mmol) en DMF (2 mL) se agregó K_2CO_3 (70 mg, 0.506 mmol) y el compuesto parte A (70 mg, 0.553 mmol). La reacción se agitó a 75°C durante 16 h, luego se enfrió a temperatura ambiente y se dividió entre EtOAc y NH_4Cl acuoso saturado. La capa acuosa se extrajo con $CHCl_3$ (10×), y los extractos orgánicos combinados se secaron ($MgSO_4$) y se concentraron *in vacuo* para dar el compuesto parte B (50 mg, 62% de rendimiento) como un sólido blanco.

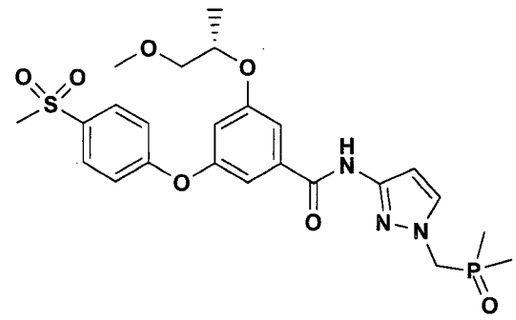
C.



A una solución agitada del compuesto parte B (50 mg, 0.246 mmol) en MeOH (3 mL) se agregó Pd/C (26.2 mg, 0.025 mmol). La reacción se agitó bajo una atmósfera de H_2 (globo) durante 1 h, luego se filtró a través de Celite® y se

concentró *in vacuo* para dar el compuesto parte C (35 mg, 82%) como un aceite amarillo ligero.

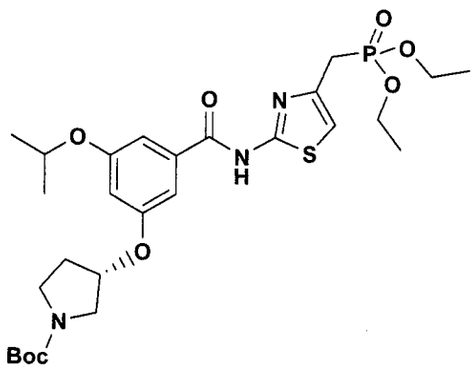
D.



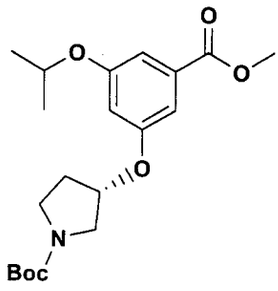
A una solución agitada del ácido del ejemplo 26 parte C (77 mg, 0.202 mmol) en DMF (2 mL) se agregó HOBT (55.0 mg, 0.404 mmol), EDC (77 mg, 0.404 mmol), y Base Hunig (0.106 mL, 0.606 mmol). La reacción se agitó a temperatura ambiente durante 30 min, después de lo cual el compuesto parte C (35 mg, 0.202 mmol) se agregó. La reacción se agitó a temperatura ambiente durante 20 h, luego se dividió entre HCl acuoso 1N y CH_2Cl_2. La fase orgánica se lavó con NH_4Cl acuoso saturado y salmuera, se secó ($MgSO_4$) y se concentró *in vacuo*. El residuo se purificó por HPLC preparativa (columna Luna 5µm 21.2 x 100 mm; relación de flujo = 20 mL/min, 0 hasta 100% solvente B durante 12 min, mantenido a 15 min, donde solvente A = 90:10:0.1 H_2O:MeOH:TFA y solvente B = 90:10:0.1 MeOH:H_2O:TFA) para dar el compuesto del título (59 mg, 55% de rendimiento) como un sólido blanco. $[M + H]^+$ = 536.3; ^1H RMN (400 MHz, CD_3OD): δ 1.31 (d, J = 6.9 Hz, 3H), 1.64 (d, J = 13.2 Hz, 6H), 2.99 (s, 3H), 3.40 (s, 3H), 3.48-3.61 (m, 2H), 4.60 (d,

J = 6.6 Hz, 2H), 4.68 (m, 1H), 6.84 (s, 1H), 6.96 (d, J = 2.2 Hz, 1H), 7.11 (d, J = 8.8 Hz, 2H), 7.21 (s, 1H), 7.34 (s, 1H), 7.52 (d, J = 2.2 Hz, 1H), 7.88 (d, J = 8.8 Hz, 2H).

EJEMPLO 109



A.

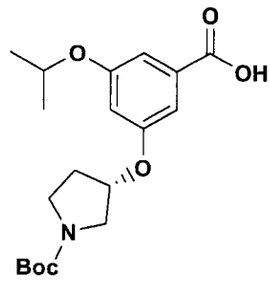


A una solución del compuesto del ejemplo 101 parte A (300 mg, 1.427 mmol) y (R) tert-butil-3-hidroxipirrolidina-carboxilato (534m g, 2.85 mmol) en tolueno (2 mL) se agregó una suspensión del Compuesto del ejempo 97 parte B (1.17g, 2.85 mmol) en DCM (2 mL). La mezcla de reacción se agitó a temperatura ambiente durante 3 h, luego se concentró *in vacuo*. El residuo se procesó por cromatografía (SiO_2; gradiente continuo 10% EtOAc/Hex hasta 60% EtOAc/Hexano) para dar el compuesto parte A (500 mg, 92%) como un sólido blanco.

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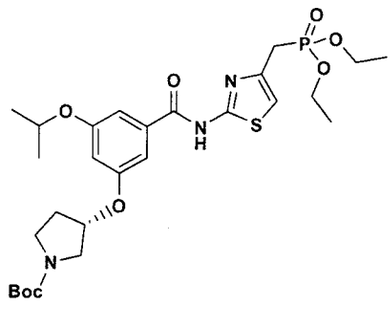
$[M + H]^+$ = 402; ^1H RMN (400 MHz, $CDCl_3$) δ 1.25 (d, *J*=6.15 Hz, 6 H), 1.39 (d, *J*=7.47 Hz, 9 H), 1.95 - 2.22 (m, 2 H), 3.25 - 3.46 (m, 4 H), 3.47 - 3.58 (m, 1 H), 3.82 (s, 3 H), 4.61 - 4.73 (m, 1 H), 5.07 (s, 1 H), 6.76 (t, *J*=2.42 Hz, 1 H), 7.00 (s, 1 H), 7.03 (s, 1 H).

B.



A una solución a 0°C del compuesto parte A (500 mg, 1.318 mmol) en THF/agua (1/1, 4 mL) se agregó $LiOH.H_2O$ (270 mg, 6.59 mmol). La mezcla se agitó a temperatura ambiente durante 18 h, luego se diluyó con EtOAc y se acidificó con HCl acuoso 1N hasta pH~4-5. La capa acuosa se extrajo con EtOAc (2x). Los extractos orgánicos combinados se lavaron con HCl acuoso 1N, H_2O, y salmuera, se secaron ($MgSO_4$) y se concentraron *in vacuo* para proporcionar el compuesto parte B (480 mg, 100% de rendimiento) como un sólido blanco. EM $[M - H]^-$ = 364.4.

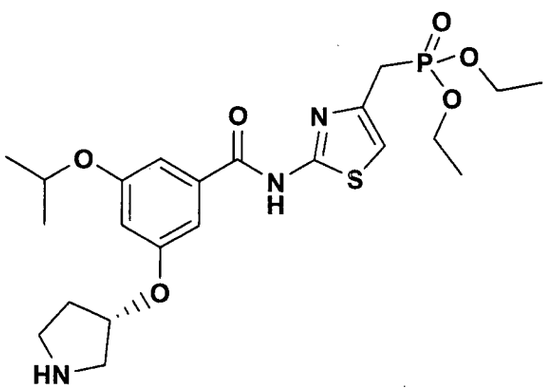
C.



A una solución del compuesto parte B (200 mg, 0.547

mmol) y compuesto del ejemplo 13 parte E (137 mg, 0.547 mmol) en DCM/DMF (1/1; amortiguada con DIEA) se agregó sucesivamente HOAT (208 mg, 1.53mmol), EDCI (210 mg, 1.094 mmol), y DIPEA (665 µL, 3.83 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 18 h, luego se diluyó con DCM. La fase orgánica se lavó con agua (2x) y salmuera, se secó ($MgSO_4$), y se concentró *in vacuo*. El residuo se procesó por cromatografía (SiO_2; gradiente continuo de 0% DCM/MeOH hasta 5% DCM/MeOH) para dar el compuesto del título (160 mg, 49% de rendimiento) como un sólido blanco. $[M + H]^+$ = 598.3; ^1H RMN (500 MHz, $CDCl_3$) δ 1.26 (t, J=7.15 Hz, 6 H), 1.33 (d, J=6.05 Hz, 6 H,) 1.45 (s, 9 H), 1.64 (s, 2 H), 2.02 - 2.24 (m, 2 H), 3.28 (d, J=21.44 Hz, 2 H), 3.41 - 3.70 (m, 4 H), 4.01 - 4.16 (m, 4 H), 4.51 - 4.63 (m, 1 H), 6.98 (s, 1 H), 7.03 (s, 1 H), 9.71 (s, 1 H).

EJEMPLO 110

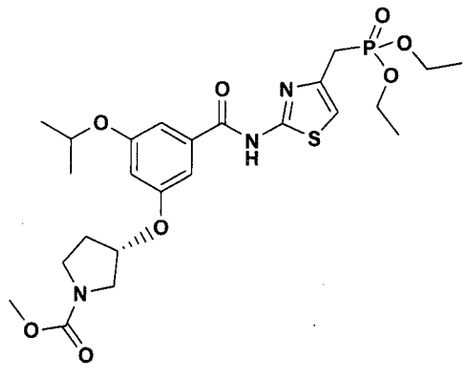


El compuesto del título (10.4 mg, 71% de rendimiento, sólido blanco) se preparó a partir del

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Compuesto del ejemplo 109 empleando la misma secuencia general usada para preparar el ejemplo 102. $[M + H]^+$ = 498.0; ^1H RMN (500 MHz, $CDCl_3$) δ 1.24 - 1.29 (m, 6 H), 1.32 (d, *J*=6.05 Hz, 6 H), 2.22 - 2.44 (m, 2 H), 3.26 (d, *J*=21.44 Hz, 2 H), 4.01 - 4.16 (m, 4 H), 4.58 - 4.70 (m, 1 H), 5.24 (s, 1 H), 6.66 (s, 1 H), 6.93 (d, *J*=3.30 Hz, 1 H), 7.29 (s, 1 H), 7.33 (s, 1 H), 9.81 (s, 1 H), 10.30 (s, 1 H).

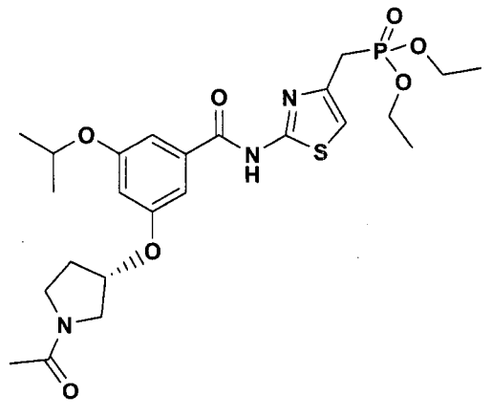
EJEMPLO 111



El compuesto del título (22.5 mg, 68% de rendimiento, aceite incoloro) se preparó a partir del Compuesto del ejemplo 110 empleando la misma secuencia general usada para preparar el ejemplo 103. $[M + H]^+$ = 556.3; ^1H RMN (500 MHz, $CDCl_3$) δ 1.29 - 1.35 (m, 12 H), 2.13 (s, 1 H), 2.20 (s, 1 H), 3.35 (d, *J*=21.44 Hz, 2 H), 3.48 - 3.65 (m, *J*=28.04 Hz, 4 H), 3.70 (d, *J*=11.55 Hz, 4 H), 4.13 - 4.20 (m, 4 H), 4.64 - 4.74 (m, 1 H), 5.14 (s, 1 H), 6.66 (t, *J*=1.92 Hz, 1 H), 7.03 (d, *J*=3.30 Hz, 1 H), 7.31 - 7.41 (m, 2 H).

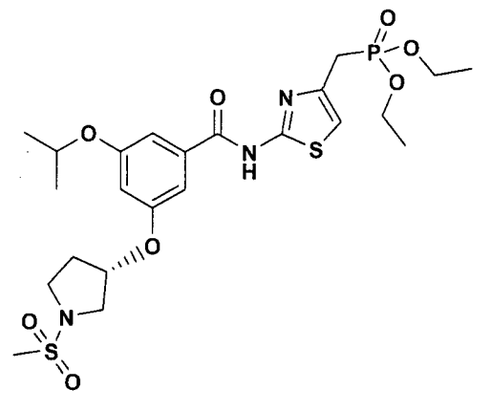
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EJEMPLO 112



El compuesto del título (24 mg, 74% de rendimiento, aceite amarillo ligero) se preparó a partir del Compuesto del ejemplo 110 empleando la misma secuencia general usada para preparar el ejemplo 104. $[M + H]^+$ = 540.4; ^1H RMN (500 MHz, $CDCl_3$) δ 1.32 - 1.35 (m, 6 H), 1.35 - 1.39 (m, 6 H), 2.09 - 2.20 (m, *J*=23.09 Hz, 3 H), 2.21 - 2.43 (m, 2 H), 3.37 (d, *J*=21.44 Hz, 2 H), 3.55 - 3.92 (m, 4 H), 4.13 - 4.24 (m, 4 H), 4.66 - 4.76 (m, 1 H), 5.19 - 5.30 (m, 1 H), 6.67 - 6.72 (m, 1 H), 7.07 (d, *J*=3.85 Hz, 1 H), 7.39 (s, 1 H), 7.40 - 7.44 (m, 1 H).

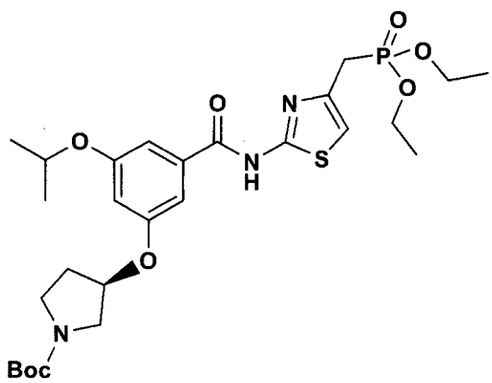
EJEMPLO 113



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El compuesto del título (28 mg, 43% de rendimiento, sólido blanco) se preparó a partir del Compuesto del ejemplo 110 empleando la misma secuencia general usada para preparar el ejemplo 105. $[M + H]^+$ = 576.3; ^1H RMN (500 MHz, $CDCl_3$) δ 1.32 (t, *J*=7.15 Hz, 6 H), 1.35 (dd, *J*=6.05, 1.10 Hz, 6 H), 2.17 - 2.37 (m, 2 H), 2.83 (s, 3 H), 3.34 (d, *J*=20.89 Hz, 2 H), 3.42 - 3.52 (m, 1 H), 3.54 - 3.71 (m, 3 H), 4.11 - 4.23 (m, 4 H), 4.65 - 4.77 (m, 1 H), 5.16 (s, 1 H), 6.64 (t, *J*=2.20 Hz, 1 H), 7.35 (s, 1 H), 7.41 (d, *J*=3.30 Hz, 1 H).

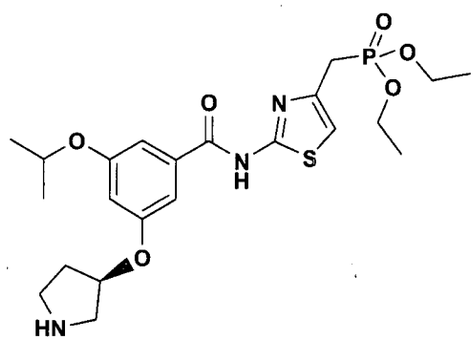
EJEMPLO 114



El compuesto del título (176 mg, 32% de rendimiento, sólido blanco) se preparó a partir de (S) tert-butil-3-hidroxipirrolidina-carboxilato empleando la misma secuencia general usada para preparar el ejemplo 109. $[M + H]^+$ = 598.4; ^1H RMN (500 MHz, $CDCl_3$) δ 1.26 (t, *J*=7.15 Hz, 6 H), 1.34 (d, *J*=5.50 Hz, 6 H), 1.45 (s, 9 H), 1.63 (s, 2 H), 2.00 - 2.27 (m, 2 H), 3.28 (d, *J*=20.89 Hz, 2 H), 3.39 - 3.70 (m, 4 H), 3.99 - 4.18 (m, 4 H), 4.50 - 4.66 (m, 1 H), 4.91 (s, 1 H), 6.59 (s, 1 H), 6.84 (s, 1 H), 6.96 - 7.10 (m, 2 H).

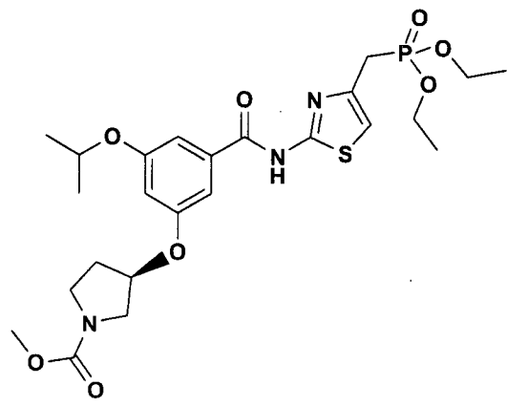
090690

EJEMPLO 115



El compuesto del título (13.4 mg, 67% de rendimiento, sólido blanco) se preparó a partir del Compuesto del ejemplo 114 empleando la misma secuencia general usada para preparar el ejemplo 110. $[M + H]^+$ = 498.3; ^1H RMN (500 MHz, $CDCl_3$) δ 1.22 - 1.28 (m, 6 H), 1.32 (d, *J*=6.05 Hz, 6 H), 2.24 - 2.40 (m, 2 H), 3.24 (d, *J*=21.44 Hz, 2 H), 3.41 - 3.69 (m, 4 H), 3.97 - 4.13 (m, 4 H), 4.56 - 4.69 (m, 1 H), 5.22 (s, 1 H), 6.64 (t, *J*=2.20 Hz, 1 H), 6.89 (d, *J*=3.85 Hz, 1 H), 7.28 (s, 1 H), 7.32 (s, 1 H).

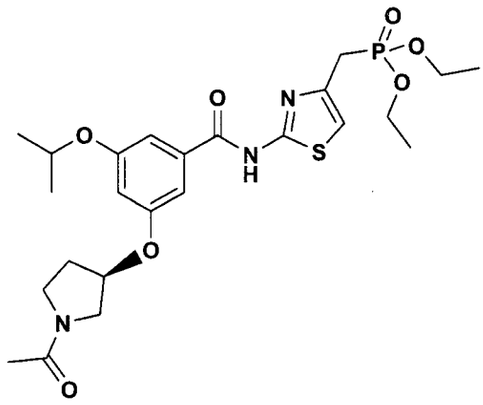
EJEMPLO 116



El compuesto del título (32.5 mg, 83% de rendimiento, aceite incoloro) se preparó a partir del Compuesto del

ejemplo 115 empleando la misma secuencia general usada para preparar el ejemplo 111. $[M + H]^+$ = 554; ^1H RMN (500 MHz, $CDCl_3$) δ 1.29 - 1.32 (m, 6 H), 1.33 (d, *J*=5.50 Hz, 6 H), 2.05 - 2.28 (m, 2 H), 3.35 (d, *J*=21.44 Hz, 2 H), 3.45 - 3.74 (m, 7 H), 4.11 - 4.22 (m, 4 H), 4.65 - 4.74 (m, 1 H), 5.14 (s, 1 H), 6.66 (t, *J*=1.92 Hz, 1 H), 7.03 (d, *J*=3.30 Hz, 1 H), 7.33 (s, 1 H), 7.38 (s, 1 H).

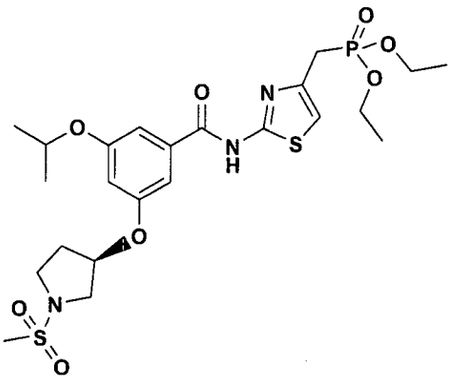
EJEMPLO 117



El compuesto del título (28.5 mg, 75% de rendimiento, aceite amarillo ligero) se preparó a partir de Compuesto del ejemplo 115 empleando la misma secuencia general usada para preparar el ejemplo 112. $[M + H]^+$ = 540.2; ^1H RMN (500 MHz, $CDCl_3$) δ 1.29 - 1.32 (m, 6 H), 1.32 - 1.36 (m, 6 H), 2.12 (d, *J*=23.09 Hz, 3 H), 2.19 - 2.39 (m, 2 H), 3.34 (d, *J*=21.44 Hz, 2 H), 3.55 - 3.88 (m, 4 H), 4.11 - 4.21 (m, 4 H), 4.64 - 4.73 (m, 1 H), 5.17 - 5.28 (m, 1 H), 6.64 - 6.69 (m, 1 H), 7.04 (d, *J*=2.75 Hz, 1 H), 7.35 (d, *J*=1.10 Hz, 1 H), 7.39 (d, *J*=9.35 Hz, 1 H).

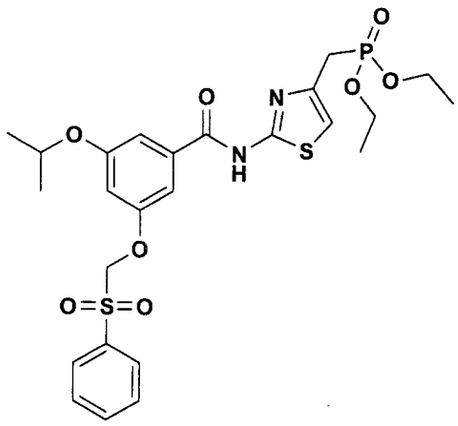
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EJEMPLO 118

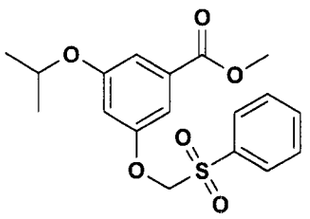


El compuesto del título (12 mg, 30% de rendimiento, aceite amarillo ligero) se preparó a partir del Compuesto del ejemplo 115 empleando la misma secuencia general usada para preparar el ejemplo 113. $[M + H]^+$ = 576.2; ^1H RMN (500 MHz, $CDCl_3$) δ 1.31 - 1.34 (m, 6 H), 1.36 (d, *J*=6.05 Hz, 6 H), 2.08 - 2.39 (m, 2 H), 2.85 (s, 3 H), 3.37 (d, *J*=21.44 Hz, 2 H), 3.44 - 3.54 (m, 1 H), 3.56 - 3.72 (m, 3 H), 4.13 - 4.25 (m, 4 H), 4.68 - 4.80 (m, 1 H), 5.18 (s, 1 H), 6.66 (s, 1 H), 7.07 (d, *J*=3.30 Hz, 1 H), 7.37 (s, 1 H), 7.43 (s, 1 H).

EJEMPLO 119



A.

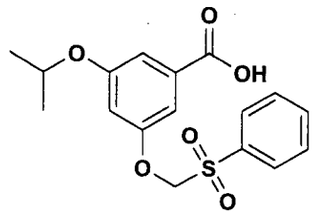


A una solución a temperatura ambiente del éster del ejemplo 101 parte A (94.7 mg, 0.450 mmol) en MeCN (2.2 mL) bajo Ar se agregó 1,4,7,10,13,16-hexaoxaciclooctadecano (16 mg, 0.061 mmol), K_2CO_3 (178 mg, 1.288 mmol), y bromometil fenil sulfona (120 mg, 0.510 mmol). La mezcla se calentó a 70°C durante 6 h, luego a 90°C durante 4 h. El DMF (1 mL) se agregó, y la reacción se calentó a 115°C durante 24 h. Después de 24 horas, más bromometil fenil sulfona (90 mg, 0.382 mmol) se agregó, y la reacción se agitó a 115°C durante 3 días, luego se enfrió a temperatura ambiente y se agitó a temperatura ambiente durante 2 días. La mezcla café oscura se dividió entre EtOAc y $NaHCO_3$ acuoso saturado. La capa orgánica se lavó con $NaHCO_3$ acuoso saturado, agua, y salmuera, se secó (Na_2SO_4), y se concentró *in vacuo*. El residuo se procesó por cromatografía (SiO_2, 12 g, eluido de 0-10%, luego 35% EtOAc:hexanos, finalmente se mojó con 100% EtOAc) para dar el compuesto parte A impuro (70 mg) como un aceite. El residuo se purificó además por HPLC preparativa (Phenomenex AXIA Luna 5µ, 75x30mm, detección a 220 nm; relación de flujo = 40 mL/min; gradiente continuo de 40% A

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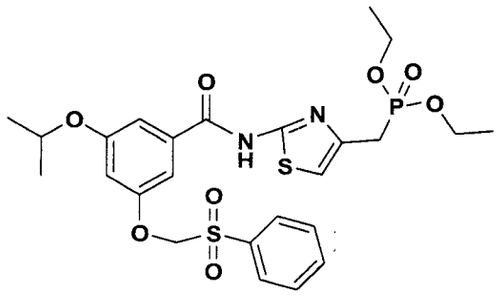
hasta 100% B durante 15 min +3 min tiempo de espera a 100% B, donde A = 90:10:0.1 H_2O:CH_3CN:TFA y B = 90:10:0.1 CH_3CN:H_2O:TFA) para dar el compuesto parte A (9.2 mg, 5.5%) como un sólido aceitoso.

B.



A una solución a temperatura ambiente del compuesto parte A (9 mg, 0.025 mmol) en THF (0.2 mL) y MeOH (0.1 mL) bajo Ar se agregó LiOH acuoso 4N (0.062 mL, 0.247 mmol). La reacción se agitó a temperatura ambiente durante 8 h, luego se almacenó a -20°C durante 18 h. Después de se calentó a temperatura ambiente y se diluyó con EtOAc, los volátiles se removieron *in vacuo* para dar un sólido incoloro. El residuo se suspendió en agua, hasta pH 1 con HCl acuoso 1N (0.3 mL), y la capa acuosa se extrajo con EtOAc (2x). Los extractos orgánicos combinados se lavaron con salmuera, se secaron (Na_2SO_4) y se concentraron *in vacuo* para dar el compuesto parte B (10.6 mg, >100% recuperación) como un sólido incoloro.

C.



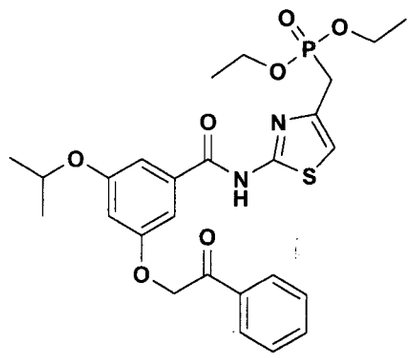
001655

Al ácido parte B (8.76 mg, 0.025 mmol) se agregó una solución a temperatura de la amina del ejemplo 13 parte E (21 mg, 0.084 mmol) en CH_2Cl_2 (0.800 mL) bajo Ar. A la mezcla resultante se agregó iPr_2NEt (0.030 mL, 0.175 mmol) seguido por la adición de HATU (14.2 mg, 0.037 mmol). La solución se agitó a temperatura ambiente durante 18 h, después de lo cual otra porción de la amina del ejemplo 13 parte E (15 mg, 0.06 mmol) se agregó, y se continuó agitando a temperatura ambiente durante 18 h. La reacción se dividió entre EtOAc y $NaHCO_3$ acuoso saturado después de agitarse durante 15 min. La capa orgánica se lavó con $NaHCO_3$ acuoso saturado y salmuera, se secó (Na_2SO_4), y se concentró *in vacuo*. El residuo se purificó por HPLC preparativa (columna Phenomenex Luna 5µm 21.2x100mm, detección a 220 nm; relación de flujo = 20 mL/min; gradiente continuo de 60% A hasta 100% B durante 10 min +2 min tiempo de espera a 100% B, donde A = 90:10:0.1 H_2O:MeOH:TFA y B = 90:10:0.1 MeOH:H_2O:TFA). Este material se purificó además por HPLC preparativa (Phenomenex Luna, 5 micron 21.2x100mm, detección a 220 nm; relación de flujo = 20 mL/min; gradiente continuo de 35% A hasta 100% B durante 10 min +2 min tiempo de espera a 100% B, donde A = 90:10:0.1 H_2O:MeOH:TFA y B = 90:10:0.1 MeOH:H_2O:TFA). El material finalmente se purificó por pasar a través de un cartucho tratado con MeOH de la resina Polymer Lab StratoSpheres TM SPE PL-HCO3 MP SPE (500 mg), se lavó bien con MeOH. El

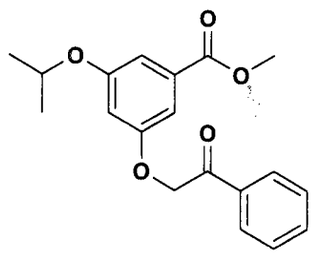
001696

filtrado se concentró *in vacuo* y el sólido resultante se disolvió en CH_2Cl_2/MeOH, se filtró y se concentró *in vacuo* para dar el compuesto del título (5 mg, 34%) como un sólido marrón. $[M + H]^+$ = 583.3; ^1H RMN (400 MHz, $CDCl_3$) δ 1.27 (t, *J*=6.87 Hz, 6 H), 1.33 (d, *J*=6.05 Hz, 6 H), 3.33 (d, *J*=20.89 Hz, 2 H), 4.07 (td, *J*=7.15, 4.40 Hz, 4 H), 4.55 - 4.58 (m, 1 H), 5.11 (s, 2 H), 6.67 (s, 1 H), 6.83 (d, *J*=3.30 Hz, 1 H), 7.08 (s, 1 H), 7.16 (s, 1 H), 7.59 (t, *J*=7.70 Hz, 2 H), 7.69 (t, *J*=7.15 Hz, 1 H), 7.97 (d, *J*=7.15 Hz, 2 H).

EJEMPLO 120



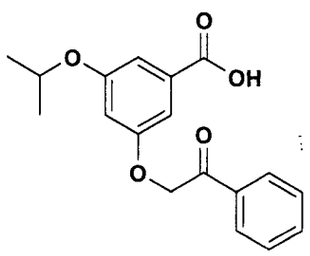
A.



A una solución a 0°C de Compuesto del ejemplo 101 parte A (183.9 mg, 0.875 mmol) en DMPU (4.5 mL) bajo Ar se agregó NaH (35.0 mg de un 60% dispersión en aceite, 0.875 mmol). A

la solución resultante se agregó 2-bromoacetofenona (174 mg, 0.875 mmol). La reacción se agitó a 0°C durante diversos min y luego se calentó a temperatura ambiente y se agitó a temperatura ambiente durante 1.5 h. Más 2-bromoacetofenona (39 mg, 0.19 mmol) se agregó, y la reacción se agitó a temperatura ambiente durante 1 h. La reacción se apagó con agua y EtOAc se agregó. La capa orgánica se lavó con agua (2x) y salmuera (1x), se secó (Na_2SO_4), y se concentró *in vacuo*. El residuo se procesó por cromatografía (SiO_2, 12 g, eluida desde 0-5% EtOAc:CH_2Cl_2, luego se mojó con 90% EtOAc) para dar el compuesto parte A (274 mg, 95%) como un aceite amarillo.

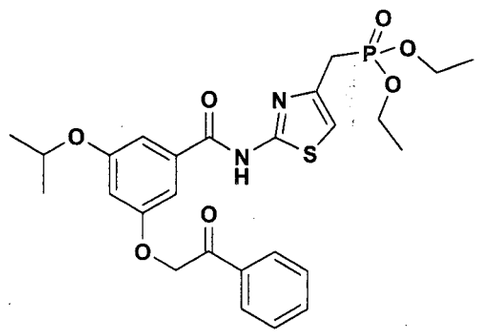
B.



A una solución a temperatura ambiente del compuesto parte A (101.4 mg, 0.309 mmol) en TF (2.4 mL) bajo Ar se agregó agua (0.6 mL), seguido por LiOH.H_2O (54.7 mg, 1.304 mmol). La reacción se agitó a temperatura ambiente durante 18 h, y LiOH acuoso (0.2 mL de una solución 4M, 0.8 mmol) se agregó. Después de agitarse durante 5.5 h, MeOH (0.5 mL) se agregó; se continuó agitando a temperatura ambiente durante 2.5 h y la reacción se almacenó a -20°C durante 18 h. Después

de calentarse a temperatura ambiente, la reacción se agitó durante otras 4.5 h. Los volátiles se removieron *in vacuo* para dar una mezcla acuosa anaranjada, la cual se acidificó con HCl acuoso 1N (1.9 mL), luego se dividió entre EtOAc y agua. La capa orgánica se lavó con agua y salmuera, se secó (Na_2SO_4) y se concentró *in vacuo* para dar el compuesto crudo parte B (88 mg, 49%) como un aceite amarillo.

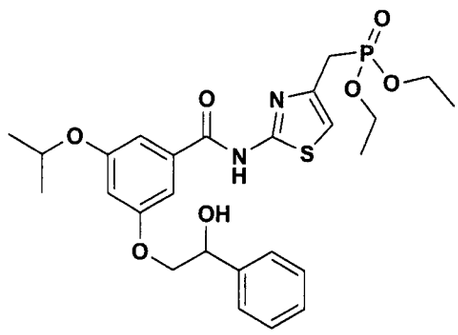
C.



A una solución a temperatura ambiente del ácido Parte B (≤88 mg, ≤0.280 mmol) en CH_2Cl_2 (1.4 mL) bajo Ar se agregó sucesivamente HATU (166 mg, 0.437 mmol), DIPEA (0.34 mL, 1.952 mmol) y una solución del Compuesto del ejemplo 13 parte E (162 mg, 0.445 mmol) en CH_2Cl_2 (0.6 mL). La reacción se agitó a temperatura ambiente durante 65 h, luego se dividió entre EtOAc y $NaHCO_3$ acuoso saturado. La capa orgánica se lavó con $NaHCO_3$ acuoso saturado y salmuera, se secó (Na_2SO_4) y se concentró *in vacuo*. El residuo se purificó por HPLC preparativa (columna YMC ODS S5 30x250mm, detección a 220 nm; relación de flujo = 25 mL/min; gradiente continuo de 50% A hasta 100% B durante 20 minutos +5 min tiempo de espera a

100% B, donde A = 90:10:0.1 H_2O:CH_3CN:TFA y B = 90:10:0.1 CH_3CN:H_2O:TFA) para dar el compuesto del título (33 mg, 22%) como un sólido amarillo gomoso. $[M + H]^+$ = 545.3; ^1H RMN (400 MHz, CD_3OD): δ 1.28 (t, *J*=7.15 Hz, 6 H), 1.34 (d, *J*=6.05 Hz, 6 H), 3.36 (d, *J*=16.49 Hz, 2 H), 4.04 - 4.14 (m, 4 H), 4.64 - 4.86 (m, 1 H), 5.55 (s, 2 H), 6.78 - 6.80 (m, 1 H), 6.95 - 6.97 (m, 1 H), 7.18 - 7.21 (m, 2 H), 7.50 - 7.58 (t, *J*=7.97 Hz 2 H), 7.65 - 7.70 (m, 1 H), 8.07 (d, *J*=7.15 Hz, 2 H).

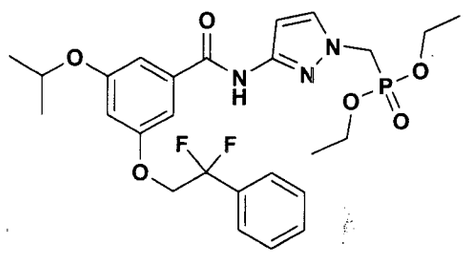
EJEMPLO 121



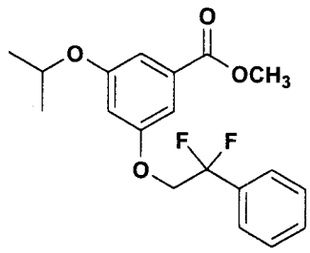
A una solución a 0°C de la cetona del ejemplo 120 (28 mg, 0.051 mmol) en MeOH (1 mL) bajo Ar se agregó $NaBH_4$ (10 mg, 0.264 mmol). Después de 15 minutos, la reacción se permitió calentar a temperatura ambiente y se agitó a temperatura ambiente durante 4 h. La mezcla se almacenó a -20°C durante 18 h, luego se trató con pH 3 solución amortiguadora de fosfato acuoso, se permitió calentar a temperatura ambiente y se agitó a temperatura ambiente durante 40 min. Los volátiles se removieron *in vacuo*, y la mezcla acuosa resultante se dividió entre agua, solución amortiguadora de fosfato y EtOAc. La capa orgánica se lavó

con agua y salmuera, se secó (Na_2SO_4) y se concentró *in vacuo*. El residuo se purificó por HPLC preparativa (Phenomenex AXIA Luna 5µm 75x30mm, detección a 220 nm; relación de flujo = 40 mL/min; gradiente continuo de 40% A hasta 100% B durante 15 min +3 min tiempo de espera a 100% B, donde A = 90:10:0.1 H_2O:CH_3CN:TFA y B = 90:10:0.1 CH_3CN:H_2O:TFA) para dar dos fracciones que contienen el compuesto del título deseado. Ambas fracciones se pasaron a través de un cartucho tratado con MeOH de la resina Polymer Lab StratoSpheres TM SPE PL-HCO3 MP SPE (500mg), se lavó bien con MeOH. Los filtrados se concentraron *in vacuo*, y los sólidos resultantes se disolvieron en CH_2Cl_2/MeOH, y se concentraron *in vacuo* para dar el compuesto del título (17 mg, 60%) como un sólido marrón. $[M + H]^+$ = 549.2; $[M - H]^-$ = 547.2; ^1H RMN (400 MHz, CD_3OD): δ 1.28 (t, *J*=6.87 Hz, 6 H), 1.33 (d, *J*=6.05 Hz, 6 H), 3.35 (d, *J*=20.89 Hz, 2 H), 4.05 - 4.17 (m, 6 H), 4.63 - 4.69 (m, 1 H), 5.02 - 5.07 (m, 1 H), 6.71 - 6.73 (m, 1 H), 6.95 (d, *J*=3.85 Hz, 1 H), 7.13 -7.15 (m, 2 H), 7.27 -7.30 (m, 1 H), 7.37 (t, *J*=7.42 Hz, 2 H), 7.48 (d, *J*=7.15 Hz, 2 H).

EJEMPLO 122

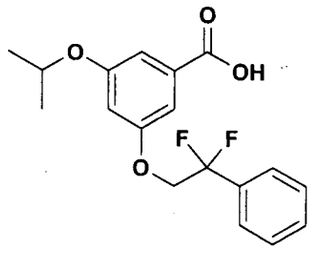


A.



A una solución a temperatura ambiente del Compuesto del ejemplo 120 parte A (53.7 mg, 0.164 mmol) en CH_2Cl_2 (0.5 mL) bajo Ar se agregó trifluoruro de bis-(2-metoxietil)aminoazufre (0.3 mL, 1.627 mmol). La solución anaranjada se agitó a temperatura ambiente bajo Ar durante 18 h, luego se diluyó con CH_2Cl_2 y se agregó cuidadosamente a una mezcla agitada de hielo y $NaHCO_3$ acuoso saturado. La mezcla se agitó durante 1 h, luego se dividió entre CH_2Cl_2 y $NaHCO_3$ acuoso saturado. La capa acuosa se extrajo CH_2Cl_2 (2x), y los extractos orgánicos combinados se lavaron con salmuera, se secaron (Na_2SO_4) y se concentraron *in vacuo* para dar el éster de la parte A crudo (54.4 mg, 95% recovered) como un aceite amarillo.

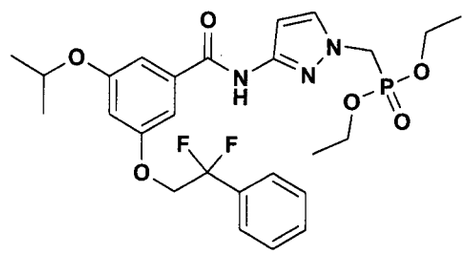
B.



A una solución a temperatura ambiente del éster parte A (54.4 mg, 0.155 mmol) en THF (0.8 mL) y MeOH (0.4 mL) bajo Ar

se agregó LiOH acuoso 4N (0.35 mL, 1.4 mmol). La reacción se agitó a temperatura ambiente durante 6 h, y los volátiles se removieron *in vacuo*. La mezcla acuosa anaranjada se acidificó con HCl acuoso 1N (1.5 mL). La mezcla resultante se dividió entre agua y EtOAc. La capa orgánica se lavó con agua y salmuera, se secó (Na_2SO_4) y se concentró *in vacuo* para dar el compuesto parte B (46.7 mg, 89% recovered) como un sólido aceitoso amarillo.

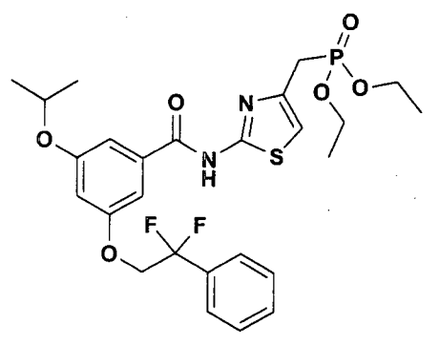
C.



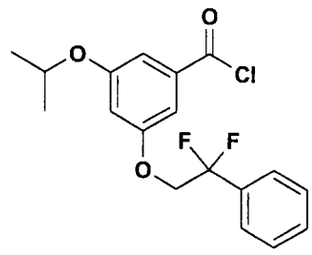
A una solución a temperatura ambiente del compuesto parte B (21.2 mg, 0.063 mmol) en CH_2Cl_2 (0.6 mL) bajo Ar se agregó sucesivamente HATU (34 mg, 0.089 mmol), iPr_2NEt (35 µL, 0.201 mmol), y una solución de la amina del ejemplo 32 Parte A (20.6 mg, 0.088 mmol) en CH_2Cl_2 (0.3 mL). La reacción se agitó durante 41 h a temperatura ambiente, luego se diluyó con CH_2Cl_2, $NaHCO_3$ acuoso saturado, y EtOAc, luego se agitó durante 15 min y se dividió entre EtOAc y $NaHCO_3$ acuoso. La capa acuosa se extrajo con EtOAc (2x), y los extractos orgánicos combinados se lavaron con salmuera, se secaron (Na_2SO_4), y se concentraron *in vacuo*. El residuo se purificó por HPLC preparativa (columna YMC ODS 30x250mm, detección a

220 nm; relación de flujo = 25 mL/min; gradiente continuo de 50% A hasta 100% B durante 25 min +7 min tiempo de espera a 100% B, donde A = 90:10:0.1 H_2O:CH_3CN:TFA y B = 90:10:0.1 CH_3CN:H_2O:TFA) para dar el compuesto del título ligeramente impuro (34.3 mg) como un aceite incoloro. El residuo se purificó además por HPLC preparativa (columna Phenomenex AXIA 5micron C18 30x100mm, detección a 220 nm; relación de flujo = 40 mL/min; gradiente continuo de 60% A hasta 100% B durante 10 min +5 min tiempo de espera a 100% B, donde A = 90:10:0.1 H_2O:MeOH:TFA y B = 90:10:0.1 MeOH:H_2O:TFA) para dar el compuesto del título (25 mg, 59%, TFA salt) como un aceite incoloro. $[M + H]^+$ = 552.2; $[M - H]^-$ = 550.3; ^1H RMN (400 MHz, $CDCl_3$): δ 1.28 (t, *J*=7.15 Hz, 6 H), 1.32 (d, *J*=6.05 Hz, 6 H), 4.04 - 4.14 (m, 4 H), 4.37 - 4.48 (m, 4 H), 4.59 (dt, *J*=12.09, 6.05 Hz, 1 H), 6.60 (s, 1 H), 6.94 (s, 1 H), 7.01 (s, 1 H), 7.08 (s, 1 H), 7.43 - 7.49 (m, 4 H), 7.55 - 7.61 (m, 2 H), 9.10 (s, 1 H), ^{19}F RMN (400 MHz, CDCl3): δ -75.98, -103.82, -103.86.

EJEMPLO 123

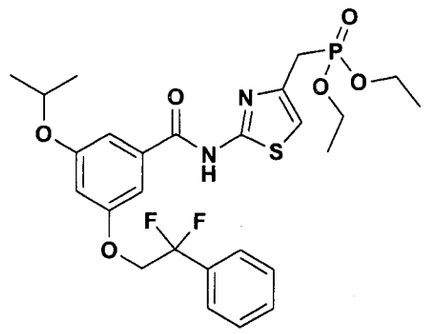


A.



A una solución a 0°C del ácido del ejemplo 122 Parte B (46.7 mg, 0.139 mmol) en CH_2Cl_2 (1.5 mL) bajo Ar se agregó sucesivamente gota a gota cloruro de oxalilo (250 µL de una solución 2M en 2 M en CH_2Cl_2; 0.5 mmol,) y DMF (15 µL). Después de 15 min, la reacción se permitió calentar a temperatura ambiente y la reacción amarilla se agitó a temperatura ambiente durante 3 h. Los volátiles se removieron *in vacuo* para dar el compuesto parte A (68.8 mg, >100% recuperación) como un sólido aceitosos anaranjado.

B.

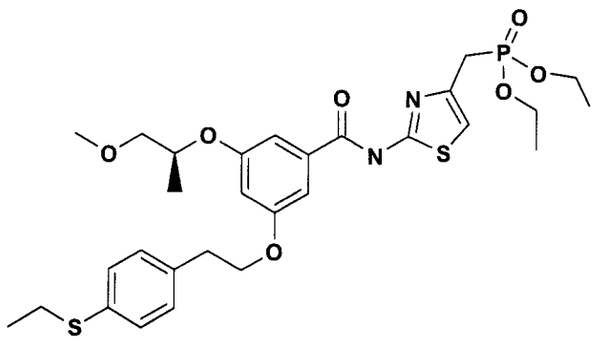


A una solución a 0°C de la amina del ejemplo 13 parte E (36.7 mg, 0.147 mmol) en THF (0.4 mL) bajo Ar se agregó sucesivamente iPr_2NEt (120 µL, 0.689 mmol), una solución del compuesto parte A (24.7 mg, 0.0695 mmol) en CH_2Cl_2 (0.4 mL) y finalmente DMAP (1.7 mg, 0.014 mmol). La reacción se permitió

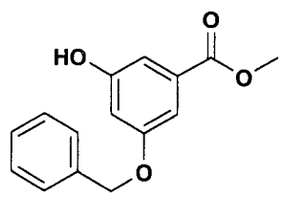
calentar a temperatura ambiente y se agitó durante 20 h a temperatura ambiente, luego se diluyó con agua y se combinó con la mezcla de reacción cruda de un experimento similar usando el cloruro ácido parte A (24.7 mg, 0.0695 mmol) y la amina del ejemplo 13 parte E (36.7 mg, 0.147 mmol). Las mezclas de reacción combinadas se dividieron entre $NaHCO_3$ acuoso diluido y CH_2Cl_2. La capa acuosa se extrajo con CH_2Cl_2 (2x), y las capas orgánicas combinadas se secaron (Na_2SO_4) y se concentraron *in vacuo*. El residuo se purificó inicialmente por HPLC preparativa (columna YMC ODS 30x250mm, detección a 220 nm; relación de flujo = 25 mL/min; gradiente continuo de 50% A hasta 100% B durante 30 min +7 min tiempo de espera a 100% B, donde A = 90:10:0.1 H_2O:CH3CN:TFA and B = 90:10:0.1 CH_3CN:H_2O:TFA). El residuo se disolvió en MeOH y se pasó a través de un cartucho tratado con MeOH de la resina Polymer Lab StratoSpheres TM SPE PL-HCO_3 MP SPE (500 mg), se lavó bien con MeOH. El filtrado se concentró *in vacuo*. El residuo se disolvió en CH_2Cl_2/MeOH, se filtró y se concentró *in vacuo* para dar el compuesto del título (5.6 mg, 7%) como un sólido gomoso canela. $[M + H]^+$ = 569.3; $[M - H]^-$ = 567.3; ^1H RMN (400 MHz, $CDCl_3$): δ 1.24 (t, J=7.15 Hz, 6 H), 1.30 (d, J=6.05 Hz, 6 H), 3.28 (d, J=20.89 Hz, 2 H), 3.98 - 4.09 (m, 4 H), 4.36 (t, J=12.37 Hz, 2 H), 4.53 (dt, J=12.09, 6.05 Hz, 1 H), 6.57 (s, 1 H), 6.77 (d, J=3.30 Hz, 1 H), 7.02 (s, 1 H), 7.09 (s, 1 H), 7.41 - 7.49 (m, 3 H), 7.51 - 7.59 (m, 2 H), 8.01 (d,

J=7.15 Hz, 1 H); ^{19}F RMN (400 MHz, CDCl3): δ -103.73, -103.76, -103.80.

EJEMPLO 124



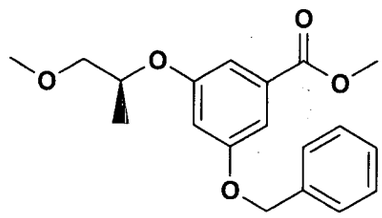
A.



A una solución de metil-3,5-dihidroxi benzoato (10.00 g; 59.5 mmol) en DMF (60.0 mL) bajo Ar se agregó K_2CO_3 (12.4 g; 89.7 mmol), seguido por la adición lenta de bromuro de bencilo (10.0 mL; 84.2 mmol) durante 10 min. La mezcla de reacción se agitó a 25°C durante 16 h, luego se apagó con NH_4Cl acuoso saturado (50 mL) y agua (350 mL). La suspensión acuosa se extrajo con CH_2Cl_2 (3 x 50mL). Los extractos orgánicos combinados se lavaron con agua y salmuera, se secaron ($MgSO_4$), y se concentraron *in vacuo*. El producto crudo se procesó por cromatografía (SiO_2; gradiente en porciones de 10-20-30-50% solvente B, donde solvente A = hexanos y solvente B = EtOAc) para dar el compuesto parte A

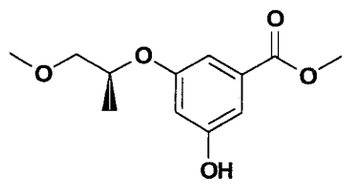
(4.599 g; 30%) como un polvo blanco opaco.

B.



A una solución a 0°C del compuesto parte A (3.130 g; 12.12 mmol) en THF (52.7 mL) se agregaron (R)-1-metoxipropan-2-ol (1.64 g; 18.18mmol) y Ph_3P (4.77 g; 18.18 mmol), seguido por la adición lenta de DIAD (3.53 mL; 18.18 mmol) por medio de una bomba de jeringa. La mezcla de reacción se agitó a 25°C durante 16 h bajo Ar, luego se diluyó con agua y se extrajo con EtOAc (3x). Los extractos orgánicos combinados se lavaron con NaOH acuoso 1N y salmuera, se secaron ($MgSO_4$) y se concentraron *in vacuo*. El producto crudo se procesó por cromatografía (SiO_2; gradiente en porciones de 5-10-30-50% solvente B, donde solvente A = hexanos y solvente B = EtOAc) para dar el compuesto parte B (2.892 g; 53%) como un aceite incoloro claro.

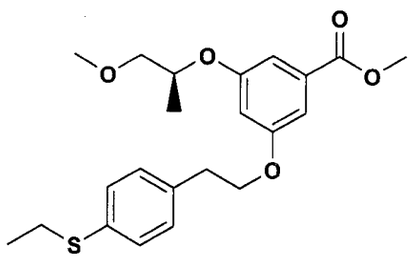
C.



Un matraz que contiene el compuesto parte B (2.892 g; 8.75 mmol) en MeOH (109 mL) se evacuó y se mojó con Ar. Se

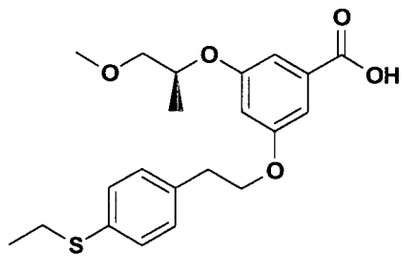
agregó 10% Pd/C (0.931 g; 0.875 mmol) seguido por la evacuación del matraz y se rellenó con H_2 (g; 1 atmósfera). La reacción se agitó durante 2 días bajo H_2. La mezcla de reacción se filtró y el catalizador se lavó con EtOAc. Los filtrados combinados se concentraron *in vacuo* para dar el compuesto parte C (2.075 g; 83%) como un aceite incoloro claro.

D.



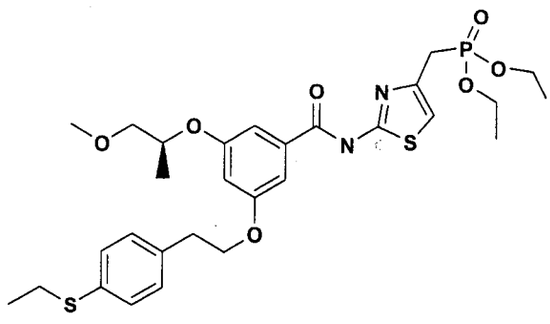
A una solución a 0°C del compuesto parte C (0.125 g; 0.519 mmol) en THF (2.60 mL) se agregaron 2-(4-(etiltio)fenil)etanol (0.208 g; 1.142 mmol) y Ph_3P (0.299 g; 1.142 mmol), seguido por la adición lenta de DIAD (0.222 mL; 1.142 mmol). La mezcla de reacción se agitó a 25°C durante 16 h bajo Ar. La mezcla de reacción se diluyó con agua y se extrajo con EtOAc (3x). Los extractos orgánicos combinados se lavaron con NaOH acuoso 1N y salmuera, se secaron ($MgSO_4$) y se concentraron *in vacuo*. El residuo se procesó por cromatografía (SiO_2; gradiente en porciones de 5-10-20-30-50% solvente B, donde solvente A = hexanos y solvente B = EtOAc) para dar el compuesto parte D (0.121 g; 49%) como un aceite amarillo claro.

E.



A una solución del Compuesto parte D (0.1208 g; 0.299 mmol) en THF (2.47 mL) y agua (0.25 mL) se agregó $LiOH.H_2O$ (0.014 g; 0.597 mmol). La mezcla de reacción se agitó a 45°C durante 1 h en un vial sellado, luego un equivalente adicional de $LiOH.H_2O$ se agregó. La mezcla de reacción se agitó a 45°C durante 16 h, luego se enfrió a temperatura ambiente. Los volátiles se removieron *in vacuo*, y la solución acuosa resultante se acidificó con 0.5N HCl acuoso hasta pH < 2. La capa acuosa se re-extrajo con EtOAc (3x). Los extractos orgánicos combinados se lavaron con salmuera, se secaron ($MgSO_4$) y se concentraron *in vacuo* para dar el compuesto parte E (0.1082 g; 76%) como un aceite incoloro claro.

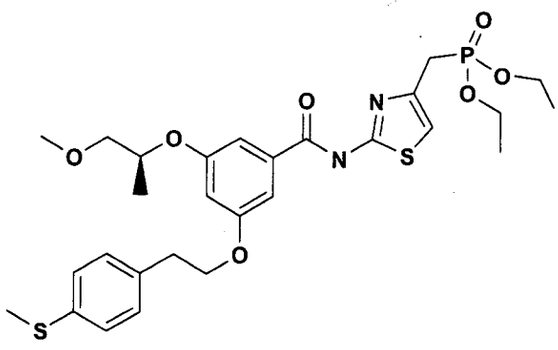
F.



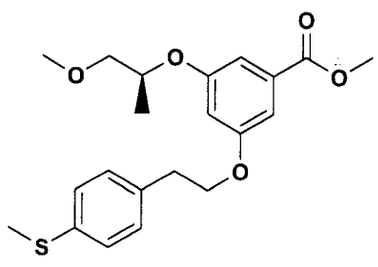
A una solución del compuesto parte E (0.160 g; 0.411 mmol) en DMF (2.05 mL) se agregaron HOAT (0.064 g; 0.47

mmol), Compuesto del ejemplo 13 parte E (0.123 g; 0.493 mmol), y DIPEA (0.08 mL; 0.47 mmol), y ultimamente, EDCI (0.091 g; 0.47 mmol). La mezcla de reacción se agitó a 25°C durante 16 h. Se agregó agua, y la mezcla se extrajo con EtOAc (3x). Los extractos orgánicos combinados se lavaron con NH_4Cl acuoso saturado, $NaHCO_3$ acuoso saturado, y salmuera, se secaron ($MgSO_4$) y se concentraron *in vacuo*. El residuo se purificó por HPLC preparativa (columna YMC fase inversa ODS-5u 30 x 100 mm; relación de flujo = 40 mL/min, 25 hasta 100% solvente B durante 12 min, donde solvente A = 90:10:0.1 H_2O:CH_3CN:TFA y solvente B = 90:10:0.1 CH_3CN:H_2O:TFA) para dar el compuesto del título (80.4 mg; 31%) como un aceite incoloro claro. $[M + H]^+$ = 623.2.

EJEMPLO 125

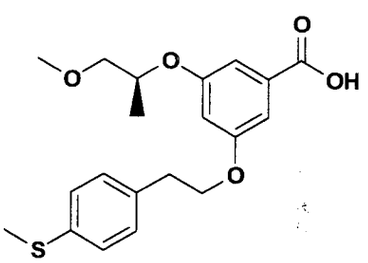


A.



A una solución a 0°C del Compuesto del ejemplo 124 parte C (0.125 g; 0.519 mmol) en THF (2.60 mL) se agregó 2-(4-(metiltio)fenil)etanol (0.208 g; 1.142 mmol) y Ph_3P (0.299 g; 1.142 mmol), seguido por la adición lenta de DIAD (0.222 mL; 1.142 mmol). La mezcla de reacción se agitó a 25°C durante 16 h bajo Ar, luego se diluyó con agua y se extrajo con EtOAc (3x). Los extractos orgánicos combinados se lavaron con NaOH acuoso 1N y salmuera, se secaron ($MgSO_4$) y se concentraron *in vacuo*. El producto crudo se procesó por cromatografía (SiO_2; etapa gradiente de 5-10-20-30-50% solvente B, donde solvente A = hexanos y solvente B = EtOAc) para dar el compuesto parte A (0.121 g; 49%) como un aceite amarillo claro.

B.

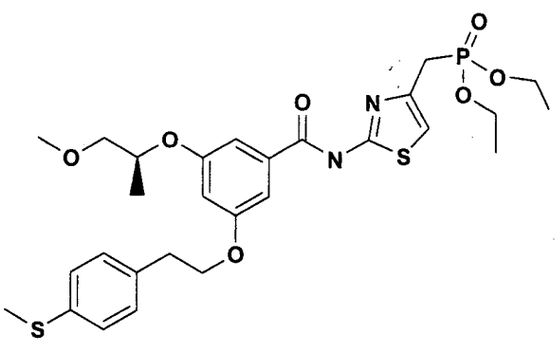


A una solución del compuesto parte A (0.1208 g; 0.299 mmol) en THF (2.47 mL) y agua (0.25 mL) se agregó $LiOH.H_2O$ (0.014 g; 0.597 mmol). La mezcla de reacción se agitó a 45°C durante 1 h en un vial sellado, luego un equivalente adicional de LiOH se agregó. La mezcla de reacción se agitó a 45°C durante 16 h, luego se enfrió a temperatura ambiente. Los volátiles se removieron *in vacuo*, y la solución acuosa resultante se acidificó con 0.5N HCl acuoso hasta pH <2. La

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capa acuosa se re-extrajo con EtOAc (3x). Los extractos orgánicos combinados se lavaron con salmuera, se secaron ($MgSO_4$) y se concentraron *in vacuo* para dar el compuesto parte B (0.1082 g; 76%) como un aceite incoloro claro.

C.

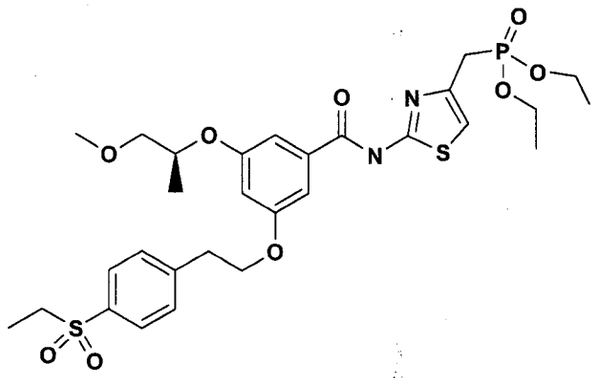


A una solución del Compuesto del ejemplo 13 parte E (0.13 g; 0.51 mmol) en DMF (2.13 mL) se agregaron HOAT (0.067 g; 0.49 mmol), El compuesto parte B (0.16 g; 0.43 mmol), DIPEA (0.63 mL; 0.49 mmol), y ultimamente, EDCI (0.094 g; 0.49 mmol). La mezcla de reacción se agitó a 25°C durante 16 h. Se agregó agua, y la mezcla se extrajo con EtOAc (3x). Los extractos orgánicos combinados se lavaron con NH_4Cl acuoso saturado, $NaHCO_3$ acuoso saturado, y salmuera, se secaron ($MgSO_4$), y se concentraron *in vacuo*. El residuo se purificó por HPLC preparativa (columna YMC fase inversa ODS-5u 30 x 100 mm; relación de flujo = 40 mL/min, 25 hasta 100% solvente B durante 12 min, donde solvente A = 90:10:0.1 H_2O: CH_3CN:TFA y solvente B = 90:10:0.1 CH_3CN:H_2O:TFA) para dar el compuesto del título (47.0 mg; 17%) como un aceite incoloro claro. [M

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+ H]$^+$ = 609.1.

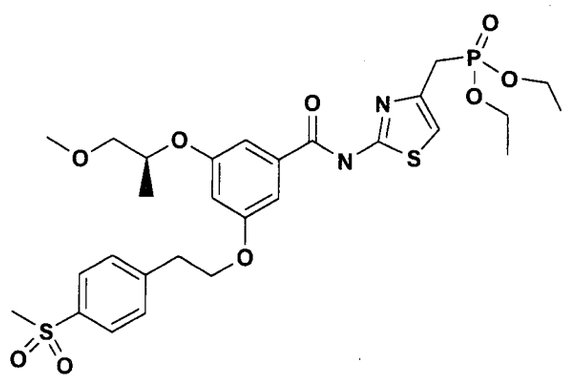
EJEMPLO 126



Al Compuesto del ejemplo 124 parte F (0.04 g; 0.07 mmol) en iPrOH (1.46 mL) y agua (0.73 mL) se agregó oxona (0.09 g; 0.15 mmol). La mezcla de reacción se agitó durante 16 h a 25°C, luego se filtró y se extrajo con EtOAc. El filtrado se dividió entre agua y salmuera. La capa orgánica se secó ($MgSO_4$) y se concentró *in vacuo*. El residuo se purificó por HPLC preparativa (columna YMC fase inversa ODS-5u 30 x 100 mm; relación de flujo = 40 mL/min, 25 hasta 100% solvente B durante 12 min, donde solvente A = 90:10:0.1 H_2O:CH_3CN:TFA y solvente B = 90:10:0.1 CH_3CN:H_2O:TFA) para dar el compuesto del título (48.0 mg; 55%) como un sólido blanco. [M + H]$^+$ = 655.3; ^{1}H RMN (400 MHz, $CDCl_3$): δ 1.16 - 1.29 (m, 12 H), 2.98 - 3.08 (m, *J*=7.33, 7.33, 7.33 Hz, 2 H), 3.08 - 3.18 (m, *J*=6.32, 6.32 Hz, 2 H), 3.22 (s, 1 H), 3.28 (s, 1 H), 3.33 (s, 3 H), 3.41 - 3.54 (m, 2 H), 4.01 - 4.13 (m, 4 H), 4.24 (t, *J*=6.32 Hz, 2 H), 4.61 - 4.70 (m, *J*=10.17, 6.32 Hz, 1 H), 6.64 - 6.70 (m, 1 H), 6.93 - 6.97 (m, *J*=3.30 Hz, 1 H), 7.29 (d,

J=17.59 Hz, 2 H), 7.42 (d, *J*=8.24 Hz, 2 H), 7.78 (d, *J*=8.25 Hz, 2 H).

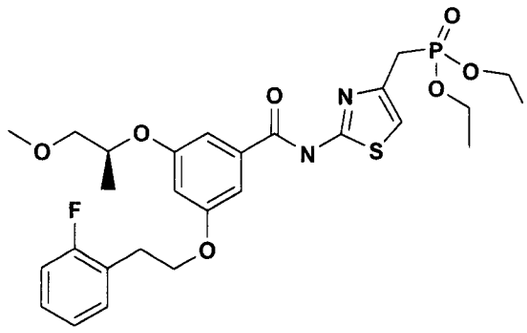
EJEMPLO 127



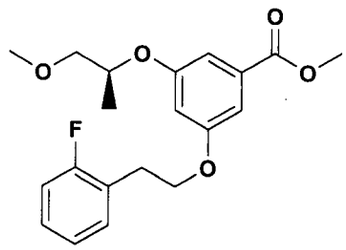
Al Compuesto del ejemplo 125 parte C (0.04 g; 0.07 mmol) en iPrOH (1.46 mL) y agua (0.73 mL) se agregó oxona (0.09 g; 0.15 mmol). La mezcla de reacción se agitó durante 16 h a 25°C, luego se filtró y se enjuagó con EtOAc. El filtrado se lavó con agua y salmuera, se secó ($MgSO_4$) y se concentró *in vacuo*. El residuo se purificó por HPLC preparativa (columna YMC fase inversa ODS-5u 30 x 100 mm; relación de flujo = 40 mL/min, 25 hasta 100% solvente B durante 12 min, donde solvente A = 90:10:0.1 H_2O: CH_3CN:TFA y solvente B = 90:10:0.1 CH_3CN:H_2O:TFA) para dar el compuesto del título (14.2 mg; 33%) como un sólido blanco. $[M + H]^+$ = 641.3; ^1H RMN (400 MHz, $CDCl_3$): δ 1.21 - 1.30 (m, *J*=7.42, 7.42 Hz, 9 H), 2.97 (s, 3 H), 3.12 (t, *J*=6.05 Hz, 2 H), 3.26 (s, 1 H), 3.29 - 3.36 (m, 4 H), 3.41 - 3.55 (m, 2 H), 4.03 - 4.16 (m, 4 H), 4.25 (t, *J*=6.32 Hz, 2 H), 4.60 - 4.72 (m, 1 H), 6.62 - 6.71 (m, 1 H), 6.91 - 7.01 (m, *J*=3.85 Hz, 1 H), 7.32 (d, *J*=16.49 Hz, 2 H),

7.43 (d, *J*=8.25 Hz, 2 H), 7.81 (d, *J*=8.24 Hz, 2 H).

EJEMPLO 128



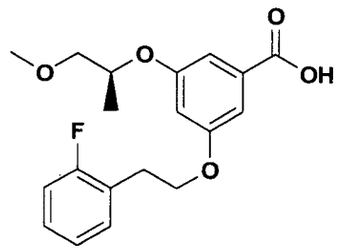
A.



Al Compuesto del ejemplo 124 parte C (0.100g; 0.416 mmol) se agregó 2-(2-fluorofenil) etanol (0.24 g; 1.67 mmol en tolueno; 2.08 mL), seguido por una suspensión de Compuesto del ejempo 97 parte B (0.68 g; 1.67 mmol) en CH_2Cl_2 (7.6 mL). La mezcla de reacción se agitó durante 16 h a 25°C, luego se diluyó con agua y se extrajo con EtOAc (3x). Los extractos orgánicos combinados se lavaron con NaOH acuoso 1N y salmuera, se secaron ($MgSO_4$) y se concentraron *in vacuo*. El producto crudo se procesó por cromatografía (SiO_2; etapa gradiente de 10-20-30% solvente B, donde solvente A = hexanos y solvente B = EtOAc) para dar el compuesto parte A (0.146 g; 90%).

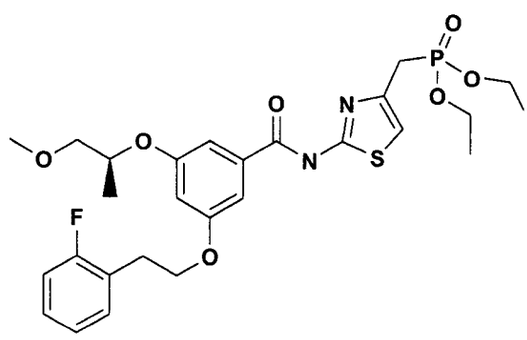
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B.



A una solución del compuesto parte A (0.100 g; 0.27 mmol) en THF (2.23 mL) y agua (0.22 mL) se agregó $LiOH.H_2O$ (0.013 g; 0.54 mmol). La mezcla de reacción se agitó a 45°C durante 1 h en un vial sellado, luego un equivalente adicional de $LiOH.H_2O$ se agregó. La mezcla de reacción se agitó a 45°C durante 16 h, luego se enfrió a temperatura ambiente. Los volátiles se removieron *in vacuo* y la solución acuosa resultante se acidificó con 0.5N HCl acuoso hasta pH <2. La capa acuosa se re-extrajo con EtOAc (3x). Los extractos orgánicos combinados se lavaron con salmuera, se secaron ($MgSO_4$) y se concentraron *in vacuo* para dar el compuesto parte B (0.107 g; 100%).

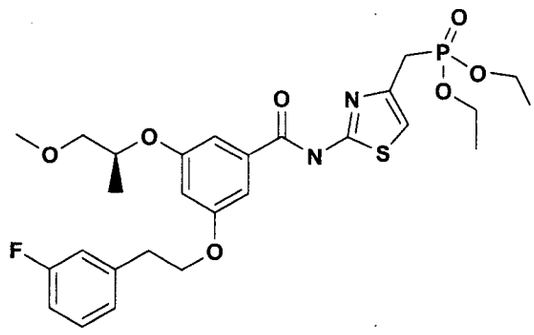
C.



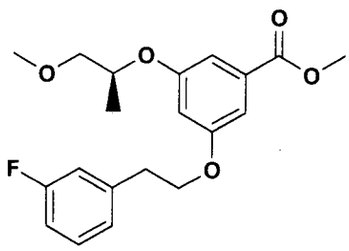
A una solución del Compuesto del ejemplo 13 parte E (0.073 g; 0.29 mmol) en DMF (1.21 mL) se agregaron HOAT

(0.038 g; 0.278 mmol), el compuesto parte B (0.084 g; 0.242 mmol), y DIPEA (0.049 mL; 0.278 mmol) y, ultimamente, EDCI (0.053 g; 0.278 mmol). La mezcla de reacción se agitó a 25°C durante 16 h. Se agregó agua, y la mezcla se extrajo con EtOAc (3x). Los extractos orgánicos combinados se lavaron con NH_4Cl acuoso saturado, $NaHCO_3$ acuoso saturado, y salmuera, se secaron ($MgSO_4$), y se concentraron *in vacuo*. El residuo se purificó por HPLC preparativa (columna YMC fase inversa ODS-5µm 30 x 100 mm; relación de flujo = 40 mL/min, 25 hasta 100% solvente B durante 12 min, donde solvente A = 90:10:0.1 H_2O:CH_3CN:TFA y solvente B = 90:10:0.1 CH_3CN:H_2O:TFA) para dar el compuesto del título (69.7 mg; 49%) como un aceite incoloro claro. $[M + H]^+$ = 581.5; ^1H RMN (400 MHz, $CDCl_3$) δ 1.21 - 1.26 (m, 9 H), 3.06 (t, *J*=6.87 Hz, 2 H), 3.21 (s, 1 H), 3.26 (s, 1 H), 3.31 - 3.35 (m, 3 H), 3.41 - 3.53 (m, 2 H), 3.98 - 4.10 (m, 4 H), 4.18 (t, *J*=6.60 Hz, 2 H), 4.61 - 4.71 (m, 1 H), 6.63 - 6.70 (m, 1 H), 6.84 - 7.06 (m, 3 H), 7.10 - 7.17 (m, 1 H), 7.18 - 7.25 (m, *J*=12.64 Hz, 3 H), 7.26 - 7.30 (m, 1 H).

EJEMPLO 129

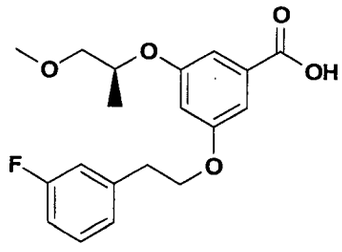


A.



Al Compuesto del ejemplo 124 parte C (0.100g; 0.416 mmol) se agregaron 2-(3-fluorofenil)etanol (0.24 g; 1.67 mmol en tolueno (2.08 mL) seguido por una suspensión de Compuesto del ejempo 97 parte B (0.68 g; 1.67 mmol) en CH_2Cl_2 (7.6 mL). La mezcla de reacción se agitó durante 16 h a 25°C, luego se diluyó con agua y se extrajo con EtOAc (3x). Los extractos orgánicos combinados se lavaron con NaOH acuoso 1N y salmuera, se secaron ($MgSO_4$), y se concentraron *in vacuo*. El producto crudo se procesó por cromatografía (SiO_2; etapa gradiente de 10-20-30% solvente B, donde solvente A = hexanos y solvente B = EtOAc) para dar el compuesto parte A (0.146 g; 90%).

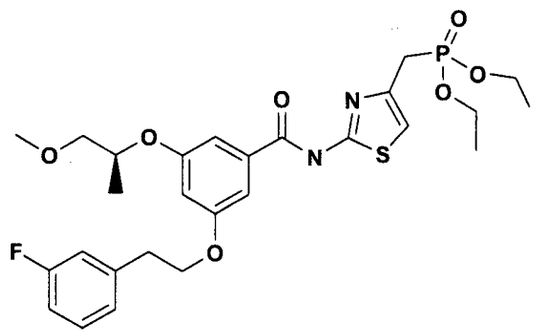
B.



A una solución del compuesto parte A (0.100 g; 0.27 mmol) en THF (2.23 mL) y agua (0.22 mL) se agregó $LiOH.H_2O$ (0.013 g; 0.54 mmol). La mezcla de reacción se agitó a 45°C

durante 1 h en un vial sellado, luego un equivalente adicional de $LiOH.H_2O$ se agregó. La mezcla de reacción se agitó a 45°C durante 16 h, luego se enfrió a temperatura ambiente. Los volátiles se removieron *in vacuo*, y la solución acuosa resultante se acidificó con 0.5N HCl acuoso hasta pH < 2. La capa acuosa se re-extrajo con EtOAc (3x). Los extractos orgánicos combinados se lavaron con salmuera, se secaron ($MgSO_4$), y se concentraron *in vacuo* para dar el compuesto parte B (0.107 g; 100%).

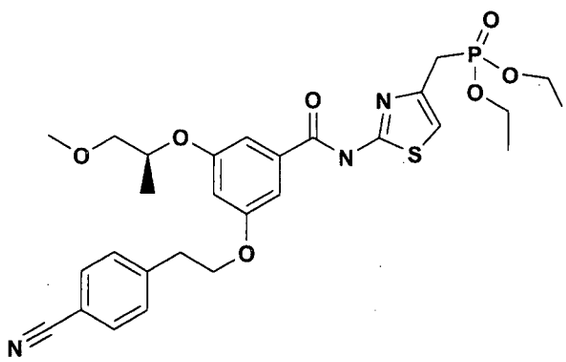
C.



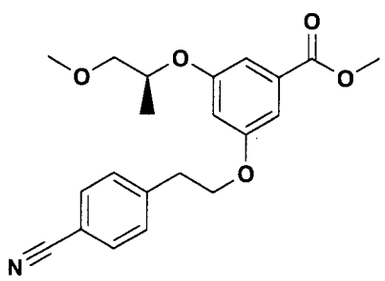
A una solución del Compuesto del ejemplo 13 parte E (0.092 g; 0.37 mmol) en DMF (1.54 mL) se agregaron HOAT (0.038 g; 0.35 mmol), el compuesto parte B (0.107 g; 0.308 mmol), DIPEA (0.062 mL; 0.35 mmol) y, ultimamente, EDCI (0.068 g; 0.35 mmol). La mezcla de reacción se agitó a 25°C durante 16 h. Agua se agregó, y la mezcla se extrajo con EtOAc (3x). Los extractos orgánicos combinados se lavaron con NH_4Cl acuoso saturado, $NaHCO_3$ acuoso saturado, y salmuera, se secaron ($MgSO_4$) y se concentraron *in vacuo*. El residuo se purificó por HPLC preparativa (columna YMC fase inversa ODS-

5μm 30 x 100 mm; relación de flujo = 40 mL/min, 25 hasta 100% solvente B durante 12 min, donde solvente A = 90:10:0.1 H_2O:CH_3CN:TFA y solvente B = 90:10:0.1 CH_3CN:H_2O:TFA) para dar el compuesto del título (78.5 mg; 44%) como un aceite incoloro claro. $[M + H]^+$ = 581.1; ^1H RMN (400 MHz, $CDCl_3$) δ 1.17 - 1.28 (m, 9 H), 3.01 (t, *J*=6.32 Hz, 2 H), 3.24 (s, 1 H), 3.26 - 3.36 (m, 4 H), 3.42 - 3.54 (m, 2 H), 4.00 - 4.14 (m, 4 H), 4.19 (t, *J*=6.32 Hz, 2 H), 4.62 - 4.73 (m, 1 H), 6.64 - 6.70 (m, 1 H), 6.79 - 6.88 (m, *J*=8.52, 8.52 Hz, 1 H), 6.88 - 7.02 (m, 3 H), 7.12 - 7.22 (m, 1 H), 7.25 - 7.30 (m, 1 H), 7.28 (s, 1 H), 7.33 (s, 1 H), 7.31 - 7.36 (m, 1 H).

EJEMPLO 130



A.

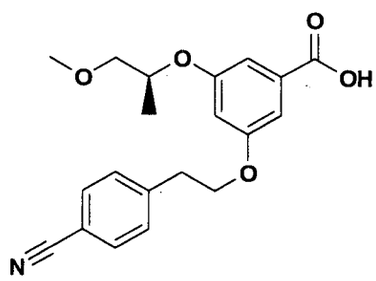


Al Compuesto del ejemplo 124 parte C (0.100g; 0.416

721

mmol) se agregó 4-(2-hidroxietil)benzonitrilo (0.09 g; 0.62 mmol en tolueno (2.08 mL) seguido por una suspensión del compuesto del ejempo 97 parte B (0.26 g; 0.62 mmol) en CH_2Cl_2 (7.14 mL). La mezcla de reacción se agitó durante 16 h a 25°C, luego se diluyó con agua y se extrajo con EtOAc (3x). Los extractos orgánicos combinados se lavaron con NaOH acuoso 1N y salmuera, se secaron ($MgSO_4$) y se concentraron *in vacuo*. El producto crudo se procesó por cromatografía (SiO_2; gradiente en porciones de 5-10-20% solvente B, donde solvente A = hexanos y solvente B = EtOAc) para dar el compuesto parte A (0.100 g; 63%).

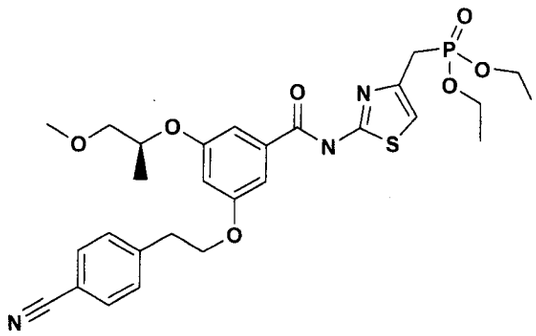
B.



A una solución del compuesto parte A (0.15 g; 0.40 mmol) en THF (3.27 mL) y agua (0.33 mL) se agregó $LiOH.H_2O$ (0.019 g; 0.79 mmol). La mezcla de reacción se agitó a 45°C durante 1 h en un vial sellado, luego un equivalente adicional de LiOH se agregó. La mezcla de reacción se agitó a 45°C durante 16 h, luego se enfrió a temperatura ambiente. Los volátiles se removieron *in vacuo*, y la solución acuosa resultante se acidificó con 0.5N HCl acuoso hasta pH <2. La capa acuosa se re-extrajo con EtOAc (3x). Los extractos orgánicos combinados

se lavaron con salmuera, se secaron ($MgSO_4$), y se concentraron *in vacuo* para dar el compuesto parte B (0.140 g; 85%).

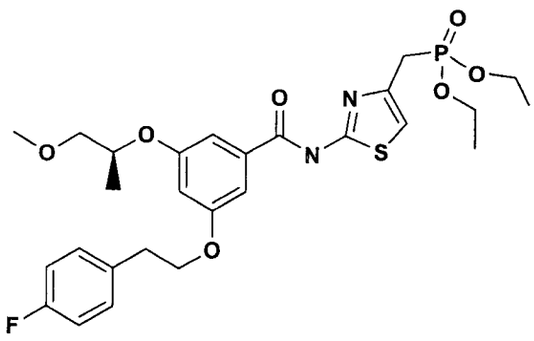
C.



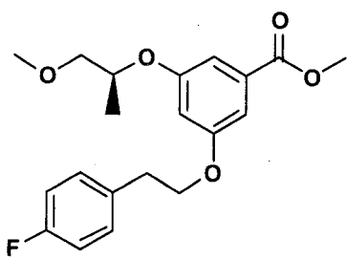
A una solución del Compuesto del ejemplo 13 parte E (0.114 g; 0.454 mmol) en DMF (1.89 mL) se agregaron HOAT (0.059 g; 0.44 mmol), compuesto parte B (0.134 g; 0.378 mmol), DIPEA (0.076 mL; 0.35 mmol), y, ultimamente, EDCI (0.083 g; 0.435 mmol). La mezcla de reacción se agitó a 25°C durante 16 h. Se agregó agua, y la mezcla se extrajo con EtOAc (3x). Los extractos orgánicos combinados se lavaron con NH_4Cl acuoso saturado, $NaHCO_3$ acuoso saturado, y salmuera, se secaron ($MgSO_4$) y se concentraron *in vacuo*. El residuo se purificó por HPLC preparativa (columna YMC fase inversa ODS-5u 30 x 100 mm; relación de flujo = 40 mL/min, 25 hasta 100% solvente B durante 12 min, donde solvente A = 90:10:0.1 H_2O:CH_3CN:TFA y solvente B = 90:10:0.1 CH_3CN:H_2O:TFA) para dar el compuesto del título (86.5 mg; 39%) como un sólido blanco transparente viscoso. $[M + H]^+$ = 588.1; ^1H RMN (400 MHz, $CDCl_3$): δ 1.18 - 1.27 (m, 9 H), 3.07 (t, J=6.32 Hz, 2 H),

3.20 (s, 1 H), 3.25 (s, 1 H), 3.33 (s, 3 H), 3.40 - 3.53 (m, 2 H), 3.97 - 4.09 (m, 4 H), 4.19 (t, *J*=6.32 Hz, 2 H), 4.55 - 4.66 (m, *J*=3.85 Hz, 1 H), 6.63 (s, 1 H), 6.84 - 6.90 (m, *J*=3.30 Hz, 1 H), 7.17 - 7.21 (m, *J*=3.85 Hz, 1 H), 7.24 (s, 1 H), 7.33 (d, *J*=8.25 Hz, 2 H), 7.53 (d, *J*=8.25 Hz, 2 H).

EJEMPLO 131



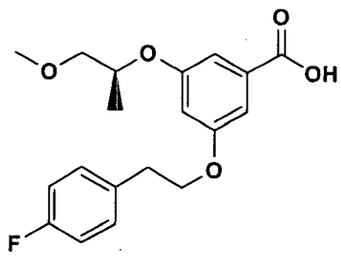
A.



Al compuesto del Ejemplo 124 Parte C (0.100 g; 0.416 mmol) se agregaron una solución de 2-(4-flurorofenil)etanol (0.58 g; 4.16 mmol) en tolueno (2.18 mL) y una suspensión del compuesto del Ejemplo 97 Parte B (1.71 g; 4.16 mmol) en CH_2Cl_2 (7.60 mL). La mezcla de reacción se agitó durante 16 h a 25°C, entonces se diluyó con agua y se extrajo con EtOAc (3x). Los extractos orgánicos combinados se lavaron con NaOH acuoso 1N y salmuera, se secaron ($MgSO_4$) y concentraron *in vacuo*. El

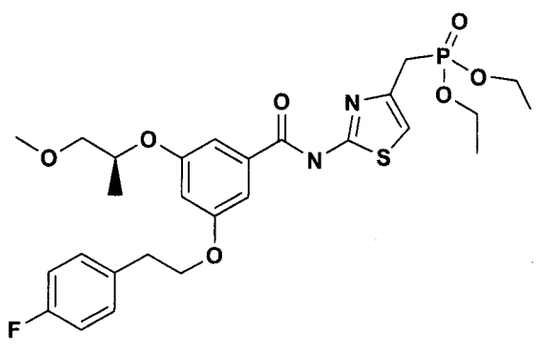
producto crudo se procesó por cromatografía (SiO_2; gradiente de etapa de 5-10-15-20% solvente B, donde solvente A = hexanos y solvente B = EtOAc) para dar compuesto de la Parte A (0.137 g; 86%).

B.



A una solución del compuesto de la Parte A (0.14 g; 0.38 mmol) en THF (3.27 mL) y agua (0.33 mL) se le agregó $LiOH.H_2O$ (0.010 g; 0.38 mmol). La mezcla de reacción se agitó a 45°C durante 1 h en un vial sellado, luego un equivalente adicional de LiOH se agregó. La mezcla de reacción se agitó a 45°C durante 16 h, luego se enfrió a temperatura ambiente. Los volátiles se removieron *in vacuo*, y la solución acuosa restante se acidificó con HCl acuoso 0.5N a un pH menos de 2. La capa acuosa se volvió a extraer con EtOAc (3x). Los extractos orgánicos combinados se lavaron con salmuera, se secaron ($MgSO_4$), y concentraron *in vacuo* para dar el compuesto de la Parte B (0.122 g; 78%).

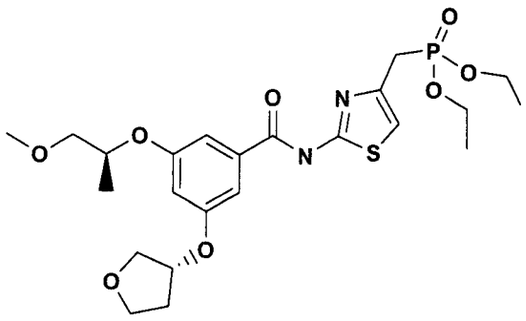
C.



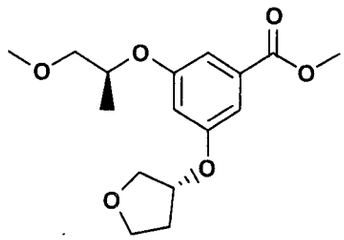
A una solución del compuesto del Ejemplo 13 Parte E

(0.106 g; 0.422 mmol) en DMF (1.76 mL) se agregaron HOAT (0.055 g; 0.404 mmol), compuesto de la Parte B (0.122 g; 0.351 mmol), DIPEA (0.071 mL; 0.404 mmol), y, finalmente, EDCI (0.077 g; 0.404 mmol). La mezcla de reacción se agitó a 25°C durante 16 h. El agua se agregó, y la mezcla se extrajo con EtOAc (3x). Los extractos orgánicos combinados se lavaron con NH_4Cl acuoso saturado, $NaHCO_3$ acuoso saturado, y salmuera, se secaron ($MgSO_4$) y concentraron *in vacuo*. El residuo se purificó por HPLC preparativa (Columna de fase inversa YMC ODS-5u 30 x 100 mm; relación de flujo = 40 mL/min, 25 hasta 100% solvente B durante 12 min, donde el solvente A = 90:10:0.1 H_2O:CH_3CN:TFA y el solvente B = 90:10:0.1 CH_3CN: H_2O: TFA) para dar el compuesto del título (80.0 mg; 39%) como un aceite amarillo pálido, transparente. $[M + H]^+$ = 581.2; ^1H RMN (400 MHz, $CDCl_3$): δ 1.21 - 1.33 (m, 9 H), 3.06 (t, 2 H), 3.25 (s, 1 H), 3.31 (s, 1 H), 3.39 (s, 3 H), 3.45 - 3.60 (m, 2 H), 4.00 - 4.15 (m, 4 H), 4.19 (t, 2 H), 4.60 - 4.70 (m, 1 H), 6.65 - 6.72 (m, 1 H), 6.88 - 6.94 (m, 1 H), 6.99 (t, 2 H), 7.13 - 7.27 (m, 4 H), 11.77 (s, 1 H).

EJEMPLO 132

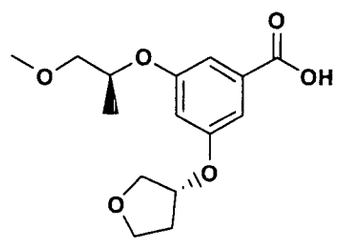


A.



A una solución fría (0°C) del compuesto del Ejemplo 124 Parte C (0.100 g; 0.416 mmol) en THF (2.08 mL) se agregaron (S)-(+)-3-Hidroxitetrahidrofurano (0.074 mL; 0.916 mmol) y Ph_3P (0.24 g; 0.916 mmol), seguido por la adición lenta de DIAD (0.178 mL; 0.916mmol). La mezcla de reacción se agitó a 25°C durante 16 h bajo una atmósfera de Ar. La mezcla de reacción se diluyó con agua y se extrajo con EtOAc (3x). Los extractos orgánicos combinados se lavaron con NaOH acuoso 1N y salmuera, se secaron ($MgSO_4$), y concentraron *in vacuo*. El producto crudo se procesó por cromatografía (SiO_2; gradiente en etapas desde 10-15-20% solvente B, donde el solvente A = hexanos y solvente B = EtOAc) para dar el compuesto de la Parte A (0.105 g; 75%).

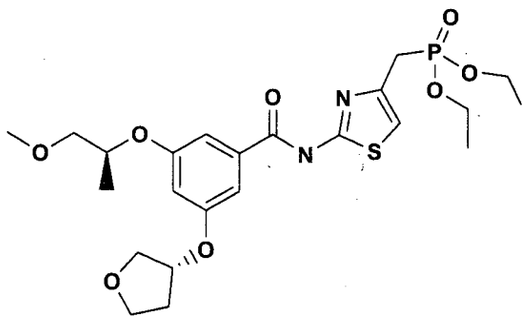
B.



A una solución del compuesto de la Parte A (0.105 g; 0.337 mmol) en THF (2.79 mL) y agua (0.279 mL) se le agregó

$LiOH.H_2O$ (0.028 g; 0.674 mmol). La mezcla de reacción se agitó a 45°C durante 1 h en un vial sellado, luego un equivalente adicional de LiOH se agregó. La mezcla de reacción se agitó a 45°C durante 16 h, luego se enfrió a temperatura ambiente. Los volátiles se removieron *in vacuo*, y la solución acuosa restante se acidificó con HCl acuoso 0.5N a un pH < 2. La capa acuosa se volvió a extraer con EtOAc (3x). Los extractos orgánicos combinados se lavaron con salmuera, se secaron ($MgSO_4$), y concentraron *in vacuo* para dar el compuesto de la Parte B (0.0964 g; 97%).

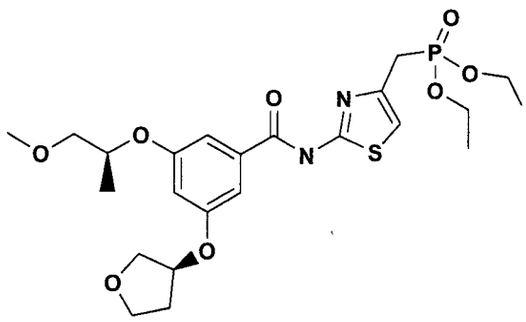
C.



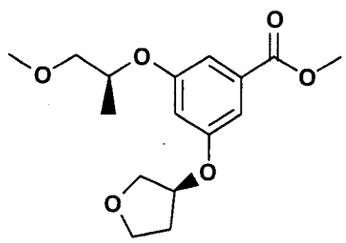
A una solución del compuesto del Ejemplo 13 Parte E (0.098 g; 0.390 mmol) en DMF (1.63 mL) se le agregaron HOAT (0.051 g; 0.374 mmol), compuesto de la Parte B (0.096 g; 0.325 mmol), DIPEA (0.065 mL; 0.374 mmol), y, finalmente, EDCI (0.072 g; 0.374 mmol). La mezcla de reacción se agitó a 25°C durante 16 h. El agua se agregó, y la mezcla se extrajo con EtOAc (3x). Los extractos orgánicos combinados se lavaron con NH_4Cl acuoso saturado, $NaHCO_3$ acuoso saturado, y salmuera, se secaron ($MgSO_4$), y concentraron *in vacuo*. El residuo se

purificó por HPLC preparativa (Columna de fase inversa YMC ODS-5u 30 x 100 mm; relación de flujo = 40 mL/min, 25 hasta 100% solvente B durante 12 min, donde el solvente A = 90:10:0.1 H_2O: CH_3CN: TFA y el solvente B = 90:10:0.1 CH_3CN: H_2O: TFA) para dar el compuesto del título (84.3 mg; 49%) como un aceite transparente, incoloro. $[M + H]^+$ = 529.1; ^1H RMN (400 MHz, $CDCl_3$): δ 1.19 - 1.34 (m, 9 H), 2.06 - 2.30 (m, 2 H), 3.25 (s, 1 H), 3.30 (s, 1 H), 3.39 (s, 3 H), 3.43 - 3.61 (m, 2 H), 3.84 - 4.00 (m, 4 H), 4.00 - 4.13 (m, 4 H), 4.54 - 4.64 (m, 1 H), 4.91 - 5.00 (m, 1 H), 6.62 - 6.70 (m, 1 H), 6.80 - 6.88 (m, *J*=3.85 Hz, 1 H), 7.06 (s, 1 H), 7.13 (s, 1 H), 10.53 (s, 1 H).

EJEMPLO 133



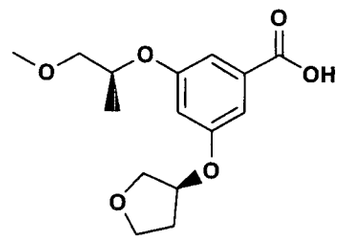
A.



A una solución 0°C del compuesto del Ejemplo 124 Parte C

(0.100 g; 0.416 mmol) en THF (2.08 mL) se le agregaron (R)-(-)-3-hidroxitetrahidrofurano (0.033 mL; 0.416 mmol) y Ph_3P (0.24 g; 0.916 mmol), seguido por la adición lenta de DIAD (0.178 mL; 0.916mmol). La mezcla de reacción se agitó a 25°C durante 16 h bajo Ar, luego se diluyó con agua y se extrajo con EtOAc (3x). Los extractos orgánicos combinados se lavaron con NaOH acuoso 1N y salmuera, se secaron ($MgSO_4$), y concentraron *in vacuo*. El producto crudo se procesó por cromatografía (SiO_2; gradiente en etapas desde 10-15-20% solvente B, donde el solvente A = hexanos y el solvente B = EOAc) para dar el compuesto de la Parte A (0.088 g; 62%).

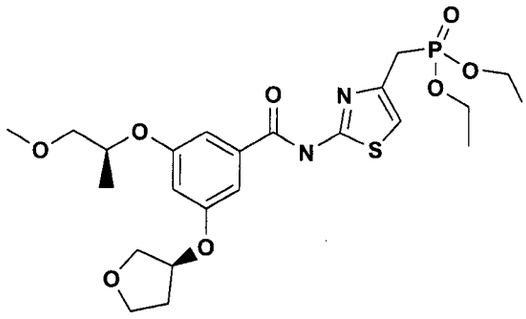
B.



A una solución del compuesto de la Parte A (0.088 g; 0.282 mmol) en THF (2.33 mL) y agua (0.233 mL) se le agregó $LiOH.H_2O$ (0.024 g; 0.565 mmol). La mezcla de reacción se agitó a 45°C durante 1 h en un vial sellado, luego un equivalente adicional de LiOH se le agregó. La mezcla de reacción se agitó a 45°C durante 16 h, luego se enfrió a temperatura ambiente. Los volátiles se removieron *in vacuo*, y la solución acuosa restante se acidificó con HCl acuoso 0.5N a un pH <2. La capa acuosa se volvió a extraer con EtOAc

(3x). Los extractos orgánicos combinados se lavaron con salmuera, se secaron ($MgSO_4$) y concentraron *in vacuo* para dar el compuesto de la Parte B (0.0654 g; 74%).

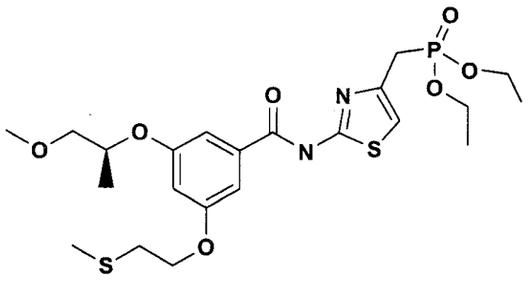
C.



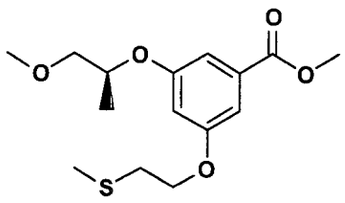
A una solución del compuesto del Ejemplo 13 Parte E (0.066 g; 0.265 mmol) en DMF (1.10 mL) se le agregaron HOAT (0.035 g; 0.254 mmol), compuesto de la Parte B (0.065 g; 0.221 mmol), DIPEA (0.044 mL; 0.254 mmol), y, finalmente, EDCI (0.049 g; 0.254 mmol). La mezcla de reacción se agitó a 25°C durante 16 h. El agua se agregó, y la mezcla se extrajo con EtOAc (3x). Los extractos orgánicos combinados se lavaron con NH_4Cl acuoso saturado, $NaHCO_3$ acuoso saturado, y salmuera, se secaron ($MgSO_4$), y concentraron *in vacuo*. El residuo se purificó por HPLC preparativa (Columna de fase inversa YMC ODS-5u 30 x 100 mm; relación de flujo = 40 mL/min, 25 hasta 100% solvente B durante 12 min, donde el solvente A = 90:10:0.1 H_2O:CH_3CN:TFA y solvente B = 90:10:0.1 CH_3CN:H_2O:TFA) para dar el compuesto del título (50.5 mg; 43%) como un aceite transparente, incoloro. $[M + H]^+$ = 529.1; ^1H RMN (400 MHz, $CDCl_3$): δ 1.21 - 1.33 (m, 9 H), 2.03 - 2.17 (m,

1 H), 2.17 - 2.28 (m, 1 H), 3.25 (s, 1 H), 3.31 (s, 1 H), 3.38 (s, 3 H), 3.44 - 3.53 (m, 1 H), 3.52 - 3.59 (m, 1 H), 3.68 (s, 2 H), 3.83 - 3.92 (m, 1 H), 3.93 - 4.01 (m, 2 H), 4.03 - 4.12 (m, 3 H), 4.57 - 4.67 (m, 1 H), 4.96 - 5.02 (m, *J*=2.20 Hz, 1 H), 6.67 (s, 1 H), 6.85 - 6.92 (m, *J*=3.85 Hz, 1 H), 7.13 (s, 1 H), 7.20 (s, 1 H).

EJEMPLO 134



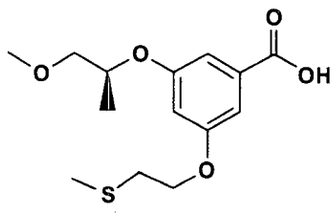
A.



A una solución 0°C del compuesto del Ejemplo 124 Parte C (0.125 g; 0.519 mmol) en THF (2.60 mL) se agregaron 2-(metiltio)etanol (0.105 mL; 1.14 mmol) y Ph_3P (0.30 g; 1.142 mmol), seguido por la adición lenta de DIAD (0.222 mL; 1.142 mmol). La mezcla de reacción se agitó a 25°C durante 16 h bajo Ar, luego se diluyó con agua y se extrajo con EtOAc (3x). Los extractos orgánicos combinados se lavaron con NaOH acuoso 1N y salmuera, se secaron ($MgSO_4$), y concentraron *in vacuo*. El producto crudo se procesó por cromatografía (SiO_2;

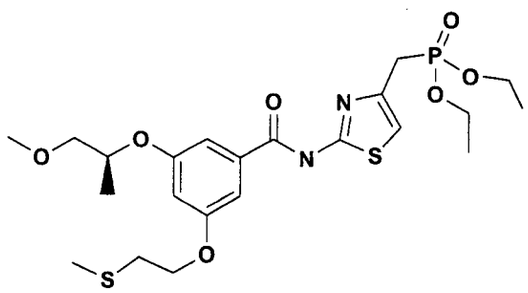
gradiente de etapa de 20-30-50-60% solvente B, donde solvente A = hexanos y solvente B = EtOAc) para dar el compuesto de la Parte A (61.8 mg; 38%).

B.



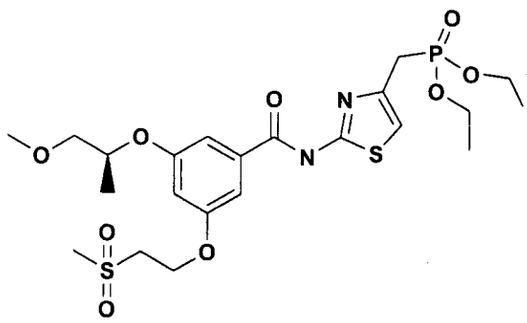
A una solución del compuesto de la Parte A (0.062 g; 0.197 mmol) en THF (1.63 mL) y agua (0.163 mL) se le agregó $LiOH.H_2O$ (0.016 g; 0.393 mmol). La mezcla de reacción se agitó a 45°C durante 1 h en un vial sellado, luego un equivalente adicional de LiOH se agregó. La mezcla de reacción se agitó a 45°C durante 16 h, luego se enfrió a temperatura ambiente. Los volátiles se removieron *in vacuo*, y la solución acuosa restante se acidificó con HCl acuoso 0.5N a un pH <2. La capa acuosa se volvió a extraer con EtOAc (3x). Los extractos orgánicos combinados se lavaron con salmuera, se secaron ($MgSO_4$), y concentraron *in vacuo* para dar el compuesto de la Parte B (0.052 g; 88%).

C.



A una solución del compuesto del Ejemplo 13 Parte E (0.059 g; 0.236 mmol) en DMF (0.98 mL) se agregaron HOAT (0.031 g; 0.226 mmol), compuesto de la Parte B (0.059 g; 0.196 mmol), DIPEA (0.034 mL; 0.196 mmol), y, finalmente, EDCI (0.043 g; 0.226 mmol). La mezcla de reacción se agitó a 25°C durante 16 h. El agua se agregó, y la mezcla se extrajo con EtOAc (3x). Los extractos orgánicos combinados se lavaron con NH_4Cl acuoso saturado, $NaHCO_3$ acuoso saturado, y salmuera, se secaron ($MgSO_4$), y concentraron *in vacuo*. El residuo se purificó por HPLC preparativa (Columna de fase inversa YMC ODS-5u 30 x 100 mm; relación de flujo = 40 mL/min, 25 hasta 100% solvente B durante 12 min, donde el solvente A = 90:10:0.1 H_2O:CH_3CN:TFA y el solvente B = 90:10:0.1 CH_3CN:H_2O:TFA) para dar el compuesto del título (62.3 mg; 60%) como un aceite transparente, incoloro. $[M + H]^+$ = 533.4; ^1H RMN (400 MHz, $CDCl_3$): δ 1.23 - 1.31 (m, 9 H), 2.15 (s, 3 H), 3.27 (s, 1 H), 3.31 - 3.37 (m, 4 H), 3.44 - 3.56 (m, 2 H), 3.99 - 4.15 (m, 4 H), 4.19 (t, 2 H), 4.65 - 4.77 (m, 1 H), 6.69 - 6.74 (m, 1 H), 6.95 - 7.00 (m, 1 H), 7.28 - 7.33 (m, 1 H), 7.35 - 7.40 (m, 1 H).

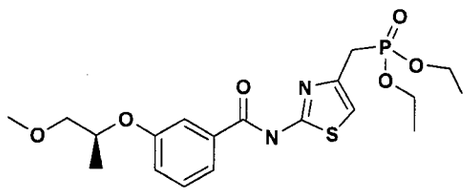
EJEMPLO 135



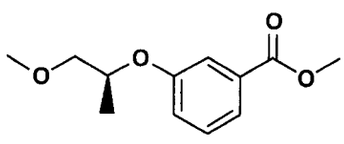
A una solución 0°C del compuesto del Ejemplo 134 Parte C (0.040 g; 0.075 mmol) en CH_2Cl_2 (0.75 mL) se le agregó *m*CPBA

(0.026 g; 0.15 mmol). La mezcla de reacción se agitó durante 1 h a 0°C, luego se entibió a temperatura ambiente. La mezcla de reacción se filtró, se apagó con $NaHCO_3$ acuoso saturado, y se extrajo con CH_2Cl_2 (3x). Los extractos orgánicos combinados se lavaron con salmuera, se secaron ($MgSO_4$), y concentraron *in vacuo*. El residuo se purificó por HPLC preparativa (Columna de fase inversa YMC ODS-5u 30 x 100 mm; relación de flujo = 40 mL/min, 25 hasta 100% solvente B durante 12 min, donde el solvente A = 90:10:0.1 H_2O: CH_3CN: TFA y el solvente B = 90:10: 0.1 CH_3CN: H_2O: TFA) para dar el compuesto del título (10.6 mg; 25%) como un aceite transparente, incoloro. $[M + H]^+$ = 565.2; ^1H RMN (400 MHz, $CDCl_3$): δ 1.26 - 1.34 (m, 9 H), 3.05 (s, 3 H), 3.29 (s, 1 H), 3.34 (s, 1 H), 3.39 (s, 4 H), 3.43 (t, 3 H), 3.49 - 3.60 (m, 2 H), 4.07 - 4.18 (m, 4 H), 4.52 (t, *J*=10.44 Hz, 3 H), 4.69 - 4.79 (m, 1 H), 6.72 - 6.78 (m, 1 H), 6.99 - 7.05 (m, 1 H), 7.40 (s, 1 H), 7.45 (s, 1 H).

EJEMPLO 136



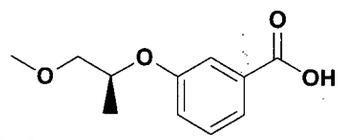
A.



20735

A una solución fría (0°C) de 2-hidroxi-metilbenzoato (0.20 g; 1.31 mmol) en THF (5.70 mL) se agregaron (R)-(-)-1-metoxi-2-propanol (0.178 g; 1.97 mmol) y Ph_3P (0.517 g; 1.97 mmol), seguido por la adición lenta de DIAD (0.398 g; 1.97 mmol). La mezcla de reacción se agitó a 25°C durante 16 h bajo Ar, luego se diluyó con agua y se extrajo con EtOAc (3x). Los extractos orgánicos combinados se lavaron con NaOH acuoso 1N y salmuera, se secaron ($MgSO_4$), y concentraron *in vacuo*. El residuo se procesó por cromatografía (SiO_2; gradiente en etapas desde 10-20-30% solvente B, donde el solvente A = hexanos y el solvente B = EtOAc) para dar el compuesto de la Parte A (0.219g; 74%).

B.

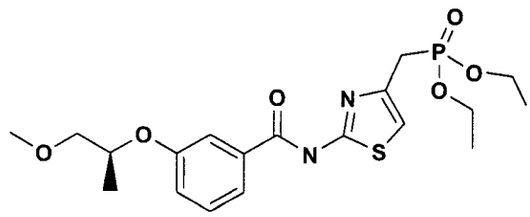


A una solución del compuesto de la Parte A (0.219 g; 0.975 mmol) en THF (3.75 mL) y agua (1.19 mL) se le agregó $LiOH.H_2O$ (0.049 g; 1.07 mmol). La mezcla de reacción se agitó a 45°C durante 1 h en un vial sellado, luego un equivalente adicional de LiOH se agregó. La mezcla de reacción se agitó a 50°C durante 2 h, luego se enfrió a temperatura ambiente. Los volátiles se removieron *in vacuo*, y la solución acuosa restante se acidificó con HCl acuoso 0.5N a un pH < 2. La capa acuosa se volvió a extraer con EtOAc (3x). Los extractos orgánicos combinados se lavaron con salmuera, se secaron

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($MgSO_4$), y concentraron *in vacuo* para dar el compuesto de la Parte B (0.221 g; 100%).

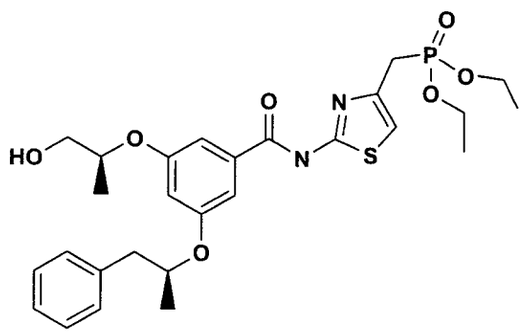
C.



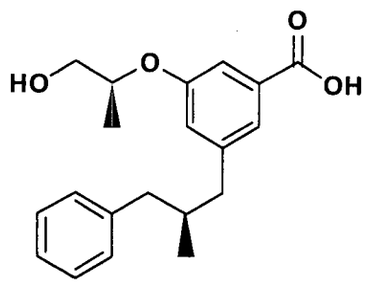
A una solución del compuesto del Ejemplo 13 Parte E (0.043 g; 0.171 mmol) en DMF (0.55 mL) se le agregaron HOAT (0.022 g; 0.164 mmol), compuesto de la Parte B (0.030 g; 0.143 mmol), DIPEA (0.029 mL; 0.164 mmol), y, finalmente, EDCI (0.031 g; 0.164 mmol). La mezcla de reacción se agitó a 25°C durante 16 h. El agua se agregó, y la mezcla se extrajo con EtOAc (3x). Los extractos orgánicos combinados se lavaron con NH_4Cl acuoso saturado, $NaHCO_3$ acuoso saturado, y salmuera, se secaron ($MgSO_4$), y concentraron *in vacuo*. El residuo se purificó por HPLC preparativa (Fase inversa YMC columna ODS-5µm, 30 x 100 mm; relación de flujo = 40 mL/min, 25 hasta 100% solvente B durante 12 min, donde el solvente A = 90: 10: 0.1 H_2O: CH_3CN: TFA y solvente B = 90: 10: 0.1 CH_3CN: H_2O: TFA) para dar el compuesto del título (17.3 mg; 27%) como un aceite pegajoso, amarillo transparente. $[M + H]^+$ = 443.3; ^1H RMN (400 MHz, $CDCl_3$): δ 1.22 - 1.30 (m, 9 H), 3.30 (s, 1 H), 3.35 (s, 3 H), 3.35 (s, 4 H), 3.47

- 3.58 (m, 2 H), 4.01 - 4.16 (m, 4 H), 4.75 - 4.83 (m, 1 H), 6.96 - 7.00 (m, *J*=3.85 Hz, 1 H), 7.14 - 7.18 (m, *J*=8.24, 2.20 Hz, 1 H), 7.37 (t, *J*=7.97 Hz, 1 H), 7.70 (d, *J*=7.70 Hz, 2 H), 7.70 (d, *J*=7.70 Hz, 1 H).

EJEMPLO 137



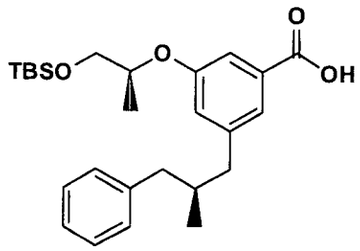
A.



A una solución del ácido del Ejemplo 33 Parte A (0.058 g; 0.17 mmol) en Et_2O (1.30 mL) bajo Ar se le agregó TMSI (0.203 g; 1.01 mmol). La mezcla de reacción se agitó a 25°C durante 16 h, luego se enfrió a -40°C, se apagó cuidadosamente con agua, y se concentró *in vacuo*. El residuo se diluyó con EtOAc y HCl acuoso 1N. La capa orgánica se lavó con 10% (p/v) $Na_2S_2O_3$ acuoso, se lavó con salmuera, se secó ($MgSO_4$),

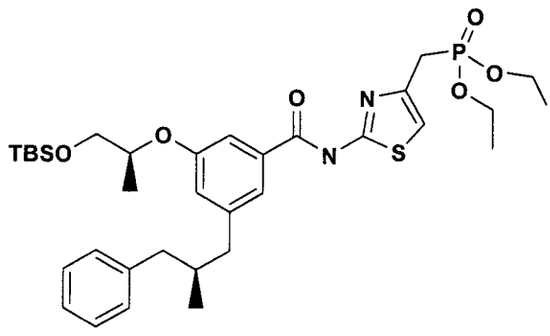
y concentró *in vacuo* para dar el compuesto de la Parte A (0.056 g; 99%) como un aceite amarillo.

B.



Una solución de TBSCl (0.076 g; 0.504 mmol) en DMF (0.37 mL) se agregó al compuesto de la Parte A (0.056 g; 0.17 mmol). El imidazol (0.069 g; 1.01 mmol) se agregó, y la mezcla de reacción se agitó durante 2 h a 25°C, luego se dividió entre EtOAc y NH_4Cl acuoso saturado. La fase orgánica se lavó con NH_4Cl acuoso saturado y salmuera, se secó ($MgSO_4$), y concentró *in vacuo*. El residuo se procesó por cromatografía (SiO_2; gradiente en etapas desde 20-25-30% solvente B, donde el solvente A = hexanos y el solvente B = EtOAc) para dar el compuesto de la Parte B (0.057 g; 76%).

C.



A una solución del compuesto del Ejemplo 13 Parte E (0.038 g; 0.152 mmol) en DMF (0.49 mL) se le agregaron HOAT

Organizacion y
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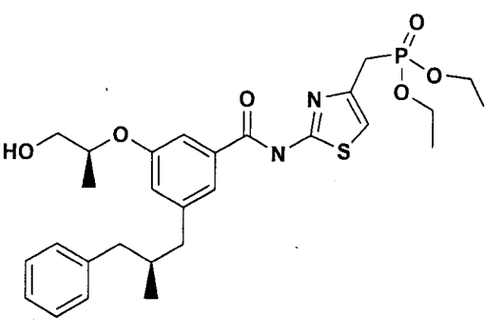
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(0.020 g; 0.146 mmol), compuesto de la Parte B (0.057 g; 0.127 mmol), DIPEA (0.026 mL; 0.146 mmol), y, finalmente, EDCI (0.028 g; 0.146 mmol). La mezcla de reacción se agitó a 25°C durante 16 h. El agua se agregó, y la mezcla se extrajo con EtOAc (3x). Los extractos orgánicos combinados se lavaron con NH_4Cl acuoso saturado, $NaHCO_3$ acuoso saturado, y salmuera. La capa orgánica se secó ($MgSO_4$), y concentró *in vacuo* para dar el compuesto de la Parte C (0.063 g; 74%) como un aceite transparente, dorado.

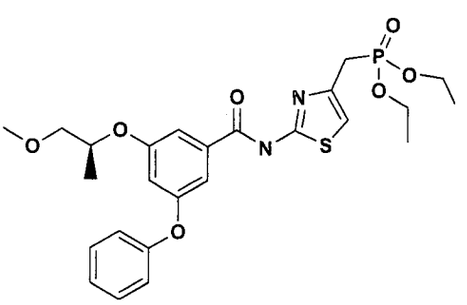
D.



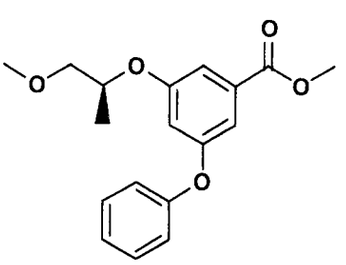
A una solución 0°C del compuesto de la Parte C (0.063; 0.094 mmol) en THF (0.47 mL) se le agregó TBAF (0.090 mL de una solución 1 M; 0.094 mmol). La reacción se agitó durante 1 h a 0°C y una adición equivalente de TBAF (0.090 mL de una solución 1 M; 0.094 mmol) se agregó. La reacción se agitó a 0°C durante otra 1 h, luego se concentró *in vacuo*. El residuo se dividió entre EtOAc y salmuera. La capa orgánica se lavó con salmuera, se secó ($MgSO_4$), y concentró *in vacuo*. El residuo se purificó por HPLC preparativa (Fase inversa YMC columna ODS-5µm 30 x 100 mm; relación de flujo = 40 mL/min,

25 hasta 100% solvente B durante 12 min, donde el solvente A = 90: 10: 0.1 H_2O: CH_3CN: TFA y el solvente B = 90:10:0.1 CH_3CN: H_2O: TFA) para dar el compuesto del título (23.6 mg; 45%) como un aceite claro, incoloro. $[M + H]^+$ = 563.5; ^1H RMN (400 MHz, $CDCl_3$): δ 1.16 - 1.31 (m, *J*=11.82, 6.32 Hz, 12 H), 1.98 (s, 1 H), 2.77 - 2.87 (m, *J*=13.74 Hz, 1 H), 2.93 - 3.02 (m, *J*=13.74 Hz, 1 H), 3.27 (s, 1 H), 3.32 (s, 1 H), 3.61 - 3.69 (m, 1 H), 3.69 - 3.76 (m, 1 H), 4.01 - 4.14 (m, 4 H), 4.60 - 4.72 (m, 2 H), 6.62 - 6.66 (m, *J*=2.20, 2.20 Hz, 1 H), 6.96 (d, *J*=3.85 Hz, 1 H), 7.09 - 7.24 (m, 5 H), 7.28 (s, 1 H) 7.32 (s, 1 H).

EJEMPLO 138



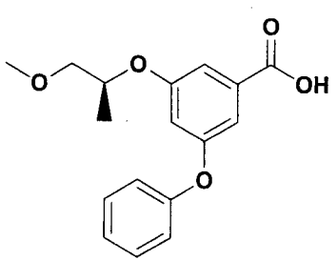
A.



Una solución del compuesto del Ejemplo 124 Parte C (0.100 g; 0.416 mmol), ácido fenilborónico (0.102 g; 0.832 mmol), acetato de cobre (II) (0.151 g; 0.832 mmol), Et_3N

(0.211 g; 2.08 mmol), y mallas moleculares 4Å recientemente activadas (1.2 g) en CH_2Cl_2 (8.32 mL) se agitó a 25°C durante 16 h. El solvente adicional (8 mL), dos equivalentes cada uno de ácido borónico, acetato de cobre (II), y Et_3N se agregaron después de 2 días. Después de un total de 5 días, 70% de conversión se observó. La mezcla de reacción se filtró y se lavó con CH_2Cl_2. Los filtrados combinados se concentraron *in vacuo*, y el residuo se dividió entre EtOAc y HCl acuoso 1N. La capa orgánica se lavó con $NaHCO_3$ acuoso saturado y salmuera, se secó ($MgSO_4$), y concentraron *in vacuo*. El producto crudo se procesó por cromatografía (SiO_2; gradiente de etapa de 10-20-30% solvente B, donde el solvente A = hexanos y el solvente B = EtOAc) para dar el compuesto de la Parte A (70.2 mg; 83% de rendimiento con base en material de partida recuperado).

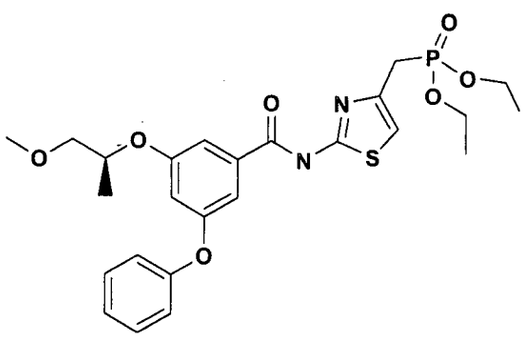
B.



A una solución del compuesto de la Parte A (0.070 g; 0.222 mmol) en THF (0.85 mL) y agua (0.27 mL) se le agregó $LiOH.H_2O$ (0.010 g; 0.244 mmol). La mezcla de reacción se agitó a 45°C durante 1 h en un vial sellado, luego un equivalente adicional de $LiOH.H_2O$ se agregó. La mezcla de

reacción se agitó a 45°C durante 3 h adicionales, luego se enfrió a temperatura ambiente. Los volátiles se removieron *in vacuo*, y la solución acuosa restante se acidificó con HCl acuoso 0.5N a un pH <2. La capa acuosa se volvió a extraer con EtOAc (3x). Los extractos orgánicos combinados se lavaron con salmuera, se secaron ($MgSO_4$), y concentraron *in vacuo* para dar el compuesto de la Parte B (0.060 g; 90%).

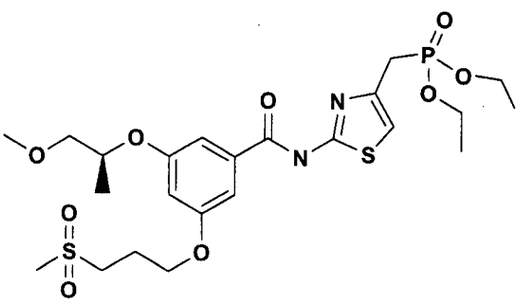
C.



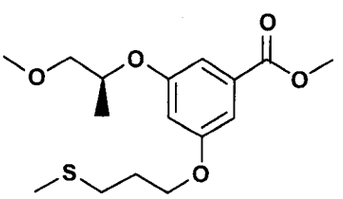
A una solución del compuesto del Ejemplo 13 Parte E (0.030 g; 0.119 mmol) en DMF (0.38 mL) se le agregaron HOAT (0.016 g; 0.114 mmol), compuesto de la Parte B (0.03 g; 0.099 mmol), DIPEA (0.020 mL; 0.114 mmol), y, finalmente, EDCI (0.022 g; 0.114 mmol). La mezcla de reacción se agitó a 25°C durante 16 h. Un equivalente adicional del compuesto del Ejemplo 13 Parte E se agregó, y la mezcla de reacción se agitó a 25°C durante 16 h adicionales sin conversión adicional. El agua se agregó, y la mezcla se extrajo con EtOAc (3x). Los extractos orgánicos combinados se lavaron con NH_4Cl acuoso saturado, $NaHCO_3$ acuoso saturado, y salmuera, se secaron ($MgSO_4$), y concentraron *in vacuo*. El residuo se

purificó por HPLC preparativa (Fase inversa YMC columna ODS-5μm 30 x 100 mm; relación de flujo = 40 mL/min, 25 hasta 100% solvente B durante 12 min, donde el solvente A = 90:10:0.1 H_2O: CH_3CN: TFA y solvente B = 90: 10: 0.1 CH_3CN: H_2O: TFA) para dar el compuesto del título (0.010 mg; 20%) como un vidrio pegajoso, viscoso. $[M + H]^+$ = 535.5; ^1H RMN (400 MHz, $CDCl_3$): δ 1.21 - 1.31 (m, 9 H), 3.26 (s, 1 H), 3.29 - 3.36 (m, 4 H), 3.46 - 3.53 (m, 2 H), 4.02 - 4.15 (m, 4 H), 4.73 - 4.87 (m, 1 H), 6.74 - 6.81 (m, 1 H), 6.92 - 7.02 (m, 3 H), 7.09 (t, *J*=7.42 Hz, 1 H), 7.25 - 7.34 (m, 3 H), 7.48 (s, 1 H).

EJEMPLO 139



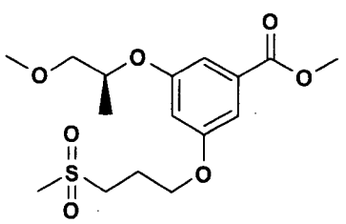
A.



A una solución 0°C del compuesto del Ejemplo 124 Parte C (0.110 g; 0.458 mmol) en THF (2.29 mL) se le agregaron 3-(metiltio)propan-1-ol (0.107 mL; 1.01 mmol) y Ph_3P (0.265 g; 1.01 mmol), seguido por la adición lenta de DIAD (0.195 mL;

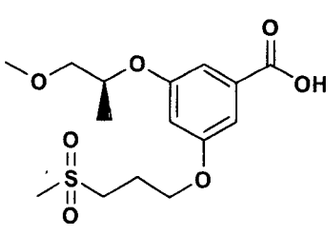
1.01 mmol). La mezcla de reacción se agitó a 25°C durante 16 h bajo Ar, luego se diluyó con agua y se extrajo con EtOAc (3x). Los extractos orgánicos combinados se lavaron con NaOH acuoso 1N y salmuera, se secaron ($MgSO_4$), y concentraron *in vacuo*. El producto crudo se procesó por cromatografía (SiO_2; gradiente en etapas desde 10-20% solvente B, donde el solvente A = hexanos y el solvente B = EtOAc) para dar el compuesto de la Parte A (0.110 g; 73%).

B.



A una solución 0°C del compuesto de la Parte A (0.110 g; 0.334 mmol) en CH_2Cl_2 (3.34 mL) se le agregó *m*CPBA (0.115 g; 0.67 mmol). La mezcla de reacción se agitó durante 1 h a 0°C, luego $NaHCO_3$ acuoso saturado se agregó y la mezcla se extrajo con CH_2Cl_2 (3x). Los extractos orgánicos combinados se lavaron con salmuera, se secaron ($MgSO_4$), y concentraron *in vacuo* para dar el compuesto de la Parte B (0.161 g; 88%).

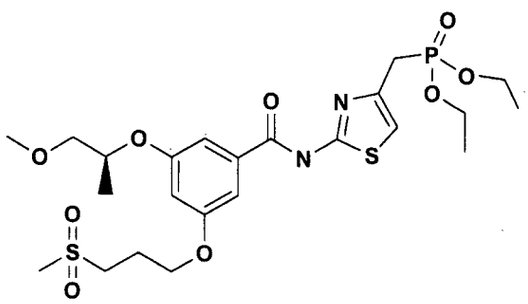
C.



A una solución del compuesto de la Parte C (0.162 g; 0.450 mmol) en THF (1.73 mL) y agua (0.549 mL) se le agregó

$LiOH.H_2O$ (0.021 g; 0.495 mmol). La mezcla de reacción se agitó a 45°C durante 1 h en un vial sellado, luego un equivalente adicional de LiOH se agregó. La mezcla de reacción se agitó a 45°C durante 16 h, luego se enfrió a temperatura ambiente. Los volátiles se removieron *in vacuo*, y la solución acuosa restante se acidificó con HCl acuoso 0.5N a un pH <2. La capa acuosa se volvió a extraer con EtOAc (3x). Los extractos orgánicos combinados se lavaron con salmuera, se secaron ($MgSO_4$), y concentraron *in vacuo* para dar el compuesto de la Parte C (0.147 g; 94%).

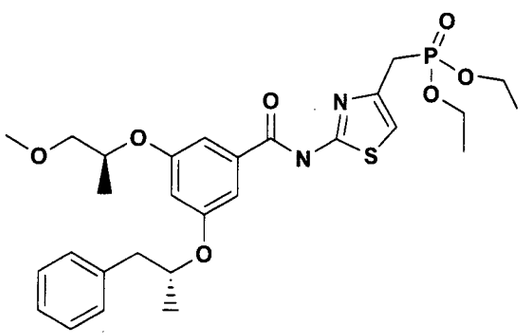
D.



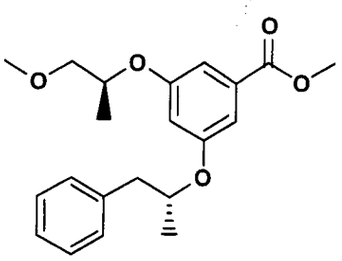
A una solución del compuesto del Ejemplo 13 Parte E (0.026 g; 0.104 mmol) en DMF (0.33 mL) se le agregaron HOAT (0.014 g; 0.100 mmol), compuesto de la Parte C (0.030 g; 0.087 mmol), DIPEA (0.017 mL; 0.100 mmol), y, finalmente, EDCI (0.019 g; 0.100 mmol). La mezcla de reacción se agitó a 25°C durante 16 h. El agua se agregó, y la mezcla se extrajo con EtOAc (3x). Los extractos orgánicos combinados se lavaron con NH_4Cl acuoso saturado, $NaHCO_3$ acuoso saturado, y salmuera, se secaron ($MgSO_4$), y concentraron *in vacuo*. El residuo se purificó por HPLC preparativa (Columna de fase inversa YMC

ODS-5u 30 x 100 mm; relación de flujo = 40 mL/min, 25 hasta 100% solvente B durante 12 min, donde el solvente A = 90:10:0.1 H_2O: CH_3CN: TFA y el solvente B = 90: 10: 0.1 CH_3CN: H_2O: TFA) para dar el compuesto del título (8 mg, 16% de rendimiento) como un liofilato sólido blanco. $[M + H]^+$ = 579.4; ^1H RMN (400 MHz, $CDCl_3$): δ 1.14 - 1.28 (m, 9 H), 2.20 - 2.33 (m, 2 H), 2.89 (s, 3 H), 3.13 - 3.26 (m, 4 H), 3.33 (s, 3 H), 3.40 - 3.54 (m, 2 H), 3.92 - 4.05 (m, 4 H), 4.05 - 4.12 (m, *J*=5.77, 5.77 Hz, 2 H), 4.53 - 4.63 (m, 1 H), 6.61 - 6.65 (m, 1 H), 6.78 - 6.86 (m, *J*=3.85 Hz, 1 H), 7.14 (s, 1 H), 7.19 (s, 1 H).

EJEMPLO 140



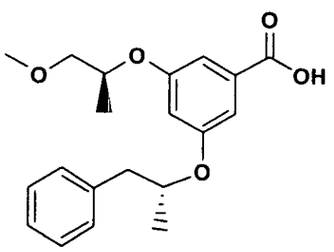
A.



A una solución 0°C del compuesto del Ejemplo 124 Parte C (0.110 g; 0.458 mmol) en THF (2.29 mL) se le agregaron (S)-(+)-1-fenil-2-propanol (0.138 mL; 1.01 mmol) y Ph_3P (0.265 g;

1.01 mmol), seguido por la adición lenta de DIAD (0.195 mL; 1.01 mmol). La mezcla de reacción se agitó a 25°C durante 16 h bajo Ar, luego se diluyó con agua y se extrajo con EtOAc (3x). Los extractos orgánicos combinados se lavaron con NaOH acuoso 1N y salmuera, se secaron ($MgSO_4$), y concentraron *in vacuo*. El residuo se procesó por cromatografía (SiO_2; gradiente en etapas desde 5-10% solvente B, donde el solvente A = hexanos y el solvente B = EtOAc) para dar el compuesto de la Parte A (0.133 g; 81%).

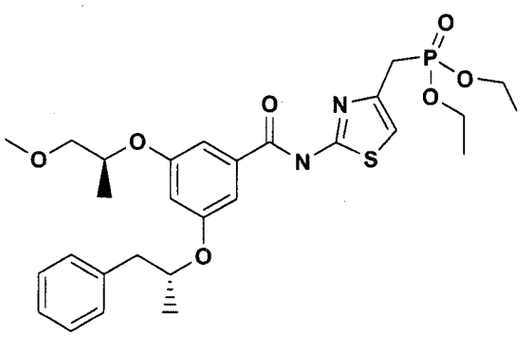
B.



A una solución del compuesto de la Parte A (0.133 g; 0.371 mmol) en THF (1.43 mL) y agua (0.45 mL) se le agregó $LiOH.H_2O$ (0.017 g; 0.408 mmol). La mezcla de reacción se agitó a 45°C durante 1 h en un vial sellado, luego un equivalente adicional de LiOH se agregó. La mezcla de reacción se agitó a 45°C durante 16 h, luego se enfrió a temperatura ambiente. Los volátiles se removieron *in vacuo*, y la solución acuosa restante se acidificó con HCl acuoso 0.5N a un pH <2. La capa acuosa se volvió a extraer con EtOAc (3x). Los extractos orgánicos combinados se lavaron con salmuera, se secaron ($MgSO_4$), y concentraron *in vacuo* para

dar el compuesto de la Parte B (0.123 g; 96%).

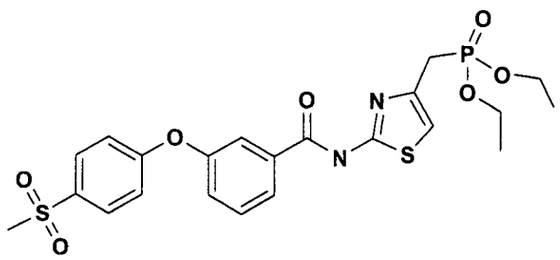
C.



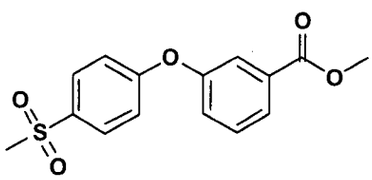
A una solución del compuesto del Ejemplo 13 Parte E (0.026 g; 0.105 mmol) en DMF (0.34 mL) se le agregaron HOAT (0.014 g; 0.100 mmol), compuesto de la Parte B (0.030 g; 0.087 mmol), DIPEA (0.017 mL; 0.100 mmol), y, finalmente, EDCI (0.019 g; 0.100 mmol). La mezcla de reacción se agitó a 25°C durante 16 h. El agua se agregó, y la mezcla se extrajo con EtOAc (3x). Los extractos orgánicos combinados se lavaron con NH_4Cl acuoso saturado, $NaHCO_3$ acuoso saturado, y salmuera, se secaron ($MgSO_4$), y concentraron *in vacuo*. El residuo se purificó por HPLC preparativa (Columna de fase inversa YMC ODS-5u 30 x 100 mm; relación de flujo = 40 mL/min, 25 hasta 100% solvente B durante 12 min, donde solvente A = 90: 10: 0.1 H_2O: CH_3CN: TFA y el solvente B = 90: 10: 0.1 CH_3CN: H_2O: TFA) para dar el compuesto del título (16.4 mg; 33%) como un aceite claro, incoloro. $[M + H]^+$ = 577.4; ^1H RMN (400 MHz, $CDCl_3$): δ 1.04 - 1.32 (m, 12 H), 2.65 - 2.86 (m, J=13.74 Hz, 1 H), 2.88 - 3.06 (m, 1 H), 3.10 - 3.25 (m, J=20.89 Hz, 2 H), 3.32 (s, 3 H), 3.36 - 3.55 (m, 2 H), 3.85 - 4.05 (m, J=7.15

Hz, 4 H), 4.34 - 4.63 (m, 2 H), 6.41 - 6.66 (m, 1 H), 6.67 - 6.81 (m, 1 H), 6.95 - 7.07 (m, 2 H), 7.08 - 7.29 (m, 5 H), 10.44 (s, 1 H), 10.44 (s, 1 H).

EJEMPLO 141



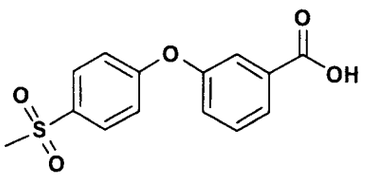
A.



A una solución de 3-hidroxi-metilbenzoato (0.500 g; 3.29 mmol) en DMF (8.23 mL) se le agregaron K_2CO_3 (0.908 g; 6.57 mmol) y fluoro-4-(metilsulfonil)benceno (0.573 g; 3.29 mmol). La mezcla de reacción se agitó a 120°C durante 2 días bajo Ar, luego se enfrió a temperatura ambiente. Los volátiles se removieron *in vacuo*. El residuo se dividió entre $NaHCO_3$ acuoso saturado y EtOAc. La capa orgánica se lavó con HCl acuoso 1N y salmuera, se secó ($MgSO_4$), y concentró *in vacuo*. El residuo se procesó por cromatografía (SiO_2; gradiente en etapas desde 20-30-40% solvente B, donde el solvente A = hexanos y el solvente B = EtOAc) para dar el

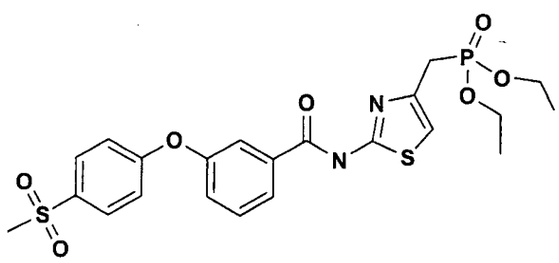
compuesto de la Parte A (0.583 g; 58%).

B.



A una solución del compuesto de la Parte A (0.200 g; 0.653 mmol) en THF (2.51 mL) y agua (0.80 mL) se le agregó $LiOH.H_2O$ (0.030 g; 0.718 mmol). La mezcla de reacción se agitó a 45°C durante 1 h en un vial sellado, luego un equivalente adicional de LiOH se agregó. La mezcla de reacción se agitó a 50°C durante 2 h, luego se enfrió a temperatura ambiente. Los volátiles se removieron *in vacuo*, y la solución acuosa restante se acidificó con HCl acuoso 0.5N a un pH < 2. La capa acuosa se volvió a extraer con EtOAc (3x). Los extractos orgánicos combinados se lavaron con salmuera, se secaron ($MgSO_4$), y concentraron *in vacuo* para dar el compuesto de la Parte B (0.176 g; 92%).

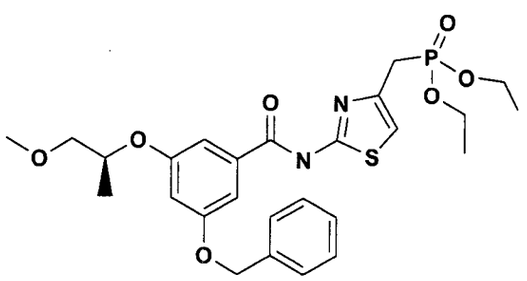
C.



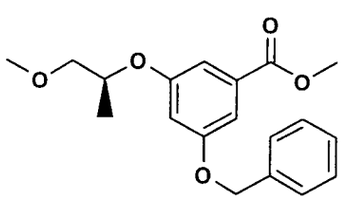
A una solución del compuesto del Ejemplo 13 Parte E (0.309 g; 0.124 mmol) en DMF (0.40 mL) se le agregaron HOAT (0.016 g; 0.118 mmol), compuesto de la Parte B (0.030 g; 0.103 mmol), DIPEA (0.021 mL; 0.118 mmol), y, finalmente, EDCI (0.023 g; 0.118 mmol). La mezcla de

reacción se agitó a 25°C durante 16 h. El agua se agregó, y la mezcla se extrajo con EtOAc (3x). Los extractos orgánicos combinados se lavaron con NH_4Cl acuoso saturado, $NaHCO_3$ acuoso saturado, y salmuera, se secaron ($MgSO_4$), y concentraron *in vacuo*. El residuo se purificó por CLAR preparativa (Columna de fase inversa YMC ODS-5u 30 x 100 mm; relación de flujo = 40 mL/min, 25 hasta 100% solvente B durante 12 min, donde el solvente A = 90: 10: 0.1 H_2O: CH_3CN: TFA y el solvente B = 90: 10: 0.1 CH_3CN: H_2O: TFA) para dar el compuesto del título (14.7 mg; 27%) como un sólido pegajoso, blanco. $[M + H]^+$ = 525.3; ^1H RMN (400 MHz, $CDCl_3$): δ 1.20 (t, J=7.15 Hz, 6 H), 2.99 (s, 3 H), 3.21 (s, 1 H), 3.26 (s, 1 H), 3.95 - 4.08 (m, 4 H), 6.85 - 6.92 (m, J=3.30 Hz, 1 H), 7.00 - 7.10 (m, J=8.79 Hz, 2 H), 7.24 - 7.32 (m, J=7.70 Hz, 1 H), 7.53 (t, J=7.97 Hz, 1 H), 7.77 (s, 1 H), 7.74 - 7.80 (m, 1 H), 7.84 (d, J=8.79 Hz, 2 H), 7.92 (d, J=7.70 Hz, 1 H).

EJEMPLO 142



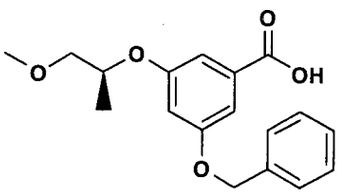
A.



A una solución 0°C del compuesto del Ejemplo 124 Parte C

(0.110 g; 0.458 mmol) en THF (2.29 mL) se le agregaron alcohol de bencilo (0.109 mL; 1.01 mmol) y Ph_3P (0.265 g; 1.01 mmol), seguido por la adición lenta de DIAD (0.195 mL; 1.01 mmol). La mezcla de reacción se agitó a 25°C durante 16 h bajo Ar, luego se diluyó con agua y se extrajo con EtOAc (3x). Los extractos orgánicos combinados se lavaron con NaOH acuoso 1N y salmuera, se secaron ($MgSO_4$), y concentraron *in vacuo*. El residuo se procesó por cromatografía (SiO_2; gradiente de etapa de 10-15-20% solvente B, donde el solvente A = hexanos y el solvente B = EtOAc) para dar el compuesto de la Parte A (0.160 g; 100%).

B.

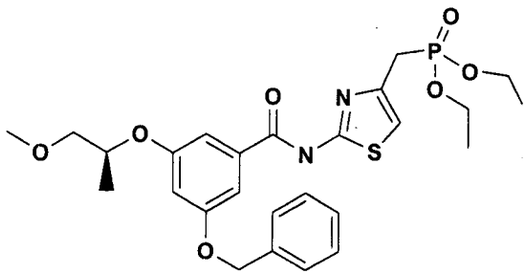


A una solución del compuesto de la Parte A (0.160 g; 0.483 mmol) en THF (1.86 mL) y agua (0.59 mL) se le agregó $LiOH.H_2O$ (0.022 g; 0.532 mmol). La mezcla de reacción se agitó a 45°C durante 2 h en un vial sellado, luego un equivalente adicional de LiOH se agregó. La mezcla de reacción se agitó a 45°C durante 16 h, luego se enfrió a temperatura ambiente. Los volátiles se removieron *in vacuo*, y la solución acuosa restante se acidificó con HCl acuoso 0.5N a un pH < 2. La capa acuosa se volvió a extraer con EtOAc (3x). Los extractos orgánicos combinados se lavaron con

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salmuera, se secaron ($MgSO_4$), y concentraron *in vacuo* para dar el compuesto de la Parte B (0.137 g; 90%).

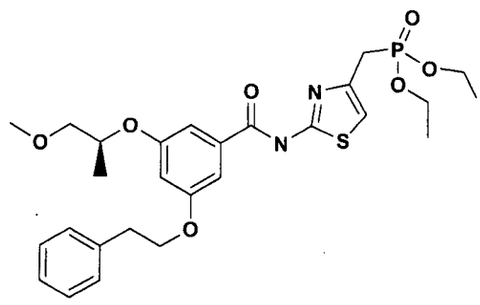
C.



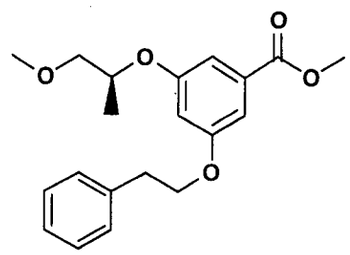
A una solución del compuesto del Ejemplo 13 Parte E (0.029 g; 0.114 mmol) en DMF (0.37 mL) se le agregaron HOAT (0.015 g; 0.109 mmol), compuesto de la Parte B (0.030 g; 0.095 mmol), DIPEA (0.019 mL; 0.109 mmol), y, finalmente, EDCI (0.021 g; 0.109 mmol). La mezcla de reacción se agitó a 25°C durante 16 h. El agua se agregó, y la mezcla se extrajo con EtOAc (3x). Los extractos orgánicos combinados se lavaron con NH_4Cl acuoso saturado, $NaHCO_3$ acuoso saturado, y salmuera, se secaron ($MgSO_4$), y concentraron *in vacuo*. El residuo se purificó por CLAR preparativa (Columna de fase inversa YMC ODS-5u 30 x 100 mm; relación de flujo = 40 mL/min, 25 hasta 100% solvente B durante 12 min, donde el solvente A = 90: 10: 0.1 H_2O: CH_3CN: TFA y el solvente B = 90: 10: 0.1 CH_3CN: H_2O: TFA) para dar el compuesto del título (18.6 mg; 36%) como un aceite claro, incoloro. $[M + H]^+$ = 549.2; ^1H RMN (400 MHz, $CDCl_3$): δ 1.13 - 1.29 (m, 9 H), 3.19 (s, 1 H), 3.24 (s, 2 H), 3.33 (s, 3 H), 3.39 - 3.46 (m, 1 H), 3.46 - 3.53 (m, 1 H),

3.89 - 4.04 (m, 4 H), 4.48 - 4.58 (m, *J*=3.85 Hz, 1 H), 5.01 (s, 2 H), 6.69 - 6.74 (m, 1 H), 6.75 - 6.80 (m, *J*=3.85 Hz, 1 H), 7.11 (s, 1 H), 7.23 - 7.38 (m, 5 H).

EJEMPLO 143



A.

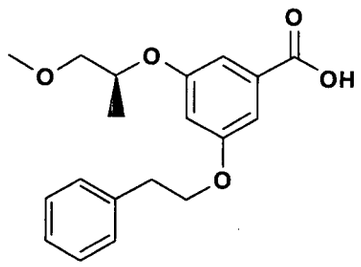


A una solución 0°C del compuesto del Ejemplo 124 Parte C (0.110 g; 0.458 mmol) en THF (2.29 mL) se le agregaron 2-feniletanol (0.121 mL; 1.01 mmol) y Ph_3P (0.265 g; 1.01 mmol), seguido por la adición lenta de DIAD (0.195 mL; 1.01 mmol). La mezcla de reacción se agitó a 25°C durante 16 h bajo Ar, luego se diluyó con agua y se extrajo con EtOAc (3x). Los extractos orgánicos combinados se lavaron con NaOH acuoso 1N y salmuera, se secaron ($MgSO_4$), y concentraron *in vacuo*. El residuo se procesó por cromatografía (SiO_2; gradiente en etapas desde 10-15-20% solvente B, donde el solvente A = hexanos y el solvente B = EtOAc) para dar el

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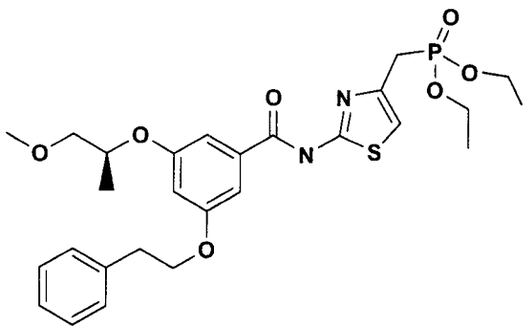
compuesto de la Parte A (0.127 g; 81%).

B.



A una solución del compuesto de la Parte A (0.127 g; 0.370 mmol) en THF (1.42 mL) y agua (0.45 mL) se le agregó $LiOH.H_2O$ (0.017 g; 0.407 mmol). La mezcla de reacción se agitó a 45°C durante 2 h en un vial sellado, luego un equivalente adicional de LiOH se agregó. La mezcla de reacción se agitó a 45°C durante 16 h, luego se enfrió a temperatura ambiente. Los volátiles se removieron *in vacuo*, y la solución acuosa restante se acidificó con HCl acuoso 0.5N a un pH <2. La capa acuosa se volvió a extraer con EtOAc (3x). Los extractos orgánicos combinados se lavaron con salmuera, se secaron ($MgSO_4$), y concentraron *in vacuo* para dar el compuesto de la Parte B (0.112 g; 91%).

C.

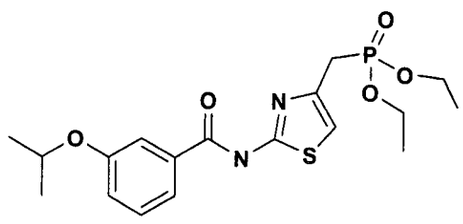


A una solución del compuesto del Ejemplo 13 Parte E

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(0.027 g; 0.109 mmol) en DMF (0.35 mL) se agregaron HOAT (0.014 g; 0.104 mmol), compuesto de la Parte B (0.030 g; 0.091 mmol), DIPEA (0.018 mL; 0.104 mmol), y, finalmente, EDCI (0.020 g; 0.104 mmol). La mezcla de reacción se agitó a 25°C durante 16 h. El agua se agregó, y la mezcla se extrajo con EtOAc (3x). Los extractos orgánicos combinados se lavaron con NH_4Cl acuoso saturado, $NaHCO_3$ acuoso saturado, y salmuera, se secaron ($MgSO_4$), y concentraron *in vacuo*. El residuo se purificó por CLAR preparativa (Columna de fase inversa YMC ODS-5u 30 x 100 mm; relación de flujo = 40 mL/min, 25 hasta 100% solvente B durante 12 min, donde el solvente A = 90: 10: 0.1 H_2O: CH_3CN: TFA y el solvente B = 90: 10: 0.1 CH_3CN: H_2O: TFA) para dar el compuesto del título (24.5 mg; 48%) como un aceite claro, incoloro. $[M + H]^+$ = 563.2; ^1H RMN (400 MHz, $CDCl_3$): δ 1.16 - 1.28 (m, 6 H), 3.02 (t, *J*=6.60 Hz, 2 H), 3.20 (s, 1 H), 3.25 (s, 1 H), 3.33 (s, 3 H), 3.41 - 3.54 (m, 2 H), 3.96 - 4.08 (m, 4 H), 4.16 (t, *J*=6.87 Hz, 2 H), 4.57 - 4.67 (m, 1 H), 6.63 - 6.69 (m, 1 H), 6.83 - 6.89 (m, *J*=3.85 Hz, 1 H), 7.13 - 7.28 (m, 7 H).

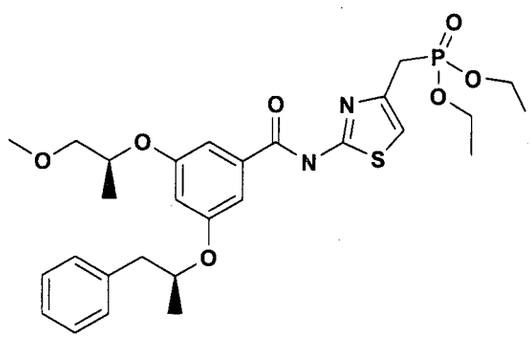
EJEMPLO 144



A una solución del compuesto del Ejemplo 13 Parte E

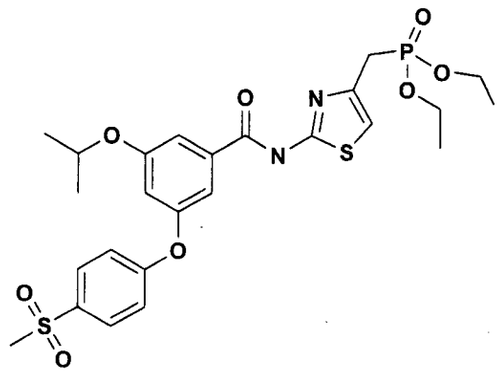
(0.100 g; 0.400 mmol) en DMF (2.0 mL) se le agregaron HOAT (0.052 g; 0.383 mmol), ácido 3-isopropoxibenzóico (0.060 g; 0.333 mmol), DIPEA (0.07 mL; 0.383 mmol), y, finalmente, EDCI (0.073 g; 0.383 mmol). La mezcla de reacción se agitó a 25°C durante 16 h. El agua se agregó, y la mezcla se extrajo con EtOAc (3x). Los extractos orgánicos combinados se lavaron con HCl acuoso 0.5N y salmuera, se secaron ($MgSO_4$), y concentraron *in vacuo*. El residuo se purificó por CLAR preparativa (Columna de fase inversa YMC ODS-5u 30 x 100 mm; relación de flujo = 40 mL/min, 25 hasta 100% solvente B durante 12 min, donde del solvente A = 90: 10: 0.1 H_2O: CH_3CN: TFA y el solvente B = 90: 10: 0.1 CH_3CN: H_2O: TFA) para dar el compuesto del título (9.4 mg; 7%) como un aceite claro, incoloro. $[M + H]^+$ = 413.1; ^1H RMN (400 MHz, $CDCl_3$): δ 1.21 - 1.34 (m, *J*=7.15, 7.15 Hz, 12 H), 3.26 (s, 1 H), 3.31 (s, 1 H), 4.00 - 4.14 (m, 4 H), 4.68 - 4.80 (m, 1 H), 6.91 - 6.99 (m, 1 H), 7.04 - 7.12 (m, *J*=8.25 Hz, 1 H), 7.31 - 7.41 (m, 1 H), 7.62 - 7.72 (m, 2 H).

EJEMPLO 145

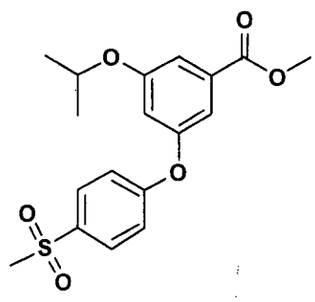


A una solución del compuesto del Ejemplo 13 Parte E (0.027 g; 0.105 mmol) en DMF (0.34 mL) se le agregaron HOAT (0.013 g; 0.093 mmol), ácido del Ejemplo 33 Parte A (0.030 g; 0.087 mmol), DIPEA (0.016 mL; 0.093 mmol), y, finalmente, EDCI (0.018 g; 0.932 mmol). La mezcla de reacción se agitó a 25°C durante 16 h. El agua se agregó, y la mezcla se extrajo con EtOAc (3x). Los extractos orgánicos combinados se lavaron con NH_4Cl acuoso saturado, $NaHCO_3$ acuoso saturado, y salmuera, se secaron ($MgSO_4$), y concentraron *in vacuo*. El residuo se purificó por CLAR preparativa (Columna de fase inversa YMC ODS-5u 30 x 100 mm; relación de flujo = 40 mL/min, 25 hasta 100% solvente B durante 12 min, donde el solvente A = 90:10:0.1 H_2O:CH_3CN:TFA y el solvente B = 90:10:0.1 CH_3CN:H_2O:TFA) para dar el compuesto del título (35.2 mg; 70%) como un aceite claro, incoloro. $[M + H]^+$ = 577.2; ^1H RMN (400 MHz, $CDCl_3$): δ 1.21 - 1.37 (m, 12 H), 2.82 - 2.93 (m, *J*=14.02, 5.22 Hz, 1 H), 2.99 - 3.09 (m, 1 H), 3.32 - 3.48 (m, 5 H), 3.51 - 3.66 (m, 2 H), 4.06 - 4.26 (m, 4 H), 4.68 - 4.84 (m, 2 H), 6.68 - 6.77 (m, 1 H), 6.96 - 7.07 (m, *J*=3.85 Hz, 1 H), 7.13 - 7.41 (m, 7 H), 10.77 (s, 1 H).

EJEMPLO 146

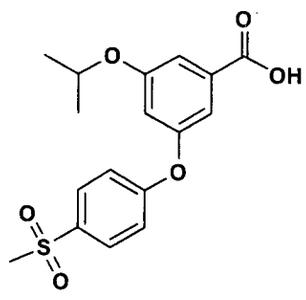


A.



A una solución 0°C del compuesto del Ejemplo 26 Parte A (0.166 g; 0.515 mmol) en THF (2.60 mL) se le agregaron iPrOH (0.087 mL; 1.13 mmol) y Ph_3P (0.30 g; 1.13 mmol), seguido por la adición lenta de DIAD (0.219 mL; 1.13 mmol). La mezcla de reacción se agitó a 25°C durante 16 h bajo Ar, luego se diluyó con agua y se extrajo con EtOAc (3x). Los extractos orgánicos combinados se lavaron con NaOH acuoso 1N y salmuera, se secaron ($MgSO_4$), y concentraron *in vacuo*. El residuo se procesó por cromatografía (SiO_2; gradiente en etapas desde 20-40% solvente B, donde el solvente A = hexanos y el solvente B = EtOAc) para dar el compuesto de la Parte A (0.258 g; >100%, contaminado con DIAD reducido).

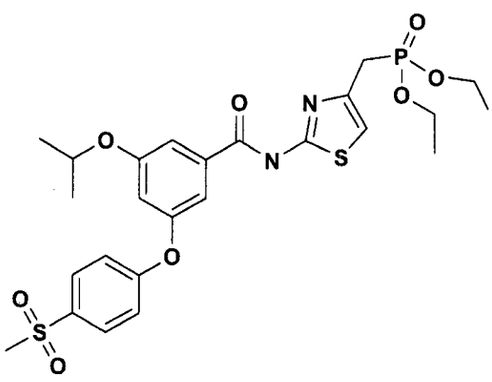
B.



A una solución del compuesto de la Parte A (0.189 g; 0.515 mmol) en THF (3.22 mL) y agua (0.62 mL) se le agregó

$LiOH.H_2O$ (0.024 g; 0.567 mmol). La mezcla de reacción se agitó a 45°C durante 1 h en un vial sellado, luego un equivalente adicional de LiOH se agregó. La mezcla de reacción se agitó a 45°C durante 16 h, luego se enfrió a temperatura ambiente. Los volátiles se removieron *in vacuo*, y la solución acuosa restante se acidificó con HCl acuoso 0.5N a un pH < 2. La capa acuosa se volvió a extraer con EtOAc (3x). Los extractos orgánicos combinados se lavaron con salmuera, se secaron ($MgSO_4$), y concentraron *in vacuo* para dar el compuesto de la Parte B (0.214 g; >100%, contaminado con DIAD reducido).

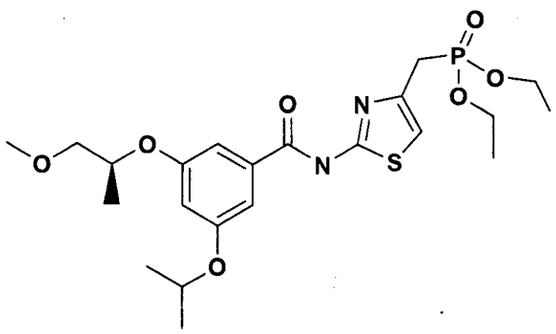
C.



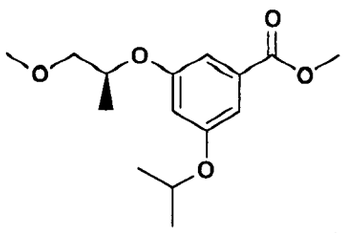
A una solución del compuesto del Ejemplo 13 Parte E (0.043 g; 0.17 mmol) en DMF (0.55 mL) se le agregaron HOAT (0.022 g; 0.164 mmol), compuesto de la Parte B (0.050 g; 0.143 mmol), DIPEA (0.029 mL; 0.164 mmol), y, finalmente, EDCI (0.031 g; 0.164 mmol). La mezcla de reacción se agitó a 25°C durante 16 h. El agua se agregó, y la mezcla se extrajo con EtOAc (3x). Los extractos orgánicos combinados se lavaron

con NH_4Cl acuoso saturado, $NaHCO_3$ acuoso saturado, y salmuera, se secaron ($MgSO_4$), y concentraron *in vacuo*. El residuo se purificó por CLAR preparativa (Columna de fase inversa YMC ODS-5u 30 x 100 mm; relación de flujo = 40 mL/min, 25 hasta 100% solvente B durante 12 min, donde el solvente A = 90:10:0.1 H_2O:CH_3CN:TFA y el solvente B = 90:10:0.1 CH_3CN:H_2O:TFA) para dar el compuesto del título (37.5 mg; 60%) como un aceite claro, incoloro. $[M + H]^+$ = 583.1; ^1H RMN (400 MHz, $CDCl_3$): δ 1.17 - 1.38 (m, 12 H), 3.04 (s, 3 H), 3.27 (s, 1 H), 3.32 (s, 1 H), 3.99 - 4.14 (m, 4 H), 4.64 - 4.77 (m, 1 H), 6.79 - 6.83 (m, 1 H), 6.88 - 6.96 (m, *J*=3.30 Hz, 1 H), 7.07 - 7.15 (m, *J*=8.79 Hz, 2 H), 7.30 - 7.36 (m, 1 H), 7.47 - 7.54 (m, 1 H), 7.84 - 7.92 (m, *J*=8.79 Hz, 2 H).

EJEMPLO 147

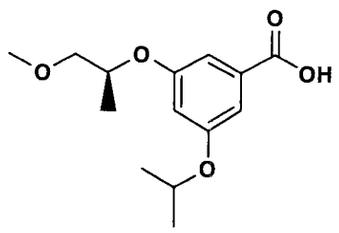


A.



A una solución 0°C del compuesto del Ejemplo 124 Parte C (0.100 g; 0.416 mmol) en THF (2.08 mL) se le agregaron iPrOH (0.019 mL; 0.916 mmol) y Ph_3P (0.240 g; 0.916 mmol), seguido por la adición lenta de DIAD (0.177 mL; 0.916 mmol). La mezcla de reacción se agitó a 25°C durante 16 h bajo Ar, luego se diluyó con agua y se extrajo con EtOAc (3x). Los extractos orgánicos combinados se lavaron con NaOH acuoso 1N y salmuera, se secaron ($MgSO_4$), y concentraron *in vacuo*. El residuo se procesó por cromatografía (SiO_2; gradiente en etapas desde 5-10% solvente B, donde el solvente A = hexanos y el solvente B = EtOAc) para dar el compuesto de la Parte A (82.2 mg; 70%).

B.

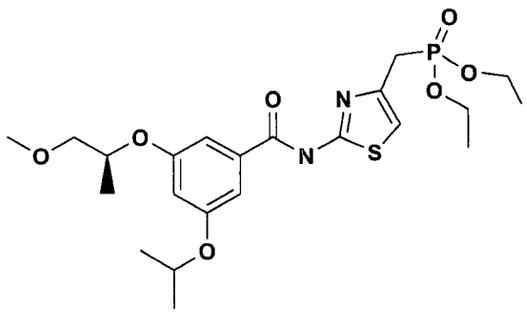


A una solución del compuesto de la Parte A (0.082 g; 0.291 mmol) en THF (1.82 mL) y agua (0.45 mL) se le agregó $LiOH.H_2O$ (0.014 g; 0.32 mmol). La mezcla de reacción se agitó a 45°C durante 3 h en un vial sellado, luego un equivalente adicional de LiOH. La mezcla de reacción se agitó a 45°C durante 16 h, luego se enfrió a temperatura ambiente. Los volátiles se removieron *in vacuo*, y la solución acuosa restante se acidificó con HCl acuoso 0.5N a un pH < 2. La

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capa acuosa se extrajo nuevamente con EtOAc (3x). Los extractos orgánicos combinados se lavaron con salmuera, se secaron ($MgSO_4$), y concentraron *in vacuo* para dar el compuesto de la Parte B (83.0 mg; 100%).

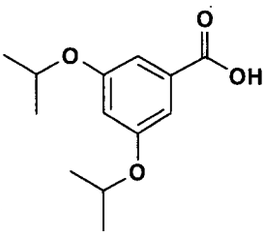
C.



A una solución del compuesto del Ejemplo 13 Parte E (0.034 g; 0.134 mmol) en DMF (0.43 mL) se le agregaron HOAT (0.018 g; 0.129 mmol), compuesto de la Parte B (0.030 g; 0.112 mmol), DIPEA (0.023 mL; 0.129 mmol), y, finalmente, EDCI (0.025 g; 0.129 mmol). La mezcla de reacción se agitó a 25°C durante 16 h. El agua se agregó, y la mezcla se extrajo con EtOAc (3x). Los extractos orgánicos combinados se lavaron con NH_4Cl acuoso saturado, $NaHCO_3$ acuoso saturado, y salmuera, se secaron ($MgSO_4$), y concentraron *in vacuo*. El residuo se purificó por CLAR preparativa (Columna de fase inversa YMC ODS-5u 30 x 100 mm; relación de flujo = 40 mL/min, 25 hasta 100% solvente B durante 12 min, donde el solvente A = 90:10:0.1 H_2O: CH_3CN: TFA y el solvente B = 90: 10: 0.1 CH_3CN: H_2O: TFA) para dar el compuesto del título (28.0 mg; 50%) como un aceite claro, incoloro. $[M + H]^+$ = 501.0; ^1H RMN (400

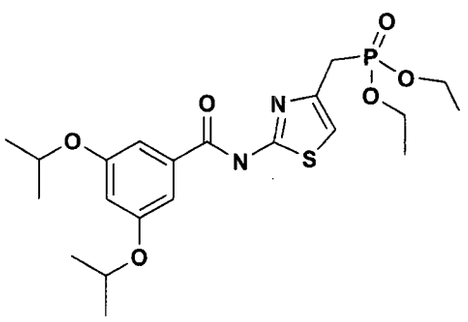
hexanos y el solvente B = EtOAc) para dar el compuesto de la Parte A (1.27 g; 85%).

B.



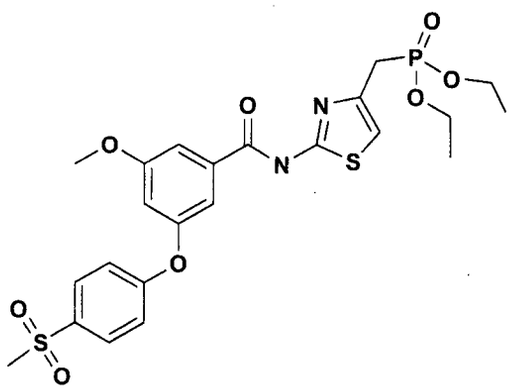
A una solución del compuesto de la Parte A (0.300 g; 1.19 mmol) en THF (7.44 mL) y agua (1.45 mL) se le agregó $LiOH.H_2O$ (0.055 g; 1.31 mmol). La mezcla de reacción se agitó a 45°C durante 3 h en un vial sellado, luego un equivalente adicional de LiOH se agregó. La mezcla de reacción se agitó a 45°C durante 16 h, luego se enfrió a temperatura ambiente. Los volátiles se removieron *in vacuo*, y la solución acuosa restante se acidificó con HCl acuoso 0.5N a un pH < 2. La capa acuosa se volvió a extraer con EtOAc (3x). Los extractos orgánicos combinados se lavaron con salmuera, se secaron ($MgSO_4$), y concentraron *in vacuo* para dar el compuesto de la Parte B (0.290 g; 100%).

C.



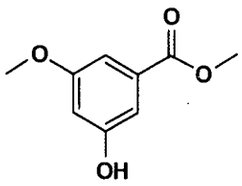
A una solución del compuesto del Ejemplo 13 Parte E (0.167 g; 0.668 mmol) en DMF (2.14 mL) se le agregaron HOAT (0.087 g; 0.641 mmol), compuesto de la Parte B (0.133 g; 0.557 mmol), DIPEA (0.116 mL; 0.641 mmol), y, finalmente, EDCI (0.123 g; 0.668 mmol). La mezcla de reacción se agitó a 25°C durante 16 h. El agua se agregó, y la mezcla se extrajo con EtOAc (3x). Los extractos orgánicos combinados se lavaron con NH_4Cl acuoso saturado, $NaHCO_3$ acuoso saturado, y salmuera, se secaron ($MgSO_4$), y concentraron *in vacuo*. El residuo se purificó por CLAR preparativa (Columna de fase inversa YMC ODS-5u 30 x 100 mm; relación de flujo = 40 mL/min, 25 hasta 100% solvente B durante 12 min, donde el solvente A = 90:10:0.1 H_2O:CH_3CN:TFA y el solvente B = 90:10:0.1 CH_3CN:H_2O:TFA) para dar el compuesto del título (95.1 mg; 36%) como un sólido blanco. $[M + H]^+$ = 471.5; ^1H RMN (400 MHz, $CDCl_3$): δ 1.24 - 1.37 (m, 18 H), 3.27 (s, 1 H), 3.32 (s, 1 H), 4.01 - 4.19 (m, 4 H), 4.58 - 4.72 (m, 2 H), 6.65 (s, 1 H), 6.92 - 7.00 (m, *J*=3.85 Hz, 1 H), 7.21 - 7.27 (m, 2 H).

EJEMPLO 149



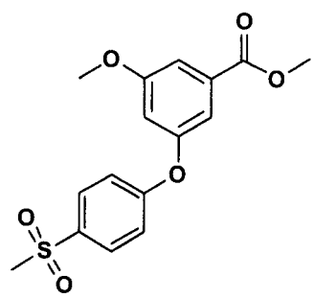
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A.



A una solución de 3,5-dihidroxibenzoato de metilo (1.75 g; 10.41 mmol) en acetona (14 mL se agregó K_2CO_3 (2.88 g; 20.82 mmol) y nBu_4NI (384 mg; 1.04 mmol), seguido por sulfato de dimetilo (985 µL; 10.41 mmol). La mezcla de reacción se calentó a reflujo (~65°C) durante 3 h, luego se enfrió a temperatura ambiente. La mezcla se filtró, y el filtrado se concentró *in vacuo*. El residuo se procesó por cromatografía (SiO_2; gradiente continuo desde 0 hasta 45% el solvente B durante 40 min, donde el solvente A = hexanos y el solvente B = EtOAc) para dar el compuesto de la Parte A (0.74 g; 39%) como un sólido blanco.

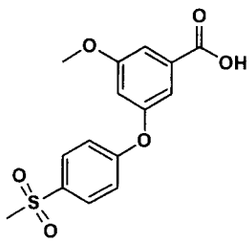
B.



A una mezcla del compuesto de la Parte A (75 mg; 0.412 mmol), 4-fluorofenil metil sulfona (72 mg; 0.412 mmol) y K_2CO_3 (114 mg; 0.824 mmol) se agregó DMF (1.6 mL). La mezcla de reacción se calentó a 120°C durante 5 h, luego se enfrió a temperatura ambiente. La mezcla se dividió entre EtOAc (10

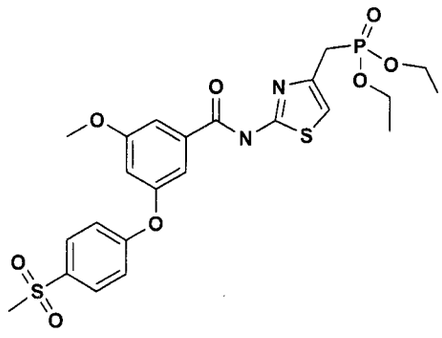
mL) y H_2O (10 mL). La fase orgánica se lavó con salmuera (5 mL), se secó ($MgSO_4$), y concentró *in vacuo*. El residuo se procesó por cromatografía (SiO_2; gradiente continuo desde 0 hasta 80% solvente B durante 12 min, donde el solvente A = hexanos y el solvente B = EtOAc) para dar el compuesto de la Parte B (119 mg; 86%) como un jarabe incoloro.

C.



A una solución del compuesto de la Parte B (118 mg; 0.351 mmol) en THF (0.47 mL), MeOH (0.47 mL), y H_2O (0.47 mL) se le agregó $LiOH \cdot H_2O$ (44 mg; 1.053 mmol). Después de 1 h de agitación, la mezcla se dividió entre EtOAc (6 mL) y HCl acuoso 0.5 N (6 mL). La fase acuosa se extrajo con EtOAc (6 mL). Los extractos orgánicos combinados se lavaron con salmuera (6 mL), se secaron ($MgSO_4$), y concentraron *in vacuo* para dar el compuesto de la Parte C (94 mg; 83%) como un sólido blanco.

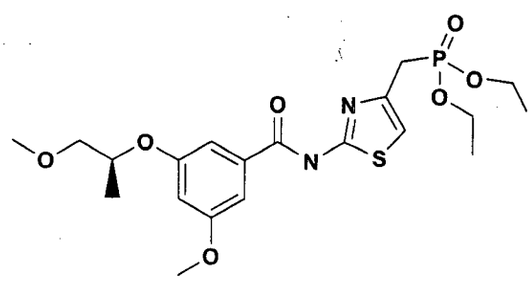
D.



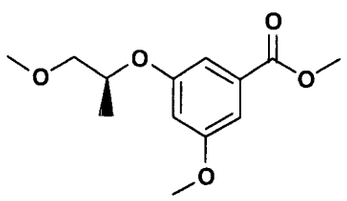
A una solución del compuesto del Ejemplo 13 Parte E

(0.038 g; 0.150 mmol) en DMF (0.48 mL) se le agregaron HOAT (0.020 g; 0.144 mmol), compuesto de la Parte C (0.040 g; 0.125 mmol), DIPEA (0.025 mL; 0.144 mmol), y, finalmente, EDCI (0.028 g; 0.144 mmol). La mezcla de reacción se agitó a 25°C durante 16 h. El agua se agregó, y la mezcla se extrajo con EtOAc (3x). Los extractos orgánicos combinados se lavaron con NH_4Cl acuoso saturado, $NaHCO_3$ acuoso saturado, y salmuera, se secaron ($MgSO_4$), y concentraron *in vacuo*. El residuo se purificó por CLAR preparativa (Columna de fase inversa YMC ODS-5u 30 x 100 mm; relación de flujo = 40 mL/min, 25 hasta 100% solvente B durante 12 min, donde el solvente A = 90:10:0.1 H_2O:CH_3CN:TFA y el solvente B = 90:10:0.1 CH_3CN:H_2O:TFA) para dar el compuesto del título (27.6 mg; 40%) como un sólido blanco. $[M + H]^+$ = 555.4; ^1H RMN (400 MHz, $CDCl_3$): δ 1.20 (t, *J*=7.15 Hz, 6 H), 3.01 (s, 3 H), 3.24 (s, 1 H), 3.30 (s, 1 H), 3.83 (s, 3 H), 3.94 - 4.09 (m, 4 H), 6.73 - 6.87 (m, 2 H), 7.08 (d, *J*=8.79 Hz, 2 H), 7.22 - 7.28 (m, 1 H), 7.36 - 7.43 (m, 1 H), 7.86 (d, *J*=8.79 Hz, 2 H).

EJEMPLO 150

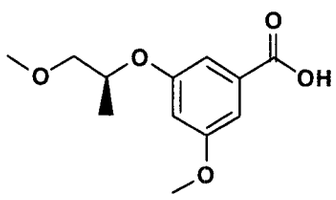


A.



A una mezcla 0°C del compuesto del Ejemplo 149 Parte A (100 mg; 0.549 mmol), R-(-)-1-metoxi-2-propanol (70 µL; 0.714 mmol), y enlace de polímero PPh_3 (0.47 g; 1.43 mmol) en THF (2 mL) sele agregó gota a gota una solución de DIAD (162 µL; 0.823 mmol) en THF (0.20 mL). La reacción se agitó a temperatura ambiente durante 18 h, luego se filtró. La resina se enjuagó con THF (2 x 4 mL), y los filtrados combinados se concentraron *in vacuo*. El residuo se procesó por cromatografía (SiO_2; gradiente continuo desde 0 hasta 45% solvente B durante 20 min, donde el solvente A = hexanos y el solvente B = EtOAc) para dar el compuesto de la Parte A (78 mg; 56%) como un aceite incoloro.

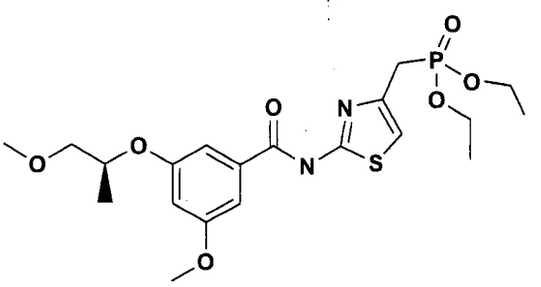
B.



A una solución del compuesto de la Parte A (74 mg; 0.291 mmol) en THF (0.39 mL), MeOH (0.39 mL), y H_2O (0.39 mL) se le agregó $LiOH \cdot H_2O$ (37 mg; 0.873 mmol). La reacción se agitó durante 1 h, luego se dividió entre EtOAc (5 mL) y HCl acuoso 0.5 N (5 mL). La fase acuosa se extrajo con EtOAc (5 mL). Los

extractos orgánicos combinados se lavaron con salmuera (5 mL), se secaron ($MgSO_4$), y concentraron *in vacuo* para dar el compuesto de la Parte B (68 mg; 97%) como un jarabe incoloro.

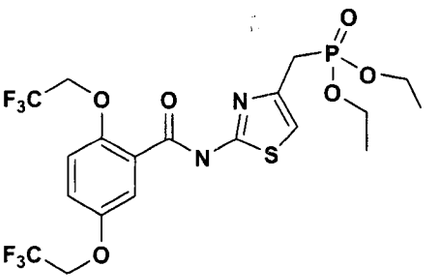
C.



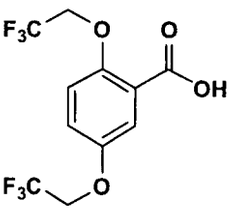
A una solución del compuesto del Ejemplo 13 Parte E (0.041 g; 0.164 mmol) en DMF (0.52 mL) se le agregaron HOAT (0.087 g; 0.641 mmol), compuesto de la Parte B (0.033 g; 0.137 mmol), y DIPEA (0.028 mL; 0.158 mmol), y, finalmente, EDCI (0.030 g; 0.158 mmol). La mezcla de reacción se agitó a 25°C durante 16 h. El agua se agregó, y la mezcla se extrajo con EtOAc (3x). Los extractos orgánicos combinados se lavaron con NH_4Cl acuoso saturado, $NaHCO_3$ acuoso saturado, y salmuera, se secaron ($MgSO_4$), y concentraron *in vacuo*. El residuo se purificó por CLAR preparativa (Columna de fase inversa YMC ODS-5 µm 30 x 100 mm; relación de flujo = 40 mL/min, 25 hasta 100% solvente B durante 12 min, donde el solvente A = 90:10:0.1 H_2O:CH_3CN:TFA y el solvente B = 90:10:0.1 CH_3CN:H_2O:TFA) para dar el compuesto del título (38.1 mg; 59%) como un aceite claro, incoloro. $[M + H]^+$ = 473.4; ^1H RMN (400 MHz, $CDCl_3$): δ 1.20 - 1.30 (m, 9 H), 3.23 (s, 1 H), 3.28 (s,

1 H), 3.35 (s, 3 H), 3.43 - 3.55 (m, 2 H), 3.80 (s, 3 H), 4.01 - 4.12 (m, 4 H), 4.60 - 4.72 (m, 1 H), 6.66 - 6.72 (m, 1 H), 6.89 - 6.94 (m, *J*=3.30 Hz, 1 H), 7.21 - 7.25 (m, 1 H), 7.25 - 7.29 (m, 1 H).

EJEMPLO 151



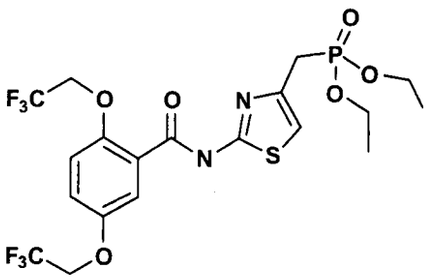
A.



A una solución de 2,5-bis(2,2,2-trifluoroetoxi)benzoato de metilo (0.029 g; 1.20 mmol) en THF (2.49 mL) y agua (0.25 mL) se le agregó $LiOH.H_2O$ (0.100 g; 0.301 mmol). La mezcla de reacción se agitó a 45°C durante 3 h en un vial sellado, luego un equivalente adicional de LiOH se agregó. La mezcla de reacción se agitó a 45°C durante 16 h, luego se enfrió a temperatura ambiente. El solvente se removió *in vacuo*, y la solución acuosa restante se acidificó con HCl acuoso 0.5N a un pH <2. La capa acuosa se volvió a extraer con EtOAc (3x). Los extractos orgánicos combinados se lavaron con salmuera,

se secaron ($MgSO_4$), y concentraron *in vacuo* para dar el compuesto de la Parte A ompound (0.0954 g; 99%).

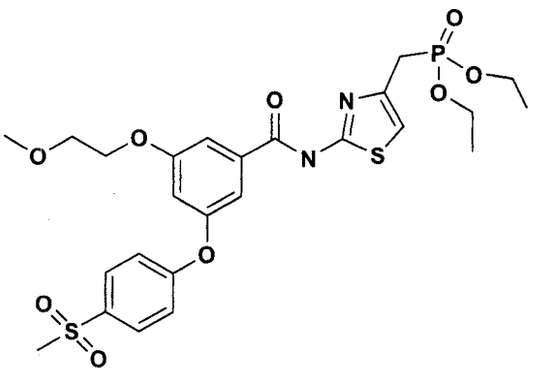
B.



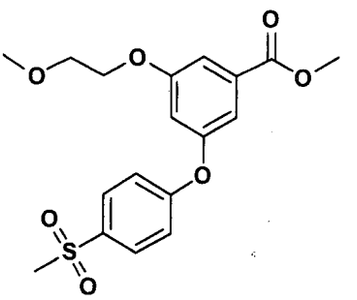
A una solución del compuesto del Ejemplo 13 Parte E (0.029 g; 0.114 mmol) en DMF (0.476 mL) se le agregaron HOAT (0.015 g; 0.11 mmol), compuesto de la Parte A (0.030 g; 0.095 mmol), DIPEA (0.019 mL; 0.110 mmol), y, finalmente, EDCI (0.021 g; 0.110 mmol). La mezcla de reacción se agitó a 25°C durante 16 h. El agua se agregó, y la mezcla se extrajo con EtOAc (3x). Los extractos orgánicos combinados se lavaron con NH_4Cl acuoso saturado, $NaHCO_3$ acuoso saturado, y salmuera, se secaron ($MgSO_4$), y concentraron *in vacuo*. El residuo se purificó por CLAR preparativa (Columna de fase inversa YMC ODS-5u 30 x 100 mm; relación de flujo = 40 mL/min, 0 hasta 100% solvente B durante 12 min, donde el solvente A = 90:10:0.1 H_2O:CH_3CN:TFA y el solvente B = 90:10:0.1 CH_3CN:H_2O:TFA) para dar el compuesto del título (13.8 mg; 26%) como un liofilado blanco. $[M + H]^+$ = 551.2; ^1H RMN (400 MHz, $CDCl_3$) δ 1.23 (t, J=7.15 Hz, 6 H), 3.23 (s, 1 H), 3.28 (s, 1 H), 3.94 - 4.10 (m, 4 H), 4.27 - 4.39 (m, J=7.88, 7.88,

7.88 Hz, 2 H), 4.46 - 4.58 (m, *J*=8.06, 8.06, 8.06 Hz, 2 H), 6.81 - 6.86 (m, *J*=3.30 Hz, 1 H), 6.93 - 6.98 (m, *J*=9.34 Hz, 1 H), 7.12 - 7.18 (m, *J*=9.34, 3.30 Hz, 1 H), 7.69 - 7.75 (m, *J*=3.30 Hz, 1 H).

EJEMPLO 152



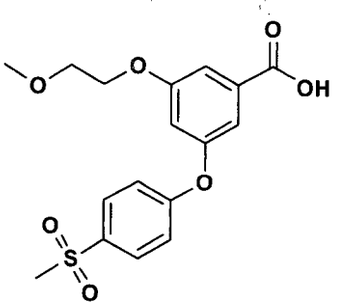
A.



Al compuesto del Ejemplo 26 Parte A (0.130 g; 0.403 mmol) se le agregaron sucesivamente 2-metoxietanol (0.046 g; 0.605 mmol) en tolueno (2.02 mL) y una suspensión del compuesto del Ejemplo 97 Parte B (0.248 g; 0.605 mmol) en CH_2Cl_2 (1.1 mL). La mezcla de reacción se agitó durante 16 h a 25°C, luego se diluyó con agua y se extrajo con EtOAc (3x). Los extractos orgánicos combinados se lavaron con NaOH acuoso 1N y salmuera, se secaron ($MgSO_4$), y concentraron *in vacuo*.

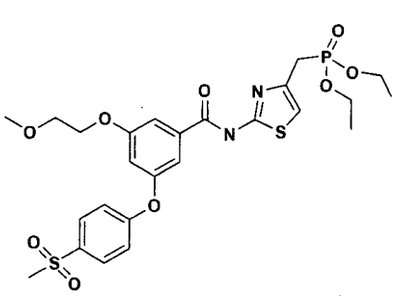
El residuo se procesó por cromatografía (SiO_2; gradiente de etapa de 50-60% solvente B, donde el solvente A = hexanos y el solvente B = EtOAc) para dar el compuesto de la Parte A (0.157 g; 93%).

B.



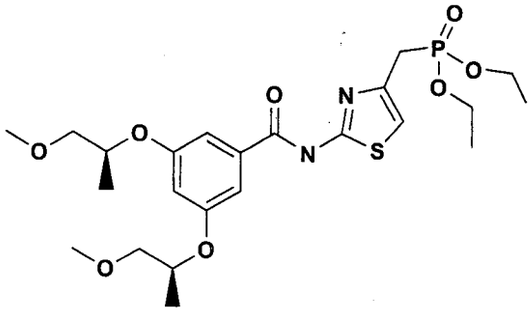
A una solución del compuesto de la Parte A (0.157 g; 0.413 mmol) en THF (3.42 mL) y agua (0.342 mL) se le agregó $LiOH.H_2O$ (0.020 g; 0.827 mmol). La mezcla de reacción se agitó a 45°C durante 3 h en un vial sellado, luego se enfrió a temperatura ambiente. Los volátiles se removieron *in vacuo*, y la solución acuosa restante se acidificó con HCl acuoso 0.5N a un pH < 2. La capa acuosa se volvió a extraer con EtOAc (3x). Los extractos orgánicos combinados se lavaron con salmuera, se secaron ($MgSO_4$), y concentraron *in vacuo* para dar el compuesto de la Parte B (0.166 g; 100%).

C.

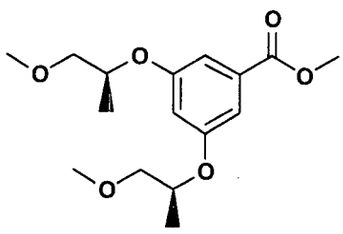


A una solución del compuesto del Ejemplo 13 Parte E (0.033 g; 0.130 mmol) en DMF (0.542 mL) se le agregaron HOAT (0.017 g; 0.125 mmol), compuesto de la Parte B (0.040 g; 0.108 mmol), DIPEA (0.022 mL; 0.125 mmol), y, finalmente, EDCI (0.024 g; 0.125 mmol). La mezcla de reacción se agitó a 25°C durante 5 h. El agua se agregó, y la mezcla se extrajo con EtOAc (3x). Los extractos orgánicos combinados se lavaron con NH_4Cl acuoso saturado, $NaHCO_3$ acuoso saturado, y salmuera, se secaron ($MgSO_4$), y concentraron *in vacuo*. El residuo se purificó por CLAR preparativa (Columna de fase inversa YMC ODS-5µm 30 x 100 mm; relación de flujo = 40 mL/min, 0 hasta 100% solvente B durante 12 min, donde el solvente A = 90:10:0.1 H_2O:CH_3CN:TFA y el solvente B = 90:10:0.1 CH_3CN:H_2O:TFA) para dar el compuesto del título (34.4 mg; 51%) como un liofilado blanco. $[M + H]^+$ = 599.2; ^1H RMN (400 MHz, $CDCl_3$): δ 1.25 (t, J=6.87 Hz, 6 H), 3.00 (s, 3 H), 3.24 (s, 1 H), 3.29 (s, 1 H), 3.39 (s, 3 H), 3.67 - 3.77 (m, 2 H), 4.00 - 4.15 (m, 4 H), 4.18 - 4.28 (m, 2 H), 6.86 - 6.93 (m, 1 H), 6.94 - 7.00 (m, J=3.30 Hz, 1 H), 7.04 - 7.12 (m, J=8.79 Hz, 2 H), 7.38 - 7.45 (m, 1 H), 7.58 - 7.64 (m, 1 H), 7.81 - 7.88 (m, J=8.79 Hz, 2 H).

EJEMPLO 153

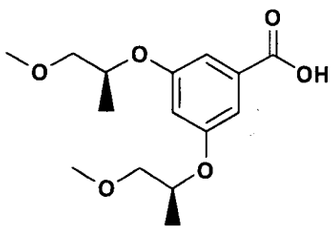


A.



A metil-3,5-dihidroxibenzoato (0.100 g; 0.595 mmol) se le agregaron (R)-1-metoxi-propan-2-ol (0.134 g; 1.487 mmol en tolueno (2.97 mL), seguido por una suspensión del compuesto del Ejemplo 97 Parte B (0.610 g; 1.487 mmol) en CH_2Cl_2 (2.72 mL). La mezcla de reacción se agitó durante 2 días a 25°C, luego a 45°C durante 2 días, luego se enfrió a temperatura ambiente. La mezcla de reacción se diluyó con agua y se extrajo con EtOAc (3x). Los extractos orgánicos combinados se lavaron con NaOH acuoso 1N y salmuera, se secaron ($MgSO_4$), y concentraron *in vacuo*. El residuo se procesó por cromatografía (SiO_2; gradiente en etapas desde 10-20% solvente B, donde el solvente A = hexanos y el solvente B = EtOAc) para dar el compuesto de la Parte A (0.080 g; 40%).

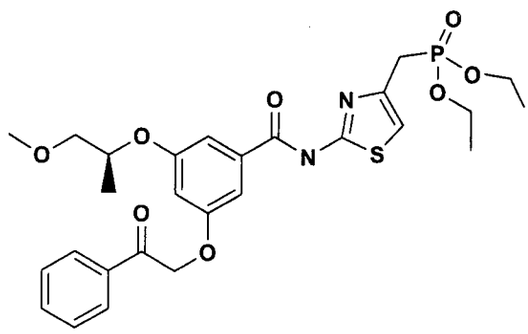
B.



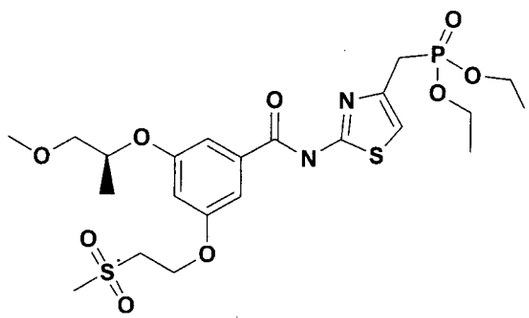
A una solución del compuesto de la Parte A (0.080 g; 0.257 mmol) en THF (2.13 mL) y agua (0.213 mL) se le agregó

ODS-5u 30 x 100 mm; relación de flujo = 40 mL/min, 0 hasta 100% solvente B durante 12 min, donde el solvente A = 90:10:0.1 H_2O:CH_3CN:TFA y el solvente B = 90:10:0.1 CH_3CN:H_2O:TFA) para dar el compuesto del título (28.2 mg; 45%) como un aceite claro, incoloro. $[M + H]^+$ = 531.3; ^1H RMN (400 MHz, $CDCl_3$) δ 1.22 - 1.29 (m, J=6.87, 6.87 Hz, 12 H), 3.28 (s, 1 H), 3.32 - 3.38 (m, 7 H), 3.44 - 3.56 (m, 4 H), 4.06 - 4.16 (m, 4 H), 4.64 - 4.73 (m, 2 H), 6.70 - 6.76 (m, 1 H), 6.94 - 7.00 (m, J=3.85 Hz, 1 H), 7.32 - 7.35 (m, J=2.20 Hz, 2 H).

EJEMPLO 154



A.

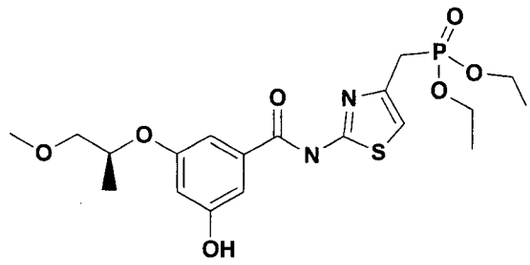


A una solución del compuesto del Ejemplo 134 (0.298 g; 0.560 mmol) en iPrOH (12.43 mL) y agua (6.22 mL) se le agregó oxona (0.791 g;

88783

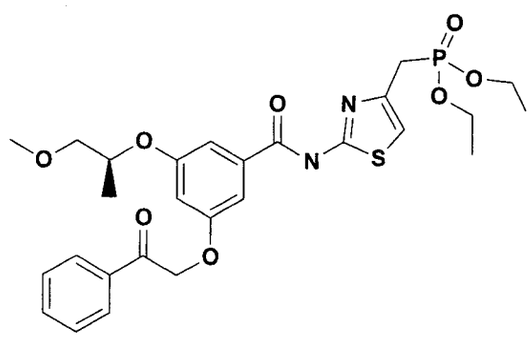
1.287 mmol). La mezcla de reacción se agitó durante 16 h a 25°C, luego se filtró y se extrajo con EtOAc. Los filtrados combinados se lavaron con agua y salmuera, se secaron ($MgSO_4$), y concentraron *in vacuo* para dar compuesto de la Parte A (0.206g; 38%).

B.



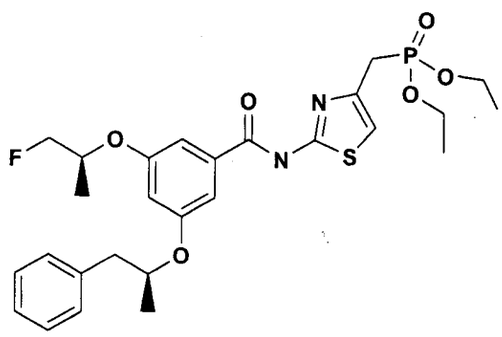
A una solución del compuesto de la Parte A (0.070 g; 0.125 mmol) en THF (1.03 mL) y agua (0.103 mL) se le agregó $LiOH.H_2O$ (0.006 g; 0.249 mmol). La mezcla de reacción se agitó a 45°C durante 1 h en un vial sellado, luego dos equivalentes más de $LiOH.H_2O$ se agregaron. La mezcla de reacción se agitó a 45°C durante 20 minutes, luego se enfrió a temperatura ambiente. Los volátiles se removieron *in vacuo*, y la solución acuosa restante se acidificó con HCl acuoso 0.5N a un pH <2. La capa acuosa se volvió a extraer con EtOAc (3x). Los extractos orgánicos combinados se lavaron con salmuera, se secaron ($MgSO_4$), y concentraron *in vacuo* para dar compuesto de la Parte B (0.082 g; 87%).

C.



A una solución 0°C del compuesto de la Parte B (0.020 g; 0.044 mmol) en NMP (0.146 mL) se le agregó LiHMDS 1M en THF (0.087 mL; 0.087 mmol). Después de 15 min, 2-bromo-1-feniletanona (0.017 g; 0.087 mmol) se le agregó. La mezcla de reacción se permitió entibiar a temperatura ambiente y se agitó a temperatura ambiente durante 15 h, luego se dividió entre NH_4Cl acuoso saturado y EtOAc. La capa orgánica se lavó con agua (2x) y salmuera, se secoó ($MgSO_4$), y concentraron *in vacuo*. El residuo se purificó por CLAR preparativa (Columna de fase inversa YMC ODS-5u 30 x 100 mm; relación de flujo = 40 mL/min, 0 hasta 100% solvente B durante 12 min, donde el solvente A = 90:10:0.1 H_2O:CH_3CN:TFA y el solvente B = 90:10:0.1 CH_3CN:H_2O:TFA) para dar el compuesto del título (6.0 mg; 24%) como un aceite amarillo. $[M + H]^+$ = 577.3; ^1H RMN (400 MHz, $CDCl_3$) δ 1.05 - 1.12 (m, *J*=6.05 Hz, 3 H), 1.24 (t, 6 H), 3.06 (s, 1 H), 3.11 (s, 1 H), 3.23 - 3.35 (m, 4 H), 3.36 - 3.42 (m, 1 H), 3.93 - 4.10 (m, 4 H), 4.24 - 4.35 (m, 1 H), 5.92 - 5.99 (m, *J*=4.40 Hz, 2 H), 6.41 - 6.48 (m, 1 H), 6.50 - 6.57 (m, 1 H), 7.11 (s, 1 H), 7.19 (s, 1 H), 7.44 - 7.54 (m, *J*=7.70 Hz, 2 H), 7.56 - 7.66 (m, *J*=7.15 Hz, 1 H), 7.99 - 8.08 (m, *J*=8.25 Hz, 2 H).

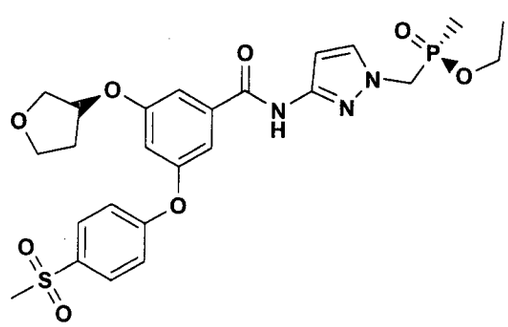
EJEMPLO 155



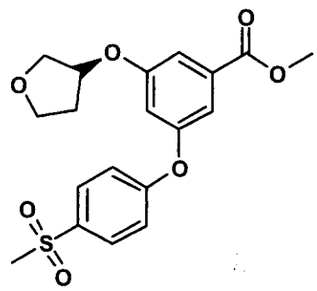
086782

A una solución 0°C del compuesto del Ejemplo 137 (0.021 g; 0.036 mmol) en CH_2Cl_2 anhidro (0.369 mL) se le agregó DAST (0.005 mL; 0.036 mmol). La mezcla de reacción se agitó durante 2 h a 0°C, seguido por adición cuidadosa de $NaHCO_3$ acuoso saturado y se agitó durante 5 min, luego se dividió entre $NaHCO_3$ acuoso saturado y CH_2Cl_2. La capa acuosa se volvió a extraer con CH_2Cl_2 (3x). Los extractos orgánicos combinados se lavaron con salmuera, se secaron ($MgSO_4$), y concentraron *in vacuo*. El residuo se purificó dos veces por CLAR preparativa (Columna de fase inversa YMC ODS-5u 30 x 100 mm; relación de flujo = 40 mL/min, 20 hasta 100% solvente B durante 12 min, donde el solvente A = 90:10:0.1 H_2O:CH_3CN:TFA y el solvente B = 90:10:0.1 CH_3CN:H_2O:TFA) para dar el compuesto del título (6.0 mg; 29%) como un aceite claro, incoloro. $[M + H]^+$ = 565.2; ^1H RMN (400 MHz, $CDCl_3$) δ 1.22 - 1.32 (m, 12 H), 2.75 - 2.87 (m, J=13.74, 5.50 Hz, 2 H), 2.92 - 3.03 (m, J=13.74, 6.60 Hz, 1 H), 3.29 (s, 1 H), 3.34 (s, 1 H), 4.06 - 4.17 (m, 4 H), 4.33 - 4.45 (m, 1 H), 4.45 - 4.57 (m, 1 H), 4.63 - 4.74 (m, 1 H), 4.74 - 4.87 (m, 1 H), 6.64 - 6.69 (m, J=2.20, 2.20 Hz, 1 H), 6.94 - 7.00 (m, J=3.30 Hz, 1 H), 7.12 - 7.24 (m, 5 H), 7.30 (s, 1 H), 7.33 (s, 1 H).

EJEMPLO 156

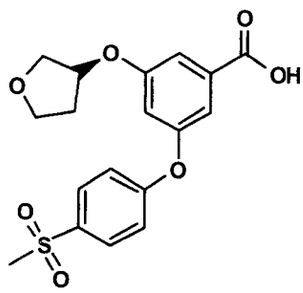


A.



A una suspensión del compuesto del Ejemplo 97 Parte B (1.4 g, 3.5 mmol) en DCM (6 mL) se le agregó una solución del compuesto del Ejemplo 26 Parte A (141 mg, 0.44 mmol) y (R)-(-)-3-hidroxitetrahidrofurano (0.081 mL, 1.00 mmol) en tolueno (2 mL). La reacción se agitó a temperatura ambiente durante 15 h, luego se diluyó con EtOAc (10 mL) y se lavó con agua y salmuera. La capa orgánica se secó ($MgSO_4$), y concentró *in vacuo*. El residuo se procesó por cromatografía (SiO_2; 40 g, 19 min gradiente continuo, desde 100% Hexano/0% EtOAc hasta 0% Hexanos/100% EtOAc) para proporcionar el compuesto de la Parte A (254 mg, 148% de rendimiento, mezclado con Ph_3PO) como un aceite incoloro.

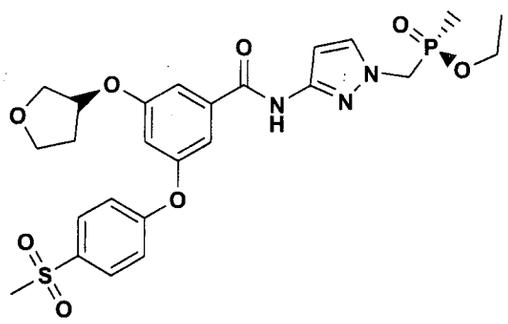
B.



A una solución del compuesto de la Parte A (254 mg, 0.65

mmol) en THF (2 mL) se le agregó NaOH acuoso 1N (1 mL, 1.00 mmol). La reacción se agitó a temperatura ambiente durante 15 h, luego se diluyó con EtOAc (6 mL) y se acidificó con HCl acuoso 1N (0.5 mL). La capa orgánica se lavó con salmuera, se secó ($MgSO_4$), y concentró *in vacuo*. El residuo se purificó por CLAR preparativa (columna Phenomenex Luna AXIA 30 x 100 mm; relación de flujo = 40 mL/min, 30 hasta 100% solvente B durante 10 min, donde el solvente A = 90:10:0.1 H_2O:MeOH:TFA y el solvente B = 90:10:0.1 MeOH:H_2O:TFA) para dar el compuesto de la Parte B (90 mg, 37% de rendimiento) como un aceite incoloro.

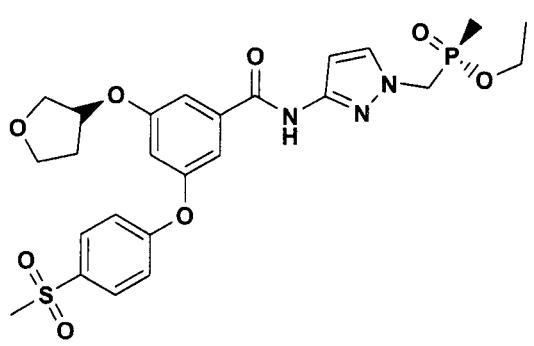
C.



A una solución del compuesto de la Parte B (25 mg, 0.066 mmol) en DMF (1 mL) se le agregaron amina del Ejemplo 60 Parte D2 (26.8 mg, 0.13 mmol), EDCI (25.3 mg, 0.13 mmol), HOBT (20.2 mg, 0.13 mmol), y DIPEA (0.035 mL, 0.20 mmol). La reacción se agitó a temperatura ambiente durante 24 h. La reacción se purificó directamente por CLAR preparativa (columna Phenomenex Luna AXIA 30 x 100 mm; relación de flujo = 40 mL/min, 30 hasta 100% solvente B durante 10 min, donde

el solvente A = 90:10:0.1 H_2O:MeOH:TFA y el solvente B = 90:10:0.1 MeOH:H_2O:TFA) para proporcionar el compuesto del título (24.6 mg, 66% de rendimiento) como un sólido blanco. $[M + H]^+$= 564.3; ^1H RMN (500 MHz, $CDCl_3$) δ 9.63 (1 H, s), 7.92 (2 H, d, J=8.80 Hz), 7.52 (1 H, d, J=2.20 Hz), 7.33 (1 H, s), 7.27 (1 H, s), 7.09 - 7.18 (2 H, m), 7.01 (1 H, d, J=2.20 Hz), 6.71 - 6.86 (1 H, m), 5.01 - 5.14 (1 H, m), 4.37 - 4.60 (2 H, m), 4.07 - 4.22 (2 H, m), 3.96 - 4.05 (3 H, m), 3.84 - 3.96 (1 H, m), 3.07 (3 H, s), 2.05 - 2.38 (2 H, m), 1.55 (3 H, d, J=14.85 Hz), 1.34 (3 H, t, J=7.15 Hz).

EJEMPLO 157

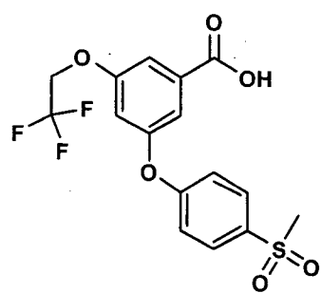


El compuesto del título (27.4 mg, 73.6% de rendimiento; sólido blanco) se sintetizó de la amina del Ejemplo 60 Parte D1 usando el procedimiento empleado en el Ejemplo 156. [M + H]$^+$ = 564.3; ^1H RMN (500 MHz, $CDCl_3$) δ 9.58 (1 H, s), 7.92 (2 H, d, J=8.25 Hz), 7.52 (1 H, s), 7.31 (1 H, s), 7.26 (1 H, s), 7.14 (2 H, d, J=8.25 Hz), 7.01 (1 H, s), 6.80 (1 H, s), 5.01 - 5.13 (1 H, m), 4.41 - 4.60 (2 H, m), 4.06 - 4.21 (2 H, m), 3.96 - 4.05 (3 H, m), 3.86 - 3.96 (1 H, m), 3.07 (3 H,

ambiente. La reacción se diluyó con agua y se agitó durante 1

h, luego se dividió entre EtOAc y $NaHCO_3$ acuoso saturado. La capa orgánica se lavó con agua (2x), y las capas acuosas combinadas se extrajeron nuevamente con EtOAc. Los extractos orgánicos combinados se lavaron con salmuera, se secaron (Na_2SO_4), y concentraron *in vacuo*. El residuo se procesó por cromatografía (12g SiO_2, eluyendo desde 0-10% EtOAc: CH_2Cl_2, luego enjuagando con 90% EtOAc) para dar el compuesto de la Parte A (44 mg, 29%) como un aceite incoloro.

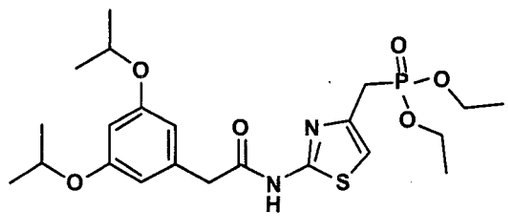
B.



A una solución a temperatura ambiente del éster de la Parte A (44 mg, 0.109 mmol) en THF (0.8 mL) y MeOH (0.4 mL) bajo Ar se le agregó LiOH.H_2O acuoso 4N (0.2 mL, 0.800 mmol). Un precipitado formado inmediatamente, y la reacción se agitó a temperatura ambiente durante 6.5 h, luego se diluyó con MeOH, y los volátiles se removieron *in vacuo*. El residuo se disolvió en agua y se acidificó con HCl acuoso 1N. La capa acuosa se extrajo con EtOAc; la capa orgánica se lavó con salmuera, se secó (Na_2SO_4), y concentró *in vacuo* para dar el ácido de la Parte B (38.6 mg, 91%)

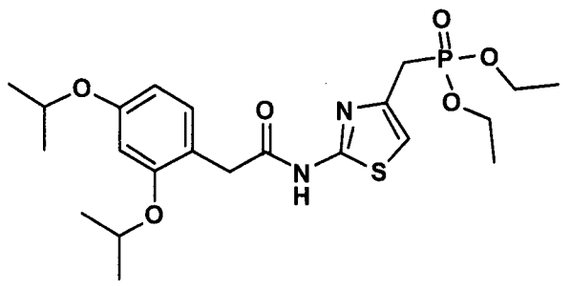
StratoSpheres TM SPE PL-HCO3 MP SPE (500mg), bien lavado con MeOH. El filtrado se concentró *in vacuo*, luego se hizo azeotrópico varias veces con MeOH. El residuo se tomó en CH_2Cl_2/MeOH; los sólidos se filtraron completamente, y el filtrado se concentró *in vacuo* para dar el compuesto del título (14.8 mg, 46%) como un sólido color canela. $[M + H]^+$ = 623.2; ^1H RMN (400 MHz, $CDCl_3$) δ 1.24 (t, *J*=7.15 Hz, 6 H), 3.09 (s, 3 H), 3.46 (d, *J*=21.5 Hz, 2 H), 3.99 - 4.10 (m, 4 H), 4.48 (q, *J*=7.70 Hz, 2 H), 6.83 (d, *J*=3.30 Hz, 1 H), 6.92 (s, 1 H), 7.16 (d, *J*=8.79 Hz, 2 H), 7.46 (s, 1 H), 7.58 (s, 1 H), 7.95 (d, *J*=8.79 Hz, 2 H), ^{19}F RMN (400 MHz, $CDCl_3$): δ -73.66.

EJEMPLO 159



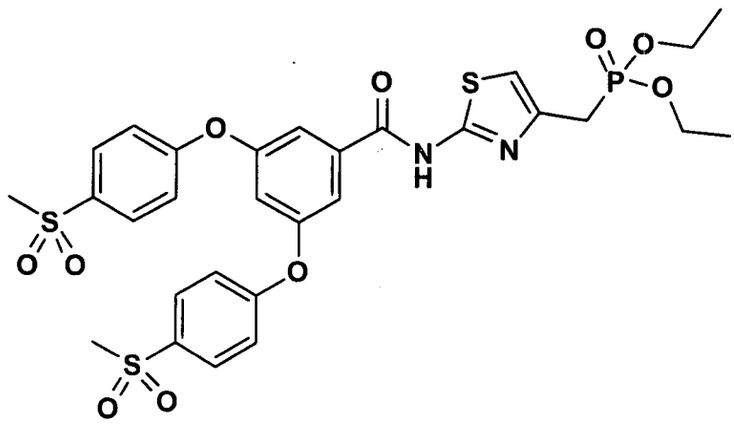
El compuesto del título (20 mg, 51% de rendimiento, aceite amarillo) se preparó empleando la misma secuencia general como se describe en la síntesis del Ejemplo 74. $[M + H]^+$ = 485.18; ^1H RMN (400 MHz, $CDCl_3$) δ ppm 6.94 (1 H, d, *J*=3.95 Hz), 6.52 (2 H, d, *J*=2.20 Hz), 6.35 (1 H, t, *J*=2.20 Hz), 4.49 - 4.57 (2 H, m), 4.10 - 4.19 (4 H, m), 3.78 (2 H, s), 3.25 - 3.34 (2 H, m), 1.27 - 1.36 (18 H, m).

EJEMPLO 160

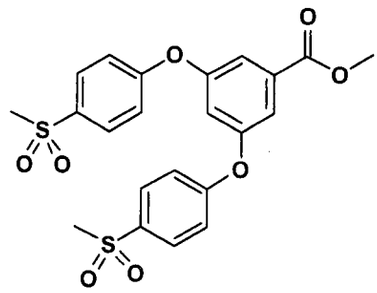


El compuesto del título (15 mg, 45% de rendimiento, aceite amarillo) se preparó empleando la misma secuencia general como se describe en la síntesis del Ejemplo 74. $[M + H]^+$ = 485.18; ^1H RMN (400 MHz, $CDCl_3$) δ 7.12 (1 H, d, J=8.79 Hz), 6.88 (1 H, d, J=3.95 Hz), 6.41 - 6.46 (2 H, m), 4.47 - 4.57 (1 H, m), 4.07 - 4.17 (4 H, m), 3.75 (2 H, s), 3.24 - 3.34 (2 H, m), 1.23 - 1.37 (18 H, m).

EJEMPLO 161



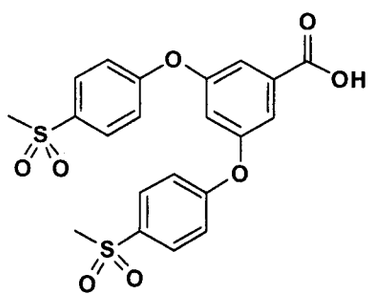
A.



010791

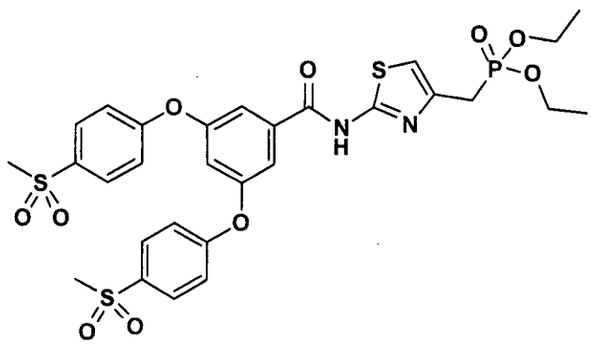
Una solución de 3,5-dihidroxibenzoato de metilo (2.5 g, 14.9 mmol), 1-fluoro-4-(metilsulfonil)benceno (5.18 g, 29.8 mmol), y K_2CO_3 anhidro (8.23 g, 59.6 mmol) en DMF seco (100 mL) se calentó a 120°C durante 10 h, luego se enfrió a temperatura ambiente y se filtró. El sólido se lavó con CH_2Cl_2 (100 mL), y el filtrado combinado se concentró *in vacuo*. El residuo se procesó por cromatografía (SiO_2; 80 g; gradiente continuo desde 100% hexano hasta 100% EtOAc durante 40 min) para proporcionar compuesto de la Parte A (6.1 g, 86% de rendimiento) como un sólido blanco. $[M + H]^+ = 477$.

B.



Una solución del compuesto de la Parte A (2.3 g, 4.83 mmol), y $LiOH.H_2O$ (4.1 g, 97.5 mmol) en THF (10 mL)/H_2O (5 mL) se agitó durante 2 h a temperatura ambiente. La reacción se acidificó a un pH 1 con HCl acuoso 1N, y se extrajo con EtOAc (3 x 15 mL). Los extractos orgánicos combinados se lavaron con salmuera (30 mL), se secaron ($MgSO_4$) y concentraron *in vacuo* para dar el compuesto de la Parte B (2.2 g, 99% de rendimiento) como un sólido blanco. [M - H] = 461.

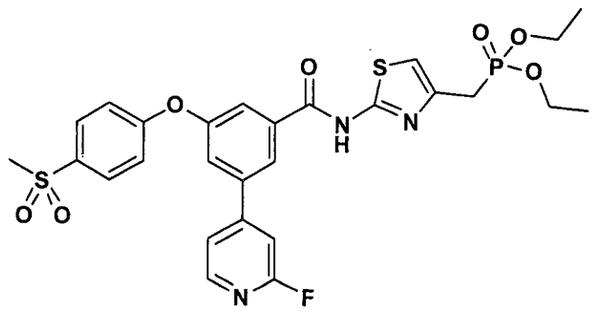
c.



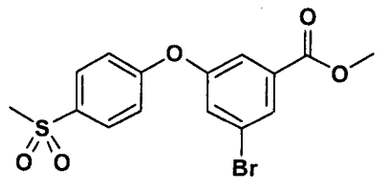
A una suspensión del compuesto de la Parte B (50 mg, 0.11 mmol) en CH_2Cl_2 (3 mL) se le agregaron compuesto del Ejemplo 13 Parte E (27 mg, 0.11 mmol), Et_3N (30 µL, 0.22 mmol), y BOP (72 mg, 0.16 mmol). La reacción se agitó durante 16 h, luego se diluyó con H_2O (1 mL), y se extrajo con CH_2Cl_2 (3 x 5 mL). Los extractos orgánicos combinados se lavaron con salmuera (3 mL), se secaron ($MgSO_4$), y concentraron *in vacuo*. El residuo se purificó por CLAR preparativa (Columna de fase inversa YMC ODS-A-5µm 30 x 250 mm; relación de flujo = 25 mL/min, 20 hasta 100% solvente B durante 30 min, espera hasta 40 min, donde el solvente A = 90:10:0.1 H_2O:MeOH:TFA y el solvente B = 90:10:0.1 MeOH:H_2O:TFA) para proporcionar el compuesto del título (50 mg, 65% de rendimiento) como un sólido blanco. $[M + H]^+$ = 695; ^1H RMN (500 MHz, $CDCl_3$): δ 7.95 (d, *J*=8.8 Hz, 4H), 7.65 (d, *J*=2.2 Hz, 2H), 7.20 (d, *J*=8.8 Hz, 4H), 7.09 (t, *J*=2.2 Hz, 1H), 7.01 (d, *J*=3.3 Hz, 1H), 4.11 (m, 4H), 3.28 (d, *J*=22.0 Hz, 2H), 3.06 (s, 6H), 1.28 (t, *J*=6.9 Hz, 6H).

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EJEMPLO 162

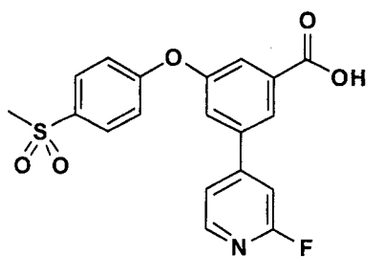


A.



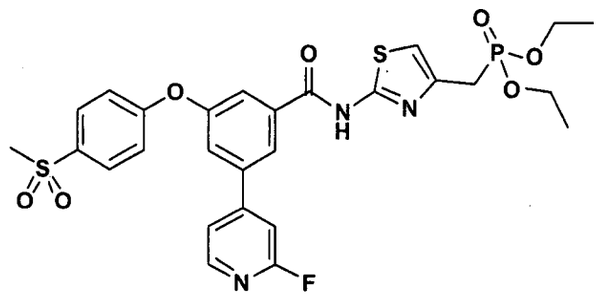
Una solución de 3-bromo-5-hidroxibenzoato de metilo (2.13 g, 9.21 mmol), 1-fluoro-4-(metilsulfonil)benceno (1.93 g, 11.1 mmol), y K_2CO_3 anhidro (2.55 g, 18.42 mmol) en DMF seco (15 mL) se calentó a 120°C durante 20 h, luego se enfrió a temperatura ambiente y se filtró. Los sólidos se lavaron con CH_2Cl_2 (100 mL), y los filtrados combinados se concentraron *in vacuo*. El residuo se procesó por cromatografía (SiO_2; 80 g; gradiente continuo desde 100% hexano hasta 100% EtOAc durante 40 min) para proporcionar compuesto de la Parte A (1.64 g, 48% de rendimiento) como un sólido blanco. [M - H] = 370.

B.



Una solución a temperatura ambiente del compuesto de la Parte A (124 mg, 0.322 mmol), ácido 2-fluoropiridin-4-ilborónico (54.4 mg, 0.386 mmol), K_2CO_3 (89 mg, 0.644 mmol), y $(PPh_3)_4Pd$ (18.6 mg, 16 µmol) en DME (4 mL) y agua (1 mL) se agitó bajo una corriente de N_2 durante 5 min. La mezcla se selló luego y se calentó en un Emrys Optimizer® a 150°C durante 30 min. La reacción se enfrió a temperatura ambiente y se acidificó a un pH 2 con HCl acuoso 1N. La mezcla se dividió entre EtOAc (3 mL) y agua (3 mL), y se extrajo con EtOAc (3 x 10 mL). Los extractos orgánicos combinados se secaron ($MgSO_4$) y concentraron *in vacuo*. El residuo se purificó por CLAR preparativa (Columna de fase inversa YMC ODS-A-5µm 30 x 250 mm; relación de flujo = 25 mL/min, 20 hasta 100% solvente B durante 30 min, luego se mantuvo durante 10 min, donde el solvente A = 90:10:0.1 H_2O: MeOH: TFA y el solvente B = 90:10:0.1 MeOH: H_2O: TFA) para proporcionar el compuesto de la Parte B (80 mg, 64%) como un sólido blanco. [M - H] = 386.

C.

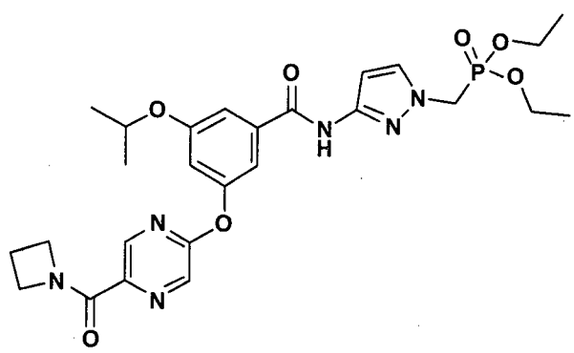


A una suspensión del compuesto de la Parte B (20 mg,

795

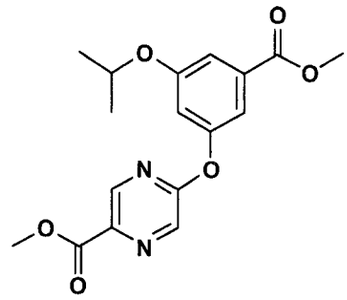
0.052 mmol) en CH_2Cl_2 (2 mL) se le agregaron compuesto del Ejemplo 13 Parte E (13 mg, 0.052 mmol), Et_3N (11 µL, 0.077 mmol), y BOP (27.4 mg, 0.062 mmol). La reacción se agitó durante 16 h, luego se diluyó con H_2O (1 mL) y se extrajo con CH_2Cl_2 (3 x 5 mL). Los extractos orgánicos combinados se lavaron con salmuera (3 mL), se secaron ($MgSO_4$) y concentraron *in vacuo*. El residuo se purificó por CLAR preparativa (Columna de fase inversa YMC ODS-A-5µm 30 x 250 mm; relación de flujo = 25 mL/min, 20 hasta 100% solvente B durante 30 min, espera hasta 40 min, donde el solvente A = 90: 10: 0.1 H_2O: MeOH: TFA y el solvente B = 90: 10: 0.1 MeOH: H_2O: TFA) para proporcionar el compuesto del título (27 mg, 84% de rendimiento) como un sólido blanco. $[M + H]^+$ = 620; ^1H RMN (500 MHz, CD_3OD): δ 8.32 - 8.29 (m, 2H), 8.0 (d, *J*=8.8 Hz, 2H), 7.85 - 7.82 (m, 2H), 7.72 - 7.69 (m, 1H), 7.51 (s, 1H), 7.30 (d, *J*=8.8 Hz, 2H), 7.00 (d, *J*=3.8 Hz, 1H), 4.12 - 4.05 (m, 4H), 3.37 (d, *J*=21.4 Hz, 2H), 3.13 (s, 3H), 1.28 (t, *J*=6.8 Hz, 6H).

EJEMPLO 163



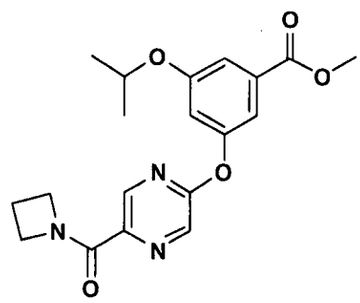
ES 2 396 796

A.



Una solución de 3-hidroxi-5-isopropoxibenzoato de metilo (*Bioorg. Med. Chem. Lett.* **2005**, 15:2103) (609 mg, 2.90 mmol), metil 5-cloropirazina-2-carboxilato (500 mg, 2.90 mmol), y K_2CO_3 (1.20 mg, 8.69 mmol) en CH_3CN (20 mL) se calentó a 80°C durante 2 h bajo Ar. La reacción se enfrió a temperatura ambiente, se diluyó con CH_2Cl_2 (50 mL), se filtró y el filtrado se concentró *in vacuo*. El residuo se procesó por cromatografía (SiO_2; 40 g; gradiente continuo desde 100% hexano hasta 100% EtOAc durante 40 min) para proporcionar el compuesto de la Parte A (1.005 g, 100% de rendimiento) como un aceite incoloro. $[M + H]^+ = 347$.

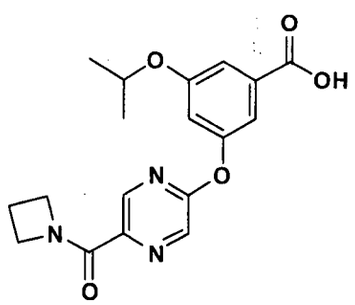
B.



Una mezcla del compuesto de la Parte B (1.005 g, 2.9 mmol), clorohidrato de azetidina (326 mg, 3.48 mmol), Et_3N

(0.485 mL, 3.48 mmol), y $MgCl_2$ (332 mg, 3.48 mmol) se agitó a temperatura ambiente durante 5 h. Más clorohidrato de azetidina (326 mg, 3.48 mmol), Et_3N (0.485 mL, 3.48 mmol), y $MgCl_2$ (332 mg, 3.48 mmol) se agregaron. La reacción se agitó a temperatura ambiente durante 30 min, luego se almacenó a 0°C durante la noche, luego se diluyó con CH_2Cl_2 (50 mL), se filtró, y el filtrado se concentró *in vacuo*. El residuo se procesó por cromatografía (SiO_2; 40 g; gradiente continuo desde 100% hexano hasta 100% EtOAc durante 40 min) para proporcionar el compuesto de la Parte B (267 mg, 25% de rendimiento) como un aceite incoloro. $[M + H]^+ = 372$.

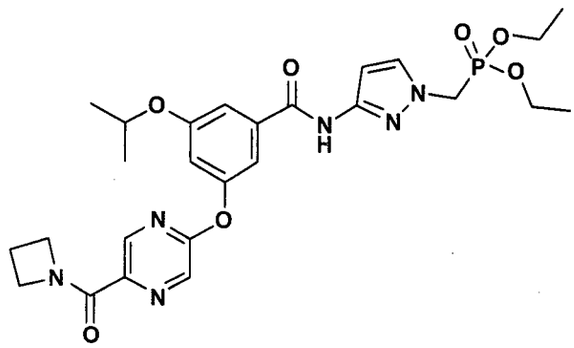
C.



Una solución del compuesto de la Parte B (267 mg, 0.72 mmol) y $LiOH.H_2O$ (90 mg, 2.16 mmol) en THF (4 mL)/H_2O (4 mL) se agitó durante 5 h a temperatura ambiente. La reacción se acidificó a un pH 2 con HCl acuoso 1N, luego se extrajo con EtOAc (3 x 10 mL). Los extractos orgánicos combinados se lavaron con salmuera (10 mL), se secaron ($MgSO_4$) y concentraron *in vacuo* para dar compuesto de la Parte C (200 mg, 78% de rendimiento) como un sólido blanco. $[M + H]^+ =$

358.

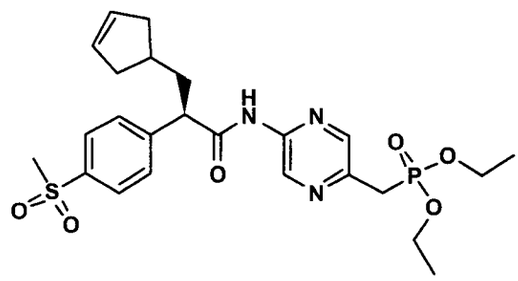
D.



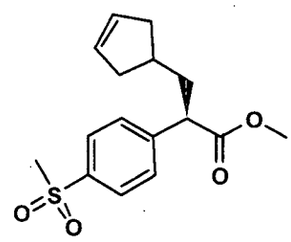
A una suspensión del compuesto de la Parte C (14 mg, 0.039 mmol) en CH_2Cl_2 (1.5 mL) se le agregaron compuesto de la Ejemplo 32 Parte A (9.1 mg, 0.039 mmol), Et_3N (11 µL, 0.078 mmol), y BOP (34.7 mg, 0.078 mmol). La reacción se agitó durante 16 h a temperatura ambiente, luego se diluyó con H_2O (1 mL) y se extrajo con CH_2Cl_2 (3 x 5 mL). Los extractos orgánicos combinados se lavaron con salmuera (3 mL), se secaron ($MgSO_4$), y concentraron *in vacuo*. El residuo se purificó por CLAR preparativa (Columna de fase inversa YMC ODS-A-5u 30 x 250 mm; relación de flujo = 25 mL/min, 20 hasta 100% solvente B durante 30 min, espera hasta 40 min, donde el solvente A = 90:10:0.1 H_2O:MeOH:TFA y el solvente B = 90:10:0.1 MeOH:H_2O:TFA) para proporcionar el compuesto del título (9.5 mg, 43% de rendimiento) como un sólido blanco. [M + H]$^+$ = 573; ^{1}H RMN (500 MHz, $CDCl_3$): δ 9.11 (s, 1H), 8.84 (s, 1H), 8.33 (s, 1H), 7.48 (s, 1H), 7.35 (s, 1H), 7.27 (s, 1H), 6.95 (d, *J*=2.2 Hz, 1H), 6.87 (d, *J*=2.2 Hz, 1H), 4.70 - 7.62

(m, 3H), 4.44 (d, *J*=8.0 Hz, 2H), 4.26 (t, *J*=7.7 Hz, 2H), 4.15 - 4.05 (m, 4H), 2.41 - 2.34 (m, 2H), 1.35 (d, *J*=6.1 Hz, 6H), 1.29 (t, *J*=7.2 Hz, 6H).

EJEMPLO 164



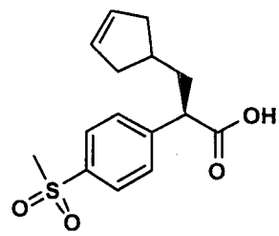
A.



A una solución -70°C de LDA (2.9 mL, 5.79 mmol, 2N en THF) y DMPU (1.75 mL, 5.79 mmoL) en THF (5.1mL) se agregó lentamente 2-(4-(metilsulfonil)fenil)acetato de metilo (1.27 g, 5.55 mmol) (ver WO 00/58293), manteniendo la temperatura debajo de -65°C. La reacción se agitó a -70°C durante 1 h y 4-(yodometil)ciclopent-1-eno (1.38 g, 6.58 mmol) se agregó, manteniendo la temperatura debajo de -60°C. La mezcla de reacción se agitó a -70°C durante 30 min y luego se entibió a temperatura ambiente y se agitó durante 18 h. La reacción se enfrió en un baño de hielo y se apagó con NH_4Cl acuoso saturado (20 mL). Los volátiles se removieron *in vacuo*, y la

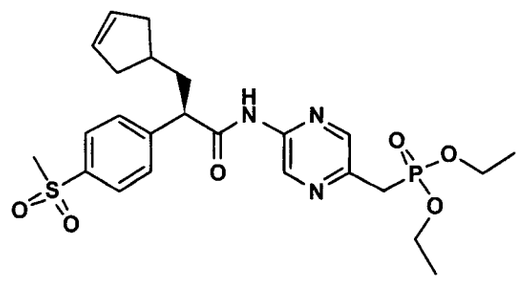
mezcla se extrajo con EtOAc (2x). La capa organica combinada se lavó con salmuera, se secó ($MgSO_4$), filtró, y concentró *in vacuo*. El residuo se procesó por cromatografía (SiO_2) para dar el compuesto de la Parte A (880 mg, 51% de rendimiento) como un sólido blanco.

B.



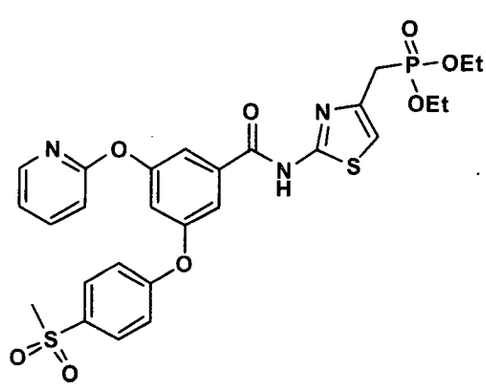
A una solución 0°C del compuesto de la Parte A (880 mg, 2.85 mmol) en MeOH (8 mL) y THF (4 mL) se le agregó NaOH acuoso 1N (6 mL). La reacción se entibió lentamente a temperatura ambiente y se agitó a temperatura ambiente durante 18 h. Los volátiles se removieron *in vacuo*, y la reacción se diluyó con agua, se acidificó con HCl acuoso 2N (5 mL), y se extrajo con EtOAc. La capa orgánica se lavó con salmuera, se secó ($MgSO_4$), filtró, y concentró *in vacuo* para dar el compuesto de la Parte B (830 mg, 96% de rendimiento) como un sólido blanco.

C.

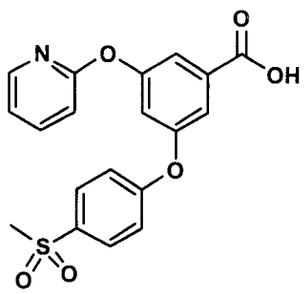


A una solución 0°C del compuesto de la Parte B (29.4 mg, 0.1 mmol) en CH_2Cl_2 (0.5 mL) bajo Ar se le agregó cloruro de oxalilo (0.065 mL, 0.13 mmol, 2M en CH_2Cl_2) y DMF (3 µL). La reacción se agitó a 0°C durante 1 h y se entibió luego a temperatura ambiente y se agitó durante 2 h. Los volátiles se removieron *in vacuo*. A una solución 0°C del residuo de cloruro ácido en CH_2Cl_2 (0.5 mL) bajo Ar se le agregó una solución de piridina (32.3 µL, 0.4 mmol) en CH_2Cl_2 (0.25 mL), seguido por la adición del compuesto del Ejemplo 7 Parte B (27 mg, 0.11 mmol). La reacción se agitó a temperatura ambiente durante 18 h y se purificó directamente por cromatografía de columna (SiO_2, 0-10% MeOH: CH_2Cl_2). El producto deseado y el ácido de la Parte B co-eluido, de manera que la mezcla se extrajo con CH_2Cl_2. La capa orgánica se lavó con HCl acuoso 0.5 N, agua, $NaHCO_3$ acuoso saturado, y salmuera. La capa orgánica se secó ($MgSO_4$), filtró, y concentró *in vacuo* para dar el compuesto del título (29 mg, 56% de rendimiento) como un aceite. $[M+H]^+$ = 522.2.

EJEMPLO 165

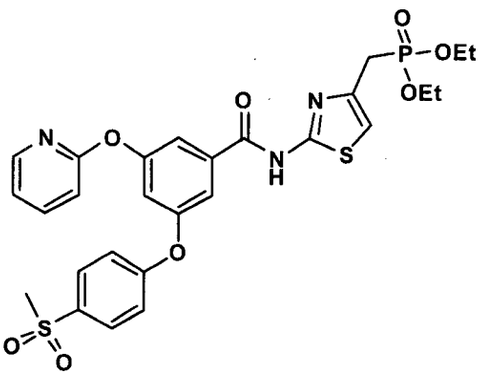


A.



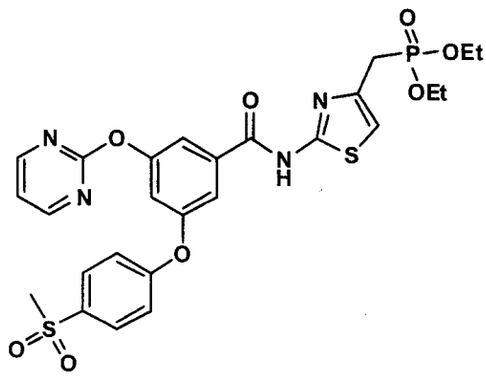
A una solución del compuesto del Ejemplo 26 Parte A (80 mg, 0.248 mmol) en DMF (1 mL), se le agregaron 2-cloropiridina (0.047 mL, 0.496 mmol) y K_2CO_3 (103 mg, 0.745 mmol). La mezcla de reacción se agitó a 120°C durante 40 h, luego se enfrió a temperatura ambiente y se filtró. El filtrado se diluyó con MeOH, luego se purificó por CLAR preparativa (columna Phenomenex Luna AXIA 30 x 100 mm; detección a 220 nm; relación de flujo = 40 mL/min.; gradiente continuo desde 80% A hasta 100% B durante 10 min., donde A = 10% MeOH/90% H_2O/0.1% TFA y B = 90% MeOH/10% H_2O/0.1% TFA) para dar el compuesto de la Parte A (26 mg, 27%) como un sólido blanco.

B.



A una solución del compuesto de la Parte A (26 mg, 0.067 mmol) en DMF (1 mL), se agregó compuesto del Ejemplo 13 Parte E (33.8 mg, 0.135 mmol), EDCI (25.9 mg, 0.135 mmol), HOBT (20.66 mg, 0.135 mmol), y DIPEA (0.035 mL, 0.202 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 2 días. La mezcla de reacción se purificó directamente por CLAR preparativa (columna Phenomenex Luna AXIA 30 x 100 mm; detección a 220 nm; relación de flujo = 40 mL/min.; gradiente continuo desde 70% A hasta 100% B durante 10 min., donde A = 10% MeOH/90% H_2O/0.1% TFA y B = 90% MeOH/10% H_2O/0.1% TFA) para dar el compuesto del título (11 mg, 26% de rendimiento) como un aceite amarillo. $[M + H]^+$ = 618.3; ^1H RMN (500 MHz, $CDCl_3$): δ 8.24 (1 H, d, J=4.95 Hz), 7.95 (2 H, d, J=8.80 Hz), 7.78 - 7.84 (2 H, m), 7.71 (1 H, s), 7.20 - 7.25 (3 H, m), 7.13 (1 H, dd, J=6.87, 4.67 Hz), 7.07 (1 H, d, J=8.25 Hz), 7.04 (1 H, d, J=3.85 Hz), 4.10 - 4.21 (4 H, m), 3.34 (2 H, d, J=21.44 Hz), 3.07 (3 H, s), 1.32 (6 H, t, J=6.87 Hz).

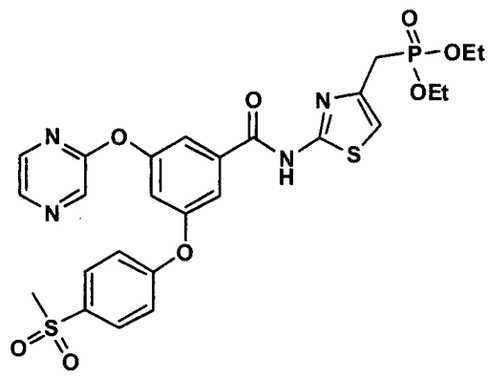
EJEMPLO 166



El compuesto del título (5 mg, 24% de rendimiento,

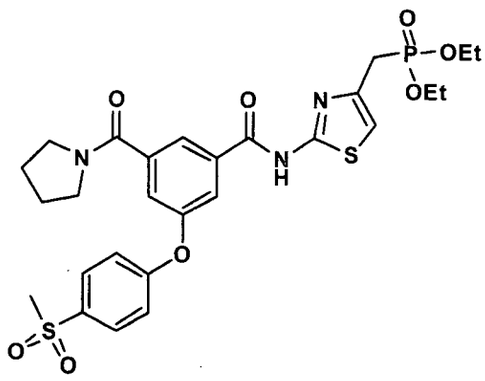
aceite amarillo) se preparó de 2-cloropirimidina siguiendo el mismo procedimiento general como se usa para la síntesis del Ejemplo 165. $[M + H]^+$ = 619.3; ^1H RMN (500 MHz, $CDCl_3$): δ 8.63 (2 H, d, *J*=4.95 Hz), 7.88 - 7.99 (3 H, m), 7.78 (1 H, s), 7.27 - 7.28 (1 H, m), 7.24 (2 H, d, *J*=9.35 Hz), 7.15 (1 H, t, *J*=4.95 Hz), 7.05 (1 H, d, *J*=3.30 Hz), 4.11 - 4.21 (4 H, m), 3.34 (2 H, d, *J*=21.44 Hz), 3.08 (3 H, s), 1.32 (6 H, t, *J*=7.15 Hz).

EJEMPLO 167

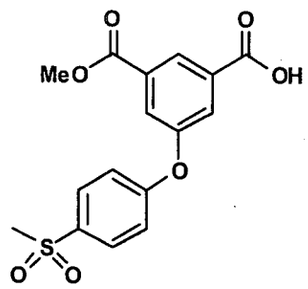


El compuesto del título (11.5 mg, 30% de rendimiento, sólido amarillo) se preparó de 2-cloropirazina siguiendo el mismo procedimiento general como se usa para la síntesis del Ejemplo 165. $[M + H]^+$ = 619.3; ^1H RMN (500 MHz, $CDCl_3$): δ 8.54 (1 H, s), 8.37 (1 H, d, *J*=2.75 Hz), 8.16 (1 H, s), 7.96 (2 H, d, *J*=8.80 Hz), 7.89 (1 H, s), 7.77 (1 H, s), 7.25 - 7.27 (1 H, m), 7.24 (2 H, d, *J*=8.80 Hz), 7.05 (1 H, d, *J*=3.85 Hz), 4.10 - 4.21 (4 H, m), 3.34 (2 H, d, *J*=21.44 Hz), 3.08 (3 H, s), 1.32 (6 H, t, *J*=6.87 Hz).

EJEMPLO 168

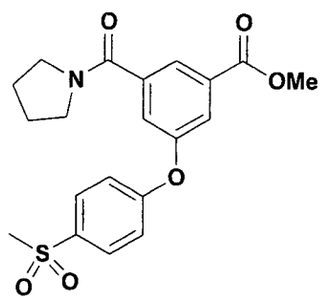


A.



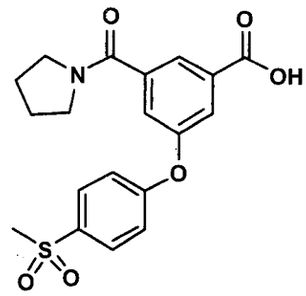
A una solución de 5-hidroxiisoftalato de dimetilo (198 mg, 0.942 mmol) en DMF (2 mL), se le agregó 1-fluoro-4-(metilsulfonil)benceno (197 mg, 1.130 mmol) y K_2CO_3 (391 mg, 2.83 mmol). La mezcla de reacción se agitó a 120°C durante 41 h, luego se enfrió a temperatura ambiente y se filtró. El filtrado se diluyó con MeOH, luego se purificó por CLAR preparativa (columna Phenomenex Luna AXIA 30 x 100 mm; detección a 220 nm; relación de flujo = 40 mL/min.; gradiente continuo desde 80% A hasta 100% B durante 10 min., donde A = 10% MeOH/90% H_2O/0.1% TFA y B = 90% MeOH/10% H_2O/0.1% TFA) para proporcionar el compuesto de la Parte A (176 mg, 53% de rendimiento) como un sólido blanco. $[M+H]^+$ = 351.2.

B.



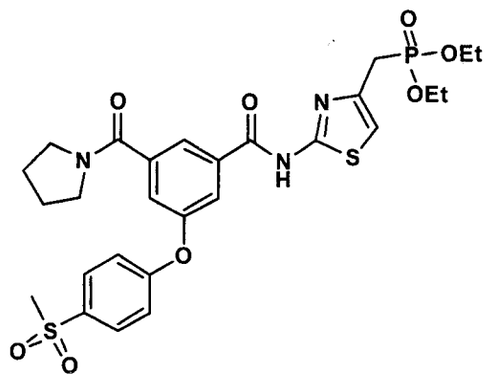
A una solución del compuesto de la Parte A (85 mg, 0.243 mmol) en CH_2Cl_2 (1.0 ml) se le agregó cloruro de oxalilo (0.243 mL, 0.485 mmol) y DMF (5.64 µL, 0.073 mmol). La mezcla se agitó a temperatura ambiente durante 1 h, luego se concentró in vacuo. El cloruro ácido crudo se tomó en THF (1.0 mL), y pirrolidina (0.041 mL, 0.485 mmol) y piridina (0.059 mL, 0.728 mmol) se agregaron. La mezcla de reacción se agitó a temperatura ambiente durante 3 h, luego se diluyó con EtOAc (10 mL), se lavó con H_2O y salmuera, se secó ($MgSO_4$), y concentró *in vacuo*. El residuo se purificó por CLAR preparativa (columna Phenomenex Luna AXIA 30 x 100 mm; detección a 220 nm; relación de flujo = 40 mL/min.; gradiente continuo desde 70% A hasta 100% B durante 10 min., donde A = 10% MeOH/90% H_2O/0.1% TFA y B = 90% MeOH/10% H_2O/0.1% TFA) para proporcionar compuesto de la Parte B (93 mg, 95% de rendimiento) como un aceite incoloro. $[M+H]^+$ = 404.3.

C.



A una solución del compuesto de la Parte B (8.5 mg, 0.021 mmol) en THF (1 mL), se le agregó NaOH acuoso 1N (0.063 mL, 0.063 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 15 h y se diluyó con EtOAc (6 mL), se acidificó con HCl acuoso 1N (0.050 mL), y se separó. La capa orgánica se lavó con salmuera, se secó ($MgSO_4$), y concentró *in vacuo* para dar el compuesto de la Parte C crudo (10 mg) como un sólido blanco, el cual se usó en la siguiente etapa sin purificación adicional. $[M+H]^+$ = 390.2.

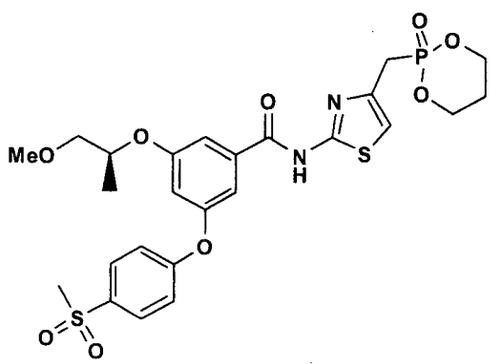
D.



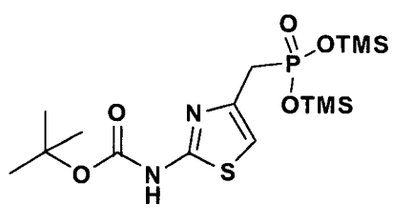
A una solución del compuesto de la Parte C (10 mg, 0.026 mmol) en DMF (1 mL), se le agregó compuesto del Ejemplo 13 Parte E (12.9 mg, 0.051 mmol), EDCI (9.9 mg, 0.051 mmol),

HOBT (7.9 mg, 0.051 mmol), y DIPEA (0.013 mL, 0.077 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 4 días, luego se purificó directamente por HPLC preparativa (columna Phenomenex Luna AXIA 30 x 100 mm; detección a 220 nm; relación de flujo = 40 mL/min.; gradiente continuo desde 70% A hasta 100% B durante 10 min., donde A = 10% MeOH/90% H_2O/0.1% TFA y B = 90% MeOH/10% H_2O/0.1% TFA) para proporcionar el compuesto del título (3 mg, 23% de rendimiento durante 2 etapas) como un sólido blanco. $[M+H]^+$ = 622.3; ^1H RMN (500 MHz, $CDCl_3$): δ 8.18 (1 H, s), 7.89 - 8.00 (3 H, m), 7.55 (1 H, s), 7.19 (2 H, d, *J*=8.80 Hz), 7.05 (1 H, d, *J*=3.30 Hz), 4.05 - 4.23 (4 H, m), 3.50 - 3.74 (4 H, m), 3.35 (2 H, d, *J*=21.44 Hz), 3.09 (3 H, s), 1.85 - 2.04 (4 H, m), 1.32 (6 H, t, *J*=7.15 Hz).

EJEMPLO 169

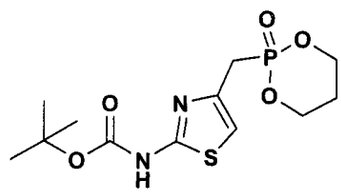


A.



A una solución del compuesto del Ejemplo 13 Parte A (377 mg, 1.08 mmol) en CH_2Cl_2 (5 mL) a temperatura ambiente bajo Ar se le agregó TMSBr (0.307 mL, 2.37 mmol). Después de la agitación a temperatura ambiente durante 15 h, la mezcla de reacción se concentró in vacuo bajo condiciones escrupulosamente secas para proporcionar compuesto de la Parte A como un aceite incoloro, el cual se usó en la siguiente etapa sin purificación adicional.

B.

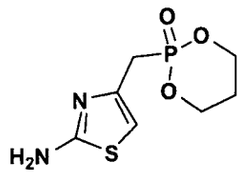


A una solución del compuesto de la Parte A en CH_2Cl_2 seco (5 mL; protegido desde la atmosfera por un tubo de secado lleno con $CaCl_2$) se le agregó cloruro de oxalilo (0.207 mL, 2.37 mmol) y DMF (8 µL, 0.1 mmol). Se observó espumado considerable, resultando eventualmente en la formación de un precipitado beige. Después de agitar a temperatura ambiente durante 3 h, la mezcla de reacción se concentró in vacuo y el residuo se tomó en THF (12 mL) y se enfrió a -65°C bajo Ar. A esta solución espesa se le agregó una solución de 1,3-propanodiol (0.086 mL, 1.18 mmol) en MeCN (6 mL) durante 2 min y se agitó durante 5 min a -65°C. La piridina (0.183 mL, 2.26 mmol) se agregó luego durante 1 min, y la mezcla de reacción se permitió entibiar a temperatura ambiente y se

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agitó durante 16 h a temperatura ambiente. La mezcla se dividió entre EtOAc y $NaHSO_4$ acuoso 5% (25 mL cada uno). La fase orgánica se secó (Na_2SO_4) y concentró in vacuo. El residuo se purificó por HPLC preparativa (columna Phenomenex Luna 21.2 x 100 mm; detección a 254 nm; relación de flujo = 20 mL/min.; gradiente continuo desde 0% A hasta 100% B durante 10 min, donde A = 10% MeCN/90% H_2O/0.1% TFA y B = 90% MeCN /10% H_2O/0.1% TFA) para proporcionar compuesto de la Parte B (71 mg, 20% de rendimiento) como un sólido amorfo blanco. $[M+H]^+$ = 335.

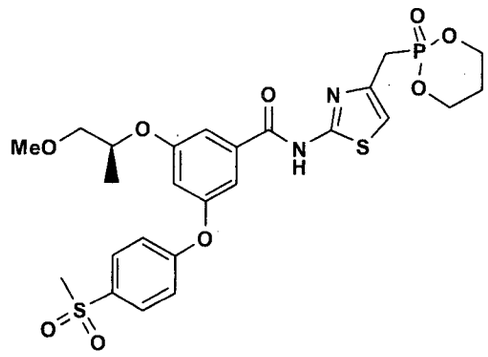
C.



A una solución agitada del compuesto de la Parte B (71 mg, 0.21 mmol) en CH_2Cl_2 seco (2 mL; protegido desde la atmosfera por un tubo de secado lleno con $CaCl_2$) a temperatura ambiente se le agregó TFA (0.5 mL). La reacción se agitó durante 4 h a temperatura ambiente, luego se concentró in vacuo. El residuo se disolvió en MeOH y se eluyó a través de un cartucho de intercambio de iones StratoSpheres™ SPE PL-HCO_3 MP (capacidad 0.9 meq) con MeOH. La concentración del eluyente in vacuo proporcionó compuesto de la Parte C como un sólido amorfo blanco (43 mg, 86% de rendimiento). $[M+H]^+$ = 235.

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D.



A una solución espesa agitada del compuesto del Ejemplo 26C (69 mg, 0.18 mmol) en CH_2Cl_2 (2 mL) a temperatura ambiente bajo Ar se le agregaron sucesivamente HOAt (25 mg, 0.18 mmol) y EDC (35 mg, 0.18 mmol). Una solución transparente formada durante 5 min. Después de 30 min, esta solución se agregó a una mezcla espesa del compuesto de la Parte C en THF (2 mL) a temperatura ambiente bajo Ar, seguido por iPr_2NEt (0.016 mL, 0.43 mmol) y DMAP (2.6 mg, 0.02 mmol). Después de agitar durante 18 h a temperatura ambiente, HPLC analítica indica que ningun producto se había formado. La mezcla de reacción se concentró in vacuo y se tomó en MeCN seco (3 mL), luego se calentó a reflujo bajo Ar, con lo cual una solución se formó. Después de 2 h a reflujo, HPLC analítica indica que casi toda la amina había sido consumida. La mezcla de reacción se enfrió a temperatura ambiente y concentró in vacuo. El residuo se dividió entre EtOAc y $NaHCO_3$ acuoso saturado (20 mL cada uno). La fase orgánica se lavó con salmuera y $NaHSO_3$ 10% acuoso, se secó (Na_2SO_4) y concentró in vacuo. La

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purificación del residuo aceitoso por HPLC preparativa (columna Phenomenex Luna 21.2 x 100 mm; detección a 220 nm; relación de flujo = 20 mL/min.; gradiente continuo desde 0% A hasta 100% B durante 10 min., donde A = 10% MeCN/90% H_2O/0.1% TFA y B = 90% MeCN/10% H_2O/0.1% TFA) proporcionó el compuesto del título (35 mg, 28% de rendimiento) como un sólido amorfo blanco. $[M+H]^+$ = 597. ^1H RMN (400 MHz, $CDCl_3$): δ 7.92 (2 H, d, *J*=7.1 Hz), 7.59 (1 H, s), 7.42 (1 H, s), 7.17 (2 H, d, *J*=8.80 Hz), 6.85 (2 H, m), 4.73 (1 H, m), 4.35 (2 H, m), 4.12 (2 H, m), 3.66-3.51 (3 H, m), 3.41 (3 H, s), 3.07 (3 H, s), 1.92-1.72 (2 H, m), 1.34 (3 H, d, *J*=6.0 Hz).

ENSAYOS PARA ACTIVACION DE GLUCOCINASA

Los compuestos de la fórmula I de la invención activan la glucocinasa. Los ensayos los cuales pueden usarse para probar los compuestos de la fórmula I de la invención en glucocinasa activada se conocen en la técnica tales como se describen en Patentes de EUA Nos. 6,320,050, 6,384,200 y 6,610,846 y WO 2004/052869 y en Castellano, A.L, Dong, H., Fyfe, M.C.T., Gardner, L.S., Kamikozawa, Y. et al. (2005) "Glucokinase activating ureas", Bioorg. Med. Chem. Letters, 15:1501-1504, and Grimsby, J., Sarabu, R., Corbett, W.L, Haynes, N-E., Bizzarro, F.T., Coffey, J.W., Guertin, K.R., Hilliard, D.W., Kester, R.F., Mahaney, P.E., Marcus, L., Qi, L., Spence, C.L., Tengi, J., Magnuson, M.A., Chu, C.A., Dvorozniak, M.T., Matschinsky, F.M., Grippo, J.F. (2003)

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"Allosteric Activators of Glucokinase: Potential Role in Diabetes Therapy", Science, 301:370-373.

En general, los compuestos de la presente invención, tales como los compuestos particulares descritos en los siguientes ejemplos, se han identificado para aumentar la actividad de glucocinasa a concentraciones equivalentes a, o más potencialmente que, 100 μM, preferiblemente 10 μM, más preferiblemente 1 μM, por ello demuestra que compuestos de la presente invención son potenciadores especialmente efectivos de la actividad de glucocinasa. Las potencias pueden calcularse y expresarse como ya sea EC_{50} (concentración para alcanzar 50% de activación completa) y/o la activación de porcentaje máxima de respaldo anterior, y se refiere a la actividad medida empleando el sistema de ensayo descrita arriba.

ENSAYO Y DATOS BIOLOGICOS

Los compuestos de la fórmula I de la invención, incluyendo los compuestos descritos en los ejemplos en la misma, se han probado en el siguiente ensayo y muestran que son activadores de la glucocinasa.

Ensayo Enzimático en Tándem de Glucocinasa

La actividad enzimática de la glucocinasa humana (GK) se midió al incubar GK, ATP, y glucosa por periodos de tiempo discretos seguido por apagado con EDTA (ácido etilendiamina tetra-acético). Se midieron cantidades relativas de producto de glucosa-6-fosfato (G6P) al correr

entonces un ensayo de detección usando deshidrogenasa G6P y midiendo la conversión de ThioNAD (dinucleótido tio-dihidronicotinamida adenina) a una longitud de onda de 405 nm. Esta reacción enzimática "desacoplada" se denota como el ensayo en "tándem" GK. La activación de GK por compuestos puede evaluarse usando este ensayo. El protocolo de ensayo en tándem GK descrito abajo se siguió usando un rango de concentraciones del compuesto activador desde 0 hasta 100 μM a 5 y 12 mM de glucosa. La glucocinasa de longitud completa humana (GK, 15 nM) se incubó con 5 ó 12 mM de glucosa en una placa de microtitulación de 384 pozos negra con un fondo transparente. Para iniciar la reacción GK, se agregó magnesio-ATP (concentración final 3 mM) al GK en solución amortiguadora (condiciones de solución amortiguadora final de solución amortiguadora 25 mM HEPES, pH 7.1, que contiene 1 mM ditiotreitol y 5% DMSO). El volumen de reacción total fue 20 μL. La reacción se permitió que procediera durante diez minutos y se apagó entonces con 5 μL EDTA; 45 mM final). Los componentes de la reacción de detección, ThioNAD y G6PDH (glucosa-6-fosfato deshidrogenasa) (concentraciones finales de 650 μM y 3.33 Unidades, respectivamente), luego se agregaron junto en un volumen de 25 μL, (para dar un volumen total de 50 μL). Las mediciones de absorbancia se hicieron a 405 nm en un lector de placa de absorbancia Spectramax Plus 384 (Molecular Devices). La absorbancia se leyó, los niveles de glucosa-6-fosfato de respaldo se substraen, después de lo cual la activación se calculó como un porcentaje de la actividad de control. La actividad de control se determinó usando GK en presencia de vehículo (DMSO), con glucosa-6-fosfato de respaldo

substraída. La glucosa-6-fosfato de respaldo se determinó por GK previamente apagado con EDTA antes de iniciar la reacción con ATP.

Expresión y Purificación de GK Humano

Se expresó GK hepático humano de longitud completa (no etiquetado) en células BL21 STAR (DE3)pLysS (Invitrogen) a 25°C como se describe por Mookhtiar et al. (1). La proteína se purificó esencialmente como se describe por Lange (2) con una modificación ligera. Brevemente, se lisaron peletizados celulares por medio de tres rondas de congelado y descongelado, centrifugado a 15000g para clarificación, y precipitado con 40-65% (NH4)2SO4. el peletizado resultante se volvïó a suspender en solución amortiguadora, se dializó, y se aplica directamente a una columna Q-Sepharose (Sigma) seguido por elución con un gradiente lineal 100-600 mM KCl. Las fracciones que contienen GK se agruparon, dializaron durante la noche contra 25 mM Hepes pH 7.2/1 mM MgCl2/1 mM EDTA/0.1 M KCl/1 mM DTT, luego se dializaron de nuevo con la misma solución amortiguadora con glicerol al 10% agregado.

REFERENCIAS

1. Mookhtiar, K.A., Kalinowski, S.S., Brown, K.S., Tsay, Y.H., Smith-Monroy, C., y Robinson, G.W. (1996) "Heterologous expression and characterization of rat liver glucokinase regulatory protein", *Diabetes,* 45:1670-1677.

2. Lange, A.J., Xu, L.Z., Van Poelwijk, F., Lin, K., Granner, D.K., and Pilkis, S.J. (1991) "Expression and site-directed mutagenesis of hepatic glucokinase", *Biochem. J.,* 277:159-163.

Los datos biológicos para los ejemplos seleccionados se muestran en la tabla a continuación.

Ejemplo No.	EC_{50} (nM) con glucocinasa humana @ 12 mM Glucosa
169	9
51	15
82	18
137	21
50	22
122	23
145	24
33	26
37	34
163	38
54	49
32	65
29	98
148	178
22	402
112	428
113	437
139	467
116	469

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Ejemplo No.	EC_{50} (nM) con glucocinasa humana @ 12 mM Glucosa
134	476
84	492
56	534
44	564

Para otros ejemplos, los valores EC_{50} no se pueden calcularse de las curvas de activación, así los datos de activación máximos (expresados como un % de activación basal) para algunos Ejemplos selectos se muestran en la tabla a continuación.

Ejemplo No.	(%) de activación máxima Glucocinasa humana @ 12 mM Glucosa
121	126%
65	162%
35	133%
79	133%

Ejemplo No.	(%) de activación máxima Glucocinasa humana @ 12 mM Glucosa
86	141%
123	135%
74	142%
23	150%

Estudios *In Vivo*: Prueba de tolerancia a la glucosa oral (OGTT)

Las pruebas de tolerancia a la glucosa oral se llevaron a cabo en ratones macho C57BL/6J DIO (obeso inducido por dieta) alimentado con una dieta alta en grasas (60% kcal de grasa) durante 26 semanas previo al experimento. Los ratones se alimentaron durante la noche antes de usarse para los experimentos. Un compuesto o vehículo de prueba (ya sea: 1) 40% PEG 400 + 10% Cremóforo + 50% agua o 2) 10% de acetamida de dimetilo + 10% de etanol + 10% de Cremóforo + 70% agua) se da oralmente 60 min antes de la administración oral de una solución de glucosa a una dosis de 2 g/kg peso corporal (prueba de tolerancia a la glucosa oral; OGTT). Los niveles de glucosa en la sangre se midieron de las muestras de tail-bled se toman en puntos de tiempo diferentes antes y después de la administración de la glucosa (tiempo de curso de 2

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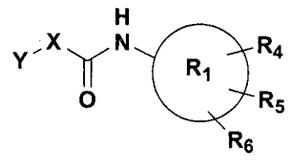
horas). Una curva de tiempo de la glucosa en la sangre se generó y el cambio del área de la línea base bajo la curva (ΔAUC) desde 0-120 min se calculó (el tiempo de la administración de glucosa es tiempo cero).

Los ejemplos en la tabla a continuación reducen los niveles AUC de glucosa en una prueba OGTT en ratones DIO como se describe anteriormente.

Ejemplo No.	Reducción en la glucosa AUC a 30 mg/kg por dosis
37	88%
148	60%
145	71%
54	68-82%
29	66-78%
44	62-80
32	79% @ 30 μmol/kg
82	44% @10 μmol/kg

REIVINDICACIONES

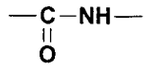
1. Compuesto, caracterizado porque tiene la estructura:



I

en donde

R_1 es un heteroarilo sustituido por R_4 y opcionalmente sustituido con uno o dos substituyentes R_5 y R_6, en donde el heteroarilo posee un átomo de nitrógeno adyacente al átomo

unido al grupo heteroarilo para  ;

R_4 se selecciona del grupo que consiste de

$-(CH_2)_n-Z-(CH_2)_m-PO(OR_7)(OR_8)$,

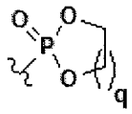
o $-(CH_2)_nZ-(CH_2)_m-PO(OR_7)R_9$,

o $-(CH_2)_n-Z-(CH_2)_m-O-PO(OR_7)R_9$,

o $-(CH_2)_nZ-(CH_2)_m-O-PO-(R_9)R_{10}$,

o $-(CH_2)_nZ-(CH_2)_m-PO(R_9)R_{10}$;

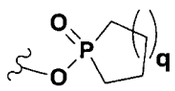
R_7 y R_8 son los mismos o diferentes y son independientemente seleccionados del grupo que consiste de hidrógeno y alquilo, o R_7 y R_8 pueden ciclizarse en un anillo



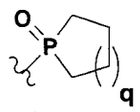
donde q = 1-3;

R_9 y R_{10} son los mismos o diferentes y son independientemente seleccionados del grupo que consiste de alquilo, arilo, arilalquilo, heteroarilo y heteroarilalquilo;

o R_9 y R_{10} pueden ciclizarse en un anillo



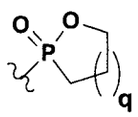
donde q = 1-3,



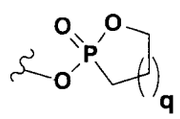
donde q = 1-3;

o

o, R_7 y R_9 pueden ciclizarse en un anillo



donde q = 1-3,



donde q = 1-3;

o

Z es seleccionado del grupo que consiste de un enlace, alquileno, alquenileno, O, S o SO_2;

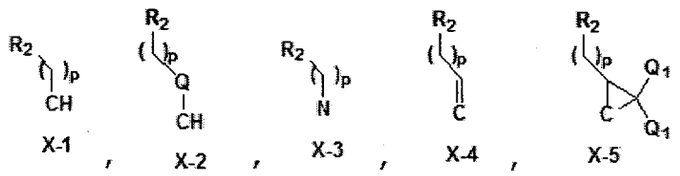
m es 0, 1 ó 2, con la condición de que cuando Z es O, S o SO_2, m es 1 ó 2;

n es 0, 1 ó 2;

R_5 y R_6 son iguales o diferentes y son seleccionados del grupo que consiste de hidrógeno,alquilo, halógeno y carboxi, o está

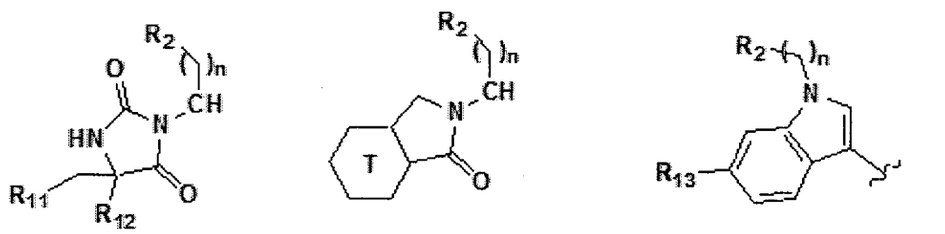
ausente;

X se selecciona del grupo que consiste de



X-1 , X-2 , X-3 , X-4 , X-5 , y un enlace X-6;

y cuando Y está ausente, X es



X-7 , X-8 , y X-9 ;

R_2 se selecciona del grupo que consiste de hidrógeno, alquilo, cicloalquilo, heterociclilo, arilo, heteroarilo, alquinilo, y alquenilo;

p es 0 ó 1;

Q se selecciona del grupo que consiste de O, $S(O)_q$ y CO, donde q es 0, 1 ó 2;

Q_1 se selecciona del grupo que consiste de hidrógeno y flúor;

R_{11} se selecciona del grupo que consiste de hidrógeno, alquilo inferior, cicloalquilo, arilo y heteroarilo;

R_{12} se selecciona del grupo que consiste de hidrógeno, y alquilo inferior, o R_{11} y R_{12} junto con el átomo de carbono al cual se enlazan forman un anillo cicloalquilo de 5 hasta 7 átomos de carbono;

R_{13} se selecciona del grupo que consiste de halo, nitro, amino, ciano, metilo, trifluorometilo, hidroxi, metoxi, trifluorometoxi, metiltio, metilsulfinilo y metilsulfonilo;

T se selecciona del grupo que consiste de arilo y heteroarilo;

Y es $R_3-(CH_2)_s-$, o está ausente;

R_3 se selecciona del grupo que consiste de arilo y heteroarilo;

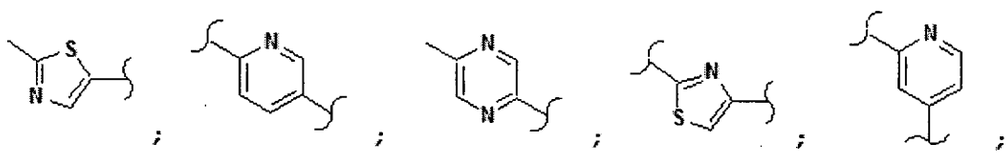
s = 0 ó 1;

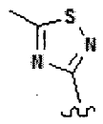
todos los estereoisómeros del mismo, un éster profármaco del mismo o una sal farmacéuticamente aceptable del mismo.

2. Compuesto de conformidad con la reivindicación 1, caracterizado porque la porción



es



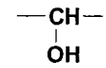
; o  .

3. Compuesto de conformidad con la reivindicación 1, caracterizado porque Z es alquileno o alquenileno, cada uno de los cuales pueden ser opcionalmente substituido con hidroxilo, alcoxi, aminoalquilo, aminoaralquilo, aminoheteroaralquilo, aminoarilo, aminoheteroarilo o carboxi.

4. Compuesto de conformidad con la reivindicación 1, caracterizado porque

R_4 es $(CH_2)_n$-Z-$(CH_2)_m$-$PO(OR_7)(OR_8)$ en donde Z es alquileno o alquenileno.

5. Compuesto de conformidad con la reivindicación 4, caracterizado porque n es 0, m es 0 y Z es

un enlace, $-CH_2-$, $-CH_3-CH=CH-$, $-CH_2CH_2-$ o  ; y

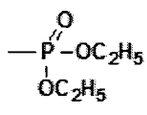
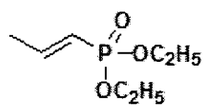
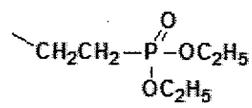
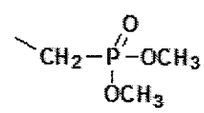
R_5 y R_6 son cada uno H;

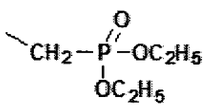
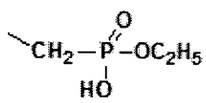
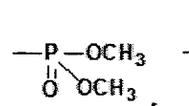
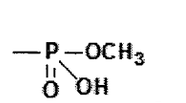
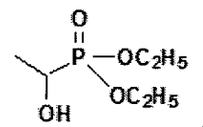
R_7 es H o alquilo; y

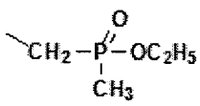
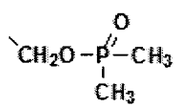
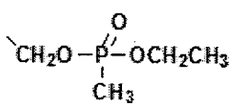
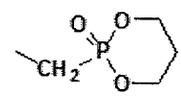
R_8 es H o alquilo.

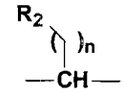
6. El compuesto de conformidad con la reivindicación 5, caracterizado porque

R_4 es

 ;  ;  ;  ;

 ;  ;  ,  ,  ;

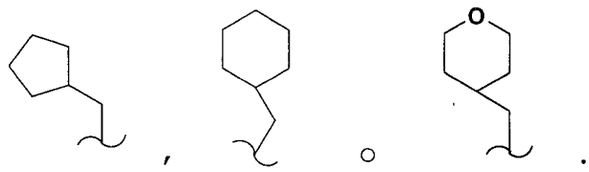
 ;  ;  o  .

7. Compuesto de conformidad con la 

reivindicación 1, caracterizado porque X es .

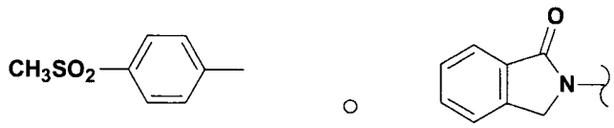
8. Compuesto de conformidad con la reivindicación 7, caracterizado porque R_2 es cicloalquilo o cicloalquilo con un oxígeno colocado, y n es 1.

9. Compuesto de conformidad con la reivindicación 7, caracterizado porque X es



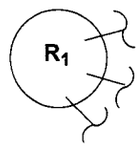
10. Compuesto de conformidad con la reivindicación 1, caracterizado porque Y es arilo o heteroarilo o está ausente.

11. Compuesto de conformidad con la reivindicación 10, caracterizado porque Y es CH_3SO_2-,

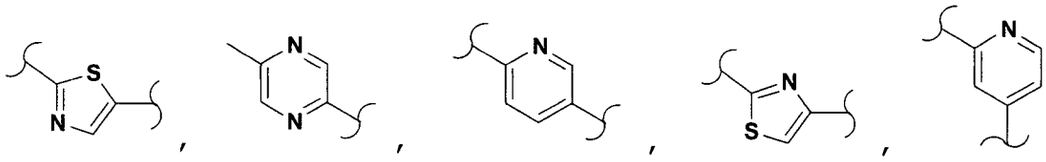


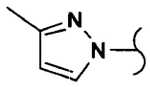
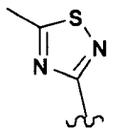
12. Compuesto de conformidad con la reivindicación 1, caracterizado porque R_5 y R_6 son cada uno H.

13. Compuesto de conformidad con la reivindicación 1, caracterizado porque



es




, o 
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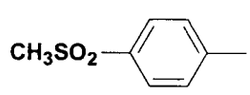
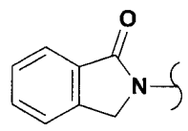
R_4 es $(CH_2)_n$-Z-$(CH_2)_m$-PO(OR_7)(OR_8), donde n es 0, m es 0, Z es alquileno o alquenileno;

R_5 y R_6 son cada uno H;

R_7 y R_8 son los mismos o diferentes y son independientemente seleccionados de H y alquilo;

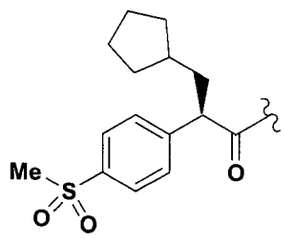
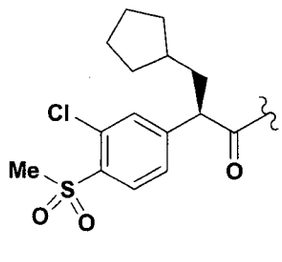
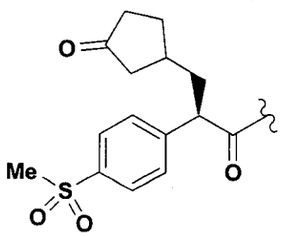
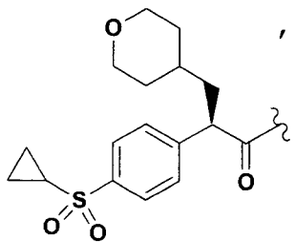
X es un enlace o  donde R_2 es ciclopentilo o ciclohexilo, y p es 0;

Y es

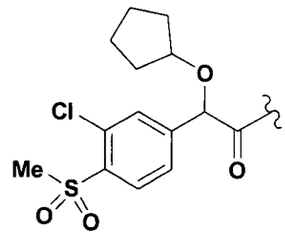

o 
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14. Compuesto de conformidad con la reivindicación 1, caracterizado porque incluye:

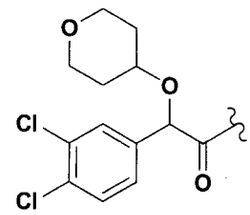
Y-X-CO- es


(a)
, 
(b)
, 
(c)
, o 
(d)
; o

Y-X-CO- es

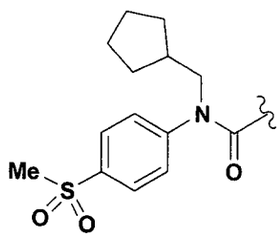


(e) , o

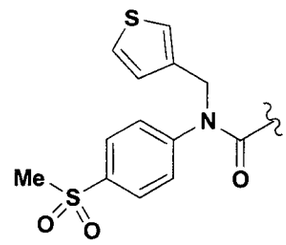


(f) ; o

Y-X-CO- es

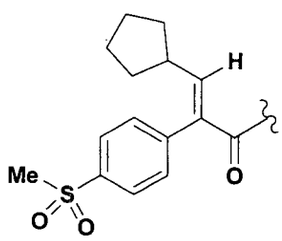


(g) o

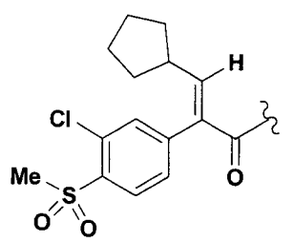


(h) ; o

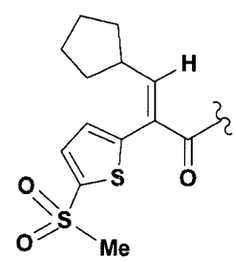
Y-X-CO- es



(i) ,

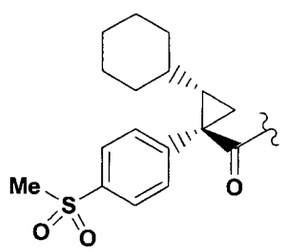


(j) o

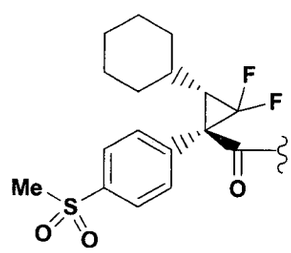


(k) ; o

Y-X-CO- es

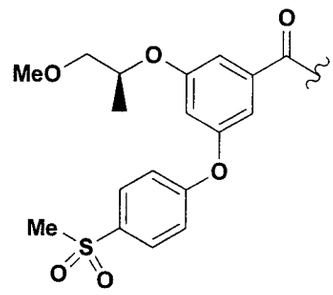


(l) o

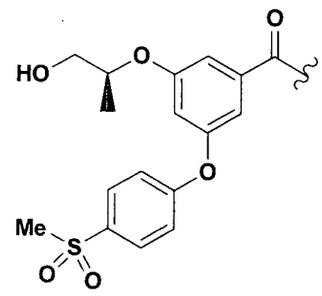


(m) ; o

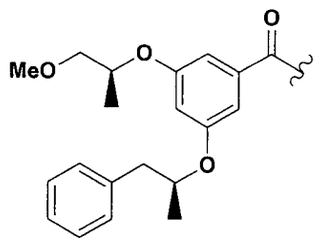
Y-X-CO- es



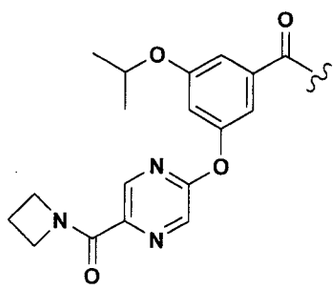
(n)



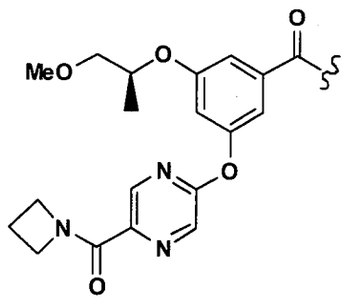
(o)



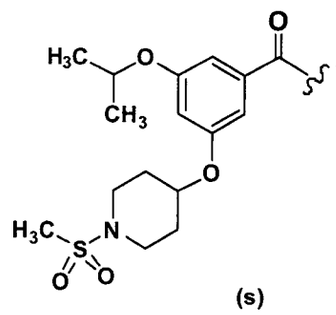
(p)



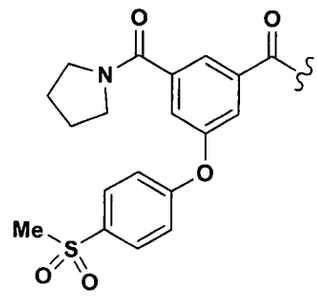
(q)



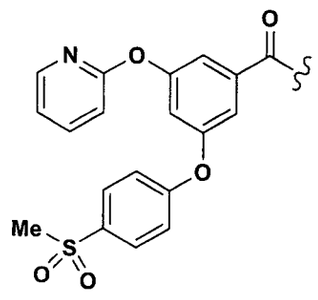
(r)



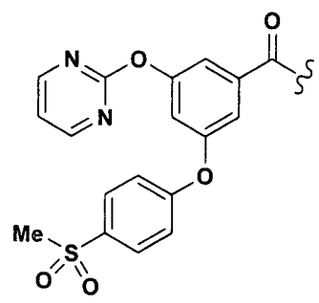
(s)



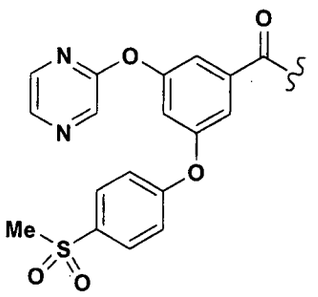
(t)



(u)

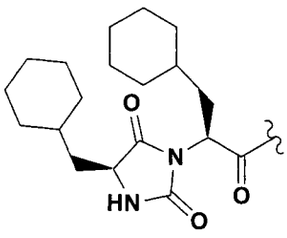


(v)

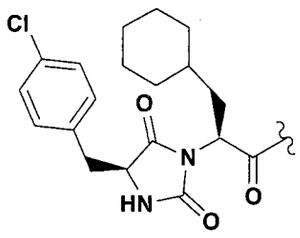


(w)

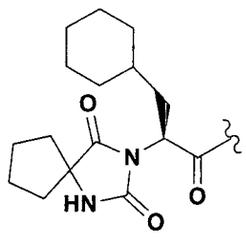
Y-X-CO- es



(x)

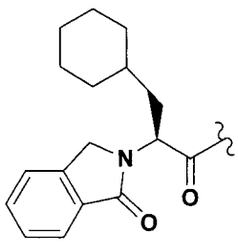


(y)



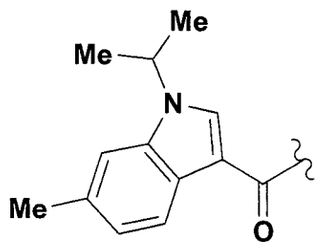
(z)

Y-X-CO- es



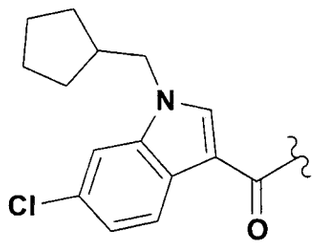
(aa)

Y-X-CO- es



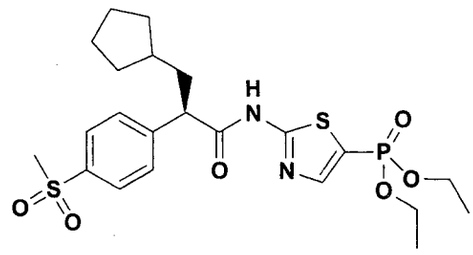
(ab)

o

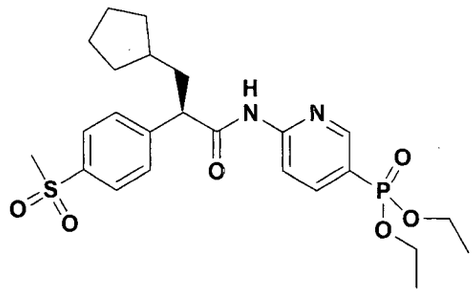


(ac)

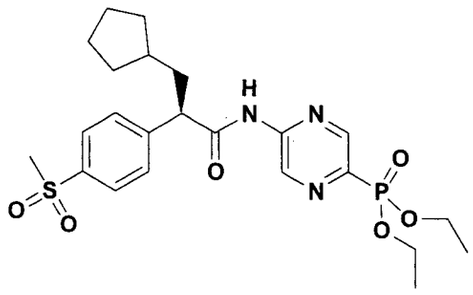
15. Compuesto de conformidad con la reivindicación 13, caracterizado porque es



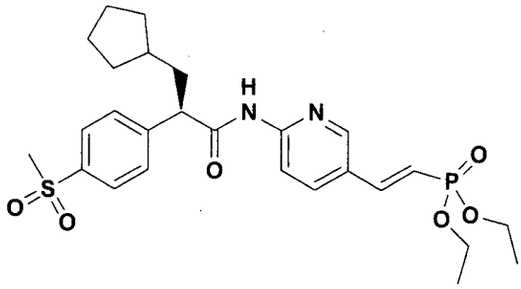
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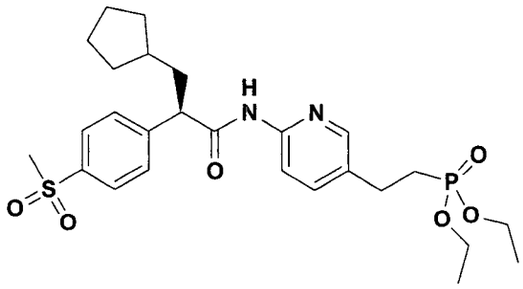


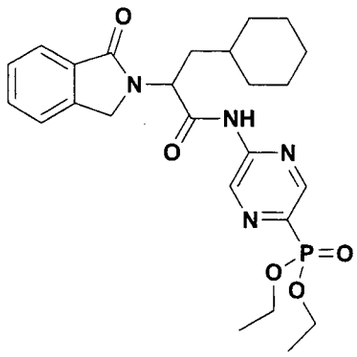
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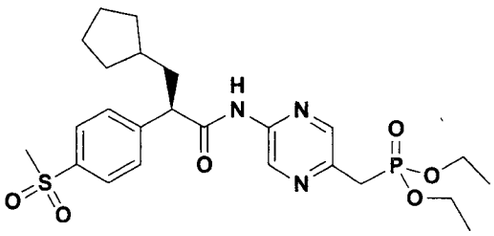


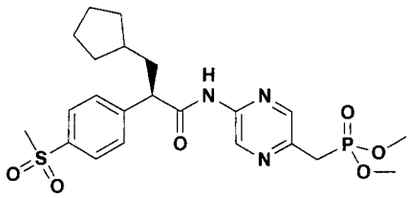
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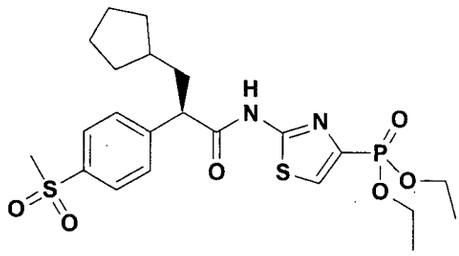




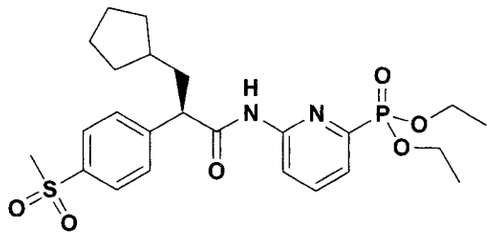




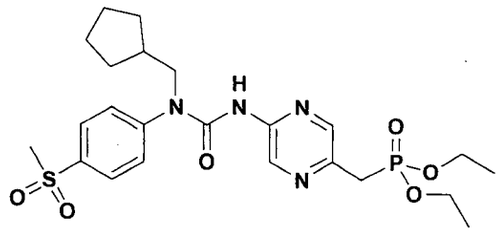




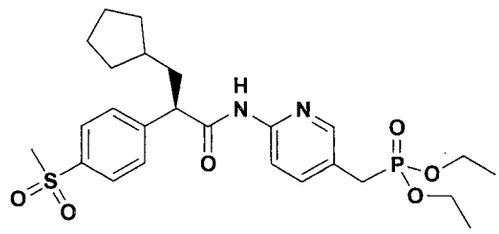
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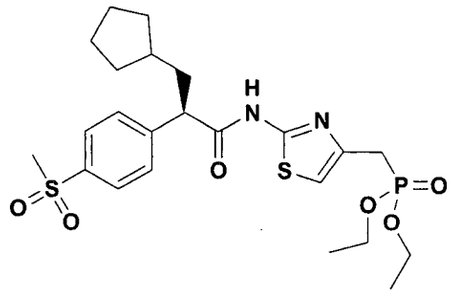
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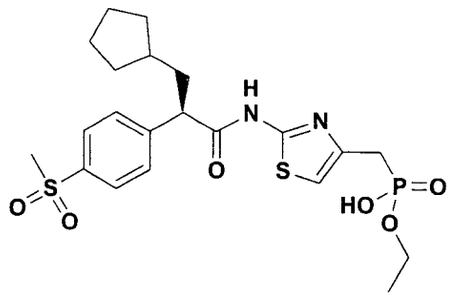
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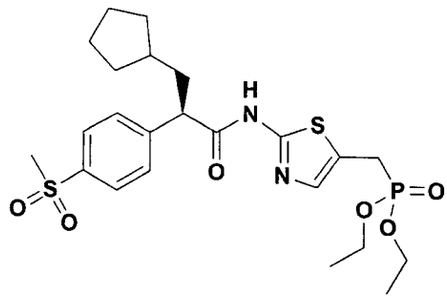


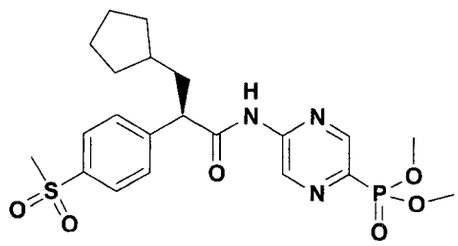
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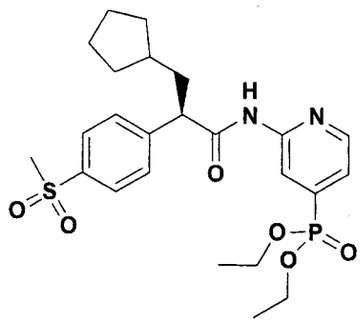


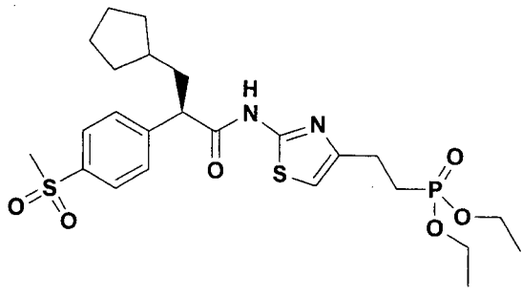
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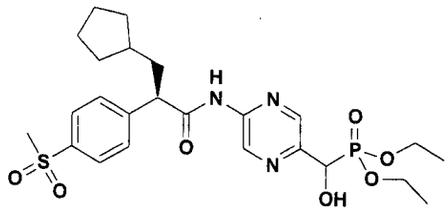


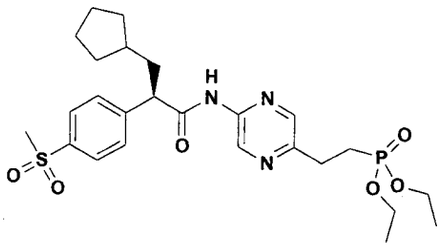


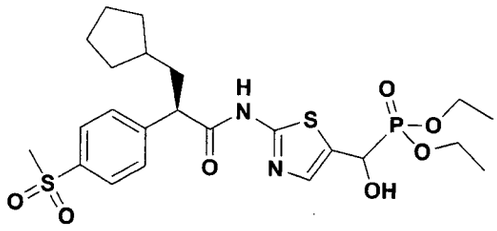


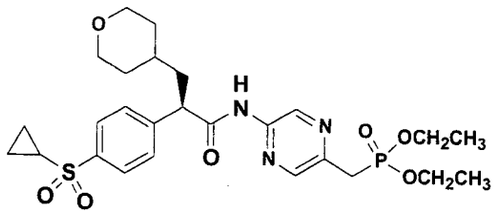


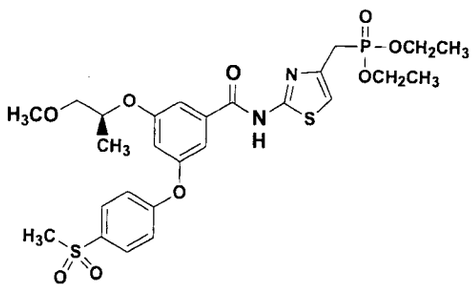


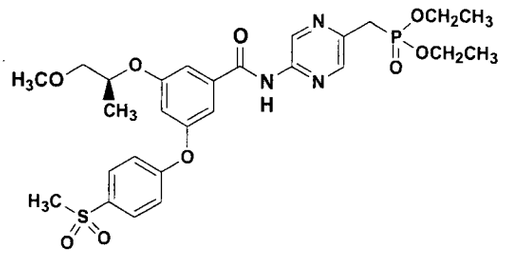


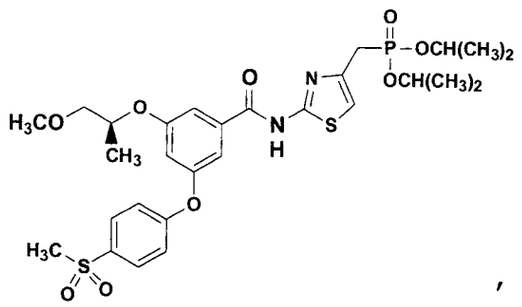


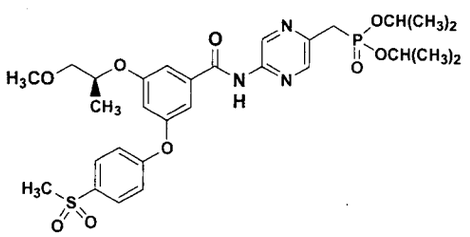


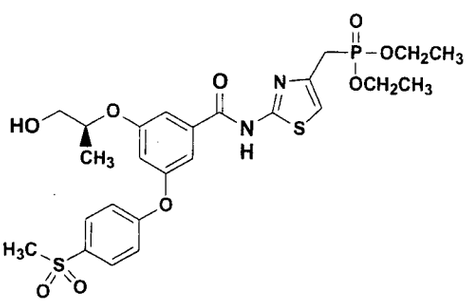


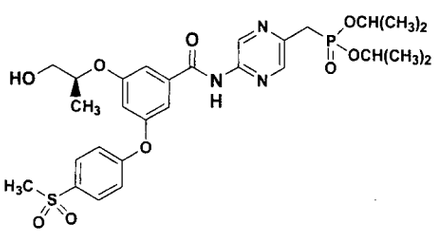


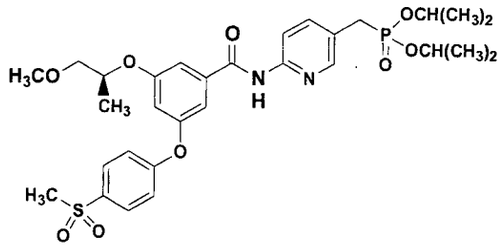


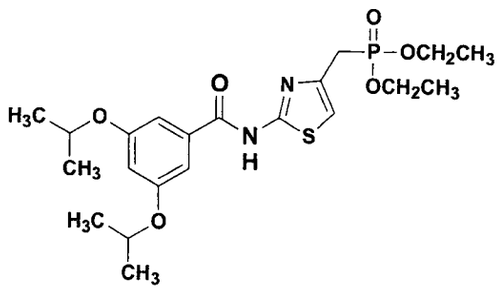


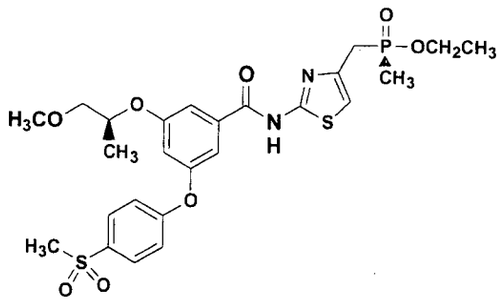


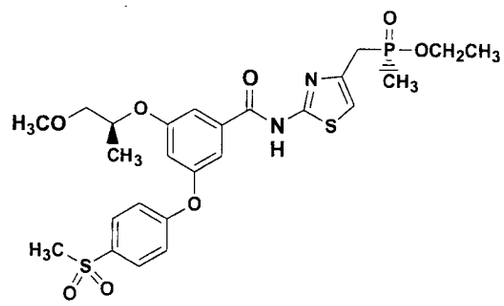


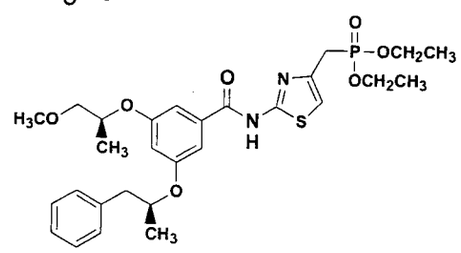




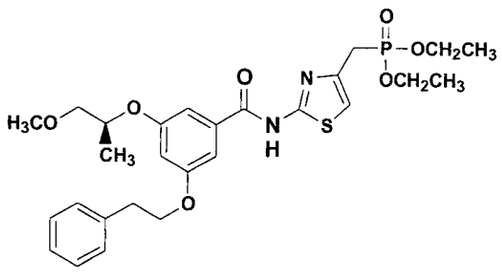


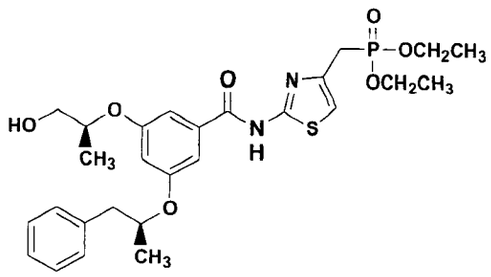


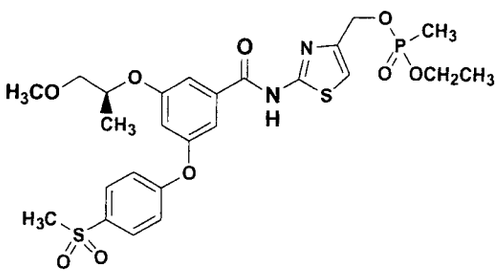


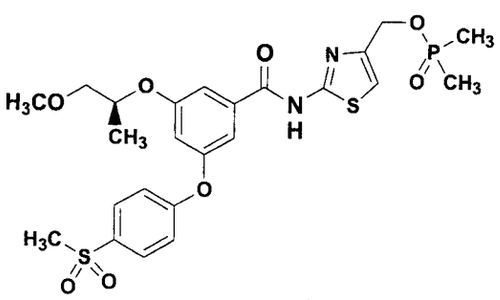


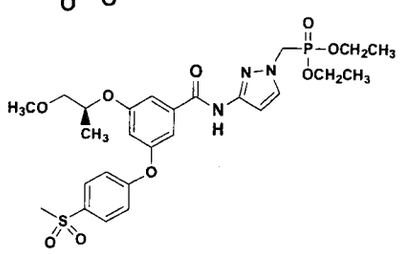
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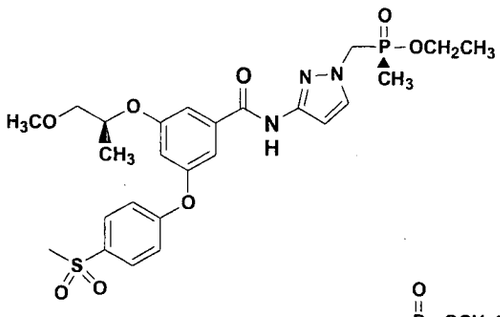


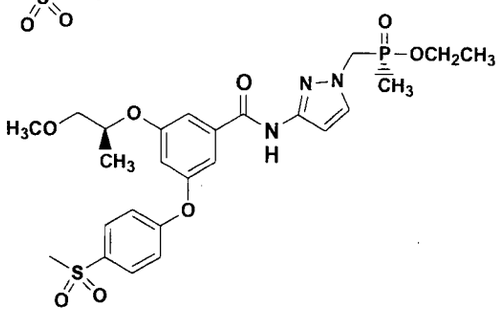


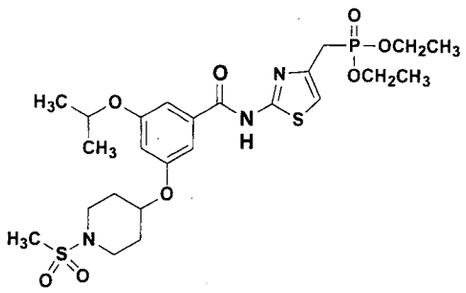


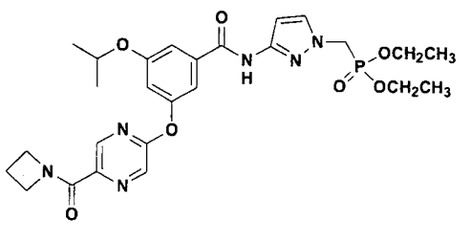


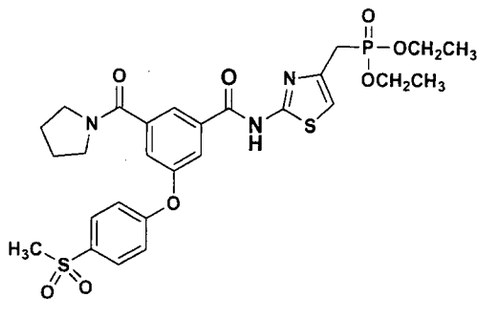
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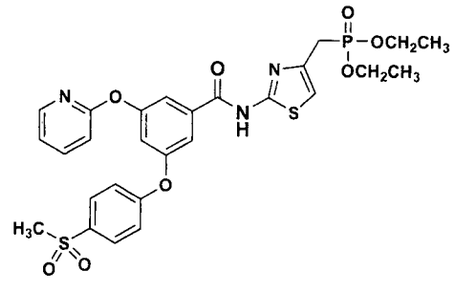


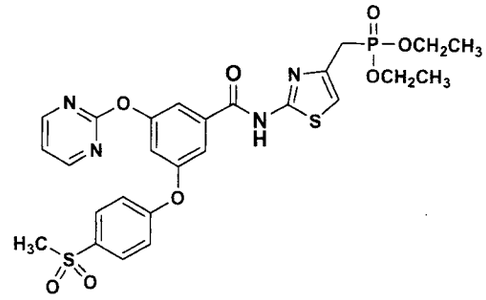


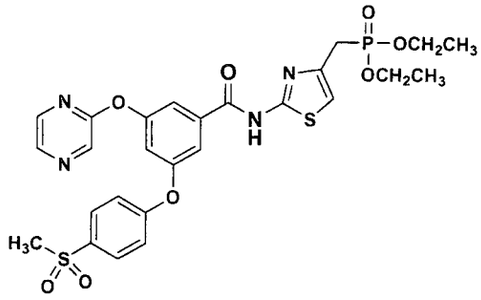


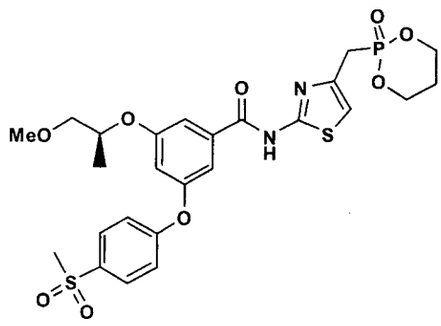


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16. Composición farmacéutica, caracterizada porque comprende un compuesto de conformidad con la reivindicación 1

y un portador farmacéuticamente aceptable del mismo.

17. Composición farmacéutica, caracterizada porque comprende un compuesto de conformidad con la reivindicación 1 y otro agente terapéutico el cual es un agente anti-diabético, agente anti-hiperglicémico, agente anti-hiperinsulinémico, agente anti-retinopático, agente anti-neuropático, agente anti-nefropático, agente anti-ateroesclerótico, agente anti-infectivo, agente anti-isquémico, agente anti-hipertensivo, agente anti-obesidad, agente anti-dislipidémico, agente anti-hiperlipidémico, agente anti-hipertrigliceridémico, agente anti-hipercolesterolémico, agente anti-isquémico, agente anti-cáncer, agente anti-citotóxico, agente anti-restenótico, agente anti-pancreático, agente que disminuye el lípido, agente supresor del apetito, agente potenciador de la memoria o agente cognitivo.

18. Método para tratar, prevenir, o disminuir el progreso de una enfermedad que requiere la terapia del activador de glucocinasa, caracterizado porque comprende administrar a un paciente mamífero que necesita del tratamiento una cantidad terapéuticamente efectiva de un compuesto de la fórmula I como se define de conformidad con la reivindicación 1.

19. Método de conformidad con la reivindicación 18, caracterizado porque la enfermedad es diabetes,

(99841

hiperglicemia, deterioro de la tolerancia a la glucosa, resistencia a la insulina, hiperinsulinemia, retinopatía, neuropatía, nefropatía, cicatrización retrasada de herida, ateroesclerosis y sus secuelas, función cardiaca anormal, isquemia miocardial, apoplejía, Sindrome metabólico, hipertensión, obesidad, dislipidemia, hiperlipidemia, hipertrigliceridemia, hipercolesterolemia, HDL bajo, LDL alto, isquemia no cardiaca, infección, cáncer, restenosis vascular, pancreatitis, enfermedad neurodegenerativa, trastornos de lípido, insuficiencia cognitiva y demencia, enfermedad del hueso, lipodistrofia asociada con la proteasa de VIH, y glaucoma.

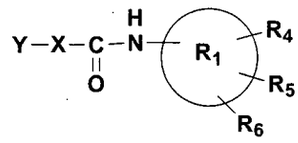
20. Método para activar la enzima glucocinasa, caracterizado porque comprende administrar a un paciente mamífero que necesita del tratamiento una cantidad terapéuticamente efectiva de un compuesto de la fórmula I de conformidad con la reivindicación 1.

21. Método para tratar la diabetes tipo II, caracterizado porque comprende administrar a un paciente que necesita del tratamiento un compuesto de conformidad con la reivindicación 1.

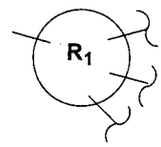
1183

RESUMEN DE LA INVENCIÓN

Se proporcionan compuestos los cuales son activadores de fosfonato y fosfinato y de esta manera son útiles en el tratamiento de diabetes y enfermedad relacionadas y tienen la estructura de la fórmula I



en donde la fórmula II



es un anillo heteroarilo;

R_4 es $-(CH_2)_n-Z-(CH_2)_m-PO(OR_7)(OR_8)$,

$-(CH_2)_nZ-(CH_2)_m-PO(OR_7)R_9$,

$-(CH_2)_n-Z-(CH_2)_m-OPO(OR_7)R_9$,

$-(CH_2)_nZ-(CH_2)_m-OPO(R_9)(R_{10})$, or

$-(CH_2)_nZ-(CH_2)_m-PO(R_9)(R_{10})$;

R_5 y R_6 son independientemente seleccionados de H, alquilo y halógeno;

Y es $R_7(CH_2)_s$ o está ausente; y

X, n, Z, m, R_4, R_5, R_6, R_7, y s son como se definen en la presente; o una sal farmacéuticamente aceptable del mismo.

También se proporciona un método para tratar diabetes y enfermedades relacionadas empleando los compuestos anteriores.

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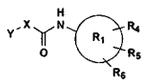
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
EXTRACTO PARA PUBLICACIÓN
SOLICITUD DE PATENTE DE INVENCIÓN PCT

(21) N° de solicitud:	(51) Int Cl: C07F 9/32 ; A61K 31/675; A61P 3/00; C07F 9/40
22) Fecha de solicitud:	(71)Solicitante(s) BRISTOL-MYERS SQUIBB COMPANY
(30) Prioridad (31) ***No.*** 32) ***Fecha*** (33) ***País*** 60/818,912 06.07.2006 US 11/769,964 28.06.2007 US	(72) Inventor(es) RYONO, Dennis E. ; CHENG, Peter T.W. Y OTROS
	(74) Apoderado: **ALVARO CORREA ORDOÑEZ**
(85) Fecha limite inicio fase nacional: 06/01/2009 (86) Datos relativos a la presentación de la solicitud PCT Fecha de presentación de la solicitud: 03.07.2007 No. de solicitud : PCT/US2007/072708	(87) Publicación internacional Fecha: 10.01.2008 N° publicación: WO/2008/005964

(54) Titulo: ACTIVADORES NOVEDOSOS DE GLUCOCINASA Y METODOS DE USO DE LOS MISMOS

Reivindicación(es):

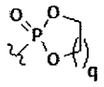
1. Compuesto, caracterizado porque tiene la estructura:



I

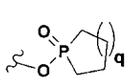
en donde
R1 es un heteroarilo sustituido por R4 y opcionalmente sustituido con uno o dos substituyentes R5 y R6, en donde el heteroarilo posee un átomo de nitrógeno adyacente al átomo

unido al grupo heteroarilo para ;
R4 se selecciona del grupo que consiste de
-(CH2)n-Z-(CH2)m-PO(OR7)(OR8),
o -(CH2)nZ-(CH2)m-PO(OR7)R9,
o -(CH2)n-Z-(CH2)m-O-PO(OR7)R9,
o -(CH2)nZ-(CH2)m-O-PO-(R9)R10,
o -(CH2)nZ-(CH2)m-PO(R9)R10;
R7 y R8 son los mismos o diferentes y son independientemente seleccionados del grupo que consiste de hidrógeno y alquilo, o R7 y R8 pueden ciclizarse en un anillo



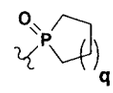
donde q = 1-3;

R9 y R10 son los mismos o diferentes y son independientemente seleccionados del grupo que consiste de alquilo, arilo, arilalquilo, heteroarilo y heteroarilalquilo;
o R9 y R10 pueden ciclizarse en un anillo



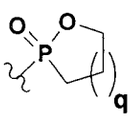
where q = 1-3

o

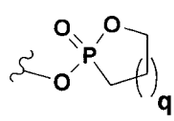


where q = 1-3

o, R7 y R9 pueden ciclizarse en un anillo



where q = 1-3



where q = 1-3

o

Z es seleccionado del grupo que consiste de un enlace, alquileno, alquenileno, O, S o SO2;

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
TARJETA ARCHIVO TEMATICO

PATENTE DE INVENCION ___ PCT _X_ MODELO DE UTILIDAD ___ DISEÑO INDUSTRIAL ___

(21) N° de solicitud: (22) Fecha de solicitud:

(51) Clasificación Internacional : C07F 9/32 ; A61K 31/675; A61P 3/00; C07F 9/40

(71)Solicitante(s)) BRISTOL-MYERS SQUIBB COMPANY

(72) Inventor(es) RYONO, Dennis E. ; CHENG, Peter T.W. ; BOLTON, Scott A. ;CHEN, Sean S; SHI, Yan ; MENG, Wei; TINO, Joseph A; ZHANG, Hao; SULSKY, Richard B

(74) Apoderado: ALVARO CORREA ORDOÑEZ

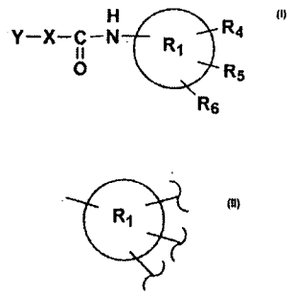
(30) Prioridad

(31) *No. Prioridad*	32) *Fecha*	(33) *País*
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11/769,964	28.06.2007	US

(85) Fecha límite inicio fase nacional: 06/01/2009

(86) Datos relativos a la presentación de la solic. PCT
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No. de solicitud : PCT/US2007/072708

(87) Publicación internacional:
Fecha: 10.01.2008
No. Publicación : WO/2008/005964



(54) Titulo: ACTIVADORES NOVEDOSOS DE GLUCOCINASA Y METODOS DE USO DE LOS MISMOS

(57) Resumen: Se proporcionan compuestos los cuales son activadores de fosfonato y fosfinato y de esta manera son útiles en el tratamiento de diabetes y enfermedad relacionadas y tienen la estructura de la fórmula I en donde la fórmula II es un anillo heteroarilo; R4 es -(CH2)n-Z-(CH2)m-PO(OR7)(OR8), -(CH2)nZ-(CH2)m-PO(OR7)R9, -(CH2)n-Z-(CH2)m-OPO(OR7)R9, -(CH2)nZ-(CH2)m-OPO(R9)(R10), or -(CH2)nZ-(CH2)m-PO(R9)(R10); R5 y R6 son independientemente seleccionados de H, alquilo y halógeno; Y es R7(CH2)s o está ausente; y X, n, Z, m, R4, R5, R6, R7, y s son como se definen en la presente; o una sal farmacéuticamente aceptable del mismo. También se proporciona un método para tratar diabetes y enfermedades relacionadas empleando los compuestos anteriores.

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
TARJETA ARCHIVO PROPIETARIOS

PATENTE DE INVENCION ___ PCT X MODELO DE UTILIDAD ___ DISEÑO INDUSTRIAL ___

(21) N° de solicitud: (22) Fecha de solicitud:

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(54) Titulo: ACTIVADORES NOVEDOSOS DE GLUCOCINASA Y METODOS DE USO DE LOS MISMOS

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2008/023

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

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Act. 411 PRESENTACION Folios: 849

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
BAKER & MCKENZIE	CONSIGNACION	BANCO DE BOGOTA	062754387	120646805	24/12/2008	46,377,000.00

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

CANT.	RENTISTICO	CONCEPTO		TOTAL CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD I	54	INFORMACION DETALLADA DE UN TRAMI	23,000.00
			TOTAL : $	23,000.00

SON: VEINTITRES MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

2008/020 847

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 08 - 86,680
FECHA : NOVIEMBRE 4 DE 2008

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 09-000418- -00000-0000
Fecha: 2009-01-05 16:46:19 Dep. 2020 NUECREACIONI
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 849

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
BAKER & MCKENZIE	CONSIGNACION	BANCO DE BOGOTA	062754387	10156473	04/11/2008	53,447,000.00

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

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD I	21 CERTIFICACIONES	11,000.00
		TOTAL : $	11,000.00

SON: ONCE MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

848

2008/023

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

CERTIFICACION DE EXCEDENTE : 08 - 100,315
FECHA : DICIEMBRE 26 DE 2008

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 09-000418- -00000-0000

Fecha: 2009-01-05 16:46:19 Dep: 2020 NUECREACIONI
Tra: 11 PATENTEIYII Eve: 378 FASENACIONALI
Act: 411 PRESENTACION Folios: 849

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
BAKER & MCKENZIE	CONSIGNACION	BANCO DE BOGOTA	062754387	120646805	24/12/2008	46,377,000.00

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

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD I	99 OTROS SERVCIOS ADMINISTRATIVOS	5,000.00
		TOTAL : $	5,000.00

SON: CINCO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

ESTA CERTIFICACION DE EXCEDENTE DE PAGO SOLO PODRA SER UTILIZADA COMO PARTE DE LA CANCELACION DE UNA TARIFA VIGENTE Y NO PODRA SER SUSTITUIDA POR NINGUN RECIBO.

849

2008/022

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

CERTIFICACION DE EXCEDENTE : 08 - 95,751
FECHA : DICIEMBRE 10 DE 2008

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 09-000418- -00000-0000

Fecha: 2009-01-05 16:46:19 Dep: 2020 NUECREACIONI
Tra: 11 PATENTEIYII Eve: 378 FASENACIONALI
Act: 411 PRESENTACION Folios: 849

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
BAKER & MCKENZIE	CONSIGNACION	BANCO DE BOGOTA	062754387	97803145	10/12/2008	39,689,000.00

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

CANT.	RENTISTICO	CONCEPTO		TOTAL CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD I	99	OTROS SERVCIOS ADMINISTRATIVOS	150,000.00
			TOTAL : $	150,000.00

SON: CIENTO CINCUENTA MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

ESTA CERTIFICACION DE EXCEDENTE DE PAGO SOLO PODRA SER UTILIZADA COMO PARTE DE LA CANCELACION DE UNA TARIFA VIGENTE Y NO PODRA SER SUSTITUIDA POR NINGUN RECIBO.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 09-000418- -00000-0000
Fecha: 2009-01-05 16:46:19 Dep. 2020 NUECREACIONE
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 849

Industria y Comercio

SUPERINTENDENCIA

Delegatura de Propiedad Industrial
División de Nuevas Creaciones

REQUISITOS NECESARIOS PARA PRESENTACIÓN Y AGILIZACIÓN DEL TRAMITE

	USUARIO	RADICADOR
PATENTE DE INVENCIÓN (X) MODELO DE UTILIDAD ( )	( )	( )
-Indicación de que se solicita la concesión de una patente.	(X)	( )
-Datos de identificación del solicitante o de la persona que se presenta la solicitud.	(X)	( )
-Descripción de la Invención.	(X)	( )
-Dibujos de ser estos pertinentes.	(X)	( )
-Comprobante de Pago de las tasas establecidas.		
COMPLETA (X) INCOMPLETA		
DISEÑO INDUSTRIAL ( )	( )	( )
-Indicación de que se solicita el registro de Diseño Industrial.	( )	( )
-Datos de identificación del solicitante o de la persona que se presenta la solicitud.	( )	( )
-Representación gráfica y fotográfica del Diseño Industrial o muestra del Material que incorpora el diseño.	( )	( )
-Comprobante de Pago de las tasas establecidas.	( )	( )
COMPLETA ( ) INCOMPLETA	( )	( )
ESQUEMA DE TRAZADO ( )		
-Indicación de que se solicita el registro de Diseño Industrial.	( )	( )
-Datos de identificación del solicitante o de la persona que se presenta la solicitud.	( )	( )
-Representación gráfica del Esquema Trazado.	( )	( )
-Comprobante de Pago de las tasas establecidas.	( )	( )
COMPLETA ( ) INCOMPLETA	( )	( )

Firma Responsable: Sandra Rodriguez

Fecha: Enero 5/09

REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Bogotá,
2020

Doctor(a)
CORREA ORDOÑEZ ALVARO
Apoderado(a) y/o Representante de
BRISTOL- MYERS SQUIBB COMPANY

REFERENCIA	Radicación No.	9 418
	Solicitud internacional	PCT/US2007/072708
	Fecha inicio fase nacional	06/02/2009
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	- 2245

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

1. La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante, conforme a lo establecido por el artículo 26 literal k) de la Decisión 486 de la Comisión de la Comunidad Andina. Cuando se trate de documentos otorgados en el extranjero, estos deberán legalizarse de conformidad con lo dispuesto por los artículos 259 y 260 del Código de Procedimiento Civil. Cuando se trate de las declaraciones a que hace referencia la Regla 4.17 ii) del Tratado de Cooperación en Materia de Patentes PCT., el alcance de las tales declaraciones se determinará según indiquen claramente una cesión de derechos del inventor al solicitante o su causante, de conformidad con lo dispuesto en el numeral 5.2.15 del Capítulo Quinto, Título X de la Circular Única de Superintendencia de Industria y Comercio.

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Unica No.10 de 2001.

DORIS ELENA POLO CORDOBA
Jefe de la división de Nuevas Creaciones (E)

El anterior requerimiento fue notificado por fijación en lista de fecha 27 FEB. 2009
adpa11