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Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
INVENTARIO

PCT

DELEGATURA DE PROPIEDAD INDUSTRIAL

DIVISIÓN DE NUEVAS CREACIONES

09-8880

SOLICITUD DE PATENTE DE INVENCIÓN

TITULO: COMPUESTOS QUIMICOS

SOLICITANTE: PRAECIS PHARMACEUTICALS INCORPORATED

DIRECCIÓN: 830 Winter Street, Waltham, MA 02451-1420 E.U.A.

APODERADO: CARLOS R. OLARTE

BOGOTÁ 29 Enero de 2009

99/

P2009/000009

Titulo Poder Cesión
FN: 01-03-2009

OLARTERAISBECK

OLARTE RAISBECK MOURE &

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 09-008880- -00000-0000
Fecha: 2009-01-30 17:01:37 Dep. 2020 NUECREACION
Tra. 11 PATENTEIYII Eve. 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 450

PETITORIO - FORMULARIO ÚNICO DE SOLICITUD
PATENTE PCT
ENTRADA EN FASE NACIONAL **P2009/000009**

SOLICITUD DE:

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

[X] Capítulo I. [ ] Capítulo II.

(2) **SOLICITANTE (71)**

Nombre: **PRAECIS PHARMACEUTICALS INCORPORATED**
Dirección: 830 Winter Street, Waltham, MA 02451-1420 E.U.A.
Nacionalidad o Domicilio: Estados unidos
Lugar de Constitución: Estadounidense

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

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

REPRESENTANTE O APODERADO

Nombre: CARLOS R. OLARTE
Dirección: World Trade Center Torre A, Calle 100 No. 8A-37 Piso 10
Teléfono: 601-7700 **Fax:** 601-7799
E-mail: office@olarteraisbeck.com

IDENTIFICACIÓN
C.C. [X] **NIT** [ ]
C.E. [ ] **Otro** [ ]
Cual _____
Número 79.782.747Bta
TP 74.295

INVENTOR (ES) (72)

Nombre: VER PAGINA ADJUNTA
Dirección: VER PAGINA ADJUNTA
Nacionalidad o Domicilio: VER PAGINA ADJUNTA

(5) **PCT (86)**

Solicitud Internacional No. PCT/US2007/017282 Fecha Agosto 1, 2007

Publicación Internacional No. WO 2008/016692 Fecha Febrero 7, 2008

(6) **Título (54)** **COMPUESTOS QUIMICOS** (Nva Hoja fol. 454)

Clasificación Internacional (51) C07D 213/38, C07D 26/108, C07D 271/10, C07D 277/28, C07D 285/12, C07D 417/12, C07F 9/6539, A61K 31/425, A61K 31/433, A61K 31/44, A61K 31/505, A61P 37/00

Prioridad
SI [X] **NO** [ ]

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US	Octubre 3, 2006	60/827,919
US	Marzo 22, 2007	60/896,431
US	Julio 12, 2007	60/959,291

(9) **Comprobante de pago No.** 09-6,736 y 09.6,731 **Fecha** Enero 27 de 2009

(10) **ANEXOS**

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

(11) **FIGURA CARACTERÍSTICA:**

(12) Solicito la concesión de la patente,

NOMBRE: CARLOS R. OLARTE FIRMA:

C.C. 79.782.747 Btá T.P. 74.295

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

3

LISTA DE INVENTORES

PCT/US2007/017282

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   Nacionalidad: Canadiense

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   Nacionalidad: Estadounidense

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   Estados Unidos de America
   Nacionalidad: China

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

OFICIAL DE CAJA : 09 - 6,736
FECHA : ENERO 27 DE 2009

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
OLARTE RAISBEK	CONSIGNACION	BANCO DE BOGOTA	062754387	20235471	27/01/2009	4,915,000.00

***** 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	540,000.00
			TOTAL : $	540,000.00

SON: QUINIENTOS CUARENTA MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

5

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 09-008880- -00000-0000

Fecha: 2009-01-30 17:01:37 Dep. 2020 NUECREACION
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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

[redacted]BO OFICIAL DE CAJA : 09 - 6,731
[redacted]HA : ENERO 27 DE 2009

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
OLARTE RAISBEK	CONSIGNACION	BANCO DE BOGOTA	062754387	20235471	27/01/2009	4,915,000.00

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

[redacted]T.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
4	50005-01-01 SOLICITUDES	*** REIVINDICACION UNITARIA ADICIONAL	100,000.00
		TOTAL : $	100,000.00

SON: CIEN MIL PESOS

RESPONSABLE : _____

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

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(51) International Patent Classification:
C07D 213/38 (2006.01) *C07F 9/6539* (2006.01)
C07D 239/26 (2006.01) *A61K 31/425* (2006.01)
C07D 261/08 (2006.01) *A61K 31/433* (2006.01)
C07D 271/10 (2006.01) *A61K 31/44* (2006.01)
C07D 277/28 (2006.01) *A61K 31/505* (2006.01)
C07D 285/12 (2006.01) *A61P 37/00* (2006.01)
C07D 417/12 (2006.01)

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60/821,101	1 August 2006 (01.08.2006)	US
60/827,919	3 October 2006 (03.10.2006)	US
60/896,431	22 March 2007 (22.03.2007)	US
60/959,291	12 July 2007 (12.07.2007)	US

(71) Applicant *(for all designated States except US)*: **PRAECIS PHARMACEUTICALS INCORPORATED** [US/US]; 830 Winter Street, Waltham, MA 02451-1420 (US).

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(75) Inventors/Applicants *(for US only)*: **EVINDAR, Ghotas** [CA/US]; 31 Middlesex Circle, Apt. 19, Waltham, MA 02452 (US). **DENG, Hongfeng** [CN/US]; 11 Brucewood Road, Acton, MA 01720 (US). **BERNIER, Sylvie** [CA/US]; 2 Maria Court, Woburn, MA 01801 (US). **YAO, Gang** [CN/US]; 20 Washbrook Rd., Sudbury, MA 01776 (US). **COFFIN, Aaron** [US/US]; 57 Radnor Road, Apt. 1, Brighton, MA 02135 (US). **YANG, Hongfang** [CN/US]; 8 Kimball Court, Apt. 308, Burlington, MA 01803 (US).

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(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).

Published:
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(54) Title: CHEMICAL COMPOUNDS

(57) Abstract: The invention provides compounds formula I, their preparation, and their use as pharmaceutically active immunosuppressive agents for the treatment of autoimmune disorders, organ transplant rejection, disorders associated with an activated immune system, as well as other disorders modulated by lymphopenia or SIP receptors.

WO 2008/016692 A2

CHEMICAL COMPOUNDS

RELATED APPLICATIONS

This application is related and claims priority to U.S. provisional application serial No. 60/821,101, filed August 1, 2006, U.S. provisional application serial No. 60/827,919, filed October 3, 2006, U.S. provisional application serial No. 60/896,431, filed March 22, 2007 and U.S. provisional application serial No. 60/959,291, filed July 12, 2007, the entire contents of each of which are incorporated herein by this reference.

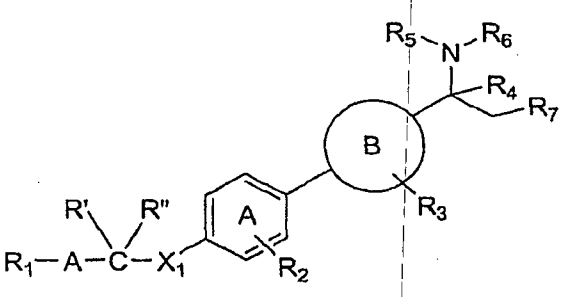
BACKGROUND OF THE INVENTION

The sphingosine-1-phosphate (S1P) receptors 1-5 constitute a family of seven transmembrane G-protein coupled receptors. These receptors, referred to as S1P-1 to S1P-5, are activated via binding by sphingosine-1-phosphate, which is produced by the sphingosine kinase-catalyzed phosphorylation of sphingosine. S1P receptors are cell surface receptors involved in a variety of cellular processes, including cell proliferation and differentiation, cell survival, cell invasion, lymphocyte trafficking, and cell migration. Sphingosine-1-phosphate is found in plasma and a variety of other tissues, and exerts autocrine and paracrine effects, including regulating the secretion of growth factors.

Administration of S1P to an animal results in sequestration of lymphocytes into the lymph nodes and Peyers patches without causing lymphocyte depletion. This activity, which is of potential utility in treating diseases or conditions associated with inappropriate immune response, including transplant rejection, autoimmune diseases, as well as other disorders modulated by lymphocyte trafficking, is believed to proceed via activation of the S1P-1 receptor. Administration of S1P *in vivo* has been shown to cause hypotension and bradycardia, which are believed to be due to signaling through one or more of the other S1P receptors, *i.e.* S1P-2 to S1P-5. Accordingly, there is a need for compounds which are potent and selective agonists of the S1P-1 receptor.

SUMMARY OF THE INVENTION

These and other needs are met by the present invention. In some aspects, the present invention is directed to a compound of formula I:



I

or a pharmaceutically acceptable salt thereof, wherein:

R_1 is hydrogen, halogen, cyano, alkyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, aralkyl, heteroalykl, -O-alkyl, -O-aryl, -O-heteroaryl, -S-alkyl, alkylene-O-alkyl, alkylene-CO_2H, alkylene-CO_2alkyl, alkylSO_2, alkylenesulfonyl, alkylene-CO-amino, alkylene-CO-alkylamino, alkylene-CO-dialkylamino, alkylene-NH-CO_2H, alkylene-NH-CO_2alkyl -CO_2alkyl, -OH, -C(O)-alkyl, -C(O)O-alkyl, -$CONH_2$, -CO-alkylamino, -CO-dialkylamino, amino, alkylamino, or dialkylamino, any of which may be optionally substituted on carbon with 1, 2, or 3 groups selected from halo, alkyl, haloalkyl, -CF_3, aryl, -CN, -OH, or –O-alkyl;

A is (C_1-C_{20})alkylene, (C_2-C_{20})alkenylene, or (C_2-C_{20})alkynylene, each of which may be optionally suibstited on carbon with 1, 2, o3 groups selected from OH, CO_2H, CO_2alkyl, halogen, amino, alkylamino, dialkylamino, -O-alkyl, alkylene-O-alkyl, alkylene-OH, or alkylene-CO_2H;

X_1 is a bond or is CH_2, O,-CH_2O-, S, -S(O), -$S(O)_2$, -C(O)-, -C(O)O-, or NR_x, wherein R_x is H or (C_1-C_6)alkyl;

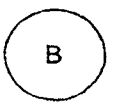
R' and R" are each independently hydrogen, halogen, alkyl optionally substituted on carbon with halogen, alkyl, or taken together with the carbon to which they are attached form C=O or a 3, 4, 5,or 6-membered ring, optionally containing 1 or 2 heteroatoms selected from O NH, N-alkyl, SO, or SO_2, any of which may be optionally substituted on carbon with alkyl or halogen

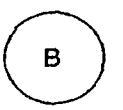
R_2 is cyano, alkyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, aralkyl, heteroalykl, -O-alkyl, -O-aryl, -O-heteroaryl, aralkoxy, heteroaralkoxy, -S-alkyl, alkylene-O-alkyl, alkylene-CO_2H, alkylene-CO_2alkyl, alkylSO_2, alkylenesulfonyl, alkylene-CO-amino, alkylene-CO-alkylamino, alkylene-CO-dialkylamino, alkylene-NH-CO_2H, alkylene-NH-CO_2alkyl -CO_2alkyl, -OH, -C(O)-alkyl, -C(O)O-alkyl, -$CONH_2$, -CO-alkylamino, -CO-dialkylamino, amino, alkylamino, and dialkylamino, any of which may be optionally substituted on carbon with 1, 2, or 3 groups selected from halo, alkyl, OH, or –O-alkyl;

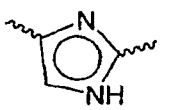
R_3 is absent, hydrogen, halogen, cyano, alkyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, aralkyl, heteroalykl, -O-alkyl, -O-aryl, -O-heteroaryl, aralkoxy, heteroaralkoxy, -S-alkyl, alkylene-O-alkyl, alkylene-CO_2H, alkylene-CO_2alkyl, alkylSO_2, alkylenesulfonyl, alkylene-CO-amino, alkylene-CO-alkylamino, alkylene-CO-dialkylamino, alkylene-NH-CO_2H, alkylene-NH-CO_2alkyl -CO_2alkyl, -OH, -C(O)-alkyl, -C(O)O-alkyl, -$CONH_2$, -CO-alkylamino, -CO-dialkylamino, amino, alkylamino, and dialkylamino, any of which may be optionally substituted on carbon with 1, 2, or 3 groups selected from halo, alkyl, OH, or –O-alkyl;



is phenyl or pyridyl;



is aryl, heteroaryl, heterocyclo, or cycloalkyl, any of which may be optionally substituted on carbon with 1, 2, or 3 groups selected form halogen, alkyl, O-alkyl, CO_2H, CO_2alkyl, halogen, amino, alkylamino, dialkylamino, -O-alkyl, alkylene-O-alkyl, alkylene-OH, or alkylene-CO_2H, provided that 

is not 

;

R_4 is hydrogen, cyano, alkyl, aryl, heteroaryl, alkylene-O-alkyl, alkylene-OH, aryl, alkylene-O-alkyl, -CO_2H, -CO_2-alkyl, alkylene-CO_2H, or alkylene-CO_2-alkyl, alkylene-OC(O)R wherein R is hydrogen or alkyl; cycloalkyl, heterocycloalkyl, alkylene-NH_2, alkylene-alkylamino, or alkylene-dialkylamino, any of which may be optionally substituted on carbon with 1, 2, or 3 groups selected from OH, CO_2H, CO_2alkyl, halogen, amino, alkylamino, dialkylamino, -O-alkyl, alkylene-O-alkyl, alkylene-OH, or alkylene-CO_2H;

R_5 and R_6 are each independently selected from the group consisting of hydrogen, alkyl, alkylene-OH, aryl, alkylene-O-alkyl, -CO_2H, CO_2-alkyl, alkylene-OC(O)alkyl, cycloalkyl, heterocyclo, -C(O)-alkyl, -C(O)-aryl, C(O)-aralkyl, -C(O)-Oalkyl, -C(O)-Oaryl, -C(O)-Oaralkyl, alkylene-amino, alkylene-alkylamino, and alkylene-dialkylamino, any of which may be optionally substituted on carbon with halogen, alkyl, hydroxyl, CO_2H, CO_2alkyl or alkoxy; or

R_5 and R_6, together with the nitrogen to which they are attached, may form a 3, 4, 5, or 6-membered saturated or unsaturated ring, optionally containing 1 or 2 additional

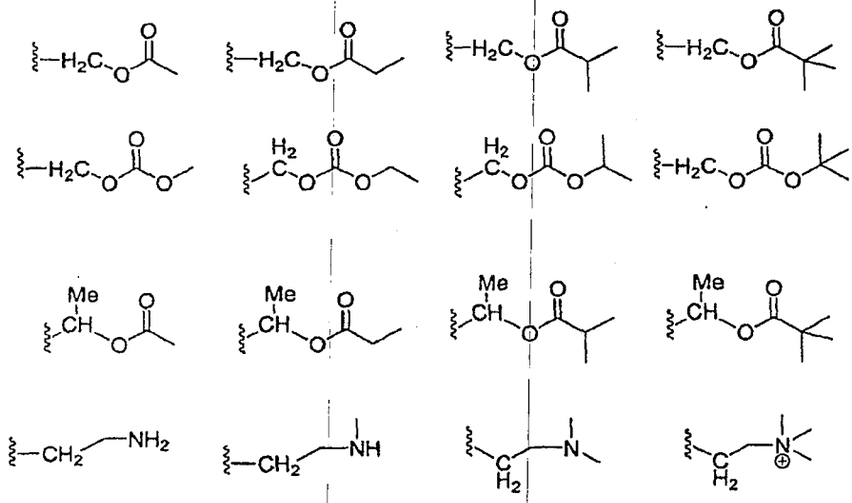
heteroatoms selected from O, S, NH, or N-alkyl, and optionally substituted on carbon with halogen, alkyl, hydroxyl, or alkoxy;

R_7 is selected from the group consisting of -OH, -O-alkyl, alkylene-OH, -CO_2H, alkylene-CO_2H, -C(O)O-alkyl, -alkylene-CO_2-alkyl, -C(O)O-aryl, -CH_2=$CHCO_2$H, -CH_2=CHC(O)O-alkyl, -CH_2=CHC(O)O-aryl, -$OPO_2R_{p1}R_{p2}$, -$OPO_3R_{p1}R_{p2}$, -$CH_2PO_3R_{p1}R_{p2}$, -OPO_2(S)$R_{p1}R_{p2}$, and -C(Z')(Z")$PO_3R_{p1}R_{p2}$, any of which may be optionally substituted on carbon with halogen, alkyl, hydroxyl, carboxy, or alkoxy; and wherein

Z' is hydroxyl or halogen;

Z" is H or halogen;

R_{p1} and R_{p2} are each independently hydrogen, C_1-C_6-alkyl, aryl, or one of the following groups:

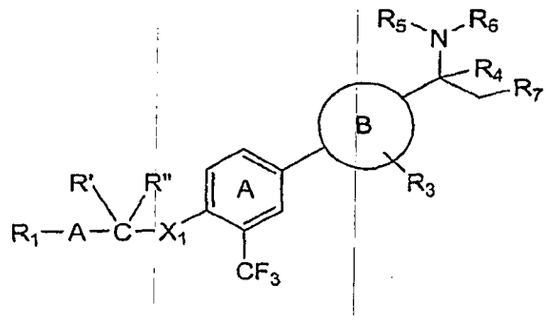


; and

Y is heterocyclo or heteroaryl.

In some embodiments, R_2 is alkyl substituted with 1, 2 or 3 halo groups. In some embodiments, R_2 is trifluoromethyl.

In other aspects, the present invention is directed to a compound of formula II:



II

or a pharmaceutically acceptable salt thereof, wherein:

R_1 is hydrogen, halogen, cyano, alkyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, aralkyl, heteroalykl, -O-alkyl, -O-aryl, -O-heteroaryl, -S-alkyl, alkylene-O-alkyl, alkylene-CO_2H, alkylene-CO_2alkyl, alkylSO_2, alkylenesulfonyl, alkylene-CO-amino, alkylene-CO-alkylamino, alkylene-CO-dialkylamino, alkylene-NH-CO_2H, alkylene-NH-CO_2alkyl -CO_2alkyl, -OH, -C(O)-alkyl, -C(O)O-alkyl, -$CONH_2$, -CO-alkylamino, -CO-dialkylamino, amino, alkylamino, or dialkylamino, any of which may be optionally substituted on carbon with 1, 2, or 3 groups selected from halo, alkyl, haloalkyl, -CF_3, -CN, -OH, or –O-alkyl;

A is (C_1-C_{20})alkylene, (C_2-C_{20})alkenylene, or (C_2-C_{20})alkynylene, each of which may be optionally suibstited on carbon with 1, 2, or 3 groups selected from OH, CO_2H, CO_2alkyl, halogen, amino, alkylamino, dialkylamino, -O-alkyl, alkylene-O-alkyl, alkylene-OH, or alkylene-CO_2H;

X_1 is a bond or is CH_2, O, -CH_2O-, S, -S(O), -$S(O)_2$, -C(O)-, -C(O)O-, or NR_x, wherein R_x is H or (C_1-C_6)alkyl;

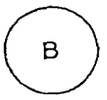
R' and R" are each independently hydrogen, halogen, alkyl optionally substituted on carbon with halogen, alkyl, or taken together with the carbon to which they are attached form C=O or a 3, 4, 5,or 6-membered ring, optionally containing 1 or 2 heteroatoms selected from O NH, N-alkyl, SO, or SO_2, any of which may be optionally substituted on carbon with alkyl or halogen

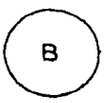
R_3 is absent, hydrogen, halogen, cyano, alkyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, aralkyl, heteroalykl, -O-alkyl, -O-aryl, -O-heteroaryl, aralkoxy, heteroaralkoxy, -S-alkyl, alkylene-O-alkyl, alkylene-CO_2H, alkylene-CO_2alkyl, alkylSO_2, alkylenesulfonyl, alkylene-CO-amino, alkylene-CO-alkylamino, alkylene-CO-dialkylamino, alkylene-NH-CO_2H, alkylene-NH-CO_2alkyl -CO_2alkyl, -OH, -C(O)-alkyl, -C(O)O-alkyl, -$CONH_2$, -CO-alkylamino,
-CO-dialkylamino, amino, alkylamino, and dialkylamino, any of which may be optionally substituted on carbon with 1, 2, or 3 groups selected from halo, alkyl, OH, or –O-alkyl;

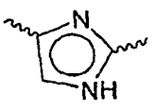


is phenyl or pyridyl;

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is aryl, heteroaryl, heterocyclo, or cycloalkyl, any of which may be optionally substituted on carbon with 1, 2, or 3 groups selected form halogen, alkyl, O-alkyl, CO_2H, CO_2alkyl, halogen, amino, alkylamino, dialkylamino, -O-alkyl, alkylene-O-alkyl, alkylene-OH, or alkylene-CO_2H, provided that 

is not 

;

R_4 is hydrogen, cyano, alkyl, aryl, heteroaryl, alkylene-O-alkyl, alkylene-OH, aryl, alkylene-O-alkyl, -CO_2H, -CO_2-alkyl, alkylene-CO_2H, or alkylene-CO_2-alkyl, alkylene-OC(O)R wherein R is hydrogen or alkyl; cycloalkyl, heterocycloalkyl, alkylene-NH_2, alkylene-alkylamino, or alkylene-dialkylamino, any of which may be optionally substituted on carbon with 1, 2, or 3 groups selected from OH, CO_2H, CO_2alkyl, halogen, amino, alkylamino, dialkylamino, -O-alkyl, alkylene-O-alkyl, alkylene-OH, or alkylene-CO_2H;

R_5 and R_6 are each independently selected from the group consisting of hydrogen, alkyl, alkylene-OH, aryl, alkylene-O-alkyl, -CO_2H, CO_2-alkyl, alkylene-OC(O)alkyl, cycloalkyl, heterocyclo, -C(O)-alkyl, -C(O)-aryl, C(O)-aralkyl, -C(O)-Oalkyl, -C(O)-Oaryl, -C(O)-Oaralkyl, alkylene-amino, alkylene-alkylamino, and alkylene-dialkylamino, any of which may be optionally substituted on carbon with halogen, alkyl, hydroxyl, CO_2H, CO_2alkyl or alkoxy; or

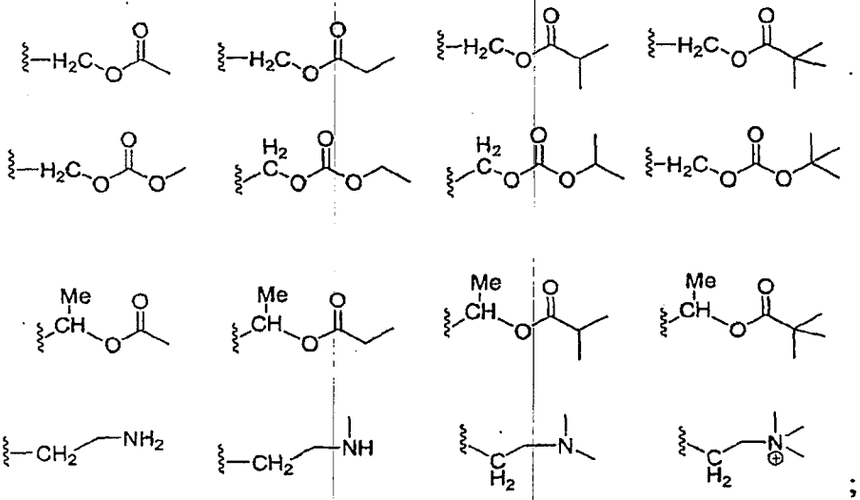
R_5 and R_6, together with the nitrogen to which they are attached, may form a 3, 4, 5, or 6-membered saturated or unsaturated ring, optionally containing 1 or 2 additional heteroatoms selected from O, S, NH, or N-alkyl, and optionally substituted on carbon with halogen, alkyl, hydroxyl, or alkoxy;

R_7 is selected from the group consisting of -OH, -O-alkyl, -alkylene-OH, -CO_2H, -alkylene-CO_2H, -C(O)O-alkyl, -alkylene-CO_2-alkyl, -C(O)O-aryl, -CH_2=$CHCO_2H$, -CH_2=CHC(O)O-alkyl, -CH_2=CHC(O)O-aryl, -$OPO_2R_{p1}R_{p2}$, -$OPO_3R_{p1}R_{p2}$, -$CH_2PO_3R_{p1}R_{p2}$, -$OPO_2(S)R_{p1}R_{p2}$; and -$C(Z')(Z'')PO_3R_{p1}R_{p2}$, any of which may be optionally substituted on carbon with halogen, alkyl, hydroxyl, carboxy, or alkoxy; and wherein

Z' is hydroxyl or halogen;

Z" is H or halogen;

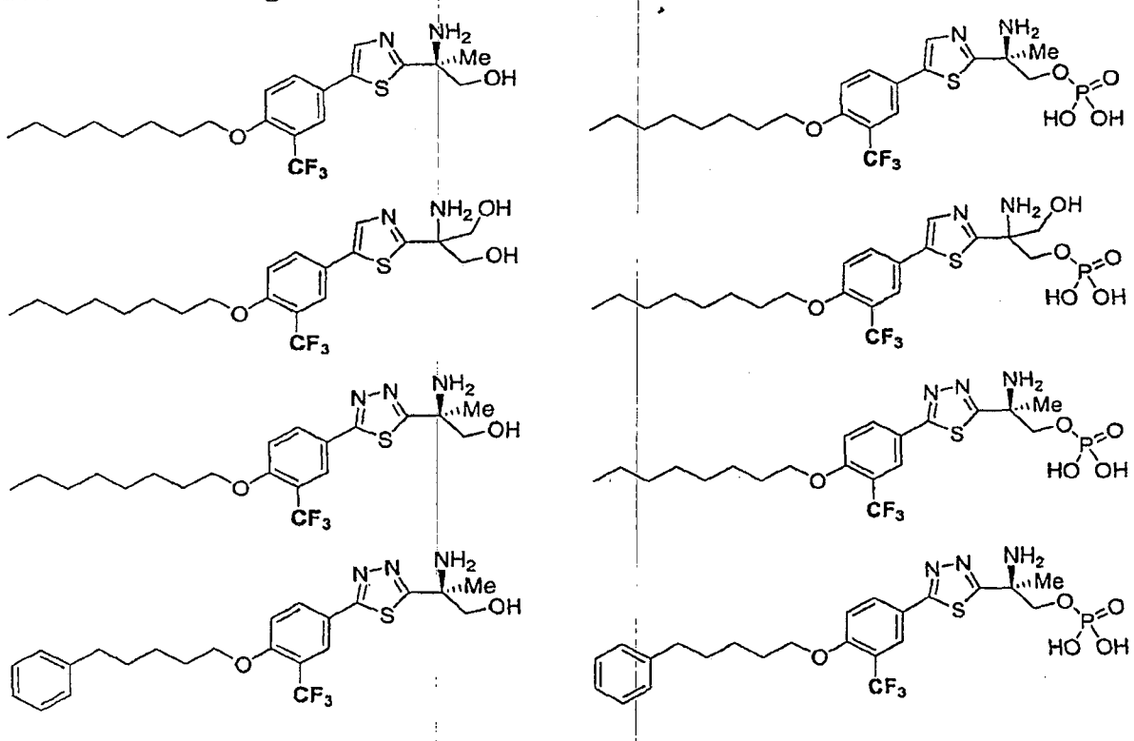
R_{p1} and R_{p2} are each independently hydrogen, C_1-C_6-alkyl, aryl, or one of the following groups:

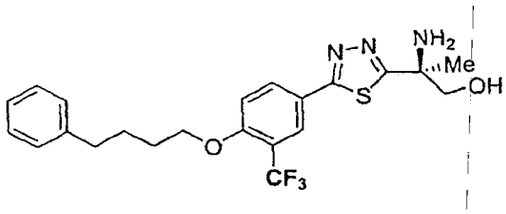


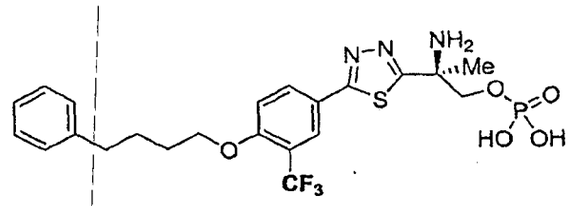
; and

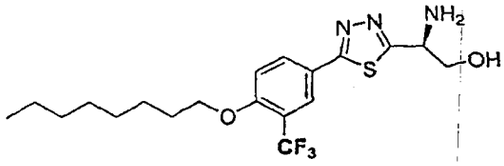
Y is heterocyclo or heteroaryl.

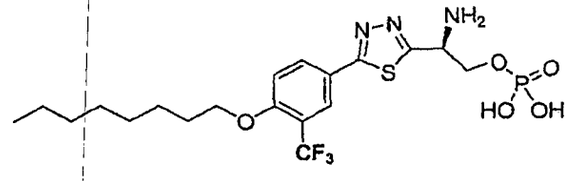
In some embodiments, compounds of the present invention include compounds listed in the following table:

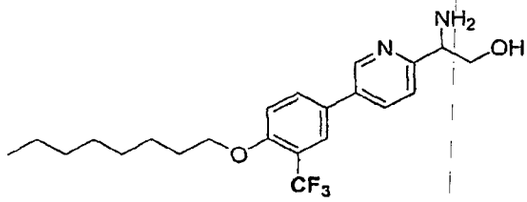


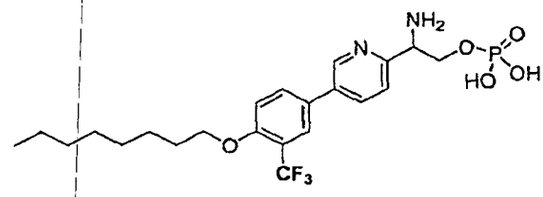


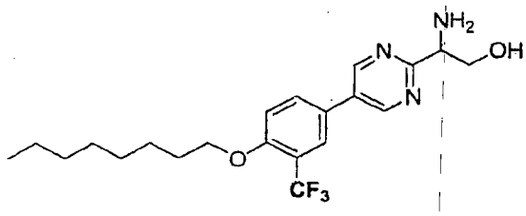


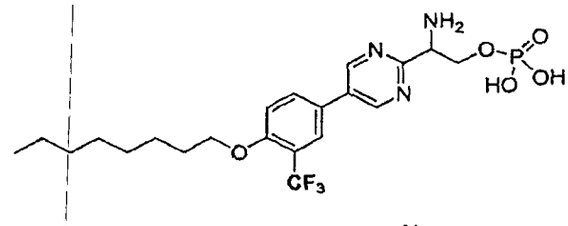


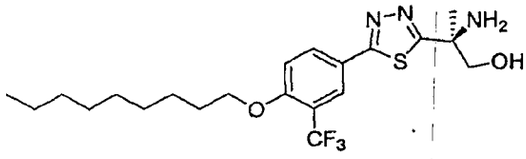


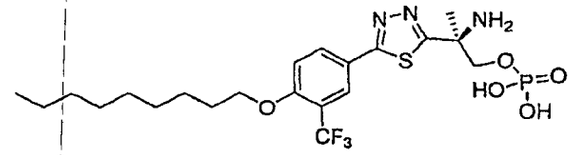


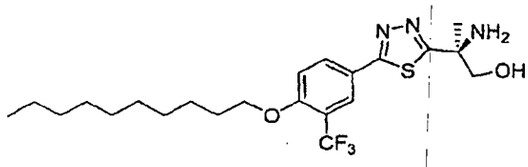


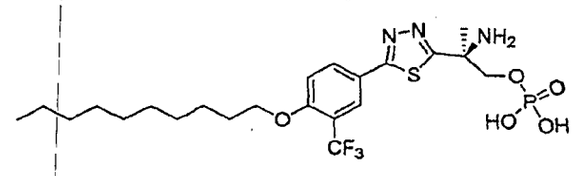


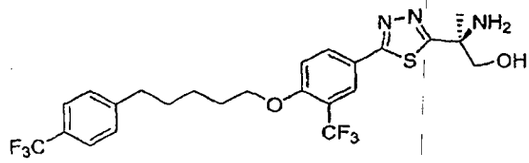


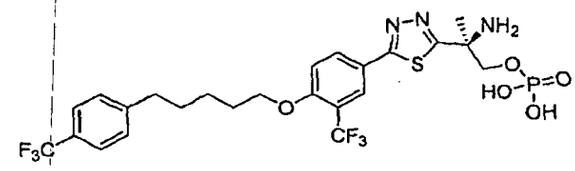


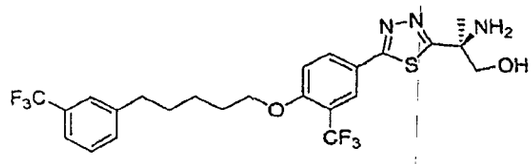


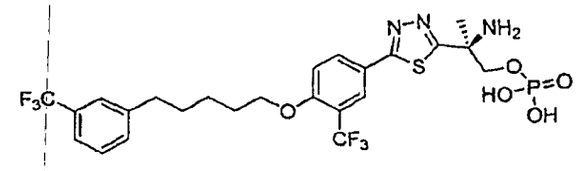




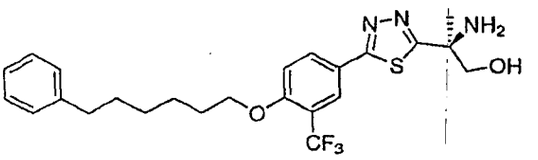
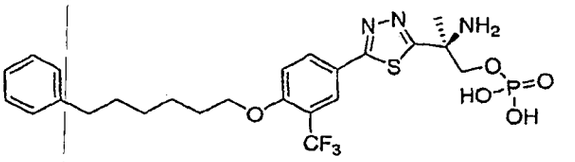
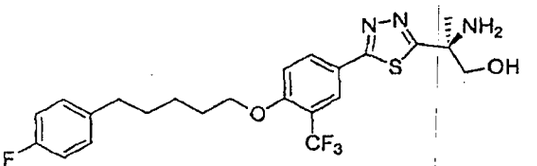
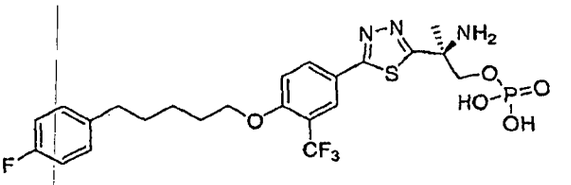
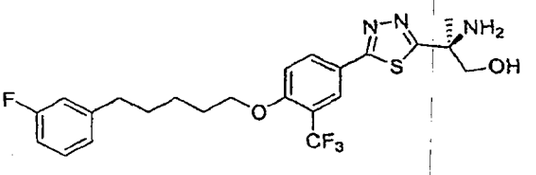
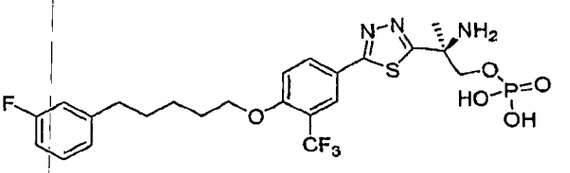
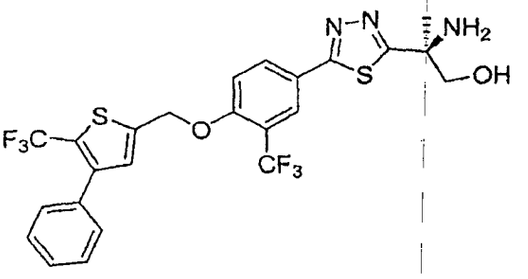
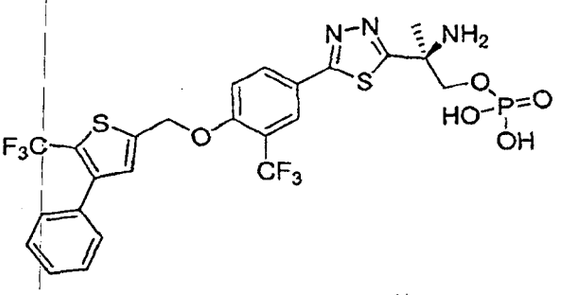
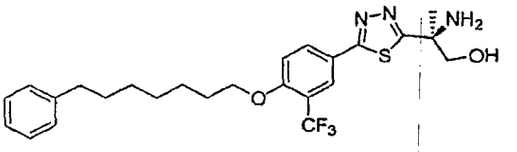
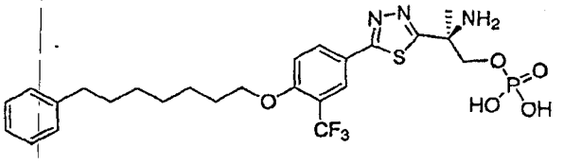
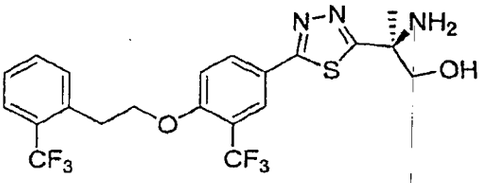
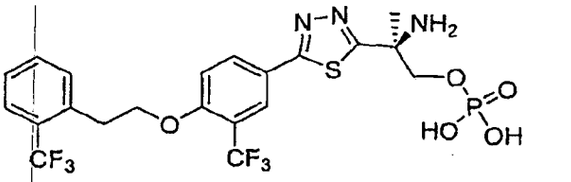
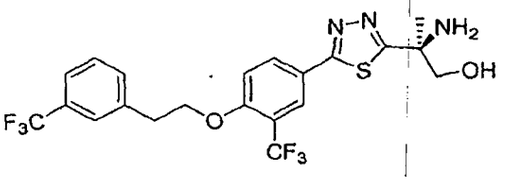
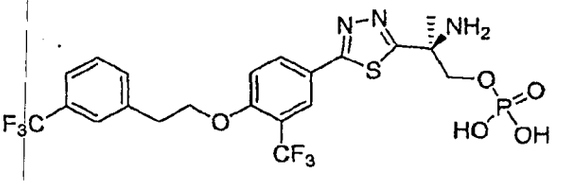
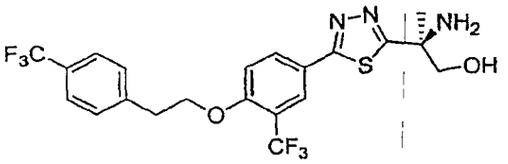
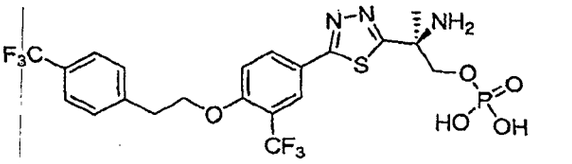




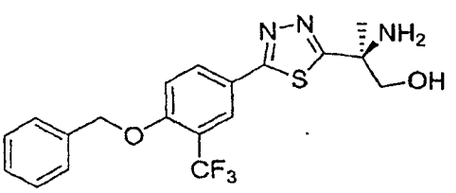


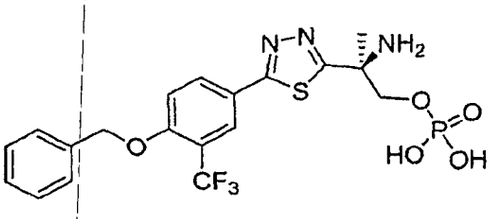


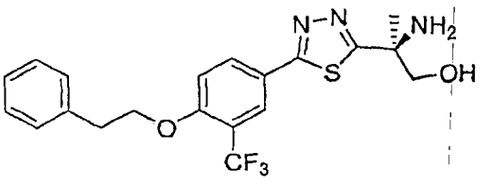


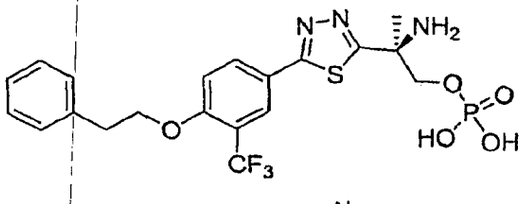

















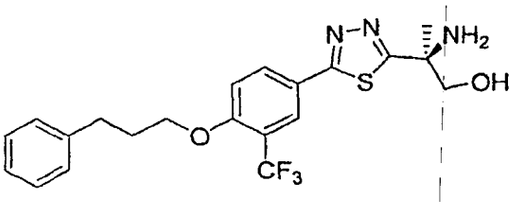
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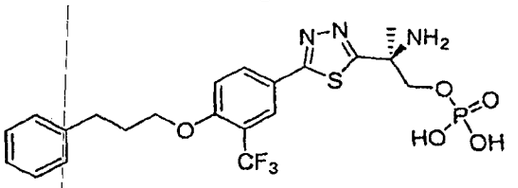


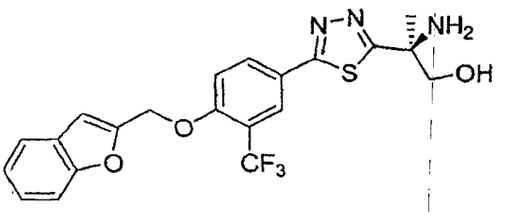


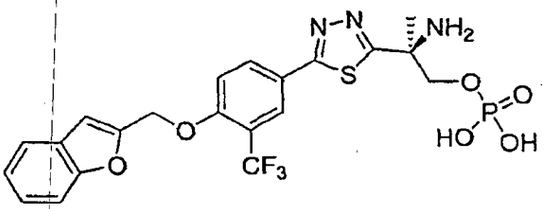


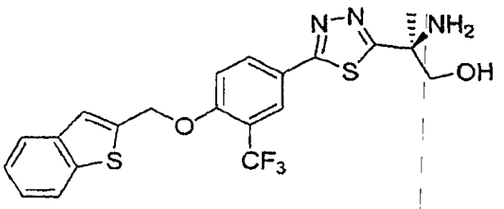


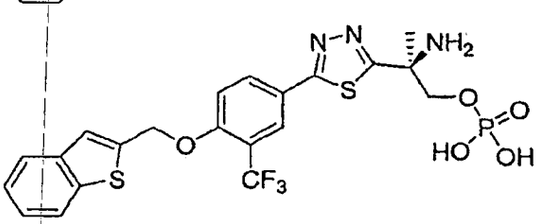


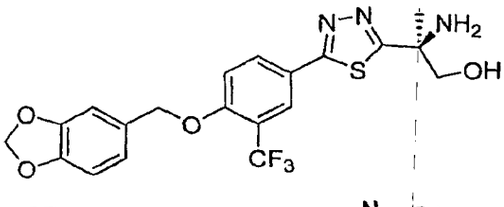


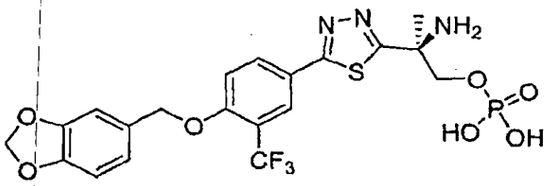


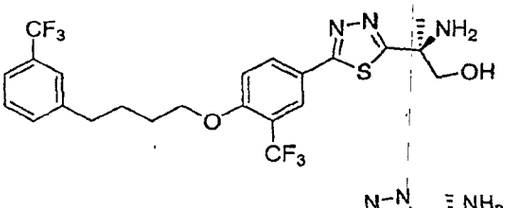


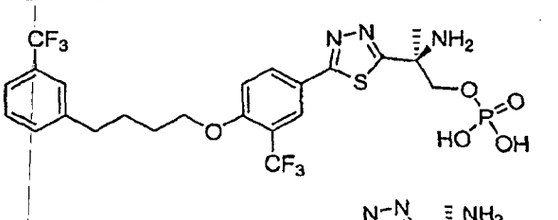


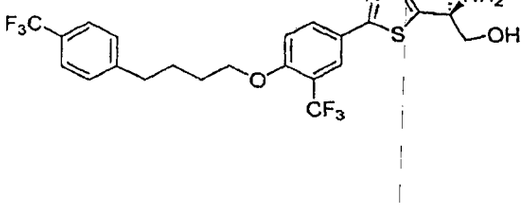


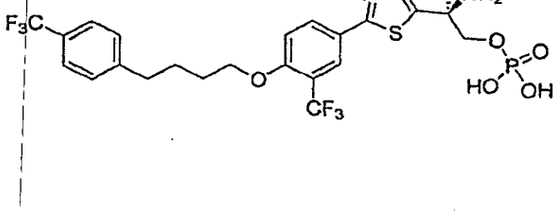






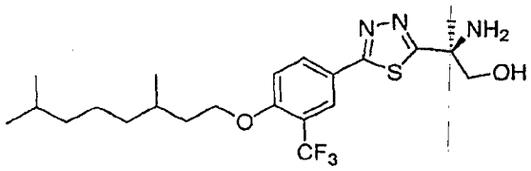
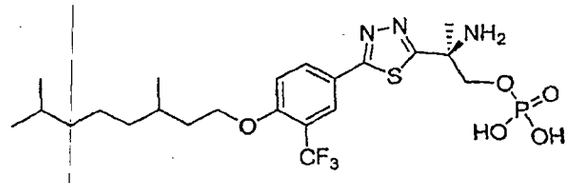
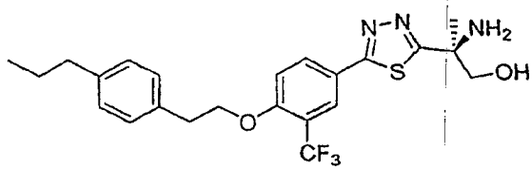
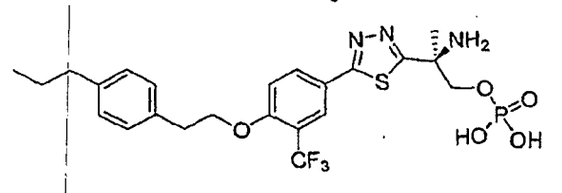
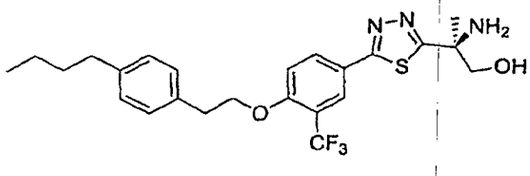
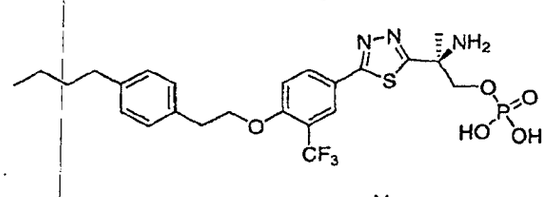
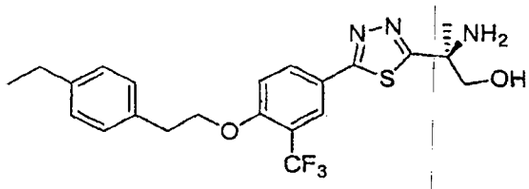
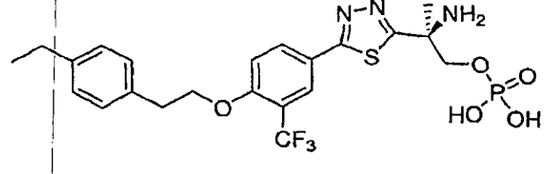
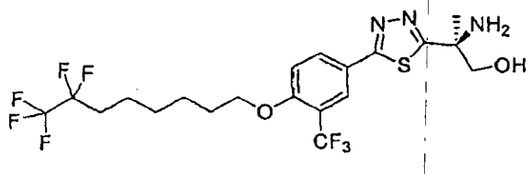
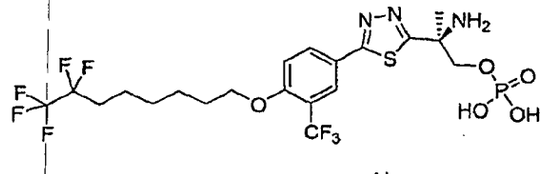
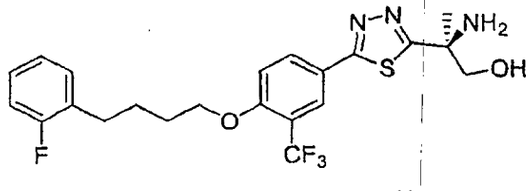
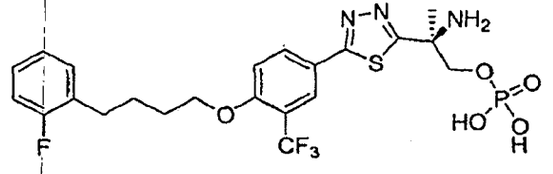
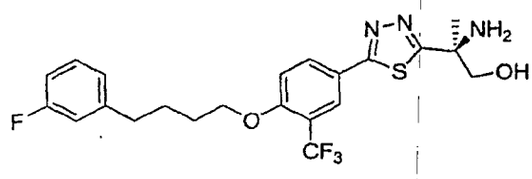
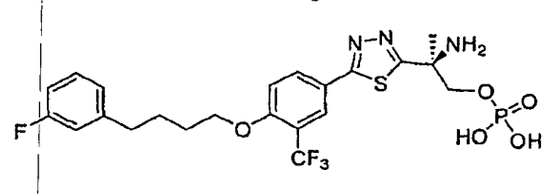
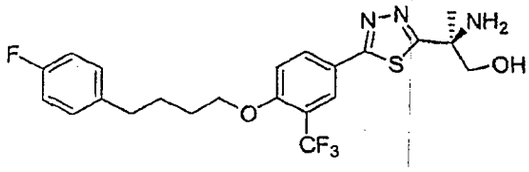
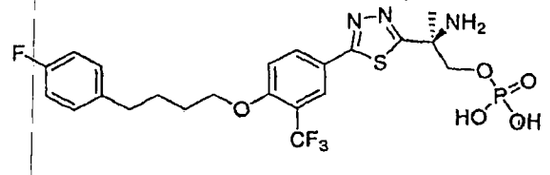
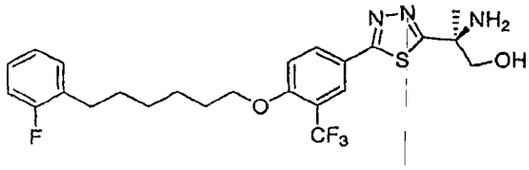
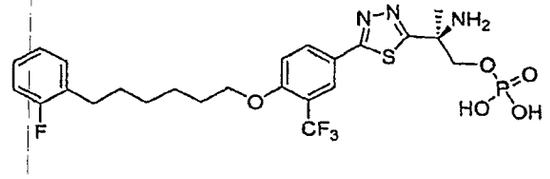




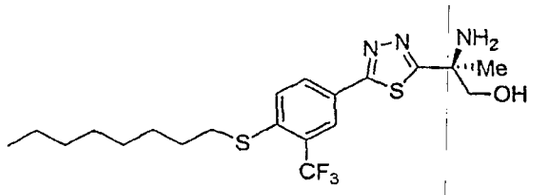


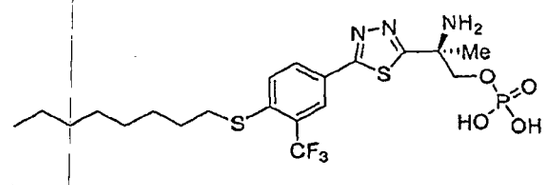


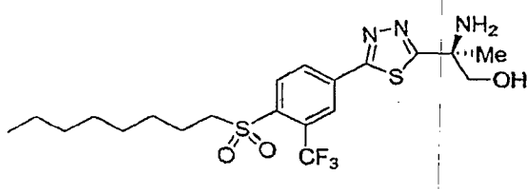


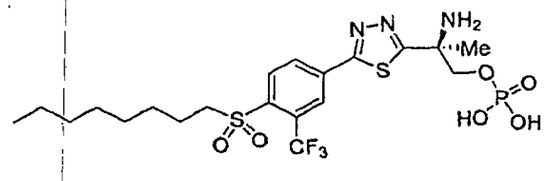



















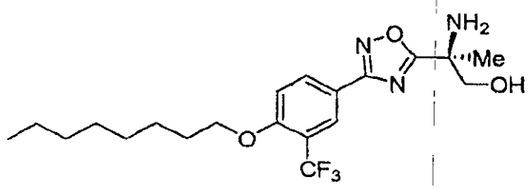


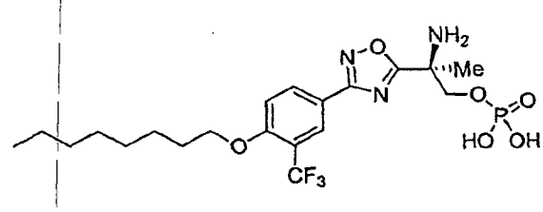


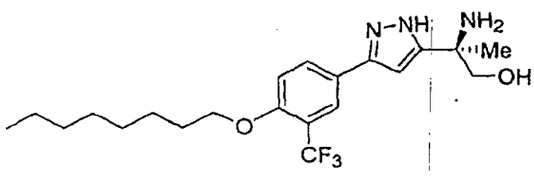


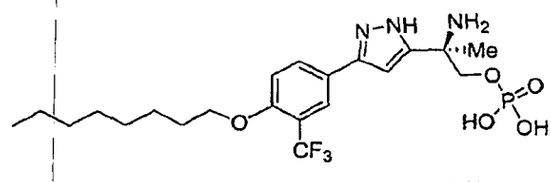


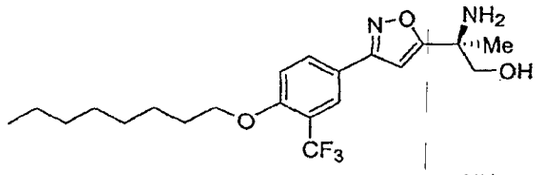


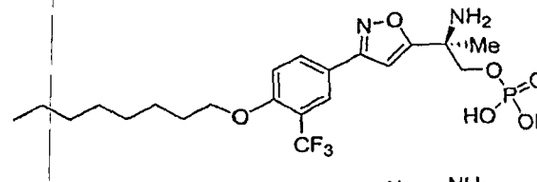


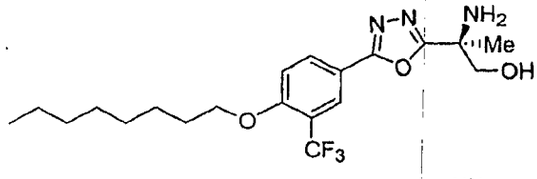


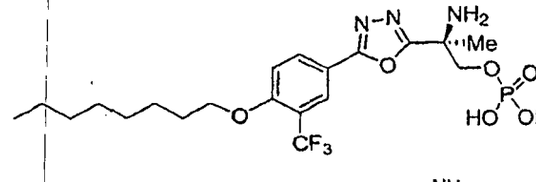


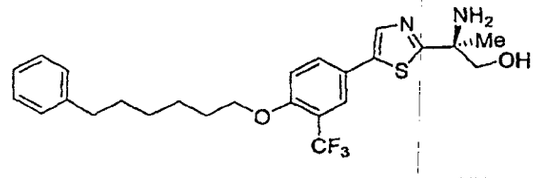


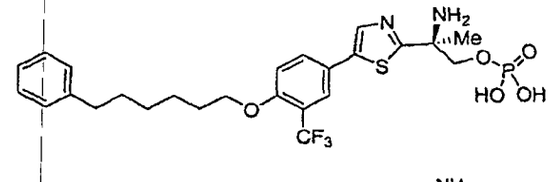


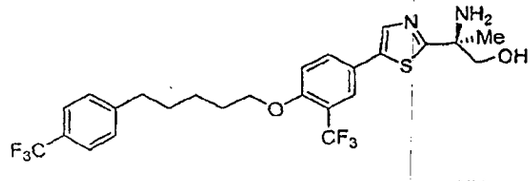


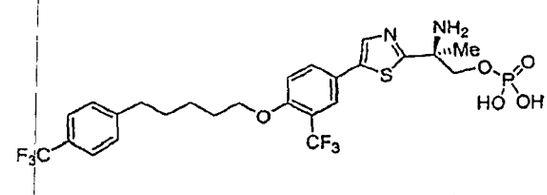


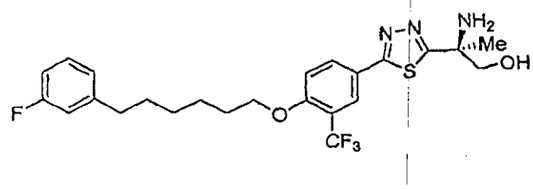


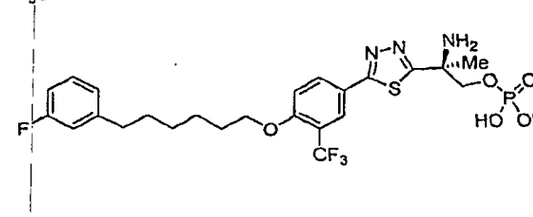






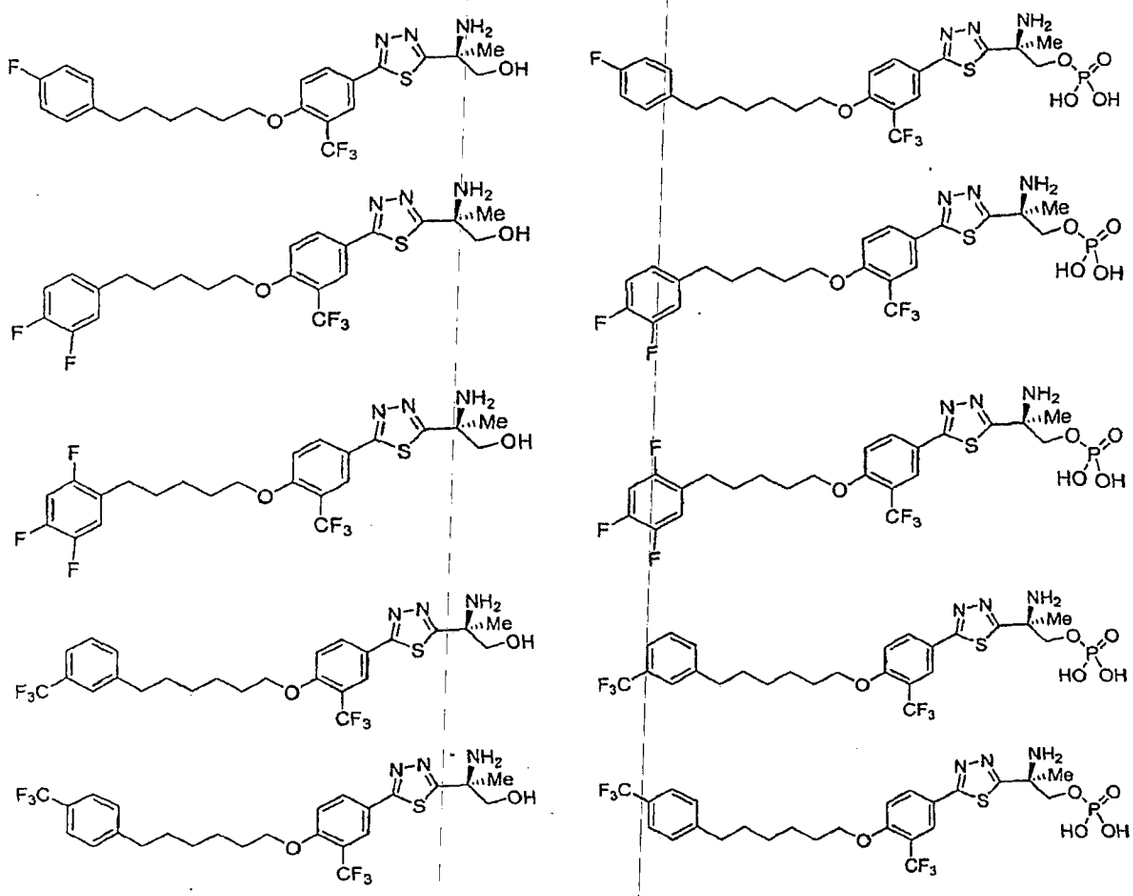






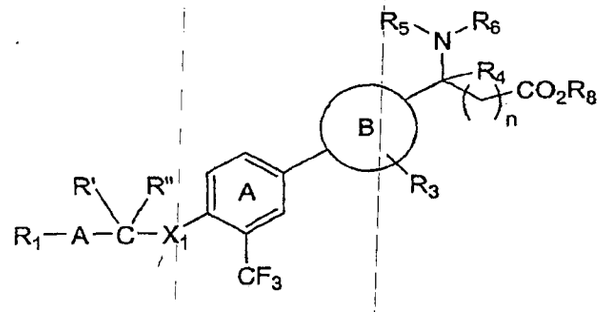






as well as pharmaceutically acceptable salts, phosphate derivatives, phosphate mimics, or phosphate precursor analogs thereof.

In some aspects, the present invention is directed to a compound of formula III:



III

or a pharmaceutically acceptable salt thereof, wherein:

R_1 is hydrogen, halogen, cyano, alkyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, aralkyl, heteroalykl, -O-alkyl, -O-aryl, -O-heteroaryl, -S-alkyl, alkylene-O-alkyl, alkylene-CO_2H, alkylene-CO_2alkyl, alkylSO_2, alkylenesulfonyl, alkylene-CO-amino, alkylene-CO-alkylamino, alkylene-CO-dialkylamino, alkylene-NH-

CO_2H, alkylene-NH-CO_2alkyl -CO_2alkyl, -OH, -C(O)-alkyl, -C(O)O-alkyl, -$CONH_2$, -CO-alkylamino, -CO-dialkylamino, amino, alkylamino, or dialkylamino, any of which may be optionally substituted on carbon with 1, 2, or 3 groups selected from halo, alkyl, haloalkyl, -CF_3, -CN, -OH, or –O-alkyl;

A is (C_1-C_{20})alkylene, (C_2-C_{20})alkenylene, or (C_2-C_{20})alkynylene, each of which may be optionally suibstited on carbon with 1, 2, or 3 groups selected from OH, CO_2H, CO_2alkyl, halogen, amino, alkylamino, dialkylamino, -O-alkyl, alkylene-O-alkyl, alkylene-OH, or alkylene-CO_2H;

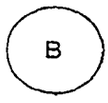
X_1 is a bond or is CH_2, O, -CH_2O-, S, -S(O), -$S(O)_2$, -C(O)-, -C(O)O-, or NR_x, wherein R_x is H or (C_1-C_6)alkyl;

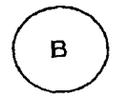
R' and R" are each independently hydrogen, halogen, alkyl optionally substituted on carbon with halogen, alkyl, or taken together with the carbon to which they are attached form C=O or a 3, 4, 5,or 6-membered ring, optionally containing 1 or 2 heteroatoms selected from O NH, N-alkyl, SO, or SO_2, any of which may be optionally substituted on carbon with alkyl or halogen

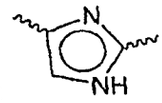
R_3 is absent, hydrogen, halogen, cyano, alkyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, aralkyl, heteroalykl, -O-alkyl, -O-aryl, -O-heteroaryl, aralkoxy, heteroaralkoxy, -S-alkyl, alkylene-O-alkyl, alkylene-CO_2H, alkylene-CO_2alkyl, alkylSO_2, alkylenesulfonyl, alkylene-CO-amino, alkylene-CO-alkylamino, alkylene-CO-dialkylamino, alkylene-NH-CO_2H, alkylene-NH-CO_2alkyl -CO_2alkyl, -OH, -C(O)-alkyl, -C(O)O-alkyl, -$CONH_2$, -CO-alkylamino, -CO-dialkylamino, amino, alkylamino, and dialkylamino, any of which may be optionally substituted on carbon with 1, 2, or 3 groups selected from halo, alkyl, OH, or –O-alkyl;



is phenyl or pyridyl;



is aryl, heteroaryl, heterocyclo, or cycloalkyl, any of which may be optionally substituted on carbon with 1, 2, or 3 groups selected form halogen, alkyl, O-alkyl, CO_2H, CO_2alkyl, halogen, amino, alkylamino, dialkylamino, -O-alkyl, alkylene-O-alkyl, alkylene-OH, or alkylene-CO_2H, provided that 

is not 

;

R_4 is hydrogen, cyano, alkyl, aryl, heteroaryl, alkylene-O-alkyl, alkylene-OH,

aryl, alkylene-O-alkyl, -CO_2H, -CO_2-alkyl, alkylene-CO_2H, or alkylene-CO_2-alkyl, alkylene-OC(O)R wherein R is hydrogen or alkyl; cycloalkyl, heterocycloalkyl, alkylene-NH_2, alkylene-alkylamino, or alkylene-dialkylamino, any of which may be optionally substituted on carbon with 1, 2, or 3 groups selected from OH, CO_2H, CO_2alkyl, halogen, amino, alkylamino, dialkylamino, -O-alkyl, alkylene-O-alkyl, alkylene-OH, or alkylene-CO_2H;

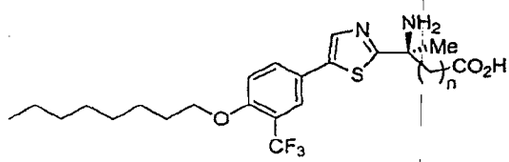
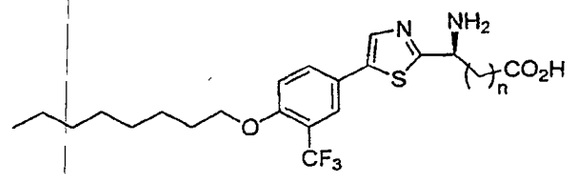
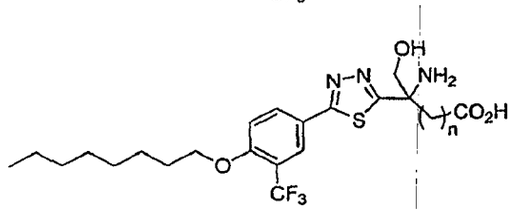
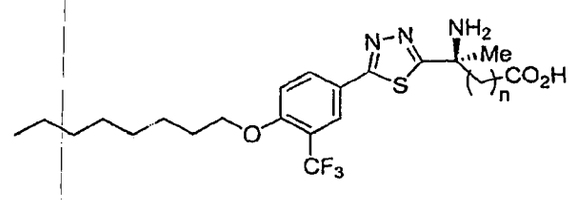
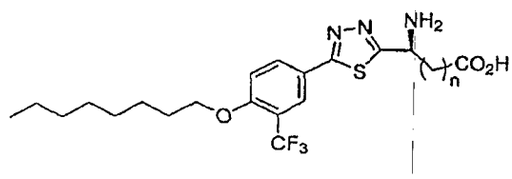
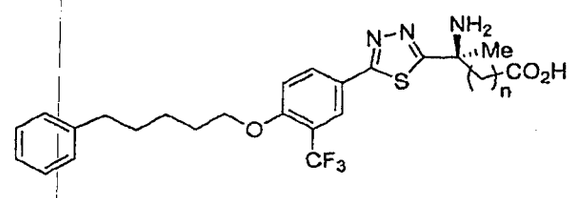
R_5 and R_6 are each independently selected from the group consisting of hydrogen, alkyl, alkylene-OH, aryl, alkylene-O-alkyl, -CO_2H, CO_2-alkyl, alkylene-OC(O)alkyl, cycloalkyl, heterocyclo, -C(O)-alkyl, -C(O)-aryl, C(O)-aralkyl, -C(O)-Oalkyl, -C(O)-Oaryl, -C(O)-Oaralkyl, alkylene-amino, alkylene-alkylamino, and alkylene-dialkylamino, any of which may be optionally substituted on carbon with halogen, alkyl, hydroxyl, CO_2H, CO_2alkyl or alkoxy; or

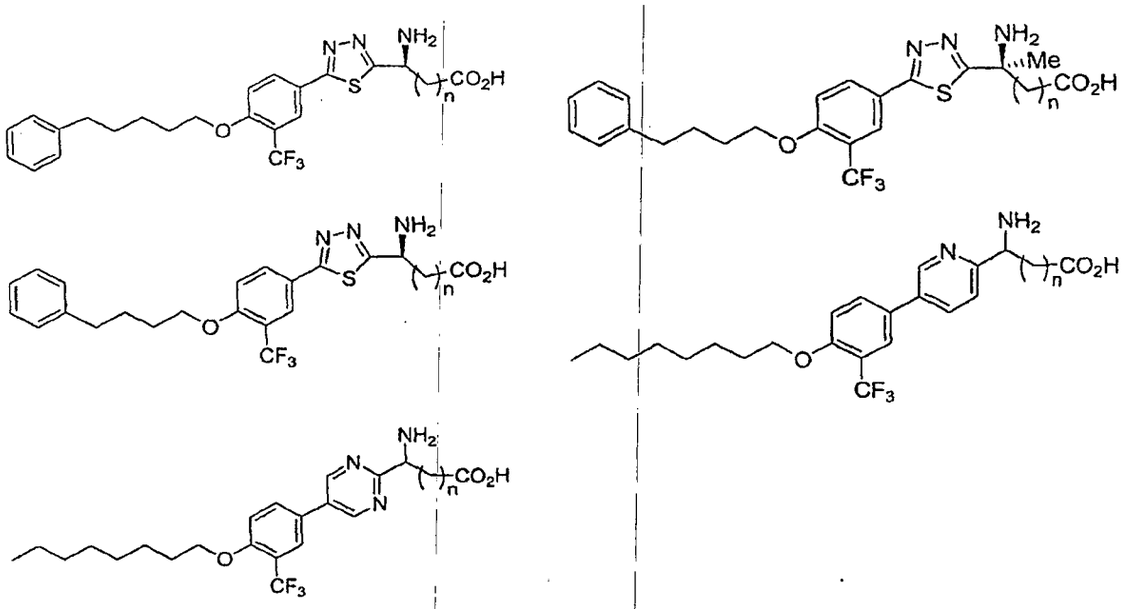
R_5 and R_6, together with the nitrogen to which they are attached, may form a 3, 4, 5, or 6-membered saturated or unsaturated ring, optionally containing 1 or 2 additional heteroatoms selected from O, S, NH, or N-alkyl, and optionally substituted on carbon with halogen, alkyl, hydroxyl, or alkoxy;

R_8 is hydrogen, alkyl or aryl; and

n is 0, 1, or 2.

In some embodiments, compounds of the present invention include compounds listed in the following table:



wherein n for each compound is 0, 1 or 2, as well as pharmaceutically acceptable salts, phosphate derivatives, phosphate mimics, or phosphate precursor analogs thereof.

In some aspects, the present invention is directed to compound selected from:

(*S*)-2-Amino-2-(5-(4-(octyloxy)-3-(trifluoromethyl)phenyl)thiazol-2-yl)propan-1-ol;

2-Amino-2-(5-(4-(octyloxy)-3-(trifluoromethyl)phenyl)thiazol-2-yl)propane-1,3-diol;

(*S*)-2-Amino-2-(5-(4-(octyloxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol;

(*S*)-2-Amino-2-(5-(4-(5-phenylpentyloxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol;

(*S*)-2-Amino-2-(5-(4-(4-phenylbutoxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol;

(*S*)-2-Amino-2-(5-(4-(nonyloxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazole-2-yl)propan-1-ol;

(*S*)-2-Amino-2-(5-(4-(decyloxy)-3(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol;

(*S*)-2-Amino-2-(5-(3-(trifluoromethyl)-4-(5-(4-(trifluoromethyl)phenyl)pentyloxy)phenyl)-1,3,4-thiadiazole-2-yl)propan-1-ol;

(*S*)-2-Amino-2-(5-(3-(trifluoromethyl)-4-(5-(3-(trifluoromethyl)phenyl)pentyloxy)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol;

(*S*)-2-Amino-2-(5-(4-(6-phenylhexyloxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol;

(*S*)-2-Amino-2-(5-(4-(5-(4-fluorophenyl)pentyloxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol;

(*S*)-2-Amino-2-(5-(4-(5-(3-fluorophenyl)pentyloxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol;

(*S*)-2-Amino-2-(5-(4-((4-phenyl-5-(trifluoromethyl)thiophen-2-yl)methoxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol;

(*S*)-2-Amino-2-(5-(4-(7-phenylheptyloxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol;

(*S*)-2-Amino-2-(5-(3-(trifluoromethyl)-4-(2-(trifluoromethyl)phenethoxy)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol;

(*S*)-2-Amino-2-(5-(3-(trifluoromethyl)-4-(3-(trifluoromethyl)phenethoxy)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol;

(*S*)-2-Amino-2-(5-(3-(trifluoromethyl)-4-(4-(trifluoromethyl)phenethoxy)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol;

(*S*)-2-Amino-2-(5-(4-(benzyloxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol;

(*S*)-2-Amino-2-(5-(4-phenethoxy-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol;

(*S*)-2-Amino-2-(5-(4-(3-phenylpropoxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol;

(*S*)-2-Amino-2-(5-(4-(benzofuran-2-ylmethoxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol;

(*S*)-2-Amino-2-(5-(4-(benzo[*b*]thiophen-2-ylmethoxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol;

(*S*)-2-Amino-2-(5-(4-(benzo[*d*][1,3]dioxol-5-ylmethoxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol;

(*S*)-2-Amino-2-(5-(3-(trifluoromethyl)-4-(4-(3-(trifluoromethyl)phenyl)butoxy)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol;

(*S*)-2-Amino-2-(5-(3-(trifluoromethyl)-4-(4-(4-(trifluoromethyl)phenyl)butoxy)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol;

(2*S*)-2-Amino-2-(5-(4-(3,7-dimethyloctyloxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol;

(*S*)-2-Amino-2-(5-(4-(4-propylphenethoxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol;

(*S*)-2-Amino-2-(5-(4-(4-butylphenethoxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol;

(*S*)-2-Amino-2-(5-(4-(4-ethylphenethoxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol;

(*S*)-2-Amino-2-(5-(4-(7,7,8,8,8-pentafluorooctyloxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol;

(*S*)-2-Amino-2-(5-(4-(4-(2-fluorophenyl)butoxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol;

(*S*)-2-Amino-2-(5-(4-(4-(3-fluorophenyl)butoxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol;

(*S*)-2-Amino-2-(5-(4-(4-(4-fluorophenyl)butoxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol;

(*S*)-2-Amino-2-(5-(4-(6-(2-fluorophenyl)hexyloxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol;

(*S*)-2-Amino-2-(5-(4-(6-(3-fluorophenyl)hexyloxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol;

(*S*)-2-Amino-2-(5-(4-(6-(4-fluorophenyl)hexyloxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol;

(*S*)-2-Amino-2-(5-(4-(5-(3,4-difluorophenyl)pentyloxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol;

(*S*)-2-Amino-2-(5-(3-(trifluoromethyl)-4-(5-(2,4,5-trifluorophenyl)pentyloxy)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol;

(*S*)-2-Amino-2-(5-(3-(trifluoromethyl)-4-(6-(3-(trifluoromethyl)phenyl)hexyloxy)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol;

(*S*)-2-Amino-2-(5-(3-(trifluoromethyl)-4-(6-(4-(trifluoromethyl)phenyl)hexyloxy)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol;

(*S*)-2-Amino-2-(5-(4-(octylthio)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol;

(*S*)-2-Amino-2-(5-(4-(octylsulfonyl)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol;

(*S*)-2-Amino-2-(3-(4-(octyloxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)propan-1-ol;
(*R*)-2-Amino-2-(5-(4-(octyloxy)-3-(trifluoromethyl)phenyl)-1*H*-pyrazol-3-yl)propan-1-ol;
(*S*)-2-Amino-2-(3-(4-(octyloxy)-3-(trifluoromethyl)phenyl)isoxazol-5-yl)propan-1-ol;
(*S*)-2-Amino-2-(5-(4-(octyloxy)-3-(trifluoromethyl)phenyl)-1,3,4-oxadiazol-2-yl)propan-1-ol;
(*S*)-2-Amino-2-(5-(4-(6-phenylhexyloxy)-3-(trifluoromethyl)phenyl)thiazol-2-yl)propan-1-ol;
(*S*)-2-Amino-2-(5-(3-(trifluoromethyl)-4-(5-(4-(trifluoromethyl)phenyl)pentyloxy)phenyl) thiazol-2-yl)propan-1-ol;
and pharmaceutically acceptable salts, phosphate derivatives, phosphate mimics, and phosphate precursor analogs thereof.

In some aspects, the present invention is directe to a compound which is (*S*)-2-Amino-2-(5-(4-(octyloxy)-3-(trifluoromethyl)phenyl)thiazol-2-yl)propan-1-ol or a pharmaceutically acceptable salt, phosphate derivative, phosphate mimic, or phosphate precursor analog thereof. In other aspects, the present invention is directe to a compound which is (*S*)-2-Amino-2-(5-(4-(octyloxy)-3-(trifluoromethyl)phenyl)thiazol-2-yl)propyl dihydrogen phosphate or a pharmaceutically acceptable salt thereof.

In some aspects, the present invention is directe to a compound which is (*S*)-2-Amino-2-(5-(4-(octyloxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol or a pharmaceutically acceptable salt, phosphate derivative, phosphate mimic, or a phosphate precursor analog thereof. In other aspects, the present invention is directe to a compound which is (*S*)-2-Amino-2-(5-(4-(octyloxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propyl dihydrogen phosphate or a pharmaceutically acceptable salt thereof.

In some aspects, the present invention is directed to a method of treating a sphingosine 1-phosphate associated disorder in a subject in need thereof comprising administering to the subject a therapeutically safe and effective amount of a compound of any of formulas I, II or III, or a pharmaceutically acceptable salt, phosphate derivative, phosphate mimic, or phosphate precursor analog thereof, such that the sphingosine 1-phosphate associated disorder is treated.

In some aspects, the present invention is directed to a method of treating an autoimmune disorder comprising administering to a subject in need thereof a pharmaceutically acceptable amount of a compound of any of formulas I, II or III, such that the autoimmune disorder is treated.

In some aspects, the present invention is directed to a method treating transplant rejection comprising administering to a subject in need thereof a pharmaceutically acceptable amount of a compound of any of formulas I, II or III, such that the transplant rejection is treated.

In some aspects, the present invention is directed to a compound of any of formulas I, II or III for use as a therapeutic substance.

In some aspects, the present invention is directed to a compound of any of formulas I, II or III for use in the treatment of sphingosine associated disorders. In some aspects, the present invention is directed to a compound of any of formulas I, II or III for use in the treatment of multiple sclerosis.

In some aspects, the present invention is directed to a compound of any of formulas I, II or III for use in the manufacture of a medicament for use in the treatment of sphingosine associated disorders. In some aspects, the present invention is directed to a compound of any of formulas I, II or III for use in the manufacture of a medicament for the treatment of multiple sclerosis.

In some aspects, the present invention is directed to a pharmaceutical composition comprising a compound of any of formulas I, II or III and a pharmaceutically acceptable carrier.

In some aspects, the present invention is directed to a process for making any of the compounds described herein.

DETAILED DESCRIPTION OF THE INVENTION

Defintions

The following definitions are used, unless otherwise described.

"Halogen" or "halo" means fluoro (F), chloro (Cl), bromo (Br), or iodo (I).

The term "hydrocarbon" used alone or as a suffix or prefix, refers to any structure comprising only carbon and hydrogen atoms up to 14 carbon atoms.

The term "hydrocarbon radical" or "hydrocarbyl" used alone or as a suffix or prefix, refers to any structure as a result of removing one or more hydrogens from a hydrocarbon.

The term "alkyl' used alone or as a suffix or prefix, refers to monovalent straight or branched chain hydrocarbon radicals comprising 1 to about 12 carbon atoms.

The term "alkylene" used alone or as suffix or prefix, refers to divalent straight or branched chain hydrocarbon radicals comprising 1 to about 12 carbon atoms, which serves to links two structures together.

The term "cycloalkyl" used alone or as suffix or prefix, refers to a saturated or partially unsaturated monovalent ring-containing hydrocarbon radical comprising at least 3 up to about 12 carbon atoms.

The term "aryl" used alone or as suffix or prefix, refers to a monovalent hydrocarbon radical having one or more polyunsaturated carbon rings having aromatic character, and comprising 5 up to about 14 carbon atoms.

The term "heterocycle" used alone or as a suffix or prefix, refers to a ring-containing structure or molecule having one or more multivalent heteroatoms, independently selected from N, O and S, as a part of the ring structure and including at least 3 and up to about 20 atoms in the ring(s). Heterocycle may be saturated or unsaturated, containing one or more double bonds, and heterocycle may contain more than one ring. When a heterocycle contains more than one ring, the rings may be fused or unfused. Fused rings generally refer to at least two rings share two atoms therebetween. Heterocycle may have aromatic character or may not have aromatic character.

The terms "heterocyclic group", "heterocyclic moiety", "heterocyclic", or "heterocyclo" used alone or as a suffix or prefix, refers to a radical derived from a heterocycle by removing one or more hydrogens therefrom.

The term "heterocyclyl" used alone or as a suffix or prefix, refers a monovalent radical derived from a heterocycle by removing one hydrogen therefrom.

The term "heteroaryl" used alone or as a suffix or prefix, refers to a heterocyclyl having aromatic character.

Heterocycle includes, for example, monocyclic heterocycles such as: aziridine, oxirane, thiirane, azetidine, oxetane, thietane, pyrrolidine, pyrroline, imidazolidine, pyrazolidine, pyrazoline, dioxolane, sulfolane 2,3-dihydrofuran, 2,5-dihydrofuran

tetrahydrofuran, thiophane, piperidine, 1,2,3,6-tetrahydro-pyridine, piperazine, morpholine, thiomorpholine, pyran, thiopyran, 2,3-dihydropyran, tetrahydropyran, 1,4-dihydropyridine, 1,4-dioxane, 1,3-dioxane, dioxane, homopiperidine, 2,3,4,7-tetrahydro-1H-azepine homopiperazine, 1,3-dioxepane, 4,7-dihydro-1,3-dioxepin, and hexamethylene oxide.

In addition, heterocycle includes aromatic heterocycles (heteroaryl groups), for example, pyridine, pyrazine, pyrimidine, pyridazine, thiophene, furan, furazan, pyrrole, imidazole, thiazole, oxazole, pyrazole, isothiazole, isoxazole, 1,2,3-triazole, tetrazole, 1,2,3-thiadiazole, 1,2,3-oxadiazole, 1,2,4-triazole, 1,2,4-thiadiazole, 1,2,4-oxadiazole, 1,3,4-triazole, 1,3,4-thiadiazole, and 1,3,4-oxadiazole.

Additionally, heterocycle encompass polycyclic heterocycles, for example, indole, indoline, isoindoline, quinoline, tetrahydroquinoline, isoquinoline, tetrahydroisoquinoline, 1,4-benzodioxan, coumarin, dihydrocoumarin, benzofuran, 2,3-dihydrobenzofuran, isobenzofuran, chromene, chroman, isochroman, xanthene, phenoxathiin, thianthrene, indolizine, isoindole, indazole, purine, phthalazine, naphthyridine, quinoxaline, quinazoline, cinnoline, pteridine, phenanthridine, perimidine, phenanthroline, phenazine, phenothiazine, phenoxazine, 1,2-benzisoxazole, benzothiophene, benzoxazole, benzthiazole, benzimidazole, benztriazole, thioxanthine, carbazole, carboline, acridine, pyrolizidine, and quinolizidine.

In addition to the polycyclic heterocycles described above, heterocycle includes polycyclic heterocycles wherein the ring fusion between two or more rings includes more than one bond common to both rings and more than two atoms common to both rings. Examples of such bridged heterocycles include quinuclidine, diazabicyclo[2.2.1]heptane and 7-oxabicyclo[2.2.1]heptane.

Heterocyclyl includes, for example, monocyclic heterocyclyls, such as: aziridinyl, oxiranyl, thiiranyl, azetidinyl, oxetanyl, thietanyl, pyrrolidinyl, pyrrolinyl, imidazolidinyl, pyrazolidinyl, pyrazolinyl, dioxolanyl, sulfolanyl, 2,3-dihydrofuranyl, 2,5-dihydrofuranyl, tetrahydrofuranyl, thiophanyl, piperidinyl, 1,2,3,6-tetrahydro-pyridinyl, piperazinyl, morpholinyl, thiomorpholinyl, pyranyl, thiopyranyl, 2,3-dihydropyranyl, tetrahydropyranyl, 1,4-dihydropyridinyl, 1,4-dioxanyl, 1,3-dioxanyl, dioxanyl, homopiperidinyl, 2,3,4,7-tetrahydro-1H-azepinyl, homopiperazinyl, 1,3-dioxepanyl, 4,7-dihydro-1,3-dioxepinyl, and hexamethylene oxidyl.

In addition, heterocyclyl includes aromatic heterocyclyls or heteroaryl, for example, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, thienyl, furyl, furazanyl, pyrrolyl, imidazolyl, thiazolyl, oxazolyl, pyrazolyl, isothiazolyl, isoxazolyl, 1,2,3-triazolyl, tetrazolyl, 1,2,3-thiadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-triazolyl, 1,2,4-thiadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-triazolyl, 1,3,4-thiadiazolyl, and 1,3,4 oxadiazolyl.

Additionally, heterocyclyl encompasses polycyclic heterocyclyls (including both aromatic or non-aromatic), for example, indolyl, indolinyl, isoindolinyl, quinolinyl, tetrahydroquinolinyl, isoquinolinyl, tetrahydroisoquinolinyl, 1,4-benzodioxanyl, coumarinyl, dihydrocoumarinyl, benzofuranyl, 2,3-dihydrobenzofuranyl, isobenzofuranyl, chromenyl, chromanyl, isochromanyl, xanthenyl, phenoxathiinyl, thianthrenyl, indolizinyl, isoindolyl, indazolyl, purinyl, phthalazinyl, naphthyridinyl, quinoxalinyl, quinazolinyl, cinnolinyl, pteridinyl, phenanthridinyl, perimidinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxazinyl, 1,2-benzisoxazolyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benzimidazolyl, benztriazolyl, thioxanthinyl, carbazolyl, carbolinyl, acridinyl, pyrolizidinyl, and quinolizidinyl.

In addition to the polycyclic heterocyclyls described above, heterocyclyl includes polycyclic heterocyclyls wherein the ring fusion between two or more rings includes more than one bond common to both rings and more than two atoms common to both rings. Examples of such bridged heterocycles include quinuclidinyl, diazabicyclo[2.2.1]heptyl; and 7-oxabicyclo[2.2.1]heptyl.

The term "six-membered" used as prefix refers to a group having a ring that contains six ring atoms.

The term "five-membered" used as prefix refers to a group having a ring that contains five ring atoms.

A five-membered heteroaryl ring is a heteroaryl with a ring having five ring atoms wherein 1, 2 or 3 ring atoms are independently selected from N, O and S. Exemplary five-membered ring heteroaryls are thienyl, furyl, pyrrolyl, imidazolyl, thiazolyl, oxazolyl, pyrazolyl, isothiazolyl, isoxazolyl, 1,2,3-triazolyl, tetrazolyl, 1,2,3-thiadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-triazolyl, 1,2,4-thiadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-triazolyl, 1,3,4-thiadiazolyl, and 1,3,4- oxadiazolyl.

A six-membered ring heteroaryl is a heteroaryl with a ring having six ring atoms wherein 1, 2 or 3 ring atoms are independently selected from N, O and S. Exemplary

six-membered ring heteroaryls are pyridyl, pyrazinyl, pyrimidinyl, triazinyl and pyridazinyl.

The term "aralkyl" refers to an alkyl group substituted with an aryl group.

The term "heteroaralkyl" refers to an alkyl group substituted with an heteroaryl group.

Unless otherwise specified, the term "substituted", when used as a prefix, refers to a structure, molecule or group, wherein one or more hydrogens are replaced with one or more alkyl groups, or one or more chemical groups containing one or more heteroatoms selected from N, O, S, F, Cl, Br, I, and P. Exemplary chemical groups containing one or more heteroatoms include heterocyclyl, $-NO_2$, -O-alkyl, halo, $-CF_3$, $-CO_2H$, $-CO_2R$, $-NH_2$, -SH, -NHR, $-NR_2$, -SR, $--SO_3H$, $-SO_2R$, --S(O)R, -CN, -OH, $-C(O)NR_2$, --NRC(O)R, oxo (=O), imino (=NR), thio (=S), and oximino (=N-OR), wherein each "R" is alkyl as defined above. For example, substituted phenyl may refer to nitrophenyl, pyridylphenyl, methoxyphenyl, chlorophenyl, aminophenyl, an so on, wherein the nitro, pyridyl, methoxy, chloro, and amino groups may replace any suitable hydrogen on the phenyl ring. It will be understood that "substitution" or "substituted with" includes the implicit proviso that such substitution is in accordance with the permitted valence of the substituted atom and the substituent, and that the substitution results in a stable compound, *e.g.*, which does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, etc.

The term "alkoxy" used alone or as a suffix or prefix, refers to radicals of the general –O-alkyl, Exemplary alkoxy groups includes methoxy, ethoxy, propoxy, isopropoxy, butoxy, t-butoxy, isobutoxy, cyclopropylnethoxy, allyloxy, and propargyloxy.

The term "amine" or "amino" used alone or as a suffix or prefix, refers $-NH_2$.

The term "alkylamino" used alone or as a suffix or prefix, refers –NH(alkyl). The term "dialkylamino" used alone or as a suffix or prefix, refers $–NH(alkyl)_2$.

"Acyl" used alone, as a prefix or suffix, means -C(O)-R, wherein R hydrogen, hydroxyl, amino, alkylamino, dialkylamino, or alkoxy, any of which may be substituted as provided by the defiontion of "substituted" given above. Acyl groups include, for example, acetyl, propionyl, benzoyl, phenyl acetyl, carboethoxy, and dimethylcarbamoyl.

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Some of the compounds in the present invention may exist as stereoisomers, including enantiomers, diastereomers, and geometric isomers. All of these forms, including (R), (S), epimers, diastereomers, cis, trans, syn, anti, solvates (including hydrates), tautomers, and mixtures thereof, are contemplated in the compounds of the present invention.

The invention also relates to salts of the compounds of the invention and, in particular, to pharmaceutically acceptable salts. A "pharmaceutically acceptable salt" is a salt that retains the desired biological activity of the parent compound and does not impart any undesired toxicological effects. The salts can be, for example, salts with a suitable acid, such as hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, nitric acid, and the like; acetic acid, oxalic acid, tartaric acid, succinic acid, malic acid, benzoic acid, pamoic acid, alginic acid, methanesulfonic acid, naphthalenesulfonic acid, and the like. Also included are salts of cations such as ammonium, sodium, potassium, lithium, zinc, copper, barium, bismuth, calcium, and the like; or organic cations such as tetralkylammonium and trialkylammonium cations. Combinations of the above salts are also useful. Salts of other acids and/or cations are also included, such as salts with trifluoroacetic acid, chloroacetic acid, and trichloroacetic acid.
The invention also includes different crystal forms, hydrates, and solvates of the compounds of the invention.

The terms "phosphate precursor" and "phosphate precursor analog," as used herein, refer to substituent moieties in invention compounds that may be directly phosphorylated *in vivo*, or which may be cleaved *in vivo* to reveal a moiety that may then be phosphorylated *in vivo*. In certain embodiments, the phosphate precursor may be L_1-O-H or L_1-O-L_2, wherein L_1 is a linking moiety and L_2 is a labile moiety. Exemplary embodiments of the phosphate precursor, include but are not limited to -alkyl-OH, -halo-alkyl-OH, alkoxy-OH, -alkyl-$OCOR^a$, -halo-alkyl-$OCOR^a$, -alkoxy-$OCOR^a$, -alkyl-$OC(O)NR^a R^b$, -halo-alkyl-$OC(O)NHR^a R^b$, -alkoxy-$OC(O)NR^aR^b$, -$(CH_2)_qCO_2R^c$, and -$(CH_2)_nCH_2$=$CHC(O)OR^c$, wherein

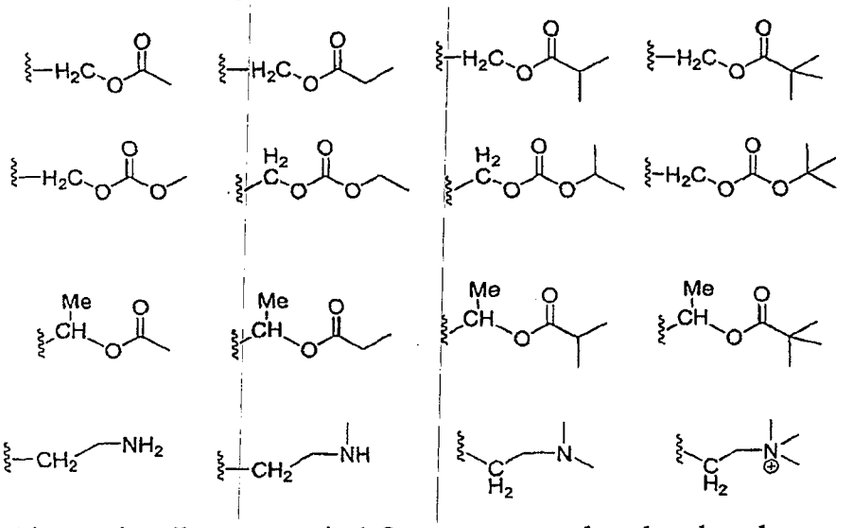
q is an integer between 0 and 4;

R^a and R^b are independently selected from the group consisting of hydrogen, straight chain or branched C_1-C_6-alkyl, all of which may be optionally substituted with OH, halogen, straight chain or branched C_1-C_6-alkoxy, straight chain or branched halo-C_1-C_6-alkyl, straight chain or branched halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl,

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hydroxyl-C_1-C_6-alkyl, carboxy-C_1-C_6-alkyl, substituted or unsubstituted C_3-C_{10} carbocyclic rings, and substituted or unsubstituted C_3-C_{10} heterocyclic rings, which may contain one or more heteroatoms and may be saturated or unsaturated; and

R^c is selected from the group consisting of hydrogen, straight chain or branched C_1-C_6-alkyl, straight chain or branched halo-C_1-C_6-alkyl, substituted or unsubstituted aryl group, or one of the following groups.



The "linking moiety," may contain 1-8 atoms or may be a bond, and serves as the connection point through which the phosphate mimic, phosphate derivative, or phosphate precursor substituent moieties are linked to the remaining structure of the compounds of the invention. In certain embodiments, the linking moiety may include, but is not limited to, substituted or unsubstituted alkyl (*e.g.*, methylene chains), substituted or unsubstituted alkenyl (*e.g.*, n-alkenes), substituted or unsubstituted alkynyl, substituted or unsubstituted halo-alkyl, substituted or unsubstituted alkoxy, and substituted or unsubstituted halo-alkoxy. In specific embodiments, the linking moiety may be carbonyl derivatized.

The language "labile moiety" refers to a moiety that is subject to cleavage, for instance, by hydrolysis or enzymatic degradation. In certain embodiments, the labile moiety is an ester moiety, which may result in a carboxylate or hydroxyl derivative, depending on the orientation of the ester functionality in the molecule prior to cleavage.

The term "phosphate derivative" refers to substituent moieties in invention compounds that contain a phosphate or phosphate ester group. When a compound of the invention containing a phosphate derivative is administered to a subject, the compound may act as is *in vivo* or the phosphate derivative (within the compound) may be cleaved

and then re-phosphorylated *in vivo* leading to an active compound. In certain embodiments, the phosphate derivative may be selected from the group consisting of -$(CH_2)_q$ $OPO_2R^dR^e$, -$(CH_2)_qOPO_3R^dR^e$, and -$(CH_2)_qOPO_2(S)R^dR^e$, wherein

q is an integer between 0 and 4; and

R^d and R^e are each independently selected from the group consisting of hydrogen, straight chain or branched C_1-C_6-alkyl, straight chain or branched halo-C_1-C_6-alkyl, substituted or unsubstituted aryl group, and a prodrug derivatizing moiety (PDM).

The term "phosphate mimic" refers to substituent moieties in invention compounds in which a phosphate substrate has been replaced with a non-hydrolyzable functional group, resulting in a moiety that mimics the biological function of a phosphate or phosphate ester moiety. In certain embodiments, the phosphate mimic is -L_1-Z_2, wherein L_1 is a linking moiety and Z_2 is a non-hydrolyzable moiety covalently bonded, to L_1. In certain embodiments, the phosphate mimic is selected from the group consisting of -$(CH_2)_qCH_2PO_3R^dR^e$, and -$(CH_2)_qC(Y_1)(Y_2)PO_3R^dR^e$, wherein

q is an integer between 0 and 4;

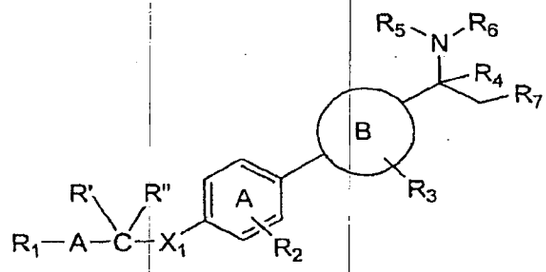
Y_1 and Y_2 are independently selected from the group consisting of hydrogen, straight chain or branched C_1-C_6-alkyl, all of which may be optionally substituted with OH, halogen, straight chain or branched C_1-C_6-alkoxy, straight chain or branched halo-C_1-C_6-alkyl, straight chain or branched halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, hydroxyl-C_1-C_6-alkyl, carboxy-C_1-C_6-alkyl, substituted or unsubstituted C_3-C_{10} carbocyclic rings, and substituted or unsubstituted C_3-C_{10} heterocyclic rings, which may contain one or more heteroatoms and may be saturated or unsaturated; and

R^d and R^e are each independently selected from the group consisting of hydrogen, straight chain or branched C_1-C_6-alkyl, straight chain or branched halo-C_1-C_6-alkyl, substituted or unsubstituted aryl group, and a prodrug derivatizing moiety (PDM).

The language "non-hydrolyzable moiety" is art-recognized, and refers to moieties containing bonds, such as carbon-phosphorous bonds, that are not hydrolyzable *in vivo*.

Compounds of the Invention

In some aspects, the present invention is directed to a compound of formula I:



I

or a pharmaceutically acceptable salt thereof, wherein:

R_1 is hydrogen, halogen, cyano, alkyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, aralkyl, heteroalykl, -O-alkyl, -O-aryl, -O-heteroaryl, -S-alkyl, alkylene-O-alkyl, alkylene-CO_2H, alkylene-CO_2alkyl, alkylSO_2, alkylenesulfonyl, alkylene-CO-amino, alkylene-CO-alkylamino, alkylene-CO-dialkylamino, alkylene-NH-CO_2H, alkylene-NH-CO_2alkyl -CO_2alkyl, -OH, -C(O)-alkyl, -C(O)O-alkyl, -$CONH_2$, -CO-alkylamino, -CO-dialkylamino, amino, alkylamino, or dialkylamino, any of which may be optionally substituted on carbon with 1, 2, or 3 groups selected from halo, alkyl, haloalkyl, -CF_3, aryl, -CN, -OH, or –O-alkyl;

A is (C_1-C_{20})alkylene, (C_2-C_{20})alkenylene, or (C_2-C_{20})alkynylene, each of which may be optionally suibstited on carbon with 1, 2, o3 groups selected from OH, CO_2H, CO_2alkyl, halogen, amino, alkylamino, dialkylamino, -O-alkyl, alkylene-O-alkyl, alkylene-OH, or alkylene-CO_2H;

X_1 is a bond or is CH_2, O,-CH_2O-, S, -S(O), -$S(O)_2$, -C(O)-, -C(O)O-, or NR_x, wherein R_x is H or (C_1-C_6)alkyl;

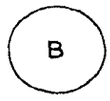
R' and R" are each independently hydrogen, halogen, alkyl optionally substituted on carbon with halogen, alkyl, or taken together with the carbon to which they are attached form C=O or a 3, 4, 5,or 6-membered ring, optionally containing 1 or 2 heteroatoms selected from O NH, N-alkyl, SO, or SO_2, any of which may be optionally substituted on carbon with alkyl or halogen

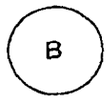
R_2 is cyano, alkyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, aralkyl, heteroalykl, -O-alkyl, -O-aryl, -O-heteroaryl, aralkoxy, heteroaralkoxy, -S-alkyl, alkylene-O-alkyl, alkylene-CO_2H, alkylene-CO_2alkyl, alkylSO_2, alkylenesulfonyl, alkylene-CO-amino, alkylene-CO-alkylamino, alkylene-CO-dialkylamino, alkylene-NH-CO_2H, alkylene-NH-CO_2alkyl -CO_2alkyl, -OH, -C(O)-alkyl, -C(O)O-alkyl, -$CONH_2$, -CO-alkylamino, -CO-dialkylamino, amino, alkylamino, and dialkylamino, any of which may be optionally substituted on carbon with 1, 2, or 3 groups selected from halo, alkyl, OH, or –O-alkyl;

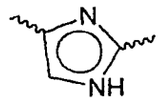
R_3 is absent, hydrogen, halogen, cyano, alkyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, aralkyl, heteroalykl, -O-alkyl, -O-aryl, -O-heteroaryl, aralkoxy, heteroaralkoxy, -S-alkyl, alkylene-O-alkyl, alkylene-CO_2H, alkylene-CO_2alkyl, alkylSO_2, alkylenesulfonyl, alkylene-CO-amino, alkylene-CO-alkylamino, alkylene-CO-dialkylamino, alkylene-NH-CO_2H, alkylene-NH-CO_2alkyl -CO_2alkyl, -OH, -C(O)-alkyl, -C(O)O-alkyl, -$CONH_2$, -CO-alkylamino, -CO-dialkylamino, amino, alkylamino, and dialkylamino, any of which may be optionally substituted on carbon with 1, 2, or 3 groups selected from halo, alkyl, OH, or –O-alkyl;



is phenyl or pyridyl;



is aryl, heteroaryl, heterocyclo, or cycloalkyl, any of which may be optionally substituted on carbon with 1, 2, or 3 groups selected form halogen, alkyl, O-alkyl, CO_2H, CO_2alkyl, halogen, amino, alkylamino, dialkylamino, -O-alkyl, alkylene-O-alkyl, alkylene-OH, or alkylene-CO_2H, provided that 

is not 

;

R_4 is hydrogen, cyano, alkyl, aryl, heteroaryl, alkylene-O-alkyl, alkylene-OH, aryl, alkylene-O-alkyl, -CO_2H, -CO_2-alkyl, alkylene-CO_2H, or alkylene-CO_2-alkyl, alkylene-OC(O)R wherein R is hydrogen or alkyl; cycloalkyl, heterocycloalkyl, alkylene-NH_2, alkylene-alkylamino, or alkylene-dialkylamino, any of which may be optionally substituted on carbon with 1, 2, or 3 groups selected from OH, CO_2H, CO_2alkyl, halogen, amino, alkylamino, dialkylamino, -O-alkyl, alkylene-O-alkyl, alkylene-OH, or alkylene-CO_2H;

R_5 and R_6 are each independently selected from the group consisting of hydrogen, alkyl, alkylene-OH, aryl, alkylene-O-alkyl, -CO_2H, CO_2-alkyl, alkylene-OC(O)alkyl, cycloalkyl, heterocyclo, -C(O)-alkyl, -C(O)-aryl, C(O)-aralkyl, -C(O)-Oalkyl, -C(O)-Oaryl, -C(O)-Oaralkyl, alkylene-amino, alkylene-alkylamino, and alkylene-dialkylamino, any of which may be optionally substituted on carbon with halogen, alkyl, hydroxyl, CO_2H, CO_2alkyl or alkoxy; or

R_5 and R_6, together with the nitrogen to which they are attached, may form a 3, 4, 5, or 6-membered saturated or unsaturated ring, optionally containing 1 or 2 additional

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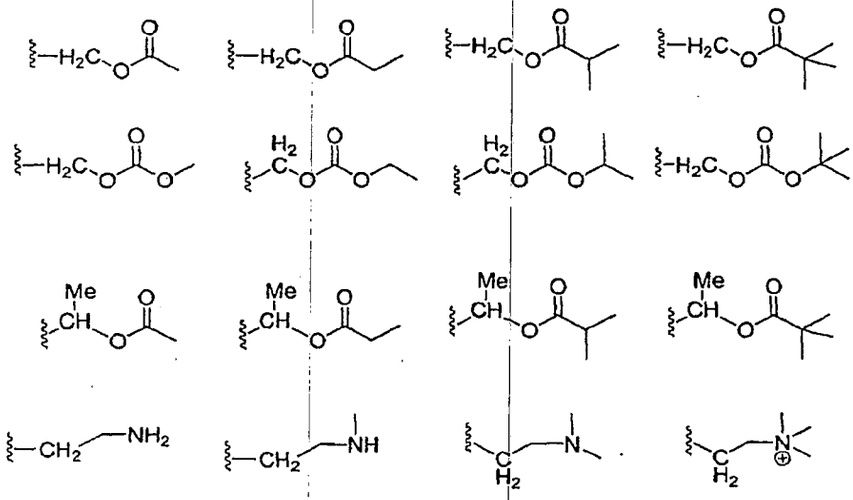
heteroatoms selected from O, S, NH, or N-alkyl, and optionally substituted on carbon with halogen, alkyl, hydroxyl, or alkoxy;

R_7 is selected from the group consisting of -OH, -O-alkyl, alkylene-OH, $-CO_2H$, alkylene-CO_2H, -C(O)O-alkyl, -alkylene-CO_2-alkyl, -C(O)O-aryl, $-CH_2=CHCO_2H$, $-CH_2=CHC(O)O$-alkyl, $-CH_2=CHC(O)O$-aryl, $-OPO_2R_{p1}R_{p2}$, $-OPO_3R_{p1}R_{p2}$, $-CH_2PO_3R_{p1}R_{p2}$, $-OPO_2(S)R_{p1}R_{p2}$, and $-C(Z')(Z'')PO_3R_{p1}R_{p2}$, any of which may be optionally substituted on carbon with halogen, alkyl, hydroxyl, carboxy, or alkoxy; and wherein

Z' is hydroxyl or halogen;

Z" is H or halogen;

R_{p1} and R_{p2} are each independently hydrogen, C_1-C_6-alkyl, aryl, or one of the following groups:



; and

Y is heterocyclo or heteroaryl.

In some embodiments, R_1 is aryl or heteroaryl, optionally substituted with 1, 2, or 3 groups selected from halo, alkyl, haloalkyl, -aryl, $-CF_3$, -CN, -OH, or –O-alkyl. In some embodiments, R_1 is aryl, *e.g.*, phenyl, optionally substituted with 1 or 2 groups selected from $-CF_3$, -CN, -OMe, -Cl or -F. In some embodiments, R_1 is heteroaryl, *e.g.*, thiophene or benzothiophene, optionally substituted with 1 or 2 groups selected from phenyl, $-CF_3$, -CN, -OMe, -Cl or -F. In some embodiments, R_1 is hydrogen. In other embodiments, R_1 is phenyl. In some embodiments, R_1 is pyridyl. In other embodiments, R_1 is thiophenyl. In still other embodiments, R_1 is cyclohexyl. In some embodiments, R_1 is cyclopentyl.

In some embodiments, A is a C_1-C_{10} alkylene. In some embodiments, A is a branched C_1-C_{10} alkylene. In other embodiments, A is n-octyl. In other embodiments, A is n-heptyl. In other embodiments, A is n-hexyl. In some embodiments, A is a C_1-C_5 alkylene. In some embodiments, A is n-pentyl. In other embodiments, A is n-butyl. In still other embodiments, A is n-propyl. In other embodiments, A is ethyl. In still other embodiments, A is methyl.

In some embodiments, X_1 is O. In other embodiments, X_1 is S. In still other embodiments, X_1 is SO_2. In some embodiments, X_1 is CH_2. In other embodiments, X_1 is C=O. In still other embodiments, CH_2O, wherein either the oxygen or the carbon may be attached to 

.

In some embodiments, R' is hydrogen. In other embodiments, R' is methyl. In some embodiments, R" is hydrogen. In other embodiments, R" is methyl. In some embodiments, R' and R" taken together with the carbon to which they are attached, is C=O, with the provision that only one of X_1 or R' and R" taken together with the carbon may form C=O.

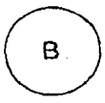
The compounds of the present invention include a selectivity enhancing moiety. The term "selectivity enhancing moiety (SEM)" is defined in United States Application Ser. No. 11/349069 filed on February 6, 2006 which is assigned to the assignee of the present application, the contents of which are incorporated herein by reference, refers to one or more moieties that provide an enhancement in the selectivity of the compound to which they are attached for the S1P-1 receptor, as compared to the compound not containing the moiety or moieties. The SEM confers selectivity to the compound to which it is attached for the S1P-1 receptor as compared to, for example, the S1P-2 to S1P-5 receptors. The enhancement conferred to a compound by the SEM may be measured by, for example, determining the binding specificity of a compound for the S1P-1 receptor and one or more of the other S1P receptors wherein enhancement conferred to a compound by the SEM may be in the form of increased potency. In some embodiments, at least one of R_2 and/or R_3 is an SEM. In some embodiments, the SEM is a halo-substituted alkyl group such as CF_3, CF_2CF_3, $CF_2CF_2CF_3$, $CFHCF_3$, CH_2CF_3, $CH_2CH_2CF_3$, $CHCl_2$, or CH_2Cl.

In certain embodiments, the SEM may possess a selectivity enhancing orientation (SEO). The term "selectivity enhancing orientation" or "SEO," is defined in

United States Application Ser. No. 11/349069 filed on February 6, 2006 which is assigned to the assignee of the present application, the contents of which are incorporated herein by reference and as used herein refers to the relative selectivity enhancement of a compound based on the orientation of the SEM as well as the additional substitutents on the ring, either alone or in combination with each other. In particular, the SEO may result from the orientation of the SEM on the ring to which it is attached, in relation to any other ring and/or moiety attached to the same ring. In one embodiment, the SEM on 

is in the *ortho* position relative to X_1 in Formula I. In another specific embodiment, the SEM is in the *meta* position relative to X_1.

Thus, in some embodiments, R_2 is alkyl substituted with 1, 2 or 3 halo groups. In some embodiments, R_2 is trifluoromethyl. In still other embodiments, R_2 is methyl.

In some embodiments, R_3 is absent. For example, in the case of compounds where 

is 

, R_3 would be considered absent, because there no substituents on the ring. In other embodiments, R_3 is halogen.

In some embodiments, R_4 is hydrogen. In other embodiments, R_4 is an alkyl, *e.g.*, a C_1-C_4 alkyl. For example, in some embodiments, R_4 is methyl. In some embodiments, R_4 is hydroxymethyl.

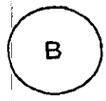
In some embodiments, R_5 is hydrogen. In some embodiments, R_6 is hydrogen. In some embodiments, R_5 is an alkyl, *e.g.*, a C_1-C_4 alkyl. In some embodiments, R_6 is an alkyl, *e.g.*, a C_1-C_4 alkyl.

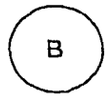
In some embodiments, R_7 is OH. In other embodiments, R_7 is CO_2H. In still other embodiments, R_7 is CO_2Me or CO_2Et. In other embodiments, R_7 is CO_2-phenyl. In still other embodiments, R_7 is $-OP(O)_3H_2$. In other embodiments, R_7 is $-CH_2P(O)_3H_2$.

In some embodiments, 

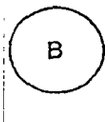
is phenyl. In other embodiments, 

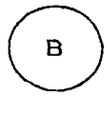
is pyridyl.

In some embodiments, 

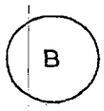
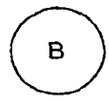
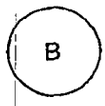
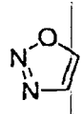
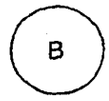
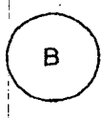
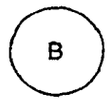
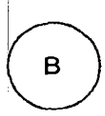
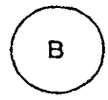
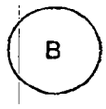
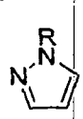
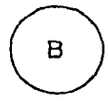
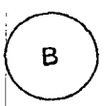
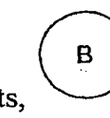
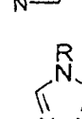
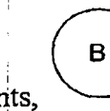
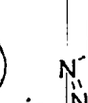
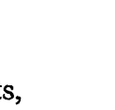
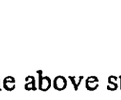
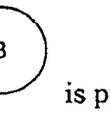
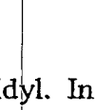
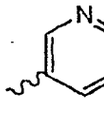
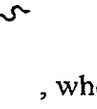
is . In some embodiments, 

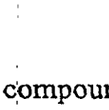
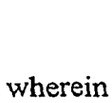
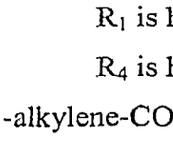
is 

. In some embodiments, 

is . In some embodiments, 

is

 . In some embodiments,  is  . In some embodiments,  is  . In some embodiments,  is  . In some embodiments,  is  . In some embodiments,  is  . In some embodiments,  is  . In some embodiments,  is  . In some embodiments,  is  . In some embodiments,  is  . In some embodiments,  is  . In some embodiments,  is  . In some embodiments,  is  . In some embodiments,  is  . In some embodiments,  is  . In some embodiments,  is  . In some embodiments, . In some embodiments,  is  . In some embodiments,  is  . In each of the above structures, R can be hydrogen or alkyl.

In some embodiments,  is pyridyl. In some embodiments,  is  , wherein "" indicates the points of attachment of the B ring to the remainder of the compound.

In some embodiments, compounds of the invention are compounds wherein

R_1 is hydrogen, aryl, cycloalkyl, or heteroaryl.

R_4 is hydrogen, alkyl, alkylene-OH, aryl, -alkylene-O-alkyl, alkylene-CO_2H, or -alkylene-CO_2-alkyl;

R_5 and R_6 are each independently hydrogen or alkyl, or alkylene-OH;

R_7 is selected from the group consisting of OH, alkylene-OH, -CO_2H, alkylene-CO_2H,
-alkylene-CO_2-alkyl, C(O)O-alkyl, -C(O)O-aryl, -CH_2=$CHCO_2$H, -CH_2=CHC(O)O-alkyl,
-CH_2=CHC(O)O-aryl, -$OPO_2R_{p1}R_{p2}$, -$OPO_3R_{p1}R_{p2}$, -$CH_2PO_3R_{p1}R_{p2}$, -OPO_2(S)$R_{p1}R_{p2}$, or
-C(Z')(Z")$PO_3R_{p1}R_{p2}$.

In some embodiments, compounds of the invention are compounds wherein

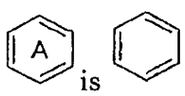
R_1 is hydrogen or aryl;

R_4 is hydrogen or alkyl;

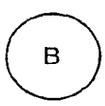
R_5 and R_6 are each independently hydrogen or alkyl, or alkylene-OH;

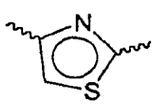
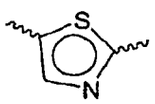
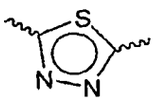
R_7 is selected from the group consisting of -OH, alkylene-OH, -CO_2H, alkylene-CO_2H,
-alkylene-CO_2-allky, C(O)O-alkyl, -C(O)O-aryl, -CH_2=$CHCO_2$H, -CH_2=CHC(O)O-alkyl,
-CH_2=CHC(O)O-aryl, -$OPO_2R_{p1}R_{p2}$, -$OPO_3R_{p1}R_{p2}$, -$CH_2PO_3R_{p1}R_{p2}$, -OPO_2(S)$R_{p1}R_{p2}$, and
-C(Z')(Z")$PO_3R_{p1}R_{p2}$.

In other embodiments, compounds of the invention are compounds wherein



is ;



is  ,  , or  ,

R_1 is phenyl;

A is (C_1-C_{10})alkyl;

R' and R" are hydrogen;

X_1 is O;

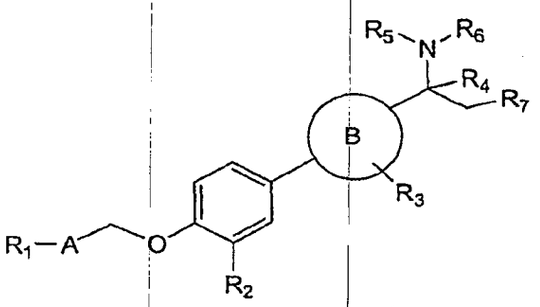
R_4 is hydrogen, alkyl, or alkylene-OH;

R_5 and R_6 are each independently hydrogen, alkyl;

R_7 is selected from the group consisting of -OH, alkylene-OH, -CO_2H, alkylene-CO_2H,
-C(O)O-alkyl, -C(O)O-aryl, -CH_2=$CHCO_2$H, -CH_2=CHC(O)O-alkyl, -CH_2=CHC(O)O-aryl,

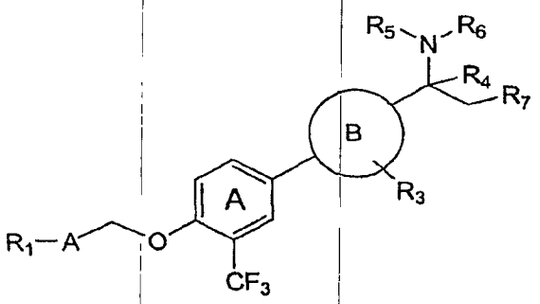
$-OPO_2R_{p1}R_{p2}$, $-OPO_3R_{p1}R_{p2}$, $-CH_2PO_3R_{p1}R_{p2}$, $-OPO_2(S)R_{p1}R_{p2}$, and $-C(Z')(Z'')PO_3R_{p1}R_{p2}$;

In some embodiments, compounds of the invention are compounds of formula I-1.



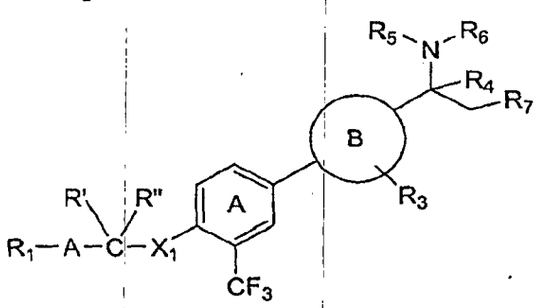
I-1

Another specific group of compounds of the invention are compounds of formula I-2.



I-2

In other aspects, the present invention is directed to a compound of formula II:



II

or a pharmaceutically acceptable salt thereof, wherein:

R_1 is hydrogen, halogen, cyano, alkyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, aralkyl, heteroalykl, -O-alkyl, -O-aryl, -O-heteroaryl, -S-alkyl, alkylene-O-alkyl, alkylene-CO_2H, alkylene-CO_2alkyl, alkylSO_2, alkylenesulfonyl,

alkylene-CO-amino, alkylene-CO-alkylamino, alkylene-CO-dialkylamino, alkylene-NH-CO_2H, alkylene-NH-CO_2alkyl -CO_2alkyl, -OH, -C(O)-alkyl, -C(O)O-alkyl, -$CONH_2$, -CO-alkylamino, -CO-dialkylamino, amino, alkylamino, or dialkylamino, any of which may be optionally substituted on carbon with 1, 2, or 3 groups selected from halo, alkyl, haloalkyl, -CF_3, -CN, -OH, or –O-alkyl;

A is (C_1-C_{20})alkylene, (C_2-C_{20})alkenylene, or (C_2-C_{20})alkynylene, each of which may be optionally suibstited on carbon with 1, 2, or 3 groups selected from OH, CO_2H, CO_2alkyl, halogen, amino, alkylamino, dialkylamino, -O-alkyl, alkylene-O-alkyl, alkylene-OH, or alkylene-CO_2H;

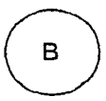
X_1 is a bond or is CH_2, O, -CH_2O-, S, -S(O), -$S(O)_2$, -C(O)-, -C(O)O-, or NR_x, wherein R_x is H or (C_1-C_6)alkyl;

R' and R" are each independently hydrogen, halogen, alkyl optionally substituted on carbon with halogen, alkyl, or taken together with the carbon to which they are attached form C=O or a 3, 4, 5,or 6-membered ring, optionally containing 1 or 2 heteroatoms selected from O NH, N-alkyl, SO, or SO_2, any of which may be optionally substituted on carbon with alkyl or halogen

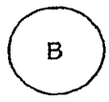
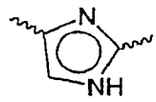
R_3 is absent, hydrogen, halogen, cyano, alkyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, aralkyl, heteroalykl, -O-alkyl, -O-aryl, -O-heteroaryl, aralkoxy, heteroaralkoxy, -S-alkyl, alkylene-O-alkyl, alkylene-CO_2H, alkylene-CO_2alkyl, alkylSO_2, alkylenesulfonyl, alkylene-CO-amino, alkylene-CO-alkylamino, alkylene-CO-dialkylamino, alkylene-NH-CO_2H, alkylene-NH-CO_2alkyl -CO_2alkyl, -OH, -C(O)-alkyl, -C(O)O-alkyl, -$CONH_2$, -CO-alkylamino,
-CO-dialkylamino, amino, alkylamino, and dialkylamino, any of which may be optionally substituted on carbon with 1, 2, or 3 groups selected from halo, alkyl, OH, or –O-alkyl;



is phenyl or pyridyl;



is aryl, heteroaryl, heterocyclo, or cycloalkyl, any of which may be optionally substituted on carbon with 1, 2, or 3 groups selected form halogen, alkyl, O-

alkyl, CO_2H, CO_2alkyl, halogen, amino, alkylamino, dialkylamino, -O-alkyl, alkylene-O-alkyl, alkylene-OH, or alkylene-CO_2H, provided that  is not  ;

R_4 is hydrogen, cyano, alkyl, aryl, heteroaryl, alkylene-O-alkyl, alkylene-OH, aryl, alkylene-O-alkyl, -CO_2H, -CO_2-alkyl, alkylene-CO_2H, or alkylene-CO_2-alkyl, alkylene-OC(O)R wherein R is hydrogen or alkyl; cycloalkyl, heterocycloalkyl, alkylene-NH_2, alkylene-alkylamino, or alkylene-dialkylamino, any of which may be optionally substituted on carbon with 1, 2, or 3 groups selected from OH, CO_2H, CO_2alkyl, halogen, amino, alkylamino, dialkylamino, -O-alkyl, alkylene-O-alkyl, alkylene-OH, or alkylene-CO_2H;

R_5 and R_6 are each independently selected from the group consisting of hydrogen, alkyl, alkylene-OH, aryl, alkylene-O-alkyl, -CO_2H, CO_2-alkyl, alkylene-OC(O)alkyl, cycloalkyl, heterocyclo, -C(O)-alkyl, -C(O)-aryl, C(O)-aralkyl, -C(O)-Oalkyl, -C(O)-Oaryl, -C(O)-Oaralkyl, alkylene-amino, alkylene-alkylamino, and alkylene-dialkylamino, any of which may be optionally substituted on carbon with halogen, alkyl, hydroxyl, CO_2H, CO_2alkyl or alkoxy; or

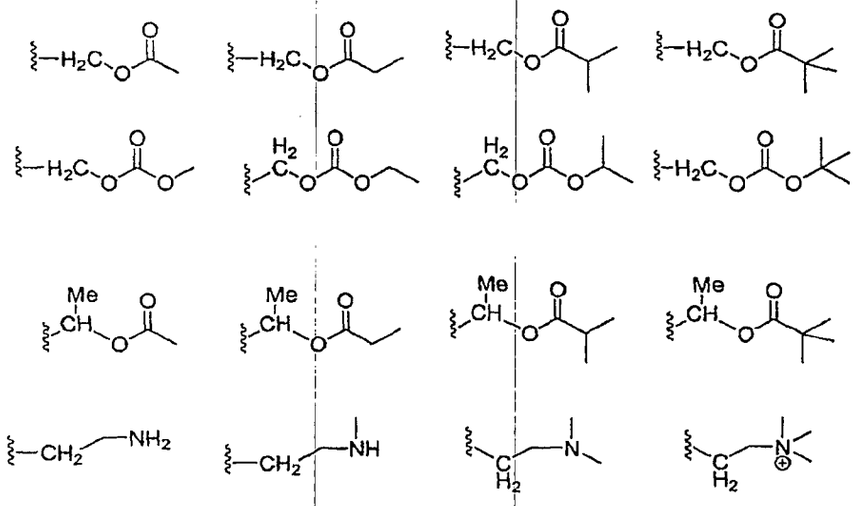
R_5 and R_6, together with the nitrogen to which they are attached, may form a 3, 4, 5, or 6-membered saturated or unsaturated ring, optionally containing 1 or 2 additional heteroatoms selected from O, S, NH, or N-alkyl, and optionally substituted on carbon with halogen, alkyl, hydroxyl, or alkoxy;

R_7 is selected from the group consisting of -OH, -O-alkyl, -alkylene-OH, -CO_2H, -alkylene-CO_2H, -C(O)O-alkyl, -alkylene-CO_2-alkyl, -C(O)O-aryl, -CH_2=$CHCO_2H$, -CH_2=CHC(O)O-alkyl, -CH_2=CHC(O)O-aryl, -$OPO_2R_{p1}R_{p2}$, -$OPO_3R_{p1}R_{p2}$, -$CH_2PO_3R_{p1}R_{p2}$, -$OPO_2(S)R_{p1}R_{p2}$, and -C(Z')(Z")$PO_3R_{p1}R_{p2}$, any of which may be optionally substituted on carbon with halogen, alkyl, hydroxyl, carboxy, or alkoxy; and wherein

Z' is hydroxyl or halogen;

Z" is H or halogen;

R_{p1} and R_{p2} are each independently hydrogen, C_1-C_6-alkyl, aryl, or one of the following groups:



; and

Y is heterocyclo or heteroaryl.

In some embodiments, R_1 is aryl or heteroaryl, optionally substituted with 1, 2, or 3 groups selected from halo, alkyl, haloalkyl, -aryl, $-CF_3$, -CN, -OH, or –O-alkyl. In some embodiments, R_1 is aryl, *e.g.*, phenyl, optionally substituted with 1 or 2 groups selected from $-CF_3$, -CN, -OMe, -Cl or -F. In some embodiments, R_1 is heteroaryl, *e.g.*, thiophene or benzothiophene, optionally substituted with 1 or 2 groups selected from phenyl, $-CF_3$, -CN, -OMe, -Cl or -F. In some embodiments, R_1 is hydrogen. In other embodiments, R_1 is phenyl. In some embodiments, R_1 is pyridyl. In other embodiments, R_1 is thiophenyl. In still other embodiments, R_1 is cyclohexyl. In some embodiments, R_1 is cyclopentyl.

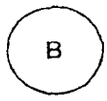
In some embodiments, A is a C_1-C_{10} alkylene. In some embodiments, A is a branched C_1-C_{10} alkylene. In other embodiments, A is n-octyl. In other embodiments, A is n-heptyl. In other embodiments, A is n-hexyl. In some embodiments, A is a C_1-C_5 alkylene. In some embodiments, A is n-pentyl. In other embodiments, A is n-butyl. In still other embodiments, A is n-propyl. In other embodiments, A is ethyl. In still other embodiments, A is methyl.

In some embodiments, X_1 is O. In other embodiments, X_1 is S. In still other embodiments, X_1 is SO_2. In some embodiments, X_1 is CH_2. In other embodiments, X_1 is C=O. In still other embodiments, CH_2O, wherein either the oxygen or the carbon may be attached to 

.

In some embodiments, R' is hydrogen. In other embodiments, R' is methyl. In some embodiments, R" is hydrogen. In other embodiments, R" is methyl. In some

embodiments, R' and R" taken together with the carbon to which they are attached, is C=O, with the provision that only one of X_1 or R' and R" taken together with the carbon may form C=O.

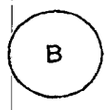
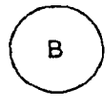
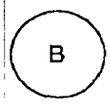
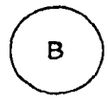
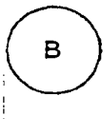
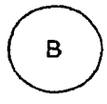
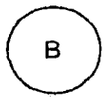
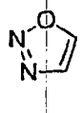
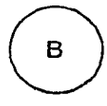
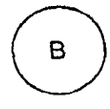
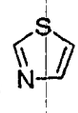
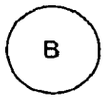
In some embodiments, R_3 is absent. For example, in the case of compounds where  is  , R_3 would be considered absent, because there no substituents on the ring. In other embodiments, R_3 is halogen.

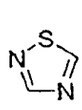
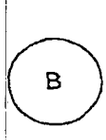
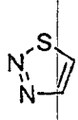
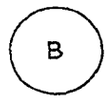
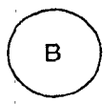
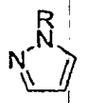
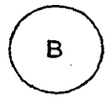
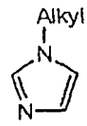
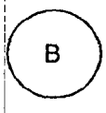
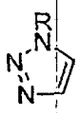
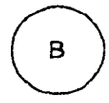
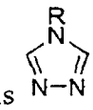
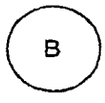
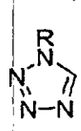
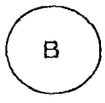
In some embodiments, R_4 is hydrogen. In other embodiments, R_4 is an alkyl, *e.g.*, a C_1-C_4 alkyl. For example, in some embodiments, R_4 is methyl. In some embodiments, R_4 is hydroxymethyl.

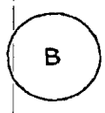
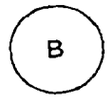
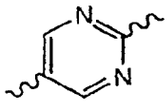
In some embodiments, R_5 is hydrogen. In some embodiments, R_6 is hydrogen. In some embodiments, R_5 is an alkyl, *e.g.*, a C_1-C_4 alkyl. In some embodiments, R_6 is an alkyl, *e.g.*, a C_1-C_4 alkyl.

In some embodiments, R_7 is OH. In other embodiments, R_7 is CO_2H. In still other embodiments, R_7 is CO_2Me or CO_2Et. In other embodiments, R_7 is CO_2-phenyl. In still other embodiments, R_7 is $-OP(O)_3H_2$. In other embodiments, R_7 is $-CH_2P(O)_3H_2$.

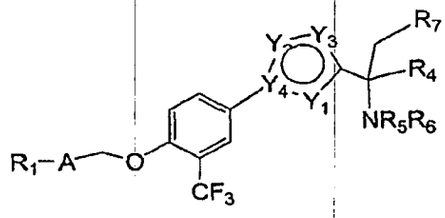
In some embodiments,  is phenyl. In other embodiments,  is pyridyl.

In some embodiments,  is  . In some embodiments,  is  . In some embodiments,  is  . In some embodiments,  is  . In some embodiments,  is  . In some embodiments,  is  . In some embodiments,  is  . In some embodiments,  is  . In some embodiments,  is  . In some embodiments,  is . In some embodiments, is . In some embodiments, is

 . In some embodiments,  is  . In some embodiments,  is  . In some embodiments,  is  . In some embodiments,  is  . In some embodiments,  is  . In some embodiments,  is  . In some embodiments,  is  . In some embodiments,  is  . In each of the above structures, R can be hydrogen or alkyl.

In some embodiments,  is pyridyl. In some embodiments,  is  , wherein "" indicates the points of attachment of the B ring to the remainder of the compound.

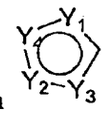
In some embodiments, compounds of formula II are compounds of formula II-1.



II-1

wherein  is a heteroaryl ring containing up to four heteroatoms selected from N, O, or S, optionally substituted on carbon with halogen or alkyl, wherein

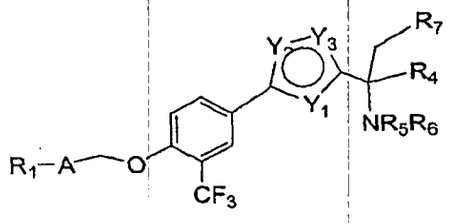
Y_1 is CH, N, S, or O;



Y_2 and Y_3 are each independently CH; N; O, or S; provided that when contains an N-H, that hydrogen may be replaced with alkyl; and

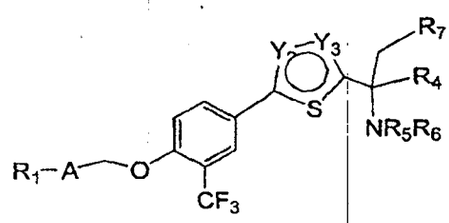
Y_4 is C or N.

In some embodiments, compounds of formula II are compounds of formula II-2.



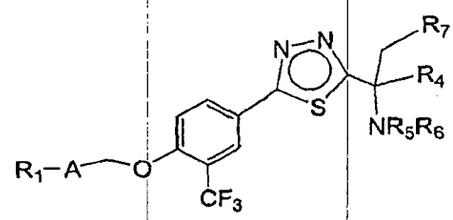
II-2

In other embodiments, compounds of formula II are compounds of formula II-3.



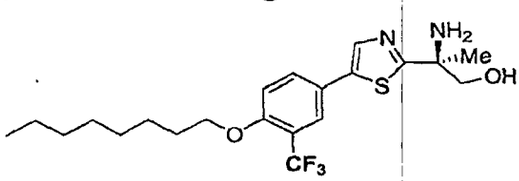
II-3

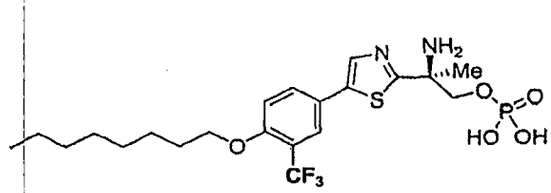
In some embodiments, compounds of formula II are compounds of formula II-4.

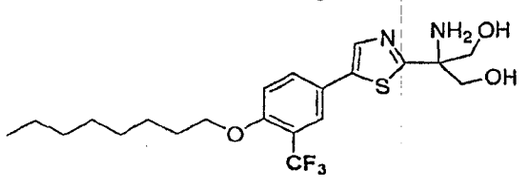


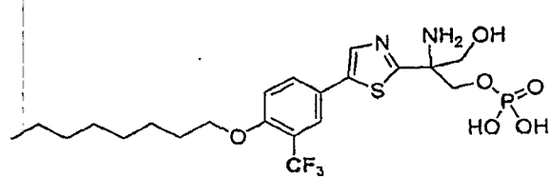
II-4

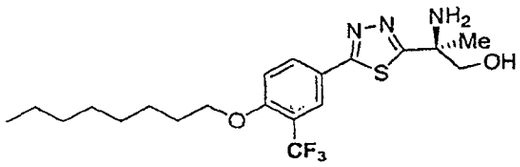
In some embodiments, compounds of the present invention include compounds listed in the following table:

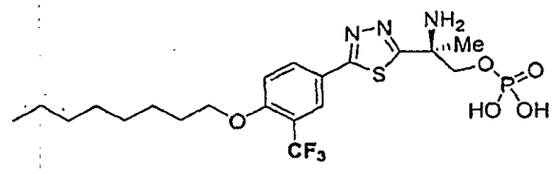


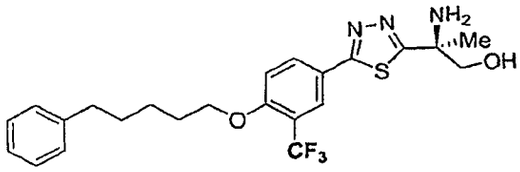


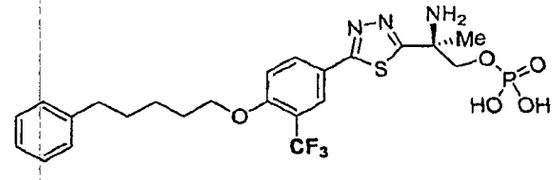


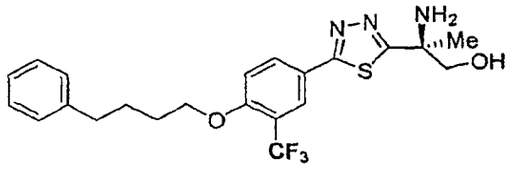


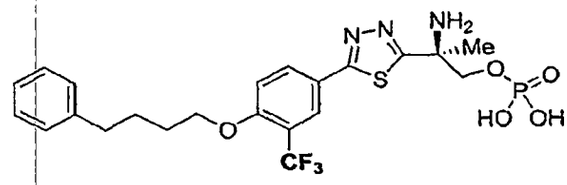


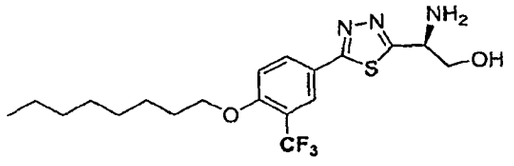


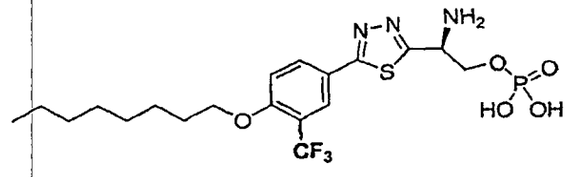


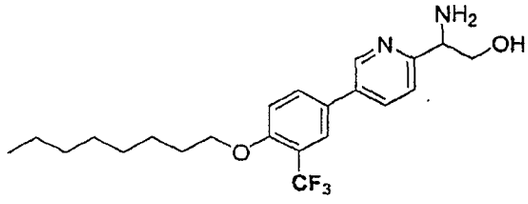


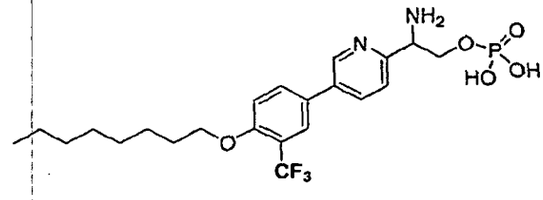


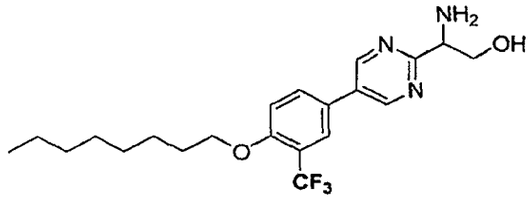


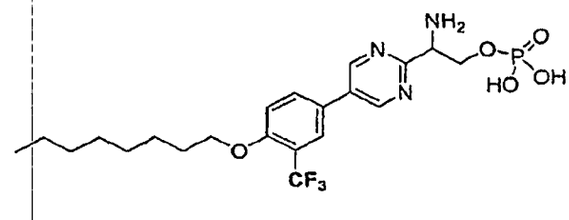


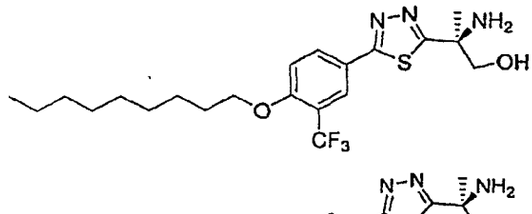


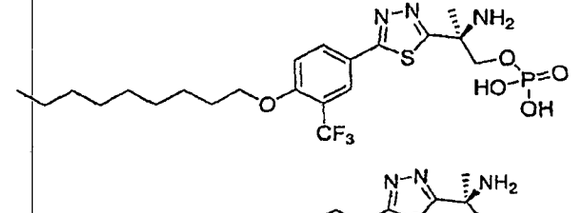


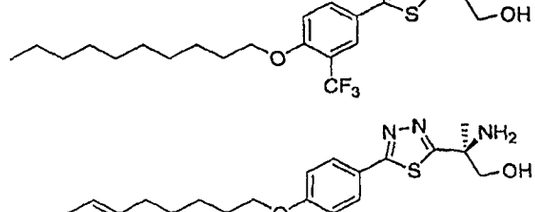


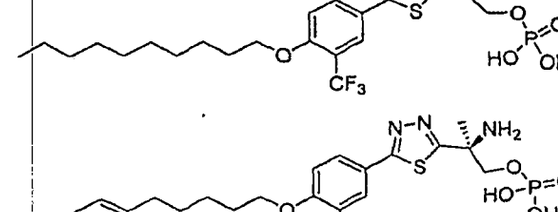


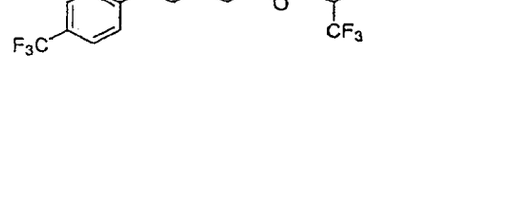


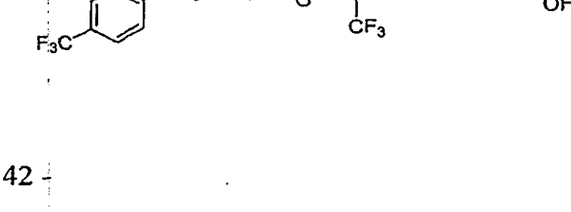


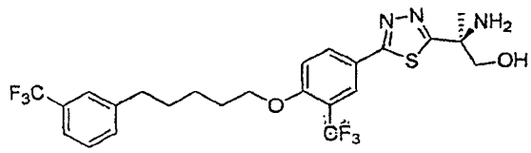
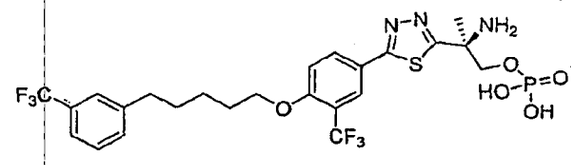
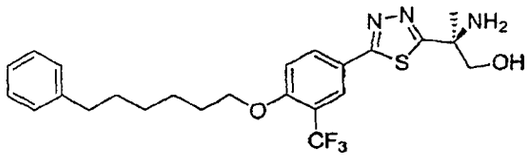
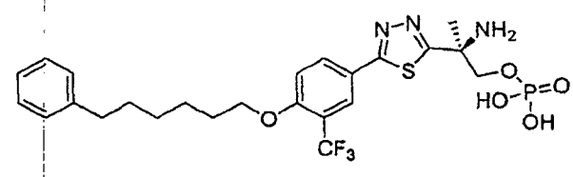
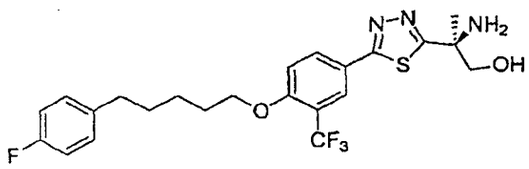
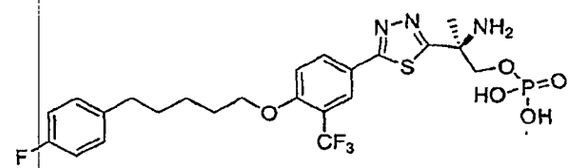
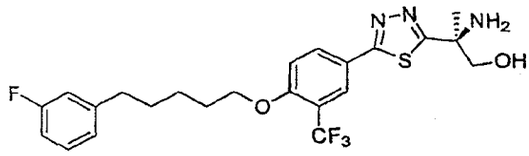
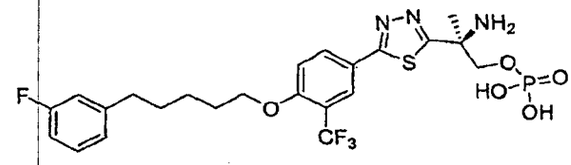
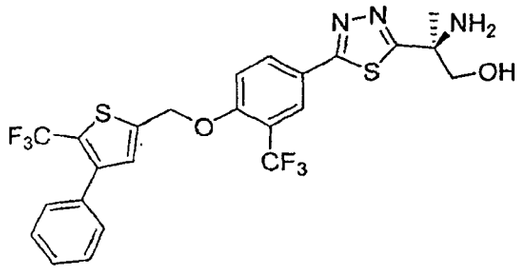
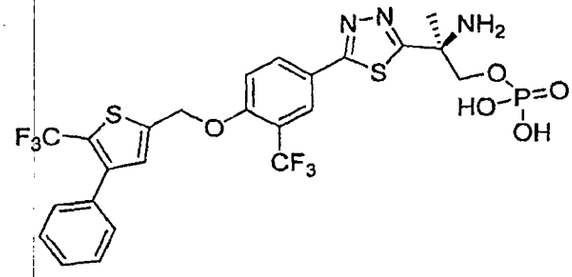
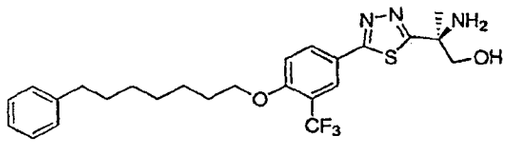
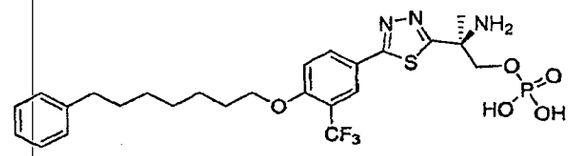
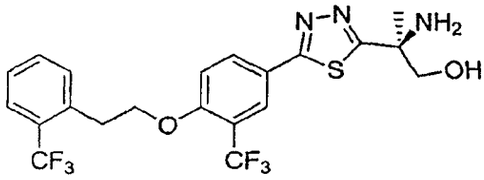
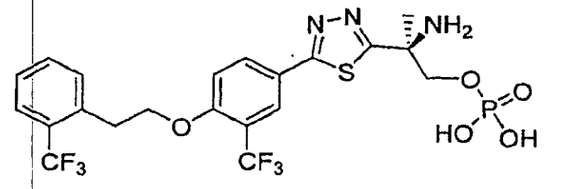
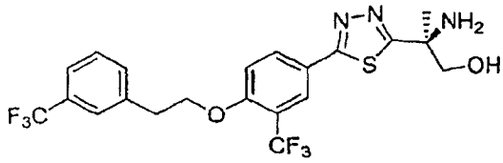
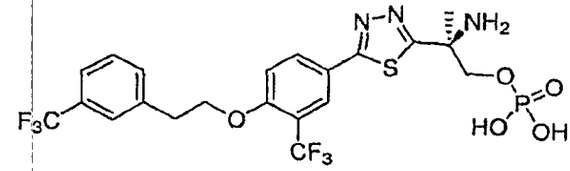
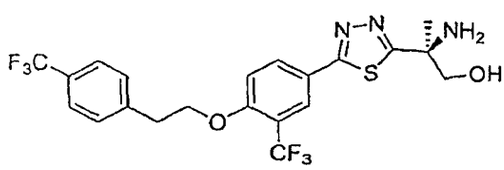
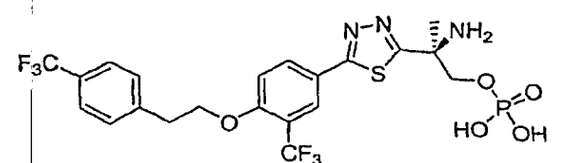


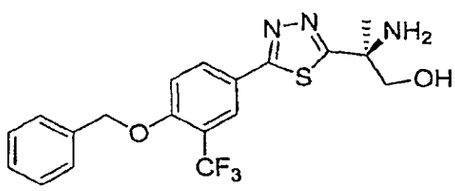


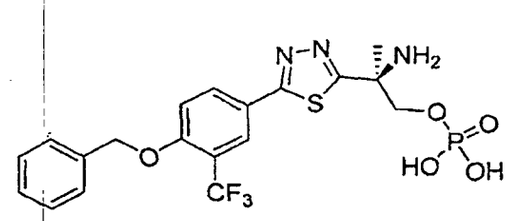


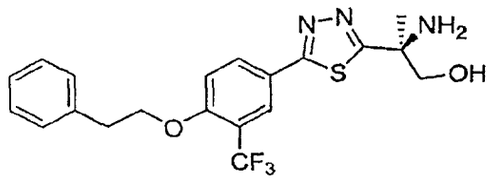


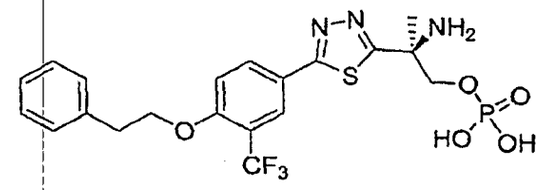


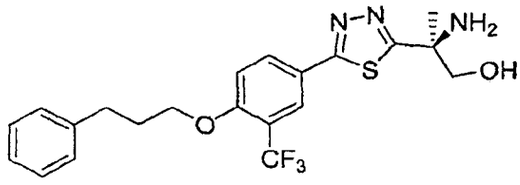



















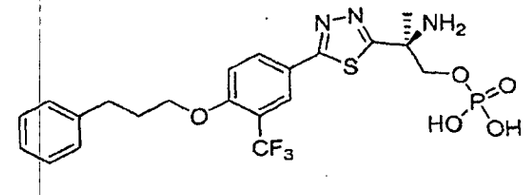


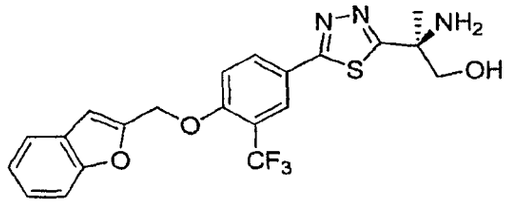


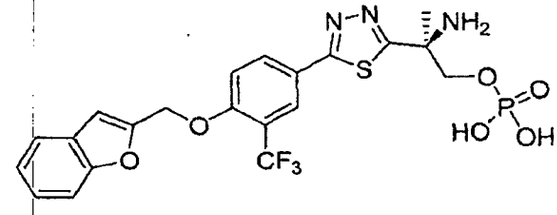


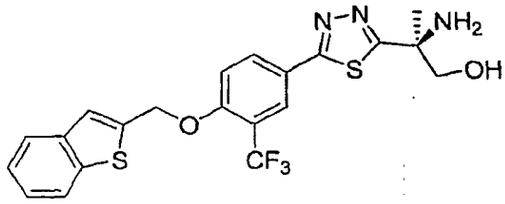


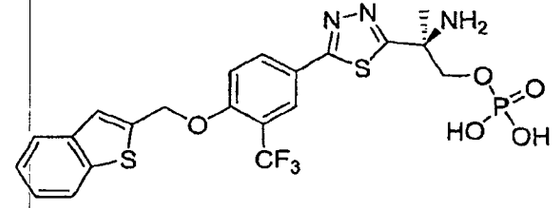


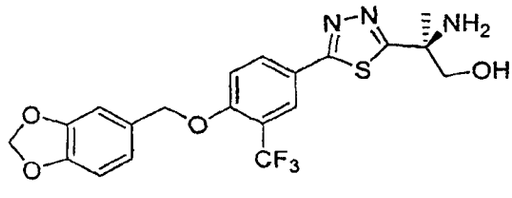


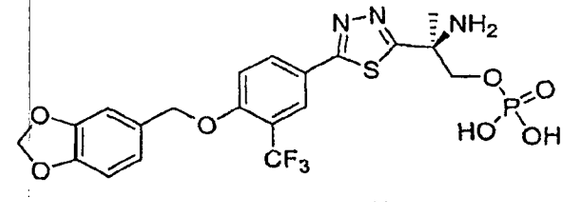


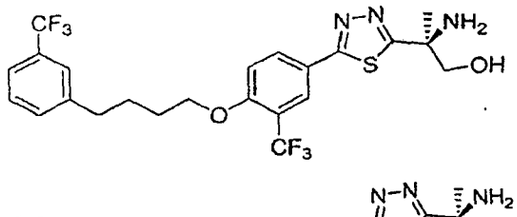


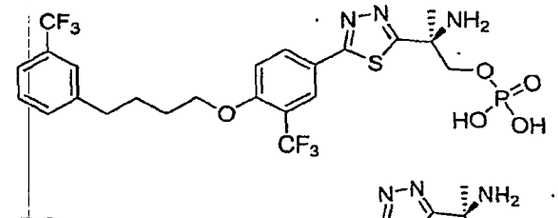


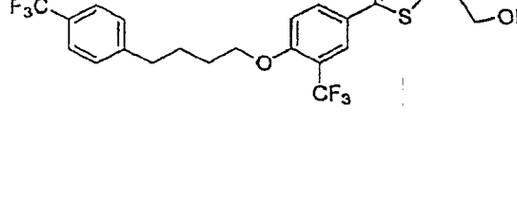


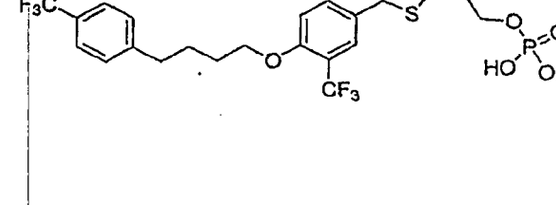






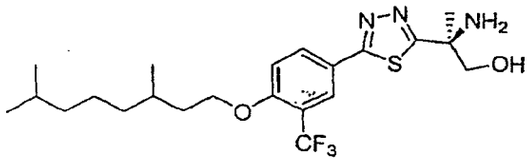
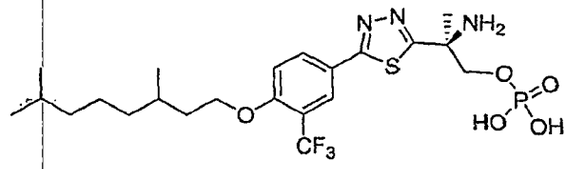
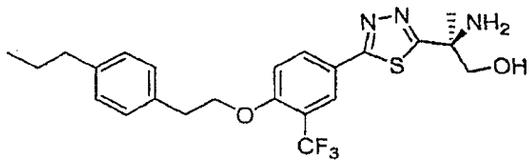
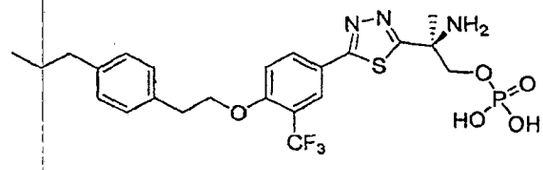
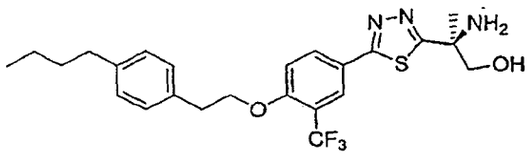
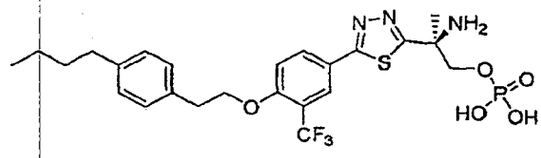
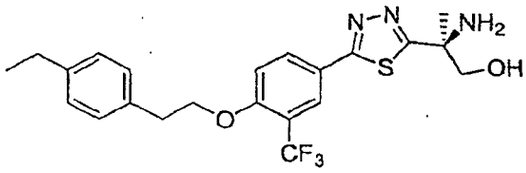
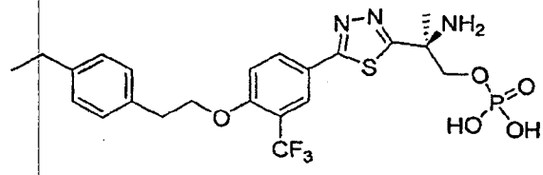
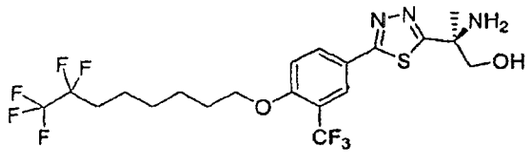
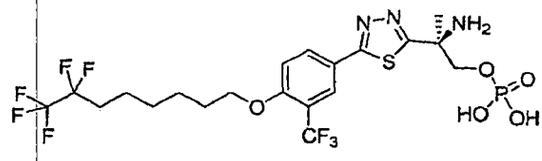
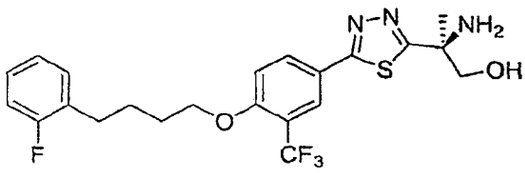
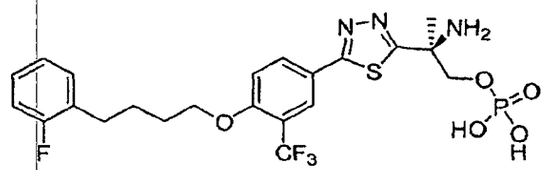
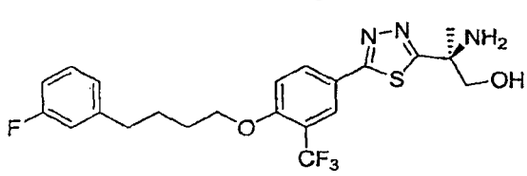
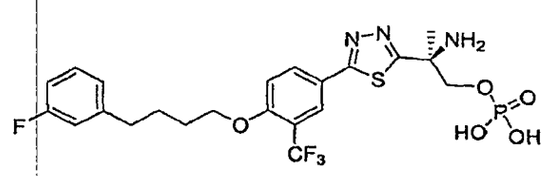
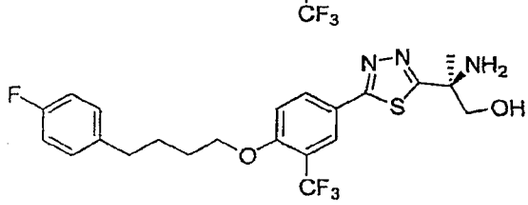
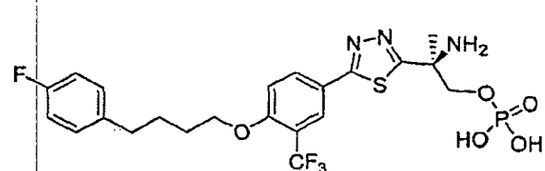
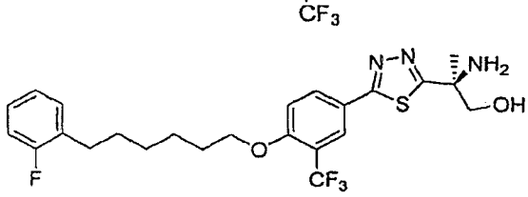
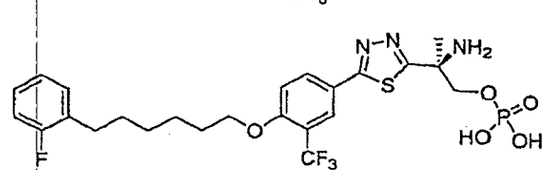


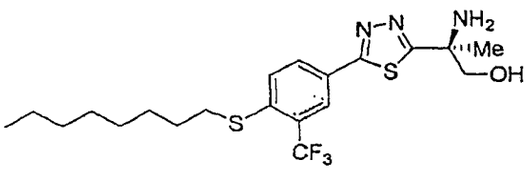


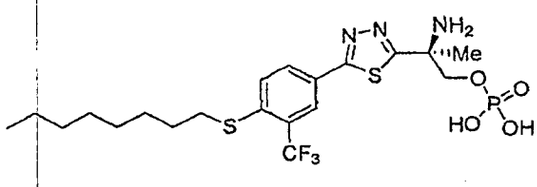


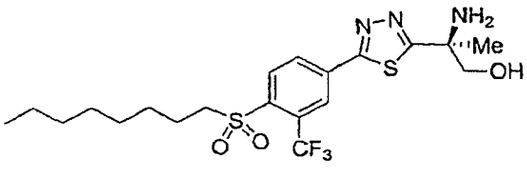


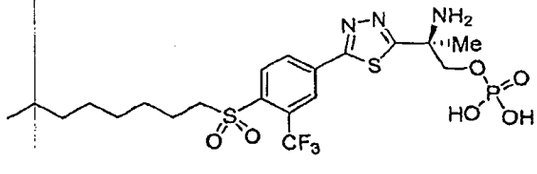
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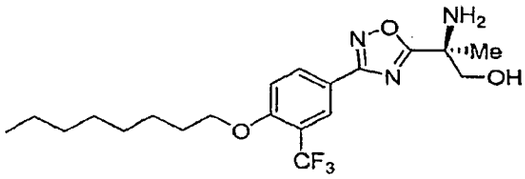



















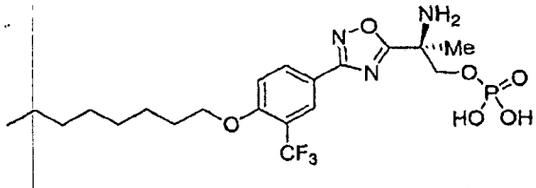


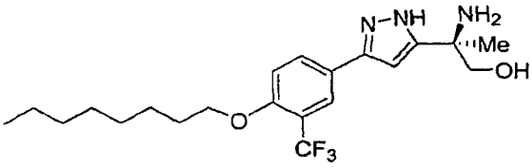


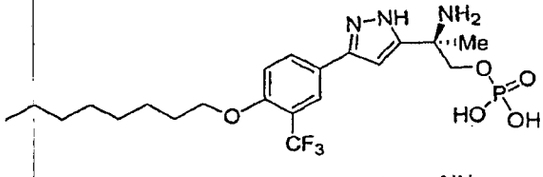


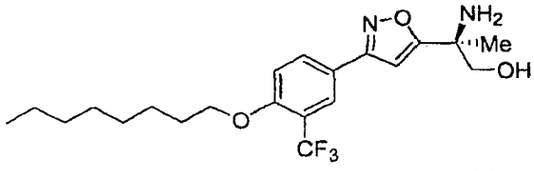


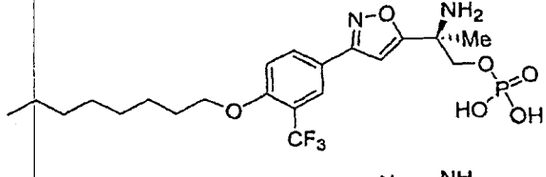


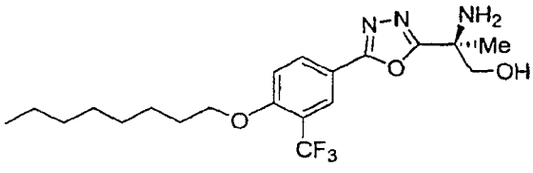


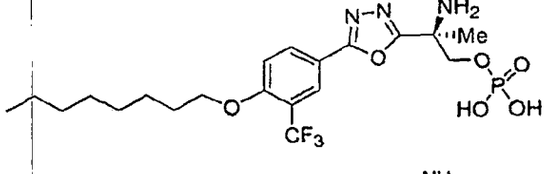


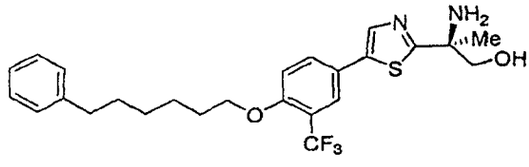


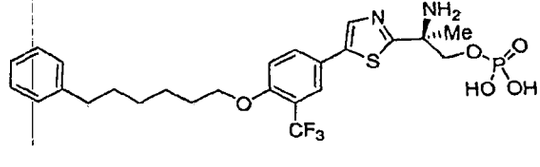


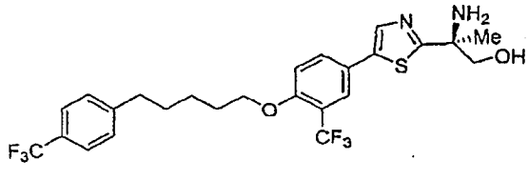


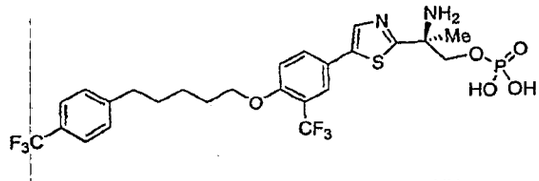


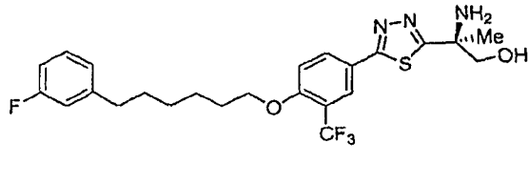


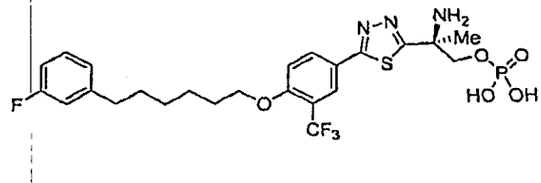




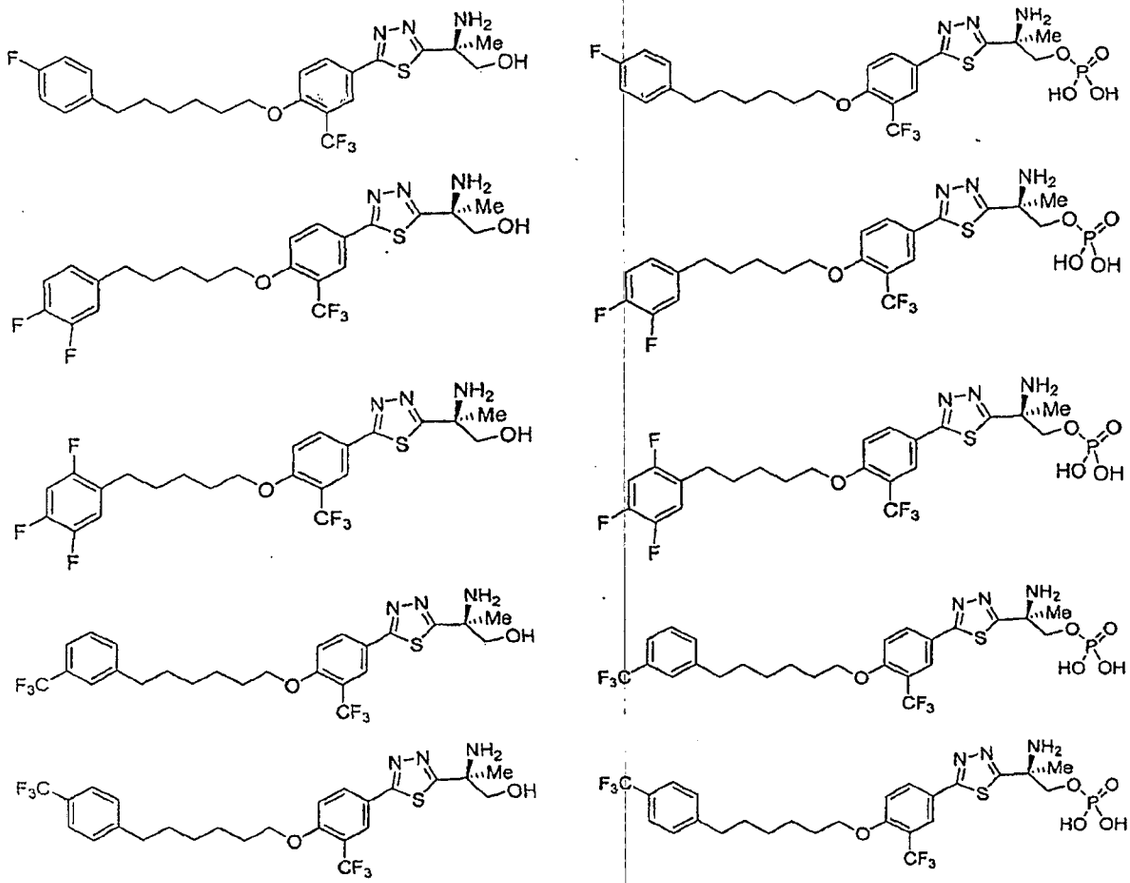






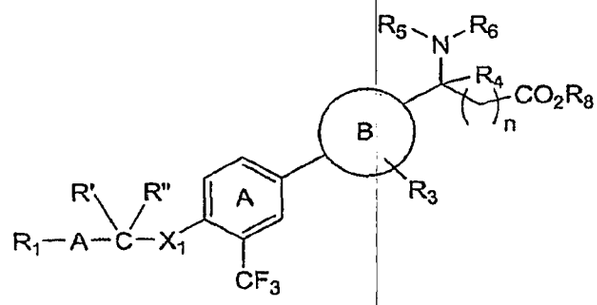






as well as pharmaceutically acceptable salts, phosphate derivatives, phosphate mimics, or phosphate precursor analogs thereof.

In some aspects, the present invention is directed to a compound of formula III:



III

or a pharmaceutically acceptable salt thereof, wherein:

R_1 is hydrogen, halogen, cyano, alkyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, aralkyl, heteroalykl, -O-alkyl, -O-aryl, -O-heteroaryl, -S-alkyl, alkylene-O-alkyl, alkylene-CO_2H, alkylene-CO_2alkyl, alkylSO_2, alkylenesulfonyl, alkylene-CO-amino, alkylene-CO-alkylamino, alkylene-CO-dialkylamino, alkylene-NH-CO_2H, alkylene-NH-CO_2alkyl -CO_2alkyl, -OH, -C(O)-alkyl, -C(O)O-alkyl, -$CONH_2$, -

CO-alkylamino, -CO-dialkylamino, amino, alkylamino, or dialkylamino, any of which may be optionally substituted on carbon with 1, 2, or 3 groups selected from halo, alkyl, haloalkyl, -CF_3, -CN, -OH, or –O-alkyl;

A is (C_1-C_{20})alkylene, (C_2-C_{20})alkenylene, or (C_2-C_{20})alkynylene, each of which may be optionally suibstited on carbon with 1, 2, or 3 groups selected from OH, CO_2H, CO_2alkyl, halogen, amino, alkylamino, dialkylamino, -O-alkyl, alkylene-O-alkyl, alkylene-OH, or alkylene-CO_2H;

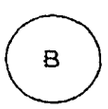
X_1 is a bond or is CH_2, O, -CH_2O-, S, -S(O), -$S(O)_2$, -C(O)-, -C(O)O-, or NR_x, wherein R_x is H or (C_1-C_6)alkyl;

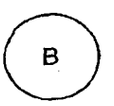
R' and R" are each independently hydrogen, halogen, alkyl optionally substituted on carbon with halogen, alkyl, or taken together with the carbon to which they are attached form C=O or a 3, 4, 5,or 6-membered ring, optionally containing 1 or 2 heteroatoms selected from O NH, N-alkyl, SO, or SO_2, any of which may be optionally substituted on carbon with alkyl or halogen

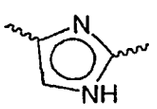
R_3 is absent, hydrogen, halogen, cyano, alkyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, aralkyl, heteroalykl, -O-alkyl, -O-aryl, -O-heteroaryl, aralkoxy, heteroaralkoxy, -S-alkyl, alkylene-O-alkyl, alkylene-CO_2H, alkylene-CO_2alkyl, alkylSO_2, alkylenesulfonyl, alkylene-CO-amino, alkylene-CO-alkylamino, alkylene-CO-dialkylamino, alkylene-NH-CO_2H, alkylene-NH-CO_2alkyl -CO_2alkyl, -OH, -C(O)-alkyl, -C(O)O-alkyl, -$CONH_2$, -CO-alkylamino, -CO-dialkylamino, amino, alkylamino, and dialkylamino, any of which may be optionally substituted on carbon with 1, 2, or 3 groups selected from halo, alkyl, OH, or –O-alkyl;



is phenyl or pyridyl;



is aryl, heteroaryl, heterocyclo, or cycloalkyl, any of which may be optionally substituted on carbon with 1, 2, or 3 groups selected form halogen, alkyl, O-alkyl, CO_2H, CO_2alkyl, halogen, amino, alkylamino, dialkylamino, -O-alkyl, alkylene-O-alkyl, alkylene-OH, or alkylene-CO_2H, provided that 

is not 

;

R_4 is hydrogen, cyano, alkyl, aryl, heteroaryl, alkylene-O-alkyl, alkylene-OH, aryl, alkylene-O-alkyl, -CO_2H, -CO_2-alkyl, alkylene-CO_2H, or alkylene-CO_2-alkyl,

alkylene-OC(O)R wherein R is hydrogen or alkyl; cycloalkyl, heterocycloalkyl, alkylene-NH_2, alkylene-alkylamino, or alkylene-dialkylamino, any of which may be optionally substituted on carbon with 1, 2, or 3 groups selected from OH, CO_2H, CO_2alkyl, halogen, amino, alkylamino, dialkylamino, -O-alkyl, alkylene-O-alkyl, alkylene-OH, or alkylene-CO_2H;

R_5 and R_6 are each independently selected from the group consisting of hydrogen, alkyl, alkylene-OH, aryl, alkylene-O-alkyl, -CO_2H, CO_2-alkyl, alkylene-OC(O)alkyl, cycloalkyl, heterocyclo, -C(O)-alkyl, -C(O)-aryl, C(O)-aralkyl, -C(O)-Oalkyl, -C(O)-Oaryl, -C(O)-Oaralkyl, alkylene-amino, alkylene-alkylamino, and alkylene-dialkylamino, any of which may be optionally substituted on carbon with halogen, alkyl, hydroxyl, CO_2H, CO_2alkyl or alkoxy; or

R_5 and R_6, together with the nitrogen to which they are attached, may form a 3, 4, 5, or 6-membered saturated or unsaturated ring, optionally containing 1 or 2 additional heteroatoms selected from O, S, NH, or N-alkyl, and optionally substituted on carbon with halogen, alkyl, hydroxyl, or alkoxy;

R_8 is hydrogen, alkyl or aryl; and

n is 0, 1, or 2.

In some embodiments, R_1 is aryl or heteroaryl, optionally substituted with 1, 2, or 3 groups selected from halo, alkyl, haloalkyl, -aryl, -CF_3, -CN, -OH, or –O-alkyl. In some embodiments, R_1 is aryl, *e.g.*, phenyl, optionally substituted with 1 or 2 groups selected from -CF_3, -CN, -OMe, -Cl or -F. In some embodiments, R_1 is heteroaryl, *e.g.*, thiophene or benzothiophene, optionally substituted with 1 or 2 groups selected from phenyl, -CF_3, -CN, -OMe, -Cl or -F. In some embodiments, R_1 is hydrogen. In other embodiments, R_1 is phenyl. In some embodiments, R_1 is pyridyl. In other embodiments, R_1 is thiophenyl. In still other embodiments, R_1 is cyclohexyl. In some embodiments, R_1 is cyclopentyl.

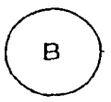
In some embodiments, A is a C_1-C_{10} alkylene. In some embodiments, A is a branched C_1-C_{10} alkylene. In other embodiments, A is n-octyl. In other embodiments, A is n-heptyl. In other embodiments, A is n-hexyl. In some embodiments, A is a C_1-C_5 alkylene. In some embodiments, A is n-pentyl. In other embodiments, A is n-butyl. In still other embodiments, A is n-propyl. In other embodiments, A is ethyl. In still other embodiments, A is methyl.

56

In some embodiments, X_1 is O. In other embodiments, X_1 is S. In still other embodiments, X_1 is SO_2. In some embodiments, X_1 is CH_2. In other embodiments, X_1 is C=O. In still other embodiments, CH_2O, wherein either the oxygen or the carbon may be attached to 

.

In some embodiments, R' is hydrogen. In other embodiments, R' is methyl. In some embodiments, R" is hydrogen. In other embodiments, R" is methyl. In some embodiments, R' and R" taken together with the carbon to which they are attached, is C=O, with the provision that only one of X_1 or R' and R" taken together with the carbon may form C=O.

In some embodiments, R_3 is absent. For example, in the case of compounds where 

is 

, R_3 would be considered absent, because there no substituents on the ring. In other embodiments, R_3 is halogen.

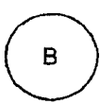
In some embodiments, R_4 is hydrogen. In other embodiments, R_4 is an alkyl, *e.g.*, a C_1-C_4 alkyl. For example, in some embodiments, R_4 is methyl. In some embodiments, R_4 is hydroxymethyl.

In some embodiments, R_5 is hydrogen. In some embodiments, R_6 is hydrogen. In some embodiments, R_5 is an alkyl, *e.g.*, a C_1-C_4 alkyl. In some embodiments, R_6 is an alkyl, *e.g.*, a C_1-C_4 alkyl.

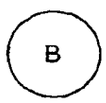
In some embodiments, 

is phenyl. In other embodiments, 

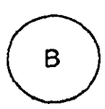
is pyridyl.

In some embodiments, 

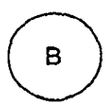
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. In some embodiments, 

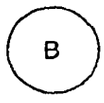
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. In some embodiments, 

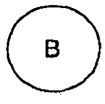
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. In some embodiments, 

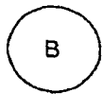
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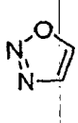
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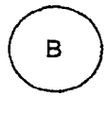
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. In some embodiments, 

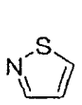
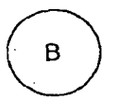
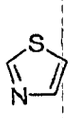
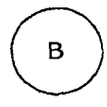
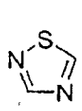
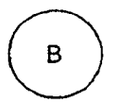
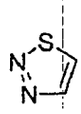
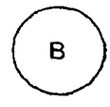
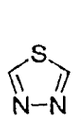
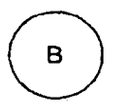
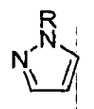
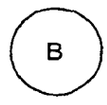
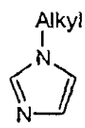
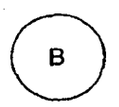
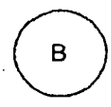
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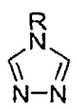
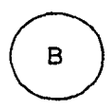
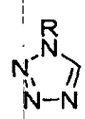
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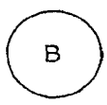
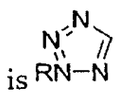
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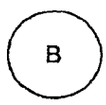
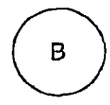
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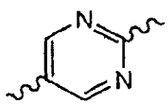
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 . In some embodiments,  is  . In some embodiments,  is  . In some embodiments,  is  . In some embodiments,  is  . In some embodiments,  is  . In some embodiments,  is  . In some embodiments,  is  . In some embodiments, 

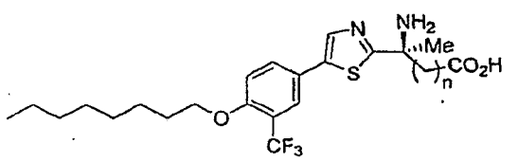
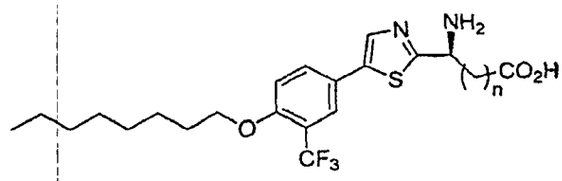
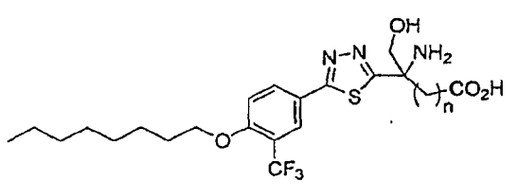
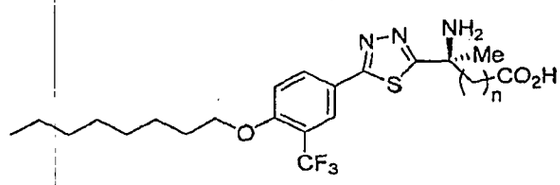
is  . In some embodiments,  is  . In some embodiments,

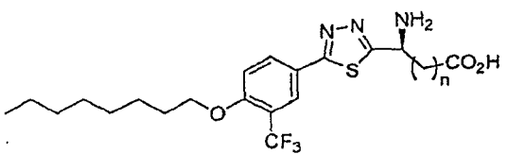
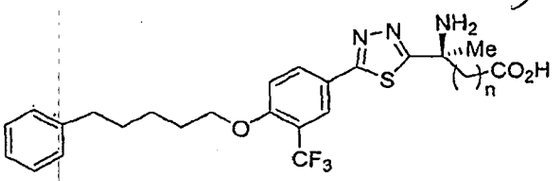
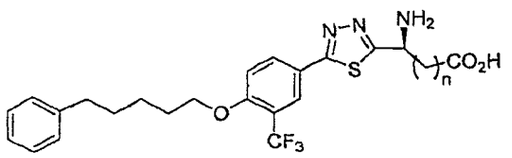
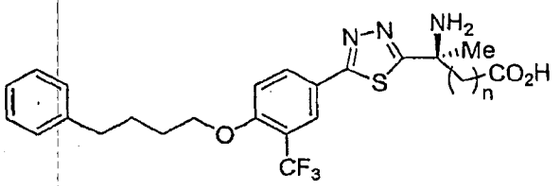
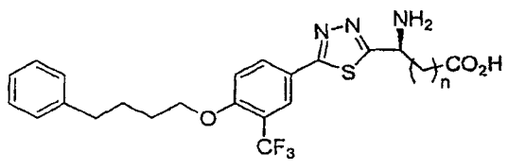
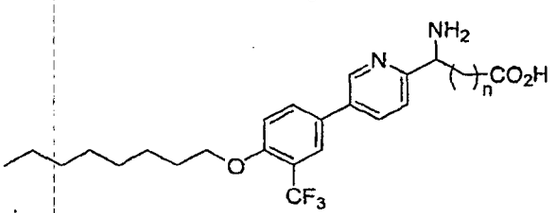
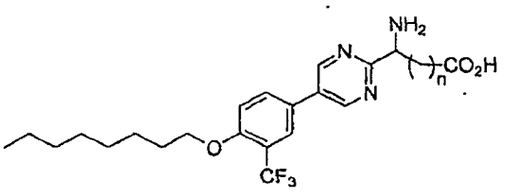
 is  . In each of the above structures, R can be hydrogen or alkyl.

In some embodiments,  is pyridyl. In some embodiments,  is

 , wherein "〰" indicates the points of attachment of the B ring to the remainder of the compound.

In some embodiments, compounds of the present invention include compounds listed in the following table:

wherein n for each compound is 0, 1 or 2, as well as pharmaceutically acceptable salts, phosphate derivatives, phosphate mimics, or phosphate precursor analogs thereof.

Compounds of the present invention include the following compounds:

(*S*)-2-Amino-2-(5-(4-(octyloxy)-3-(trifluoromethyl)phenyl)thiazol-2-yl)propan-1-ol;

2-Amino-2-(5-(4-(octyloxy)-3-(trifluoromethyl)phenyl)thiazol-2-yl)propane-1,3-diol;

(*S*)-2-Amino-2-(5-(4-(octyloxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol;

(*S*)-2-Amino-2-(5-(4-(5-phenylpentyloxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol;

(*S*)-2-Amino-2-(5-(4-(4-phenylbutoxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol;

(*S*)-2-Amino-2-(5-(4-(nonyloxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazole-2-yl)propan-1-ol;

(*S*)-2-Amino-2-(5-(4-(decyloxy)-3(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol;

(*S*)-2-Amino-2-(5-(3-(trifluoromethyl)-4-(5-(4-(trifluoromethyl)phenyl)pentyloxy)phenyl)-1,3,4-thiadiazole-2-yl)propan-1-ol;

(*S*)-2-Amino-2-(5-(3-(trifluoromethyl)-4-(5-(3-(trifluoromethyl)phenyl)pentyloxy)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol;
(*S*)-2-Amino-2-(5-(4-(6-phenylhexyloxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol;
(*S*)-2-Amino-2-(5-(4-(5-(4-fluorophenyl)pentyloxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol;
(*S*)-2-Amino-2-(5-(4-(5-(3-fluorophenyl)pentyloxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol;
(*S*)-2-Amino-2-(5-(4-((4-phenyl-5-(trifluoromethyl)thiophen-2-yl)methoxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol;
(*S*)-2-Amino-2-(5-(4-(7-phenylheptyloxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol;
(*S*)-2-Amino-2-(5-(3-(trifluoromethyl)-4-(2-(trifluoromethyl)phenethoxy)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol;
(*S*)-2-Amino-2-(5-(3-(trifluoromethyl)-4-(3-(trifluoromethyl)phenethoxy)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol;
(*S*)-2-Amino-2-(5-(3-(trifluoromethyl)-4-(4-(trifluoromethyl)phenethoxy)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol;
(*S*)-2-Amino-2-(5-(4-(benzyloxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol;
(*S*)-2-Amino-2-(5-(4-phenethoxy-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol;
(*S*)-2-Amino-2-(5-(4-(3-phenylpropoxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol;
(*S*)-2-Amino-2-(5-(4-(benzofuran-2-ylmethoxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol;
(*S*)-2-Amino-2-(5-(4-(benzo[*b*]thiophen-2-ylmethoxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol;
(*S*)-2-Amino-2-(5-(4-(benzo[*d*][1,3]dioxol-5-ylmethoxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol
(*S*)-2-Amino-2-(5-(3-(trifluoromethyl)-4-(4-(3-(trifluoromethyl)phenyl)butoxy)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol;

(*S*)-2-Amino-2-(5-(3-(trifluoromethyl)-4-(4-(4-(trifluoromethyl)phenyl)butoxy)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol;

(2*S*)-2-Amino-2-(5-(4-(3,7-dimethyloctyloxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol;

(*S*)-2-Amino-2-(5-(4-(4-propylphenethoxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol;

(*S*)-2-Amino-2-(5-(4-(4-butylphenethoxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol;

(*S*)-2-Amino-2-(5-(4-(4-ethylphenethoxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol;

(*S*)-2-Amino-2-(5-(4-(7,7,8,8,8-pentafluorooctyloxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol;

(*S*)-2-Amino-2-(5-(4-(4-(2-fluorophenyl)butoxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol;

(*S*)-2-Amino-2-(5-(4-(4-(3-fluorophenyl)butoxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol;

(*S*)-2-Amino-2-(5-(4-(4-(4-fluorophenyl)butoxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol;

(*S*)-2-Amino-2-(5-(4-(6-(2-fluorophenyl)hexyloxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol;

(*S*)-2-Amino-2-(5-(4-(6-(3-fluorophenyl)hexyloxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol;

(*S*)-2-Amino-2-(5-(4-(6-(4-fluorophenyl)hexyloxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol;

(*S*)-2-Amino-2-(5-(4-(5-(3,4-difluorophenyl)pentyloxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol;

(*S*)-2-Amino-2-(5-(3-(trifluoromethyl)-4-(5-(2,4,5-trifluorophenyl)pentyloxy)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol;

(*S*)-2-Amino-2-(5-(3-(trifluoromethyl)-4-(6-(3-(trifluoromethyl)phenyl)hexyloxy)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol;

(*S*)-2-Amino-2-(5-(3-(trifluoromethyl)-4-(6-(4-(trifluoromethyl)phenyl)hexyloxy)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol;

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(*S*)-2-Amino-2-(5-(4-(octylthio)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol;

(*S*)-2-Amino-2-(5-(4-(octylsulfonyl)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol;

(*S*)-2-Amino-2-(3-(4-(octyloxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)propan-1-ol;

(*R*)-2-Amino-2-(5-(4-(octyloxy)-3-(trifluoromethyl)phenyl)-1*H*-pyrazol-3-yl)propan-1-ol;

(*S*)-2-Amino-2-(3-(4-(octyloxy)-3-(trifluoromethyl)phenyl)isoxazol-5-yl)propan-1-ol;

(*S*)-2-Amino-2-(5-(4-(octyloxy)-3-(trifluoromethyl)phenyl)-1,3,4-oxadiazol-2-yl)propan-1-ol;

(*S*)-2-Amino-2-(5-(4-(6-phenylhexyloxy)-3-(trifluoromethyl)phenyl)thiazol-2-yl)propan-1-ol;

(*S*)-2-Amino-2-(5-(3-(trifluoromethyl)-4-(5-(4-(trifluoromethyl)phenyl)pentyloxy)phenyl) thiazol-2-yl)propan-1-ol;

and pharmaceutically acceptable salts, phosphate derivatives, phosphate mimics, or phosphate precursor analogs thereof.

Compounds of the present invention further include the following compounds:

(*S*)-2-amino-2-(5-(4-(octyloxy)-3-(trifluoromethyl)phenyl)thiazol-2-yl)propyl dihydrogen phosphate;

(*S*)-2-Amino-2-(5-(4-(octyloxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propyl dihydrogen phosphate;

(*S*)-2-Amino-2-(5-(4-(5-phenylpentyloxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propyl dihydrogen phosphate;

(*S*)-2-Amino-2-(5-(4-(4-phenylbutoxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propyl dihydrogen phosphate;

(*S*)-2-Amino-2-(5-(4-(octylthio)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propyl dihydrogen phosphate;

(*S*)-2-Amino-2-(5-(4-(nonyloxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propyl dihydrogen phosphate;

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(*S*)-2-Amino-2-(5-(3-(trifluoromethyl)-4-(5-(3-(trifluoromethyl)phenyl)pentyloxy)phenyl)-1,3,4-thiadiazol-2-yl)propyl dihydrogen phosphate;

(*S*)-2-Amino-2-(5-(3-(trifluoromethyl)-4-(5-(4-(trifluoromethyl)phenyl)pentyloxy)phenyl)-1,3,4-thiadiazol-2-yl)propyl dihydrogen phosphate;

(*S*)-2-Amino-2-(5-(4-((4-phenyl-5-(trifluoromethyl)thiophen-2-yl)methoxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propyl dihydrogen phosphate;

(*S*)-2-Amino-2-(5-(4-(6-phenylhexyloxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propyl dihydrogen phosphate;

(*S*)-2-Amino-2-(5-(4-(5-(3-fluorophenyl)pentyloxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propyl dihydrogen phosphate;

(*S*)-2-Amino-2-(5-(4-(5-(4-fluorophenyl)pentyloxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propyl dihydrogen phosphate;

(*S*)-2-Amino-2-(5-(3-(trifluoromethyl)-4-(4-(3-(trifluoromethyl)phenyl)butoxy)phenyl)-1,3,4-thiadiazol-2-yl)propyl dihydrogen phosphate;

(*S*)-2-Amino-2-(5-(4-(4-(4-fluorophenyl)butoxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propyl dihydrogen phosphate;

(*S*)-2-Amino-2-(5-(4-(6-(3-fluorophenyl)hexyloxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propyl dihydrogen phosphate;

(*S*)-2-Amino-2-(5-(4-(6-(4-fluorophenyl)hexyloxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propyl dihydrogen phosphate;

(*S*)-2-Amino-2-(5-(4-(5-(3,4-difluorophenyl)pentyloxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propyl dihydrogen phosphate;

(*S*)-2-Amino-2-(5-(3-(trifluoromethyl)-4-(5-(2,4,5-trifluorophenyl)pentyloxy)phenyl)-1,3,4-thiadiazol-2-yl)propyl dihydrogen phosphate;

(*S*)-2-Amino-2-(3-(4-(octyloxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)propyl dihydrogen phosphate;

(*R*)-2-Amino-2-(3-(4-(octyloxy)-3-(trifluoromethyl)phenyl)-1*H*-pyrazol-5-yl)propyl dihydrogen phosphate;

(*S*)-2-Amino-2-(3-(4-(octyloxy)-3-(trifluoromethyl)phenyl)isoxazol-5-yl)propyl dihydrogen phosphate;

(*S*)-2-Amino-2-(5-(4-(octyloxy)-3-(trifluoromethyl)phenyl)-1,3,4-oxadiazol-2-yl)propyl dihydrogen phosphate;
(*S*)-2-Amino-2-(5-(4-(6-phenylhexyloxy)-3-(trifluoromethyl)phenyl)thiazol-2-yl)propyl dihydrogen phosphate; and
(*S*)-2-Amino-2-(5-(3-(trifluoromethyl)-4-(5-(4-(trifluoromethyl)phenyl)pentyloxy)phenyl) thiazol-2-yl)propyl dihydrogen phosphate.

Biological Activity of Invention Compounds

Lymphopenia Assay

Several of the compounds described herein were evaluated for the ability to induce lymphopenia in mice. Male C57Bl/6 mice were divided into groups of three. A control group received the 3% BSA vehicle only. The other groups received a single dose of either a specified dose of test compound in vehicle administered orally (PO) and intravenously (IV). After 6 hours, the mice were anesthesized with isoflurane and approximately 250 μL of blood was removed from the retroorbital sinus and collected in an EDTA microtainer, mixed with an anticoagulant and placed on a tilt table until complete blood count (CBC) analysis. Oral administration (10 mg/K) of these compounds induced increased lymphopenia versus the vehicle.

A 10mg/Kg oral dose of (*S*)-2-amino-2-(5-(4-(octyloxy)-3-(trifluoromethyl)phenyl)thiazol-2-yl)propan-1-ol produced a lymphopenia of 75% in this assay.

A 10mg/Kg oral dose of (*S*)-2-amino-2-(5-(4-(octyloxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol produced a lymphopenia of 77% in this assay.

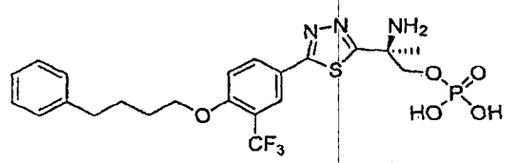
Binding to S1P-1 or S1P-3 Receptors

In certain embodiments, the compounds of the invention selective for the S1P-1 receptor as compared to one or more of the other S1P receptors. For example, one set of compounds includes compounds which are selective for the S1P-1 receptor relative to the S1P-3 receptor. Compounds selective for the S1P-1 receptor can be agonists of the S1P-1 receptor, significantly weaker agonists of one or more other receptors and/or antagonists of one or more other receptors. A compound is "selective" for the S1P-1

receptor relative to a second receptor, if the EC_{50} of the compound for the second receptor is at least two-fold greater than the EC_{50} for the S1P-1 receptor. The EC_{50} of a compound is determined using the ^{35}S-GTPγS binding assay, as described in WO 03/061567, the entire contents of which are incorporated herein by reference.

Additionally or alternatively, a compound is "selective" for the S1P-1 receptor relative to a second receptor, if the IC_{50} of the compound for the second receptor is at least two-fold greater than the IC_{50} for the S1P-1 receptor. The IC_{50} of a compound is determined using the [^{33}P]sphingosine 1-phosphate binding assay, as described in Davis, M.D. *et al.*, Sphingosine 1-Phosphate Analogs as Receptor Antagonists. *J. Biol. Chem.* (2005) 280:9833-9841, the entire contents of which are incorporated herein by this reference.

The terms "agonist" or "S1P-1 receptor agonist" as used herein include the compounds described herein which bind to and/or agonize the S1P-1 receptor. In one embodiment, the S1P receptor agonists have an IC_{50} for the S1P-1 receptor of about 100 nM - 0.25 nM, about 50 nM – 0.25 nM, about 25 nM – 0.5 nM, about 100 nM or less, about 75 nM or less, about 50 nM or less, about 40 nM or less, about 30 nM or less, about 20 nM or less, about 10 nM or less, about 5 nM or less, about 1 nM or less, about 0.5 nM or less, or about 0.25 nM or less. The compounds' IC_{50} for the S1P-1 receptor can be measured using the binding assays described in Example 13 or those described in WO 03/061567. Compounds of the invention generally had an IC_{50} in the range of 100 pM (picomolar) to 100 M.

For example,  had an IC_{50} 3.23 nM

Ranges intermediate to the above recited values are also intended to be part of this invention. For example, ranges using a combination of any of the above recited values as upper and/or lower limits are intended to be included.

In a further embodiment, the S1P receptor agonist has an IC_{50} value for the S1P-3 receptor of about 10 nM - 10,000 nM, about 100 nM – 5000 nM, about 100 nM – 3000 nM, about 10 nM or greater, about 20 nM or greater, about 40 nM or greater, about 50 nM or greater, about 75 nM or greater, or about 100 nM or greater. In another embodiment, the S1P compound of the invention binds the S1P-3 receptor with an IC_{50} of 1000 nM or greater, 2000 nM or greater, 3000 nM or greater, 5000 nM or greater,

10,000 nM or greater. The IC_{50} for of S1P-3 receptor can be measured using the binding assays described herein or those described in WO 03/061567.

In addition, it should be understood that the ranges intermediate to the above recited values are also intended to be part of this invention. For example, ranges using a combination of any of the above recited values as upper and/or lower limits are intended to be included.

In yet another embodiment, the S1P receptor agonists described herein have an IC_{50} value for the S1P-1 receptor that is about 5-fold lower, about 10-fold lower, about 20-fold lower, about 50-fold lower, about 100-fold lower, about 200-fold lower, about 500-fold lower or about 1000-fold lower than their IC_{50} value for the S1P-3 receptor.

Ranges intermediate to the above recited values are also intended to be part of this invention. For example, ranges using a combination of any of the above recited values as upper and/or lower limits are intended to be included.

The ability of several of the compounds described herein to bind to the S1P-1 or S1P-3 receptor was also tested as follows.

For the membrane preparation, plasmid DNA was transfected into HEK 293 T cells using the FuGENE 6 transfection protocol (publicly available from Roche). Briefly, subconfluent monolayers of HEK 293 T cells were transfected with the DNA mixture containing FuGENE 6 (using a 1:3 ratio). The dishes containing the cells were then placed in a tissue culture incubator (5% CO_2, 37°C). The cells were harvested 48 hours after addition of the DNA by scraping in HME buffer (in mM: 20 HEPES, 5 $MgCl_2$, 1 EDTA, pH 7.4, 1 mM PMSF) containing 10% sucrose on ice, and disrupted using a Dounce homogenizer. After centrifugation at 800 × *g*, the supernatant was diluted with HME without sucrose and centrifuged at 17,000 × *g* for 1 hour. This crude membrane pellet was resuspended in HME with sucrose, aliquoted, and snap-frozen by immersion in liquid nitrogen. The membranes were stored at -70 C. Protein concentration was determined spectroscopically by Bradford protein assay.

For the binding assay, [^{33}P]sphingosine 1-phosphate (obtained from American Radiolabeled Chemicals, Inc) was added to membranes in 200 µl in 96-well plates with assay concentrations of 2.5 pM [^{33}P]sphingosine 1-phosphate, 4 mg/ml BSA, 50 mM HEPES, pH 7.5, 100 mM NaCl, 5 mM MgCl2, and 5 µg of protein. Binding was performed for 60 minutes at room temperature with gentle mixing and terminated by collecting the membranes onto GF/B filter plates. After drying the filter plates for 10

minutes, 50 µl of Microscint 40 was added to each well, and filter-bound radionuclide was measured on a Packard Top Count. Nonspecific binding was defined as the amount of radioactivity remaining in the presence of excess of unlabeled S1P.

GTPgS assay Protocol

Membrane preparation

For membrane preparations all steps were performed at 4°C. Rat hepatoma cells stably expressing the human S1P1 receptor or Rat Basophilic Leukaemia cells (RBL) stably expressing human S1P3 receptor were grown to 80% confluency before being harvested into 10ml Phospho-Buffered Saline (PBS) and centrifuged at 1200rpm for 5 minutes. After removal of the supernatant, the pellet was re-suspended and cells were homogenised within a glass Waring blender for 2 bursts of 15secs in 200mls of buffer (50mM HEPES, 1mM leupeptin, 25ug/ml bacitracin, 1mM EDTA, 1mM PMSF, 2uM pepstatin A). The blender was plunged into ice for 5 mins after the first burst and 10-40 mins after the final burst to allow foam to dissipate. The material was then spun at 500g for 20 mins and the supernatant spun for 36 mins at 48,000g. The pellet was resuspended in the same buffer as above but without PMSF and pepstatin A. The material was then forced through a 0.6mm needle, made up to the required volume, (usually x4 the volume of the original cell pellet), aliquoted and stored frozen at –80°C.

GTPgS assay

Human S1P1 rat hepatoma or S1P3 expressing RBL membranes (1.5ug/well) were adhered to WGA-coated SPA beads (0.125mg/well) in assay buffer (HEPES 20mM, $MgCl_2$ 3mM, NaCl 100mM and pH adjusted to 7.4 using KOH 5M, GDP 10uM FAC and saponin 90ug/well FAC was also added).

After 30minutes pre-coupling at 4°C the bead and membrane suspension was dispensed into a white Greiner polypropylene LV384-well plate (5ul/well), containing 0.1ul of test compound or S1P. 5ul/well [^{35}S]-GTP□S (0.5nM final radio-ligand conc) made up in assay buffer was then added to the plates. The final assay cocktail (10.1ul) was centrifuged at 1000rpm for 5minutes then read immediately on a Viewlux.

All test compounds were dissolved in DMSO at a concentration of 10mM and were prepared in 100% DMSO using a 1 in 4 dilution step to provide 11 point dose

response curves. The dilutions were transferred to the assay plates ensuring that the DMSO concentration was constant across the plate for all assays.

All data was normalized to the mean of 16 high and 16 low control wells on each plate. A four parameter curve fit was then applied.

The trifluoracetic acid salt of (*S*)-2-amino-2-(5-(4-(octyloxy)-3-(trifluoromethyl)phenyl)thiazol-2-yl)propyl dihydrogen phosphate had a pEC50 of 8.5 in the S1P1 assay and pEC50 of 6.5 in the S1P3 assay.

The trifluoracetic acid salt of (*S*)-2-Amino-2-(5-(4-(octyloxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propyl dihydrogen phosphate had a pEC50 of 9.2 in the S1P1 assay and pEC50 of 6.1 in the S1P3 assay.

Methods of Using Invention Compounds

The compounds of the invention have been determined to be useful in the treatment of sphingosine 1-phosphate associated disorders. Accordingly, in one embodiment, the invention relates to a method for treating a subject suffering from a sphingosine 1-phosphate associated disorder, comprising administering to a subject an effective amount of a compound of the invention; that is, a compound of formula I or compounds otherwise described herein, such that the subject is treated for a sphingosine 1-phosphate associated disorder.

The term "sphingosine 1-phosphate associated disorder" includes disorders, diseases or conditions which are associated with or caused by a misregulation in S1P receptor function and/or signaling or S1P receptor ligand function. The term also includes diseases, disorders or conditions which can be treated by administering to a subject an effective amount of a sphingosine 1-phosphate receptor agonist. Such disorders include disorders that are associated with an inappropriate immune response and conditions associated with an overactive immune response, *e.g.*, autoimmune diseases. In some embodiments, sphingosine 1-phosphate associated disorders include autoimmune diseases. In other embodiments, sphingosine 1-phosphate associated disorders include inflammation. In further embodiments, sphingosine 1-phosphate associated disorders include transplant rejection. In still other embodiments,

sphingosine 1-phosphate associated disorders include acute respiratory distress syndrome (ARDS). In other embodiments, sphingosine 1-phosphate associated disorders include asthma. In yet other embodiments, sphingosine 1-phosphate associated disorders include any combination of the disorders listed herein.

"Treatment", or "treating" as used herein, is defined as the application or administration of a therapeutic agent such as a compound of formula I to a subject who has a shingosine 1-phosphate associated disorder as described herein, with the purpose to cure, heal, alleviate, delay, relieve, alter, remedy, ameliorate, improve or affect the disease or disorder, or symptoms of the disease or disorder. The term "treatment" or "treating" is also used herein in the context of administering agents prophylactically.

In some embodiments, the efficacy of the compounds of the present invention can be measured by comparing a value, level, feature, characteristic, property, *etc.* to a "suitable control". A "suitable control" is any control or standard familiar to one of ordinary skill in the art useful for comparison purposes. In one embodiment, a "suitable control" is a value, level, feature, characteristic, property, *etc.* determined prior to administering a composition of the present invention. For example, the immune response, *etc.* can be determined prior to introducing a compound of the invention into a cell or subject. In another embodiment, a "suitable control" is a value, level, feature, characteristic, property, *etc.* determined in a cell or organism, *e.g.*, a control or normal cell or organism, exhibiting, for example, normal traits. In yet another embodiment, a "suitable control" is a predefined value, level, feature, characteristic, property, *etc.* For example a "suitable control" can be a pre-defined level of binding to a specified S1P receptor.

An additional embodiment of the invention pertains to a method for treating a subject suffering from a sphingosine 1-phosphate associated disorder, comprising administering to a subject a compound, such that the subject is treated for a sphingosine 1-phosphate associated disorder by a compound of the invention; that is, a compound of formulae I or compounds otherwise described herein.

The present invention is also directed to a method of selectively treating a sphingosine 1-phosphate associated disorder, comprising administering to a subject an effective amount of a compound of the invention, *e.g.*, compounds of any of Formulae I-VIII or compounds otherwise described herein, such that the subject is selectively treated for a sphingosine 1-phosphate associated disorder. In certain embodiments, the

sphingosine 1-phosphate associated disorder is a sphingosine 1-phosphate-(1) associated disorder. In a particular embodiment, the sphingosine 1-phosphate-(1) associated disorder is selectively treated as compared with a sphingosine 1-phosphate-(3) associated disorder.

Another embodiment of the invention is a method of selectively treating a sphingosine 1-phosphate associated disorder, comprising administering to a subject a compound, such that the subject is selectively treated for a sphingosine 1-phosphate associated disorder by a compound of the invention, *e.g.*, compounds of any of Formulae I-VIII or compounds otherwise described herein. In certain embodiments, the sphingosine 1-phosphate associated disorder is a sphingosine 1-phosphate-(1) associated disorder. In a particular embodiment, the sphingosine 1-phosphate-(1) associated disorder is selectively treated as compared with a sphingosine 1-phosphate-(3) associated disorder.

In another embodiment, the present invention provides a method of treating a condition associated with an activated immune system. Such diseases or disorders include multiple sclerosis as well as rejection of transplanted organs, tissue or cells; graft-versus-host diseases brought about by transplantation; autoimmune syndromes including rheumatoid arthritis; systemic lupus erythematosus; antiphospholipid syndrome; Hashimoto's thyroiditis; lymphocytic thyroiditis;; myasthenia gravis; type I diabetes; uveitis; episcleritis; scleritis; Kawasaki's disease, uveo-retinitis; posterior uveitis; uveitis associated with Behcet's disease; uveomeningitis syndrome; allergic encephalomyelitis; chronic allograft vasculopathy; post-infectious autoimmune diseases including rheumatic fever and post-infectious glomerulonephritis; inflammatory and hyperproliferative skin diseases; psoriasis; psoriatic arthritis; atopic dermatitis; myopathy; myositis; osteomyelitis; contact dermatitis; eczematous dermatitis; seborrhoeic dermatitis; lichen planus; pemphigus; bullous pemphigoid; epidermolysis bullosa; urticaria; angioedema; vasculitis; erythema; cutaneous eosinophilia; acne; scleroderma; alopecia areata; keratoconjunctivitis; vernal conjunctivitis; keratitis; herpetic keratitis; dystrophia epithelialis corneas; corneal leukoma; ocular pemphigus; Mooren's ulcer; ulcerative keratitis; scleritis; Graves' ophthalmopathy; Vogt-Koyanagi-Harada syndrome; sarcoidosis; pollen allergies; reversible obstructive airway disease; bronchial asthma; allergic asthma; intrinsic asthma; extrinsic asthma; dust asthma; chronic or inveterate asthma; late asthma and airway hyper-responsiveness;

bronchiolitis; bronchitis; endometriosis; orchitis; gastric ulcers; ischemic bowel diseases; inflammatory bowel diseases; necrotizing enterocolitis; intestinal lesions associated with thermal burns; coeliac disease; proctitis; eosinophilic gastroenteritis; mastocytosis; Crohn's disease; ulcerative colitis; vascular damage caused by ischemic diseases and thrombosis; atherosclerosis; fatty heart; myocarditis; cardiac infarction; aortitis syndrome; cachexia due to viral disease; vascular thrombosis; migraine; rhinitis; eczema; interstitial nephritis; IgA-induced nephropathy; Goodpasture's syndrome; hemolytic- uremic syndrome; diabetic nephropathy; glomerulosclerosis; glomerulonephritis; tubulointerstitial nephritis; interstitial cystitis; multiple myositis; Guillain-Barre syndrome; Meniere's disease; polyneuritis; multiple neuritis; myelitis; mononeuritis; radiculopathy; hyperthyroidism; Basedow's disease; thyrotoxicosis; pure red cell aplasia; aplastic anemia; hypoplastic anemia; idiopathic thrombocytopenic purpura; autoimmune hemolytic anemia; autoimmune thrombocytopenia; agranulocytosis; pernicious anemia; megaloblastic anemia; anerythroplasia; osteoporosis; fibroid lung; idiopathic interstitial pneumonia; dermatomyositis; leukoderma vulgaris; ichthyosis vulgaris; photoallergic sensitivity; cutaneous T cell lymphoma; polyarteritis nodosa; Huntington's chorea; Sydenham's chorea; myocardosis; myocarditis; scleroderma; Wegener's granuloma; Sjogren's syndrome; adiposis; eosinophilic fascitis; lesions of gingiva, periodontium, alveolar bone, substantia ossea dentis; male pattern alopecia or alopecia senilis; muscular dystrophy; pyoderma; Sezary's syndrome; hypophysitis; chronic adrenal insufficiency; Addison's disease; ischemia-reperfusion injury of organs which occurs upon preservation; endotoxin shock; pseudomembranous colitis; colitis caused by drug or radiation; ischemic acute renal insufficiency; chronic renal insufficiency; lung solid cancer; malignancy of lymphoid origin; acute or chronic lymphocytic leukemias; lymphoma; psoriasis; pulmonary emphysema; cataracts; siderosis; retinitis pigmentosa; senile macular degeneration; vitreal scarring; corneal alkali burn; dermatitis erythema; ballous dermatitis; cement dermatitis; gingivitis; periodontitis; sepsis; pancreatitis; peripheral artery disease; carcinogenesis; solid cancer tumors; metastasis of carcinoma; hypobaropathy; autoimmune hepatitis; primary biliary cirrhosis; sclerosing cholangitis; partial liver resection; acute liver necrosis; cirrhosis; alcoholic cirrhosis; hepatic failure; fulminant hepatic failure; late-onset hepatic failure; "acute-on-chronic" liver failure.

As used herein, the term "subject" includes warm-blooded animals, *e.g.*, mammals, including humans, cats, dogs, horses, bears, lions, tigers, ferrets, rabbits, mice, cows, sheep, pigs, etc. In a particular embodiment, the subject is a primate. In a specific embodiment, the primate is a human.

As used herein, the term "administering" to a subject includes dispensing, delivering or applying a compound of the invention in a pharmaceutical formulation (as described herein), to a subject by any suitable route for delivery of the compound to the desired location in the subject, including delivery by either the parenteral or oral route, intramuscular injection, subcutaneous/intradermal injection, intravenous injection, buccal administration, topical delivery, transdermal delivery and administration by the rectal, colonic, vaginal, intranasal or respiratory tract route.

As used herein, the term "effective amount" includes an amount effective, at dosages and for periods of time necessary, to achieve the desired result, *e.g.*, sufficient to treat the condition in a subject. An effective amount of a compound of the invention, as defined herein, may vary according to factors such as the disease state, age, and weight of the subject, and the ability of the compound to elicit a desired response in the subject. Dosage regimens may be adjusted to provide the optimum therapeutic response. An effective amount is also one in which any toxic or detrimental effects (*e.g.*, side effects) of the compound are outweighed by the therapeutically beneficial effects.

A therapeutically effective amount of a compound of the invention (i.e., an effective dosage) may range from about 0.001 to 30 mg/kg body weight, for example, about 0.01 to 25 mg/kg body weight, for example, about 0.1 to 20 mg/kg body weight. It is to be understood that all values and ranges between those listed are intended to be encompassed by the present invention. The skilled artisan will appreciate that certain factors may influence the dosage required to effectively treat a subject, including but not limited to the severity of the disease or disorder, previous treatments, the general health and/or age of the subject, and other diseases present. Moreover, treatment of a subject with a therapeutically effective amount of a compound of the invention can include a single treatment or, for example, can include a series of treatments. It will also be appreciated that the effective dosage of the compound used for treatment may increase or decrease over the course of a particular treatment.

The methods of the invention further include administering to a subject a therapeutically effective amount of a compound of the invention in combination with

another pharmaceutically active compound known to treat the disease or condition, *e.g.*, an immunomodulatory agent or an anti-inflammatory agent. Pharmaceutically active compounds that may be used depend upon the condition to be treated, but include as examples cyclosporin, rapamycin, FK506, methotrexate, etanercept, infliximab, adalimumab, non-steroidal anti-inflammatory agents, cyclooxygenase-2-inhibitors, such as celecoxib and rofecoxib, and corticosteroids. Other suitable compounds can be found in Harrison's Principles of Internal Medicine, Thirteenth Edition, Eds. T. R. Harrison et al. McGraw-Hill N.Y., N.Y.; and the Physicians Desk Reference 50th Edition 1997, Oradell New Jersey, Medical Economics Co., the complete contents of which are expressly incorporated herein by reference. The compound of the invention and the additional pharmaceutically active compound may be administered to the subject in the same pharmaceutical composition or in different pharmaceutical compositions (at the same time or at different times).

Pharmaceutical Compositions Comprising Invention Compounds

The present invention also provides pharmaceutically acceptable formulations and compositions comprising one or more compounds of the invention; that is, compounds of formula I or compounds otherwise described herein. In certain embodiments, the compound of the invention is present in the formulation in a therapeutically effective amount; that is, an amount effective to treat a sphingosine 1-phosphate associated disorder.

Accordingly, in one embodiment, the invention pertains to a pharmaceutical composition comprising a therapeutically effective amount of a compound of the invention; that is, compounds of formula I or compounds otherwise described herein, and a pharmaceutically acceptable carrier.

In another embodiment, the invention is directed to a packaged pharmaceutical composition comprising a container holding a therapeutically effective amount of a compound of the invention; that is, compounds of formula I or compounds otherwise described herein; and instructions for using the compound to treat a sphingosine 1-phosphate associated disorder in a subject.

The term "container" includes any receptacle for holding the pharmaceutical composition. For example, in one embodiment, the container is the packaging that contains the pharmaceutical composition. In other embodiments, the container is not the

packaging that contains the pharmaceutical composition, *i.e.*, the container is a receptacle, such as a box or vial that contains the packaged pharmaceutical composition or unpackaged pharmaceutical composition and the instructions for use of the pharmaceutical composition. Moreover, packaging techniques are well known in the art. It should be understood that the instructions for use of the pharmaceutical composition may be contained on the packaging containing the pharmaceutical composition, and as such the instructions form an increased functional relationship to the packaged product. However, it should be understood that the instructions can contain information pertaining to the compound's ability to perform its intended function, *e.g.*, treating, preventing, or reducing a sphingosine 1-phosphate associated disorder in a subject.

Another embodiment of the invention relates to a packaged pharmaceutical composition comprising a container holding a therapeutically effective amount of a compound of the invention; that is, a compound of formula I or compounds otherwise described herein, and instructions for using the compound to selectively treat a sphingosine 1-phosphate associated disorder in a subject.

Such pharmaceutically acceptable formulations typically include one or more compounds of the invention as well as one or more pharmaceutically acceptable carriers and/or excipients. As used herein, "pharmaceutically acceptable carrier" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like that are physiologically compatible. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the compounds of the invention, use thereof in the pharmaceutical compositions is contemplated.

Supplementary pharmaceutically active compounds known to treat transplant or autoimmune disease, i.e., immunomodulatory agents and anti-inflammatory agents, as described above, can also be incorporated into the compositions of the invention. Suitable pharmaceutically active compounds that may be used can be found in Harrison's Principles of Internal Medicine.

A pharmaceutical composition of the invention is formulated to be compatible with its intended route of administration. Examples of routes of administration include parenteral, *e.g.*, intravenous, intradermal, subcutaneous, oral (*e.g.*, inhalation), transdermal (topical), transmucosal, and rectal administration. Solutions or suspensions

used for parenteral, intradermal, or subcutaneous application can include the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose. pH can be adjusted with acids or bases, such as hydrochloric acid or sodium hydroxide. The parenteral preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic.

Pharmaceutical compositions suitable for injection include sterile aqueous solutions (where water soluble) or dispersions, or sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. For intravenous administration, suitable carriers include physiological saline, bacteriostatic water, Cremophor El™ (BASF, Parsippany, N.J.) or phosphate buffered saline (PBS). In all cases, the pharmaceutical composition must be sterile and should be fluid to the extent that easy syringability exists. It must also be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyetheylene glycol, and the like), and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Prevention of the action of microorganisms can be achieved by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, ascorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as mannitol, sorbitol, or sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, aluminum monostearate and gelatin.

Sterile injectable solutions can be prepared by incorporating the compound of the invention in the required amount in an appropriate solvent with one or a combination of the ingredients enumerated above, as needed, followed by filtered sterilization.

Generally, dispersions are prepared by incorporating the compound into a sterile vehicle which contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and freeze-drying which yields a powder of the compound plus any additional desired ingredient from a previously sterile-filtered solution thereof.

Oral compositions generally include an inert diluent or an edible carrier. They can be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic administration, the compound of the invention can be incorporated with excipients and used in the form of tablets, troches, or capsules. Oral compositions can also include an enteric coating. Oral compositions can also be prepared using a fluid carrier for use as a mouthwash, wherein the compound in the fluid carrier is applied orally and swished and expectorated or swallowed. Pharmaceutically compatible binding agents, and/or adjuvant materials can be included as part of the composition. The tablets, pills, capsules, troches and the like can contain any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate or Sterotes; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring.

For administration by inhalation, the compounds of the invention are delivered in the form of an aerosol spray from a pressured container or dispenser which contains a suitable propellant, *e.g.*, a gas such as carbon dioxide, or a nebulizer.

Systemic administration can also be by transmucosal or transdermal means. For transmucosal or transdermal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art, and include, for example, for transmucosal administration, detergents, bile salts, and fusidic acid derivatives. Transmucosal administration can be accomplished through the use of nasal sprays or suppositories. For transdermal administration, the compounds of the invention are formulated into ointments, salves, gels, or creams as generally known in the art.

The present pharmaceutical compositions can also be prepared in the form of suppositories (*e.g.*, with conventional suppository bases such as cocoa butter and other glycerides) or retention enemas for rectal delivery.

In one embodiment, the compounds are prepared with carriers that will protect the compound against rapid elimination from the body, such as a controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Methods for preparation of such formulations will be apparent to those skilled in the art. The materials can also be obtained commercially from Alza Corporation and Nova Pharmaceuticals, Inc. Liposomal suspensions can also be used as pharmaceutically acceptable carriers. These can be prepared according to methods known to those skilled in the art, for example, as described in U.S. Pat. No. 4,522,811, U.S. Pat. No. 5,455,044 and U.S. Pat. No. 5,576,018, and U.S. Pat. No. 4,883,666, the contents of all of which are incorporated herein by reference.

The compounds of the invention can also be incorporated into pharmaceutical compositions which allow for the sustained delivery of the compounds to a subject for a period of at least several weeks to a month or more. Such formulations are described in published PCT application no. WO 02/74247, incorporated herein by reference.

It is especially advantageous to formulate oral or parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the subject to be treated; each unit containing a predetermined quantity of a compound of the invention calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the unit dosage forms of the invention are dictated by and directly dependent on the unique characteristics of the compound and the particular therapeutic effect to be achieved, and the limitations inherent in the art of compounding such compounds for the treatment of individuals.

This invention is further illustrated by the following examples, which should not be construed as limiting. The contents of all references, patents, patent applications cited throughout this application are incorporated herein by reference. It should be understood that the use of any of the compounds described herein are within the scope of

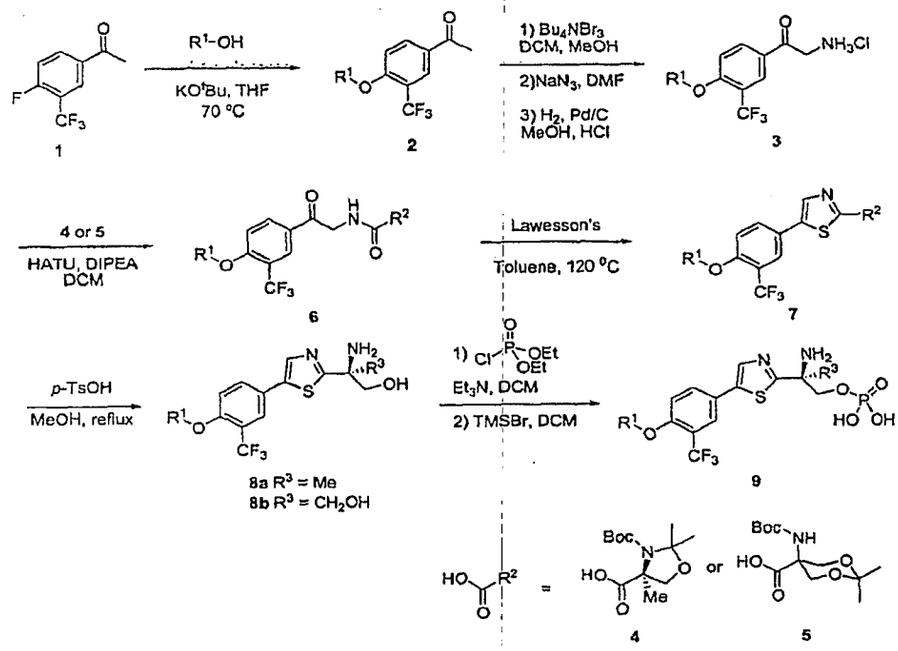
the present invention and are intended to be encompassed by the present invention and are expressly incorporated herein for all purposes.

Examples

General Approach to the Synthesis of 2,5-Disubstituted Thiazoles

The synthesis of 2,5-substituted thiazoles is described in Scheme 1. Reaction of alcohol R^1-OH wherein R^1 alkyl, aralkyl, heteroaryl, heterocyclo, or cycloalkyl with substituted 4-fluoroacetophenone **1** afforded the ether-acetophenone intermediate **2**. Ether-acetophenone intermediate **2** was then converted to the corresponding bromo-acetophenone using Bu_4NBr_3, which, upon reaction with NaN_3, provided the azido-acetophenone intermediate. Hydrogenation of the azido-acetophenone intermediate afforded amine **3**, followed by coupling with orthogonally protected amino acid **4** or amino diol-carboxylic acid **5** gave amide **6**. As a note, compound **4** was synthesized from (*S*)-2-(*tert*-butoxycarbonylamino)-3-hydroxy-2-methylpropanoic acid in three steps in overall 52-64% yield. A synthesis of (*R*)-3-(*tert*-butoxycarbonyl)-2,2,4-trimethyloxazolidine-4-carboxylic acid is described in Clemens, J. J.; Davis, M. D.; Lynch, K. R.; Macdonald, T. L. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3568-3572. Compound **5** was synthesized from 2-amino-2-(hydroxymethyl)propane-1,3-diol in five steps in overall 30% yield, also as described in Clemens, J. J.; Davis, M. D.; Lynch, K. R.; Macdonald, T. L. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3568-3572. Under conditions using Lawesson's reagent, amide **6** was converted to thiazole **7** in good yield. Removal of the protecting groups afforded the final alcohol **8**, which upon reaction with diethyl chlorophosphate and subsequent deprotection with TMSBr gave the phosphate **9**.

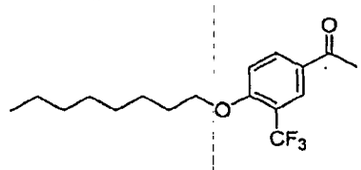
Scheme 1



General Protocol for Synthesis of Substituted Acetophenones (Williamson Ether Synthesis) (2)

To a solution of the desired alcohol (1.0 equivalent) in dry THF under nitrogen atmosphere was added KO'Bu (either 1.0 M solution in THF or solid, 1.1 equivalent). The reaction mixture was heated at 60-70 °C for 10 minutes, then substituted 4-flouroacetophenone **1** (1.0 equivalent) was added. The reaction was then stirred for 1 to 3 hours before cooling to room temperature (RT). The solvent removed *in vacuo*. The product was purified by silica gel column chromatography using the Combi-Flash system (Hex:EtOAc).

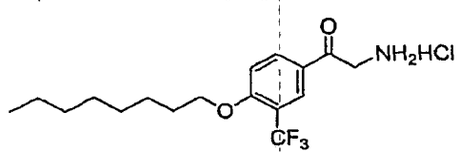
1-(4-(Octyloxy)-3-(trifluoromethyl)phenyl)ethanone (2)



The product was purified by silica gel column chromatography using the Combi-Flash system (Hex:EtOAc) as white solid in 60% (1.20 g). TLC (1:5 EtOAc:Hex), R_f = 0.4; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, 1H, J = 2.0 Hz), 8.10 (dd, 1H, J = 8.8 Hz, J

= 2.3 Hz), 7.02 (d, 1H, J = 8.8 Hz), 4.12 (t, 2H, J = 6.4 Hz), 2.58 (m, 3H), 1.80-1.89 (m, 2H), 1.42-1.54 (m, 2H), 1.22-1.40 (m, 8H), 0.89 (t, 3H, J = 6.7 Hz).

2-Amino-1-(4-(octyloxy)-3-(trifluoromethyl)phenyl)ethanone hydrochloride (3)

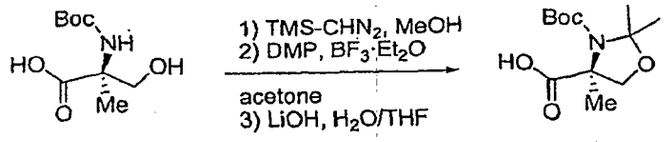


To a solution of the substituted acetophenone **2** (390 mg, 1.0 equivalent) in dry CH_2Cl_2 (9 mL) under nitrogen atmosphere was added Bu_4NBr_3 (0.60 g, 1.0 equiv). To the solution was added anhydrous MeOH (1.0 mL). The reaction mixture was stirred at room temperature overnight. The solvent was removed *in vacuo*, and the bromo-acetophenone product was used as is in the next step. TLC (4:1, Hex/EtOAc), R_f = 0.6.

To the desired bromo-acetophenone (from last step, 1.0 equivalents), in DMF (10 mL) was added NaN_3 (0.24 g, 3.0 equiv). The resulting mixture was then stirred in DMF for 1 hour. The reaction mixture was diluted with EtOAc (50 mL) and washed with H_2O (2 x 50). The solvent removed *in vacuo* and the product was purified by silica gel column chromatography using the Combi-Flash system (Hex:EtOAc) to give the azido-acetophenone product as a white solid in 99% (0.44 g) yield. TLC (4:1, Hex/EtOAc), R_f = 0.4.

To a solution of the azido-acetophenone (0.44 g, 1.0 equivalent) in MeOH (10 mL) was added concentrated HCl (1.5 mL), and 10% Pd/C (44 mg). The reaction mixture was stirred under an atmosphere of H_2 (g) for 2 hours. The reaction mixture was then filtered through a thin layer of Celite and the solvent was removed *in vacuo*. The amino-acetophenone **3** was obtained a white solid in quantitative yield (0.46 mg) with 90% purity. TLC (1:5 EtOAc:Hex), R_f = 0.4; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, 1H, J = 2.0 Hz), 8.10 (dd, 1H, J = 8.8 Hz, J = 2.3 Hz), 7.02 (d, 1H, J = 8.8 Hz), 4.52 (s, 2H), 4.12 (t, 2H, J = 6.4 Hz), 1.80-1.89 (m, 2H), 1.42-1.54 (m, 2H), 1.22-1.40 (m, 8H), 0.89 (t, 3H, J = 6.7 Hz).

(*R*)-3-(*tert*-Butoxycarbonyl)-2,2,4-trimethyloxazolidine-4-carboxylic acid (4)



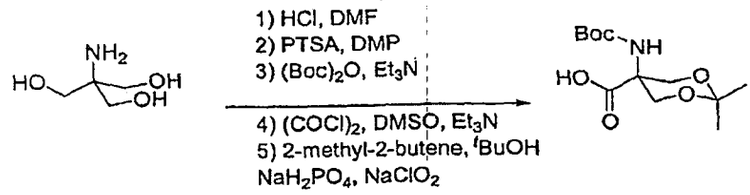
To a solution of the (*S*)-2-(*tert*-butoxycarbonylamino)-3-hydroxy-2-methylpropanoic acid (5.0 g, 1.0 equivalent) in CH_2Cl_2/MeOH(4:1, 50 mL) at 0 °C was added a solution of TMS-CHN_2 (2.0 M in diethyl ether or hexanes, 12.5mL, 1.1 equivalents) drop-wise until the colourless solution turned a light yellow color. The reaction mixture was stirred for 20 minutes then a few drops of acetic acid were added to quench the last unreacted TMS-CHN_2 (the solution turns colorless from light yellow). The solvent was removed *in vacuo*. TLC (2:1, Hex/EtOAc), R_f = 0.4.

The residue was dissolved in acetone (30 mL). To the resulting solution was then added 2,2-dimethoxypropane (DMP) (15 mL). To the mixture was added $BF_3 \cdot OEt_2$ (2 mL) drop-wise and the solution was stirred at RT for 4-18 hours. The solvent was removed *in vacuo* and the product was purified by silica gel column chromatography using the Combi-Flash system (Hex:EtOAc). TLC (3:1, Hex/EtOAc), R_f = 0.6; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.06-4.12 (m, 1H), 3.73-3.83 (m, 4H), 1.55-1.64 (m, 9H), 1.48 (br s, 3H), 1.41 (br s, 6H).

The purified residue was dissolved in THF (40 mL) and to the solution was added LiOH (1.15 g, 1.20 equiv) in H_2O (20 mL). The solution was heated at reflux for 6-18 hours, then concentrated *in vacuo* to remove most of the THF. The solution was diluted with H_2O (150 mL) and washed with Et_2O (2 x 150 mL). The aqueous layer was cooled to 0 °C then acidified to a pHof approximately 3 using concentrated HCl, then extracted with EtOAc (2 x 200 mL). The EtOAc layers were combined, dried ($MgSO_4$), filtered, and the solvent was removed *in vacuo* to afford carboxylate **4** as a white solid in 52-64% yield (3.78 g) yield. TLC (1:1 EtOAc:Hex), R_f = 0.2; ^{1}H NMR (400 MHz, $CDCl_3$) δ (rotamers) 4.47 (br d, 0.5H, J = 8.8 Hz), 4.17 (br d, 0.5H, J = 8.8 Hz), 3.85 (br d, 0.5H, J = 8.8 Hz), 3.78 (br d, 0.5H, J = 8.8 Hz), 1.38-1.67 (m, 18H).

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5-(*tert*-butoxycarbonylamino)-2,2-dimethyl-1,3-dioxane-5-carboxylic acid (5)



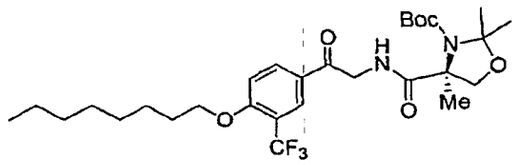
To a solution of the 2-amino-2-(hydroxymethyl)propane-1,3-diol (2.0 g, 1.0 equivalent) in DMF (20 mL) at RT was added 1M HCl (16.5 mL, 1.0 equiv) in diethyl ether. The resulting mixture was stirred for 20 minutes, then *para*-toluenesulfonic acid (PTSA) (157 mg, 0.05 equivalent) and 2,2-dimethoxypropaneor (2.23 mL, 1.1 equivalents) were added. The reaction mixture was stirred for 24 hours,then Et_3N (3.0 equivalent, 6.90 mL) and $(Boc)_2O$ (1.0 equiv, 3.60 g) were added and the mixture wasstirred overnight. The reaction mixture was diluted with EtOAc (50 mL) and washed with H_2O (2 x 50 mL). The solvent removed *in vacuo* and the product was purified by silica gel column chromatography using the Combi-Flash system (Hex:EtOAc) as a white solid in 58% (2.49 g) yield. TLC (2:1, Hex/EtOAc), R_f = 0.3; ^1H NMR (400 MHz, $CDCl_3$) δ 5.33 (br s, 1H), 4.27 (br s, 1H), 3.79–3.84 (m, 4H), 3.72 (d, 2H, J = 6.4 Hz), 1.46 (s, 12H), 1.44 (s, 3H).

To a solution of oxalyl chloride (2.0 M in CH_2Cl_2, 5.74 mL, 3.0 equivalents) in dry CH_2Cl_2 (10 mL) at -78 °C was added DMSO (1.36 ml, 5.0 equivalents). The resulting mixture was stirred for 15 minutes, then a solution of the desired alcohol (from last step, 1.0 g) in dry CH_2Cl_2 (10 mL) was added drop-wise. The mixture was stirred for 2 hours, then Et_3N (5.33 mL, 10 equivalents) was added. The reaction mixture was stirred for 10 minutes then the cooling bath was removed and the mixture was allowed to warm to RT. The reaction mixture was then diluted with EtOAc (50 mL) and washed with 10% NH_4Cl (2 x 50 mL). The organic layer was dried over $MgSO_4$, filtered, and the solvent was removed *in vacuo* to afford aldehyde intermediate as a white solid in >99% yield (1.00 g). For more detailed Swern oxidation conditions see: a) Blaskovich, M. A.; Evindar, G.; Rose, N. G. W.; Wilkinson, S.; Luo, Y.; Lajoie, G. A. *J. Org. Chem.* **1998**, *63*, 3631-3646. and b) Rose, N. G. W.; Blaskovich, M. A.; Evindar, G.; Wilkinson, S.; Luo, Y.; Fishlock, D.; Reid, C.; Lajoie, G. A. *Organic Syntheses* **2002**, *79*, 216-227. TLC (2:1, Hex/EtOAc), R_f = 0.7; ^1H NMR (400 MHz, $CDCl_3$) δ 9.63 (s, 1H), 5.55 (br s, 1H), 4.07 (d, 2H, J = 12.0 Hz), 3.95 (d, 2H, J = 12.0 Hz), 1.47 (s, 18H).

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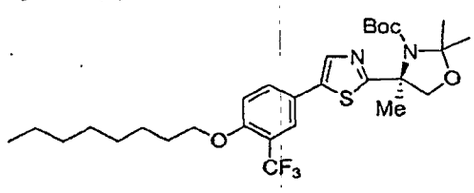
To a solution of the aldehyde (from last step, 1.0 g) in *t*-BuOH (20 mL) and 2-methyl-2-butene (10 mL) at room temerature was added a sluotion of NaH_2PO_4 (1.06 g, 2.0 equivalents), and $NaClO_2$ (1.40 g, 4.0 equivalents) in H_2O (10 mL). The reaction was stirred for 3 hours and then was diluted with H_2O (10 mL). The mixture was extracted with EtOAc (30 mL). The organic layer was dried over $MgSO_4$, filtered, and the solvent was removed *in vacuo* to afford carboxylate **5** as a white solid in 52% yield (550 mg). For more detailed procedure for oxidation of aldehyde to carboyxlate see: Taylor, R. E.; Galvin, G. M.; Hilfiker, K. A.; Chen, Y. *J. Org. Chem.* **1998**, *63*, 9580-9583. TLC (1:1 EtOAc:Hex), R_f = 0.2; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.50 (br s, 1H), 4.18 (d, 2H, *J* = 11.8 Hz), 4.10 (d, 2H, *J* = 11.8 Hz), 1.47 (br s, 18H).

(*R*)-*tert*-Butyl 2,2,4-trimethyl-4-(2-(4-(octyloxy)-3-(trifluoromethyl)phenyl)-2-oxoethylcarbamoyl)oxazolidine-3-carboxylate (6)



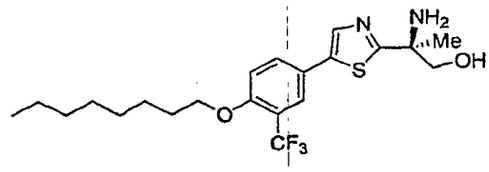
To a solution of protected oxazolidine-4-carboxylic acid **4** (176 mg, 1 equivalents), HATU (310 mg, 1.2 equivalents), and DIEA (1.2 mL, 10 equivalents) in CH2CL2/DMF (1:1, 10 mL) was added amino-acetophenone **3** (250 mg, 1.0 equivalents). The resultant mixture was stirred at room temperature overnight. The reaction mixture was diluted with EtOAc (50 mL) and washed with 10% NH_4Cl (2 x 50 mL) and saturated NaCl (1 x 50 mL). The solvent removed *in vacuo* and the product was obtained, silica gel column chromatography using the Combi-Flash system (Hex:EtOAc), as a white solid in 40% yield (185 mg). TLC (1:2 EtOAc:Hex), R_f = 0.3; MS (ESI, M+Na) = 572.99; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (s, 1H), 8.11 (d, 1H, *J* = 8.4 Hz), 7.05 (d, 1H, *J* = 8.4 Hz), 4.62-4.79 (m, 2H), 4.13 (t, 2H, *J* = 6.4 Hz), 3.28 (br s, 1H), 1.22-1.90 (m, 30H), 0.89 (t, 3H, *J* = 6.4 Hz).

(*R*)-*tert*-Butyl 2,2,4-trimethyl-4-(5-(4-(octyloxy)-3-(trifluoromethyl)phenyl)thiazol-2-yl)oxazolidine-3-carboxylate (7)



A suspension of protected oxazolidine-amide **6** (180 mg, 1.0 equivalent) and Lawesson's Reagent (390 mg, 3.0 equivalents) in toluene (5 mL) was sealed and heated at 100 ^{0}C for 1 hour. After cooling to room temperature, the reaction mixture was purified by silica gel column chromatography using the Combi-Flash system (Hex:EtOAc) as a thick colourless oil in 67% yield (120 mg). TLC (1:2 EtOAc:Hex), R_f = 0.8; MS (ESI, M+H$^+$) = 571.11; ^{1}H NMR (400 MHz, CDCl3) δ 7.73 (br s, 1H), 7.70 (s, 1H), 7.61 (d, 1H, *J* = 6.8 Hz), 7.01 (d, 1H, *J* = 6.8 Hz), 3.96-4.28 (m, 4H), 1.21-1.99 (m, 30H), 0.89 (t, 3H, *J* = 7.6 Hz).

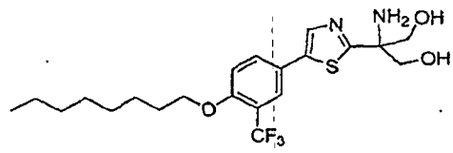
(*S*)-2-Amino-2-(5-(4-(octyloxy)-3-(trifluoromethyl)phenyl)thiazol-2-yl)propan-1-ol (8a)



A solution of thiazole **7** (120 mg) and para toluenesulfonic acid (PTSA, 400 mg, 10 equivalents) in MeOH (6 mL) was refluxed for 6 hours. The solvent was removed *in vacuo* and the product was purified by reverse phase preparative HPLC, then lyophilized to dryness to obtain the trifluoroacetate salt of the product as a white solid in 79% yield (90.5 mg). MS (ESI, M+H$^+$) = 431.01; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.27 (s, 1H), 7.88 (dd, 1H, *J* = 8.8 Hz, *J* = 2.4 Hz), 7.85 (d, 1H, *J* = 2.4 Hz), 7.34 (d, 1H, *J* = 8.4 Hz), 5.77 (br s, 1H), 4.14 (t, 2H, *J* = 6.4 Hz), 3.76 (dd, 1H, *J* = 11.2, Hz, *J* = 1.2 Hz), 3.66 (dd, 1H, *J* = 11.2 Hz, *J* = 1.2 Hz), 1.73 (q, 2H, *J* = 6.8 Hz), 1.58 (s, 3H), 1.36-1.48 (m, 2H), 1.20-1.36 (m, 8H), 0.85 (t, 3H, *J* = 6.4 Hz).

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2-Amino-2-(5-(4-(octyloxy)-3-(trifluoromethyl)phenyl)thiazol-2-yl)propane-1,3-diol (8b)

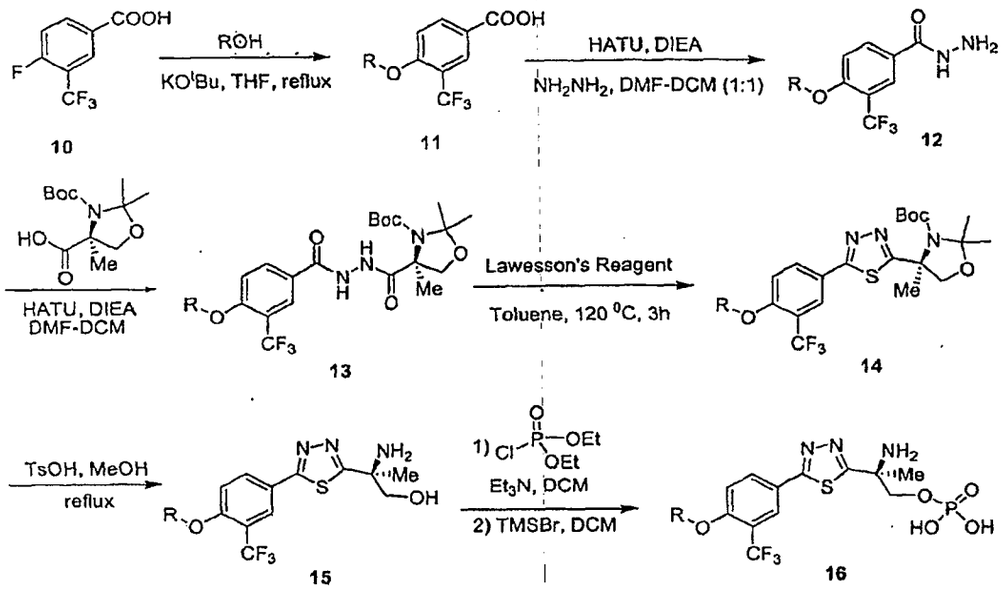


The diol **8b** was prepared from carboxylate **5** and amino-acetophenone **3** analogously to thiazole **8a** in 35% yield over three steps. MS (ESI, $M+H^+$) = 447.01; ^1H NMR (400 MHz, DMSO-d_6) δ 8.27 (s, 1H), 7.87 (dd, 1H, J = 8.8 Hz, J = 2.4 Hz), 7.84 (d, 1H, J = 2.4 Hz), 7.32 (d, 1H, J = 8.4 Hz), 5.71 (br s, 1H), 4.13 (t, 2H, J = 6.4 Hz), 3.71-3.85 (m, 4H), 1.72 (q, 2H, J = 6.4 Hz), 1.36-1.46 (m, 2H), 1.19-1.35 (m, 8H), 0.84 (t, 3H, J = 6.4 Hz).

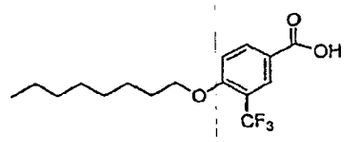
General Approach to the Synthesis of 2,5-Disubstituted-1,3,4-Thiadiazoles

The synthesis of 2,5-substituted thiadizoles is described in Scheme 2. Reaction of alcohol ROH with substituted 4-fluorobezoic acid **10** afforded ether-benzoate intermediate **11**. The ether-benzoate intermediate **11** was then coupled with hydrazine to afford benzohydrazide **13**. Reaction of benzohydrazide **13** with orthogonally protected amino Note, this phrase used here and elsewhere in the application is new to me acid **4** under using *N*,*N*,*N*',*N*'-Tetramethyl-O-(7-azabenzotriazol-1-yl)uronium hexafluorophosphate (HATU) followed by cyclization with Lawesson's reagent provided thiadizole **14** in good yield. Removal of the protecting groups afforded final alcohol **15**. Alcohol **15** was then converted to corresponding phosphate as reported in scheme 1.

Scheme 2

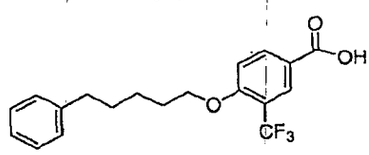


4-(Octyloxy)-3-(trifluoromethyl)benzoic acid (11a)



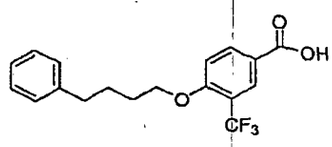
To a solution of 1-octanol (315 μL, 2.0 mmol) in anhydrous THF (5 mL) was added potassium *t*-butoxide (5 mL, 1M solution in THF). The mixture was heated at 70 °C for 15 min then cooled down to room temperature. 4-Fluoro-3-trifluoromethylbenzoid acid (**10**) (417 mg, 2.0 mmol) in THF (5 mL) was added and the resultant was heated at 75 °C overnight. After cooling down to room temperature, the reaction mixture was diluted with ethyl acetate and washed with water. The water layer was acidified to a pH of approximately 3 with HCl (2M) and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo* to afford the title compound (632 mg, HPLC purity > 95%), which was used for next reaction without further purification. HPLC retention time on a C8(2) column (30 × 3.00 mm, 3 μ) was 3.28 min with gradient 50-98% acetonitrile-H_2O (0.1% trifluoroacetic acid (TFA)) in 3.5 min as mobile phase.

4-(5-Phenylpentyloxy)-3-(trifluoromethyl)benzoic acid (11b)



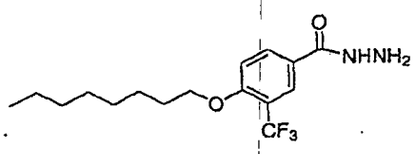
The title compound was prepared analogously to 4-(octyloxy)-3-(trifluoromethyl)benzoic acid **(11a)** in > 95% yield. HPLC retention time on a C8(2) column (30 × 3.00 mm, 3 μ) is 3.31 min with gradient 20-98% acetonitrile-H_2O (0.1% TFA) in 3.5 min as mobile phase.

4-(4-Phenylbutoxy)-3-(trifluoromethyl)benzoic acid (11c)



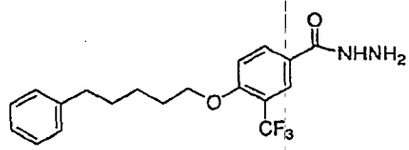
The title compound was prepared analogously to 4-(octyloxy)-3-(trifluoromethyl)benzoic acid **(11a)** in > 95% yield. HPLC retention time on a C8(2) column (30 × 3.00 mm, 3 μ) is 3.14 min with gradient 20-98% acetonitrile-H_2O (0.1% TFA) in 3.5 min as mobile phase.

4-(Octyloxy)-3-(trifluoromethyl)benzohydrazide (12a)



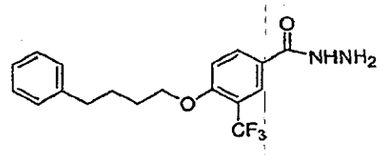
4-(Octyloxy)-3-(trifluoromethyl)benzoic acid **(11a)** (632 mg, crude, approximately 1.89 mmol) was stirred with HATU (905 mg) and DIEA (1.7 mL) in CH_2Cl_2-DMF (10 mL, 4:1) for 10 min followed by addition of hydrazine (297 μL) dropwise. The reaction mixture was continuously stirred for another hour, then was diluted with ethyl acetate (30 mL) and washed with water (10 mL) and brine (3 × 15 mL). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo* to afford the title compound (661 mg, HPLC purity > 90%), which was used for next reaction without further purification. MS (ESI): 333.08 (MH^+); HPLC retention time on a C8(2) column (30 × 3.00 mm, 3 μ) is 1.61 min with gradient 50-98% acetonitrile-H_2O (0.1% TFA) in 3.5 min as mobile phase.

4-(5-Phenylpentyloxy)-3-(trifluoromethyl)benzohydrazide (12b)



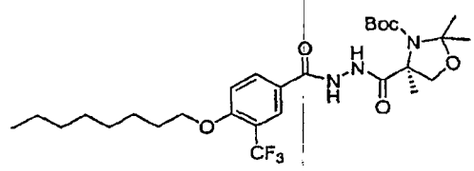
The title compound was prepared analogously to 4-(octyloxy)-3-(trifluoromethyl)-benzo-hydrazide (**12a**) in > 95% yield. MS (ESI): 367.14 (MH^+); HPLC retention time on a C8(2) column (30 × 3.00 mm, 3 μ) is 2.44 min with gradient 20-98% acetonitrile-H_2O (0.1% TFA) in 3.5 min as mobile phase.

4-(4-Phenylbutoxy)-3-(trifluoromethyl)benzohydrazide (12c)



The title compound was prepared analogously to 4-(octyloxy)-3-(trifluoromethyl)-benzo-hydrazide (**12a**) in > 95% yield. MS (ESI): 353.11 (MH^+); HPLC retention time on a C8(2) column (30 × 3.00 mm, 3 μ) is 2.30 min with gradient 20-98% acetonitrile-H_2O (0.1% TFA) in 3.5 min as mobile phase.

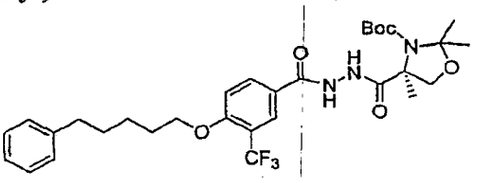
(*S*)-*tert*-Butyl 2,2,4-trimethyl-4-(2-(4-(octyloxy)-3-(trifluoromethyl)benzoyl)-hydrazinecarbonyl)oxazolidine-3-carboxylate (13a)



(*R*)-3-(*tert*-Butoxycarbonyl)-2,2,4-trimethyloxazolidine-4-carboxylic acid (4) (210 mg, 0.81 mmol) was stirred with HATU (372 mg, 0.98 mmol) and diisopropylethyl amine (DIEA) (0.705 mL, 4.1 mmol) in CH_2Cl_2-DMF (2:1, 6 mL) for 10 min followed by addition of 4-(octyloxy)-3-(trifluoromethyl)benzohydrazide (**12a**) (270 mg, 0.81 mmol) in CH_2Cl_2 (2 mL). The reaction was stirred at room temperature for 1 hour and then was concentrated under vacuum. The residue was diluted with ethyl acetate (20 mL) and washed with water (5 mL), brine (2 × 10 mL) and dried over Na_2SO_4. The organic layer was concentrated *in vacuo* and chromatographed on a silica gel column (ethyl acetate-hexane, 0-33%, as eluent) to afford the title compound (428 mg, 82% yield). MS (ESI): 573.84 (MH^+); ^1H NMR (400 MHz, $CDCl_3$) δ 9.43 (br, 2H), 8.06 (d,

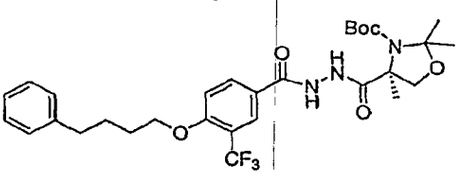
1H, J = 2.0 Hz), 7.94 (dd, 1H, J = 8.8 Hz, J = 2.0 Hz), 6.96 (d, 1H, J = 8.8 Hz), 4.52 (br, 1H), 4.07 (t, 2H, J = 6.4 Hz), 3.76 (br, 1H), 1.82 (m, 2H), 1.67 (s, 6H), 1.57 (s, 3H), 1.51 (s, 9H), 1.51-1.43 (m, 4H), 1.38-1.24 (m, 6H), 0.88 (t, 3H, J = 7.2 Hz).

(*S*)-*tert*-Butyl 2,2,4-trimethyl-4-(2-(4-(5-phenylpentyloxy)-3-(trifluoromethyl)-benzoyl)hydrazinecarbonyl)oxazolidine-3-carboxylate (13b)



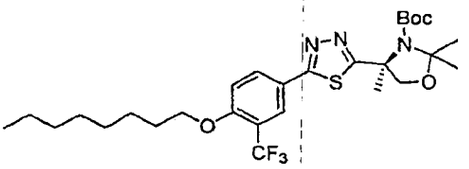
The title compound was prepared analogously to (*S*)-*tert*-butyl 2,2,4-trimethyl-4-(2-(4-(octyloxy)-3-(trifluoromethyl)benzoyl)-hydrazinecarbonyl)oxazolidine-3-carboxylate (**13a**) in 95% yield. MS (ESI): 607.81 (MH^+); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.94 (br, 1H), 9.04 (br, 1H), 8.05 (d, 1H, J = 2.4 Hz), 7.93 (dd, 1H, J = 8.8 Hz, J = 2.4 Hz), 7.29-7.25 (m, 2H), 7.18-7.15 (m, 3H), 6.97 (d, 1H, J = 8.8 Hz), 4.55 (br, 1H), 4.07 (t, 2H, J = 6.4 Hz), 3.77 (br, 1H), 2.64 (d, 2H, J = 7.6 Hz), 1.86 (m, 2H), 1.73-1.65 (m, 9H), 1.58-1.52 (m, 13 H).

(*S*)-*tert*-Butyl 2,2,4-trimethyl-4-(2-(4-(4-phenylbutoxy)-3-(trifluoromethyl)benzoyl)-hydrazinecarbonyl)oxazolidine-3-carboxylate (13c)



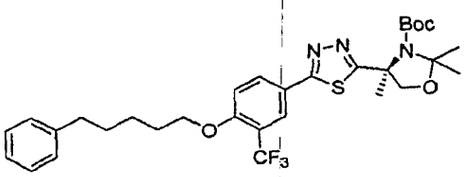
The title compound was prepared analogously to (*S*)-*tert*-butyl 2,2,4-trimethyl-4-(2-(4-(octyloxy)-3-(trifluoromethyl)benzoyl)-hydrazinecarbonyl)oxazolidine-3-carboxylate (**13a**) in 97% yield. MS (ESI): 593.87 (MH^+); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.94 (br, 1H), 8.79 (br s, 1H), 8.05 (d, 1H, J = 2.4 Hz), 7.93 (dd, 1H, J = 8.8 Hz, J = 2.4 Hz), 7.30-7.25 (m, 2H), 7.20-7.16 (m, 3H), 6.98 (d, 1H, J = 8.8 Hz), 4.55 (br, 1H), 4.10 (t, 2H, J = 6.4 Hz), 3.78 (br s, 1H), 2.69 (d, 2H, J = 7.6 Hz), 1.86 (m, 4H), 1.68 (s, 6H), 1.58 (s, 3H), 1.52 (s, 9H).

(*R*)-*tert*-Butyl 2,2,4-trimethyl-4-(5-(4-(octyloxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)oxazolidine-3-carboxylate (14a)



A solution of (*S*)-*tert*-butyl 2,2,4-trimethyl-4-(2-(4-(octyloxy)-3-(trifluoromethyl)-benzoyl)hydrazinecarbonyl)oxazolidine-3-carboxylate (**13a**) (228 mg, 0.39 mmol) in toluene (5 mL) was treated with Lawesson's reagent (473 mg, 1.17 mmol) at 85 ^{0}C for 2 hours. The reaction was cooled down to room temperature and the supernatant was chromatographed on a silica gel column eluted with ethyl acetate-hexane (0-30%, v/v) to afford the title compound (156 mg, 70% yield). MS (ESI): 572.17 (MH^+), ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, 1H, J = 8.8 Hz), 8.08 (d, 1H, J = 6.8 Hz), 7.06 (d, 1H, J = 8.0 Hz), 4.41 (d, 1H, J = 8.0 Hz), 4.18 (d, 1H, J = 9.6 Hz), 4.13-4.07 (m, 3H), 2.00 (s, 3H), 1.85 (m, 2H), 1.78 (s, 3H), 1.68 (m, 4H), 1.51 (s, 3H), 1.47 (m, 2H), 1.39-1.28 (m, 13H), 0.89 (t, 3H, J = 7.2 Hz).

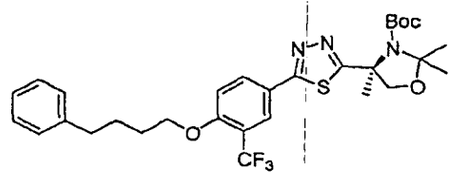
(*R*)-*tert*-Butyl 2,2,4-trimethyl-4-(5-(4-(5-phenylpentyloxy)-3-(trifluoromethyl)-phenyl)-1,3,4-thiadiazol-2-yl)oxazolidine-3-carboxylate (14b)



The title compound was prepared analogously to (*R*)-*tert*-butyl 2,2,4-trimethyl-4-(5-(4-(octyloxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)oxazolidine-3-carboxylate (**14a**) in 80% yield. MS (ESI): 606.19 (MH^+), HPLC retention time on a C8(2) column (30 × 3.00 mm, 3 μ) is 3.78 min with gradient 50-98% acetonitrile-H_2O (0.1% TFA) in 3.5 min as mobile phase.

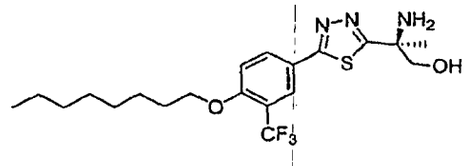
90

(*R*)-*tert*-Butyl 2,2,4-trimethyl-4-(5-(4-(4-phenylbutoxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)oxazolidine-3-carboxylate (14c)



The title compound was prepared analogously to (*R*)-*tert*-butyl 2,2,4-trimethyl-4-(5-(4-(octyloxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)oxazolidine-3-carboxylate (**14a**) in 75% yield. MS (ESI): 592.14 (MH^+), HPLC retention time on a C8(2) column (30 × 3.00 mm, 3 μ) is 3.55 min with gradient 50-98% acetonitrile-H_2O (0.1% TFA) in 3.5 min as mobile phase

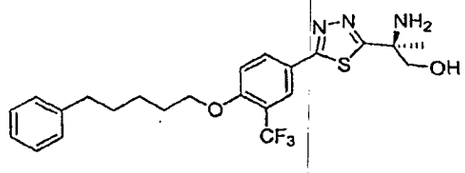
(*S*)-2-Amino-2-(5-(4-(octyloxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol (15a)



A solution of (*S*)-*tert*-butyl 2,2,4-trimethyl-4-(2-(4-(octyloxy)-3-(trifluoromethyl)-benzoyl)hydrazinecarbonyl)oxazolidine-3-carboxylate (**14a**) (156 mg, 0.27 mmol) in methanol (5 mL) was treated with *p*-toluenesulfonic acid monohydrate (259 mg, 1.36 mmol) at 70 °C for 2 hours. The reaction mixture was then cooled to room temperature and purified by prep HPLC on a C8(2) column ((Luna, 5μ, 100 × 21.10 mm) with acetonitrile-H_2O (0.1% TFA) as mobile phase and gradient 30-98% in 20 min. The title compound was obtained as the bis-TFA salt (36 mg, 20%). MS (ESI): 432.00 (MH^+); ^1H NMR (400 MHz, DMSO-d_6) δ 8.21 (dd, 1H, J = 2.0 Hz, J = 8.8 Hz), 8.15 (d, 1H, J = 2.0 Hz), 8.09 (br s, 2H), 7.45 (d, 1H, J = 8.8 Hz), 5.96 (t, 1H, J = 4.8 Hz), 4.21 (t, 2H, J = 6.4 Hz), 3.81 (dd, 1H, J = 11.2 Hz, J = 5.2 Hz), 3.73 (dd, 1H, J = 11.2 Hz, J = 5.2 Hz), 1.76 (m, 2H), 1.66 (s, 3H), 1.44 (m, 2H), 1.28 (m, 8H), 0.86 (t, 3H, J = 6.8 Hz).

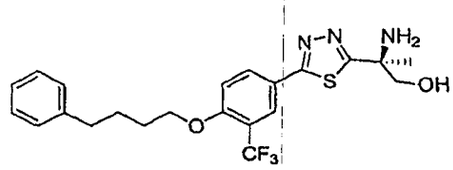
41

(*S*)-2-Amino-2-(5-(4-(5-phenylpentyloxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol (15b)



The title compound was prepared analogously to (*S*)-2-amino-2-(5-(4-(octyloxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol (**15a**) in 67% yield. MS (ESI): 466.05 (MH^+); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.87 (br s, 2H), 8.22 (dd, 1H, *J* = 8.8 Hz, *J* = 2.0 Hz), 8.16 (d, 1H, *J* = 2.0 Hz), 7.45 (d, 1H, *J* = 8.8 Hz), 7.26 (t, 2H, *J* = 7.6 Hz), 7.20-7.14 (m, 3H), 6.10 (br, 1H), 4.22 (t, 2H, *J* = 6.4 Hz), 3.83 (d, 1H, *J* = 11.2 Hz), 3.77 (d, 1H, *J* = 11.2Hz), 2.59 (t, 2H, *J* = 7.2 Hz), 1.80 (m, 2H), 1.70 (s, 3H), 1.46 (m, 2H), 1.46 (m, 2H).

(*S*)-2-Amino-2-(5-(4-(4-phenylbutoxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol (15c)



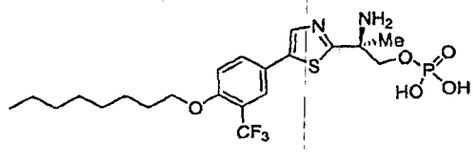
The title compound was prepared analogously to (*S*)-2-amino-2-(5-(4-(octyloxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol (**15a**) in 70% yield. MS (ESI): 452.06 (MH^+); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.60 (br s, 2H), 8.23 (dd, 1H, *J* = 8.8 Hz, *J* = 2.4 Hz), 8.16 (d, 1H, *J* = 2.4 Hz), 7.45 (d, 1H, *J* = 8.8 Hz), 7.28 (t, 2H, *J* = 7.2 Hz), 7.21-7.15 (m, 3H), 4.25, 4.22 (t, 2H, *J* = 5.6 Hz), 3.82 (d, 1H, *J* = 9.6 Hz), 3.75 (d, 1H, *J* = 9.6 Hz), 2.65 (t, 2H, *J* = 7.2 Hz), 1.80-172 (m, 4H), 1.68 (s, 3H).

General Method for Phosphate Synthesis

Synthetic strategy for synthesis of desired phosphates is illustrated in Scheme 1 above. To a solution of unprotected amino alcohol (1.0 equiv) in dry CH_2Cl_2 at room temperature was added excess diethyl chlorophosphate (10.0 equiv) and triethylamine (20.0 equivalents) and the reaction stirred for 12-18 hours. The reaction was monitored by LC-MS. The crude reaction mixture was then evaporated to dryness *in vacuo*. The obtained phospho-diester intermediate was reacted with excess bromotrimethylsilane (10.0-20.0 equiv) in dry CH_2Cl_2 at room temperature over a period of 6-10 hours to

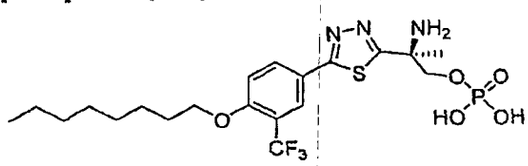
afford the final phosphate which was purified by reverse-phase preparative HPLC after evaporation of the solvent and excess reagent.

(*S*)-2-amino-2-(5-(4-(octyloxy)-3-(trifluoromethyl)phenyl)thiazol-2-yl)propyl dihydrogen phosphate (9a)



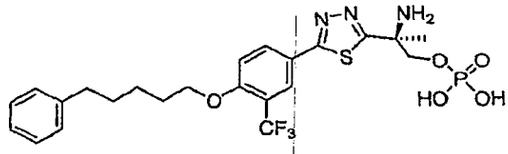
The product was obtained as a white solid in 28% (10 mg) yield from the alcohol precursor. MS (ESI, $M+H^+$) = 511.1.

(*S*)-2-Amino-2-(5-(4-(octyloxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propyl dihydrogen phosphate (16a)



MS (ESI): 511.98 (MH^+), HPLC retention time on a C8(2) column (30 × 3.00 mm, 3 μ) is 1.88 min with gradient 40-98% acetonitrile-H_2O (0.1% TFA) in 3.5 min as mobile phase.

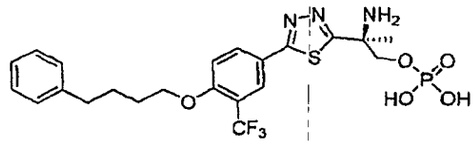
(*S*)-2-Amino-2-(5-(4-(5-phenylpentyloxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propyl dihydrogen phosphate (16b)



MS (ESI): 546.01 (MH^+), HPLC retention time on a C8(2) column (30 × 3.00 mm, 3 μ) is 2.06 min with gradient 30-98% acetonitrile-H_2O (0.1% TFA) in 3.5 min as mobile phase.

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(*S*)-2-Amino-2-(5-(4-(4-phenylbutoxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propyl dihydrogen phosphate (16c)



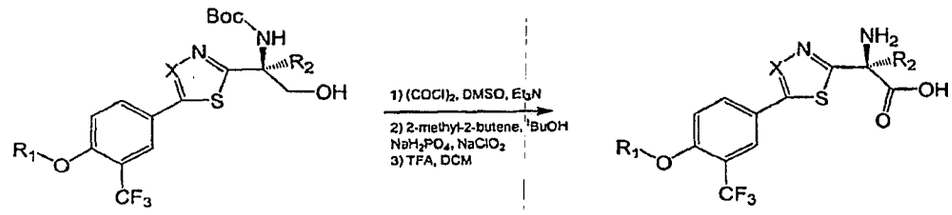
MS (ESI): 532.01 (MH^+), HPLC retention time on a C8(2) column (30 x 3.00 mm, 3 μ) is 1.96 min with gradient 30-98% acetonitrile-H_2O (0.1% TFA) in 3.5 min as mobile phase.

General Approach to Synthesis of Compounds of Formula III

The synthesis of compounds of formula III is described in Scheme 3. Synthesis of compounds **1a** and **1b** in strategy A and compound **3** in strategy B were described in schemes 1 and 2. Oxidation of the compounds **1a** and **1b** in strategy A followed by deprotection afforded compounds **2a** and **2b**. In strategy B, coupling of the free amine in compound **3** with the desired protected-amino acid gave compound **4** which upon cyclization under Lawesson's reagent conditions provided the desired azole **5**. Removal of the protecting groups afforded the final carboxylate **6**.

Scheme 3

Strategy A:

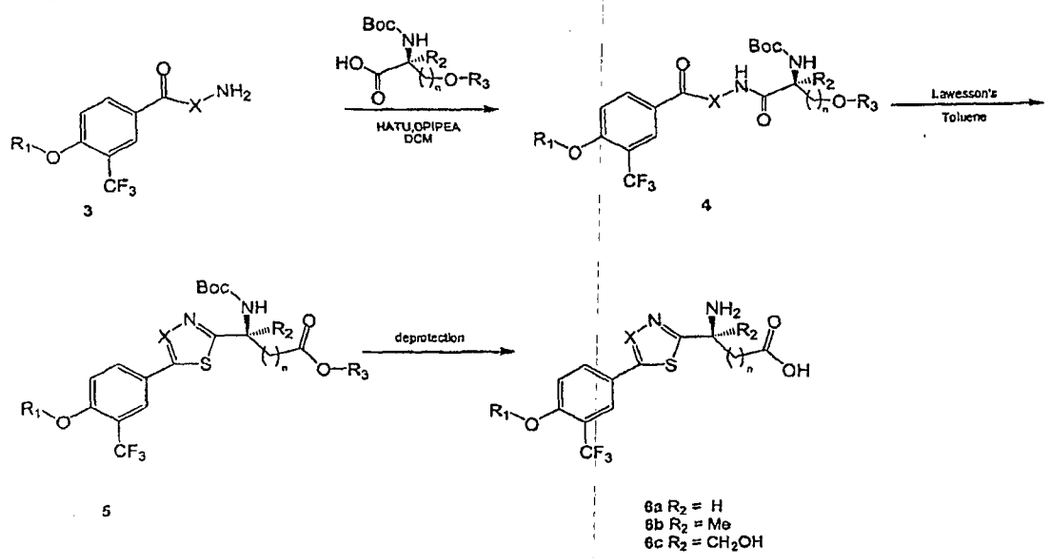


1a R_2 = H
1b R_2 = Me

2a R_2 = H
2b R_2 = Me

94

Strategy B:

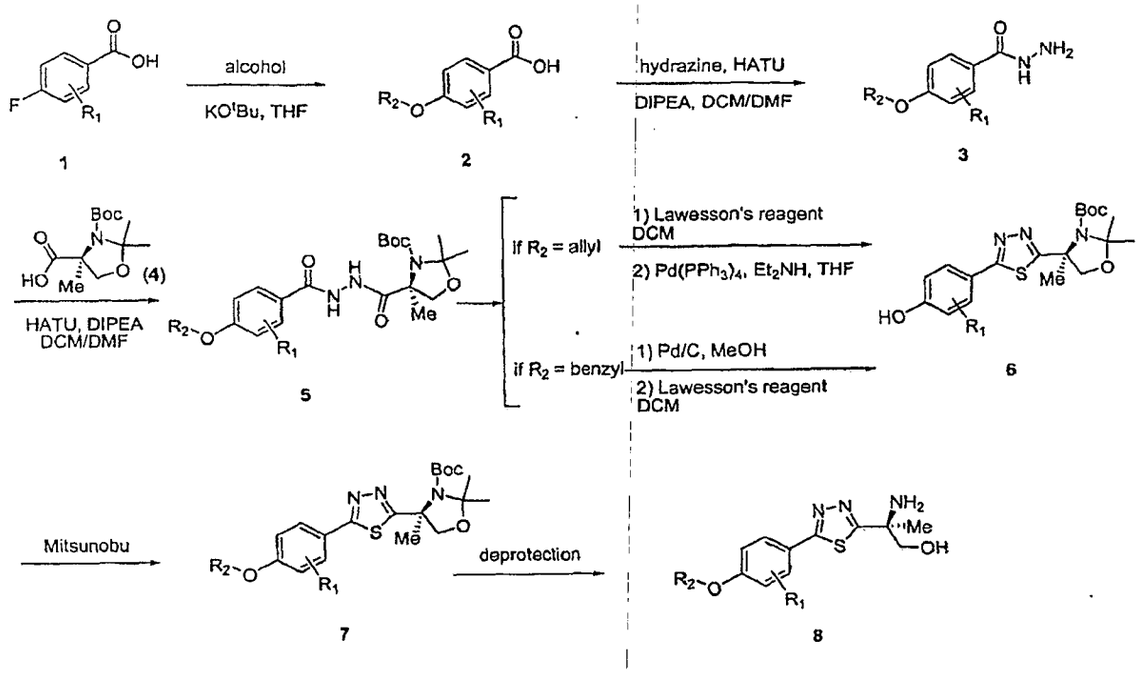


General approach to synthesis of ether-phenyl-thiadiazoles

Synthesis of phenyl-thiazoles is described in Scheme 4. Reaction of benzyl or allyl alcohol with substituted 4-fluorobenzoic acid **1** afforded the substituted ether-benzoate **2**. The substituted ether-benzoate **2** was then coupled with hydrazine to afford benzohydrazide **3**. Reaction of benzohydrazide **3** with orthogonally protected amino acid **4** under HATU conditions followed by cyclization and deprotection (or vis versa) provided phenol **6** in good yield. Mitsunobu reaction of phenol **6** with desired alcohol followed by deprotection afforded the desired final compound **8**. Reaction of the alcohol **8** with diethyl chlorophosphate followed by deprotection with TMSBr gave the corresponding phosphate.

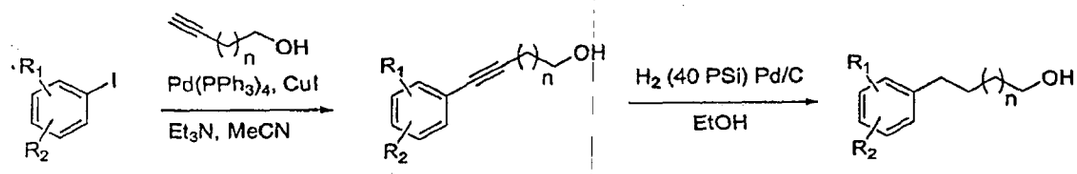
95

Scheme 4:



General procedure for preparation of substituted phenyl alcohols

Various starting material alcohols for Mitsunobu reaction were prepared as described below.



General procedure for Sonogashira cross-coupling

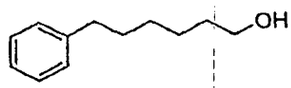
To a mixture of a substituted 4-iodobenzene (1.0 equiv), $Pd(PPh_3)_4$ (0.02 equiv) and CuI (0.04 equiv) in MeCN was added the alkynol (1.5 equiv) and Et_3N (1.5 equiv). The reaction mixture was stirred for 2-16 hours at reflux, then the solvent removed *in vacuo*. The crude product was purified by silica gel column chromatography using the Combi-Flash system (Hex:EtOAc) as needed.

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General Method for hydrogenation of alkyne

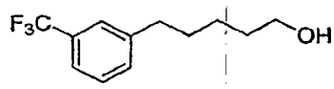
The desired alkyne is dissolved in ethanol and a heterogeneous mixture of palladium on carbon is added. The reaction is shaken for 2 hours under 40 psi of H_2. Filtration through celite and removal of the solvent *in vacuo* gives the desired product.

6-Phenylhexan-1-ol



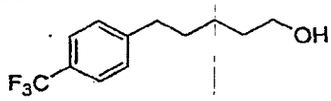
The title compound was prepared from 6-phenylhex-5-yn-1-ol in 70 % (241 mg) yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18-7.27 (m, 2H), 7.16-7.18 (m, 3H) 3.63 (t, 2H, J = 6.4 Hz), 2.61 (t, 2H, J = 8.0 Hz), 1.56-1.69 (m, 4H), 1.37-1.40 (m, 5H).

5-(3-(Trifluoromethyl)phenyl)pentan-1-ol



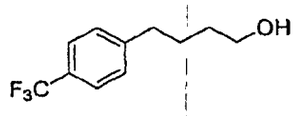
The title compound was prepared from 5-(3-(trifluoromethyl)phenyl)pent-4-yn-1-ol in 85 % (241 mg) yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.42 (m, 4H), 3.65 (t, 2H, J = 6.8 Hz), 2.68 (t, 2H, J = 6.0 Hz), 1.59-1.68 (m, 4H), 1.37-1.44 (m, 3H).

5-(4-(Trifluoromethyl)phenyl)pentan-1-ol



The title compound was prepared from 5-(4-(trifluoromethyl)phenyl)pent-4-yn-1-ol in 60 % (140 mg) yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, 2H, J = 8.4 Hz), 7.27 (d, 2H, J = 7.3 Hz), 3.64 (t, 2H, J = 6.8 Hz), 2.68 (t, 2H, J = 8.0 Hz), 1.57-1.70 (m, 4H), 1.39-1.45 (m, 3H).

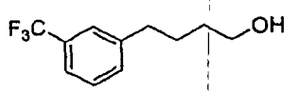
4-(4-(Trifluoromethyl)phenyl)butan-1-ol



The title compound was prepared from 4-(4-(trifluoromethyl)phenyl)but-3-yn-1-ol in 28 % (183 mg) yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, 2H, J = 8.0 Hz), 7.29

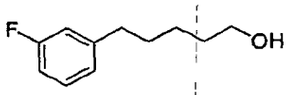
(d, 2H, J = 7.6 Hz), 3.67 (t, 2H, J = 6.4 Hz), 2.71 (t, 2H, J = 7.6 Hz), 1.69-1.76 (m, 2H), 1.59-1.64 (m, 3H).

4-(3-(Trifluoromethyl)phenyl)butan-1-ol



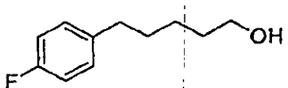
The title compound was prepared from 4-(3-(trifluoromethyl)phenyl)but-3-yn-1-ol in 70 % (453 mg) yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26-7.67 (m, 4H), 3.67 (t, 2H, J = 6.4 Hz), 2.70 (t, 2H, J = 6.4 Hz), 1.71-1.92 (m, 2H), 1.57-1.70 (m, 3H).

5-(3-Fluorophenyl)pentan-1-ol



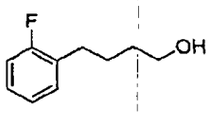
The title compound was prepared from 5-(3-fluorophenyl)pent-4-yn-1-ol in 73 % (405 mg) yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19-7.26 (m, 1H), 6.94 (d, 1H, J = 7.6 Hz), 6.84-6.88 (m, 2H), 3.64 (t, 2H, J = 6.8 Hz), 2.62 (t, 2H, J = 7.6 Hz), 1.56-1.69 (m, 4H), 1.36-1.46 (m, 5H).

5-(4-Fluorophenyl)pentan-1-ol



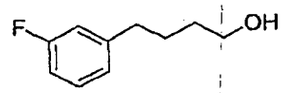
The title compound was prepared from 5-(4-fluorophenyl)pent-4-yn-1-ol in 60 % (325 mg) yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10-7.13 (m, 2H), 6.93-6.97 (m, 2H), 3.64 (t, 2H, J = 6.8 Hz), 2.59 (t, 2H, J = 7.2 Hz), 1.56-1.66 (m, 5H), 1.37-1.43 (m, 4H).

4-(2-Fluorophenyl)butan-1-ol



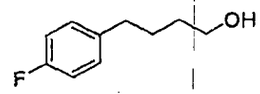
The title compound was prepared from 4-(2-fluorophenyl)but-3-yn-1-ol in 50 % (246 mg) yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13-7.25 (m, 2H), 6.97-7.03 (m, 2H), 3.66 (t, 2H, J = 6.0 Hz), 2.68 (t, 2H, J = 6.8 Hz), 1.59-1.73 (m, 4H), 1.37 (br s, 1H).

4-(3-Fluorophenyl)butan-1-ol



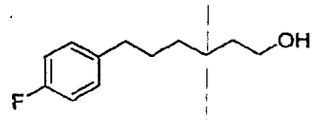
The title compound was prepared from 4-(3-fluorophenyl)but-3-yn-1-ol in 60 % (295 mg) yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19-7.29 (m, 1H), 6.95 (d, 1H, J = 7.2 Hz), 6.83-6.89 (m, 2H), 3.66 (t, 2H, J = 6.4 Hz), 2.64 (t, 2H, J = 7.6 Hz), 1.56-1.74 (m, 4H), 1.39 (br s, 1H).

4-(4-Fluorophenyl)butan-1-ol



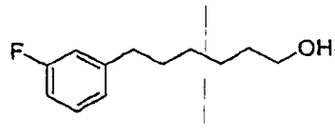
The title compound was prepared from 4-(4-fluorophenyl)but-3-yn-1-ol in 47 % (233 mg) yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10-7.15 (m, 2H), 6.93-6.98 (m, 2H), 3.66 (t, 2H, J = 6.4 Hz), 2.61 (t, 2H, J = 7.6 Hz), 1.56-1.72 (m, 4H), 1.35 (s, 1H).

6-(4-Fluorophenyl)hexan-1-ol



The title compound was prepared from 6-(4-fluorophenyl)hex-5-yn-1-ol in 17 % (95 mg) yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15–7.18 (m, 2H), 6.98-7.07 (m, 2H), 3.65 (t, 2H, 6.8 Hz), 2.65 (t, 2H, J = 7.6 Hz), 1.57-1.65 (m, 4H), 1.38-1.42 (m, 4H), 1.31 (s, 1H).

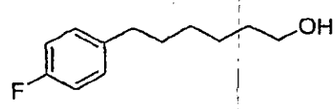
6-(3-fluorophenyl)hexan-1-ol



The title compound was prepared from 6-(3-(trifluoromethyl)phenyl)hex-5-yn-1-ol in 17 % (100 mg) yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19-7.25 (m, 1H), 6.93 (d, 1H, J = 8.0 Hz), 6.83-6.88 (m, 2H), 3.63 (t, 2H, J = 6.4 Hz), 2.60 (t, 2H, J = 7.6 Hz), 1.53-1.66 (m, 4H), 1.31-1.43 (m, 5H)

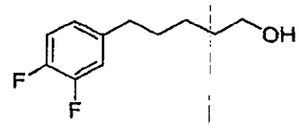
99

6-(4-fluorophenyl)hexan-1-ol



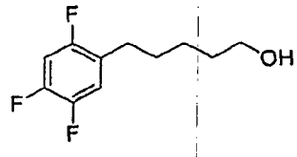
The title compound was prepared from 6-(3-(trifluoromethyl)phenyl)hex-5-yn-1-ol in 27 % (162 mg) yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19-7.27 (m, 1H), 7.09-7.13 (m, 1H), 6.92-7.04 (m, 2H), 3.63 (t, 2H, J = 6.4 Hz), 2.57 (t, 2H, J = 7.6 Hz), 1.49-1.66 (m, 5H), 1.34-1.42 (m, 4H).

5-(3,4-difluorophenyl)pentan-1-ol



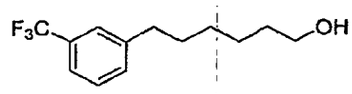
The title compound was prepared from 6-(3-(trifluoromethyl)phenyl)hex-5-yn-1-ol in 67 % (404 mg) yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.93-7.05 (m, 2H), 6.84-6.87 (m, 1H), 3.64 (t, 2H, J = 6.8 Hz), 2.58 (t, 2H, J = 7.6 Hz), 1.56-1.66 (m, 4H), 1.35-1.43 (m, 3H)

5-(2,4,5-trifluorophenyl)pentan-1-ol



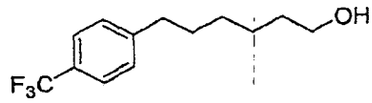
The title compound was prepared from 6-(3-(trifluoromethyl)phenyl)hex-5-yn-1-ol in 57 % (0.376g) yield. ^{1}H NMR (400 MHz, $CDCl_3$) d 6.96-7.01 (m, 1H), 6.83-6.89 (m, 1H), 3.64 (t, 2H, J=6.8 Hz), 2.59 (t, 2H, J=7.2 Hz), 1.56-1.65 (m, 4H), 1.34-1.44 (m, 3H)

6-(3-(trifluoromethyl)phenyl)hexan-1-ol



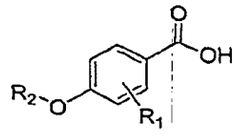
The title compound was prepared from 6-(3-(trifluoromethyl)phenyl)hex-5-yn-1-ol in 50 % (362 mg) yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.44 (m, 4H), 3.64 (t, 2H, J = 6.8 Hz), 2.67 (t, 2H, J = 7.2 Hz), 1.54-1.69 (m, 4H), 1.24-1.44 (m, 5H).

6-(4-(trifluoromethyl)phenyl)hexan-1-ol



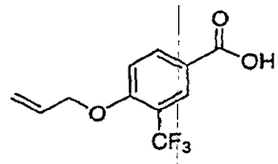
The title compound was prepared from 6-(4-(trifluoromethyl)phenyl)hex-5-yn-1-ol in 72 % (534 mg) yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, 2H, J = 8.0 Hz), 7.27 (d, 2H, J = 8.0 Hz), 3.64 (t, 2H, J = 6.4 Hz), 2.66 (t, 2H, J = 7.2 Hz), 1.53-1.68 (m, 4H), 1.35-1.42 (m, 5H).

General protocol for synthesis of substituted 4-(allyloxy)benzoic acid (2)



To a solution of the desired alcohol (1.05 equiv) in anhydrous THF was added potassium *t*-butyloxide (2.05 equiv). The mixture was heated at 65 °C for 10 minutes then added substituted 4-fluorobenzoic acid (**1**) (1.00 equiv) in THF. The resultant solution was heated at 65 °C 1 to 3 hours. After cooling down to room temperature, the reaction was diluted with ethyl acetate and washed with 10% $KHSO_4$ or 1N HCl (1x), and saturated NaCl (1x). The organic layer was dried over $MgSO_4$, filtered, and the solvent was removed *in vacuo* to afford intermediate **2**.

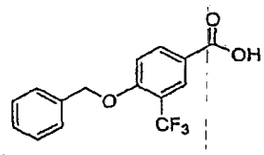
4-(Allyloxy)-3-(trifluoromethyl)benzoic acid (2a)



The title compound was prepared from 4-fluoro-3-(trifluoromethyl)benzoic acid (1a) in >99% (5.65 g) yield. HPLC retention time on a C8(2) column (30 × 3.00 mm, 3 μ) was 2.53 min with gradient 20-98% acetonitrile-H_2O (0.1% TFA) in 4.0 min as mobile phase. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.10 (br s, 1H), 8.15 (dd, 1H, J = 8.8 Hz, J = 2.4 Hz), 8.08 (d, 1H, J = 2.4 Hz), 7.35 (d, 1H, J = 8.8 Hz), 5.95-6.80 (m, 1H), 5.38-5.45 (m, 1H), 5.26-5.32 (m, 1H), 4.77-4.82 (m, 2H).

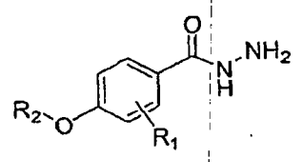
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4-(Benzyloxy)-3-(trifluoromethyl)benzoic acid (2b)



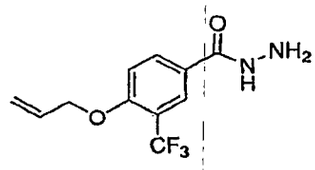
The title compound was prepared from 4-fluoro-3-(trifluoromethyl)benzoic acid (**1a**) in >99% (7.22g) yield.

General protocol for synthesis of substituted benzohydrazide (3)



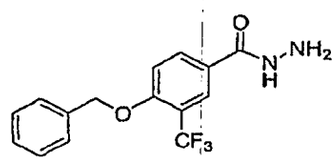
Benzoic acid **2** (1.0 equiv) was stirred with HATU (1.1 equiv) and DIEA (3.0 equiv) in DCM-DMF (2:1) for 20 minutes. The solution was then added to a solution of hydrazine mono-hydrate (3.0-5.0) in DCM-DMF (2:1). The reaction mixture was stirred at rt for 1 hour, then diluted with ethyl acetate and washed with 10% NH_4Cl (2x) and saturated NaCl (1x). The organic layer was dried over $MgSO_4$, filtered, and the solvent was removed *in vacuo* to afford benzohydrazide **3**.

4-(Allyloxy)-3-(trifluoromethyl)benzohydrazide (3a)



The title compound was prepared from 4-(allyloxy)-3-(trifluoromethyl)benzoic acid (**1a**) in >99% (6.00 g) yield. HPLC retention time on a C8(2) column (30 × 3.00 mm, 3 μ) was 1.79 min with gradient 20-98% acetonitrile-H_2O (0.1% TFA) in 4.0 min as mobile phase. MS (ESI, $M+H^+$) = 261.09

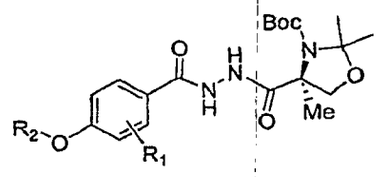
4-(Benzyloxy)-3-(trifluoromethyl)benzohydrazide (3b)



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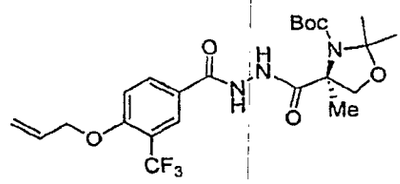
The title compound was prepared from 4-(Benzyloxy)-3-(trifluoromethyl)benzoic acid **2b** in >99% (14.7 g) yield. MS (ESI, $M+H^+$) = 311.1.

General protocol for synthesis of acyl-benzohydrazide (5)



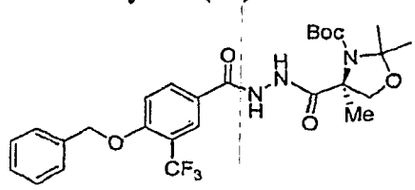
(*R*)-3-(*tert*-Butoxycarbonyl)-2,2,4-trimethyloxazolidine-4-carboxylic acid **4** (1.0 equiv) was stirred with HATU (1.1 equiv) and DIEA (3.0 equiv) in DCM-DMF (2:1) for 10 min followed by addition of substituted benzohydrazide **3** (1.0 equiv). The reaction mixture was stirred at rt for 1 hour, then diluted with ethyl acetate and washed with 10% NH_4Cl (2x) and saturated NaCl (1x). The organic layer was dried over $MgSO_4$, filtered, and the solvent was removed *in vacuo* to afford acyl-benzohydrazide **5**.

(*R*)-*tert*-Butyl 4-(2-(4-(allyloxy)-3-(trifluoromethyl)benzoyl)hydrazinecarbonyl)-2,2,4-trimethyloxazolidine-3-carboxylate (5a)



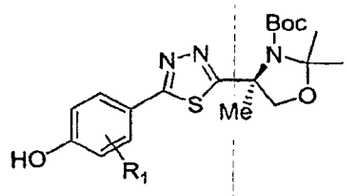
The title compound was prepared from 4-(allyloxy)-3-(trifluoromethyl)benzohydrazide **3a** in >99% (11.51 g) yield. HPLC retention time on a C8(2) column (30 × 3.00 mm, 3 μ) was 2.92 min with gradient 20-98% acetonitrile-H_2O (0.1% TFA) in 4.0 min as mobile phase. MS (ESI, $M+Na^+$) = 524.1

(*R*)-*tert*-Butyl 4-(2-(4-(benzyloxy)-3-(trifluoromethyl)benzoyl)hydrazinecarbonyl)-2,2,4-trimethyloxazolidine-3-carboxylate (5b)



The title compound was prepared from 4-(benzyloxy)-3-(trifluoromethyl)benzohydrazide **3b** in 83% (13.1 g) yield. MS (ESI, $M+Na^+$) = 574.1; TLC (2:1, Hex/EtOAc), R_f = 0.34.

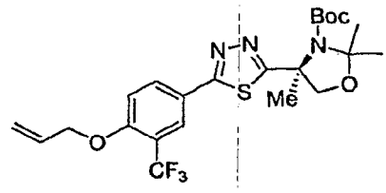
General protocol for synthesis of phenyl-thiadiazole from allyl protected precursor (6)



A solution of allyl protected acyl-benzohydrazide **5a** (1.0 equiv) in DCM was treated with Lawesson's reagent (1.0 equiv) at 50 ^{0}C overnight. The reaction was cooled down to room temperature and the supernatant was chromatographed on a silica gel column eluted with ethyl acetate in hexanes (0-40%, v/v) to afford phenyl-thiadiazole.

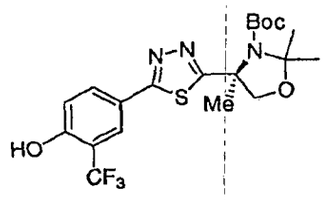
A solution of phenyl-thiadiazole (1.0 equiv) and Et_2NH (1.5 equiv) in THF was treated with $Pd(PPh_3)_4$ (0.02 to 0.05 equiv) at rt for 1-3 hours. The solvent removed *in vacuo* and the product was purified by silica gel column chromatography using the Combi-Flash system (Hex:EtOAc).

(*R*)-*tert*-Butyl 4-(5-(4-(allyloxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)-2,2,4-trimethyloxazolidine-3-carboxylate



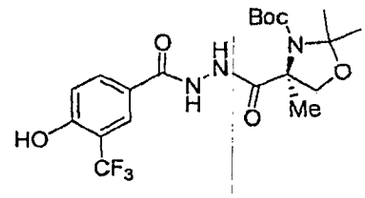
The title compound was prepared from acyl-benzohydrazide **5a** in 88% (8.35 g) yield. HPLC retention time on a C8(2) column (30 × 3.00 mm, 3 μ) was 2.84 min with gradient 50-98% acetonitrile-H_2O (0.1% TFA) in 4.0 min as mobile phase. MS (ESI, $M+H^+$) = 500.0; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.13-8.24 (m, 2H), 7.42 (d, 1H, J = 8.4 Hz), 5.98-6.10 (m, 1H), 5.40-5.50 (m, 1H), 5.25-5.34 (m, 1H), 4.80-4.84 (m, 2H), 4.10-4.40 (m, 2H), 1.88 (s, 3H), 1.66 (s, 3H), 1.56 (s, 3H), 1.41 (s, 3H), 1.18 (s, 6H).

(*R*)-*tert*-Butyl 4-(5-(4-hydroxy-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)-2,2,4-trimethyloxazolidine-3-carboxylate (6a)



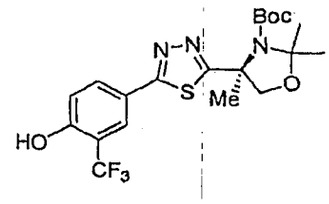
The title compound was prepared from allyl protected phenyl-thiadiazole **6a** in 64% (4.86 g) yield. HPLC retention time on a C8(2) column (30 × 3.00 mm, 3 μ) was 2.06 min with gradient 50-98% acetonitrile-H_2O (0.1% TFA) in 4.0 min as mobile phase. MS (ESI, $M+H^+$) = 460.0; ^1H NMR (400 MHz, DMSO-d_6) δ 11.40 (s, 1H), 8.00-8.10 (m, 2H), 7.18 (d, 1H, J = 8.8 Hz), 4.07-4.21 (m, 2H), 1.88 (s, 3H), 1.67 (s, 3H), 1.57 (s, 3H), 1.42 (s, 3H), 1.19 (s, 6H).

(*R*)-*tert*-Butyl 4-(2-(4-hydroxy-3-(trifluoromethyl)benzoyl)hydrazinecarbonyl)-2,2,4-trimethyloxazolidine-3-carboxylate (5c)



A solution of benzyl protected acyl-benzohydrazide **5b** (1.0 equiv) in MeOH was subjected to hydrogenation in the presence of Pd/C (10% w) for 1 h. The reaction mixture was filtered through celite and concentrated to give compound **5c** (6.86 g, 99% yield). MS (ESI, $M+Na^+$): 484.0; TLC (2:1, Hex/EtOAc), R_f = 0.20; ^1H NMR (400 MHz, CD_3OD) δ 8.11 (s, 1H,), 7.95 (d, 1H, J = 8.8 Hz), 7.01 (d, 1H, J = 8.8 Hz), 4.28 (br s, 1H), 3.91 (br s, 1H), 1.69 (s, 3H,), 1.64 (s, 3H), 1.58 (s, 3H), 1.49 (s, 9H).

(*R*)-*tert*-Butyl 4-(5-(4-hydroxy-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)-2,2,4-trimethyloxazolidine-3-carboxylate (6a)



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The phenyl-thiazole 6a was prepared through two different protocols (A and B) from 5c:

Protocol A:

A solution of acyl-benzohydrazide **5c** (1 equiv) in DCM was treated with Lawesson's reagent (3.0 equiv) at 50 ^{0}C overnight. The reaction was cooled down to room temperature and the supernatant was chromatographed on a silica gel column eluted with ethyl acetate in hexanes (0-40%, v/v) to afford phenyl-thiadiazole **6** in 37% (670 mg) yield.

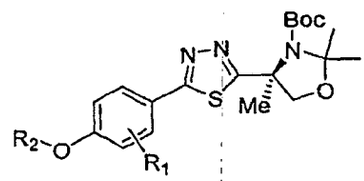
Protocol B:

A solution of acyl-benzohydrazide **5c** (1 equiv) in DCM was added acetyl anhydride (1.1 equiv) and pyridine (1.1 equiv). The mixture was stirred at rt for 4 h. The solvent was removed under vacuum and the residue was dissolved in ethyl acetate, washed with brine (3x), dried over $MgSO_4$ and concentrated to afford crude acylated **5c** in quantitative (5.46 g) yield. TLC (4:1, Hex/EtOAc), R_f = 0.40; MS (ESI, M+H$^+$) = 504.1.

To a solution of acylated intermediate **5c** (1.0 equiv) in toluene was added Lawesson's reagent (1.1 equiv). The mixture was heated at 85 °C for 3 h. The reaction was cooled down to room temperature and the supernatant was chromatographed on a silica gel column eluted with ethyl acetate in hexanes (15%–30%, v/v) to afford acylated **6a** in 82% (5.1 g) yield. MS (ESI, M+H$^+$) = 502.0.

Acylated **6a** was dissolved in a mixture of methanol and saturated $NaHCO_3$ (2:1, v/v) and stirred at rt overnight. The methanol was removed and the aqueous phase was extracted with ethyl acetate (3x). The combined organic phase was washed with brine, dried over $MgSO_4$ and concentrated to afford **6 a** in 76% (3.1g) yield.

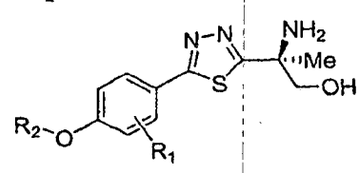
General protocol for Mitsunobu reaction (7)



To a suspension of triphenyl phosphine, polymer bound [3mmol/g loading] (1.2-6.0 equiv) in DCM or PPh_3 (1.0 equiv) in DCM or THF, was added a phenol **6** (1.0 equiv) and the desired alcohol (1.0 equiv). The reaction was then cooled to 0 °C in an ice bath and added diisopropyl azodicarboxylate (DIAD) (1.0 equiv). The reaction was

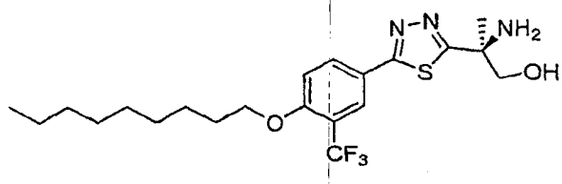
then allowed to warm to rt and stirred for 4-12 hours. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure to give a crude product, which was taken on to the next step without any further purification.

General protocol for one pot deprotection of both Boc and oxazolidine (8)



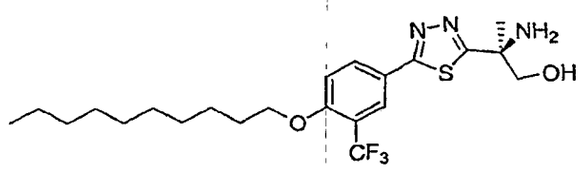
To a solution of compound **8** in DCM added TFA (10-50% v/v) and 1% anisole or triisopropyl silane (TIPS) as scavenger. The reaction mixture was allowed to stir at rt for 0.5-2 hours, dried under vacuum and was subjected directly to prep HPLC purification. The product was purified by prep HPLC on a C8(2) column ((Luna, 5μ, 100 × 21.10 mm) with acetonitrile-H_2O (0.1% TFA) as mobile phase and gradient 30-98% in 20 min.

(*S*)-2-Amino-2-(5-(4-(nonyloxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazole-2-yl)propan-1-ol (8a)



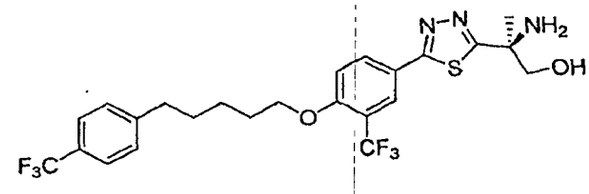
The title compound was prepared from protected phenyl-thiadiazole **6a** in 90% (579 mg) yield. HPLC retention time on a C8(2) column (30 x 50 mm, 3 μL) is 1.68 min with gradient 50-98% acetonitrile-H_2O (0.1 % TFA) in 3.5 min as mobile phase. MS (ESI, $M+H^+$) = 446.2; ^1H NMR (400 MHz, DMSO-d_6) δ 8.21 (dd, 1H, J = 9.0 Hz, J = 2.0 Hz), 8.15 (d, 1H, J = 2.0 Hz), 7.45 (d, 1H, J = 8.4), 4.21 (t, 2H, J = 6.2 Hz), 3.74-3.85 (m, 3H), 1.68-1.77 (m, 5H), 1.25-1.45 (m, 12H), 0.849 (t, 3H, J = 6.4).

(*S*)-2-Amino-2-(5-(4-(decyloxy)-3(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol (8b)



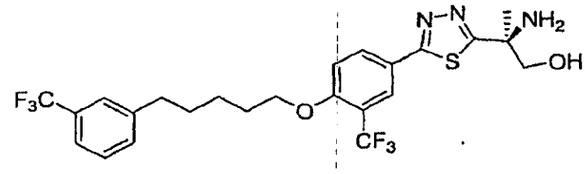
The title compound was prepared from protected phenyl-thiadiazole **6a** in 50% (208 mg) yield. HPLC retention time on a C8(2) column (30 x 50 mm, 3 μL) is 1.95 min with gradient 50-98% acetonitrile-H_2O (0.1 % TFA) in 3.5 min as mobile phase. MS (ESI, $M+H^+$) = 460.2; ^1H NMR (400 MHz, DMSO-d_6) δ 8.2 (d, 1H, J = 8.8 Hz), 8.15 (s, 1H), 7.44 (d, 1H, J = 8.8 Hz), 4.21 (t, 2H, J = 4.8 Hz), 3.74-3.78 (m, 3H), 1.75 (t, 3H, J = 6.8 Hz), 1.65 (s, 3H), 1.25-1.43 (m, 14H), 0.83-0.86 (m, 3H).

(*S*)-2-Amino-2-(5-(3-(trifluoromethyl)-4-(5-(4-(trifluoromethyl)phenyl)pentyloxy)phenyl)-1,3,4-thiadiazole-2-yl)propan-1-ol (8c)



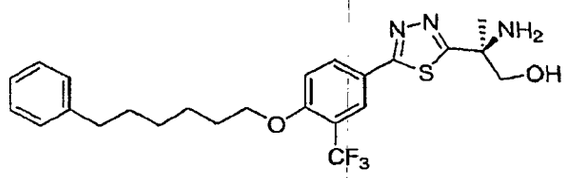
The title compound was prepared from protected phenyl-thiadiazole **6a** in 20% (149 mg) yield. HPLC retention time on a C8(2) column (30 x 50 mm, 3 μL) is 1.66 min with gradient 50-98% acetonitrile-H_2O (0.1 % TFA) in 3.5 min as mobile phase. MS (ESI, $M+H^+$) = 534.1; ^1H NMR (400 MHz, DMSO-d_6) δ 8.87 (br s, 2H), 8.22 (d, 1H, J = 8 Hz), 8.16 (s, 1H), 7.44-7.55 (m, 5H), 4.22 (t, 2H, J = 6 Hz), 3.77-3.83 (m, 3H), 2.71 (t, 2H, J = 7.6 Hz), 1.68-1.82 (m, 7H), 1.46-1.48 (m, 2H).

(*S*)-2-Amino-2-(5-(3-(trifluoromethyl)-4-(5-(3-(trifluoromethyl)phenyl)pentyloxy)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol (8d)



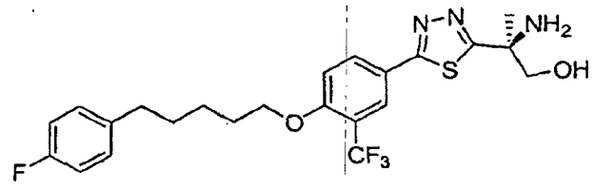
The title compound was prepared from protected phenyl-thiadiazole **6a** in 50% (379 mg) yield. HPLC retention time on a C8(2) column (30 x 50 mm, 3 μL) is 2.52 min with gradient 30-98% acetonitrile-H_2O (0.1 % TFA) in 3.5 min as mobile phase. MS (ESI, $M+H^+$) = 534.1; ^1H NMR (400 MHz, DMSO-d_6) δ 8.22 (d, 1H, J = 8 Hz), 8.15 (d, 1H, J = 2.0 Hz), 7.43-7.55 (m, 4H), 7.44 (d, 1H, J = 8.8 Hz), 4.22 (t, 2H, J = 6.0 Hz), 3.75-3.80 (m, 3H), 2.70 (t, 2H, J = 7.6 Hz), 1.78-1.82 (m, 2H), 1.67-1.70 (m, 5H), 1.45-1.47 (m, 2H).

(*S*)-2-Amino-2-(5-(4-(6-phenylhexyloxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol (8e)



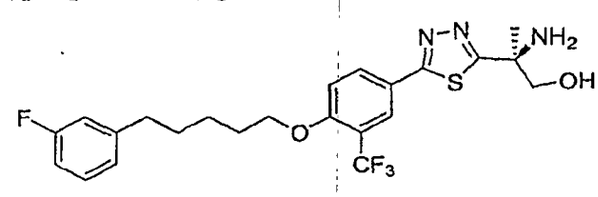
The title compound was prepared from protected phenyl-thiadiazole **6a** in 40% (271 mg) yield. HPLC retention time on a C8(2) column (30 x 50 mm, 3 μL) is 2.48 min with gradient 30-98% acetonitrile-H_2O (0.1 % TFA) in 3.5 min as mobile phase. MS (ESI, $M+H^+$) = 480.1; ^1H NMR (400 MHz, DMSO-d_6) δ 8.21 (d, 1H, J = 9.6 Hz), 8.16 (s, 1H), 7.44 (d, 1H, J = 8.8 Hz), 7.13-7.27 (m, 5H), 4.21 (t, 2H, J = 6.4 Hz), 3.74-3.84 (m, 3H), 2.57 (t, 2H, J = 7.6 Hz), 1.69-1.79 (m, 5H), 1.55-1.62 (m, 2H), 1.44-1.51 (m, 2H), 1.33-1.39 (m, 2H).

(*S*)-2-Amino-2-(5-(4-(5-(4-fluorophenyl)pentyloxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol (8f)



The title compound was prepared from protected phenyl-thiadiazole **6a** in 25% (155 mg) yield. HPLC retention time on a C8(2) column (30x50 mm, 3 μL) is 1.92 min with gradient 40-98% acetonitrile-H_2O (0.1 % TFA) in 3.5 min as mobile phase. MS (ESI, $M+H^+$) = 484.1; ^1H NMR (400 MHz, DMSO-d_6) δ 8.19 (d, 1H, J = 9.6 Hz), 8.13 (s, 1H), 7.43 (d, 1H, J = 8.8 Hz), 7.19-7.22 (m, 2H), 7.03-7.08 (m, 2H), 4.20 (t, 2H, J = 6.0 Hz), 3.74-3.79 (m, 3H), 2.57 (t, 2H, J = 7.6 Hz), 1.76-1.79 (m, 2H), 1.60-1.67 (m, 5H), 1.42-1.45 (m, 2H).

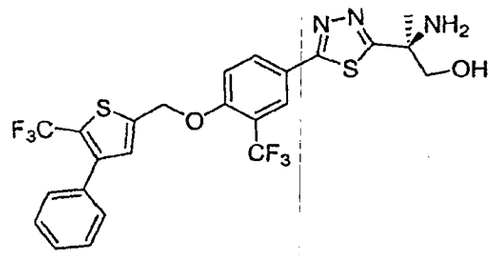
(*S*)-2-Amino-2-(5-(4-(5-(3-fluorophenyl)pentyloxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol (8g)



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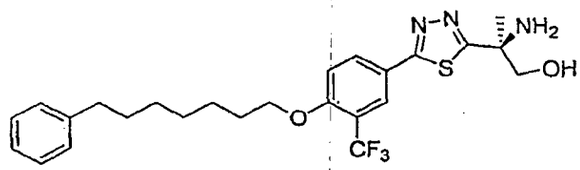
The title compound was prepared from protected phenyl-thiadiazole **6a** in 35% (304 mg) yield. HPLC retention time on a C8(2) column (30 x 50 mm, 3 μL) is 2.71 min with gradient 20-95% acetonitrile-H_2O (0.1 % TFA) in 3.5 min as mobile phase. MS (ESI, $M+H^+$) = 484.1; ^1H NMR (400 MHz, DMSO-d_6) δ 8.21 (dd, 1H, J = 8.4 Hz, J = 2.0 Hz), 8.15 (s, 1H), 7.44 (d, 1H, J = 8.8 Hz), 7.26-7.31 (m, 1H), 6.94-7.09 (m, 3H), 4.21 (t, 2H, J = 6.0 Hz), 3.74-3.83 (m, 3H), 2.61 (t, 2H, J = 7.6 Hz), 1.75-1.82 (m, 2H), 1.60-1.68 (m, 5H), 1.38-1.48 (m, 4H).

(*S*)-2-Amino-2-(5-(4-((4-phenyl-5-(trifluoromethyl)thiophen-2-yl)methoxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol (8h)



The title compound was prepared from 4-(5-(4-hydroxy-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)-2,2,4-trimethyoxyazolidine-3-carboxylate **6a** in 38% (254 mg) yield. HPLC retention time on a Synergi-Max RP column (2 x 20 mm, 2 μL) is 1.47 min with gradient 30-99% acetonitrile-H_2O (0.1 % TFA) in 2 min as mobile phase. MS (ESI, $M+H^+$) = 560.0; ^1H NMR (400 MHz, DMSO-d_6) δ 8.88 (br s, 2H), 8.31 (dd, 1H, J = 9.2 Hz, J = 2.4 Hz), 8.23 (d, 1H, J = 2.0 Hz), 7.44-7.51 (m, 6H), 6.11 (s, 1H), 5.72 (s, 2H), 3.79-3.85 (m, 3H), 1.72 (s, 3H).

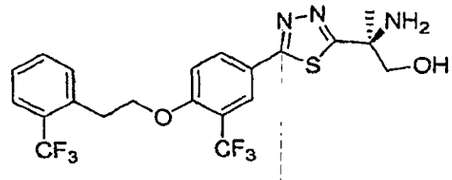
(*S*)-2-Amino-2-(5-(4-(7-phenylheptyloxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol (8i)



The title compound was prepared from 4-(5-(4-hydroxy-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)-2,2,4-trimethyoxyazolidine-3-carboxylate **6a** in 50% (306 mg) yield. HPLC retention time on a Synergi-Max RP column (2 x 20 mm, 2 μL) is 1.32 min with gradient 40-99% acetonitrile-H_2O (0.1 %

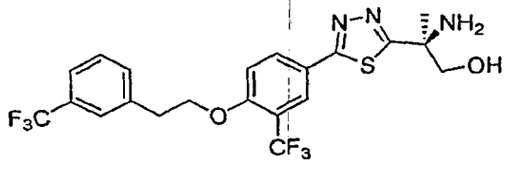
TFA) in 2 min as mobile phase. MS (ESI, M+H$^+$) = 494.2; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.87 (br s, 2H), 8.22 (dd, 1H, J = 8.8, J = 2.4), 8.16 (d, 1H, J = 2.0 Hz), 7.45 (d, 1H, J = 8.4 Hz), 7.24-7.25 (m, 4H), 7.13-7.17 (m, 2H), 7.04 (s, 1H), 4.21 (t, 2H, J = 6.0 Hz), 3.78-3.85 (m, 3H), 2.56 (t. 2H, J = 7.6 Hz), 1.67-1.78 (m, 4H), 1.53-1.61 (m, 2H), 1.27-1.47 (m, 5H).

(*S*)-2-Amino-2-(5-(3-(trifluoromethyl)-4-(2-(trifluoromethyl)phenethoxy)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol (8j)



The title compound was prepared from 4-(5-(4-hydroxy-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)-2,2,4-trimethyoxyazolidine-3-carboxylate **6a** in 58% (35 mg) yield. HPLC retention time on a Synergi-Max RP column (2 x 20 mm, 2 μL) is 0.70 min with gradient 40-99% acetonitrile-H_2O (0.1 % TFA) in 2 min as mobile phase. MS (ESI, M+H$^+$) = 492.0; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.79 (br s, 2H), 8.22 (dd, 1H, J = 9.0 Hz, J = 2.0 Hz), 8.15 (d, 1H, J = 2.4 Hz), 7.73 (d, 1H, J = 8 Hz), 7.45-7.52 (m, 4H), 4.49 (t, 2H, J = 6.4 Hz), 3.75-3.85 (m, 3H), 3.28 (t, 2H, J = 6.4 Hz), 1.70 (s, 3H).

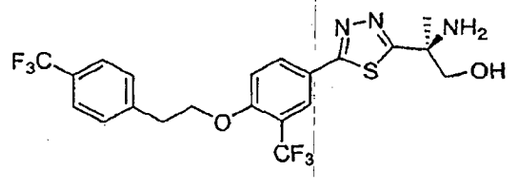
(*S*)-2-Amino-2-(5-(3-(trifluoromethyl)-4-(3-(trifluoromethyl)phenethoxy)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol (8k)



The title compound was prepared from 4-(5-(4-hydroxy-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)-2,2,4-trimethyoxyazolidine-3-carboxylate **6a** in 51% (30.7 mg) yield. HPLC retention time on a Synergi-Max RP column (2 x 20 mm, 2 μL) is 0.68 min with gradient 40-99% acetonitrile-H_2O (0.1 % TFA) in 2 min as mobile phase. MS (ESI, M+H$^+$) = 491.9; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.88 (br s, 2H), 8.21 (dd, 1H, J = 8.6 Hz, J = 2.0 Hz), 8.14 (d, 1H, J = 2.4 Hz),

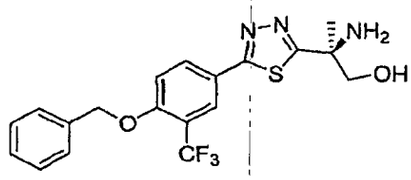
7.49-7.70 (m, 5H), 4.48 (t, 2H, J = 6.4 Hz), 3.77-3.85 (m, 3H), 3.20 (t, 2H, J = 6.0 Hz), 1.71 (s, 3H).

(*S*)-2-Amino-2-(5-(3-(trifluoromethyl)-4-(4-(trifluoromethyl)phenethoxy)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol (8l)



The title compound was prepared from 4-(5-(4-hydroxy-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)-2,2,4-trimethyoxyazolidine-3-carboxylate **6a** in 64% (39 mg) yield. HPLC retention time on a Synergi-Max RP column (2 x 20 mm, 2 μL) is 0.77 min with gradient 50-98% acetonitrile-H_2O (0.1 % TFA) in 2 min as mobile phase. MS (ESI, M+H$^+$) = 491.9; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.91 (br s, 2H), 8.22 (dd, 1H, J = 9.0 Hz, J = 2.0 Hz), 8.15 (d, 1H, J = 2.4 Hz), 7.44-7.68 (m, 5H), 4.49 (t, 2H, J = 6.0 Hz), 3.74-3.86 (m, 3H), 3.20 (t, 2H, J = 6.4 Hz), 1.71 (s, 3H).

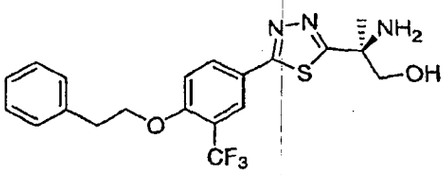
(*S*)-2-Amino-2-(5-(4-(benzyloxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol (8m)



The title compound was prepared from 4-(5-(4-hydroxy-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)-2,2,4-trimethyoxyazolidine-3-carboxylate **6a** in 19% (10 mg) yield. HPLC retention time on a Synergi-Max RP column (2 x 20 mm, 2 μL) is 1.37 min with gradient 20-95% acetonitrile-H_2O (0.1 % TFA) in 2 min as mobile phase. MS (ESI, M+H$^+$) = 409.9; ^{1}H NMR (400 MHz, CD_3OD) δ 8.25 (d, 1H, J = 2.4 Hz), 8.16 (dd, 1H, J = 8.4 Hz, J = 2.4 Hz), 7.32-7.48 (m, 6H), 5.34 (s, 2H), 3.89-3.96 (m, 2H, 1.83 (s, 3H).

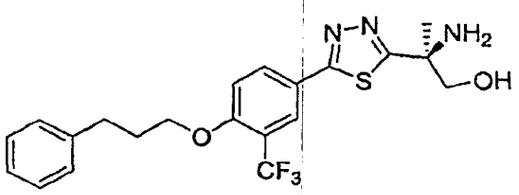
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(*S*)-2-Amino-2-(5-(4-phenethoxy-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol (8n)



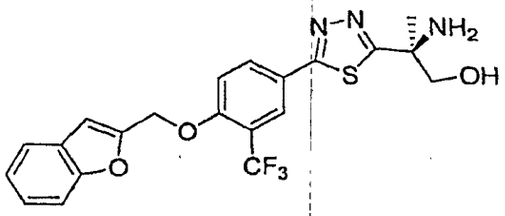
The title compound was prepared from 4-(5-(4-hydroxy-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)-2,2,4-trimethyoxyazolidine-3-carboxylate **6a** in 12% (6.2 mg) yield. HPLC retention time on a Synergi-Max RP column (2 x 20 mm, 2 μL) is 1.45 min with gradient 20-95% acetonitrile-H_2O (0.1 % TFA) in 2 min as mobile phase. MS (ESI, $M+H^+$) = 423.9; ^1H NMR (400 MHz, CD_3OD) δ 8.25 (d, 1H, J = 2.4 Hz), 8.16 (dd, 1H, J = 8.4 Hz, J = 2.4 Hz), 7.26-7.35 (m, 6H), 4.40 (t, 2H, J = 6.8 Hz), 3.89-3.96 (m, 2H), 3.14 (t, 2H, J = 6.8 Hz), 1.82 (s, 3H).

(*S*)-2-Amino-2-(5-(4-(3-phenylpropoxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol (8o)



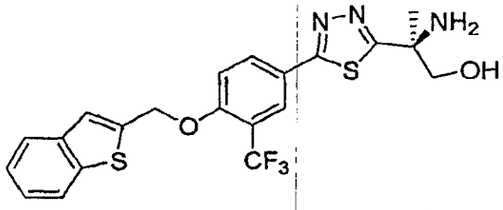
The title compound was prepared from 4-(5-(4-hydroxy-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)-2,2,4-trimethyoxyazolidine-3-carboxylate **6a** in 12% (6.0 mg) yield. HPLC retention time on a Synergi-Max RP column (2 x 20 mm, 2 μL) is 1.26 min with gradient 30-99% acetonitrile-H_2O (0.1 % TFA) in 2 min as mobile phase. MS (ESI, $M+H^+$) = 437.9; ^1H NMR (400 MHz, CD_3OD) δ 8.25 (d, 1H, J = 2.4 Hz), 8.16 (dd, 1H, J = 8.4 Hz, J = 2.4 Hz), 7.16-7.31 (m, 6H), 4.16 (t, 2H, J = 6.0 Hz), 3.89-3,96 (m, 2H), 2.85 (t, 2H, J = 7.6 Hz), 2.13-2.17 (m, 2H), 1.83 (s, 3H).

(*S*)-2-Amino-2-(5-(4-(benzofuran-2-ylmethoxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol (8p)



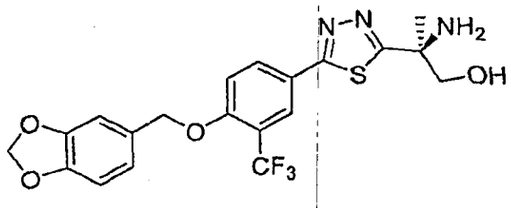
The title compound was prepared from 4-(5-(4-hydroxy-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)-2,2,4-trimethyoxyazolidine-3-carboxylate **6a** in 29% (16 mg) yield. HPLC retention time on a C8(2) column (30 x 50 mm, 3 μL) is 2.12 min with gradient 20-98% acetonitrile-H_2O (0.1 % TFA) in 2 min as mobile phase. MS (ESI, $M+H^+$) = 450.0; ^1H NMR (400 MHz, DMSO-d_6) δ 8.85 (br s, 2H), 8.28 (dd, 1H, J = 8.4 Hz, J = 2.4 Hz), 8.20 (d, 1H, J = 2.0 Hz), 7.89-7.74 (m, 3H), 7.25-7.37 (m, 2H), 6.97-7.23 (m, 1H), 5.59 (s, 3H), 3.75-3.85 (m, 3H), 1.71 (s, 3H).

(*S*)-2-Amino-2-(5-(4-(benzo[*b*]thiophen-2-ylmethoxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol (8q)



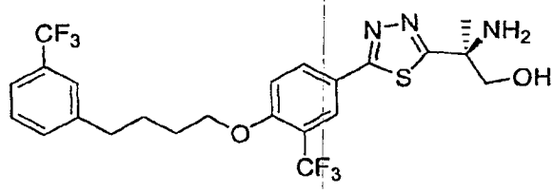
The title compound was prepared from 4-(5-(4-hydroxy-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)-2,2,4-trimethyoxyazolidine-3-carboxylate **6a** in 16% (9 mg) yield. HPLC retention time on a Synergi-Max RP column (2 x 20 mm, 2 μL) is 1.49 min with gradient 20-95% acetonitrile-H_2O (0.1 % TFA) in 2 min as mobile phase. MS (ESI, $M+H^+$) = 465.9; ^1H NMR (400 MHz, DMSO-d_6) δ 8.82 (br s, 2H), 8.28 (dd, 1H, J = 8.6 Hz, J = 2.0 Hz), 8.19 (d, 1H, J = 2.4 Hz), 8.02-8.04 (m, 1H), 7.91-7.93 (m, 1H), 7.74 (d, 1H, J = 8.8 Hz), 7.40-7.46 (m, 2H), 6.95-7.21 (m, 1H), 5.66 (s, 2H), 3.75-3.85 (m, 3H), 1.70 (s, 3H).

(*S*)-2-Amino-2-(5-(4-(benzo[*d*][1,3]dioxol-5-ylmethoxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol (8r)



The title compound was prepared from 4-(5-(4-hydroxy-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)-2,2,4-trimethyoxyazolidine-3-carboxylate **6a** in 41% (232 mg) yield. HPLC retention time on a Synergi-Max RP column (2 x 20 mm, 2 μL) is 1.38 min with gradient 20-95% acetonitrile-H_2O (0.1 % TFA) in 2 min as mobile phase. MS (ESI, $M+H^+$) = 453.9; ^1H NMR (400 MHz, DMSO-d_6) δ 8.87 (br s, 2H), 8.26 (dd, 1H, J = 9.2 Hz, J = 2.4 Hz), 8.19 (d, 1H, J = 2.4 Hz), 7.58 (d, 1H, J = 8.8 Hz), 6.87-7.12 (m, 3H), 6.07 (s, 2H), 5.34 (s, 2H), 3.76-3.85 (m, 2H), 1.71 (s, 3H).

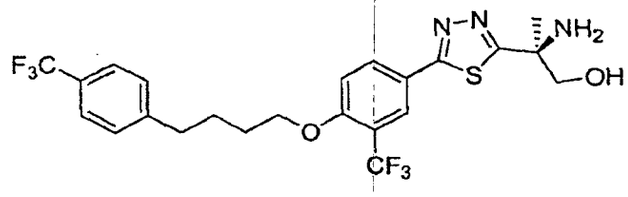
(*S*)-2-Amino-2-(5-(3-(trifluoromethyl)-4-(4-(3-(trifluoromethyl)phenyl)butoxy)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol (8s)



The title compound was prepared from 4-(5-(4-hydroxy-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)-2,2,4-trimethyoxyazolidine-3-carboxylate **6a** in 29% (184 mg) yield. HPLC retention time on a Synergi-Max RP column (2 x 20 mm, 2 μL) is 1.67 min with gradient 20-95% acetonitrile-H_2O (0.1 % TFA) in 2 min as mobile phase. MS (ESI, $M+H^+$) = 519.9; ^1H NMR (400 MHz, CD_3OD) δ 8.22 (d, 1H, J = 2.4 Hz), 8.16 (dd, 1H, J = 8.6 Hz, J = 2.4 Hz), 7.56 (d, 2H, J = 8.4 Hz), 7.4 (d, 2H, J = 8.0 Hz), 7.33 (d, 1H, J = 8.8 Hz), 4.23 (t, 2H, J = 5.2 Hz), 3.92-4.00 (m, 2H), 2.80 (t, 2H, J = 6.8 Hz), 1.88-1.92 (m, 4H), 1.84 (s, 3H).

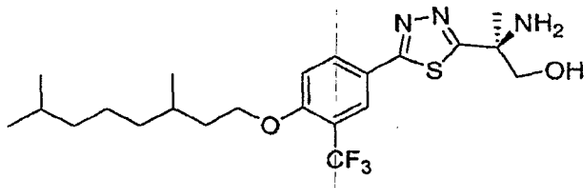
15

(*S*)-2-Amino-2-(5-(3-(trifluoromethyl)-4-(4-(4-(trifluoromethyl)phenyl)butoxy)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol (8t)



The title compound was prepared from 4-(5-(4-hydroxy-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)-2,2,4-trimethyoxyazolidine-3-carboxylate **6a** in 12% (7.8 mg) yield. HPLC retention time on a Synergi-Max RP column (2 x 20 mm, 2 μL) is 1.64 min with gradient 20-95% acetonitrile-H_2O (0.1 % TFA) in 2 min as mobile phase. MS (ESI, $M+H^+$) = 519.9; ^1H NMR (400 MHz, CD_3OD) δ 8.22 (d, 1H, J = 2.0 Hz), 8.16 (dd, 1H, J = 8.6 Hz, J = 2.0 Hz), 7.46-7.51 (m, 4H), 7.34 (d, 1H, J = 9.2 Hz), 4.24 (s, 2H), 3.90-3.98 (m, 2H), 2.80 (t, 2H, J = 6.8 Hz), 1.88-1.91 (m, 4H), 1.83 (s, 3H).

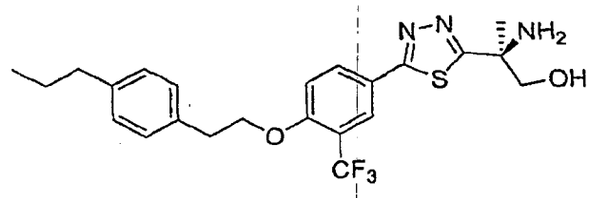
(2*S*)-2-Amino-2-(5-(4-(3,7-dimethyloctyloxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol (8u)



The title compound was prepared from 4-(5-(4-hydroxy-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)-2,2,4-trimethyoxyazolidine-3-carboxylate **6a** in 41% (19 mg) yield. HPLC retention time on a Synergi-Max RP column (2 x 20 mm, 2 μL) is 1.79 min with gradient 50-98% acetonitrile-H_2O (0.1 % TFA) in 2 min as mobile phase. MS (ESI, $M+H^+$) = 460.0; ^1H NMR (400 MHz, CD_3OD) δ 8.21 (d, 1H, J = 2.4 Hz), 8.17 (dd, 1H, J = 8.8 Hz, J = 2.4 Hz), 7.36 (d, 1H, J = 8.4 Hz), 4.86 (s, 5H), 4.22-4.27 (m, 2H), 3.90-3.98 (m, 2H), 1.87-1.90 (m, 1H), 1.83 (s, 3H), 1.74-1.78 (m, 1H), 1.61-1.65 (m, 1H), 1.50-1.55 (m, 1H), 1.30-1.40 (m, 3H), 1.16-1.22 (m, 3H), 0.97 (d, 3H, J = 6.4 Hz), 0.88 (d, 6H, J = 6.8 Hz)

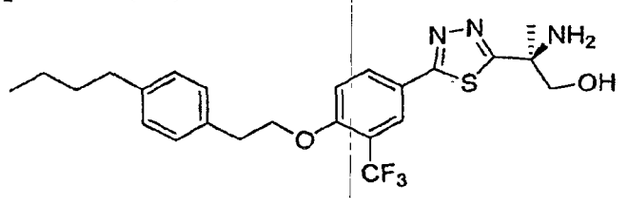
116

(*S*)-2-Amino-2-(5-(4-(4-propylphenethoxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol (8v)



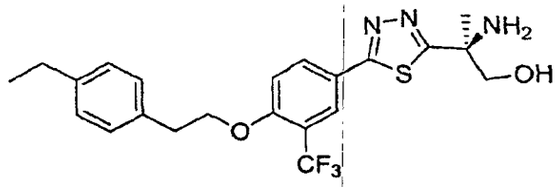
The title compound was prepared from 4-(5-(4-hydroxy-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)-2,2,4-trimethyoxyazolidine-3-carboxylate **6a** in 47% (27 mg) yield. HPLC retention time on a Synergi-Max RP column (2 x 20 mm, 2 μL) is 1.66 min with gradient 50-98% acetonitrile-H_2O (0.1 % TFA) in 2 min as mobile phase. MS (ESI, $M+H^+$) = 466.0; ^1H NMR (400 MHz, CD_3OD) δ 8.20 (d, 1H, J = 1.6 Hz), 8.13 (dd, 1H, J = 8.8 Hz, J = 2.4 Hz), 7.32 (d, 1H, J = 8.8 Hz), 7.22 (d, 2H, J = 8.4 Hz), 7.10 (d, 2H, J = 8.4 Hz), 4.44 (t, 2H, J = 6.6 Hz), 3.90-3.98 (m, 2H), 3.10 (t, 2H, J = 6.6 Hz), 2.55 (t, 2H, J = 7.6 Hz), 1.83 (s, 3H), 1.58-1.64 (m, 2H), 1.25 (d, 5H, J = 6.4), 0.91 (t, 3H, J = 7.6).

(*S*)-2-Amino-2-(5-(4-(4-butylphenethoxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol (8w)



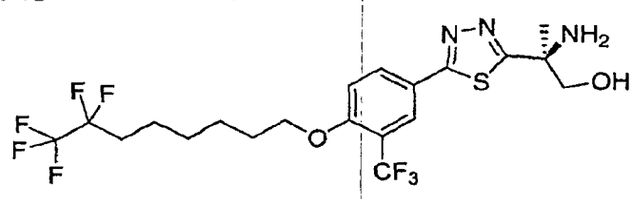
The title compound was prepared from 4-(5-(4-hydroxy-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)-2,2,4-trimethyoxyazolidine-3-carboxylate **6a** in 38% (23 mg) yield. HPLC retention time on a Synergi-Max RP column (2 x 20 mm, 2 μL) is 1.73 min with gradient 20-95% acetonitrile-H_2O (0.1 % TFA) in 2 min as mobile phase. MS (ESI, $M+H^+$) = 479.9; ^1H NMR (400 MHz, CD_3OD) δ 8.20 (d, 1H, J = 1.6 Hz), 8.13 (dd, 1H, J = 2.4 Hz, J = 8.8 Hz), 7.32 (d, 1H, J = 8.8 Hz), 7.22 (d, 2H, J = 8 Hz), 7.10 (d, 2H, J = 8 Hz), 4.36 (t, 2H, J = 6.4), 3.90-3.98 (m, 2H), 3.10 (t, 2H, J = 6.8 Hz), 2.57 (t, 2H, J = 7.6 Hz), 1.83 (s, 3H), 1.53-1.61 (m, 2H), 1.31-1.36 (m, 2H), 0.917 (t, 3H, J = 7.2 Hz).

(*S*)-2-Amino-2-(5-(4-(4-ethylphenethoxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol (8x)



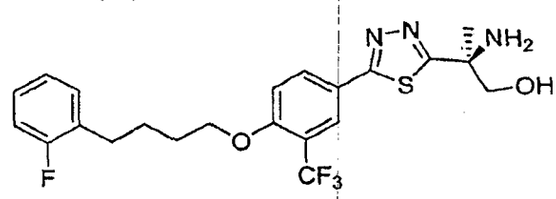
The title compound was prepared from 4-(5-(4-hydroxy-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)-2,2,4-trimethyoxyazolidine-3-carboxylate **6a** in 63% (36 mg) yield. HPLC retention time on a Synergi-Max RP column (2 x 20 mm, 2 μL) is 1.59 min with gradient 20-95% acetonitrile-H_2O (0.1 % TFA) in 2 min as mobile phase. MS (ESI, $M+H^+$) = 451.9; ^1H NMR (400 MHz, CD_3OD) δ 8.20 (d, 1H, J = 1.6 Hz), 8.14 (dd, 1H, J = 8.8 Hz, J = 2.4 Hz), 7.32 (d, 1H, J = 8.4 Hz), 7.23 (d, 2H, J = 8.4 Hz), 7.12 (d, 2H, J = 8.0 Hz),.4.36 (t, 2H, J = 6.8 Hz), 3.90-3.98 (m, 2H), 3.10 (t, 2H, J = 6.8 Hz), 2.55-2.65 (m, 2H), 1.83 (s, 3H), 1.20 (t, 3H, J = 7.6 Hz).

(*S*)-2-Amino-2-(5-(4-(7,7,8,8,8-pentafluorooctyloxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol (8y)



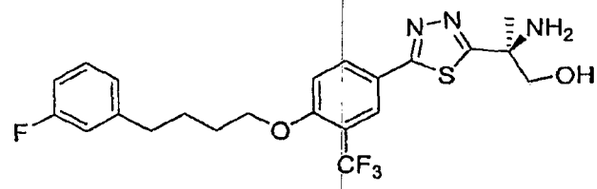
The title compound was prepared from 4-(5-(4-hydroxy-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)-2,2,4-trimethyoxyazolidine-3-carboxylate **6a** in 35% (22 mg) yield. HPLC retention time on a Synergi-Max RP column (2 x 20 mm, 2 μL) is 1.68 min with gradient 20-95% acetonitrile-H_2O (0.1 % TFA) in 2 min as mobile phase. MS (ESI, $M+H^+$) = 522.0; ^1H NMR (400 MHz, CD_3OD) δ 8.21 (d, 1H, J = 2.4 Hz), 8.16 (dd, 1H, J = 8.6 Hz, J = 2.4 Hz), 7.34 (d, 1H, J = 9.2 Hz), 4.21 (t, 2H, J = 6.0 Hz), 3.90-3.96 (m, 2H), 2.05-2.19 (m, 2H), 1.84-1.91 (m, 2H), 1.81 (s, 3H), 1.48-1.67 (m, 6H).

(*S*)-2-Amino-2-(5-(4-(4-(2-fluorophenyl)butoxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol (8z)



The title compound was prepared from 4-(5-(4-hydroxy-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)-2,2,4-trimethyoxyazolidine-3-carboxylate **6a** in 8% (5 mg) yield. HPLC retention time on a Synergi-Max RP column (2 x 20 mm, 2 μL) is 1.59 min with gradient 20-95% acetonitrile-H_2O (0.1 % TFA) in 2 min as mobile phase. MS (ESI, $M+H^+$) = 469.9; ^1H NMR (400 MHz, CD_3OD) δ 8.21 (d, 1H, J = 1.6 Hz), 8.16 (dd, 1H, J = 8.4 Hz, J = 2.4 Hz), 7.34 (d, 1H, J = 8.4 Hz), 7.16-7.27 (m, 2H), 6.99-7.10 (m, 2H), 4.22 (t, 2H, J = 5.6 Hz), 3.90-3.97 (m, 2H), 2.74 (t, 2H, J = 7.2 Hz), 1.82-1.90 (m, 4H), 1.82 (s, 2H).

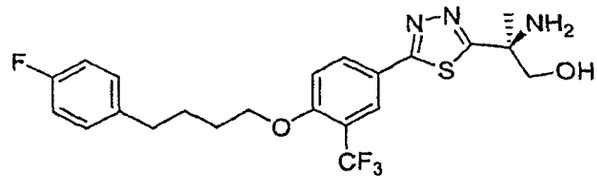
(*S*)-2-Amino-2-(5-(4-(4-(3-fluorophenyl)butoxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol (8aa)



The title compound was prepared from 4-(5-(4-hydroxy-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)-2,2,4-trimethyoxyazolidine-3-carboxylate **6a** in 16% (9 mg) yield. HPLC retention time on a Synergi-Max RP column (2 x 20 mm, 2 μL) is 1.60 min with gradient 20-95% acetonitrile-H_2O (0.1 % TFA) in 2 min as mobile phase. MS (ESI, $M+H^+$) = 469.9; ^1H NMR (400 MHz, CD_3OD) δ 8.21 (d, 1H, J = 2.4 Hz), 8.16 (dd, 1H, J = 8.4 Hz, J = 2.4 Hz), 7.34 (d, 1H, J = 8.4 Hz), 7.23-7.29 (m, 1H), 7.02 (d, 1H, J = 5.0 Hz), 6.85-6.96 (m, 2H), 4.22, (t, 2H, J = 5.6 Hz), 3.91-3.97 (m, 2H), 2.70-2.74 (m, 2H), 1.83-1.88 (m, 4H), 1.83 (s, 3H).

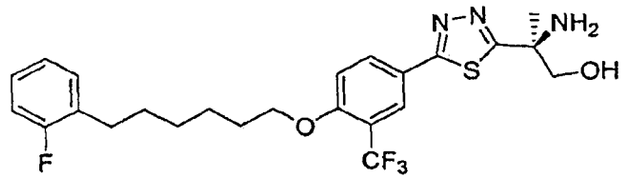
119

(*S*)-2-Amino-2-(5-(4-(4-(4-fluorophenyl)butoxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol (8ab)



The title compound was prepared from 4-(5-(4-hydroxy-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)-2,2,4-trimethyoxyazolidine-3-carboxylate **6a** in 16% (9 mg) yield. HPLC retention time on a Synergi-Max RP column (2 x 20 mm, 2 μL) is 1.91 min with gradient 20-95% acetonitrile-H_2O (0.1 % TFA) in 2 min as mobile phase. MS (ESI, $M+H^+$) = 469.9; ^1H NMR (400 MHz, CD_3OD) δ 8.21 (d, 1H, J = 2.4 Hz), 8.16 (dd, 1H, J = 8.6 Hz, J = 2.4 Hz), 7.34 (d, 1H, J = 8.0 Hz), 7.2 (m, 2H), 6.95-6.70 (m, 2H), 4.21 (t, 2H, J = 5.5 Hz), 3.90-3.98 (m, 2H), 2.69 (t, 2H, J = 6.8 Hz), 1.83-1.86 (m, 4H), 1.82 (s, 3H).

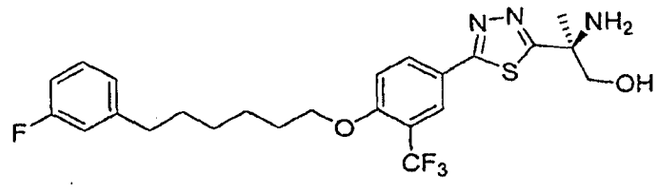
(*S*)-2-Amino-2-(5-(4-(6-(2-fluorophenyl)hexyloxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol (8ac)



The title compound was prepared from 4-(5-(4-hydroxy-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)-2,2,4-trimethyoxyazolidine-3-carboxylate **6a** in 15% (9 mg) yield. HPLC retention time on a Synergi-Max RP column (2 x 20 mm, 2 μL) is 1.73 min with gradient 20-95% acetonitrile-H_2O (0.1 % TFA) in 2 min as mobile phase. MS (ESI, $M+H^+$) = 498.1; ^1H NMR (400 MHz, CD_3OD) δ 8.21 (d, 1H, J = 2.4 Hz), 8.16 (dd, 1H, J = 8.4 Hz, J = 2.4 Hz), 7.34 (d, 1H, J = 8.4 Hz), 7.14-7.23 (m, 2H), 6.87-7.07 (m, 2H), 4.19 (t, 2H, J = 6.0 Hz), 3.90-3.97 (m, 2H), 3.79 (s, 2H), 2.66 (t, 2H, J = 8.0 Hz), 1.83-1.88 (m, 1H), 1.82 (s, 3H), 1.53-1.69 (m, 3H), 1.41-1.47 (m, 2H), 1.25-1.27 (m, 3H).

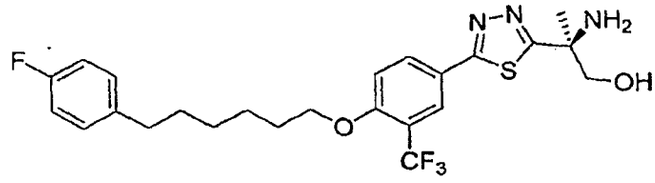
120

(*S*)-2-Amino-2-(5-(4-(6-(3-fluorophenyl)hexyloxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol (8ad)



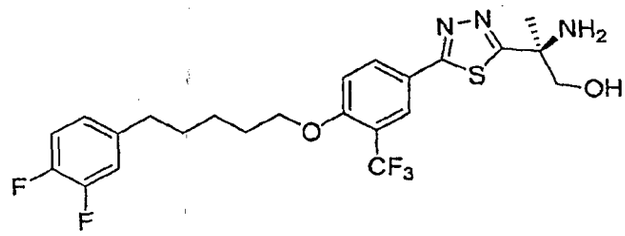
The title compound was prepared from deprotected acyl-benzohydrazide **5b** in 23% (11.3 mg) yield. HPLC retention time on a Synergi-Max RP column (2 x 20 mm, 2 μL) is 1.69 min with gradient 20-95% acetonitrile-H_2O (0.1 % TFA) in 2 min as mobile phase. MS (ESI): 497.98 (MH^+); ^1H NMR (400 MHz, CD_3OD) δ 8.21 (d, 1H, J = 2.4 Hz), 8.16 (dd, 1H, J = 8.6 Hz, J = 2.4 Hz), 7.34 (d, 1H, J = 8.4 Hz), 7.20-7.24 (m, 1H), 6.98 (d, 1H, J = 7.6 Hz), 6.85-6.91 (m, 2H), 4.19 (t, 2H, J = 6.4 Hz), 3.90-3.96 (m, 2H), 2.64 (t, 1H, J = 7.6 Hz), 1.85-2.01 (m, 2H), 1.83 (s, 3H), 1.63-1.68 (m, 2H), 1.55-1.59 (m, 2H), 1.40-1.46 (m, 2H).

(*S*)-2-Amino-2-(5-(4-(6-(4-fluorophenyl)hexyloxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol (8ae)



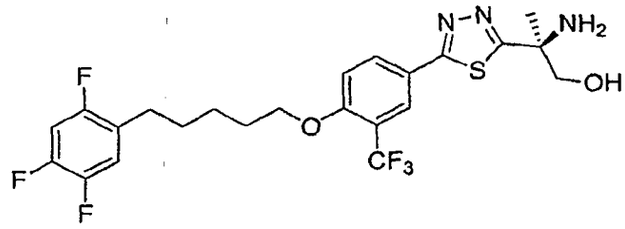
The title compound was prepared from deprotected acyl-benzohydrazide **5b** in 35% (17.4 mg) yield. HPLC retention time on a Synergi-Max RP column (2 x 20 mm, 2 μL) is 1.69 min with gradient 20-95% acetonitrile-H_2O (0.1 % TFA) in 2 min as mobile phase. MS (ESI): 497.98 (MH^+); ^1H NMR (400 MHz, CD_3OD) δ 8.21 (d, 1H, J = 2.0 Hz), 8.16 (dd, 1H, J = 8.4 Hz, J = 2.0 Hz), 7.32 (d, 1H, J = 8.4 Hz), 7.14-7.17 (m, 2H), 6.92-6.96 (m, 2H), 4.18 (t, 2H, J = 6.4 Hz), 3.90-3.98 (m, 2H), 2.60 (t, 1H, J = 8.0 Hz), 1.85-2.01 (m, 2H), 1.83 (s, 3H), 1.60-1.68 (m, 2H), 1.52-1.58 (m, 2H), 1.38-1.44 (m, 2H).

(*S*)-2-Amino-2-(5-(4-(5-(3,4-difluorophenyl)pentyloxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol (8af)



The title compound was prepared from deprotected acyl-benzohydrazide **5b** in 44% (22.0 mg). HPLC retention time on a Synergi-Max RP column (2 x 20 mm, 2 μL) is 1.46 min with gradient 30-99% acetonitrile-H_2O (0.1 % TFA) in 2 min as mobile phase. MS (ESI): 501.86 (MH^+); ^1H NMR (400 MHz, CD_3OD) δ 8.21 (d, 1H, J = 2.4 Hz), 8.16 (dd, 1H, J = 8.4 Hz, J = 2.4 Hz), 7.34 (d, 1H, J = 8.4 Hz), 7.05-7.14 (m, 2H), 6.94-6.98 (m, 1H), 4.20 (t, 2H, J = 6.0 Hz), 3.89-3.96 (m, 2H), 2.64 (t, 2H, J = 7.2 Hz), 1.85-1.91 (m, 2H), 1.83 (s, 3H), 1.66-1.74 (m, 2H), 1.52-1.58 (m, 2H).

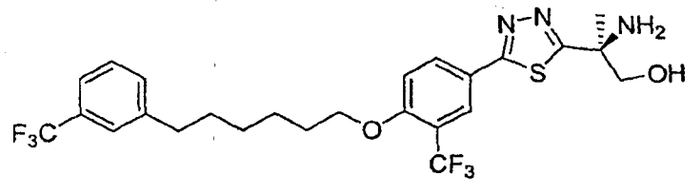
(*S*)-2-Amino-2-(5-(3-(trifluoromethyl)-4-(5-(2,4,5-trifluorophenyl)pentyloxy)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol (8ag)



The title compound was prepared from deprotected acyl-benzohydrazide **5b** in 28% (14.7 mg). HPLC retention time on a Synergi-Max RP column (2 x 20 mm, 2 μL) is 1.69 min with gradient 20-95% acetonitrile-H_2O (0.1 % TFA) in 2 min as mobile phase. MS (ESI): 497.98 (MH^+); ^1H NMR (400 MHz, CD_3OD) δ 8.21 (d, 1H, J=2 Hz), 8.16 (dd, 1H, J = 8.4 Hz, J = 2.0 Hz), 7.34 (d, 1H, J = 9.2 Hz), 7.14-7.21 (m, 1H), 7.02-7.08 (m, 1H), 4.20 (t, 2H, J = 6.0 Hz), 3.89-3.98 (m, 2H), 2.65 (t, 2H, J = 7.2 Hz), 1.83-1.90 (m, 5H), 1.65-1.71 (m, 2H), 1.53-1.59 (m, 2H).

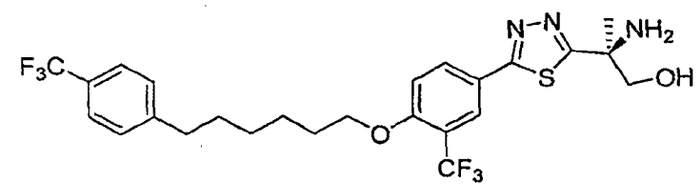
122

(*S*)-2-Amino-2-(5-(3-(trifluoromethyl)-4-(6-(3-(trifluoromethyl)phenyl)hexyloxy)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol (8ah)



The title compound was prepared from deprotected acyl-benzohydrazide **5b** in 60% (33.1 mg). HPLC retention time on a Synergi-Max RP column (2 x 20 mm, 2 μL) is 1.73 min with gradient 20-95% acetonitrile-H_2O (0.1 % TFA) in 2 min as mobile phase. MS (ESI): 548.00 (MH^+); ^1H NMR (400 MHz, CD_3OD) δ 8.21 (d, 1H, J = 1.6 Hz), 8.16 (dd, 1H, J = 8.4 Hz, J = 2.4 Hz), 7.44-7.46 (m, 4H), 7.33 (d, 1H, J = 8.4 Hz), 4.19 (t, 2H, J = 6.4 Hz), 3.90-3.99 (m, 2H), 2.71 (t, 2H, J = 7.6 Hz), 1.81-1.88 (m, 2H), 1.65-1.73 (m, 2H), 1.54-1.61 (m, 2H), 1.39-1.47 (m, 2H), 1.24-1.28 (m, 3H).

(*S*)-2-Amino-2-(5-(3-(trifluoromethyl)-4-(6-(4-(trifluoromethyl)phenyl)hexyloxy)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol (8ai)



The title compound was prepared from deprotected acyl-benzohydrazide **5b** in 59% (32.0 mg). HPLC retention time on a Synergi-Max RP column (2 x 20 mm, 2 μL) is 1.74 min with gradient 20-95% acetonitrile-H_2O (0.1 % TFA) in 2 min as mobile phase. MS (ESI): 547.92 (MH^+); ^1H NMR (400 MHz, CD_3OD) δ 8.22 (d, 1H, J = 2.0 Hz), 8.16 (dd, 1H, J = 8.6 Hz, J = 2.0 Hz), 7.53 (d, 2H, J = 8.0 Hz), 7.32-7.37 (m, 3H), 4.19 (t, 2H, J = 6.4 Hz), 3.90-3.98 (m, 2H), 2.72 (t, 2H, J = 7.6 Hz), 1.81-1.88 (m, 2H), 1.66-1.73 (m, 2H), 1.54-1.61 (m, 2H), 1.41-1.47 (m, 2H), 1.24-1.27 (m, 3H).

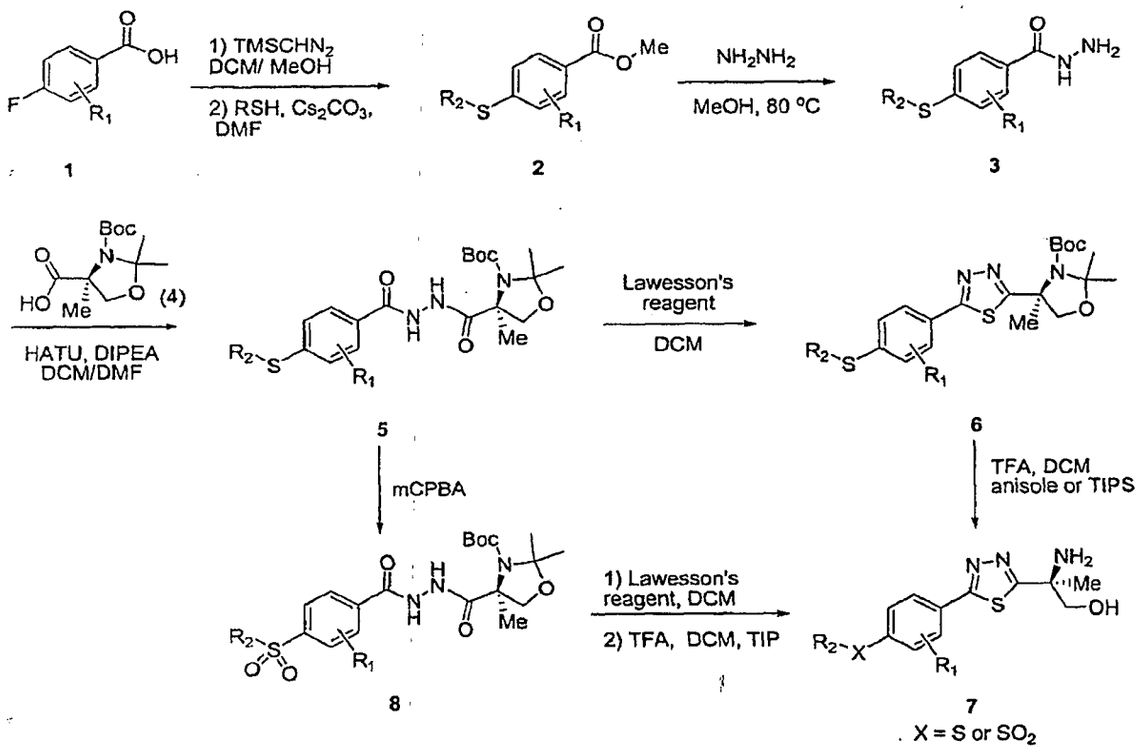
General approach to synthesis of thio-ether-phenyl-thiadiazoles

Synthesis of thio-ether-phenyl-thiazoles is described in Scheme 5. Treatment of substituted 4-fluorobenzoic acid 1 with TMS-CHN_2 afforded corresponding methyl ester with upon reaction with various thiols afforded the substituted thio-ether 2. The substituted thio-ether **2** was then condensed with hydrazine to afford benzohydrazide **3**.

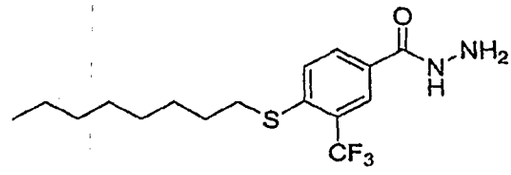
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Reaction of benzohydrazide **3** with orthogonally protected amino acid **4** under HATU conditions to give acyl-benzohydrazide **5** which upon treatment with Lawesson's reagent provided phenol **6** in good yield. Mitsunobu reaction of phenol **6** with desired alcohol followed by deprotection afforded the desired final compound **7**. Acyl-benzohydrazide **5** could also be oxidized with mCPBA to afford acyl-benzohydrazide **8** before treatment with Lawesson's reagent and deprotection. Reaction of the alcohol **7** with diethyl chlorophosphate followed by deprotection with TMSBr gave the corresponding phosphate.

Scheme 5:



4-(Octylthio)-3-(trifluoromethyl)benzohydrazide (3a)



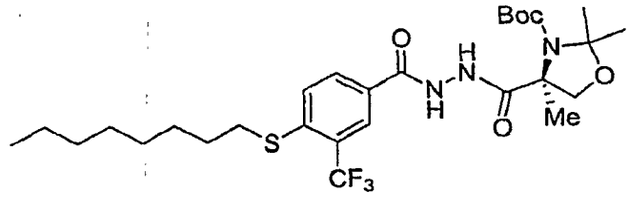
To a solution of 4-fluoro-3-(trifluoromethyl)benzoic acid **1a** (1.04 g, 5 mmol) in DCM/MeOH (4:1, 10 mL) at 0 °C was added drop-wise a solution of $TMSCHN_2$ (2.0 M

in ether, 2.6 mL, 5.1 mmol). The reaction mixture was stirred at 0 °C until the colorless solution started to turn light yellow and maintained its light yellow color. The reaction was stirred for an additional 20 minutes then a few drops of acetic acid was added to quench the last few drops of TMS-CHN_2 (the solution turns colorless from light yellow). The solvent was removed *in vacuo* to give a crude product which was used directly for next step. MS (ESI, $M+H^+$) = 223.0

To a solution of the crude methyl ester in DMF (5 mL) was added octane-1-thiol (0.87 mL, 5 mmol) and Cs_2CO_3 (2.44g, 7.5 mmol). The reaction mixture was stirred at 60 °C for 1 h, concentrated, quenched with NH_4Cl, extracted with EtOAc. The organics was dried over Na_2SO_4, concentrated under reduced pressure to leave the crude methyl 4-(octylthio)-3-(trifluoromethyl)benzoate **2a**. MS (ESI, $M+H^+$) = 349.0

The crude methyl 4-(octylthio)-3-(trifluoromethyl)benzoate was dissolved in 2 mL of MeOH and treated with 2 mL of hydrazine hydrate. The reaction mixture was left to stir at 80 °C for 1 hour, poured into ice-water. The solid was filtered, washed with H_2O and dried under vacuum to provide the 4-(octylthio)-3-(trifluoromethyl)benzohydrazide **3a** as a yellow solid. HPLC retention time on a C18 column (30 × 4.6 mm, 3.5 μ) was 2.69 min with gradient 10-95% acetonitrile-H_2O (0.1% TFA) in 3.5 min as mobile phase. MS (ESI, $M+H^+$) = 349.3; ^1H NMR (400 MHz, $CDCl_3$) δ 9.99 (s, 1H), 8.13 (d, 1H, J=1.6 Hz), 8.03 (dd, 1H, J= 8.2 Hz, J= 1.6 Hz), 7.67 (d, 1H, J= 8.8 Hz), 4.59 (s, 2H), 3.13 (t, 2H, J= 7.2 Hz), 1.61 (pentet, 2H, J= 6.8 Hz), 1.44-1.36 (m, 2H), 1.30-1.20 (m, 8H), 0.85 (t, 3H, J= 6.8 Hz).

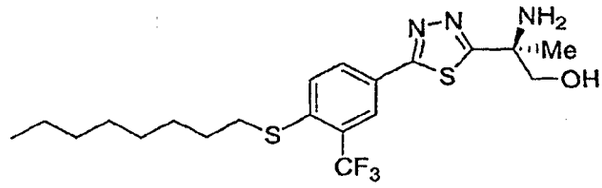
(*R*)-*tert*-Butyl 2,2,4-trimethyl-4-(2-(4-(octylthio)-3-(trifluoromethyl)benzoyl)hydrazine carbonyl)oxazolidine-3-carboxylate (5a)



To a solution of (R)-3-(tert-butoxycarbonyl)-2,2,4-trimethyloxazolidine-4-carboxylic acid **4** (129.6 mg, 0.5 mmol) in DMF (1 mL) was added HATU (209 mg, 0.55 mol) and DIPEA (0.436 mL, 2.5 mmol). After being stirred at rt for 10 min, the reaction mixture was traeted with 4-(octylthio)-3-(trifluoromethyl)benzohydrazide **3a** (174 mg, 0.5 mmol) in THF (2 mL) and was left stirred overnight. Aqueous $NaHCO_3$

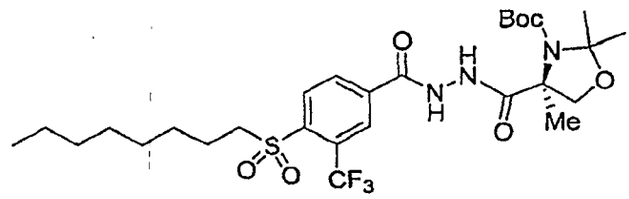
solution was added and the mixture was extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure to give a residue, which was purified by SiO_2 column chromatograph (n-hexane/EtOAc =3:7) to give (*R*)-tert-butyl 2,2,4-trimethyl-4-(2-(4-(octylthio)-3-(trifluoromethyl)benzoyl)hydrazinecarbonyl)oxazolidine-3-carboxylate **5a** (247 mg, 84%). HPLC retention time on a C18 column (30 × 4.6 mm, 3.5 μ) was 3.08 min with gradient 10-95% acetonitrile-H_2O (0.1% TFA) in 3.5 min as mobile phase. MS (ESI, $M+H^+$) = 590.5

(*S*)-2-Amino-2-(5-(4-(octylthio)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol (7a)



The title product was obtained in 32% yield from (*R*)-tert-butyl 2,2,4-trimethyl-4-(2-(4-(octylthio)-3-(trifluoromethyl)benzoyl)hydrazinecarbonyl)oxazolidine-3-carboxylate **6a**. HPLC retention time on a C18 column (30 x 4.6 mm, 3.5 μ) was 2.46 min with gradient 10-95% acetonitrile-H_2O (0.1% TFA) in 3.5 min as mobile phase. MS (ESI, $M+H^+$) = 448.4. ^1H NMR (400 MHz, CD_3OD) δ 8.17 (s, 1H), 8.13 (d, 1H, J = 8.4 Hz), 7.75 (d, 1H, J = 8.4 Hz), 3.80 (AB, 1H, J_{AB} =11.2 Hz), 3.73 (AB, 1H, J_{AB} =11.2 Hz), 3.14 (t, 2H, J = 7.2 Hz), 1.67 (s, 3H), 1.61 (pentet, 2H, J = 6.8 Hz), 1.40-1.35 (m, 2H), 1.25-1.20 (m, 8H), 0.81 (t, 3H, J = 6.6 Hz).

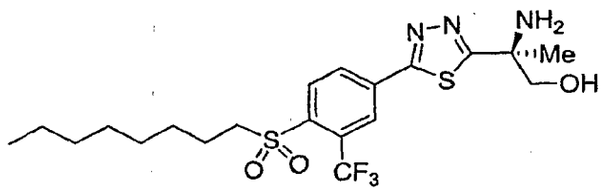
(*R*)-*tert*-Butyl 2,2,4-trimethyl-4-(2-(4-(octylsulfonyl)-3-(trifluoromethyl)benzoyl)hydrazine carbonyl)oxazolidine-3-carboxylate (8a)



A solution of (*R*)-*tert*-butyl 2,2,4-trimethyl-4-(2-(4-(octylthio)-3-(trifluoromethyl)benzoyl)hydrazinecarbonyl)oxazolidine-3-carboxylate **5a** (123 mg, 0.21 mmol) in DCM (10 mL) was treated with mCPBA (164 mg, 77%, 722 mmol) at rt.

The reaction mixture was stirred at rt overnight, quenched with saturated aqueous $NaHCO_3$, extracted with DCM. The organic layer was washed with saturated aqueous $NaHCO_3$ (3X), dried over Na_2SO_4, and evaporated under reduced pressure to give a residue, which was purified by SiO_2 column chromatograph (n-hexane/EtOAc =3:7) to leave (*R*)-*tert*-butyl 2,2,4-trimethyl-4-(2-(4-(octylsulfonyl)-3-(trifluoromethyl)benzoyl)hydrazinecarbonyl)oxazolidine-3-carboxylate **8a** (112 mg, 92%). HPLC retention time on a C18 column (30 x 4.6 mm, 3.5 μ) was 3.27 min with gradient 10-95% acetonitrile-H_2O (0.1% TFA) in 3.5 min as mobile phase. MS (ESI, $M+H^+$) = 622.5.

(*S*)-2-Amino-2-(5-(4-(octylsulfonyl)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol (7b)



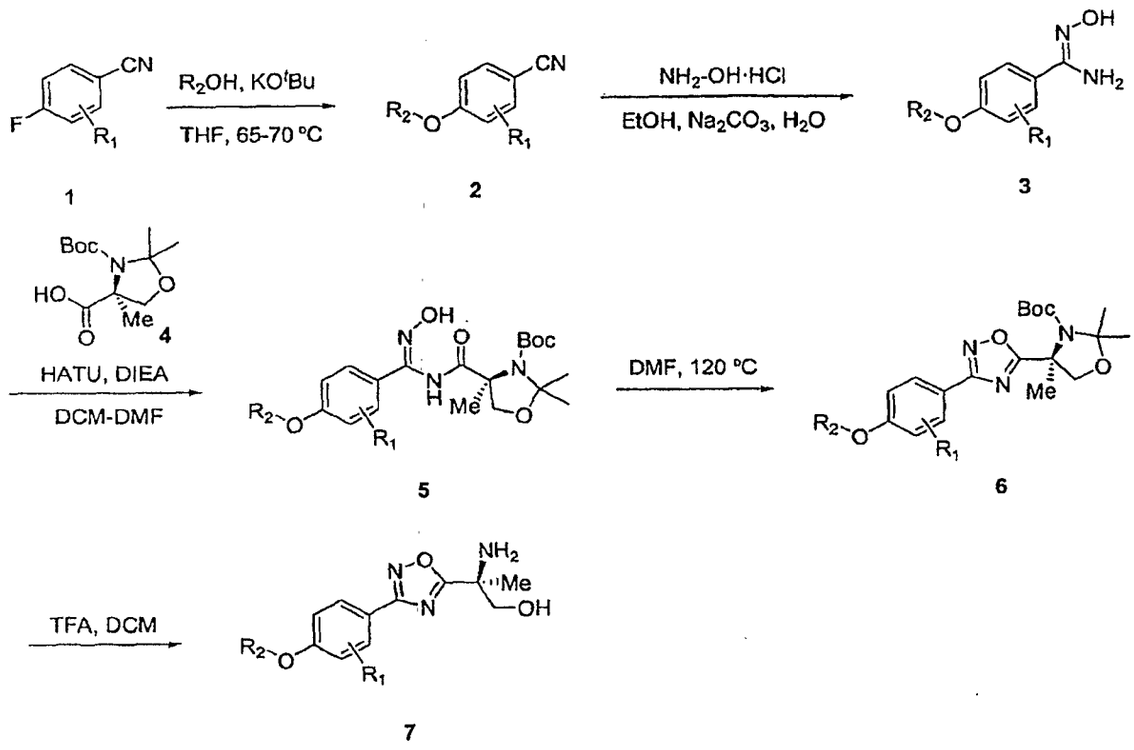
The title compound was prepared according to general procedure from (*R*)-*tert*-butyl 2,2,4-trimethyl-4-(2-(4-(octylsulfonyl)-3-(trifluoromethyl)benzoyl)hydrazinecarbonyl) oxazolidine-3-carboxylate **8a**. HPLC retention time on a C18 column (30 x 4.6 mm, 3.5 μ) was 2.11 min with gradient 10-95% acetonitrile-H_2O (0.1% TFA) in 3.5 min as mobile phase. MS (ESI, $M+H^+$) = 480.3; ^1H NMR (400 MHz, DMSO-d6) δ 8.56 (dd, 1H, J = 8.2 Hz, J = 1.6 Hz), 8.53 (d, 1H, J = 1.6 Hz), 8.38 (d, 1H, J = 8.8 Hz), 3.87 (AB, 1H, J_{AB} = 10.8 Hz), 3.80 (AB, 1H, J_{AB} = 10.8 Hz), 3.44 (t, 1H, J = 7.8 Hz), 1.68 (s, 3H), 1.66-1.60 (m, 2H), 1.37-1.31 (m, 2H), 1.25-1.16 (m, 8H), 0.83 (t, 3H, J = 7.2 Hz).

General approach to synthesis of phenyl-oxadiazoles

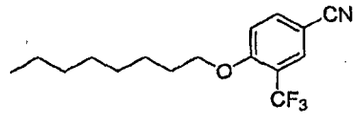
Synthesis of phenyl-oxadiazoles is described in Scheme 6. Reaction of the desired alcohol with substituted 4-fluorobenzonitrile 1 afforded the substituted benzonitrile **2**. The substituted benzonitrile **2** was then condensed with hydroxylamine to afford hydroxybenzimidamide **3**. Coupling of the hydroxyamindine intermediate **3** with orthogonally protected amino acid **4** under HATU conditions followed by cyclization

provided orthogonally protected oxadiazole **6**. Treatment of protected oxadiazole **6** with TFA gave the desired final amino-alcohol **7**.

Scheme 6:

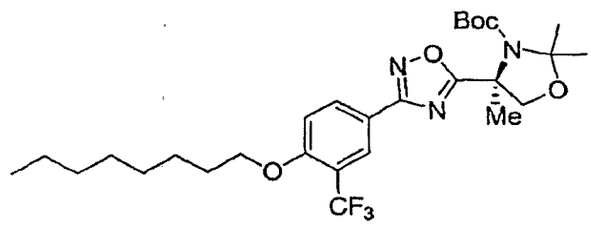


4-(Octyloxy)-3-(trifluoromethyl)benzonitrile (2a)



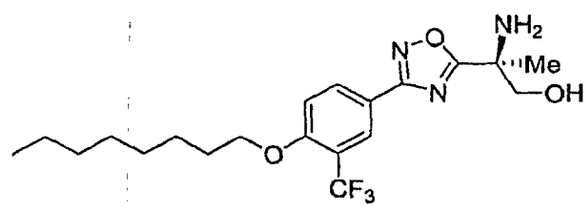
The title compound was prepared analogously to compound **2** (Scheme 4) in >95% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, 1H, J = 0.2 Hz), 7.77 (dd, 1H, J = 8.8 Hz, J = 2.0 Hz), 7.04 (d, 1H, J = 8.8 Hz), 4.11 (t, 2H, J = 5.6 Hz), 1.84 (m, 2H), 1.47 (m, 2H), 1.32 (m, 8H), 0.89 (t, 3H, J = 7.2 Hz).

(*R*)-tert-Butyl 2,2,4-trimethyl-4-(3-(4-(octyloxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)oxazolidine-3-carboxylate (6a)



A suspension of 4-(octyloxy)-3-(trifluoromethyl)benzonitrile (600 mg, 1.0 equiv), $NH_2OH{\cdot}HCl$ (280 mg, 2.0 equiv), Na_2CO_3 (636 mg, 3.0 equiv) in ethanol-water (12 mL, 5:1) was refluxed for 3 h. The reaction was condensed under vacuum and the residue was treated with water followed by extraction with ethyl acetate. The ethyl acetate layer was washed with saturated NaCl (1x), dried over Na_2SO_4, and condensed to afford hydroxyamindine intermediate (750 mg). Part of the intermediate (166 mg, 1.0 equiv) was treated with HATU (190 mg, 1.0 equiv), DIEA (260 μL, 3.0 equiv) and (*R*)-3-(tert-butoxycarbonyl)-2,2,4-trimethyloxazolidine-4-carboxylic acid (130 mg, 1.0 equiv) in DMF (1 mL) for 1 hour. The reaction was diluted with ethyl acetate and washed with water followed by saturated NaCl (1x), dried over Na_2SO_4, and condensed under vacuum. The residue was dissolved in DMF and heated at 120 ^{0}C for 2 hours. Aqueous workup followed by Isco system purification provided the title compound in 28% (70 mg) yield over three steps. MS (ESI, $M+H^+$) = 558.1 ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, 1H, J = 1.6 Hz), 8.18 (dd, 1H, J = 8.4 Hz, J = 1.6 Hz), 7.07 (d, 1H, J = 8.4 Hz), 4.23, 4.00 (AB, 2H, J = 9.2 Hz), 4.11 (t, 2H, J = 7.2 Hz), 1.92 (s, 3H), 1.84 (m, 2H), 1.76 (s, 3H), 1.70 (s, 3H), 1.51-1.46 (m, 4H), 1.25 (m, 9H), 1.25 (s, 6H), 0.89 (t, 3H, J = 7.2 Hz).

(*S*)-2-Amino-2-(3-(4-(octyloxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)propan-1-ol (7a)



The title compound was prepared analogously to compound **8** (Scheme 4) from compound **7a**. MS (ESI, $M+H^+$) = 416.0; ^{1}H NMR (400 MHz, CD_3OD) δ 8.28 (m 2H),

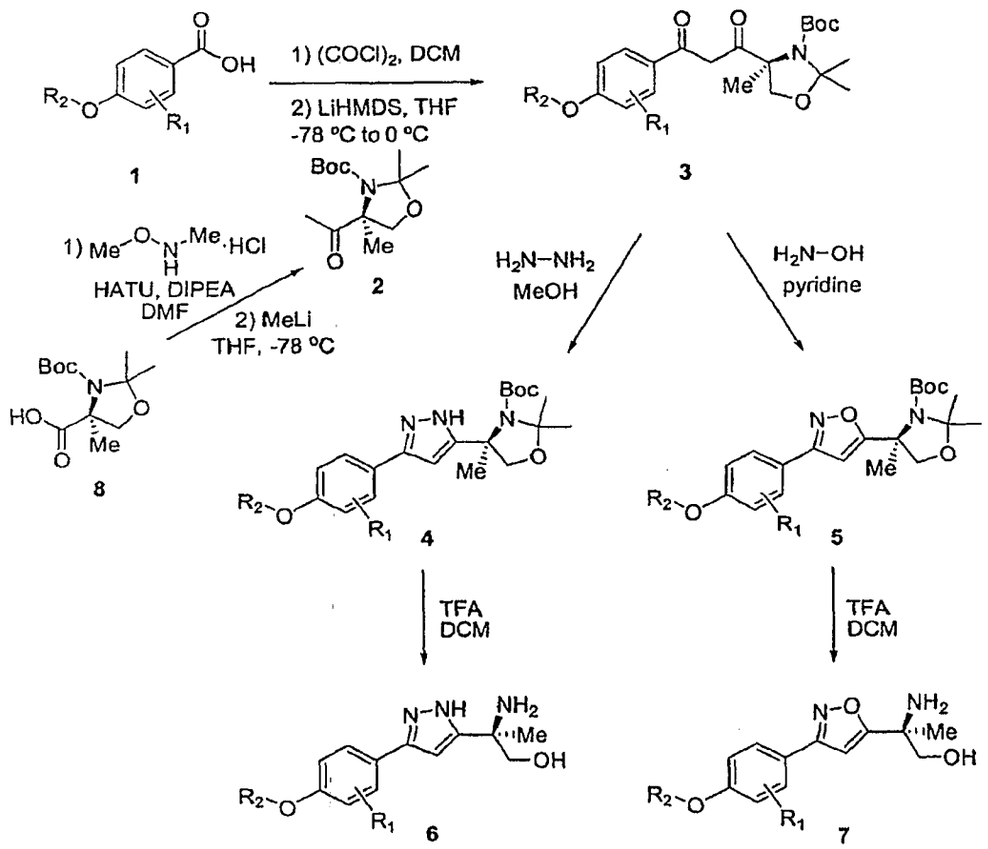
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7.34 (d, 1H, J = 9.6 Hz), 4.19 (t, 2H, J = 5.6 Hz), 4.11, 3.89 (AB, 2H, J = 11.6 Hz), 1.84 (m, 2H), 1.77 (s, 3H), 1.53 (m, 2H), 1.40-1.32 (m, 8H), 0.91 (t, 3H, J = 7.2 Hz).

General approach to synthesis of phenyl-isoxazoles and phenyl-pyrazoles

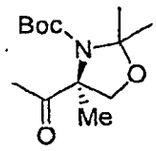
Synthesis of phenyl-isoxazoles and phenyl-pyrazoles are described in Scheme 7. Reaction of the desired benzoic acid with oxalyl chloride and trapping the acid chloride with enolate of oxazolidine-ketone **2** afforded 1,3-dione **3**. Oxazolidine-ketone **2** was synthesized from oxazolidine-carboxylate **8** after conversion of **8** to corresponding Weinreb amide followed by addition of methyl lithium. Reaction of the 1,3-dione **3** with either hydrazine or hydroxylamine followed by deprotection afforded the desired final compound **6** and **7** respectively.

Scheme 7:



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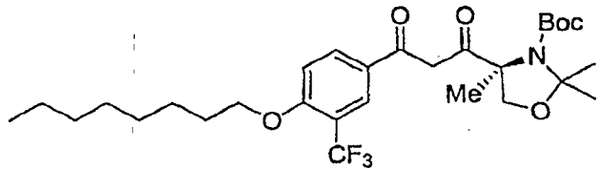
(*R*)-*tert*-Butyl 4-acetyl-2,2,4-trimethyloxazolidine-3-carboxylate (2)



To a solution of (*R*)-3-(*tert*-butoxycarbonyl)-2,2,4-trimethyloxazolidine-4-carboxylic acid **8** (2.6 g, 10 mmol, 1.0 equiv) in DMF (25 mL) was added HATU (4.6 g, 12 mmol, 1.2 equiv) and DIPEA (8.7 mL, 50 mmol, 5.0 equiv). The reaction mixture was stirred at rt for 10 min and treated with N,O-dimethylhydroxylamine hydrochloride (2.9 g, 30 mmol, 3.0 equiv), stirred for 2 days at rt, quenched with half saturated $NaHCO_3$, extracted with EtOAc. The organics was dried over Na_2SO_4, concentrated to afford corresponding Weinreb amide in 92% (2.78 g) yield. HPLC retention time on a C18 column (30 x 4.6 mm, 3.5 μ) was 2.20 min with gradient 10-95% acetonitrile-H_2O (0.1% TFA) in 3.5 min as mobile phase. MS (ESI, $M+H^+$) = 303.3.

The crude corresponding Weinreb amide (2.78g, 9.2 mmol, 1.0 equiv) was dissolved in THF (50 mL), cooled to -78 °C and treated with a solution of 1.6 M MeLi (14.7 mL, 23 mmol, 2.5 equiv) in ether drop-wise. After being stirred at -78 °C for 3 h, the reaction mixture was allowed to warm to rt, quenched with saturated aqueous NH_4Cl, extracted with EtOAc. The organics was dried over Na_2SO_4, concentrated *in vacuo* to afforded an oil which was purified by silica gel column chromatograph (n-hexane/EtOAc =85:15) to give (*R*)-*tert*-butyl 4-acetyl-2,2,4-trimethyloxazolidine-3-carboxylate as a white solid in 82% (1.94 g) yield. HPLC retention time on a C18 column (30 x 4.6 mm, 3.5 μ) was 2.39 min with gradient 10-95% acetonitrile-H_2O (0.1% TFA) in 3.5 min as mobile phase. MS (ESI, $M+H^+$) = 258.4; ^1H NMR (400 MHz, $CDCl_3$) δ 3.95 (d, 1H, J = 9.6 Hz), 3.74 (d, 1H, J = 9.6 Hz), 2.21 (s, 3H), 1.69 (s, 2H), 1.65-1.64 (m, 1H), 1.61 (s, 2H), 1.57-1.55 (m, 2H), 1.49 (s, 5H), 1.42 (s, 6H).

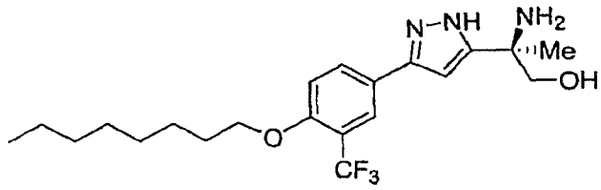
(*S*)-tert-Butyl 2,2,4-trimethyl-4-(3-(4-(octyloxy)-3-(trifluoromethyl)phenyl)-3-oxo-propanoyl)oxazolidine-3-carboxylate (3a)



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4-(Octyloxy)-3-(trifluoromethyl)benzoic acid (460 mg, 1.0 equiv) was treated with oxalyl chloride (244 μL, 2.0 equiv) for 30 min. The reaction was condensed and part of the reside (81 mg, 1.2 equiv) was dissolved in THF and transferred to a solution of (*S*)-tert-butyl 4-acetyl-2,2,4-trimethyloxazolidine-3-carboxylate (51 mg, 1.0 equiv) and 1.0M LiHMDS (0.72 mL, 3.0 equiv) in THF at -78 °C. The resultant was stirred at 0 °C for 1 hour. The reaction was quenched with aqueous NH_4Cl and extracted with ethyl acetate. The organic layer was washed with brine and dried over Na_2SO_4 and condensed *in vacuo*. The residue was purified on a silica gel column with ethyl acetate-hexane (0-30%) as eluent system to afford the title compound in 39% (55 mg) yield. MS (ESI, $M+H^+$) = 557.9

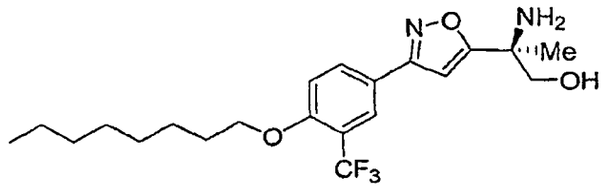
(*R*)-2-Amino-2-(5-(4-(octyloxy)-3-(trifluoromethyl)phenyl)-1*H*-pyrazol-3-yl)propan-1-ol (6a)



The solution of (*S*)-tert-butyl 2,2,4-trimethyl-4-(3-(4-(octyloxy)-3-(trifluoromethyl)-phenyl)-3-oxo-propanoyl)oxazolidine-3-carboxylate (27 mg, 0.05 mmol, 1.0 equiv) and hydrazine monohydrate (2.7 μL, 0.055 mmol, 1.1 equiv) in methanol (0.2 mL) was stirred at room temperature for 2 hours. The reaction was condensed and the residue was treated with 20 % TFA-DCM for 30 min. After removal of excess amount of TFA and DCM, the crude product was purified by prep. HPLC and afforded the title compound as mono-TFA salt (5.0 mg). MS (ESI, $M+H^+$) = 414.0; ^1H NMR (400 MHz, CD_3OD) δ 7.81 (s, 1H), 7.76 (d, 1H, J = 9.2 Hz), 7.14 (d, 1H, J = 9.2 Hz), 6.56 (s, 1H), 4.03 (t, 2H, J = 6.0 Hz), 3.79, 3.67 (AB, 2H, J = 12.0 Hz), 1.76-1.69 (m, 2H), 1.59 (s, 3H), 1.46-1.38 (m, 2H), 1.32-1.16 (m, 8H), 0.81 (t, 3H, J = 7.2 Hz).

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(*S*)-2-Amino-2-(3-(4-(octyloxy)-3-(trifluoromethyl)phenyl)isoxazol-5-yl)propan-1-ol (7a)



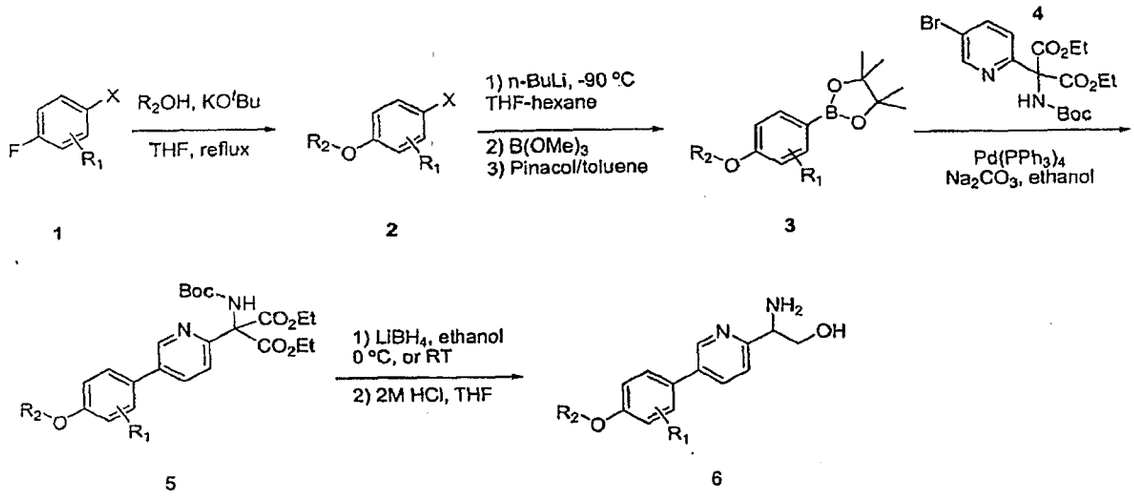
The solution of (*S*)-tert-butyl 2,2,4-trimethyl-4-(3-(4-(octyloxy)-3-(trifluoromethyl)-phenyl)-3-oxo-propanoyl)oxazolidine-3-carboxylate (27 mg, 0.05 mmol, 1.0 equiv) and hydroxylamine hydrochloride (6.6 mg, 0.10 mmol, 2.0 equiv) in pyridine (0.5 mL) was stirred at 60 ^{0}C for 2 days. The reaction was condensed and the residue was treated with 20 % TFA-DCM for 30 min. After removal of excess amount of TFA and DCM, the crude product was purified by prep. HPLC and afforded the title compound as mono-TFA salt (6.0 mg). MS (ESI, M+H^{+}) = 415.0; ^{1}H NMR (400 MHz, CD_3OD) δ 8.06 (s, 1H), 8.04 (d, 1H, J = 9.6 Hz), 7.31 (d, 1H, J = 9.6 Hz), 7.03 (s, 1H), 4.16 (t, 2H, J = 6.0 Hz), 4.01, 3.83 (AB, 2H, J = 12.0 Hz), 1.87-1.80 (m, 2H), 1.75 (s, 3H), 1.56-1.47 (m, 2H), 1.40-1.32 (m, 8H), 0.91 (t, 3H, J = 7.2 Hz).

General approach to synthesis of phenyl-pyridine analogs

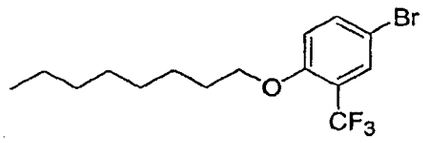
Synthesis of phenyl-pyridine analogs is described in Scheme 8. Reaction of desired alcohol with substituted halo-benzene **1** afforded the halo-benzene-ether **2**. The substituted halo-benzene-ether **2** was then treated with *n*-butyl lithium, $B(OMe)_3$, and pinacol respectively to afford ester **3**. Suzuki cross-coupling of ester **3** with compound **4** gave biaryl **5** which upon reduction and deprotection afforded amino alcohol **6**.

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Scheme 8:

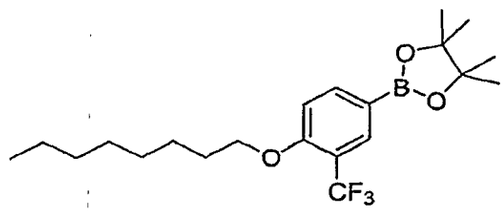


4-Bromo-1-(octyloxy)-2-(trifluoromethyl)benzene (2a)



Using 4-bromo-1-fluoro-2-(trifluoromethyl)benzene as starting material, standard aromatic fluoro-substitution with *n*-octanol provided the title compound in quantitative yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (δ, 1H, J = 2.4 Hz), 7.55 (dd, 1H, J = 8.8 Hz, J = 2.4 Hz), 6.85 (d, 1H, J = 8.8 Hz), 4.01 (t, 2H, J = 6.4 Hz), 1.80 (m, 2H), 1.46 (m, 2H), 1.32 (m, 8H), 0.90 (t, 2H, J = 5.6 Hz).

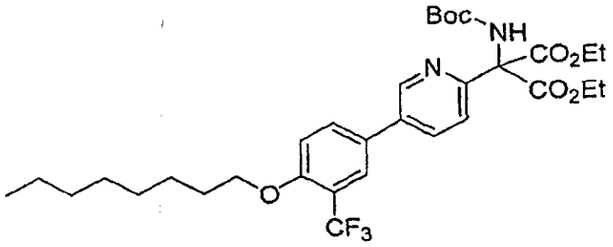
4,4,5,5-Tetramethyl-2-(4-(octyloxy)-3-(trifluoromethyl)phenyl)-1,3,2-dioxaborolane (3a)



Using 4-bromo-1-(octyloxy)-2-(trifluoromethyl)benzene as starting material, the title compound was prepared using a literature procedure in 96% yield (J. Am. Chem. Soc. **2004**, *126*, 14316-14317). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.89

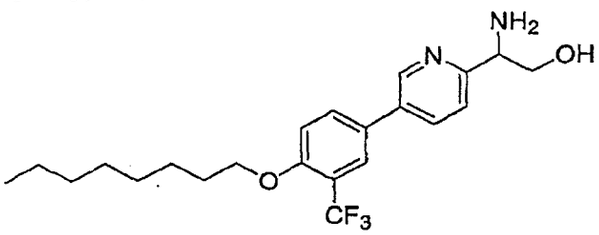
(dd, 1H, J = 8.4 Hz, J = 1.2 Hz), 6.95 (d, 1H, J = 8.4 Hz), 4.06 (t, 2H, J = 6.0 Hz), 1.81 (m, 2H), 1.47 (m, 2H), 1.36-1.28 (m, 8H), 0.88 (t, 2H, J = 7.2 Hz).

Diethyl 2-(*tert*-butoxycarbonylamino)-2-(5-(4-(octyloxy)-3-(trifluoromethyl)-phenyl)pyridin-2-yl)malonate (5a)



The suspension of 4,4,5,5-tetramethyl-2-(4-(octyloxy)-3-(trifluoromethyl)phenyl)-1,3,2-dioxaborolane **3a** (136 mg, 0.34 mmol, 1.5 equiv), diethyl 2-(5-bromopyridin-2-yl)-2-(*tert*-butoxycarbonylamino)malonate (98 mg, 0.23 mmol, 1.0 equiv), $Pd(PPh_3)_4$ (26.3 mg, 0.023 mmol, 0.1 equiv), and Na_2CO_3 (120 mg, 1.14 mmol, 4.0 equiv) in ethanol-H_2O was heated at 80 °C for 1 hour. The reaction mixture was filtered and the filtrate was purified by silica gel column to afford the title compound in 77% (110 mg) yield. MS (ESI, M+H$^+$) = 625.1; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (s, 1H), 7.88 (s, 1H), 7.86 (dd, 1H, J = 8.4 Hz, J = 2.0 Hz), 7.75 (d, J = 2.5 Hz), 7.66 (d, 1H, J = 8.4 Hz), 7.08 (d, 1H, J = 8.4 Hz), 6.82 (s, 1H), 4.30 (m, 4H), 4.09 (t, 2H, J = 6.0 Hz), 1.84 (m, 2H), 1.46 (m, 11H), 1.28 (m, 14H), 0.90 (t, 3H, J = 7.2 Hz).

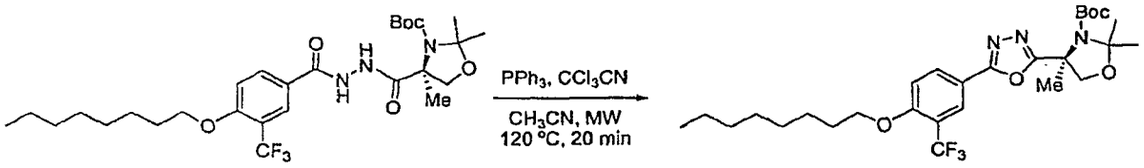
2-Amino-2-(5-(4-(octyloxy)-3-(trifluoromethyl)phenyl)pyridin-2-yl)ethanol (6a)



Diethyl 2-(*tert*-butoxycarbonylamino)-2-(5-(4-(octyloxy)-3-(trifluoromethyl)-phenyl)-pyridin-2-yl)malonate **5a** (110 mg, 0.176 mmol, 1.0 equiv) in THF (2.0 mL) was added $LiBH_4$ (57 mg, 2.64 mmol, 15.0 equiv) at 0 °C, followed by addition of ethanol (0.8 mL) carefully. The resultant was warmed up to room temperature for 10 minutes. LC-MS indicated the completion of the reaction. The reaction was terminated by addition of water. Extraction with ethyl acetate and the organic layer was washed

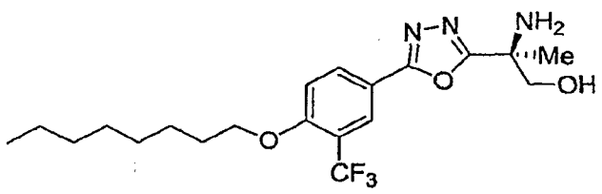
with brine and dried over sodium sulfate and condensed. The residue (crude reduction product with significant decarboxylation) was treated with 2M HCl in THF to afford the title compound after preparative HPLC purification. MS (ESI, M+H$^+$) = 411.1; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.95 (d, 1H, J = 2.4 Hz), 8.39 (s, 3H), 8.22 (dd, 1H, J = 8.4 Hz, J = 2.4 Hz), 8.01 (dd, 1H, J = 8.4 Hz, J = 2.0 Hz), 7.93 (d, 1H, J = 2.0 Hz), 7.60 (d, 1H, J = 8.4 Hz), 7.39 (d, 1H, J = 9.2 Hz), 5.48 (br, 1H), 4.48 (br, 1H), 4.17 (t, 2H, J = 6.0 Hz), 3.86-3.72 (m, 2H), 1.75 (m, 2H), 1.44 (m, 2H), 1.29 (m, 8H), 0.86 (t, 3H, J = 6.8 Hz).

(*R*)-t-Butyl 2,2,4-trimethyl-4-(5-(4-(octyloxy)-3-(trifluoromethyl)phenyl)-1,3,4-oxadi-azol-2-yl)oxazolidine-3-carboxylate



The title compound was prepared from (*S*)-*t*-butyl- 2,2,4-trimethyl-4-(2-(4-(octyloxy)benzoyl)hydrazinecarbonyl)oxazolidine-3-carboxylate using published procedure (Tet. Letters, **2006**, 47, 105-108) in 85% yield. MS (ESI, M+H$^+$) = 556.1; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, 1H, J = 1.6 Hz), 8.14 (d, 1H, J = 8.8 Hz), 8.10 (dd, 1H, J = 8.8 Hz, J = 1.6 Hz), 4.22 (d, 1H, J = 8.8 Hz), 4.12 (t, 2H, J = 6.0 Hz), 4.01 (m, 1H), 1.94 (s, 3H), 1.85 (m, 2H), 1.76 (s, 3H), 1.72 (s, 3H), 1.51-1.46 (m, 4H), 1.22 (m, 7H), 1.25 (s, 6H), 0.89 (t, 3H, J = 7.2 Hz).

(*S*)-2-Amino-2-(5-(4-(octyloxy)-3-(trifluoromethyl)phenyl)-1,3,4-oxadiazol-2-yl)propan-1-ol



Standard 20% TFA deprotection of (*R*)-t-butyl 2,2,4-trimethyl-4-(5-(4-(octyloxy)-3-(trifluoromethyl)phenyl)-1,3,4-oxadi-azol-2-yl)oxazolidine-3-carboxylate afforded the title compound in 55% yield. (ESI, M+H$^+$) = 416.0; ^{1}H NMR (400 MHz, CD_3OD) δ 8.18 (d, 1H, J = 8.8 Hz), 8.18 (s, 1H), 7.30 (d, 1H, J = 8.8 Hz), 4.12 (t, 2H, J

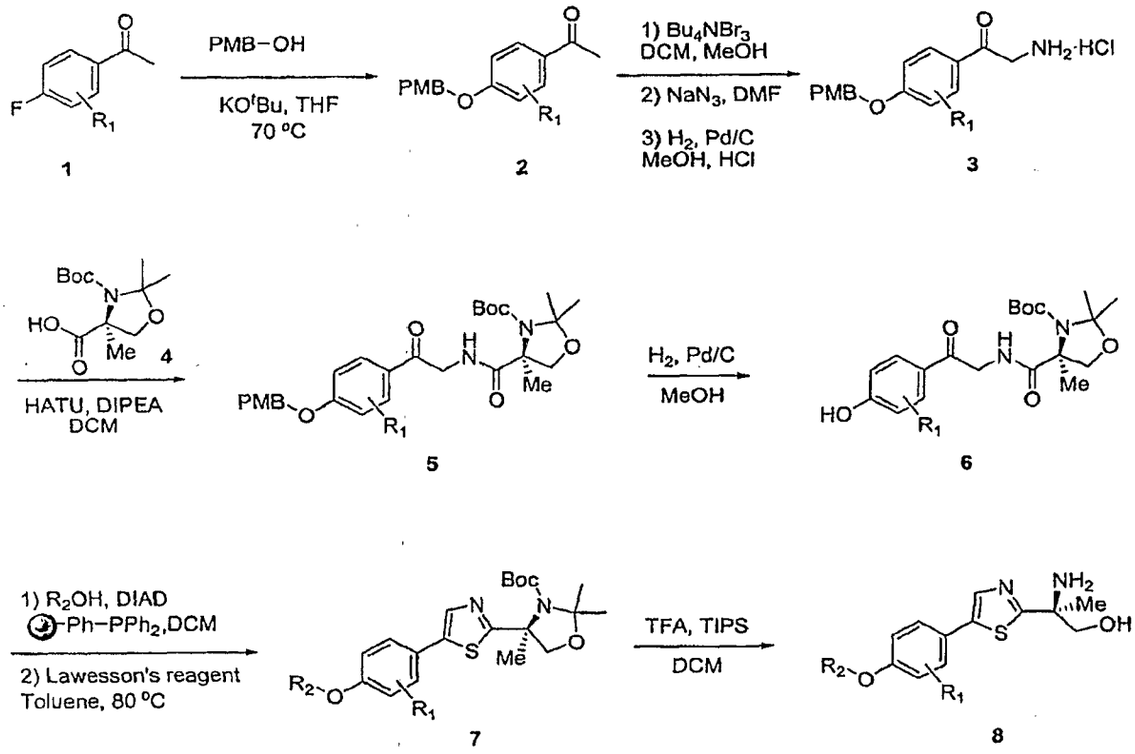
136

= 6.0 Hz), 4.01, 3.79 (AB, 2H, J = 11.6 Hz), 1.74 (m, 2H), 1.68 (s, 3H), 1.43 (m, 2H), 1.31-1.19 (m, 8H), 0.81 (t, 3H, J = 2.8 Hz).

General approach to synthesis of ether-phenyl-thiazoles

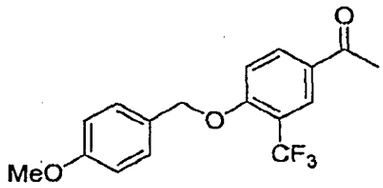
The synthesis of 2,5-substituted thiazoles is described in Scheme 9. Reaction of the desired alcohol *para*-methoxybenzyl alcohol (PMB-OH) with substituted 4-fluoroacetophenone 1 afforded the acetophenone intermediate **2**. Acetophenone intermediate **2** was then converted to the corresponding bromo-acetophenone using Bu_4NBr_3 which, upon reaction with NaN_3, provided the azido-acetophenone intermediate. Hydrogenation of the azido-acetophenone intermediate afforded amine **3**, followed by coupling with orthogonally protected amino acid **4** gave amide **5**. Removal of PMB group under hydrogenation gave phenol **6**. Mitsunobu reaction of the phenol **6** with the desired alcohol followed by thiazole formation under Lawesson's reagent conditions afforded intermediate **7** in good yield. Removal of the protecting group from intermediate **7** afforded the final amino-alcohol **8**.

Scheme 9:



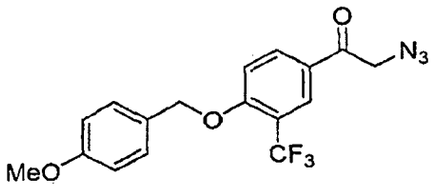
For general protocol for synthesis of compound **2**, **3**, **4**, and **5** refer to scheme 1.

1-(4-(4-Methoxybenzyloxy)-3-(trifluoromethyl)phenyl)ethanone (2a)



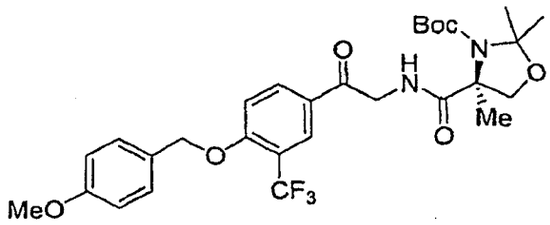
For general protocol for synthesis of compound **2** refer to scheme 1. The product was purified by silica gel column chromatography using the Combi-Flash system (Hex:EtOAc) as colorless oil in 90% (4.25 g). HPLC retention time on a C8(2) column (30 × 3.00 mm, 3 μ) is 2.02 min with gradient 50-98% acetonitrile-H_2O (0.1% TFA) in 4.0 min as mobile phase. TLC (1:3 EtOAc:Hex), R_f = 0.4; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, 1H, *J* = 1.6 Hz), 8.09 (dd, 1H, *J* = 8.8 Hz, *J* = 2.0 Hz), 7.35 (d, 2H, *J* = 8.4 Hz), 7.09 (d, 1H, *J* = 8.4 Hz), 6.93 (d, 2H, *J* = 8.4 Hz), 5.21 (s, 2H), 3.82 (s, 3H), 2.58 (s, 3H).

2-Azido-1-(4-(4-methoxybenzyloxy)-3-(trifluoromethyl)phenyl)ethanone



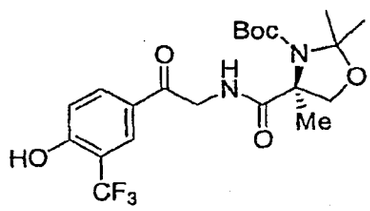
For general protocol for synthesis of azido intermediate refer to scheme 1. The product was purified by silica gel column chromatography using the Combi-Flash system (Hex:EtOAc) as yellow solid in 76% (3.64 g) yield from acetophenone **2a**. HPLC retention time on a C8(2) column (30 × 3.00 mm, 3 μ) is 2.20 min with gradient 50-98% acetonitrile-H_2O (0.1% TFA) in 4.0 min as mobile phase. TLC (1:3 EtOAc:Hex), R_f = 0.3; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, 1H, *J* = 2.0 Hz), 8.05 (dd, 1H, *J* = 8.8 Hz, *J* = 2.4 Hz), 7.33–7.36 (m, 2H), 7.12 (d, 1H, *J* = 8.8 Hz), 6.90–6.94 (m, 2H), 5.22 (s, 2H), 4.51 (s, 2H), 3.82 (s, 3H).

(*R*)-*tert*-Butyl 4-(2-(4-(4-methoxybenzyloxy)-3-(trifluoromethyl)phenyl)-2-oxoethylcarbamoyl)-2,2,4-trimethyloxazolidine-3-carboxylate (5a)



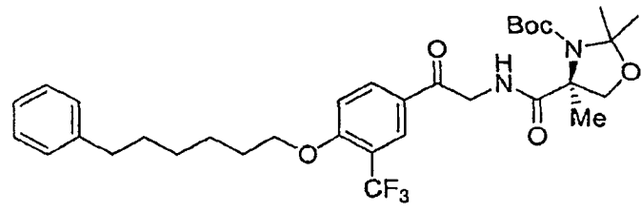
For general protocol for synthesis of compound **5** refer to scheme 1. The reaction was stirred at room temperature for 2 hours. The product was purified by silica gel column chromatography using the Combi-Flash system (Hex:EtOAc) as yellow foam in 72% (2.44 g) yield from amino-acetophenone **3a**. HPLC retention time on a C8(2) column (30 × 3.00 mm, 3 μ) is 2.51 min with gradient 50-98% acetonitrile-H_2O (0.1% TFA) in 4.0 min as mobile phase. TLC (1:1 EtOAc:Hex), R_f = 0.5; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (br s, 1H), 8.09 (br d, 1H, J = 8.4 Hz), 7.32–7.39 (m, 2H), 7.12 (d, 1H, J = 8.4 Hz), 6.90–6.97 (m, 2H), 5.22 (s, 2H), 4.70 (t, 2H, J = 5.2 Hz), 4.30 (br s, 1H), 3.78-3.86 (m, 5H), 1.38-1.85 (m, 18H).

(*R*)-*tert*-Butyl 4-(2-(4-hydroxy-3-(trifluoromethyl)phenyl)-2-oxoethylcarbamoyl)-2,2,4-trimethyloxazolidine-3-carboxylate (6a)



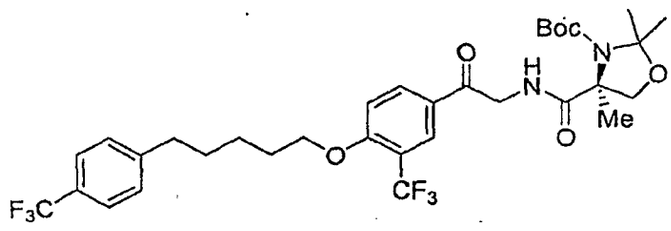
To a solution of (*R*)-*tert*-butyl 4-(2-(4-(4-methoxybenzyloxy)-3-(trifluoromethyl)phenyl)-2-oxoethylcarbamoyl)-2,2,4-trimethyloxazolidine-3-carboxylate (**4**) (2.4 g, 4.1 mmol, 1.0 equiv) in methanol (20 mL) was added 10% Pd/C (240 mg). The reaction mixture was stirred for 3 hours at rt under H_2 atmosphere using a H_2 balloon, filtered through celite and concentrated to give (*R*)-*tert*-butyl 4-(2-(4-hydroxy-3-(trifluoromethyl)phenyl)-2-oxoethylcarbamoyl)-2,2,4-trimethyloxazolidine-3-carboxylate (**6a**) as a white foam in quantitative yield. HPLC retention time on a C18 column (30 x 4.6 mm, 3.5 μ) was 2.62 min with gradient 10-95% acetonitrile-H_2O (0.1% TFA) in 3.5 min as mobile phase. MS (ESI, M+H$^+$) = 461.4.

(*R*)-*tert*-Butyl 2,2,4-trimethyl-4-(2-oxo-2-(4-(6-phenylhexyloxy)-3-(trifluoromethyl)phenyl)ethylcarbamoyl)oxazolidine-3-carboxylate



To a solution of (*R*)-tert-butyl 4-(2-(4-hydroxy-3-(trifluoromethyl)phenyl)-2-oxoethylcarbamoyl)-2,2,4-trimethyloxazolidine-3-carboxylate (114 mg, 0.25 mmol, 1.0 equiv) and 6-phenylhexan-1-ol (45 mg, 0.25 mmol, 1.0 equiv) in DCM (1 mL) was added polymer bond PPh_3 (125 mg, 0.75 mmol, 3.0 equiv). The reaction mixture was stirred at rt for 0.5 hour and cooled to 0 °C. A solution of DIAD (0.053 mL, 0.25 mmol, 1.0 equiv) in DCM (0.5 mL) was added drop wise to the reaction mixture. The reaction mixture was stirred at rt for 2 hours, filtered and evaporated under reduced pressure to give a residue, which was purified by SiO_2 column chromatograph (30-50% EtOAc in hexanes) to give (*R*)-*tert*-butyl 2,2,4-trimethyl-4-(2-oxo-2-(4-(6-phenylhexyloxy)-3-(trifluoromethyl)phenyl)ethylcarbamoyl)oxazolidine-3-carboxylate in 75% (155 mg) yield. HPLC retention time on a C18 column (30 x 4.6 mm, 3.5 μ) was 3.31 min with gradient 50-95% acetonitrile-H_2O (0.1% TFA) in 3.5 min as mobile phase. MS (ESI, $M+H^+$) = 621.6.

(*R*)-*tert*-Butyl 2,2,4-trimethyl-4-(2-oxo-2-(3-(trifluoromethyl)-4-(5-(4-(trifluoromethyl)phenyl)pentyloxy)phenyl)ethylcarbamoyl)oxazolidine-3-carboxylate

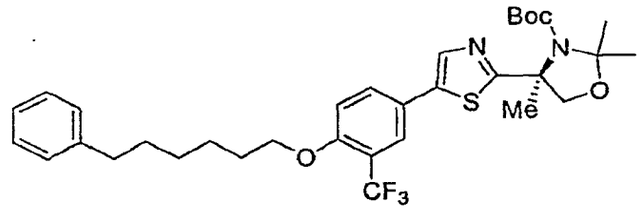


The title compound was prepared from (*R*)-tert-butyl 4-(2-(4-hydroxy-3-(trifluoromethyl)phenyl)-2-oxoethylcarbamoyl)-2,2,4-trimethyloxazolidine-3-carboxylate (0.25 mmol, 1.0 equiv) and 5-(4-(trifluoromethyl)phenyl)pentan-1-ol (0.25 mmol, 1.0 equiv) according to the general procedure in 31 % yield. HPLC retention time

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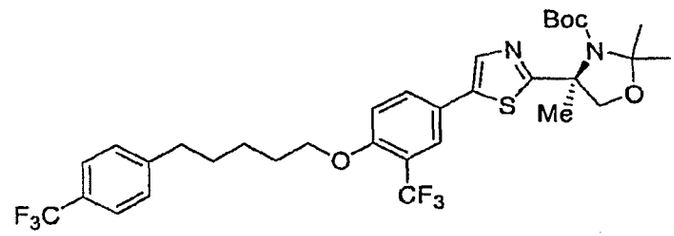
on a C18 column (30 x 4.6 mm, 3.5 μ) was 3.26 min with gradient 50-95% acetonitrile-H_2O (0.1% TFA) in 3.5 min as mobile phase. MS (ESI, $M+H^+$) = 675.6.

(*R*)-*tert*-Butyl 2,2,4-trimethyl-4-(5-(4-(6-phenylhexyloxy)-3-(trifluoromethyl)phenyl)thiazol-2-yl)oxazolidine-3-carboxylate (7a)



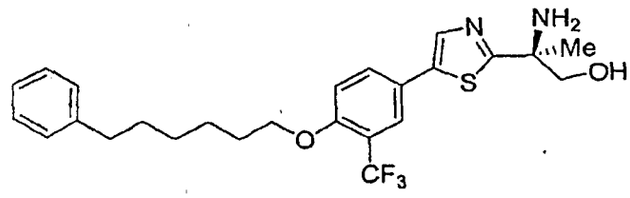
To a solution of (*R*)-tert-butyl 2,2,4-trimethyl-4-(2-oxo-2-(4-(6-phenylhexyloxy)-3-(trifluoromethyl)phenyl)ethylcarbamoyl)oxazolidine-3-carboxylate (49 mg, 0.079 mmol, 1.0 equiv) in toluene (1 mL) was added Lawesson's reagent (32 mg, 0.087 mmol, 1.1 equiv). The reaction mixture was heated at 80 °C for 3 h. The crude product was purified directly by SiO_2 column chromatograph (EtOAc/hexanes, 3:7) to give (*R*)-*tert*-butyl 2,2,4-trimethyl-4-(5-(4-(6-phenylhexyloxy)-3-(trifluoromethyl)phenyl)thiazol-2-yl)oxazolidine-3-carboxylate. HPLC retention time on a C8(2) column (30 x 50 mm, 3 μ) is 3.29 min with gradient 70-98% acetonitrile-H_2O (0.1 % TFA) in 3.5 min as mobile phase. MS (ESI, $M+H^+$) = 619.0.

(*R*)-*tert*-Butyl 2,2,4-trimethyl-4-(5-(3-(trifluoromethyl)-4-(5-(4-(trifluoromethyl)phenyl)pentyloxy)phenyl)thiazol-2-yl)oxazolidine-3-carboxylate (7b)



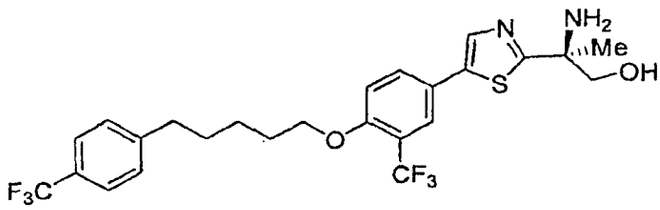
The title compound was prepared from (*R*)-*tert*-butyl 2,2,4-trimethyl-4-(2-oxo-2-(3-(trifluoromethyl)-4-(5-(4-(trifluoromethyl)phenyl)pentyloxy)phenyl)ethylcarbamoyl)-oxazolidine-3-carboxylate. HPLC retention time on a C8(2) column (30 x 50 mm, 3 μ) is 3.29 min with gradient 70-98% acetonitrile-H_2O (0.1 % TFA) in 3.5 min as mobile phase. MS (ESI, $M+H^+$) = 673.0.

(*S*)-2-Amino-2-(5-(4-(6-phenylhexyloxy)-3-(trifluoromethyl)phenyl)thiazol-2-yl)propan-1-ol (8a)



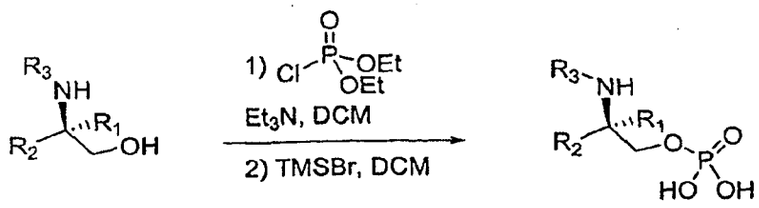
The title compound was prepared from (*R*)-*tert*-butyl 2,2,4-trimethyl-4-(5-(4-(6-phenylhexyloxy)-3-(trifluoromethyl)phenyl)thiazol-2-yl)oxazolidine-3-carboxylate. HPLC retention time on a C18 column (30 x 4.6 mm, 3.5 μ) was 2.41 min with gradient 10-95% acetonitrile-H_2O (0.1% TFA) in 3.5 min as mobile phase. MS (ESI, $M+H^+$) = 479.4; ^1H NMR (400 MHz, $CDCl_3$) δ 7.76 (s, 1H), 7.65 (d, 1H, J = 2.0 Hz), 7.55 (dd, 1H, J = 8.8 Hz, J = 2.0 Hz), 7.28-7.23 (m, 2H), 7.18-7.15 (m, 3H), 6.96 (d, 1H, J = 9.2 Hz), 4.06-3.99 (m, 4H), 2.62 (t, 2H, J = 7.6 Hz), 1.85-1.78 (m, 5H), 1.69-1.62 (m, 2H), 1.56-1.50 (m, 2H), 1.44-1.38 (m, 2H).

(*S*)-2-Amino-2-(5-(3-(trifluoromethyl)-4-(5-(4-(trifluoromethyl)phenyl)pentyloxy)phenyl)thiazol-2-yl)propan-1-ol (8b)



The title compound was prepared from (*R*)-tert-butyl 2,2,4-trimethyl-4-(5-(3-(trifluoromethyl)-4-(5-(4-(trifluoromethyl)phenyl)pentyloxy)phenyl)thiazol-2-yl)oxazolidine-3-carboxylate. HPLC retention time on a C18 column (30 x 4.6 mm, 3.5 μ) was 2.50 min with gradient 10-95% acetonitrile-H_2O (0.1% TFA) in 3.5 min as mobile phase. MS (ESI, $M+H^+$) = 533.4; ^1H NMR (400 MHz, $CDCl_3$) δ 7.77 (s, 1H), 7.66 (d, 1H, J = 2.0 Hz), 7.56 (dd, 1H, J = 9.0 Hz, J = 2.4 Hz), 7.52 (d, 2H, J = 8.0 Hz), 7.28 (d, 2H, J = 8.0 Hz), 6.97 (d, 1H, J = 8.8 Hz), 4.07-4.03 (m, 4H), 2.70 (t, 2H, J = 7.8 Hz), 1.89-1.82 (m, 5H), 1.74-1.67 (m, 2H), 1.57-1.50 (m, 2H).

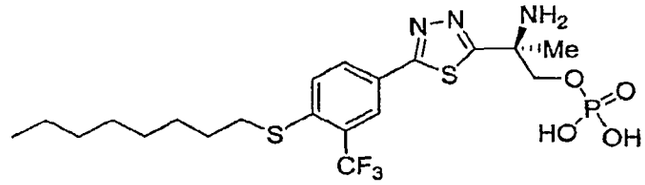
General method for phosphate synthesis



R_3 = H or protecting group

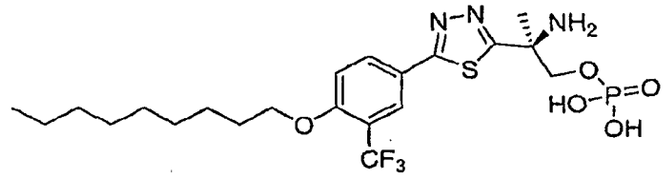
Synthetic strategy for synthesis of desired phosphates is illustrated above. To a solution of unprotected amino alcohol (1.0 equiv) in dry CH_2Cl_2 at RT was added excess diethyl chlorophosphate (10.0 equiv) and triethylamine (20.0 equiv) and the reaction stirred for 12-18 hours. The reaction was monitored by LC-MS. The crude reaction mixture was then evaporated to dryness *in vacuo*. The obtained phospho-diester intermediate was reacted with excess bromotrimethylsilane (10.0-20.0 equiv) in dry CH_2Cl_2 at RT over a period of 6-10 hours to afford the final phosphate which was purified by reverse-phase preparative HPLC after evaporation of the solvent and excess reagent.

(*S*)-2-Amino-2-(5-(4-(octylthio)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propyl dihydrogen phosphate (a)



MS (ESI, $M+H^+$) = 528.0; HPLC retention time on a C8(2) column (30 × 3.00 mm, 3 μ) is 2.27 min with gradient 30-98% acetonitrile-H_2O (0.1% TFA) in 3.5 min as mobile phase.

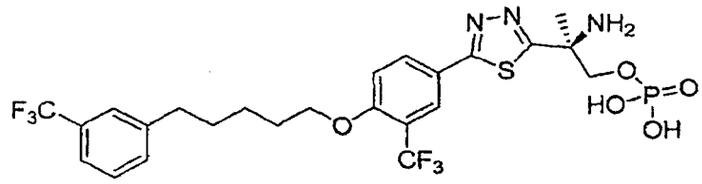
(*S*)-2-Amino-2-(5-(4-(nonyloxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propyl dihydrogen phosphate (b)



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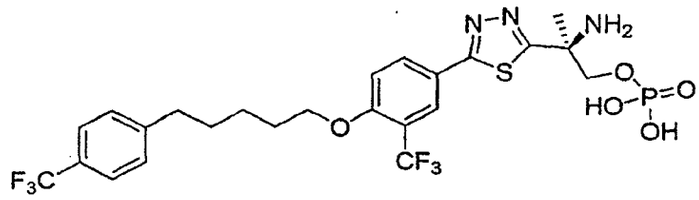
MS (ESI, M+H$^+$) = 526.0; HPLC retention time on a Synergi-Max RP column (2 x 20 mm, 2 μL) is 1.51 min with gradient 30-99% acetonitrile-H_2O (0.1 % TFA) in 2 min as mobile phase.

(*S*)-2-Amino-2-(5-(3-(trifluoromethyl)-4-(5-(3-(trifluoromethyl)phenyl)pentyloxy)phenyl)-1,3,4-thiadiazol-2-yl)propyl dihydrogen phosphate (c)



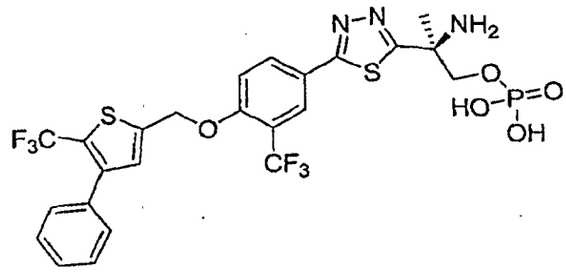
MS (ESI, M+H$^+$) = 614.0; HPLC retention time on a Synergi-Max RP column (2 x 20 mm, 2 μL) is 1.44 min with gradient 30-99% acetonitrile-H_2O (0.1 % TFA) in 2 min as mobile phase.

(*S*)-2-Amino-2-(5-(3-(trifluoromethyl)-4-(5-(4-(trifluoromethyl)phenyl)pentyloxy)phenyl)-1,3,4-thiadiazol-2-yl)propyl dihydrogen phosphate (d)



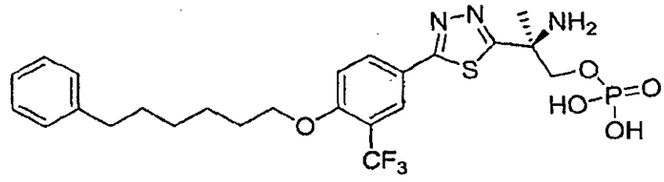
MS (ESI, M+H$^+$) = 614.0; HPLC retention time on a Synergi-Max RP column (2 x 20 mm, 2 μL) is 1.44 min with gradient 30-99% acetonitrile-H_2O (0.1 % TFA) in 2 min as mobile phase.

(*S*)-2-Amino-2-(5-(4-((4-phenyl-5-(trifluoromethyl)thiophen-2-yl)methoxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propyl dihydrogen phosphate (e)



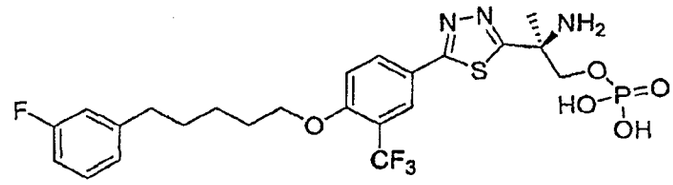
MS (ESI, $M+H^+$) = 639.8; HPLC retention time on a Synergi-Max RP column (2 x 20 mm, 2 μL) is 1.37 min with gradient 30-99% acetonitrile-H_2O (0.1 % TFA) in 2 min as mobile phase.

(*S*)-2-Amino-2-(5-(4-(6-phenylhexyloxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propyl dihydrogen phosphate (f)



MS (ESI, $M+H^+$) = 599.9; HPLC retention time on a Synergi-Max RP column (2 x 20 mm, 2 μL) is 1.41 min with gradient 30-99% acetonitrile-H_2O (0.1 % TFA) in 2 min as mobile phase.

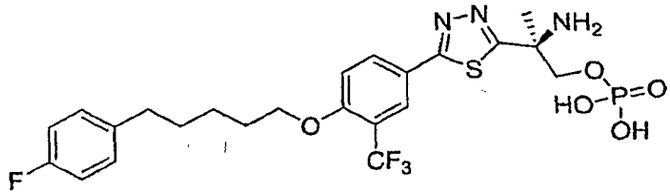
(*S*)-2-Amino-2-(5-(4-(5-(3-fluorophenyl)pentyloxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propyl dihydrogen phosphate (g)



MS (ESI, $M+H^+$) = 563.9; HPLC retention time on a Synergi-Max RP column (2 x 20 mm, 2 μL) is 1.53 min with gradient 20-95% acetonitrile-H_2O (0.1 % TFA) in 2 min as mobile phase.

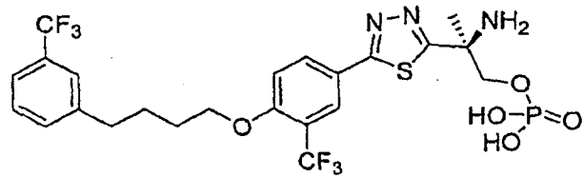
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(*S*)-2-Amino-2-(5-(4-(5-(4-fluorophenyl)pentyloxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propyl dihydrogen phosphate (h)



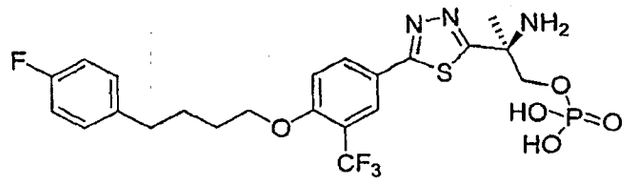
MS (ESI, $M+H^+$) = 593.9; HPLC retention time on a Synergi-Max RP column (2 x 20 mm, 2 μL) is 1.57 min with gradient 20-95% acetonitrile-H_2O (0.1 % TFA) in 2 min as mobile phase.

(*S*)-2-Amino-2-(5-(3-(trifluoromethyl)-4-(4-(3-(trifluoromethyl)phenyl)butoxy)phenyl)-1,3,4-thiadiazol-2-yl)propyl dihydrogen phosphate (i)



MS (ESI, $M+H^+$) = 599.9; HPLC retention time on a Synergi-Max RP column (2 x 20 mm, 2 μL) is 2.03 min with gradient 20-95% acetonitrile-H_2O (0.1 % TFA) in 2 min as mobile phase.

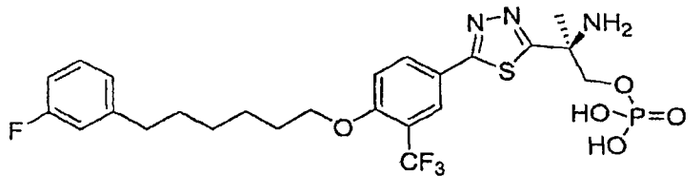
(*S*)-2-Amino-2-(5-(4-(4-(4-fluorophenyl)butoxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propyl dihydrogen phosphate (j)



MS (ESI, $M+H^+$) = 549.9; HPLC retention time on a Synergi-Max RP column (2 x 20 mm, 2 μL) is 1.51 min with gradient 20-95% acetonitrile-H_2O (0.1 % TFA) in 2 min as mobile phase.

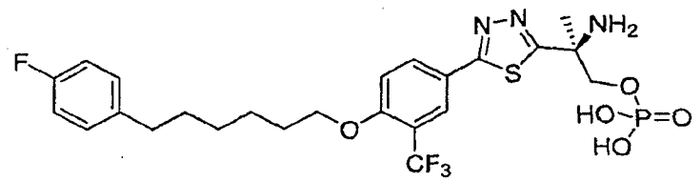
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(*S*)-2-Amino-2-(5-(4-(6-(3-fluorophenyl)hexyloxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propyl dihydrogen phosphate (k)



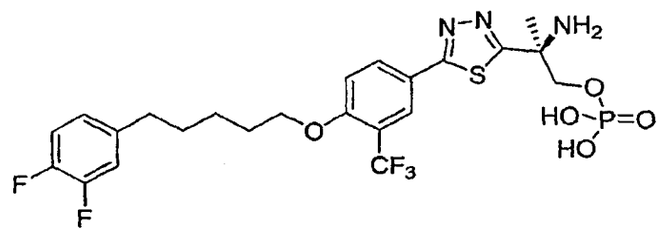
MS (ESI, $M+H^+$) = 577.9; HPLC retention time on a Synergi-Max RP column (2 x 20 mm, 2 μL) is 1.65 min with gradient 20-95% acetonitrile-H_2O (0.1 % TFA) in 2 min as mobile phase.

(*S*)-2-Amino-2-(5-(4-(6-(4-fluorophenyl)hexyloxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propyl dihydrogen phosphate (l)



MS (ESI, $M+H^+$) = 578.0; HPLC retention time on a Synergi-Max RP column (2 x 20 mm, 2 μL) is 1.63 min with gradient 20-95% acetonitrile-H_2O (0.1 % TFA) in 2 min as mobile phase.

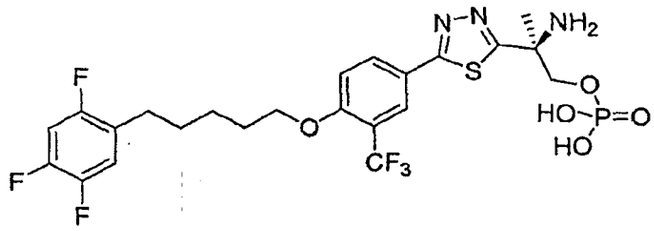
(*S*)-2-Amino-2-(5-(4-(5-(3,4-difluorophenyl)pentyloxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propyl dihydrogen phosphate (m)



MS (ESI, $M+H^+$) = 582.0; HPLC retention time on a Synergi-Max RP column (2 x 20 mm, 2 μL) is 1.58 min with gradient 20-95% acetonitrile-H_2O (0.1 % TFA) in 2 min as mobile phase.

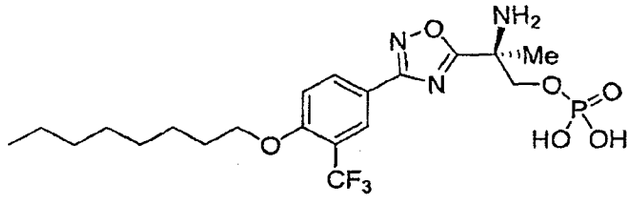
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(*S*)-2-Amino-2-(5-(3-(trifluoromethyl)-4-(5-(2,4,5-trifluorophenyl)pentyloxy)phenyl)-1,3,4-thiadiazol-2-yl)propyl dihydrogen phosphate (n)



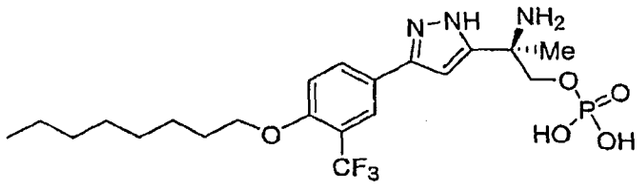
MS (ESI, M+H$^+$) = 599.9; HPLC retention time on a Synergi-Max RP column (2 x 20 mm, 2 μL) is 1.59 min with gradient 20-95% acetonitrile-H_2O (0.1 % TFA) in 2 min as mobile phase.

(*S*)-2-Amino-2-(3-(4-(octyloxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)propyl dihydrogen phosphate (o)



The title product was obtained according to general procedure from compound **7a** (Scheme 6). MS (ESI, M+H$^+$) = 496.0

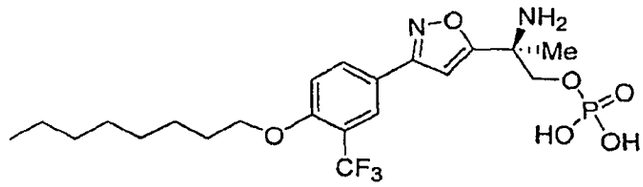
(*R*)-2-Amino-2-(3-(4-(octyloxy)-3-(trifluoromethyl)phenyl)-1*H*-pyrazol-5-yl)propyl dihydrogen phosphate (p)



The title product was obtained according to general procedure from compound **3a** (Scheme 7). MS (ESI, M+H$^+$) = 494.1

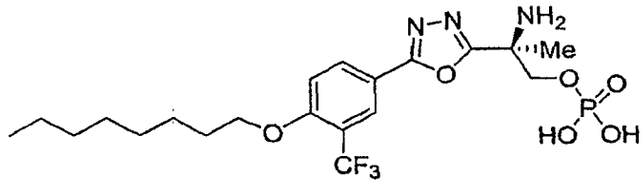
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(*S*)-2-Amino-2-(3-(4-(octyloxy)-3-(trifluoromethyl)phenyl)isoxazol-5-yl)propyl dihydrogen phosphate (q)



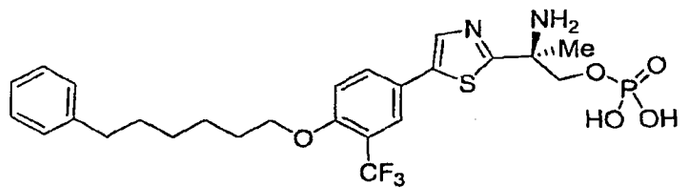
The title product was obtained according to general procedure from compound **3a** (Scheme 7). MS (ESI, $M+H^+$) = 495.0

(*S*)-2-Amino-2-(5-(4-(octyloxy)-3-(trifluoromethyl)phenyl)-1,3,4-oxadiazol-2-yl)propyl dihydrogen phosphate (q)



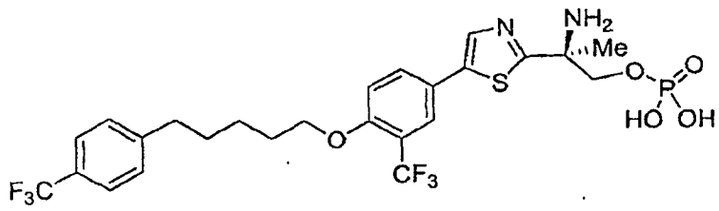
The title product was obtained according to general procedure from the corresponding amino-alcohol. MS (ESI, $M+H^+$) = 496.0

(*S*)-2-Amino-2-(5-(4-(6-phenylhexyloxy)-3-(trifluoromethyl)phenyl)thiazol-2-yl)propyl dihydrogen phosphate (r)



The title compound was prepared from (*S*)-2-amino-2-(5-(4-(6-phenylhexyloxy)-3-(trifluoromethyl)phenyl)thiazol-2-yl)propan-1-ol. HPLC retention time on a C18 column (30 x 4.6 mm, 3.5 μ) was 2.48 min with gradient 10-95% acetonitrile-H_2O (0.1% TFA) in 3.5 min as mobile phase. MS (ESI, $M+H^+$) = 559.5.

(*S*)-2-Amino-2-(5-(3-(trifluoromethyl)-4-(5-(4-(trifluoromethyl)phenyl)pentyloxy) phenyl)thiazol-2-yl)propyl dihydrogen phosphate (s)

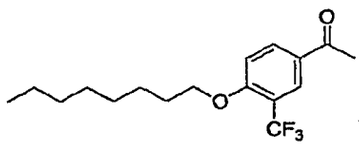


The title compound was prepared from (*S*)-2-amino-2-(5-(3-(trifluoromethyl)-4-(5-(4-(trifluoromethyl)phenyl)pentyloxy)phenyl)thiazol-2-yl)propan-1-ol. HPLC retention time on a C18 column (30 x 4.6 mm, 3.5 μ) was 2.53 min with gradient 10-95% acetonitrile-H_2O (0.1% TFA) in 3.5 min as mobile phase. MS (ESI, $M+H^+$) = 613.5.

<u>Examples of specific methods used to make (*S*)-2-Amino-2-(5-(4-(octyloxy)-3-(trifluoromethyl)phenyl)thiazol-2-yl)propan-1-ol and (*S*)-2-Amino-2-(5-(4-(octyloxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol.</u>

Description 1

1-(4-(Octyloxy)-3-(trifluoromethyl)phenyl)ethanone (D1)



1-octanol (2mL), 1-[4-fluoro-3-(trifluoromethyl)phenyl]ethanone (2.62g), potassium tert-butoxide (14mL, 1.0M) and tetrahydrofuran (30mL) were heated at 65°C for 3hrs to produce the title product as a brownish oil (4.00g). The product was purified by silica gel column chromatography using the Combi-Flash system (Hex:EtOAc) as white solid in 60% (1.20 g). TLC (1:5 EtOAc:Hex), R_f = 0.4; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, 1H, *J* = 2.0 Hz), 8.10 (dd, 1H, *J* = 8.8 Hz, *J* = 2.3 Hz), 7.02 (d, 1H, *J* = 8.8 Hz), 4.12 (t, 2H, *J* = 6.4 Hz), 2.58 (m, 3H), 1.80-1.89 (m, 2H), 1.42-1.54 (m, 2H), 1.22-1.40 (m, 8H), 0.89 (t, 3H, *J* = 6.7 Hz).

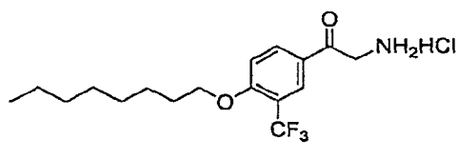
Description 1 Alternative Method (D1A)

1-(4-(Octyloxy)-3-(trifluoromethyl)phenyl)ethanone (D1)

A solution of *n*-octanol (13.3 g, 0.102 mol), in THF (224 mL) was treated with 1.0 M potassium *t*-butoxide in THF (112 mL, 1.1 equiv) at room temperature and heated to 65 °C. After 15 minutes, a solution of 1-[4-fluoro-3-(trifluoromethyl)phenyl]ethanone (21 g, 1.0 equiv) in THF (224 mL) was charged slowly over 30 minutes. Vigorous gas evolution was noted during the addition. The reaction was monitored by HPLC and deemed complete after 1.5 h. The reaction mixture was cooled to ambient temperature, treated with 10% aqueous citric acid (250 mL), extracted with MTBE (2 × 500 mL), dried, and concentrated to afford the product (31.99 g, 99.3%, 88.1% AUC by HPLC). This reaction was repeated with slight modification as described above (reducing the amount of THF used to dissolve the acetophenone to 3 mL/g from 10.7 mL/g with improved control of gas evolution) on a 100 g scale to give 137.1 g, >100% yield). The two lots were combined and purified by column chromatography using silica-gel (1 kg), eluted with 10% ethyl acetate: 90% heptane to afford the title product (105 g, 75% yield) as a pale yellow color oil. Impure fractions were collected and provided 22.8 g (16.3% yield) of the product.

Description 2

2-Amino-1-(4-(octyloxy)-3-(trifluoromethyl)phenyl)ethanone hydrochloride (D2)



To a solution of 1-(4-(Octyloxy)-3-(trifluoromethyl)phenyl)ethanone (D1) (0.5g, 1.0 equivalent) in CH_2Cl_2 /MeOH (4:1, 10mL) was added Bu_4NBr_3 (0.76 g, 1.0 equiv). The reaction mixture was stirred at room temperature for 3hours. TLC (4:1, Hex/EtOAc), R_f = 0.6. The solvent was removed *in vacuo*, and re-dissolved in DMF (10mL). NaN_3 (0.31g, 3.0 equiv) was added to the reaction and the resulting mixture was then stirred at room temperature for 2hrs. The solvent was removed *in vacuo* and the product was purified by silica gel column chromatography using the Combi-Flash system (Hex:EtOAc) to give the azido-acetophenone product. TLC (4:1, Hex/EtOAc), R_f = 0.4. The residue was then dissolved in concentrated HCl (1.0 mL) and MeOH (20mL). 10% Pd/C (100 mg) was added and the mixture stirred under an atmosphere of H_2 (g) for 3 hours. The reaction mixture was then filtered and evaporated to dryness to

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give the title product as a yellow solid 98% (570mg yield). TLC (4:1, Hex/EtOAc), R_f = 0.6.

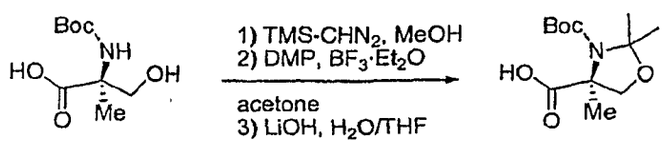
Description 2 Alternative Method (D2A)

2-Amino-1-(4-(octyloxy)-3-(trifluoromethyl)phenyl)ethanone hydrochloride (D2)

A 5 L round bottom flask was charged with 1-(4-(Octyloxy)-3-(trifluoromethyl)phenyl)ethanone (D1A) (128 g, 0.40 mol), anhydrous dichloromethane (3.2 L), tetrabutylammonium tribromide (175 g, 0.36 mol, 0.9 equiv), methanol (640 mL) and stirred for 1 hour at room temperature (18 to 23 °C) and then treated with additional tetrabutylammonium tribromide (20 g, 0.1 equiv) and held for five additional hours. The reaction was deemed complete by TLC analysis (10% ethyl acetate in toluene) and concentrated to a residue. The residue was purified by column chromatography using silica gel (2.7 kg), eluted with 10% ethyl acetate: 90% heptane to afford a foamy solid (128 g, 80% yield). A 3 L round bottom flask was charged with a solution of the foamy solid (128 g, 0.32 mol) in acetonitrile (1 L) and sodium diformylamide (36.9 g, 0.38 mol, 1.2 equiv), and heated to 65 °C for 2 hours. The reaction was assayed by TLC and appeared to be approximately 50% complete. The reaction was allowed to continue for a further 10 hours, at which point was found to be complete by TLC. The mixture was cooled to room temperature (18 to 23 °C) and charged with MTBE (1 L), stirred for 15 minutes, filtered, the solids washed twice with MTBE (2 × 250 mL). The filtrates were combined and concentrated to thick oil. The oil was taken up in reagent alcohol (1.1 L), charged with 10 N HCl (100 mL) and heated to 70 °C and held for 3 hours, at which point TLC indicated the reaction to be complete. The mixture was cooled to 40–50 °C and transferred to a rotavap and the ethanol removed, and azeotroped three times with toluene (3 × 1 L) to afford the title product (149 g, quantitative yield) as gummy oil.

Description 3

(*R*)-3-(*tert*-Butoxycarbonyl)-2,2,4-trimethyloxazolidine-4-carboxylic acid (D3)



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To a solution of the (*S*)-2-(*tert*-butoxycarbonylamino)-3-hydroxy-2-methylpropanoic acid (5.0 g, 1.0 equiv) in CH_2Cl_2/MeOH(4:1, 50 mL) at 0 °C was added a solution of TMS-CHN_2 (2.0 M in diethyl ether or hexanes, 12.5mL, 1.1 equiv) drop-wise until the colourless solution turned a light yellow colour. The reaction mixture was stirred for 20 minutes at 0°C then a few drops of acetic acid were added to quench the last unreacted TMS-CHN_2 (the solution turns colourless from light yellow). The solvent was removed *in vacuo*. TLC (2:1, Hex/EtOAc), R_f = 0.4.

The residue was dissolved in acetone (30 mL), 2,2-dimethoxypropane (DMP) (12 mL) and $BF_3 \cdot OEt_2$ (2 mL). The solution was stirred at RT for 4hours. The solvent was removed *in vacuo* and the product was purified by silica gel column chromatography using the Combi-Flash system (Hex:EtOAc). TLC (3:1, Hex/EtOAc), R_f = 0.6; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.06-4.12 (m, 1H), 3.73-3.83 (m, 4H), 1.55-1.64 (m, 9H), 1.48 (br s, 3H), 1.41 (br s, 6H).

The purified residue was dissolved in THF (40 mL) and to the solution was added LiOH (1.15 g, 1.20 equiv) in H_2O (20 mL). The solution was heated at reflux for 6hours then stirred overnight, then concentrated *in vacuo* to remove most of the THF. The solution was diluted with H_2O (150 mL) and washed with Et_2O (2 x 150 mL). The aqueous layer was cooled to 0 °C then acidified to pH2 using concentrated HCl, then extracted with EtOAc (2 x 200 mL). The EtOAc layers were combined, dried ($MgSO_4$), filtered, and the solvent was removed *in vacuo* to afford the carboxylate title compound as a white solid in 64% yield (3.78 g). TLC (1:1 EtOAc:Hex), R_f = 0.2; ^{1}H NMR (400 MHz, $CDCl_3$) δ (rotamers) 4.47 (br d, 0.5H, J = 8.8 Hz), 4.17 (br d, 0.5H, J = 8.8 Hz), 3.85 (br d, 0.5H, J = 8.8 Hz), 3.78 (br d, 0.5H, J = 8.8 Hz), 1.38-1.67 (m, 18H).

Description 3 Alternative Method (D3A)

(*R*)-3-(*tert*-Butoxycarbonyl)-2,2,4-trimethyloxazolidine-4-carboxylic acid (D3)

A 22 L round bottom flask was inerted and charged with (*S*)-2-(*tert*-butoxycarbonylamino)-3-hydroxy-2-methylpropanoic acid (564 g, 2.57 mol), acetone (8.4 L) and stirred. The mixture was slowly charged with 1,8-Diazabicyclo[5.4.0]undec-7-ene (770 mL, 5.1 mol, 2 equiv.). The addition was exothermic and the temperature was maintained below 25 °C. The mixture was stirred for 45 minutes at ambient conditions, and then cautiously charged with iodomethane (320 mL, 5.1 mol, 2 equiv). The addition was exothermic and the temperature was maintained below 25 °C. The

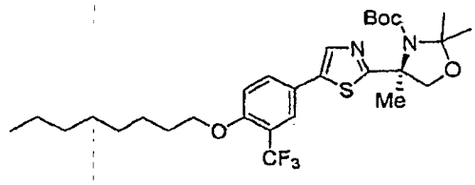
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mixture was allowed to stir overnight at room temperature (18 to 23 °C). After 16 hours, TLC indicated starting material remained. The reaction was charged with iodomethane (320 mL, 5.1 mol, 2 equiv), warmed to 30 °C for 4 hours, and then allowed to stir overnight at room temperature (18 to 23 °C). After 16 hours, assay by TLC indicated the reaction was complete. The reaction mixture was combined with another reaction mixture of a scale of 275 g. The combined reaction mixtures were concentrated under vacuum to a residue, transferred into a reactor, charged with water (8.4 L), ethyl acetate (8.4 L), mixed thoroughly, phases split, extracted aqueous phase once more with ethyl acetate (8.4 L), combined organic phases, washed with 5% w/v citric acid (900 mL), brine (1 L), dried with magnesium sulfate, filtered over Celite, and concentrated to afford an oil (925 g, 104% yield). A 22 L round bottom flask was charged with this crude product (925 g, 3.8 mol based on theoretical output from previous step), dichloromethane (10 L), 2,2-Dimethoxypropane (2.6 L), and mixed. Boron trifluoride diethyl etherate (200 mL, 1.62 mol, 0.42 equiv) in dichloromethane (1.2 L) was cautiously charged over 45 minutes. The resulting dark solution was stirred over night at room temperature (18 to 23 °C). After 16 hours TLC indicated the reaction was complete. The mixture was slowly quenched with saturated sodium bicarbonate (3.5 L) while maintaining the temperature below 25 °C. Once the quench was complete, the mixture was stirred for 30 minutes, the phases separated, and the aqueous extracted with dichloromethane (3.5 L), the organic phases were combined, washed with saturated sodium bicarbonate (3 L), concentrated to obtain compound a yellow oil (1070 g, quantitative). A 22 L round bottom flask was charge with lithium hydroxide monohydrate (482 g, 11.4 mol, 3 equiv), water (2.3 L), methanol (2.1 L), a solution of crude yellow oil (1046 g – based on theoretical output of previous step, 3.82 mol) in tetrahydrofuran (6.5 L). The mixture was stirred for 72 hours at room temperature (18 to 23 °C). TLC indicated the reaction was complete. The mixture was concentrated under vacuum at 40 °C, the residue was charged with water (10 L), MTBE (6 L), mixed thoroughly, and the phases split. The organic phase was washed with water (4 L), the aqueous phases were combined, and solid citric acid was charged in portions until a pH of 3 was obtained. The aqueous was extracted with ethyl acetate (2 × 10 L), ethyl acetate phases were combined, washed with brine (7 L), dried with magnesium sulfate, filtered over Celite, and concentrated to afford the title product (770 g, 77.6% yield) as an off white solid.

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Description 4

(*R*)-*tert*-Butyl 2,2,4-trimethyl-4-(5-(4-(octyloxy)-3-(trifluoromethyl)phenyl)thiazol-2-yl)oxazolidine-3-carboxylate (D4)



To a solution of (*R*)-3-(*tert*-Butoxycarbonyl)-2,2,4-trimethyloxazolidine-4-carboxylic acid (D3) (100 mg, 1 equiv), HATU (220 mg, 1.5 equiv), and DIEA (0.67 mL, 10 equiv) in DCM (5 mL) was added 2-amino-1-(4-(octyloxy)-3-(trifluoromethyl)phenyl)ethanone hydrochloride (D2) (142 mg, 1.0 equivalents). The solvent removed *in vacuo* and the product was purified with silica gel column chromatography using the Combi-Flash system (Hex:EtOAc). This resulted in a colourless, thick oil which was dissolved in toluene (5mL) with Lawesson's reagent (280mg, 3 equiv). The resultant mixture was heated at 120°C for 2 hours to produce the title product as a colourless oil 41% yield (90mg). TLC (1:2 EtOAc:Hex), R_f = 0.3; MS (ESI, M+Na) = 572.99; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (s, 1H), 8.11 (d, 1H, J = 8.4 Hz), 7.05 (d, 1H, J = 8.4 Hz), 4.62-4.79 (m, 2H), 4.13 (t, 2H, J = 6.4 Hz), 3.28 (br s, 1H), 1.22-1.90 (m, 30H), 0.89 (t, 3H, J = 6.4 Hz).

Description 4 Alternative method (D4A)

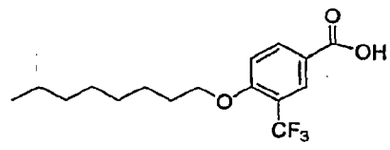
(*R*)-*tert*-Butyl 2,2,4-trimethyl-4-(5-(4-(octyloxy)-3-(trifluoromethyl)phenyl)thiazol-2-yl)oxazolidine-3-carboxylate (D4)

A 5 L, round bottom flask was charged with HATU (147 g, 0.38 mol, 1.2 equiv), methylene chloride (600 mL), *N,N*-dimethylformamide (300 mL), diisopropylethylamine(83.5 g, 0.64 mol, 2 equiv) and the mixture cooled to 10–15 °C. A solution of (*R*)-3-(*tert*-Butoxycarbonyl)-2,2,4-trimethyloxazolidine-4-carboxylic acid (D3A) (83.7 g, 0.32 mol, 1 equiv) in methylene chloride (600 mL) was charged over a period of 30 minutes. The mixture was warmed to room temperature (18 to 23 °C) and stirred for 1 hour. A separate flask was charged with solution of 2-Amino-1-(4-(octyloxy)-3-(trifluoromethyl)phenyl)ethanone hydrochloride (D2A) (149 g, 0.32 mol – based on theoretical output) in methylene chloride (1 L), *N,N*-dimethylformamide (400

mL) and diisopropylethylamine (125 g, 0.96 mol, 3 equiv). The solution of the second flask was slowly charged to the first flask over a period of 35 minutes. The resulting brown solution was stirred for 1 hour, at which point TLC analysis indicated the reaction was complete. The mixture was transferred to a rotavap and concentrated to remove the methylene chloride. The mixture was transferred once more to the round bottom flask and charge with MTBE (3 L), 10% w/v aqueous sodium chloride solution (3 L), stirred for 10 minutes, phases separated, and the aqueous extracted once more with MTBE (1 L). The organic phases were combined, washed twice with 10% w/v aqueous sodium chloride solution (2 × 1 L), dried with magnesium sulfate, and concentrated to a residue which was purified by column chromatography using silica-gel (1.3 kg), eluted with 5% ethyl acetate: 95% heptane to 30% ethyl acetate: 70% heptane to afford the product as a yellow-coloured oil (137.5 g, 74% yield). A 5 L round bottom flask was charged with Lawesson's reagent (116.2 g, 0.28 mol, 1.2 equiv), a solution of the yellow-coloured oil (137 g, 0.239 mol) in toluene (2 L). The resulting slurry was heated to 80 °C which after 30 minutes became a clear solution. The solution was held at 80 °C for another 2 hours, at which point TLC (25% ethyl acetate: 75% heptane) indicated the reaction was complete. The reaction mixture was cooled to room temperature (18 to 23 °C), charged with saturated sodium bicarbonate solution (1 L), 10% w/v sodium chloride (1 L), ethyl acetate (1 L), and stirred for 30 minutes. The phases were separated and the aqueous extracted once more with ethyl acetate (1 L). The organic phases were combined and concentrated to a residue. The residue was purified by column chromatography using silica-gel (1.3 kg), eluted with 100% heptane to 30% ethyl acetate: 70% heptane to afford the title product (91.1 g, 67% yield, 96.6% AUC by HPLC) as a brown oil.

Description 5

4-(Octyloxy)-3-(trifluoromethyl)benzoic acid (D5)



1-octanol (315 μL, 2.0 mmol), THF (5 mL), potassium *t*-butoxide (5 mL, 1M solution in THF), 4-Fluoro-3-trifluoromethylbenzoic acid (417 mg, 2.0 mmol) were mixed and heated at 75 °C for 3-4hrs. The reaction mixture was then diluted with ethyl acetate and washed with water. The water layer was acidified and extracted with ethyl acetate. The

organic layer was washed with brine and dried over Na_2SO_4 and concentrated to afford the title compound (632 mg, HPLC purity > 95%), which was used for next reaction without further purification. HPLC retention time on a C8(2) column (30 × 3.00 mm, 3 μ) was 3.28 min with gradient 50-98% acetonitrile-H_2O (0.1% trifluoroacetic acid (TFA)) in 3.5 min as mobile phase.

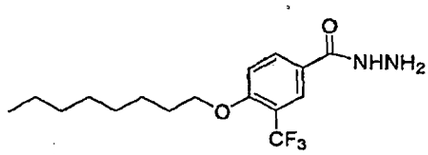
Description 5 Alternative Method A (D5A)

4-(Octyloxy)-3-(trifluoromethyl)benzoic acid (D5)

A 12 L round bottom flask was inerted and charged with 1-octanol (103 g, 0.793 mol, 1 equiv), THF (2 L), 1 M potassium *tert*-butoxide (2 L, 2.5 equiv) and heated to 65 °C and held for 45 minutes. The reaction was charged over 1 hour with 4-fluoro-3-trifluoromethyl benzoic acid (165 g, 0.793 mol) while maintaining the temperature at 64 to 67 °C. After 2 hours, the reaction mixture was sampled. The sample was concentrated, quenched into 1 N HCl, extracted with ethyl acetate, removed the ethyl acetate, diluted with acetonitrile and injected in to the HPLC. The reaction was complete. The reaction mixture was stirred overnight at 18 to 23 °C. The mixture was cooled to 5 to 10 °C and cautiously quenched with water (1.6 L). The quench was exothermic and the temperature was maintained at T<10 °C. The resulting mixture was concentrated under vacuum until no noticeable THF was coming off. The resulting aqueous mixture was acidified to pH 1 to 2 using 6 N HCl (400 mL). The mixture was extracted with MTBE (2 × 2.5 L). The MTBE phases were combined, washed with brine (2 L), dried with magnesium sulfate, filtered over Celite, concentrated to afford the title product (279 g, 111% yield, 95.6% AUC by HPLC) as a tan solid.

Description 6

4-(Octyloxy)-3-(trifluoromethyl)benzohydrazide (D6)



4-(Octyloxy)-3-(trifluoromethyl)benzoic acid (**D5**) (600 mg, 1 equiv) was stirred with HATU (859 mg, 1.2 equiv) and DIEA (1.63 mL, 5 equiv) in CH_2Cl_2-DMF (10 mL, 4:1, 3 equivalents) followed by addition of hydrazine (282 μL, 3 equiv). The reaction mixture was then diluted with ethyl acetate and washed with water and brine. The

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organic layer was dried over Na_2SO_4 and concentrated *in vacuo* to afford the title compound (661 mg). MS (ESI): 333.08 (MH^+)

Another batch was also made using **D5** (32 mg, 1 equivalent), HATU (46 mg, 1.2 equivalents), DIEA (87μL, 5 equiv) in CH_2Cl_2-DMF (1.5 mL, 2:1) followed by addition of hydrazine (15 μL, 3 equiv).

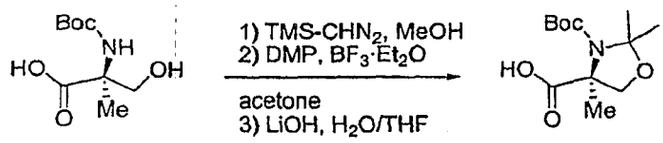
Description 6 Alternative Method (D6A)

4-(Octyloxy)-3-(trifluoromethyl)benzohydrazide (D6)

A 5 L 3 neck, round bottom flask was inerted and charged with CDI (153 g, 0.94 mol, 1.2 equiv), 4-(Octyloxy)-3-(trifluoromethyl)benzoic acid (D5A) (250 g based on theoretical output of previous step, 0.78 mol), THF (2.5 L) and stirred at 18 to 23 °C for 1 hour. A separate 12 L round bottom flask was inerted and charged with hydrazine monohydrate (235 g, 4.71 mol, 6 equiv) and THF (1.2 L). The contents of the first flask was charged to the second flask over 1 hour. During the addition, the temperature was maintained at T<25 °C. Once the addition was complete, the mixture was stirred for 2 hours at 18 to 23 °C, at which point TLC indicated the reaction was complete. The mixture was concentrated under vacuum at 35 to 40 °C until approximately 10 to 15% of the original volume was attained. Water (2 L) and brine (2 L) were charged to the mixture which was then extracted with dichloromethane (2 × 2.5 L). There was a small emulsion during each extraction. The organic phases were combined, washed with brine (500 mL), dried with magnesium sulfate, filtered over Celite, and concentrated to afford the title product (247 g, 94% yield, 96% AUC by HPLC) as a yellow solid.

Description 7

(*R*)-3-(*tert*-Butoxycarbonyl)-2,2,4-trimethyloxazolidine-4-carboxylic acid (D7)



To a solution of the (*S*)-2-(*tert*-butoxycarbonylamino)-3-hydroxy-2-methylpropanoic acid (5.0 g, 1.0 equiv) in CH_2Cl_2/MeOH (4:1, 50 mL) was added a solution of TMS-CHN_2.

The residue was dissolved in acetone (30 mL), 2,2-dimethoxypropane (DMP) (12 mL) and $BF_3 \cdot OEt_2$ (2 mL). The solution was stirred at RT for 4hours. The solvent

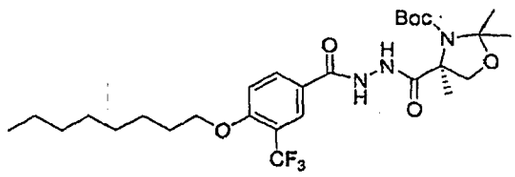
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was removed *in vacuo* and the product was purified by silica gel column chromatography using the Isco system (0-30% Hex:EtOAc) to give the oxazoline methyl ester intermediate.

The purified residue was dissolved in H_2O-THF (1:4) and to the solution was added LiOH (1.16 g). The solution was heated at refluxed for overnight, cooled to room temperature and condensed to remove the THF. The aqueous material was diluted with H_2O (~100 mL), acidified to pH2 with 10%$KHSO_4$ and then extracted with EtOAc. The Eorganic layers were dried over Na_2SO_4, and condensed to afford the title compound in 66% yield (3.29 g).

Description 8

(*S*)-*tert*-Butyl 2,2,4-trimethyl-4-(2-(4-(octyloxy)-3-(trifluoromethyl)benzoyl)-hydrazinecarbonyl)oxazolidine-3-carboxylate (D8)



(*R*)-3-(*tert*-Butoxycarbonyl)-2,2,4-trimethyloxazolidine-4-carboxylic acid (D7) (210 mg, 0.81 mmol), HATU (372 mg, 0.98 mmol), diisopropylethyl amine (DIEA) (0.705 mL, 4.1 mmol), CH_2Cl_2-DMF and 4-(octyloxy)-3-(trifluoromethyl)benzohydrazide (D6) (270 mg, 0.81 mmol) were mixed together. The reaction was condensed, diluted with ethyl acetate, washed with water and brine, and condensed again. Another batch was made using this method with (D7) (0.1 mmol), HATU (46 mg, 0.12 mmol), DIEA (87 μL, 0.5 mmol), CH_2Cl_2-DMF and 4-(octyloxy)-3-(trifluoromethyl)benzohydrazide (D6) (>6 mg, 0.1 mmol). The batches were chromatographed and combined to provide the title product (428mg). MS (ESI): 573.84 (MH^+); ^1H NMR (400 MHz, $CDCl_3$) δ 9.43 (br, 2H), 8.06 (d, 1H, J = 2.0 Hz), 7.94 (dd, 1H, J = 8.8 Hz, J = 2.0 Hz), 6.96 (d, 1H, J = 8.8 Hz), 4.52 (br, 1H), 4.07 (t, 2H, J = 6.4 Hz), 3.76 (br, 1H), 1.82 (m, 2H), 1.67 (s, 6H), 1.57 (s, 3H), 1.51 (s, 9H), 1.51-1.43 (m, 4H), 1.38-1.24 (m, 6H), 0.88 (t, 3H, J = 7.2 Hz).

Description 8 Alternative Method (D8A)

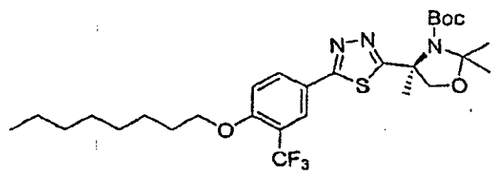
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(*S*)-*tert*-Butyl 2,2,4-trimethyl-4-(2-(4-(octyloxy)-3-(trifluoromethyl)benzoyl)-hydrazinecarbonyl)oxazolidine-3-carboxylate (D8)

A 5 L round bottom flask was inerted and charged with HATU (199 g, 0.52 mol, 1.2 equiv), *N,N*-dimethylformamide (380 mL), and mixed. A solution of (*R*)-3-(*tert*-butoxycarbonyl)-2,2,4-trimethyloxazolidine-4-carboxylic acid (D3A) (133.1 g, 0.43 mol, 1 equiv), dichloromethane (870 mL), and *N,N*-diisopropylethylamine (155 mL, 0.88 mol, 2 equiv) was charged to the flask over 15 minutes. The resulting mixture was stirred at 18 to 23 °C for 1 hour. A solution of benzohydrazide (D6) (145 g, 0.43 mol, 1 equiv) in dichloromethane (1120 mL), and *N,N*-Dimethylformamide (420 mL) was charged over 15 minutes then stirred at 18 to 23 °C for 1 hour. After 1 hour, TLC indicated the reaction was complete. The mixture was concentrated, partitioned between ethyl acetate (2.5 L) and water (2.5 L). The phases were split and the aqueous extracted once more with ethyl acetate (1 L). The organic phases were combined, washed with 10% w/v sodium chloride (2 × 1 L), dried with magnesium sulfate, filtered over Celite, and concentrated under vacuum to afford the crude product (367 g, 146% yield). The crude material was purified using a silica-gel column (2 kg) which was eluted with 5 to 25% ethyl acetate in heptane to give the title product (270 g, 108% yield, 95.9% AUC by HPLC) as a yellow oil.

Description 9

(*R*)-*tert*-Butyl 2,2,4-trimethyl-4-(5-(4-(octyloxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)oxazolidine-3-carboxylate (D9)



A solution of (*S*)-*tert*-butyl 2,2,4-trimethyl-4-(2-(4-(octyloxy)-3-(trifluoromethyl)-benzoyl)hydrazinecarbonyl)oxazolidine-3-carboxylate (D8) (228 mg, 0.39 mmol) in toluene (5 mL) was treated with Lawesson's reagent (321 mg, 0.79 mmol). The reaction was chromatographed on a silica gel column eluted with ethyl acetate-hexane to afford the title compound (~156 mg). MS (ESI): 572.17 (MH^+), ^1H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, 1H, J = 8.8 Hz), 8.08 (d, 1H, J = 6.8 Hz), 7.06 (d, 1H, J = 8.0 Hz), 4.41 (d, 1H, J = 8.0 Hz), 4.18 (d, 1H, J = 9.6 Hz), 4.13-4.07 (m, 3H),

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2.00 (s, 3H), 1.85 (m, 2H), 1.78 (s, 3H), 1.68 (m, 4H), 1.51 (s, 3H), 1.47 (m, 2H), 1.39-1.28 (m, 13H), 0.89 (t, 3H, J = 7.2 Hz).

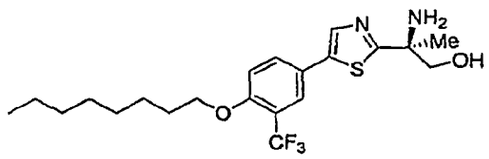
Description 9 Alternative Method (D9A)

(*R*)-*tert*-Butyl 2,2,4-trimethyl-4-(5-(4-(octyloxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)oxazolidine-3-carboxylate (D9)

A 12 L, round bottom flask was inerted and charged with Lawesson's reagent (211.5 g, 0.52 mol, 1.2 equiv), a solution of (*S*)-*tert*-butyl 2,2,4-trimethyl-4-(2-(4-(octyloxy)-3-(trifluoromethyl)benzoyl)-hydrazinecarbonyl)oxazolidine-3-carboxylate (D8A) (250 g – based on theoretical output, 0.43 mol) in toluene (2.5 L), and the resulting slurry was heated to 80 °C and held for 3 hours. TLC indicated the reaction was complete. The mixture was cooled to 18–23 °C, charged with saturated $NaHCO_3$ solution (2 L), which was slightly exothermic. The aqueous was extracted twice with ethyl acetate (2 L, 1.5 L), the organic phases were combined, concentrated, dissolved in dichloromethane (500 mL), charged with silica-gel (500 g), concentrated to remove dichloromethane, and purified using a silica-gel (2.5 kg) column which was eluted with 5% ethyl acetate: 95% heptane to afford the title product (185 g, 74% yield, 95% AUC by HPLC) as a yellow color oil.

Example 1

(*S*)-2-Amino-2-(5-(4-(octyloxy)-3-(trifluoromethyl)phenyl)thiazol-2-yl)propan-1-ol (E1)



(*R*)-*tert*-Butyl 2,2,4-trimethyl-4-(5-(4-(octyloxy)-3-(trifluoromethyl)phenyl)thiazol-2-yl)oxazolidine-3-carboxylate (D4) (90 mg, 1 equiv) and para toluenesulfonic acid (PTSA, 300 mg, 10 equiv) in MeOH (6 mL) was refluxed for 4 hours. The solvent was removed from 2/3 of the reaction mixture and the product was purified by preparative HPLC to give the title product as the trifluoroacetate salt (35mg). MS (ESI, $M+H^+$) = 431.01; ^1H NMR (400 MHz, DMSO-d_6) δ 8.27 (s, 1H), 7.88 (dd, 1H, J = 8.8 Hz, J = 2.4 Hz), 7.85 (d, 1H, J = 2.4 Hz), 7.34 (d, 1H, J = 8.4 Hz), 5.77 (br s, 1H), 4.14 (t, 2H, J = 6.4 Hz), 3.76 (dd, 1H, J = 11.2, Hz, J = 1.2 Hz), 3.66 (dd, 1H,

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J = 11.2 Hz, J = 1.2 Hz), 1.73 (q, 2H, J = 6.8 Hz), 1.58 (s, 3H), 1.36-1.48 (m, 2H), 1.20-1.36 (m, 8H), 0.85 (t, 3H, J = 6.4 Hz).

Example 1 Alternative method (E1A)

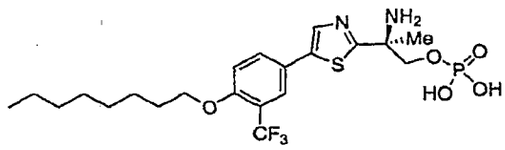
(*S*)-2-Amino-2-(5-(4-(octyloxy)-3-(trifluoromethyl)phenyl)thiazol-2-yl)propan-1-ol (E1)

(*R*)-*tert*-Butyl 2,2,4-trimethyl-4-(5-(4-(octyloxy)-3-(trifluoromethyl)phenyl)thiazol-2-yl)oxazolidine-3-carboxylate (47 g, 82.35 mmol), was reacted with *p*-TSA (2 equiv) in methanol (470 mL) at reflux for 4 h at which point HPLC indicated the reaction was complete. The mixture was cooled to rt, concentrated to a residue, and triturated with IPAc (235 mL). The resulting solid was filtered, washed with IPAc (470 mL) to afford PPI-5325 *p*-TSA salt (45 g) as a white solid. The solid was converted to freebase by treating with 6 N NaOH and DCM as a solvent.

To form a hydrochloriode salt of E1, the freebase (30 g, 69.84 mmol) was taken up in 4 M HCl in dioxane (70 mL) and stirred at rt for 0.25hours. The 1,4-dioxane was concentrated to dryness and the crude was triturated with acetonitrile (200 mL). The resulting mixture was stirred for 1 h and filtered the white solid (23.3 g, 60%, ^{1}H-NMR was consistent with structure).

Example 2

(*S*)-2-amino-2-(5-(4-(octyloxy)-3-(trifluoromethyl)phenyl)thiazol-2-yl)propyl dihydrogen phosphate (E2)

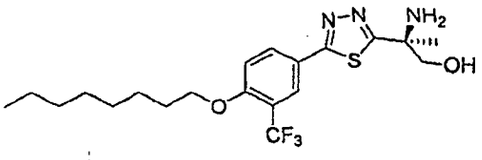


E1 (25mg, 1.0 equiv), DCM (5mL), diethyl chlorophosphate (85μL, 10.0 equiv) and triethylamine (165μL, 20.0 equiv) were stirred overnight. The obtained phospho-diester intermediate was reacted with excess bromotrimethylsilane in DCM for 5 hrs. The resulting phosphate was purified by preparative HPLC as thettriflouroacetate salt (10mg). MS (ESI, M+H$^+$) = 511.1.

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Example 3

(*S*)-2-Amino-2-(5-(4-(octyloxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol (E3)



A solution of (*S*)-*tert*-butyl 2,2,4-trimethyl-4-(2-(4-(octyloxy)-3-(trifluoromethyl)-benzoyl)hydrazinecarbonyl)oxazolidine-3-carboxylate (D9) (156 mg, 0.27 mmol) in methanol (10 mL) was treated with *p*-toluenesulfonic acid monohydrate (259 mg, 1.36 mmol) at 70 ^{0}C for 3 hours. Two thirds of the reaction mixture was then purified by prep HPLC on a C8(2) column ((Luna, 5μ, 100 × 21.10 mm) with acetonitrile-H_2O (0.1% TFA) as mobile phase and gradient 30-98% in 20 min. The title compound was obtained as the bis-TFA salt (24 mg). MS (ESI): 432.00 (MH^+); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.21 (dd, 1H, J = 2.0 Hz, J = 8.8 Hz), 8.15 (d, 1H, J = 2.0 Hz), 8.09 (br s, 2H), 7.45 (d, 1H, J = 8.8 Hz), 5.96 (t, 1H, J = 4.8 Hz), 4.21 (t, 2H, J = 6.4 Hz), 3.81 (dd, 1H, J = 11.2 Hz, J = 5.2 Hz), 3.73 (dd, 1H, J = 11.2 Hz, J = 5.2 Hz), 1.76 (m, 2H), 1.66 (s, 3H), 1.44 (m, 2H), 1.28 (m, 8H), 0.86 (t, 3H, J = 6.8 Hz).

The remaining third of the reaction was condensed and the residue re-dissolved in ethyl acetate and washed with aqueous NaHCO3, brine, dried over brine and condensed again to provide crude product for use in Example 4.

Example 3 Alternative Method (E3A)

(*S*)-2-Amino-2-(5-(4-(octyloxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol (E3)

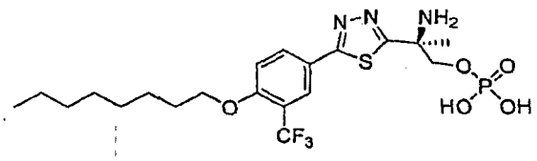
A 5 L round bottom flask was inerted and charged with *p*-toluene sulfonic acid monohydrate (208 g, 1.09 mol, 5 equiv) and a solution of (*R*)-*tert*-Butyl 2,2,4-trimethyl-4-(5-(4-(octyloxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)oxazolidine-3-carboxylate (125 g, 0.22 mol) in methanol (2.5 L), and heated to reflux. After 1.5 h HPLC indicated reaction complete. The heat was turned off and the mixture was allowed to cool to room temperature (18 to 23 °C) and stirred for 12 hours. The mixture was concentrated under vacuum to a residue to provide the title product.

The residue was taken up in dioxane (2 L), charged with 4 M HCl in dioxane (820 mL, 3.28 mol, 15 equiv), heated to 50 °C for 45 minutes, cooled to 18–23 °C, stirred for 2 hours, filtered over a glass fritted filter, displaced once with MTBE (300 mL), slurried once with MTBE (300 mL), and dried on the filter to afford a hydrochloride of E3 (72 g, solvent wet).

Three batches of the hydrochloride of E3 synthesised using this method were combined (totaling 143 g, solvent wet), slurried twice in MTBE (750 mL, 500 mL), the solvent was filtered off each time, the material was transferred to a vacuum oven and dried overnight at room temperature (18 to 23 °C). ^{1}H-NMR indicated the presence of dioxane (0.24% by weight). Further drying at an increased temperature of 30 to 35 °C for 72 hours afforded a hydrochloride (135 g, 98.6% AUC by HPLC) as a white solid.

Example 4

(*S*)-2-Amino-2-(5-(4-(octyloxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propyl dihydrogen phosphate (E4)

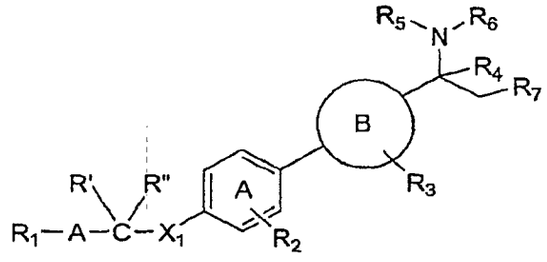


Crude product from E3 (30mg, 0.069mmol) was added to diethylchlorophosphate (100μL, 0.69mmol) and triethylamine (194μL, 1.39mmol,) in DCM and stirred for approx 36hrs. The reaction mixture was then condensed and treated with bromotrimethylsilan (0.3mL) in DCM (5mL) to provide the title compound (~2mg). MS (ESI): 511.98 (MH^+),

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CLAIMS

1. A compound of formula I



I

or a pharmaceutically acceptable salt thereof, wherein:

R_1 is hydrogen, halogen, cyano, alkyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, aralkyl, heteroalykl, -O-alkyl, -O-aryl, -O-heteroaryl, -S-alkyl, alkylene-O-alkyl, alkylene-CO_2H, alkylene-CO_2alkyl, alkylSO_2, alkylenesulfonyl, alkylene-CO-amino, alkylene-CO-alkylamino, alkylene-CO-dialkylamino, alkylene-NH-CO_2H, alkylene-NH-CO_2alkyl -CO_2alkyl, -OH, -C(O)-alkyl, -C(O)O-alkyl, -$CONH_2$, -CO-alkylamino, -CO-dialkylamino, amino, alkylamino, or dialkylamino, any of which may be optionally substituted on carbon with 1, 2, or 3 groups selected from halo, alkyl, haloalkyl, -CF_3, aryl, -CN, -OH, or –O-alkyl;

A is (C_1-C_{20})alkylene, (C_2-C_{20})alkenylene, or (C_2-C_{20})alkynylene, each of which may be optionally suibstited on carbon with 1, 2, o3 groups selected from OH, CO_2H, CO_2alkyl, halogen, amino, alkylamino, dialkylamino, -O-alkyl, alkylene-O-alkyl, alkylene-OH, or alkylene-CO_2H;

X_1 is a bond or is CH_2, O,-CH_2O-, S, -S(O), -$S(O)_2$, -C(O)-, -C(O)O-, or NR_x, wherein R_x is H or (C_1-C_6)alkyl;

R' and R" are each independently hydrogen, halogen, alkyl optionally substituted on carbon with halogen, alkyl, or taken together with the carbon to which they are attached form C=O or a 3, 4, 5,or 6-membered ring, optionally containing 1 or 2 heteroatoms selected from O NH, N-alkyl, SO, or SO_2, any of which may be optionally substituted on carbon with alkyl or halogen

R_2 is cyano, alkyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, aralkyl, heteroalykl, -O-alkyl, -O-aryl, -O-heteroaryl, aralkoxy, heteroaralkoxy, -S-alkyl, alkylene-O-alkyl, alkylene-CO_2H, alkylene-CO_2alkyl, alkylSO_2, alkylenesulfonyl, alkylene-CO-amino, alkylene-CO-alkylamino, alkylene-CO-dialkylamino, alkylene-NH-

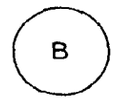
165

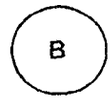
CO_2H, alkylene-NH-CO_2alkyl -CO_2alkyl, -OH, -C(O)-alkyl, -C(O)O-alkyl, -$CONH_2$, -CO-alkylamino, -CO-dialkylamino, amino, alkylamino, and dialkylamino, any of which may be optionally substituted on carbon with 1, 2, or 3 groups selected from halo, alkyl, OH, or –O-alkyl;

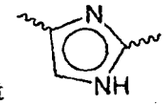
R_3 is absent, hydrogen, halogen, cyano, alkyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, aralkyl, heteroalykl, -O-alkyl, -O-aryl, -O-heteroaryl, aralkoxy, heteroaralkoxy, -S-alkyl, alkylene-O-alkyl, alkylene-CO_2H, alkylene-CO_2alkyl, alkylSO_2, alkylenesulfonyl, alkylene-CO-amino, alkylene-CO-alkylamino, alkylene-CO-dialkylamino, alkylene-NH-CO_2H, alkylene-NH-CO_2alkyl -CO_2alkyl, -OH, -C(O)-alkyl, -C(O)O-alkyl, -$CONH_2$, -CO-alkylamino, -CO-dialkylamino, amino, alkylamino, and dialkylamino, any of which may be optionally substituted on carbon with 1, 2, or 3 groups selected from halo, alkyl, OH, or –O-alkyl;



is phenyl or pyridyl;



is aryl, heteroaryl, heterocyclo, or cycloalkyl, any of which may be optionally substituted on carbon with 1, 2, or 3 groups selected form halogen, alkyl, O-alkyl, CO_2H, CO_2alkyl, halogen, amino, alkylamino, dialkylamino, -O-alkyl, alkylene-O-alkyl, alkylene-OH, or alkylene-CO_2H, provided that 

is not 

;

R_4 is hydrogen, cyano, alkyl, aryl, heteroaryl, alkylene-O-alkyl, alkylene-OH, aryl, alkylene-O-alkyl, -CO_2H, -CO_2-alkyl, alkylene-CO_2H, or alkylene-CO_2-alkyl, alkylene-OC(O)R wherein R is hydrogen or alkyl; cycloalkyl, heterocycloalkyl, alkylene-NH_2, alkylene-alkylamino, or alkylene-dialkylamino, any of which may be optionally substituted on carbon with 1, 2, or 3 groups selected from OH, CO_2H, CO_2alkyl, halogen, amino, alkylamino, dialkylamino, -O-alkyl, alkylene-O-alkyl, alkylene-OH, or alkylene-CO_2H;

R_5 and R_6 are each independently selected from the group consisting of hydrogen, alkyl, alkylene-OH, aryl, alkylene-O-alkyl, -CO_2H, CO_2-alkyl, alkylene-OC(O)alkyl, cycloalkyl, heterocyclo, -C(O)-alkyl, -C(O)-aryl, C(O)-aralkyl, -C(O)-Oalkyl, -C(O)-Oaryl, -C(O)-Oaralkyl, alkylene-amino, alkylene-alkylamino, and

alkylene-dialkylamino, any of which may be optionally substituted on carbon with halogen, alkyl, hydroxyl, CO_2H, CO_2alkyl or alkoxy; or

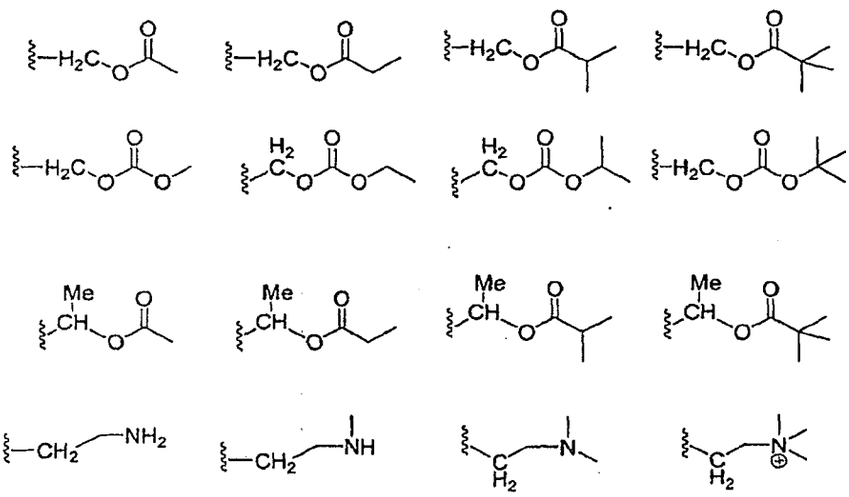
R_5 and R_6, together with the nitrogen to which they are attached, may form a 3, 4, 5, or 6-membered saturated or unsaturated ring, optionally containing 1 or 2 additional heteroatoms selected from O, S, NH, or N-alkyl, and optionally substituted on carbon with halogen, alkyl, hydroxyl, or alkoxy;

R_7 is selected from the group consisting of -OH, -O-alkyl, alkylene-OH, $-CO_2H$, alkylene-CO_2H, -C(O)O-alkyl, -alkylene-CO_2-alkyl, -C(O)O-aryl, $-CH_2$=$CHCO_2H$, -CH_2=CHC(O)O-alkyl, $-CH_2$=CHC(O)O-aryl, $-OPO_2R_{p1}R_{p2}$, $-OPO_3R_{p1}R_{p2}$, -$CH_2PO_3R_{p1}R_{p2}$, $-OPO_2(S)R_{p1}R_{p2}$, and $-C(Z')(Z'')PO_3R_{p1}R_{p2}$, any of which may be optionally substituted on carbon with halogen, alkyl, hydroxyl, carboxy, or alkoxy; and wherein

Z' is hydroxyl or halogen;

Z" is H or halogen;

R_{p1} and R_{p2} are each independently hydrogen, C_1-C_6-alkyl, aryl, or one of the following groups:



; and

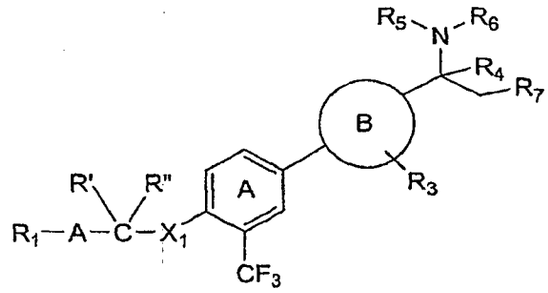
Y is heterocyclo or heteroaryl.

2. A compound of claim 1, wherein R2 is alkyl substituted with 1, 2 or 3 halo groups.

3. A compound of claim 1, wherein R2 is trifluoromethyl.

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4. A compound of formula II



II

or a pharmaceutically acceptable salt thereof, wherein:

R_1 is hydrogen, halogen, cyano, alkyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, aralkyl, heteroalykl, -O-alkyl, -O-aryl, -O-heteroaryl, -S-alkyl, alkylene-O-alkyl, alkylene-CO_2H, alkylene-CO_2alkyl, alkylSO_2, alkylenesulfonyl, alkylene-CO-amino, alkylene-CO-alkylamino, alkylene-CO-dialkylamino, alkylene-NH-CO_2H, alkylene-NH-CO_2alkyl -CO_2alkyl, -OH, -C(O)-alkyl, -C(O)O-alkyl, -$CONH_2$, -CO-alkylamino, -CO-dialkylamino, amino, alkylamino, or dialkylamino, any of which may be optionally substituted on carbon with 1, 2, or 3 groups selected from halo, alkyl, haloalkyl, -CF_3, -CN, -OH, or –O-alkyl;

A is (C_1-C_{20})alkylene, (C_2-C_{20})alkenylene, or (C_2-C_{20})alkynylene, each of which may be optionally suibstited on carbon with 1, 2, or 3 groups selected from OH, CO_2H, CO_2alkyl, halogen, amino, alkylamino, dialkylamino, -O-alkyl, alkylene-O-alkyl, alkylene-OH, or alkylene-CO_2H;

X_1 is a bond or is CH_2, O, -CH_2O-, S, -S(O), -$S(O)_2$, -C(O)-, -C(O)O-, or NR_x, wherein R_x is H or (C_1-C_6)alkyl;

R' and R" are each independently hydrogen, halogen, alkyl optionally substituted on carbon with halogen, alkyl, or taken together with the carbon to which they are attached form C=O or a 3, 4, 5,or 6-membered ring, optionally containing 1 or 2 heteroatoms selected from O NH, N-alkyl, SO, or SO_2, any of which may be optionally substituted on carbon with alkyl or halogen

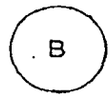
R_3 is absent, hydrogen, halogen, cyano, alkyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, aralkyl, heteroalykl, -O-alkyl, -O-aryl, -O-heteroaryl, aralkoxy, heteroaralkoxy, -S-alkyl, alkylene-O-alkyl, alkylene-CO_2H, alkylene-CO_2alkyl, alkylSO_2, alkylenesulfonyl, alkylene-CO-amino, alkylene-CO-alkylamino, alkylene-CO-dialkylamino, alkylene-NH-CO_2H, alkylene-NH-CO_2alkyl -CO_2alkyl, -OH, -C(O)-alkyl, -C(O)O-alkyl, -$CONH_2$, -CO-alkylamino,

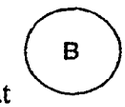
168

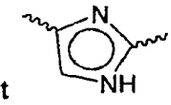
-CO-dialkylamino, amino, alkylamino, and dialkylamino, any of which may be optionally substituted on carbon with 1, 2, or 3 groups selected from halo, alkyl, OH, or –O-alkyl;



is phenyl or pyridyl;



is aryl, heteroaryl, heterocyclo, or cycloalkyl, any of which may be optionally substituted on carbon with 1, 2, or 3 groups selected form halogen, alkyl, O-alkyl, CO_2H, CO_2alkyl, halogen, amino, alkylamino, dialkylamino, -O-alkyl, alkylene-O-alkyl, alkylene-OH, or alkylene-CO_2H, provided that 

is not 

;

R_4 is hydrogen, cyano, alkyl, aryl, heteroaryl, alkylene-O-alkyl, alkylene-OH, aryl, alkylene-O-alkyl, -CO_2H, -CO_2-alkyl, alkylene-CO_2H, or alkylene-CO_2-alkyl, alkylene-OC(O)R wherein R is hydrogen or alkyl; cycloalkyl, heterocycloalkyl, alkylene-NH_2, alkylene-alkylamino, or alkylene-dialkylamino, any of which may be optionally substituted on carbon with 1, 2, or 3 groups selected from OH, CO_2H, CO_2alkyl, halogen, amino, alkylamino, dialkylamino, -O-alkyl, alkylene-O-alkyl, alkylene-OH, or alkylene-CO_2H;

R_5 and R_6 are each independently selected from the group consisting of hydrogen, alkyl, alkylene-OH, aryl, alkylene-O-alkyl, -CO_2H, CO_2-alkyl, alkylene-OC(O)alkyl, cycloalkyl, heterocyclo, -C(O)-alkyl, -C(O)-aryl, C(O)-aralkyl, -C(O)-Oalkyl, -C(O)-Oaryl, -C(O)-Oaralkyl, alkylene-amino, alkylene-alkylamino, and alkylene-dialkylamino, any of which may be optionally substituted on carbon with halogen, alkyl, hydroxyl, CO_2H, CO_2alkyl or alkoxy; or

R_5 and R_6, together with the nitrogen to which they are attached, may form a 3, 4, 5, or 6-membered saturated or unsaturated ring, optionally containing 1 or 2 additional heteroatoms selected from O, S, NH, or N-alkyl, and optionally substituted on carbon with halogen, alkyl, hydroxyl, or alkoxy;

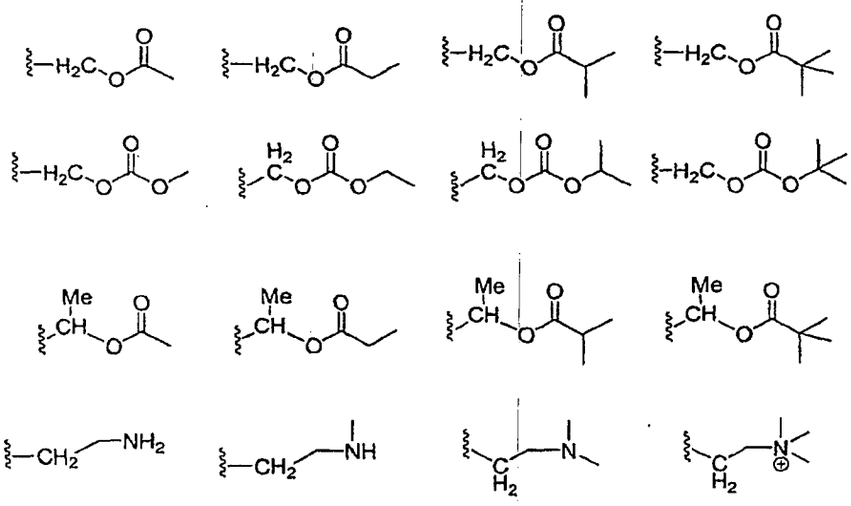
R_7 is selected from the group consisting of -OH, -O-alkyl, -alkylene-OH, -CO_2H, -alkylene-CO_2H, -C(O)O-alkyl, -alkylene-CO_2-alkyl, -C(O)O-aryl, -CH_2=$CHCO_2H$, -CH_2=CHC(O)O-alkyl, -CH_2=CHC(O)O-aryl, -$OPO_2R_{p1}R_{p2}$, -$OPO_3R_{p1}R_{p2}$, -$CH_2PO_3R_{p1}R_{p2}$, -$OPO_2(S)R_{p1}R_{p2}$, and -$C(Z')(Z'')PO_3R_{p1}R_{p2}$, any of which may be

optionally substituted on carbon with halogen, alkyl, hydroxyl, carboxy, or alkoxy; and wherein

Z' is hydroxyl or halogen;

Z" is H or halogen;

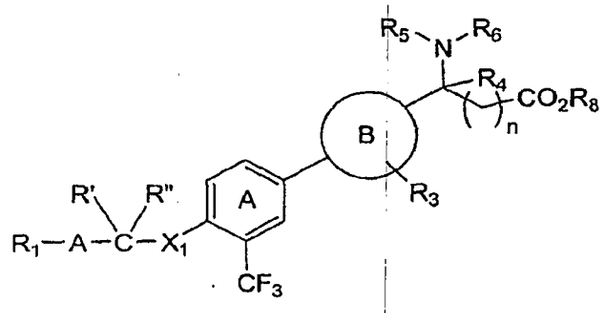
R_{p1} and R_{p2} are each independently hydrogen, C_1-C_6-alkyl, aryl, or one of the following groups:



; and

Y is heterocyclo or heteroaryl.

5. A compound of formula III



III

or a pharmaceutically acceptable salt thereof, wherein:

R_1 is hydrogen, halogen, cyano, alkyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, aralkyl, heteroalykl, -O-alkyl, -O-aryl, -O-heteroaryl, -S-alkyl, alkylene-O-alkyl, alkylene-CO_2H, alkylene-CO_2alkyl, alkylSO_2, alkylenesulfonyl, alkylene-CO-amino, alkylene-CO-alkylamino, alkylene-CO-dialkylamino, alkylene-NH-CO_2H, alkylene-NH-CO_2alkyl -CO_2alkyl, -OH, -C(O)-alkyl, -C(O)O-alkyl, -$CONH_2$, -CO-alkylamino, -CO-dialkylamino, amino, alkylamino, or dialkylamino, any of which

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may be optionally substituted on carbon with 1, 2, or 3 groups selected from halo, alkyl, haloalkyl, -CF_3, -CN, -OH, or –O-alkyl;

A is (C_1-C_{20})alkylene, (C_2-C_{20})alkenylene, or (C_2-C_{20})alkynylene, each of which may be optionally suibstited on carbon with 1, 2, or 3 groups selected from OH, CO_2H, CO_2alkyl, halogen, amino, alkylamino, dialkylamino, -O-alkyl, alkylene-O-alkyl, alkylene-OH, or alkylene-CO_2H;

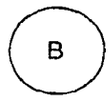
X_1 is a bond or is CH_2, O, -CH_2O-, S, -S(O), -$S(O)_2$, -C(O)-, -C(O)O-, or NR_x, wherein R_x is H or (C_1-C_6)alkyl;

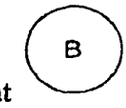
R' and R" are each independently hydrogen, halogen, alkyl optionally substituted on carbon with halogen, alkyl, or taken together with the carbon to which they are attached form C=O or a 3, 4, 5,or 6-membered ring, optionally containing 1 or 2 heteroatoms selected from O NH, N-alkyl, SO, or SO_2, any of which may be optionally substituted on carbon with alkyl or halogen

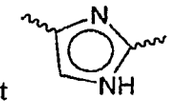
R_3 is absent, hydrogen, halogen, cyano, alkyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, aralkyl, heteroalykl, -O-alkyl, -O-aryl, -O-heteroaryl, aralkoxy, heteroaralkoxy, -S-alkyl, alkylene-O-alkyl, alkylene-CO_2H, alkylene-CO_2alkyl, alkylSO_2, alkylenesulfonyl, alkylene-CO-amino, alkylene-CO-alkylamino, alkylene-CO-dialkylamino, alkylene-NH-CO_2H, alkylene-NH-CO_2alkyl -CO_2alkyl, -OH, -C(O)-alkyl, -C(O)O-alkyl, -$CONH_2$, -CO-alkylamino, -CO-dialkylamino, amino, alkylamino, and dialkylamino, any of which may be optionally substituted on carbon with 1, 2, or 3 groups selected from halo, alkyl, OH, or –O-alkyl;



is phenyl or pyridyl;



is aryl, heteroaryl, heterocyclo, or cycloalkyl, any of which may be optionally substituted on carbon with 1, 2, or 3 groups selected form halogen, alkyl, O-alkyl, CO_2H, CO_2alkyl, halogen, amino, alkylamino, dialkylamino, -O-alkyl, alkylene-O-alkyl, alkylene-OH, or alkylene-CO_2H, provided that 

is not 

;

R_4 is hydrogen, cyano, alkyl, aryl, heteroaryl, alkylene-O-alkyl, alkylene-OH, aryl, alkylene-O-alkyl, -CO_2H, -CO_2-alkyl, alkylene-CO_2H, or alkylene-CO_2-alkyl, alkylene-OC(O)R wherein R is hydrogen or alkyl; cycloalkyl, heterocycloalkyl,

alkylene-NH_2, alkylene-alkylamino, or alkylene-dialkylamino, any of which may be optionally substituted on carbon with 1, 2, or 3 groups selected from OH, CO_2H, CO_2alkyl, halogen, amino, alkylamino, dialkylamino, -O-alkyl, alkylene-O-alkyl, alkylene-OH, or alkylene-CO_2H;

R_5 and R_6 are each independently selected from the group consisting of hydrogen, alkyl, alkylene-OH, aryl, alkylene-O-alkyl, -CO_2H, CO_2-alkyl, alkylene-OC(O)alkyl, cycloalkyl, heterocyclo, -C(O)-alkyl, -C(O)-aryl, C(O)-aralkyl, -C(O)-Oalkyl, -C(O)-Oaryl, -C(O)-Oaralkyl, alkylene-amino, alkylene-alkylamino, and alkylene-dialkylamino, any of which may be optionally substituted on carbon with halogen, alkyl, hydroxyl, CO_2H, CO_2alkyl or alkoxy; or

R_5 and R_6, together with the nitrogen to which they are attached, may form a 3, 4, 5, or 6-membered saturated or unsaturated ring, optionally containing 1 or 2 additional heteroatoms selected from O, S, NH, or N-alkyl, and optionally substituted on carbon with halogen, alkyl, hydroxyl, or alkoxy;

R_8 is hydrogen, alkyl or aryl; and

n is 0, 1, or 2.

6. A compound selected from the group consisting of:

(*S*)-2-Amino-2-(5-(4-(octyloxy)-3-(trifluoromethyl)phenyl)thiazol-2-yl)propan-1-ol;

2-Amino-2-(5-(4-(octyloxy)-3-(trifluoromethyl)phenyl)thiazol-2-yl)propane-1,3-diol;

(*S*)-2-Amino-2-(5-(4-(octyloxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol;

(*S*)-2-Amino-2-(5-(4-(5-phenylpentyloxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol;

(*S*)-2-Amino-2-(5-(4-(4-phenylbutoxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol;

(*S*)-2-Amino-2-(5-(4-(nonyloxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazole-2-yl)propan-1-ol;

(*S*)-2-Amino-2-(5-(4-(decyloxy)-3(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol;

(*S*)-2-Amino-2-(5-(3-(trifluoromethyl)-4-(5-(4-(trifluoromethyl)phenyl)pentyloxy)phenyl)-1,3,4-thiadiazole-2-yl)propan-1-ol;

(*S*)-2-Amino-2-(5-(3-(trifluoromethyl)-4-(5-(3-(trifluoromethyl)phenyl)pentyloxy)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol;
(*S*)-2-Amino-2-(5-(4-(6-phenylhexyloxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol;
(*S*)-2-Amino-2-(5-(4-(5-(4-fluorophenyl)pentyloxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol;
(*S*)-2-Amino-2-(5-(4-(5-(3-fluorophenyl)pentyloxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol;
(*S*)-2-Amino-2-(5-(4-((4-phenyl-5-(trifluoromethyl)thiophen-2-yl)methoxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol;
(*S*)-2-Amino-2-(5-(4-(7-phenylheptyloxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol;
(*S*)-2-Amino-2-(5-(3-(trifluoromethyl)-4-(2-(trifluoromethyl)phenethoxy)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol;
(*S*)-2-Amino-2-(5-(3-(trifluoromethyl)-4-(3-(trifluoromethyl)phenethoxy)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol;
(*S*)-2-Amino-2-(5-(3-(trifluoromethyl)-4-(4-(trifluoromethyl)phenethoxy)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol;
(*S*)-2-Amino-2-(5-(4-(benzyloxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol;
(*S*)-2-Amino-2-(5-(4-phenethoxy-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol;
(*S*)-2-Amino-2-(5-(4-(3-phenylpropoxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol;
(*S*)-2-Amino-2-(5-(4-(benzofuran-2-ylmethoxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol;
(*S*)-2-Amino-2-(5-(4-(benzo[*b*]thiophen-2-ylmethoxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol;
(*S*)-2-Amino-2-(5-(4-(benzo[*d*][1,3]dioxol-5-ylmethoxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol;
(*S*)-2-Amino-2-(5-(3-(trifluoromethyl)-4-(4-(3-(trifluoromethyl)phenyl)butoxy)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol;

(*S*)-2-Amino-2-(5-(3-(trifluoromethyl)-4-(4-(4-(trifluoromethyl)phenyl)butoxy)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol;

(2*S*)-2-Amino-2-(5-(4-(3,7-dimethyloctyloxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol;

(*S*)-2-Amino-2-(5-(4-(4-propylphenethoxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol;

(*S*)-2-Amino-2-(5-(4-(4-butylphenethoxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol;

(*S*)-2-Amino-2-(5-(4-(4-ethylphenethoxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol;

(*S*)-2-Amino-2-(5-(4-(7,7,8,8,8-pentafluorooctyloxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol;

(*S*)-2-Amino-2-(5-(4-(4-(2-fluorophenyl)butoxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol;

(*S*)-2-Amino-2-(5-(4-(4-(3-fluorophenyl)butoxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol;

(*S*)-2-Amino-2-(5-(4-(4-(4-fluorophenyl)butoxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol;

(*S*)-2-Amino-2-(5-(4-(6-(2-fluorophenyl)hexyloxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol;

(*S*)-2-Amino-2-(5-(4-(6-(3-fluorophenyl)hexyloxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol;

(*S*)-2-Amino-2-(5-(4-(6-(4-fluorophenyl)hexyloxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol;

(*S*)-2-Amino-2-(5-(4-(5-(3,4-difluorophenyl)pentyloxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol;

(*S*)-2-Amino-2-(5-(3-(trifluoromethyl)-4-(5-(2,4,5-trifluorophenyl)pentyloxy)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol;

(*S*)-2-Amino-2-(5-(3-(trifluoromethyl)-4-(6-(3-(trifluoromethyl)phenyl)hexyloxy)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol;

(*S*)-2-Amino-2-(5-(3-(trifluoromethyl)-4-(6-(4-(trifluoromethyl)phenyl)hexyloxy)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol;

(*S*)-2-Amino-2-(5-(4-(octylthio)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol;
(*S*)-2-Amino-2-(5-(4-(octylsulfonyl)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol;
(*S*)-2-Amino-2-(3-(4-(octyloxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)propan-1-ol;
(*R*)-2-Amino-2-(5-(4-(octyloxy)-3-(trifluoromethyl)phenyl)-1*H*-pyrazol-3-yl)propan-1-ol;
(*S*)-2-Amino-2-(3-(4-(octyloxy)-3-(trifluoromethyl)phenyl)isoxazol-5-yl)propan-1-ol;
(*S*)-2-Amino-2-(5-(4-(octyloxy)-3-(trifluoromethyl)phenyl)-1,3,4-oxadiazol-2-yl)propan-1-ol;
(*S*)-2-Amino-2-(5-(4-(6-phenylhexyloxy)-3-(trifluoromethyl)phenyl)thiazol-2-yl)propan-1-ol;
(*S*)-2-Amino-2-(5-(3-(trifluoromethyl)-4-(5-(4-(trifluoromethyl)phenyl)pentyloxy)phenyl) thiazol-2-yl)propan-1-ol;
and pharmaceutically acceptable salts, phosphate derivatives, phosphate mimics, and phosphate precursor analogs thereof.

7. A compound which is (*S*)-2-Amino-2-(5-(4-(octyloxy)-3-(trifluoromethyl)phenyl)thiazol-2-yl)propan-1-ol or a pharmaceutically acceptable salt, phosphate derivative, phosphate mimic, or phosphate precursor analog thereof.

8. A compound which is (*S*)-2-Amino-2-(5-(4-(octyloxy)-3-(trifluoromethyl)phenyl)thiazol-2-yl)propyl dihydrogen phosphate or a pharmaceutically acceptable salt thereof.

9. A compound which is (*S*)-2-Amino-2-(5-(4-(octyloxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propan-1-ol or a pharmaceutically acceptable salt, phosphate derivative, phosphate mimic, or a phosphate precursor analog thereof.

10. A compound which is (*S*)-2-Amino-2-(5-(4-(octyloxy)-3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)propyl dihydrogen phosphate or a pharmaceutically acceptable salt thereof.

11. A compound as defined in any one of claims 1 to 10 or a pharmaceutically acceptable salt, phosphate derivative, phosphate mimic, or phosphate precursor analog thereof for use as a therapeutic substance.

12. A compound as defined in any one of claims 1 to 10 or a pharmaceutically acceptable salt, phosphate derivative, phosphate mimic, or phosphate precursor analog thereof for use in the treatment of a sphingosine associated disorder.

13. A compound as defined in any one of claims 1 to 10 or a pharmaceutically acceptable salt, phosphate derivative, phosphate mimic, or phosphate precursor analog thereof for use in the treatment of multiple sclerosis.

14. A compound as defined in any one of claims 1 to 10 or a pharmaceutically acceptable salt, phosphate derivative, phosphate mimic, or phosphate precursor analog thereof for use in the manufacture of a medicament for use in the treatment of a sphingosine associated disorder.

15. A compound as defined in any one of claims 1 to 10 or a pharmaceutically acceptable salt, phosphate derivative, phosphate mimic, or phosphate precursor analog thereof for use in the manufacture of a medicament for the treatment of multiple sclerosis.

16. A method of treating a sphingosine 1-phosphate associated disorder comprising admisitering to a subject a therapeutically effective amount of a compound as defined in any one of claims 1 to 10 or a pharmaceutically acceptable salt, phosphate derivative, phosphate mimic, or phosphate precursor analog thereof, such that the sphingosine 1-phosphate associated disorder is treated.

17. A pharmaceutical composition comprising a compound as defined in any one of claims 1 to 10 or a pharmaceutically acceptable salt, phosphate derivative, phosphate mimic, or phosphate precursor analog thereof.

18. A process for the preparation of a pharmaceutical composition according to claim 17.

19. A process for the preparation of a compound as defined in any one of claims 1 to 10 or a pharmaceutically acceptable salt, phosphate derivative, phosphate mimic, or phosphate precursor analog thereof.

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COMPUESTOS QUIMICOS

SOLICITUDES RELACIONADAS

Esta solicitud está relacionada con, y reclama prioridad para, la solicitud provisional de E.U.A. serie No. 60/821,101, presentada el 1 de agosto de 2006, solicitud provisional de E.U.A. serie No. 60/827,919, presentada el 3 de octubre de 2006, solicitud provisional de E.U.A. serie No. 60/896,431, presentada el 22 de marzo de 2007 y solicitud provisional de E.U.A. serie No. 60/959,291, presentada el 12 de julio de 2007, el contenido de cada una de las cuales se incorpora aquí por referencia en su totalidad.

ANTECEDENTES DE LA INVENCION

Los receptores de 1-fosfato de esfingosina (S1P) 1-5 constituyen una familia de receptores acoplados a proteína G de siete-transmembrana. Estos receptores, referidos como S1P-1 a S1P-5, son activados mediante unión por 1-fosfato de esfingosina, que es producida por la fosforilación de esfingosina catalizada por esfingosina cinasa. Los receptores de S1P son receptores de superficie celular implicados en una variedad de procesos celulares, incluyendo proliferación y diferenciación celular, supervivencia celular, invasión celular, tráfico de linfocitos y migración celular. El 1-fosfato de esfingosina se encuentra en el plasma y una variedad de otros tejidos, y

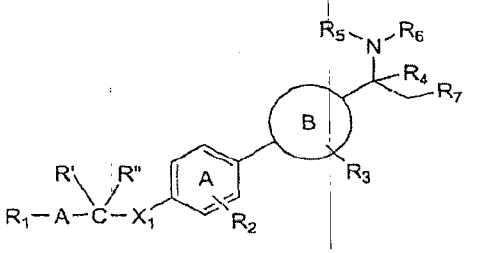
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ejerce efectos autocrinos y paracrinos, incluyendo regulación de la secreción de factores de crecimiento.

La administración de S1P a un animal da por resultado el secuestro de linfocitos en los nodos linfáticos y parches de Peyers sin causar agotamiento de linfocitos. Esta actividad, que es de utilidad potencial en el tratamiento de enfermedades o condiciones asociadas con respuesta inmune inapropiada, incluyendo rechazo de trasplante, enfermedades autoinmunes, así como otros trastornos modulados por tráfico de linfocitos, se cree que procede por activación del receptor S1P-1. Se ha mostrado que la administración de S1P *in vivo* causa hipotensión y bradicardia, que se cree que se deben a señalización a través de uno o más de los otros receptores de S1P, es decir, S1P-2 a S1P-5. Por consiguiente, existe la necesidad de compuestos que son agonistas potentes y selectivos del receptor S1P-1.

BREVE DESCRIPCION DE LA INVENCION

Estas y otras necesidades son satisfechas por la presente invención. En algunos aspectos, la presente invención está dirigida a un compuesto de la fórmula I:



I

o una sal farmacéuticamente aceptable del mismo, en donde:

R_1 es hidrógeno, halógeno, ciano, alquilo, arilo, heteroarilo, cicloalquilo, heterocicloalquilo, aralquilo, heteroalquilo, -O-alquilo, -O-arilo, -O-heteroarilo, -S-alquilo, alquileno-O-alquilo, alquileno-CO_2H, alquileno-CO_2alquilo, alquiloSO_2, alquilensulfonilo, alquileno-CO-amino, alquileno-CO-alquilamino, alquileno-CO-dialquilamino, alquileno-NH- CO_2H, alquileno-NH-CO_2alquilo-CO_2alquilo, -OH, -C(O)-alquilo, -C(O)O-alquilo, -$CONH_2$, -CO-alquilamino, -CO-dialquilamino, amino, alquilamino o dialquilamino, cualquiera de los cuales puede ser opcionalmente sustituido en carbono con 1, 2 ó 3 grupos seleccionados de halógeno, alquilo, halogenoalquilo, -CF_3, arilo, -CN, -OH, o -O-alquilo;

A es alquileno(C_1-C_{20}), alquenileno(C_2-C_{20}), o alquinileno(C_2-C_{20}), cada uno de los cuales puede ser opcionalmente sustituido en carbono con 1, 2 ó 3 grupos seleccionados de OH, CO_2H, CO_2alquilo, halógeno, amino, alquilamino, dialquilamino, -O-alquilo, alquileno-O-alquilo, alquileno-OH, o alquileno-CO_2H;

X_1 es un enlace o es CH_2, O, -CH_2O-, S, -S(O), -$S(O)_2$, -C(O)-, -C(O)O-, o NR_x, en donde R_x es H o alquilo (C_1-C_6);

R' y R" son cada uno independientemente hidrógeno, halógeno, alquilo opcionalmente sustituido en carbono con halógeno, alquilo, o tomados junto al carbono al cual están unidos forman C=O o un anillo de 3, 4, 5 ó 6 miembros, que contiene opcionalmente 1 ó 2 heteroátomos seleccionados de O NH, N-alquilo, SO o SO_2, cualquiera de los cuales puede ser opcionalmente

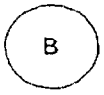
sustituido en carbono con alquilo o halógeno;

R_2 es ciano, alquilo, arilo, heteroarilo, cicloalquilo, heterocicloalquilo, aralquilo, heteroalquilo, -O-alquilo, -O-arilo, -O-heteroarilo, aralcoxi, heteroaralcoxi, -S-alquilo, alquileno-O-alquilo, alquileno-CO_2H, alquileno-CO_2alquilo, alquiloSO_2, alquilensulfonilo, alquileno-CO-amino, alquileno-CO-alquilamino, alquileno-CO-dialquilamino, alquileno-NH-CO_2H, alquileno-NH-CO_2alquilo -CO_2alquilo, -OH, -C(O)-alquilo, -C(O)O-alquilo, -$CONH_2$, -CO-alquilamino, -CO-dialquilamino, amino, alquilamino y dialquilamino, cualquiera de los cuales puede ser opcionalmente sustituido en carbono con 1, 2 ó 3 grupos seleccionados de halógeno, alquilo, OH, o -O-alquilo;

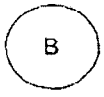
R_3 está ausente, es hidrógeno, halógeno, ciano, alquilo, arilo, heteroarilo, cicloalquilo, heterocicloalquilo, aralquilo, heteroalquilo, -O-alquilo, -O-arilo, -O-heteroarilo, aralcoxi, heteroaralcoxi, -S-alquilo, alquileno-O-alquilo, alquileno-CO_2H, alquileno-CO_2alquilo, alquiloSO_2, alquiloensulfonilo, alquileno-CO-amino, alquileno-CO-alquilamino, alquileno-CO-dialquilamino, alquileno-NH-CO_2H, alquileno-NH-CO_2alquilo -CO_2alquilo, -OH, -C(O)-alquilo, -C(O)O-alquilo, -$CONH_2$, -CO-alquilamino, -CO-dialquilamino, amino, alquilamino y dialquilamino, cualquiera de los cuales puede ser opcionalmente sustituido en carbono con 1, 2 ó 3 grupos seleccionados de halógeno, alquilo, OH, o -O-alquilo;

A

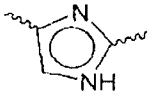
es fenilo o piridilo;



es arilo, heteroarilo, heterociclo o cicloalquilo, cualquiera de los cuales puede ser opcionalmente sustituido en carbono con 1, 2 ó 3 grupos seleccionados de halógeno, alquilo, O-alquilo, CO_2H, CO_2alquilo, halógeno, amino, alquilamino, dialquilamino, -O-alquilo, alquileno-O-alquilo, alquileno-OH, o alquileno-CO_2H, siempre que



no sea



;

R_4 es hidrógeno, ciano, alquilo, arilo, heteroarilo, alquileno-O-alquilo, alquileno-OH, arilo, alquileno-O-alquilo, -CO_2H, -CO_2-alquilo, alquileno-CO_2H, o alquileno-CO_2-alquilo, alquileno-OC(O)R en donde R es hidrógeno o alquilo; cicloalquilo, heterocicloalquilo, alquileno-NH_2, alquileno-alquilamino, o alquileno-dialquilamino, cualquiera de los cuales puede ser opcionalmente sustituido en carbono con 1, 2 ó 3 grupos seleccionados de OH, CO_2H, CO_2alquilo, halógeno, amino, alquilamino, dialquilamino, -O-alquilo, alquileno-O-alquilo, alquileno-OH, o alquileno-CO_2H;

R_5 y R_6 se seleccionan cada uno independientemente del grupo que consiste de hidrógeno, alquilo, alquileno-OH, arilo, alquileno-O-alquilo,

-CO_2H, CO_2-alquilo, alquileno- OC(O)alquilo, cicloalquilo, heterociclo, -C(O)-alquilo, -C(O)-arilo, C(O)-aralquilo, -C(O)-Oalquilo, -C(O)-Oarilo, -C(O)-Oaralquilo, alquileno-amino, alquileno-alquilamino, y alquileno-dialquilamino, cualquiera de los cuales puede ser opcionalmente sustituido en carbono con halógeno, alquilo, hidroxilo, CO_2H, CO_2alquilo o alcoxi; o

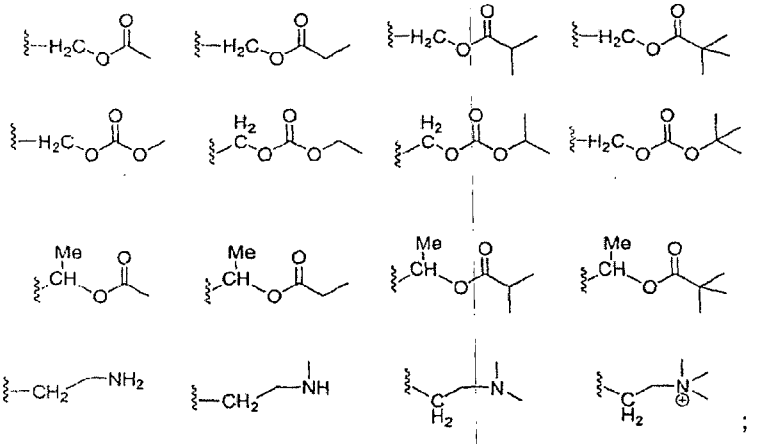
R_5 y R_6, junto con el nitrógeno al cual están unidos, pueden formar un anillo saturado o insaturado de 3, 4, 5 ó 6 miembros, que contiene opcionalmente 1 ó 2 heteroátomos adicionales seleccionados de O, S, NH_5 o N-alquilo, y opcionalmente sustituido en carbono con halógeno, alquilo, hidroxilo, o alcoxi;

R_7 se selecciona del grupo que consiste de -OH, -O-alquilo, alquileno-OH, -CO_2H, alquileno-CO_2H, -C(O)O-alquilo, -alquileno-CO_2-alquilo, -C(O)O-arilo, -CH_2=$CHCO_2H$, - CH_2=CHC(O)O-alquilo, -CH_2=CHC(O)O-arilo, -OPO_2R_p,R_{p2}, -$OPO_3R_{p1}R_{p2}$, -$CH_2PO_3R_{p1}R_{p2}$, -$OPO_2(S)R_{p1}R_{p2}$ y -$C(Z')(Z'')PO_3R_{p1}R_{p2}$, cualquiera de los cuales puede ser opcionalmente sustituido en carbono con halógeno, alquilo, hidroxilo, carboxi o alcoxi; y en donde

Z' es hidroxilo o halógeno;

Z'' es H o halógeno;

R_{p1} y R_{p2} son cada uno independientemente hidrógeno, alquilo de C_1-C_6, arilo, o uno de los siguientes grupos:

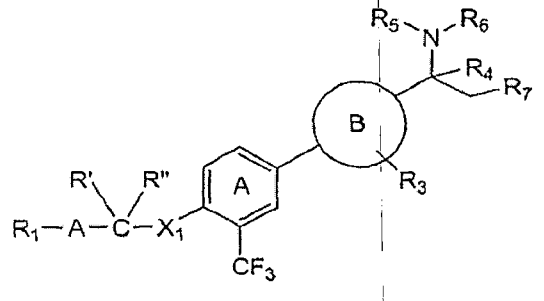


; y

Y es heterociclo o heteroarilo.

En algunas modalidades, R_2 es alquilo sustituido con 1, 2 ó 3 grupos halógeno. En algunas modalidades, R_2 es trifluorometilo.

En otros aspectos, la presente invención está dirigida a un compuesto de la fórmula II:



II

o una sal farmacéuticamente aceptable del mismo, en donde:

R_1 es hidrógeno, halógeno, ciano, alquilo, arilo, heteroarilo, cicloalquilo, heterocicloalquilo, aralquilo, heteroalquilo, -O-alquilo, -O-arilo, -O-heteroarilo, -S-alquilo, alquileno-O-alquilo, alquileno-CO_2H, alquileno-CO_2alquilo, alquiloSO_2, alquilensulfonilo, alquileno-CO-amino, alquileno-CO-alquilamino, alquileno-CO-dialquilamino, alquileno-NH-CO_2H, alquileno-NH-

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CO_2alquilo -CO_2alquilo, -OH, -C(O)-alquilo, -C(O)O-alquilo, -$CONH_2$, - CO-alquilamino, -CO-dialquilamino, amino, alquilamino, o dialquilamino, cualquiera de los cuales puede ser opcionalmente sustituido en carbono con 1, 2 ó 3 grupos seleccionados de halógeno, alquilo, halogenoalquilo, -CF_3, -CN, -OH, o -O-alquilo;

A es alquileno (C_1-C_{20}), alquenileno (C_2-C_{20}), o alquinileno(C_2-C_{20}), cada uno de los cuales puede ser substituido en carbono con 1, 2 ó 3 grupos seleccionados de OH, CO_2H, CO_2alquilo, halógeno, amino, alquilamino, dialquilamino, -O-alquilo, alquileno-O-alquilo, alquileno-OH, o alquileno-CO_2H;

X_1 es un enlace o es CH_2, O, -CH_2O-, S, -S(O), -$S(O)_2$, -C(O)-, -C(O)O-, o NR_x, en donde R_x es H o alquilo(C_1-C_6);

R' y R" son cada uno independientemente hidrógeno, halógeno, alquilo opcionalmente sustituido en carbono con halógeno, alquilo, o tomados junto al carbono al cual están unidos forman C=O o un anillo de 3, 4, 5 ó 6 miembros, que contiene opcionalmente 1 ó 2 heteroátomos seleccionados de O NH, N-alquilo, SO o SO_2, cualquiera de los cuales puede ser opcionalmente sustituido en carbono con alquilo o halógeno;

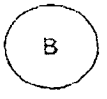
R_3 está ausente, es hidrógeno, halógeno, ciano, alquilo, arilo, heteroarilo, cicloalquilo, heterocicloalquilo, aralquilo, heteroalquilo, -O-alquilo, -O-arilo, -O-heteroarilo, aralcoxi, heteroaralcoxi, -S-alquilo, alquileno-O-alquilo, alquileno-CO_2H, alquileno-CO_2alquilo, alquiloSO_2. alquilensulfonilo, alquileno-CO-amino, alquileno-CO-alquilamino, alquileno-CO-dialquilamino, alquileno-

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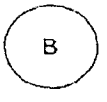
NH-CO_2H, alquileno-NH-CO_2alquilo -CO_2alquilo, -OH, -C(O)-alquilo, -C(O)O-alquilo, -$CONH_2$, -CO-alquilamino, -CO-dialquilamino, amino, alquilamino y dialquilamino, cualquiera de los cuales puede ser opcionalmente sustituido en carbono con 1, 2 ó 3 grupos seleccionados de halógeno, alquilo, OH, o -O-alquilo;



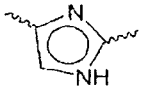
es fenilo o piridilo;



es arilo, heteroarilo, heterociclo o cicloalquilo, cualquiera de los cuales puede ser opcionalmente sustituido en carbono con 1, 2 ó 3 grupos seleccionados de halógeno, alquilo, O-alquilo, CO_2H, CO_2alquilo, halógeno, amino, alquilamino, dialquilamino, -O-alquilo, alquileno-O-alquilo, alquileno-OH, o alquileno-CO_2H, siempre que



no sea



;

R_4 es hidrógeno, ciano, alquilo, arilo, heteroarilo, alquileno-O-alquilo, alquileno-OH, arilo, alquileno-O-alquilo, -CO_2H, -CO_2-alquilo, alquileno-CO_2H, o alquileno-CO_2-alquilo, alquileno-OC(O)R en donde R es

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hidrógeno o alquilo; cicloalquilo, heterocicloalquilo, alquileno-NH_2, alquileno-alquilamino, o alquileno-dialquilamino, cualquiera de los cuales puede ser opcionalmente sustituido en carbono con 1, 2 ó 3 grupos seleccionados de OH, CO_2H, CO_2alquilo, halógeno, amino, alquilamino, dialquilamino, -O-alquilo, alquileno-O-alquilo, alquileno-OH, o alquileno-CO_2H;

R_5 y R_6 se seleccionan cada uno independientemente del grupo que consiste de hidrógeno, alquilo, alquileno-OH, arilo, alquileno-O-alquilo, -CO_2H, CO_2-alquilo, alquileno- OC(O)alquilo, cicloalquilo, heterociclo, -C(O)-alquilo, -C(O)-arilo, C(O)-aralquilo, -C(O)-Oalquilo, -C(O)-Oarilo, -C(O)-Oaralquilo, alquileno-amino, alquileno-alquilamino, y alquileno-dialquilamino, cualquiera de los cuales puede ser opcionalmente sustituido en carbono con halógeno, alquilo, hidroxilo, CO_2H_5 CO_2alquilo o alcoxi; o;

R_5 y R_6, junto con el nitrógeno al cual están unidos, pueden formar un anillo saturado o insaturado de 3, 4, 5 ó 6 miembros, que contiene opcionalmente 1 ó 2 heteroátomos adicionales seleccionados de O, S, NH, o N-alquilo, y opcionalmente sustituido en carbono con halógeno, alquilo, hidroxilo o alcoxi;

R_7 se selecciona del grupo que consiste de -OH, -O-alquilo, -alquileno-OH, -CO_2H, -alquileno-CO_2H, -C(O)O-alquilo, -alquileno-CO_2-alquilo, -C(O)O-arilo, -CH_2=$CHCO_2H$, -CH_2=CHC(O)O-alquilo, -CH_2=CHC(O)O-arilo, -$OPO_2R_{p1}R_{p2}$, -$OPO_3R_{p1}R_{p2}$, -$CH_2PO_3R_{p1}R_{p2}$, -$OPO_2(S)R_{p1}R_{p2}$, y -$C(Z')(Z'')PO_3R_{p1}R_{p2}$, cualquiera de los cuales puede ser opcionalmente sustituido en carbono con halógeno, alquilo, hidroxilo, carboxi,

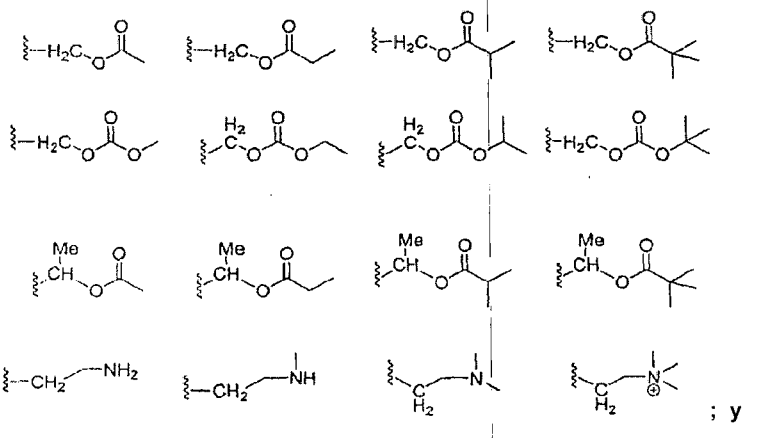
187

o alcoxi; y en donde

Z' es hidroxilo o halógeno;

Z" es H o halógeno;

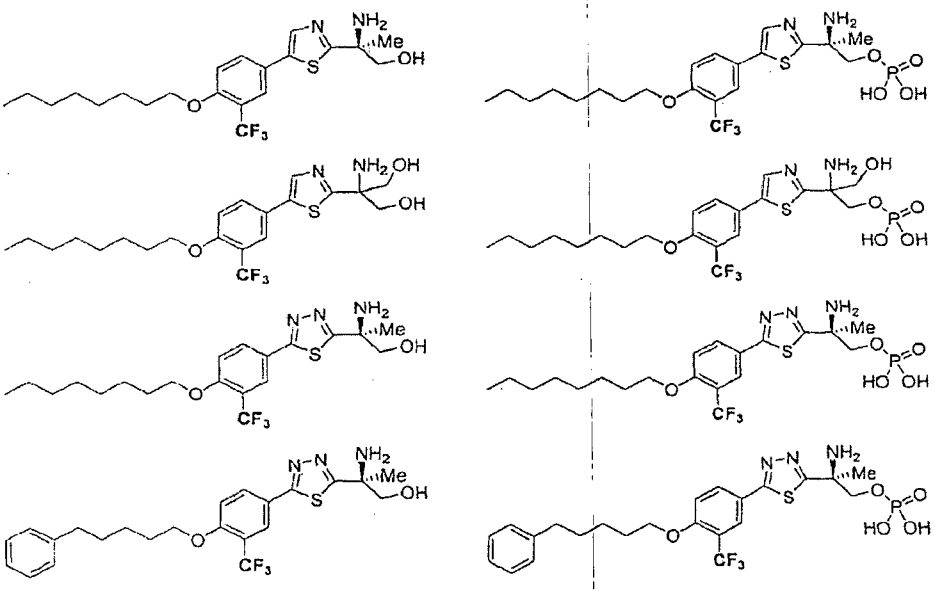
R_{p1} y R_{p2} son cada uno independientemente hidrógeno, alquilo de C_1-C_6, arilo, o uno de los siguientes grupos:

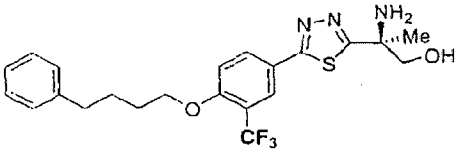
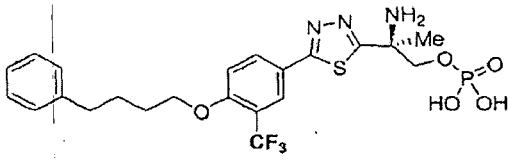
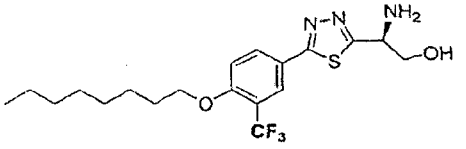
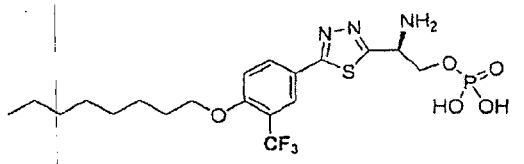
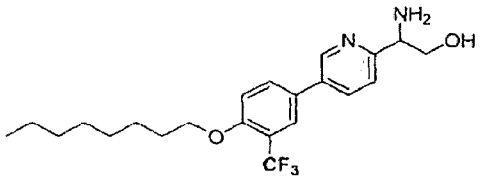
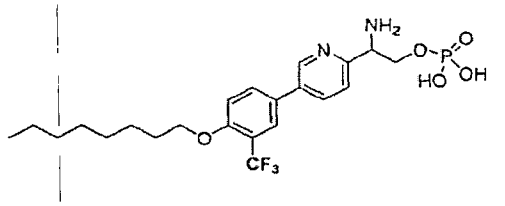
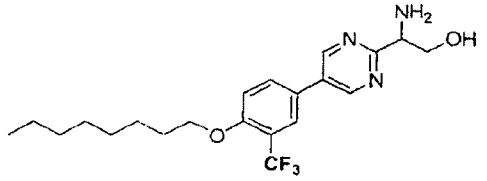
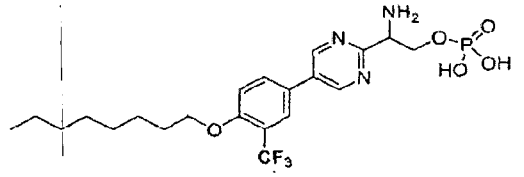
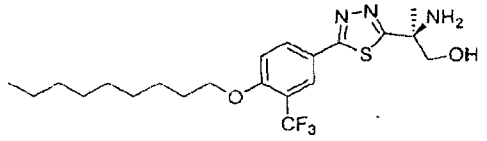
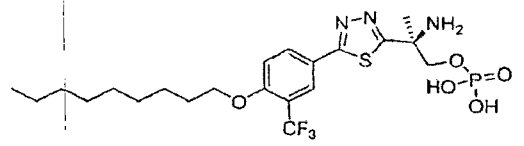
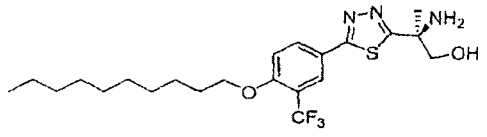
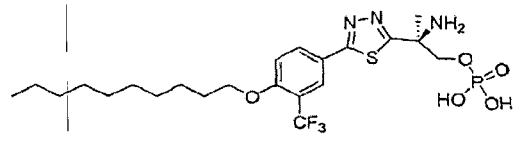
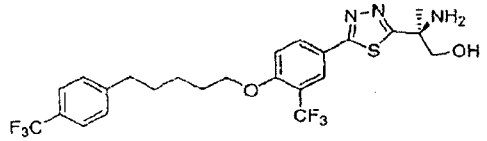
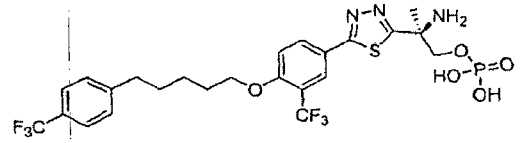
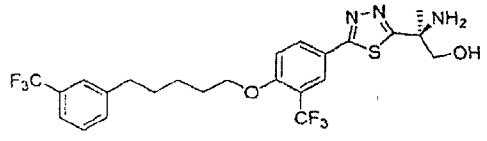
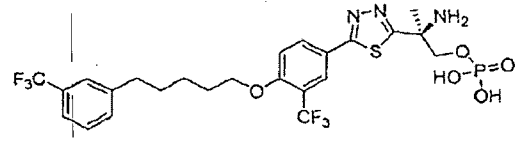


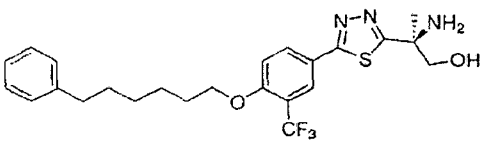
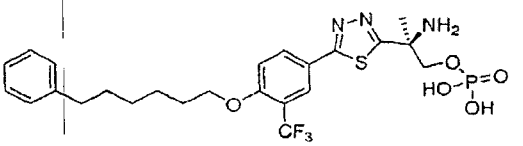
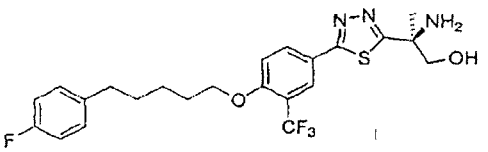
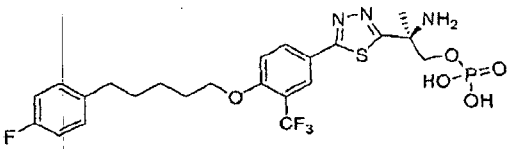
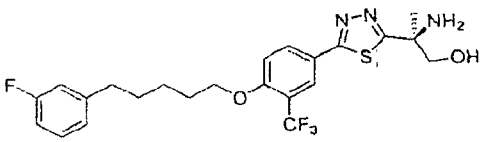
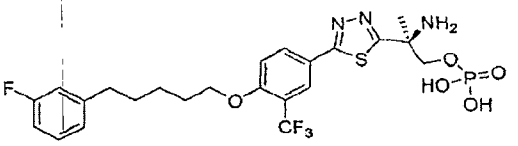
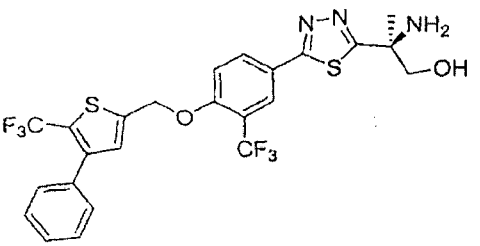
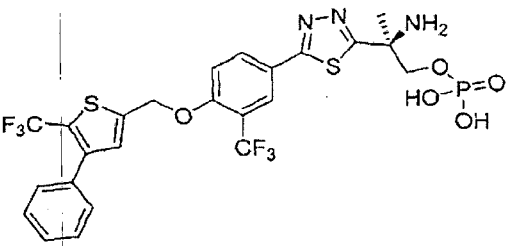
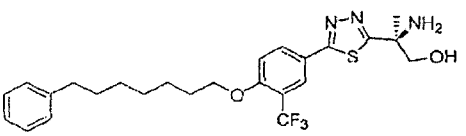
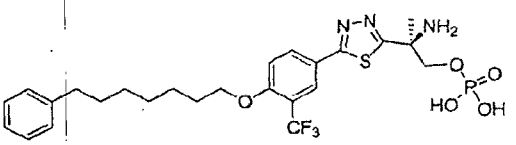
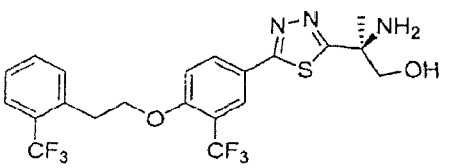
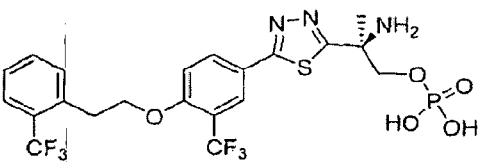
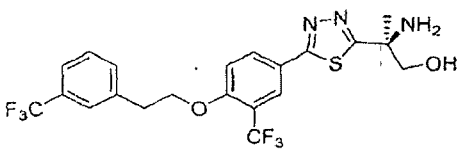
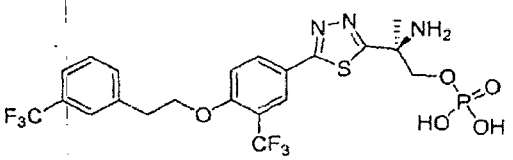
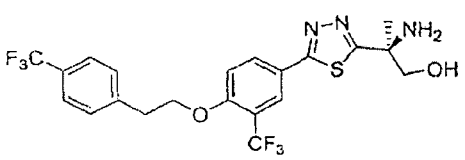
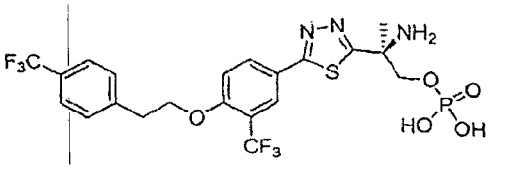
; y

Y es heterociclo o heteroarilo.

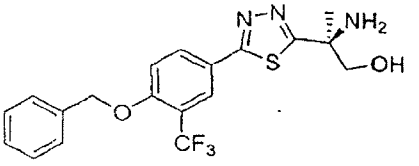
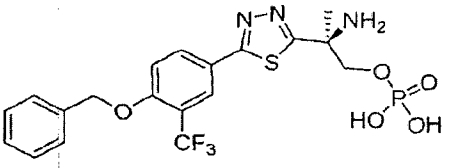
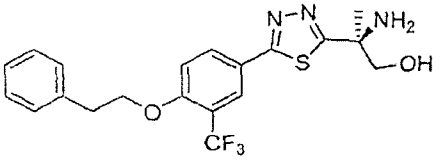
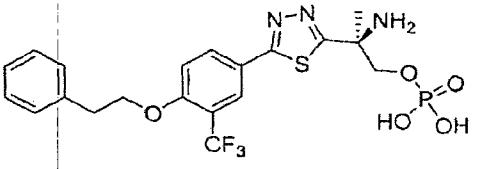
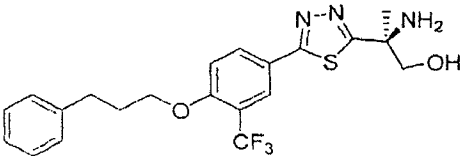
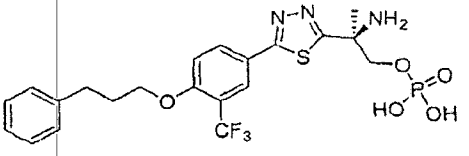
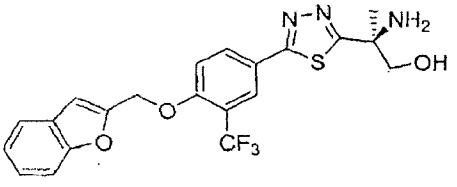
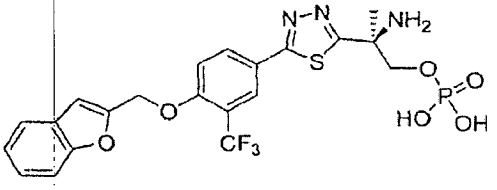
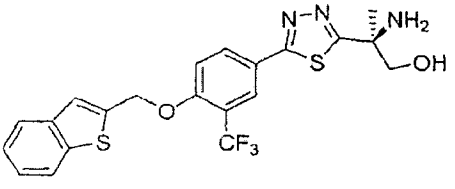
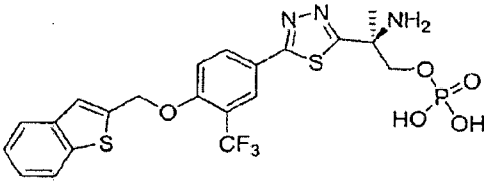
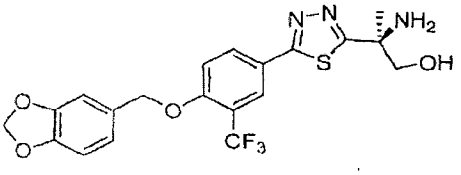
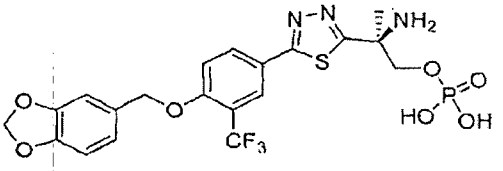
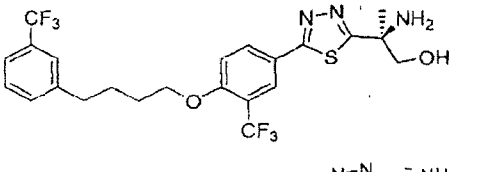
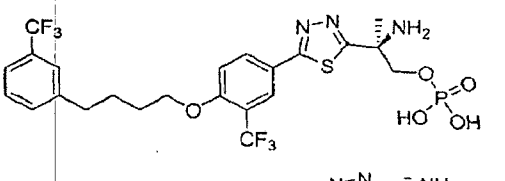
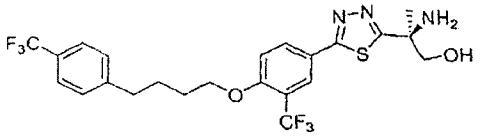
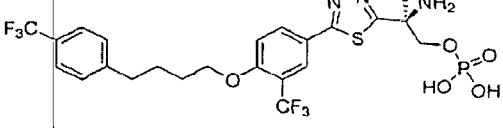
En algunas modalidades, los compuestos de la presente invención incluyen compuestos listados en el siguiente cuadro:

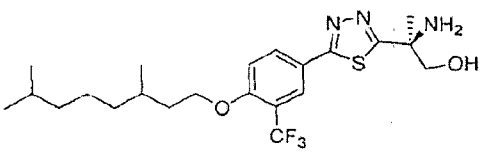
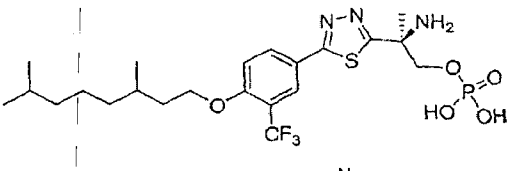
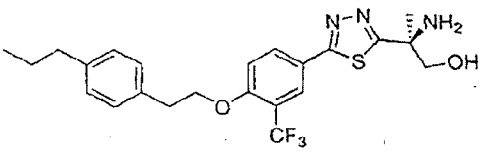
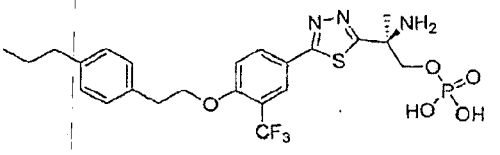
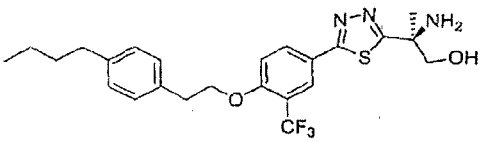
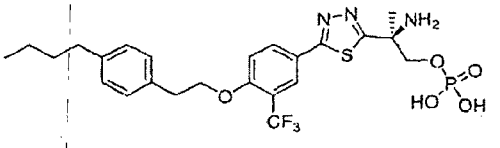
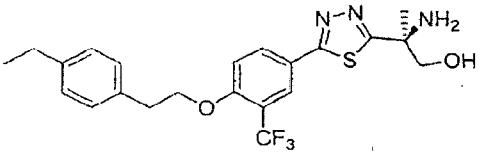
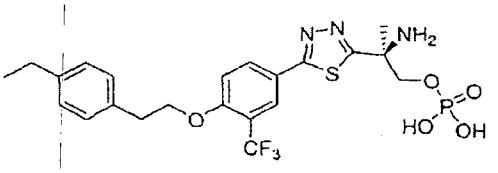
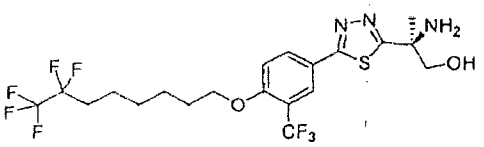
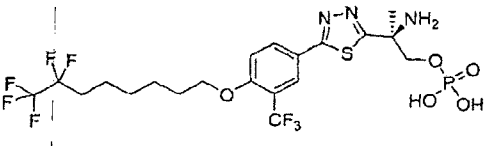
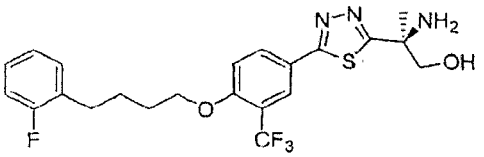
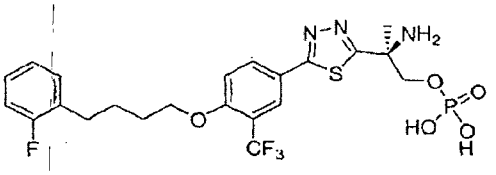
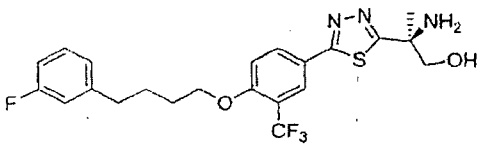
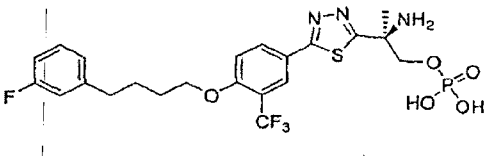
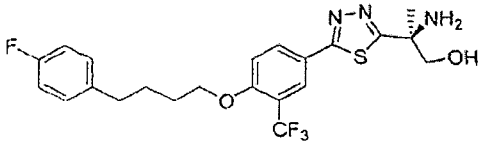
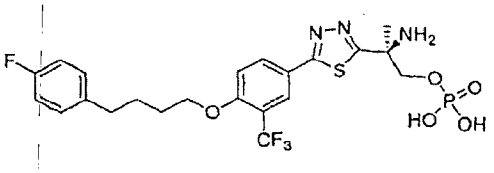
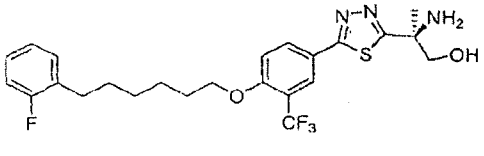
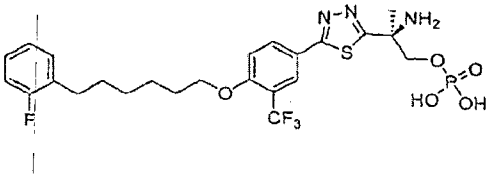


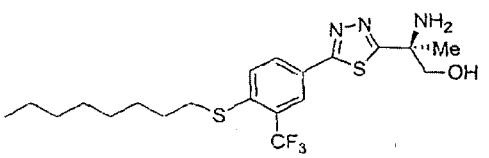

















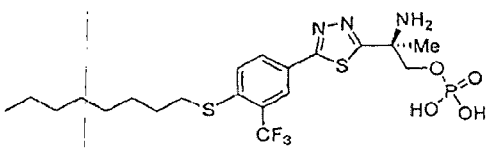

















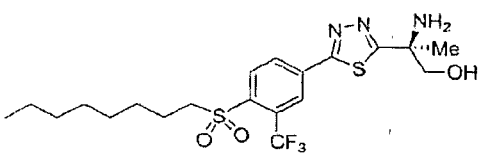
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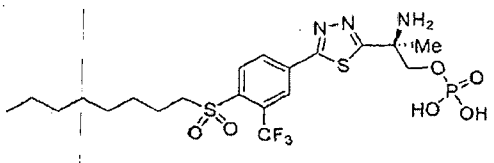

















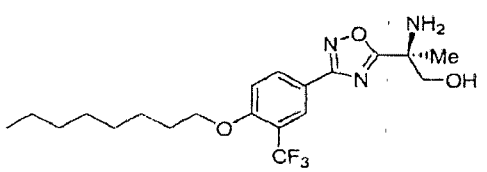



















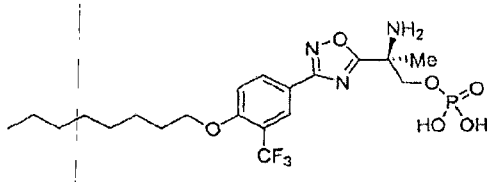



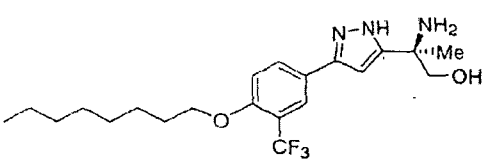


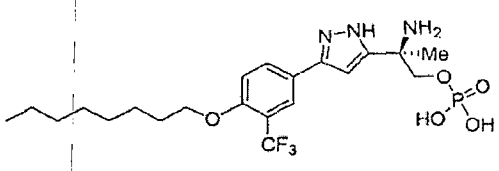


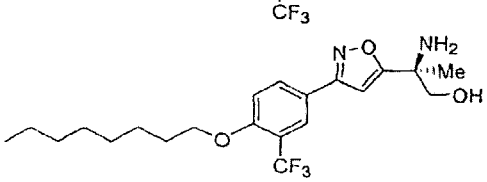


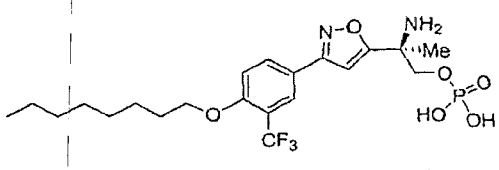


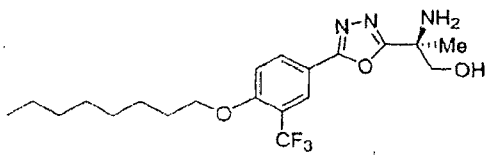


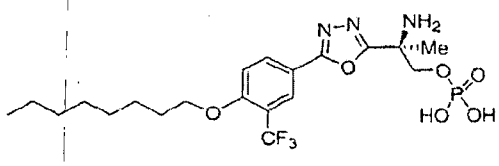


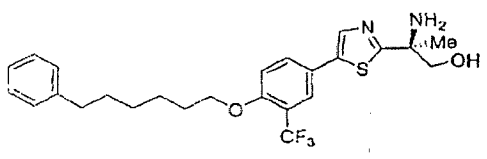


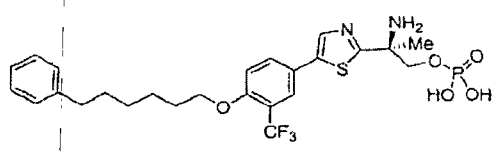


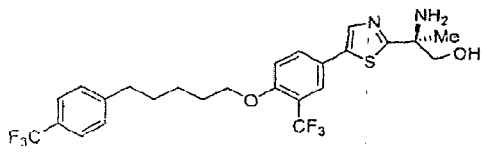


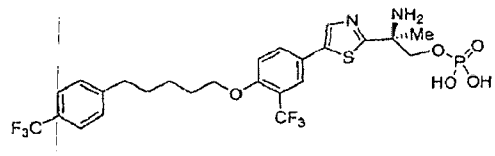


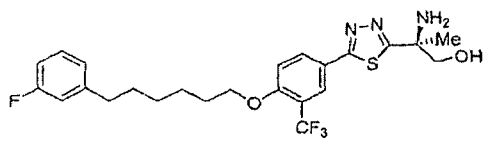


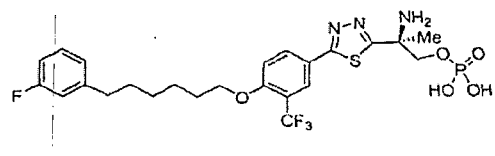




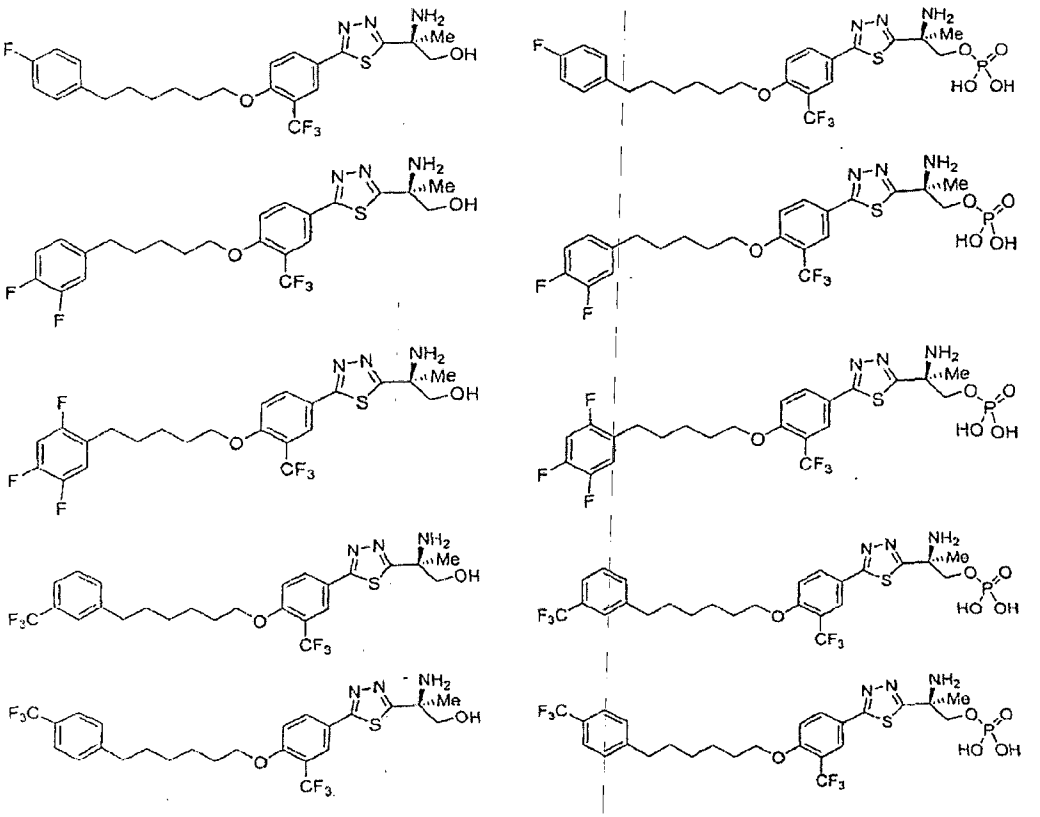






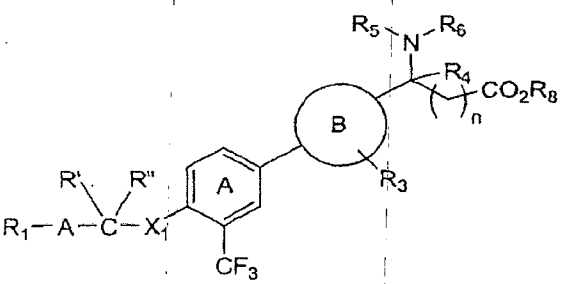


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así como sales farmacéuticamente aceptables, derivados de fosfato, simuladores de fosfato, o análogos de precursor de fosfato de los mismos.

En algunos aspectos, la presente invención está dirigida a un compuesto de la fórmula III:



III

o una sal farmacéuticamente aceptable del mismo, en donde:

R_1 es hidrógeno, halógeno, ciano, alquilo, arilo, heteroarilo, cicloalquilo, heterocicloalquilo, aralquilo, heteroalquilo, -O-alquilo, -O-arilo, -O-heteroarilo, -S-alquilo, alquileno-O-alquilo, alquileno-CO_2H, alquileno-CO_2alquilo, alquiloSO_2, alquilensulfonilo, alquileno-CO-amino, alquileno-CO-alquilamino, alquileno-CO-dialquilamino, alquileno-NH-CO_2H, alquileno-NH-CO_2alquilo -CO_2alquilo, -OH, -C(O)-alquilo, -C(O)O-alquilo, -$CONH_2$, -CO-alquilamino, -CO-dialquilamino, amino, alquilamino, o dialquilamino, cualquiera de los cuales puede ser opcionalmente sustituido en carbono con 1, 2 ó 3 grupos seleccionados de halógeno, alquilo, halogenoalquilo, -CF_3, -CN, -OH, o -O-alquilo;

A es alquileno(C_1-C_{20}), alquenileno(C_2-C_{20}), o alquinileno(C_2-C_{20}), cada uno de los cuales puede ser opcionalmente sustituido en carbono con 1, 2 ó 3 grupos seleccionados de OH, CO_2H, CO_2alquilo, halógeno, amino, alquilamino, dialquilamino, -O-alquilo, alquileno-O-alquilo, alquileno-OH, o alquileno-CO_2H;

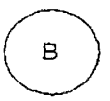
X_1 es un enlace o es CH_2, O, -CH_2O-, S, -S(O), -$S(O)_2$, -C(O)-, -C(O)O-, OrNR_x, en donde R_x es H o alquilo(C_1-C_6);

R' y R" son cada uno independientemente hidrógeno, halógeno, alquilo opcionalmente sustituido en carbono con halógeno, alquilo, o tomados junto al carbono al cual están unidos forman C=O o un anillo de 3, 4, 5 ó 6 miembros, que contiene opcionalmente 1 ó 2 heteroátomos seleccionados de O NH, N-alquilo, SO, o SO_2, cualquiera de los cuales puede ser opcionalmente sustituido en carbono con alquilo o halógeno;

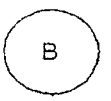
R_3 está ausente, hidrógeno, halógeno, ciano, alquilo, arilo, heteroarilo, cicloalquilo, heterocicloalquilo, aralquilo, heteroalquilo, -O-alquilo, -O-arilo, -O-heteroarilo, aralcoxi, heteroaralcoxi, -S-alquilo, alquileno-O-alquilo, alquileno-CO_2H, alquileno-CO_2alquilo, alquiloSO_2, alquilensulfonilo, alquileno-CO-amino, alquileno-CO-alquilamino, alquileno-CO-dialquilamino, alquileno-NH-CO_2H, alquileno-NH-CO_2alquilo -CO_2alquilo, -OH, -C(O)-alquilo, -C(O)O-alquilo, -$CONH_2$, -CO-alquilamino, -CO-dialquilamino, amino, alquilamino y dialquilamino, cualquiera de los cuales puede ser opcionalmente sustituido en carbono con 1, 2 ó 3 grupos seleccionados de halógeno, alquilo, OH, o -O-alquilo;



es fenilo o piridilo;

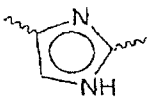


es arilo, heteroarilo, heterociclo, o cicloalquilo, cualquiera de los cuales puede ser opcionalmente sustituido en carbono con 1, 2 ó 3 grupos seleccionados de halógeno, alquilo, O-alquilo, CO_2H, CO_2alquilo, halógeno, amino; alquilamino, dialquilamino. -O-alquilo, alquileno-O-alquilo, alquileno-OH, o alquileno-CO_2H, siempre que



no sea

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;

R_4 es hidrógeno, ciano, alquilo, arilo, heteroarilo, alquileno-O-alquilo, alquileno-OH, arilo, alquileno-O-alquilo, $-CO_2H$, $-CO_2$-alquilo, alquileno-CO_2H, o alquileno-CO_2-alquilo, alquileno-OC(O)R en donde R es hidrógeno o alquilo; cicloalquilo, heterocicloalquilo, alquileno-NH_2, alquileno-alquilamino, o alquileno-dialquilarnino, cualquiera de los cuales puede ser opcionalmente sustituido en carbono con 1, 2 ó 3 grupos seleccionados de OH, CO_2H, CO_2alquilo, halógeno, amino, alquilamino, dialquilo amino, -O-alquilo, alquileno-O-alquilo, alquileno-OH, o alquileno-CO_2H;

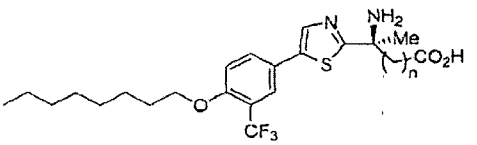
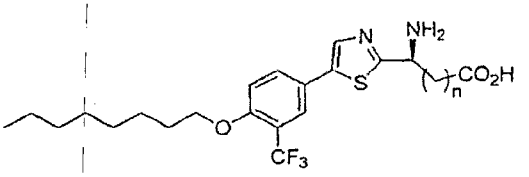
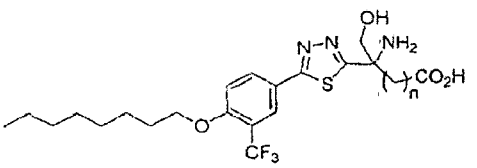
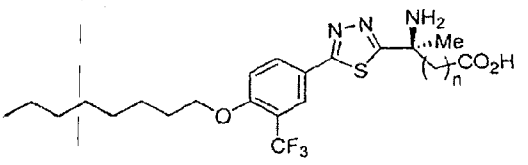
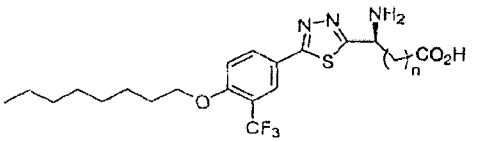
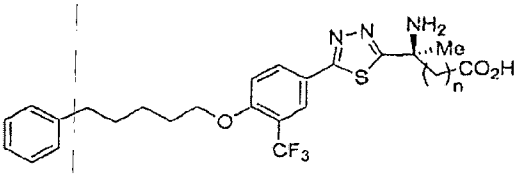
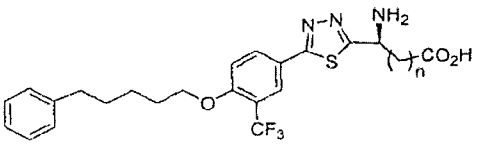
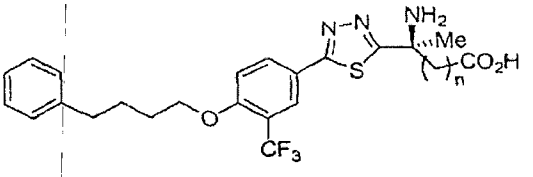
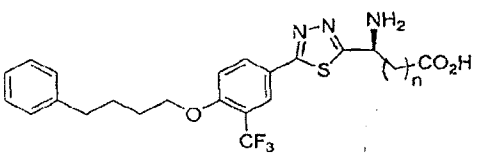
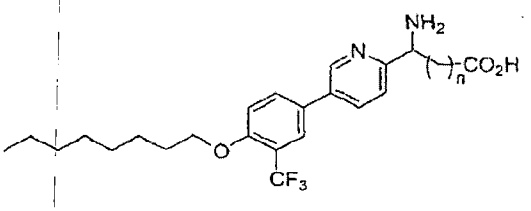
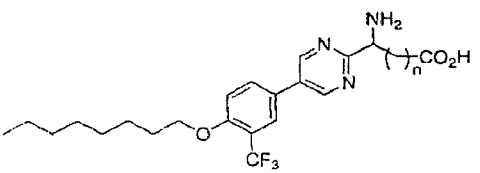
R_5 y R_6 se seleccionan cada uno independientemente del grupo que consiste de hidrógeno, alquilo, alquileno-OH, arilo, alquileno-O-alquilo, $-CO_2H$, CO_2-alquilo, alquileno- OC(O)alquilo, cicloalquilo, heterociclo, -C(O)-alquilo, -C(O)-arilo, C(O)-aralquilo, -C(O)- Oalquilo, -C(O)-Oarilo, -C(O)-Oaralquilo, alquileno-amino, alquileno-alquilamino, y alquileno-dialquilamino, cualquiera de los cuales puede ser opcionalmente sustituido en carbono con halógeno, alquilo, hidroxilo, CO_2H, CO_2alquilo o alcoxi; o

R_5 y R_6, junto con el nitrógeno al cual están unidos, pueden formar un anillo saturado o insaturado de 3, 4, 5 ó 6 miembros, que contiene opcionalmente 1 ó 2 heteroátomos adicionales seleccionados de O, S, NH, o N-alquilo, y opcionalmente sustituido en carbono con halógeno, alquilo, hidroxilo o alcoxi;

R_8 es hidrógeno, alquilo o arilo; y

n es 0, 1 ó 2.

En algunas modalidades, los compuestos de la presente invención incluyen compuestos listados en el siguiente cuadro:

en donde n para cada compuesto es 0, 1 ó 2, así como sales farmacéuticamente aceptables, derivados de fosfato, simuladores de fosfato, o análogos de precursor de fosfato de los mismos.

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En algunos aspectos, la presente invención está dirigida un compuesto seleccionado de:

(*S*)-2-Amino-2-(5-(4-(octiloxi)-3-(trifluorometil)fenil)tiazol-2-il)propan-1-ol;

2-Amino-2-(5-(4-(octiloxi)-3-(trifluorometil)fenil)tiazol-2-il)propano-1,3-diol;

(*S*)-2-Amino-2-(5-(4-(octiloxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol;

(*S*)-2-Amino-2-(5-(4-(5-fenilpentiloxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol;

(*S*)-2-Amino-2-(5-(4-(4-fenilbutoxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol;

(*S*)-2-Amino-2-(5-(4-(noniloxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol;

(*S*)-2-Amino-2-(5-(4-(deciloxi)-3(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol;

(*S*)-2-Ammo-2-(5-(3-(trifluorometil)-4-(5-(4-(trifluorometil)fenil)-pentiloxi)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol;

(*S*)-2-Amino-2-(5-(3-(trifluorometil)-4-(5-(3-(trifluorometil)fenil)pentiloxi)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol;

(*S*)-2-Amino-2-(5-(4-(6-fenilhexiloxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol;

(*S*)-2-Amino-2-(5-(4-(5-(4-fluorofenil)pentiloxi)-3-

(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol;

(*S*)-2-Amino-2-(5-(4-(5-(3-fluorofenil)pentiloxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol;

(*S*)-2-Amino-2-(5-(4-((4-fenil-5-(trifluorometil)tiofen-2-il)metoxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol;

(*S*)-2-Amino-2-(5-(4-(7-fenilheptiloxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol;

(*S*)-2-Amino-2-(5-(3-(trifluorometil)-4-(2-(trifluorometil)fenetoxi)fenil)-1,3,4- tiadiazol-2-il)propan-1-ol;

(*S*)-2-Amino-2-(5-(3-(txifluorometil)-4-(3-(trifluorometil)fenetoxi)fenil)-1,3,4- tiadiazol-2-il)propan-1-ol;

(*S*)-2-Amino-2-(5-(3-(trifluorometil)-4-(4-(trifluorometil)fenetoxi)fenil)-1,3,4- tiadiazol-2-il)propan-1-ol;

(*S*)-2-Amino-2-(5-(4-(benziloxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol;

(*S*)-2-Amino-2-(5-(4-fenetoxi-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol;

(*S*)-2-Amino-2-(5-(4-(3-fenilpropoxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol;

(*S*)-2-Amino-2-(5-(4-(benzofuran-2-ilmetoxi)-3-(trifluorometil)fenil)-1,3,4- tiadiazol-2-il)propan-1-ol;

(*S*)-2-Amino-2-(5-(4-(benzo[*b*]tiofen-2-ilmetoxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol;

(*S*)-2-Amino-2-(5-(4-(benzo[*d*][1,3]dioxol-5-ilmetoxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol;

(*S*)-2-Amino-2-(5-(3-(trifluorometil)-4-(4-(3-(trifluorometil)fenil)butoxi)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol;

(*S*)-2-Amino-2-(5-(3-(trifluorometil)-4-(4-(4-(trifluorometil)fenil)butoxi)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol;

(2*S*)-2-Amino-2-(5-(4-(3,7-dimetiloctiloxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol;

(*S*)-2-Amino-2-(5-(4-(4-propilfenetoxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol;

(*S*)-2-Amino-2-(5-(4-(4-butilfenetoxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol;

(*S*)-2-Amino-2-(5-(4-(4-etilfenetoxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol;

(*S*)-2-Amino-2-(5-(4-(7,7,8,8,8-pentafluorooctiloxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol;

(*S*)-2-Amino-2-(5-(4-(4-(2-fluorofenil)butoxi)-3-(trifluorometil)fenil)-1,3,4- tiadiazol-2-il)propan-1-ol;

(*S*)-2-Amino-2-(5-(4-(4-(3-fluorofenil)butoxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol;

(*S*)-2-Amino-2-(5-(4-(4-(4-fluorofenil)butoxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol;

(*S*)-2-Amino-2-(5-(4-(6-(2-fluorofenil)hexiloxi)-3-

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(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol;

(*S*)-2-Amino-2-(5-(4-(6-(3-fluorofenil)hexiloxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol;

(*S*)-2-Amino-2-(5-(4-(6-(4-fluorofenil)hexiloxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol;

(*S*)-2-Amino-2-(5-(4-(5-(3,4-difluorofenil)pentiloxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol;

(*S*)-2-Amino-2-(5-(3-(trifluorometil)-4-(5-(2,4,5-trifluorofenil)pentiloxi)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol;

(*S*)-2-Amino-2-(5-(3-(trifluorometil)-4-(6-(3-(trifluorometil)fenil)hexiloxi)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol;

(*S*)-2-Amino-2-(5-(3-(trifluorometil)-4-(6-(4-(trifluorometil)fenil)hexiloxi)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol;

(*S*)-2-Amino-2-(5-(4-(octiltio)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol;

(*S*)-2-Amino-2-(5-(4-(octilsulfonil)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol;

(*S*)-2-Amino-2-(3-(4-(octiloxi)-3-(trifluorometil)fenil)-1,2,4-oxadiazol-5-il)propan-1-ol;

(*R*)-2-Amino-2-(5-(4-(octiloxi)-3-(trifluorometil)fenil)-1H-pirazol-3-il)propan-1-ol;

(*S*)-2-Amino-2-(3-(4-(octiloxi)-3-(trifluorometil)fenil)isoxazol-5-il)propan-1-ol;

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(*S*)-2-Amino-2-(5-(4-(octiloxi)-3-(trifluorometil)fenil)-1,3,4-oxadiazol-2-il)propan-1-ol;

(*S*)-2-Amino-2-(5-(4-(6-fenilhexiloxi)-3-(trifluorometil)fenil)tiazol-2-il)propan-1-ol;

(*S*)-2-Amino-2-(5-(3-(trifluorometil)-4-(5-(4-(trifluorometil)fenil)pentiloxi)fenil)tiazol-2-il)propan-1-ol;

y sales farmacéuticamente aceptables, derivados de fosfato, simuladores de fosfato, y análogos de precursor de fosfato de los mismos.

En algunos aspectos, la presente invención está dirigida a un compuesto que es (*S*)-2-Amino-2-(5-(4-(octiloxi)-3-(trifluorometil)fenil)tiazol-2-il)propan-1-ol o una sal farmacéuticamente aceptable, derivado de fosfato, simulador de fosfato o análogo de precursor de fosfato del mismo. En otros aspectos, la presente invención está dirigida a un compuesto que es fosfato diácido de (*S*)-2-Amino-2-(5-(4-(octiloxi)-3-(trifluorometil)fenil)tiazol-2-il)propilo o una sal farmacéuticamente aceptable del mismo.

En algunos aspectos, la presente invención está dirigida a un compuesto que es (*S*)-2-Amino-2-(5-(4-(octiloxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol o una sal farmacéuticamente aceptable, derivado de fosfato, simulador de fosfato, o un análogo de precursor de fosfato del mismo. En otros aspectos, la presente invención está dirigida a un compuesto que es fosfato diácido de (*S*)-2-Amino-2-(5-(4-(octiloxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propilo o una sal farmacéuticamente aceptable del mismo.

En algunos aspectos, la presente invención está dirigida a un

método de tratamiento de un trastorno asociado con fosfato de 1-esfingosina en un sujeto que necesita el mismo que comprende administrar al sujeto una cantidad segura y efectiva de un compuesto de cualquiera de las fórmulas I, II o III, o una sal farmacéuticamente aceptable, derivado de fosfato, simulador de fosfato, o análogo de precursor de fosfato del mismo, de tal manera que se trata el trastorno asociado con 1-fosfato de esfingosina.

En algunos aspectos, la presente invención está dirigida a un método de tratamiento de un trastorno autoinmune que comprende administrar a un sujeto que necesita el mismo una cantidad farmacéuticamente efectiva de un compuesto de cualquiera de las fórmulas I, II o III, de tal manera que se trata el trastorno autoinmune.

En algunos aspectos, la presente invención está dirigida a un método de tratamiento de rechazo de trasplante que comprende administrar a un sujeto que necesita el mismo una cantidad farmacéuticamente efectiva de un compuesto de cualquiera de las fórmulas I, II o III, de tal manera que se trata el rechazo de trasplante.

En algunos aspectos, la presente invención está dirigida a un compuesto de cualquiera de las fórmulas I, II o III para usarse como una sustancia terapéutica.

En algunos aspectos, la presente invención está dirigida a un compuesto de cualquiera de las fórmulas I, II o III para usarse en el tratamiento de trastornos asociados con esfingosina. En algunos aspectos, la presente invención está dirigida a un compuesto de cualquiera de las fórmulas

I, II o III para usarse en el tratamiento de esclerosis múltiple.

En algunos aspectos, la presente invención está dirigida a un compuesto de cualquiera de las fórmulas I, II o III para usarse en la fabricación de un medicamento para usarse en el tratamiento de trastornos asociados con esfingosina. En algunos aspectos, la presente invención está dirigida a un compuesto de cualquiera de las fórmulas I, II o III para usarse en la fabricación de un medicamento para el tratamiento de esclerosis múltiple.

En algunos aspectos, la presente invención está dirigida a una composición farmacéutica que comprende un compuesto de cualquiera de las fórmulas I, II o III y un vehículo farmacéuticamente aceptable.

En algunos aspectos, la presente invención está dirigida a un procedimiento para hacer cualquiera de los compuestos descritos aquí.

DESCRIPCION DETALLADA DE LA INVENCION

Definiciones

Se usan las siguientes definiciones, a menos que se describa de otra manera.

"Halógeno" o "halo" significa fluoro (F), cloro (Cl), bromo (Br) o yodo (I).

El término "hidrocarburo" usado solo o como sufijo o prefijo, se refiere a cualquier estructura que comprende sólo átomos de carbono e hidrógeno hasta 14 átomos de carbono.

El término "radical hidrocarburo" o "hidrocarbilo" usado solo o como sufijo o prefijo, se refiere a cualquier estructura como resultado de remover uno o más hidrógenos de un hidrocarburo.

El término "alquilo", usado solo o como sufijo o prefijo, se refiere a radicales hidrocarburo de cadena recta o ramificada monovalentes que comprenden 1 a aproximadamente 12 átomos de carbono.

El término "alquileno", usado solo o como sufijo o prefijo, se refiere a radicales hidrocarburo de cadena recta o ramificad divalentes que comprenden 1 a aproximadamente 12 átomos de carbono, que sirve para enlazar dos estructuras entre sí.

El término "cicloalquilo", usado solo o como sufijo o prefijo, se refiere a un radical hidrocarburo que contiene un anillo monovalente saturado o parcialmente insaturado que comprende por lo menos 3 hasta aproximadamente 12 átomos de carbono.

El término "arilo", usado solo o como sufijo o prefijo, se refiere a un radical hidrocarburo monovalente que tiene uno o más anillos de carbono poliinsaturados que tienen carácter aromático, y que comprenden 5 hasta aproximadamente 14 átomos de carbono.

El término "heterociclo", usado solo o como sufijo o prefijo, se refiere a una estructura o molécula que contiene anillo que tiene uno o más heteroátomos multivalentes, independientemente seleccionados de N, O y S, como parte de la estructura de anillo y que incluye por lo menos 3 y hasta aproximadamente 20 átomos en el anillo(s). El heterociclo puede ser saturado

o insaturado, que contiene uno o más dobles enlaces, y heterociclo puede contener más de un anillo. Cuando un heterociclo contiene más de un anillo, los anillos pueden ser fusionados o no fusionados. Los anillos fusionados generalmente se refieren a por lo menos dos anillos comparten dos átomos entre los mismos. El heterociclo puede tener carácter aromático o puede no tener carácter aromático.

Los términos "grupo heterocíclico", "porción heterocíclica", "heterocíclico" o "heterociclo", usados solos o como sufijo o prefijo, se refiere a un radical derivado de un heterociclo removiendo uno o más hidrógenos de los mismos.

El término "heterociclilo", usado solo o como sufijo o prefijo, se refiere a un radical monovalente derivado de un heterociclo al remover un hidrógeno del mismo.

El término "heteroarilo", usado solo o como sufijo o prefijo, se refiere a un heterociclilo que tiene carácter aromático.

Los heterociclos incluyen, por ejemplo, heterociclos monocíclicos tales como: aziridina, oxirano, tiirano, azetidina, oxetano, tietano, pirrolidina, pirrolina, imidazolidina, pirazolidina, pirazolina, dioxolano, sulfolano, 2,3-dihidrofurano, 2,5-dihidrofurano, tetrahidrofurano, tiofano, piperidina, 1,2,3,6-tetrahidropiridina, piperazina, morfolina, tiomorfolina, pirano, tiopirano, 2,3-dihidropirano, tetrahidropirano, 1,4-dihidropiridina, 1,4-dioxano, 1,3-dioxano, dioxano, homopiperidina, 2,3,4,7-tetrahidro-1H-azepina, homopiperazina, 1,3-dioxepano, 4,7-dihidro-1,3-dioxepina y óxido de hexametileno.

Además, los heterociclos incluyen heterociclos aromáticos (grupos heteroarilo), por ejemplo, piridina, pirazina, pirimidina, piridazina, tiofeno, furan, furazan, pirrol, imidazol, tiazol, oxazol, pirazol, isotiazol, isoxazol, 1,2,3-triazol, tetrazol, 1,2,3-tiadiazol, 1,2,3-oxadiazol, 1,2,4-triazol, 1,2,4-tiadiazol, 1,2,4-oxadiazol, 1,3,4-triazol, 1,3,4-tiadiazol y 1,3,4-oxadiazol.

Además, el heterociclo abarca heterociclos policíclicos, por ejemplo, indol, indolina, isoindolina, quinolina, tetrahidroquinolina, isoquinolina, tetrahidroisoquinolina, 1,4-benzodioxano, cumarina, dihidrocumarina, benzofurano, 2,3-dihidrobenzofurano, isobenzofurano, cromeno, cromano, isocromano, xanteno, fenoxatina, tiantreno, indolizina, isoindol, indazol, purina, ftalazina, naftiridina, quinoxalina, quinazolina, cinolina, pteridina, fenantridina, perimidina, fenantrolina, fenazina, fenotiazina, fenoxazina, 1,2-bencisoxazol, benzotiofeno, benzoxazol, benztiazol, bencimidazol, benztriazol, tioxantina, carbazol, carbolina, acridina, pirolizidina y quinolizidina.

Además de los heterociclos policíclicos descritos anteriormente, los heterociclos incluyen heterociclos policíclicos en donde la fusión de anillos entre dos o más anillos incluye más que un enlace común a ambos anillos y más de dos átomos comunes a ambos anillos. Ejemplos de dichos heterociclos de puente incluyen quinuclidina, diazabiciclo[2.2.1]heptano y 7-oxabiciclo[2.2.1]heptano.

Los heterociclilos incluyen, por ejemplo, heterociclilos monocíclicos, tales como: aziridinilo, oxiranilo, tiiranilo, azetidinilo, oxetanilo, tietanilo, pirrolidinilo, pirrolinilo, imidazolidinilo, pirazolidinilo, pirazolinilo,

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dioxolanilo, sulfolanilo, 2,3-dihidrofuranilo, 2,5-dihidrofuranilo, tetrahidrofuranilo, tiofanilo, piperidinilo, 1,2,3,6-tetrahidropiridinilo, piperazinilo, morfolinilo, tiomorfolinilo, piranilo, tiopiranilo, 2,3-dihidropiranilo, tetrahidropiranilo, 1,4-dihidropiridinilo, 1,4-dioxanilo, 1,3-dioxanilo, dioxanilo, homopiperidinilo, 2,3,4,7-tetrahidro-1H-azepinilo, homopiperazinilo, 1,3-dioxepanilo, 4,7-dihidro-1,3-dioxepinilo y hexametilenoxidilo.

Además, los heterociclilos incluyen heterociclilos aromáticos o heteroarilo, por ejemplo, piridinilo, pirazinilo, pirimidinilo, piridazinilo, tienilo, furilo, furazanilo, pirrolilo, imidazolilo, tiazolilo, oxazolilo, pirazolilo, isotiazolilo, isoxazolilo, 1,2,3-triazolilo, tetrazolilo, 1,2,3-tiadiazolilo, 1,2,3-oxadiazolilo, 1,2,4-triazolilo, 1,2,4-tiadiazolilo, 1,2,4-oxadiazolilo, 1,3,4-triazolilo, 1,3,4-tiadiazolilo, y 1,3,4-oxadiazolilo.

Además, el heterociclilo abarca heterociclilos policíclicos (incluyendo aromáticos o no aromáticos), por ejemplo, indolilo, indolinilo, isoindolinilo, quinolinilo, tetrahidroquinolinilo, isoquinolinilo, tetrahidroisoquinolinilo, 1,4-benzodioxanilo, cumarinilo, dihidrocumarinilo, benzofuranilo, 2,3-dihidrobenzofuranilo, isobenzofuranilo, cromenilo, cromanilo, isocromanilo, xantenilo, fenoxatiinilo, tiantrenilo, indolizinilo, isoindolilo, indazolilo, purinilo, ftalazinilo, naftiridinilo, quinoxalinilo, quinazolinilo, cinolinilo, pteridinilo, fenantridinilo, perimidinilo, fenantrolinilo, fenazinilo, fenotiazinilo, fenoxazinilo, 1,2-bencisoxazolilo, benzotiofenilo, benzoxazolilo, benztiazolilo, bencimidazolilo, benztriazolilo, tioxantinilo, carbazolilo, carbolinilo, acridinilo, pirolizidinilo y quinolizidinilo.

Además de los heterociclilos policíclicos descritos anteriormente, los heterociclilos incluyen heterociclilos policíclicos en donde la fusión de anillos entre dos o más anillos incluyen más de un enlace común a ambos anillos y más de dos átomos comunes a ambos anillos. Ejemplos de dichos heterociclos de puente incluyen quinuclidinilo, diazabiciclo[2.2.1]heptilo; y 7-oxabiciclo[2.2.1]heptilo.

El término "seis miembros" usados como prefijo se refiere a un grupo que tiene un anillo que contiene seis átomos de anillo.

El término "cinco miembros" usado como prefijo se refiere a un grupo que tiene un anillo que contiene cinco átomos de anillo.

Un anillo de heteroarilo de cinco miembros es un heteroarilo con un anillo que tiene cinco átomos de anillo en donde 1, 2 ó 3 átomos de anillo son independientemente seleccionados de N, O y S. Heteroarilos de anillo de cinco miembros ilustrativos son tienilo, furilo, pirrolilo, imidazolilo, tiazolilo, oxazolilo, pirazolilo, isotiazolilo, isoxazolilo, 1,2,3-triazolilo, tetrazolilo, 1,2,3-tiadiazolilo, 1,2,3-oxadiazolilo, 1,2,4-triazolilo, 1,2,4-tiadiazolilo, 1,2,4-oxadiazolilo, 1,3,4-triazolilo, 1,3,4-tiadiazolilo y 1,3,4-oxadiazolilo.

Un heteroarilo de anillo de seis miembros es un heteroarilo con un anillo que tiene seis átomos de anillo en donde 1, 2 ó 3 átomos de anillo se seleccionan independientemente de N, O y S. Heteroarilo de anillo de seis miembros ilustrativos son piridilo, pirazinilo, pirimidinilo, triazinilo y piridazinilo.

El término "aralquilo" se refiere a un grupo alquilo sustituido con un grupo arilo.

El término "heteroaralquilo" se refiere a un grupo alquilo sustituido con un grupo heteroarilo.

A menos que se especifique otra cosa, el término "sustituido", cuando se usa como un prefijo, se refiere a una estructura, molécula o grupo, en donde uno o más hidrógenos son reemplazados con uno o más grupos alquilo, o uno o más grupos químicos que contienen uno o más heteroátomos seleccionados de N, O, S, F, Cl, Br, I y P. Grupos químicos ilustrativos que contienen uno o más heteroátomos incluyen heterociclilo, $-NO_2$, -O-alquilo, halógeno, $-CF_3$, $-CO_2H$, $-CO_2R$, $-NH_2$, -SH, -NHR, $-NR_2$, -SR, $-SO_3H$, $-SO_2R$, -S(O)R, -CN, -OH, $-C(O)NR_2$, -NRC(O)R, oxo (=O), imino (=NR), tio (=S), y oximino (=N-OR), en donde cada "R" es alquilo como se definió antes. Por ejemplo, fenilo sustituido puede referirse a nitrofenilo, piridilfenilo, metoxifenilo, clorofenilo, aminofenilo, etc., en donde los grupos nitro, piridilo, metoxi, cloro, y amino pueden reemplazar cualquier hidrógeno adecuado sobre el anillo de fenilo. Se entenderá que "sustitución" o "sustituido con" incluye la condición implícita de que dicha sustitución es de conformidad con la valencia permitida del átomo sustituido y el sustituyente, y que la sustitución da por resultado un compuesto estable, v.gr., que no sufre espontáneamente transformación tal como por reordenamiento, ciclización, eliminación, etc.

El término "alcoxi", usado solo o como sufijo o prefijo, se refiere a radicales de la fórmula general -O-alquilo. Grupos alcoxi ilustrativos incluyen metoxi, etoxi, propoxi, isopropoxi, butoxi, t-butoxi, isobutoxi, ciclopropilnetoxi, aliloxi y propargiloxi.

El término "amina" o "amino", usado solo o como sufijo o prefijo, se refiere a $-NH_2$.

El término "alquilamino", usado solo o como sufijo o prefijo, se refiere a -NH(alquilo). El término "dialquiloamino", usado solo o como sufijo o prefijo, se refiere a $-NH(alquilo)_2$.

"Acilo", usado solo, como un prefijo o sufijo, significa -C(O)-R, en donde R es hidrógeno, hidroxilo, amino, alquilamino, dialquilamino o alcoxi, cualquiera de los cuales puede ser sustituido como se provee por la definición de "sustituido" dada anteriormente. Grupos acilo incluyen, por ejemplo, acetilo, propionilo, benzoilo, fenilo acetilo, carboetoxi y dimetilcarbamoilo.

Algunos de los compuestos en la presente invención pueden existir como estereoisómeros, incluyendo enantiómeros, diastereómeros e isómeros geométricos. Todas estas formas, incluyendo (R), (S), epímeros, diastereómeros, cis, trans, sin, anti, solvatos (incluyendo hidratos), tautómeros y mezclas de los mismos, se contemplan en los compuestos de la presente invención.

La invención también se refiere a sales de los compuestos de la invención y, en particular, a sales farmacéuticamente aceptables. Una "sal farmacéuticamente aceptable" es una sal que retiene la actividad biológica deseada del compuesto progenitor y no imparte ningún efecto toxicológico deseado. Las sales pueden ser, por ejemplo, sales con un adecuado, tal como ácido clorhídrico, ácido bromhídrico, ácido sulfúrico, ácido fosfórico, ácido nítrico y similares; ácido acético, ácido oxálico, ácido tartárico, ácido

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succínico, ácido málico, ácido benzoico, ácido pamoico, ácido algínico, ácido metansulfónico, ácido naftalensulfónico y similares. También se incluyen sales de cationes tales como amonio, sodio, potasio, litio, zinc, cobre, bario, bismuto, calcio, y similares; o catires orgánicos tales como cationes de tetralquilamonio y trialquilamonio. Combinaciones de las sales anteriores también son útiles. También se incluyen sales de otros ácidos y/o cationes, tales como ácido trifluoroacético, ácido cloroacético y ácido tricloroacético. La invención también incluye diferentes formas de cristal, hidratos y solvatos de los compuestos de la invención.

Los términos "precursor de fosfato" y "análogo de precursor de fosfato," como se usa aquí, se refiere a porciones sustituyentes en compuestos de la invención que pueden ser directamente fosforilados *in vivo*, o que pueden ser digeridos *in vivo* para revelar una porción que entonces puede ser fosforilada *in vivo*. En ciertas modalidades, el precursor de fosfato puede ser Li-O-H o Li-O-L_2, en donde Li es una porción enlazadora y L_2 es una porción lábil. Modalidades ilustrativas del precursor de fosfato, incluyen pero no se limitan a -alquilo-OH, -halógeno-alquilo-OH, alcoxi-OH, -alquilo-$OCOR^a$, -halógeno-alquilo-$OCOR^a$ -alcoxi-$OCOR^a$, -alquilo-$OC(O)NR^a$ R^b, -halógeno-alquilo-$OC(O)NHR^aR^b$, -alcoxi-$OC(O)NR^aR^b$, -$(CH_2)_qCO_2R^c$, y -$(CH_2)_nCH_2$=$CHC(O)OR^c$, en donde

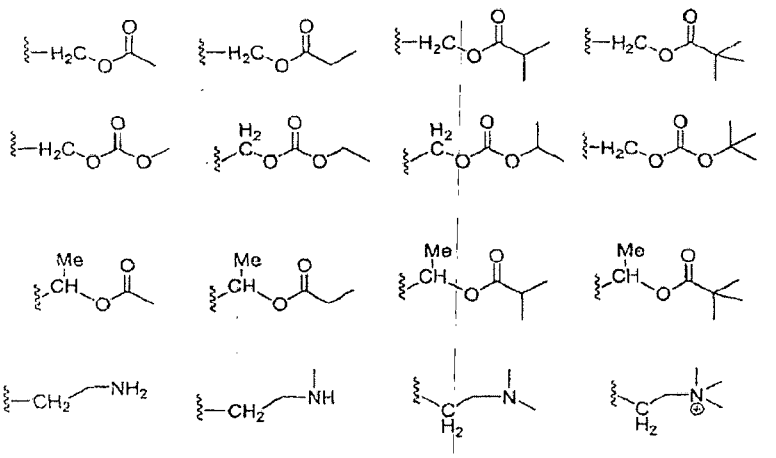
q es un entero entre 0 y 4;

R^a y R^b se seleccionan independientemente del grupo que consiste de hidrógeno, alquilo de C_1-C_6 de cadena recta o ramificada, todos

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los cuales pueden ser opcionalmente sustituidos con OH, halógeno, alcoxi de C_1-C_6 de cadena recta o ramificada, halogenoalquilo de C_1-C_6 de cadena recta o ramificada, halogenoalcoxi de C_1-C_6 de cadena recta o ramificada, alcoxi de C_1-C_6-alquilo de C_1-C_6, hidroxilo-alquilo de C_1-C_6, carboxi-alquilo de C_1-C_6, anillos carbocíclicos de C_3-C_{10} sustituidos o no sustituidos, y anillos heterocíclicos de C_3-C_{10} sustituidos o no sustituido, que pueden contener uno o más heteroátomos y pueden ser saturados o insaturado; y

R^c se selecciona del grupo que consiste de hidrógeno, alquilo de C_1-C_6 de cadena recta o ramificada, halogenoalquilo de C_1-C_6 de cadena recta o ramificada, grupo arilo sustituido o no sustituido, o uno de los siguientes grupos.



La "porción enlazadora" puede contener 1-8 átomos o puede ser un enlace, y sirve como el punto de conexión a través del cual las porciones sustituyentes del simulador de fosfato, derivado de fosfato, o precursor de fosfato son enlazadas a la estructura restante de los compuestos de la invención. En ciertas modalidades, la porción enlazadora puede may incluir

pero no se limita a, alquilo sustituido o no sustituido (v.gr., cadenas de metileno), alquenilo sustituido o no sustituido (v.gr., n-alquenos), alquinilo sustituido o no sustituido, halogenoalquilo sustituido o no sustituido, alcoxi sustituido o no sustituido, y halogenoalcoxi sustituido o no sustituido. En modalidades específicas, la porción enlazadora puede ser derivada de carbonilo.

El término "porción lábil" se refiere a una porción que susceptible de ser digerida, por ejemplo, por hidrólisis o degradación enzimática. En ciertas modalidades, la porción lábil es una porción éster, que pueden dar por resultado un carboxilato o derivado de hidroxilo, dependiendo de la orientación de la funcionalidad éster en la molécula antes de la digestión.

El término "derivado de fosfato" se refiere a porciones sustituyentes en compuestos de la invención que contienen un grupo fosfato o éster de fosfato. Cuando un compuesto de la invención que contiene un derivado de fosfato se administra a un sujeto, el compuesto puede actuar como tal *in vivo* o el derivado de fosfato (dentro del compuesto) puede ser digerido y después re-fosforilado *in vivo* conduciendo a un compuesto activo. En ciertas modalidades, el derivado de fosfato se puede seleccionar del grupo que consiste de $-(CH_2)_q\ OPO_2R^dR^e$, $-(CH_2)_qOPO_3R^dR^e$, y $-(CH_2)_qOPO_2(S)R^dR^e$, en donde

q es un entero entre 0 y 4; y

R^d y R^e se seleccionan cada uno independientemente del grupo que consiste de hidrógeno, alquilo de C_1-C_6 de cadena recta o ramificada,

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halogenoalquilo de C_1-C_6 de cadena recta o ramificada, grupo arilo sustituido o no sustituido, y una porción derivadora de profármaco (PDM).

El término "simulador de fosfato" se refiere a porciones sustituyentes en compuestos de la invención en los cuales un sustrato de fosfato ha sido reemplazado por un grupo funcional no hidrolizable, dando por resultado una porción que simula la función biológica de una porción de fosfato o éster de fosfato. En ciertas modalidades, el simulador de fosfato es $-L_1-Z_2$, en donde L_1 es una porción enlazadora y Z_2 es una porción no hidrolizable covalentemente unida a L_1. En ciertas modalidades, el simulador de fosfato se selecciona del grupo que consiste de $-(CH_2)_qCH_2PO_3R^dR^e$, y $-(CH_2)_qC(Yi)(Y_2)PO_3R^dR^e$, en donde

q es un entero entre 0 y 4;

Y_1 y Y_2 se seleccionan independientemente del grupo que consiste de hidrógeno, alquilo de C_1-C_6 de cadena recta o ramificada, todos los cuales pueden ser opcionalmente sustituidos con OH, halógeno, alcoxi de C_1-C_6 de cadena recta o ramificada, halogenoalquilo de C_1-C_6 de cadena recta o ramificada, halogenoalcoxi de C_1-C_6 de cadena recta o ramificada, alcoxi de C_1-C_6-alquilo de C_1-C_6, hidroxilo-alquilo de C_1-C_6, carboxi-alquilo de C_1-C_6, anillos carbocíclicos de C_3-C_{10} sustituidos o no sustituidos, y anillos heterocíclicos de C_3-C_{10} sustituidos o no sustituido, que pueden contener uno o más heteroátomos y pueden ser saturados o insaturado; y

R^d y R^e se seleccionan cada uno independientemente del grupo que consiste de hidrógeno, alquilo de C_1-C_6 de cadena recta o ramificada,

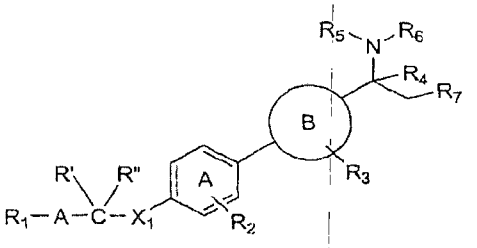
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halogenoalquilo de C_1-C_6 de cadena recta o ramificada, grupo arilo sustituido o no sustituido, y una porción derivadora de profármaco (PDM).

El término "porción no hidrolizable" es reconocida en la técnica, y se refiere a porciones que contienen enlaces, tales como enlaces carbono-fósforo, que son no hidrolizables *in vivo*.

Compuestos de la invención

En algunos aspectos, la presente invención está dirigida a un compuesto de la fórmula I:



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o una sal farmacéuticamente aceptable del mismo, en donde:

R_1 es hidrógeno, halógeno, ciano, alquilo, arilo, heteroarilo, cicloalquilo, heterocicloalquilo, aralquilo, heteroalquilo, -O-alquilo, -O-arilo, -O-heteroarilo, -S-alquilo, alquileno-O-alquilo, alquileno-CO_2H, alquileno-CO_2alquilo, alquiloSO_2, alquilensulfonilo, alquileno-CO-amino, alquileno-CO-alquilamino, alquileno-CO-dialquilamino, alquileno-NH- CO_2H, alquileno-NH-CO_2alquilo-CO_2alquilo, -OH, -C(O)-alquilo, -C(O)O-alquilo, -$CONH_2$, -CO-alquilamino, -CO-dialquilamino, amino, alquilamino o dialquilamino, cualquiera de los cuales puede ser opcionalmente sustituido en carbono con 1, 2 ó 3 grupos seleccionados de halógeno, alquilo, halogenoalquilo, -CF_3, arilo, -CN,

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-OH, o -O-alquilo;

A es alquileno(C_1-C_{20}), alquenileno(C_2-C_{20}), o alquinileno(C_2-C_{20}), cada uno de los cuales puede ser opcionalmente sustituido en carbono con 1, 2 ó 3 grupos seleccionados de OH, CO_2H, CO_2alquilo, halógeno, amino, alquilamino, dialquilamino, -O-alquilo, alquileno-O-alquilo, alquileno-OH, o alquileno-CO_2H;

X_1 es un enlace o es CH_2, O, -CH_2O-, S, -S(O), -$S(O)_2$, -C(O)-, -C(O)O-, o NR_x, en donde R_x es H o alquilo (C_1-C_6);

R' y R" son cada uno independientemente hidrógeno, halógeno, alquilo opcionalmente sustituido en carbono con halógeno, alquilo, o tomados junto al carbono al cual están unidos forman C=O o un anillo de 3, 4, 5 ó 6 miembros, que contiene opcionalmente 1 ó 2 heteroátomos seleccionados de O NH, N-alquilo, SO o SO_2, cualquiera de los cuales puede ser opcionalmente sustituido en carbono con alquilo o halógeno;

R_2 es ciano, alquilo, arilo, heteroarilo, cicloalquilo, heterocicloalquilo, aralquilo, heteroalquilo, -O-alquilo, -O-arilo, -O-heteroarilo, aralcoxi, heteroaralcoxi, -S-alquilo, alquileno-O-alquilo, alquileno-CO_2H, alquileno-CO_2alquilo, alquiloSO_2, alquilensulfonilo, alquileno-CO-amino, alquileno-CO-alquilamino, alquileno-CO-dialquilamino, alquileno-NH-CO_2H, alquileno-NH-CO_2alquilo -CO_2alquilo, -OH, -C(O)-alquilo, -C(O)O-alquilo, -$CONH_2$, -CO-alquilamino, -CO-dialquilamino, amino, alquilamino y dialquilamino, cualquiera de los cuales puede ser opcionalmente sustituido en carbono con 1, 2 ó 3 grupos seleccionados de halógeno, alquilo, OH, o -O-

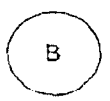
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alquilo;

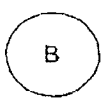
R_3 está ausente, es hidrógeno, halógeno, ciano, alquilo, arilo, heteroarilo, cicloalquilo, heterocicloalquilo, aralquilo, heteroalquilo, -O-alquilo, -O-arilo, -O-heteroarilo, aralcoxi, heteroaralcoxi, -S-alquilo, alquileno-O-alquilo, alquileno-CO_2H, alquileno-CO_2alquilo, alquiloSO_2, alquiloensulfonilo, alquileno-CO-amino, alquileno-CO-alquilamino, alquileno-CO-dialquilamino, alquileno-NH-CO_2H, alquileno-NH-CO_2alquilo -CO_2alquilo, -OH, -C(O)-alquilo, -C(O)O-alquilo, -$CONH_2$, -CO-alquilamino, -CO-dialquilamino, amino, alquilamino y dialquilamino, cualquiera de los cuales puede ser opcionalmente sustituido en carbono con 1, 2 ó 3 grupos seleccionados de halógeno, alquilo, OH, o -O-alquilo;



es fenilo o piridilo;

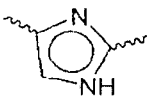


es arilo, heteroarilo, heterociclo o cicloalquilo, cualquiera de los cuales puede ser opcionalmente sustituido en carbono con 1, 2 ó 3 grupos seleccionados de halógeno, alquilo, O-alquilo, CO_2H, CO_2alquilo, halógeno, amino, alquilamino, dialquilamino, -O-alquilo, alquileno-O-alquilo, alquileno-OH, o alquileno-CO_2H, siempre que



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no sea



;

R_4 es hidrógeno, ciano, alquilo, arilo, heteroarilo, alquileno-O-alquilo, alquileno-OH, arilo, alquileno-O-alquilo, $-CO_2H$, $-CO_2$-alquilo, alquileno-CO_2H, o alquileno-CO_2-alquilo, alquileno-OC(O)R en donde R es hidrógeno o alquilo; cicloalquilo, heterocicloalquilo, alquileno-NH_2, alquileno-alquilamino, o alquileno-dialquilamino, cualquiera de los cuales puede ser opcionalmente sustituido en carbono con 1, 2 ó 3 grupos seleccionados de OH, CO_2H, CO_2alquilo, halógeno, amino, alquilamino, dialquilamino, -O-alquilo, alquileno-O-alquilo, alquileno-OH, o alquileno-CO_2H;

R_5 y R_6 se seleccionan cada uno independientemente del grupo que consiste de hidrógeno, alquilo, alquileno-OH, arilo, alquileno-O-alquilo, $-CO_2H$, CO_2-alquilo, alquileno- OC(O)alquilo, cicloalquilo, heterociclo, -C(O)-alquilo, -C(O)-arilo, C(O)-aralquilo, -C(O)-Oalquilo, -C(O)-Oarilo, -C(O)-Oaralquilo, alquileno-amino, alquileno-alquilamino, y alquileno-dialquilamino, cualquiera de los cuales puede ser opcionalmente sustituido en carbono con halógeno, alquilo, hidroxilo, CO_2H, CO_2alquilo o alcoxi; o

R_5 y R_6, junto con el nitrógeno al cual están unidos, pueden formar un anillo saturado o insaturado de 3, 4, 5 ó 6 miembros, que contiene opcionalmente 1 ó 2 heteroátomos adicionales seleccionados de O, S, NH_5 o N-alquilo, y opcionalmente sustituido en carbono con halógeno, alquilo, hidroxilo, o alcoxi;

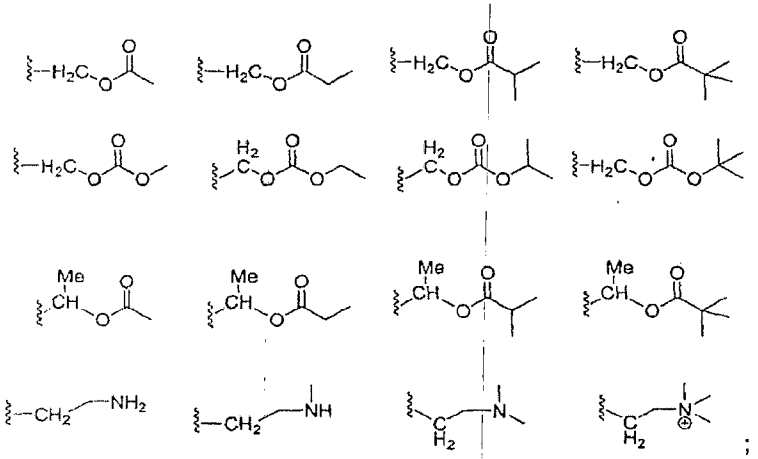
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R_7 se selecciona del grupo que consiste de -OH, -O-alquilo, alquileno-OH, $-CO_2H$, alquileno-CO_2H, -C(O)O-alquilo, -alquileno-CO_2-alquilo, -C(O)O-arilo, $-CH_2=CHCO_2H$, - $CH_2=CHC(O)O$-alquilo, $-CH_2=CHC(O)O$-arilo, $-OPO_2R_p,R_{p2}$, $-OPO_3R_{p1}R_{p2}$, $-CH_2PO_3R_{p1}R_{p2}$, $-OPO_2(S)R_{p1}R_{p2}$ y $-C(Z')(Z'')PO_3R_{p1}R_{p2}$, cualquiera de los cuales puede ser opcionalmente sustituido en carbono con halógeno, alquilo, hidroxilo, carboxi o alcoxi; y en donde

Z' es hidroxilo o halógeno;

Z" es H o halógeno;

R_{p1} y R_{p2} son cada uno independientemente hidrógeno, alquilo de C_1-C_6, arilo, o uno de los siguientes grupos:



; y

Y es heterociclo o heteroarilo.

En algunas modalidades, R_1 es arilo o heteroarilo, opcionalmente sustituido con 1, 2 ó 3 grupos seleccionados de halógeno, alquilo, halogenoalquilo, -arilo, $-CF_3$, -CN, -OH, o -O-alquilo. En algunas modalidades, R_1 es arilo, v.gr., fenilo, opcionalmente sustituido con 1 ó 2 grupos

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seleccionados de $-CF_3$, -CN, -OMe, -Cl o -F. En algunas modalidades, R_1 es heteroarilo, v.gr., tiofeno o benzotiofeno, opcionalmente sustituido con 1 ó 2 grupos seleccionados de fenilo, $-CF_3$, -CN, -OMe, -Cl o -F. En algunas modalidades, R_1 es hidrógeno. En otras modalidades, R_1 es fenilo. En algunas modalidades, R_1 es piridilo. En otras modalidades, R_1 es tiofenilo. En otras modalidades adicionales, R_1 es ciclohexilo. En algunas modalidades, R_1 es ciclopentilo.

En algunas modalidades, A es un alquileno de C_1-C_{10}. En algunas modalidades, A es un alquileno de C_1-C_{10} ramificado. En otras modalidades, A es n-octilo. En otras modalidades, A es n-heptilo. En otras modalidades, A es n-hexilo. En algunas modalidades, A es un alquileno de C_1-C_5. En algunas modalidades, A es n-pentilo. En otras modalidades, A es n-butilo. En otras modalidades adicionales, A es n-propilo. En otras modalidades, A es etilo. En otras modalidades adicionales, A es metilo.

En algunas modalidades, X_1 es O. En otras modalidades, X_1 es S. En otras modalidades adicionales, X_1 es SO_2. En algunas modalidades, X_1 es CH_2. En otras modalidades, X_1 es C=O. En otras modalidades adicionales, CH_2O, en donde ya sea el oxígeno o el carbono puede ser unido a



En algunas modalidades, R' es hidrógeno. En otras modalidades, R' es metilo. En algunas modalidades, R" es hidrógeno. En otras modalidades, R" es metilo. En algunas modalidades, R' y R" tomados junto con el carbono al

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cual están unidos, es C=O, con la condición de que sólo uno de X_1 o R' y R" tomados junto con el carbono pueden formar C=O.

Los compuestos de la presente invención incluyen una porción que incrementa selectivamente. El término "porción que incrementa selectivamente (SEM)" se define en la solicitud de los Estados Unidos Ser. No. 11/349069 presentada el 9 de febrero de 2006 que es cedida a la cesionaria de la presente solicitud, el contenido de la cual se incorpora aquí por referencia, se refiere a una o más porciones que proveen un incremento en la selectividad del compuesto al cual están unidas para el receptor S1P-1, en comparación con el compuesto que no contiene la porción o porciones. La SEM confiere selectividad al compuesto al cual está unida para el receptor S1P-1 en comparación con, por ejemplo, los receptores S1P-2 a S1P-5. El incremento conferido a un compuesto por la SEM se puede medir, por ejemplo, determinando la especificidad de unión de un compuesto para el receptor de S1P-1 y uno o más de los otros receptores S1P en donde el incremento conferido a un compuesto por la SEM puede estar en forma de potencia incrementada. En algunas modalidades, por lo menos uno de R_2 y/o R_3 es una SEM. En algunas modalidades, la SEM es un grupo alquilo halógeno-sustituido tal como CF_3, CF_2CF_3, $CF_2CF_2CF_3$, $CFHCF_3$, CH_2CF_3, $CH_2CH_2CF_3$, $CHCl_2$, o CH_2Cl.

En ciertas modalidades, la SEM puede poseer una orientación incrementadora de selectividad (SEO). El término "orientación incrementadora de selectividad " o "SEO," se define en la solicitud de los Estados Unidos Ser.

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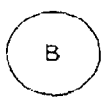
No. 11/349069 presentada el 9 de febrero de 2006 que es cedida a la cesionaria de la presente solicitud, el contenido de la cual se incorpora aquí por referencia y como se usa aquí se refiere al incremento de selectividad relativo de un compuesto basado en la orientación del SEM así como los sustituyentes adicionales en el anillo, ya sea solo o en combinación uno con otro. En particular, la SEO puede resultar de la orientación de la SEM a la derecha de la cual está unida, en relación con cualquier otro anillo y/o porción unida al mismo anillo. En una modalidad, la SEM en



está en la posición *orto* en relación con X_1 en la fórmula I. En otra modalidad específica, la SEM está en la posición *meta* en relación con X_1.

Por lo tanto, en algunas modalidades, R_2 es alquilo sustituido con 1, 2 ó 3 grupos halógeno. En algunas modalidades, R_2 es trifluorometilo. En otras modalidades adicionales, R_2 es metilo.

En algunas modalidades, R_3 está ausente. Por ejemplo, en el caso de compuestos en donde



es



,

R_3 se consideraría ausente, porque no hay sustituyentes en el anillo. En otras

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modalidades, R_3 es halógeno.

En algunas modalidades, R_4 es hidrógeno. En otras modalidades, R_4 es an alquilo, v.gr., un alquilo de C_1-C_4. Por ejemplo, en algunas modalidades, R_4 es metilo. En algunas modalidades, R_4 es hidroximetilo.

En algunas modalidades, R_5 es hidrógeno. En algunas modalidades, R_6 es hidrógeno. En algunas modalidades, R_5 es an alquilo, v.gr., un alquilo de C_1-C_4. En algunas modalidades, R_6 es an alquilo, v.gr., un alquilo de C_1-C_4.

En algunas modalidades, R_7 es OH. En otras modalidades, R_7 es CO_2H. En otras modalidades adicionales, R_7 es CO_2Me o CO_2Et. En otras modalidades, R_7 es CO_2-fenilo. En otras modalidades adicionales, R_7 es $-OP(O)_3H_2$. En otras modalidades, R_7 es $-CH_2P(O)_3H_2$.

En algunas modalidades,

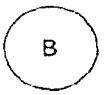


es fenilo. En otras modalidades,



es piridilo.

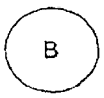
En algunas modalidades,



es



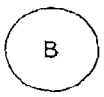
En algunas modalidades,



es



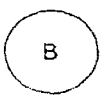
En algunas modalidades,



es



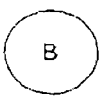
En algunas modalidades,



es



En algunas modalidades,

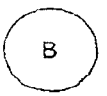


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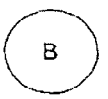
En algunas modalidades,



es



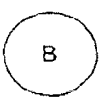
En algunas modalidades,



es



En algunas modalidades,

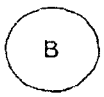


es



En algunas modalidades,

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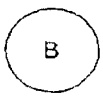


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En algunas modalidades,

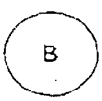


es



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En algunas modalidades,

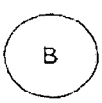


es



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En algunas modalidades,



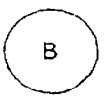
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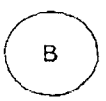
En algunas modalidades,



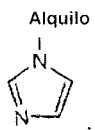
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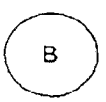
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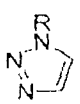
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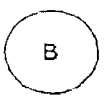
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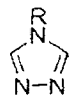
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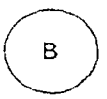
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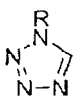
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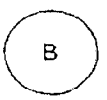
En algunas modalidades,



es



En algunas modalidades,

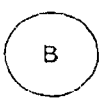


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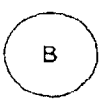


En cada una de las estructuras anteriores, R puede ser hidrógeno o alquilo.

En algunas modalidades,

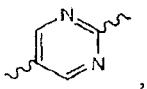


es piridilo. En algunas modalidades,



es

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en donde "~~~" indica los puntos de unión del anillo B al resto del compuesto.

En algunas modalidades, los compuestos de la invención son compuestos en donde

R_1 es hidrógeno, arilo, cicloalquilo o heteroarilo.

R_4 es hidrógeno, alquilo, alquileno-OH, arilo, -alquileno-O-alquilo, alquileno-CO_2H, o -alquileno-CO_2-alquilo;

R_5 y R_6 son cada uno independientemente hidrógeno o alquilo, o alquileno-OH;

R_7 se selecciona del grupo que consiste de OH, alquileno-OH, -CO_2H, alquileno- CO_2H, -alquileno-CO_2-alquilo, C(O)O-alquilo, -C(O)O-arilo, -CH_2=$CHCO_2H$, -CH_2=CHC(O)O-alquilo, -CH_2=CHC(O)O-arilo, -$OPO_2R_{p1}R_{p2}$, -$OPO_3R_{p1}R_{P2}$, -$CH_2PO_3R_{p1}R_{P2}$, -$OPO_2(S)R_{p1}R_{P2}$, o -C(Z')(Z")$PO_3R_{p1}R_{P2}$.

En algunas modalidades, los compuestos de la invención son compuestos en donde

R_1 es hidrógeno o arilo;

R_4 es hidrógeno o alquilo;

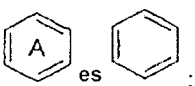
R_5 y R_6 son cada uno independientemente hidrógeno o alquilo, o alquileno-OH;

R_7 se selecciona del grupo que consiste de -OH, alquileno-OH, -CO_2H, alquileno- CO_2H, -alquileno-CO_2-alquilo, C(O)O-alquilo, -C(O)O-arilo,

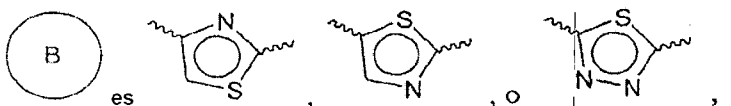
231

-CH_2=$CHCO_2H$, -CH_2=CHC(O)O-alquilo, -CH_2=CHC(O)O-arilo, -$OPO_2R_{p1}R_{p2}$, -$OPO_3R_{p1}R_{P2}$, -$CH_2PO_3R_{p1}R_{P2}$, -$OPO_2(S)R_{p1}R_{P2}$, y -C(Z')(Z'')$PO_3R_{p1}R_{P2}$.

En otras modalidades, los compuestos de la invención son compuestos en donde



;



R_1 es fenilo;

A es alquilo(C_1-C_{10})alquilo;

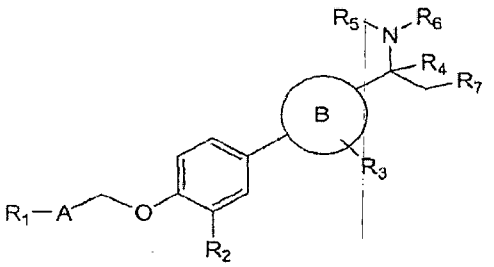
R' y R'' son hidrógeno; X, es O;

R_4 es hidrógeno, alquilo, o alquileno-OH;

R_5 y R_6 son cada uno independientemente hidrógeno, alquilo;

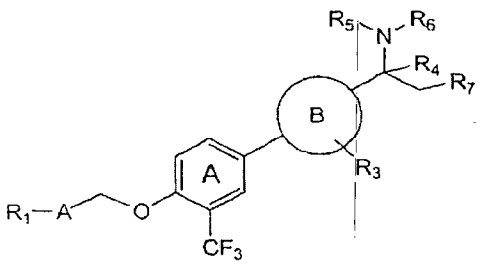
R_7 se selecciona del grupo que consiste de -OH, alquileno-OH, -CO_2H, alquileno- CO_2H, -C(O)O-alquilo, -C(O)O-arilo, -CH_2=$CHCO_2H$, -CH_2=CHC(O)O-alquilo, -CH_2=CHC(O)O- arilo, -$OPO_2R_{p1}R_{P2}$, -$OPO_3R_{p1}R_{P2}$, -$CH_2PO_3R_{p1}R_{P2}$, -$OPO_2(S)R_{p1}R_{P2}$, y - C(Z')(Z'')$PO_3R_{p1}R_{P2}$;

En algunas modalidades, los compuestos de la invención son compuestos de la fórmula I-1.



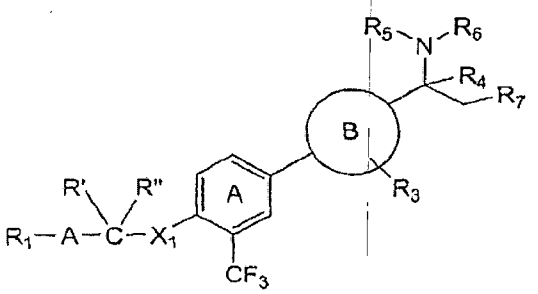
I-1

Otro grupo específico de compuestos de la invención son compuestos de la fórmula I-2.



I-2

En otros aspectos, la presente invención está dirigida a un compuesto de la fórmula II:



II

o una sal farmacéuticamente aceptable del mismo, en donde:

R_1 es hidrógeno, halógeno, ciano, alquilo, arilo, heteroarilo, cicloalquilo, heterocicloalquilo, aralquilo, heteroalquilo, -O-alquilo, -O-arilo, -O-heteroarilo, -S-alquilo, alquileno-O-alquilo, alquileno-CO_2H, alquileno-

CO_2alquilo, alquiloSO_2, alquilensulfonilo, alquileno-CO-amino, alquileno-CO-alquilamino, alquileno-CO-dialquilamino, alquileno-NH-CO_2H, alquileno-NH-CO_2alquilo -CO_2alquilo, -OH, -C(O)-alquilo, -C(O)O-alquilo, -$CONH_2$, - CO-alquilamino, -CO-dialquilamino, amino, alquilamino, o dialquilamino, cualquiera de los cuales puede ser opcionalmente sustituido en carbono con 1, 2 ó 3 grupos seleccionados de halógeno, alquilo, halogenoalquilo, -CF_3, -CN, -OH, o -O-alquilo;

A es alquileno (C_1-C_{20}), alquenileno (C_2-C_{20}), o alquinileno(C_2-C_{20}), cada uno de los cuales puede ser substituido en carbono con 1, 2 ó 3 grupos seleccionados de OH, CO_2H, CO_2alquilo, halógeno, amino, alquilamino, dialquilamino, -O-alquilo, alquileno-O-alquilo, alquileno-OH, o alquileno-CO_2H;

X_1 es un enlace o es CH_2, O, -CH_2O-, S, -S(O), -$S(O)_2$, -C(O)-, -C(O)O-, o NR_x, en donde R_x es H o alquilo(C_1-C_6);

R' y R" son cada uno independientemente hidrógeno, halógeno, alquilo opcionalmente sustituido en carbono con halógeno, alquilo, o tomados junto al carbono al cual están unidos forman C=O o un anillo de 3, 4, 5 ó 6 miembros, que contiene opcionalmente 1 ó 2 heteroátomos seleccionados de O NH, N-alquilo, SO o SO_2, cualquiera de los cuales puede ser opcionalmente sustituido en carbono con alquilo o halógeno;

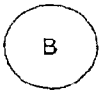
R_3 está ausente, es hidrógeno, halógeno, ciano, alquilo, arilo, heteroarilo, cicloalquilo, heterocicloalquilo, aralquilo, heteroalquilo, -O-alquilo, -O-arilo, -O-heteroarilo, aralcoxi, heteroaralcoxi, -S-alquilo, alquileno-O-alquilo,

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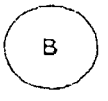
alquileno-CO_2H, alquileno-CO_2alquilo, alquiloSO_2. alquilensulfonilo, alquileno-CO-amino, alquileno-CO-alquilamino, alquileno-CO-dialquilamino, alquileno-NH-CO_2H, alquileno-NH-CO_2alquilo -CO_2alquilo, -OH, -C(O)-alquilo, -C(O)O-alquilo, -$CONH_2$, -CO-alquilamino, -CO-dialquilamino, amino, alquilamino y dialquilamino, cualquiera de los cuales puede ser opcionalmente sustituido en carbono con 1, 2 ó 3 grupos seleccionados de halógeno, alquilo, OH, o -O-alquilo;



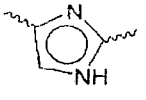
es fenilo o piridilo;



es arilo, heteroarilo, heterociclo o cicloalquilo, cualquiera de los cuales puede ser opcionalmente sustituido en carbono con 1, 2 ó 3 grupos seleccionados de halógeno, alquilo, O-alquilo, CO_2H, CO_2alquilo, halógeno, amino, alquilamino, dialquilamino, -O-alquilo, alquileno-O-alquilo, alquileno-OH, o alquileno-CO_2H, siempre que



no sea



;

R_4 es hidrógeno, ciano, alquilo, arilo, heteroarilo, alquileno-O-

alquilo, alquileno-OH, arilo, alquileno-O-alquilo, $-CO_2H$, $-CO_2$-alquilo, alquileno-CO_2H, o alquileno-CO_2-alquilo, alquileno-OC(O)R en donde R es hidrógeno o alquilo; cicloalquilo, heterocicloalquilo, alquileno-NH_2, alquileno-alquilamino, o alquileno-dialquilamino, cualquiera de los cuales puede ser opcionalmente sustituido en carbono con 1, 2 ó 3 grupos seleccionados de OH, CO_2H, CO_2alquilo, halógeno, amino, alquilamino, dialquilamino, -O-alquilo, alquileno-O-alquilo, alquileno-OH, o alquileno-CO_2H;

R_5 y R_6 se seleccionan cada uno independientemente del grupo que consiste de hidrógeno, alquilo, alquileno-OH, arilo, alquileno-O-alquilo, $-CO_2H$, CO_2-alquilo, alquileno- OC(O)alquilo, cicloalquilo, heterociclo, -C(O)-alquilo, -C(O)-arilo, C(O)-aralquilo, -C(O)-Oalquilo, -C(O)-Oarilo, -C(O)-Oaralquilo, alquileno-amino, alquileno-alquilamino, y alquileno-dialquilamino, cualquiera de los cuales puede ser opcionalmente sustituido en carbono con halógeno, alquilo, hidroxilo, CO_2H_5 CO_2alquilo o alcoxi; o;

R_5 y R_6, junto con el nitrógeno al cual están unidos, pueden formar un anillo saturado o insaturado de 3, 4, 5 ó 6 miembros, que contiene opcionalmente 1 ó 2 heteroátomos adicionales seleccionados de O, S, NH, o N-alquilo, y opcionalmente sustituido en carbono con halógeno, alquilo, hidroxilo o alcoxi;

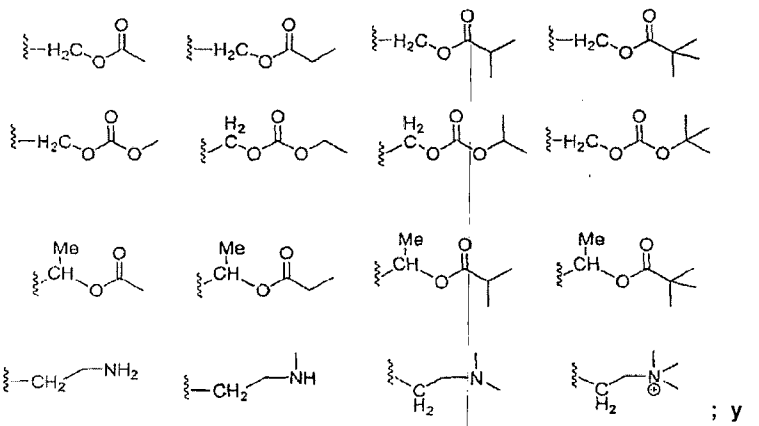
R_7 se selecciona del grupo que consiste de -OH, -O-alquilo, -alquileno-OH, $-CO_2H$, -alquileno-CO_2H, -C(O)O-alquilo, -alquileno-CO_2-alquilo, -C(O)O-arilo, $-CH_2$=$CHCO_2H$, $-CH_2$=CHC(O)O-alquilo, $-CH_2$=CHC(O)O-arilo, $-OPO_2R_{p1}R_{p2}$, $-OPO_3R_{p1}R_{p2}$, $-CH_2PO_3R_{p1}R_{p2}$,

$-OPO_2(S)R_{p1}R_{p2}$, y $-C(Z')(Z'')PO_3R_{p1}R_{p2}$, cualquiera de los cuales puede ser opcionalmente sustituido en carbono con halógeno, alquilo, hidroxilo, carboxi, o alcoxi; y en donde

Z' es hidroxilo o halógeno;

Z'' es H o halógeno;

R_{p1} y R_{p2} son cada uno independientemente hidrógeno, alquilo de C_1-C_6, arilo, o uno de los siguientes grupos:



; y

Y es heterociclo o heteroarilo.

En algunas modalidades, R_1 es arilo o heteroarilo, opcionalmente sustituido con 1, 2 ó 3 grupos seleccionados de halógeno, alquilo, halogenoalquilo, -arilo, $-CF_3$, -CN, -OH, o -O-alquilo. En algunas modalidades, R_1 es arilo, v.gr., fenilo, opcionalmente sustituido con 1 ó 2 grupos seleccionados de $-CF_3$, -CN, -OMe, -Cl o -F. En algunas modalidades, R_1 es heteroarilo, v.gr., tiofeno o benzotiofeno, opcionalmente sustituido con 1 ó 2 grupos seleccionados de fenilo, $-CF_3$, -CN, -OMe, -Cl o -F. En algunas modalidades, R_1 es hidrógeno. En otras modalidades, R_1 es fenilo. En algunas

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modalidades, R_1 es piridilo. En otras modalidades, R_1 es tiofenilo. En otras modalidades adicionales, R_1 es ciclohexilo. En algunas modalidades, R_1 es ciclopentilo.

En algunas modalidades, A es un alquileno de C_1-C_{10}. En algunas modalidades, A es un alquileno de C_1-C_{10} ramificado. En otras modalidades, A es n-octilo. En otras modalidades, A es n-heptilo. En otras modalidades, A es n-hexilo. En algunas modalidades, A es un alquileno de C_1-C_5. En algunas modalidades, A es n-pentilo. En otras modalidades, A es n-butilo. En otras modalidades adicionales, A es n-propilo. En otras modalidades, A es etilo. En otras modalidades adicionales, A es metilo.

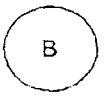
En algunas modalidades, X_1 es O. En otras modalidades, X_1 es S. En otras modalidades adicionales, X_1 es SO_2. En algunas modalidades, X_1 es CH_2. En otras modalidades, X_1 es C=O. En otras modalidades adicionales, CH_2O, en donde ya sea el oxígeno o el carbono puede ser unido a



En algunas modalidades, R' es hidrógeno. En otras modalidades, R' es metilo. En algunas modalidades, R" es hidrógeno. En otras modalidades, R" es metilo. En algunas modalidades, R' y R" tomados junto con el carbono al cual están unidos, es C=O, con la condición de que sólo uno de X_1 o R' y R" tomados junto con el carbono pueden formar C=O.

En algunas modalidades, R_3 está ausente. Por ejemplo, en el caso de compuestos en donde

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es



R_3 se consideraría ausente, poque no hay sustituyentes en el anillo. En otras modalidades, R_3 es halógeno.

En algunas modalidades, R_4 es hidrógeno. En otras modalidades, R_4 es an alquilo, v.gr., un alquilo de C_1-C_4. Por ejemplo, en algunas modalidades, R_4 es metilo. En algunas modalidades, R_4 es hidroximetilo.

En algunas modalidades, R_5 es hidrógeno. En algunas modalidades, R_6 es hidrógeno. En algunas modalidades, R_5 es an alquilo, v.gr., un alquilo de C_1-C_4. En algunas modalidades, R_6 es an alquilo, v.gr., un alquilo de C_1-C_4.

En algunas modalidades, R_7 es OH. En otras modalidades, R_7 es CO_2H. En otras modalidades adicionales, R_7 es CO_2Me o CO_2Et. En otras modalidades, R_7 es CO_2-fenilo. En otras modalidades adicionales, R_7 es $-OP(O)_3H_2$. En otras modalidades, R_7 es $-CH_2P(O)_3H_2$.

En algunas modalidades,

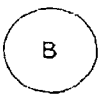


es fenilo. En otras modalidades,



es piridilo.

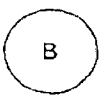
En algunas modalidades,



es



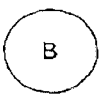
En algunas modalidades,



es



En algunas modalidades,

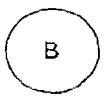


es



En algunas modalidades,

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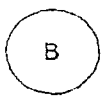


es



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En algunas modalidades,

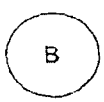


es



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En algunas modalidades,

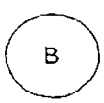


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En algunas modalidades,



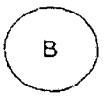
es



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En algunas modalidades,

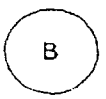


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En algunas modalidades,

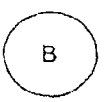


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En algunas modalidades,

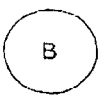


es



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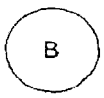
En algunas modalidades,



es



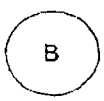
En algunas modalidades,



es



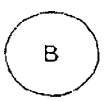
En algunas modalidades,



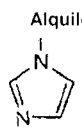
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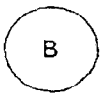
En algunas modalidades,



es



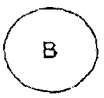
En algunas modalidades,



es



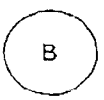
En algunas modalidades,



es



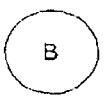
En algunas modalidades,



es



En algunas modalidades,



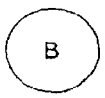
es



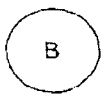
244

En cada una de las estructuras anteriores, R puede ser hidrógeno o alquilo.

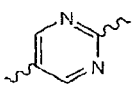
En algunas modalidades,



es piridilo. En algunas modalidades,



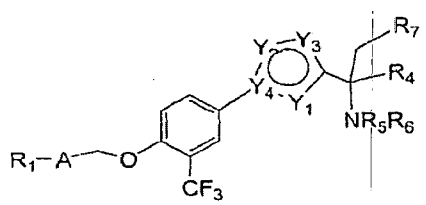
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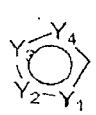
en donde "~~~" indica los puntos de unión del anillo B al resto del compuesto.

En algunas modalidades, los compuestos de la fórmula II son compuestos de la fórmula II-1.



II-1

en donde



es un anillo de heteroarilo que contiene hasta cuatro heteroátomos seleccionados de N, O, o S, opcionalmente sustituidos en carbono con

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halógeno o alquilo, en donde

Y_1 es CH, N, S, o O;

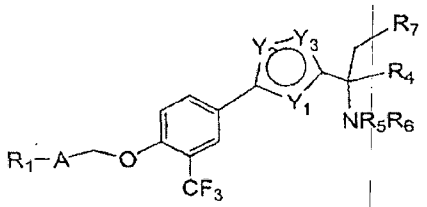
Y_2 y Y_3 son cada uno independientemente CH; N; O, o S; siempre que cuando



contiene un N-H, ese hidrógeno puede ser reemplazado por alquilo; y

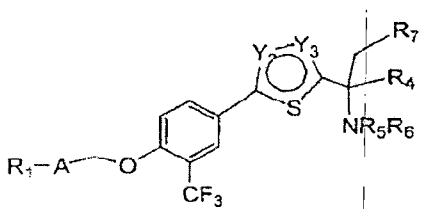
Y_4 es C o N.

En algunas modalidades, los compuestos de la fórmula II son compuestos de la fórmula II-2.



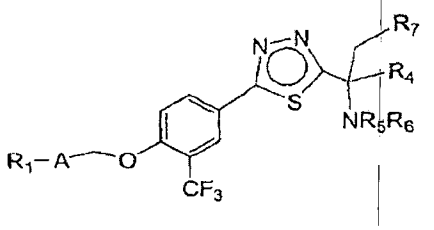
II-2

En otras modalidades, compuestos de la fórmula II son compuestos de la fórmula II-3.



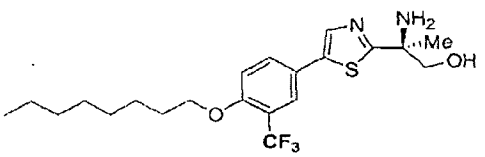
II-3

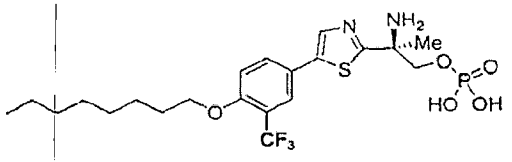
En algunas modalidades, los compuestos de la fórmula II son compuestos de la fórmula II-4.

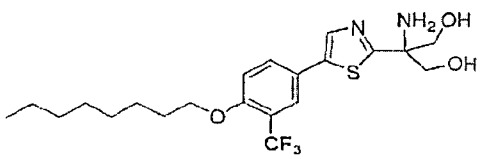


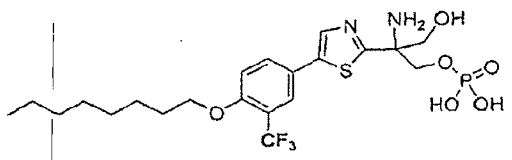
II-4

En algunas modalidades, los compuestos de la presente invención incluyen compuestos listados en el siguiente cuadro:

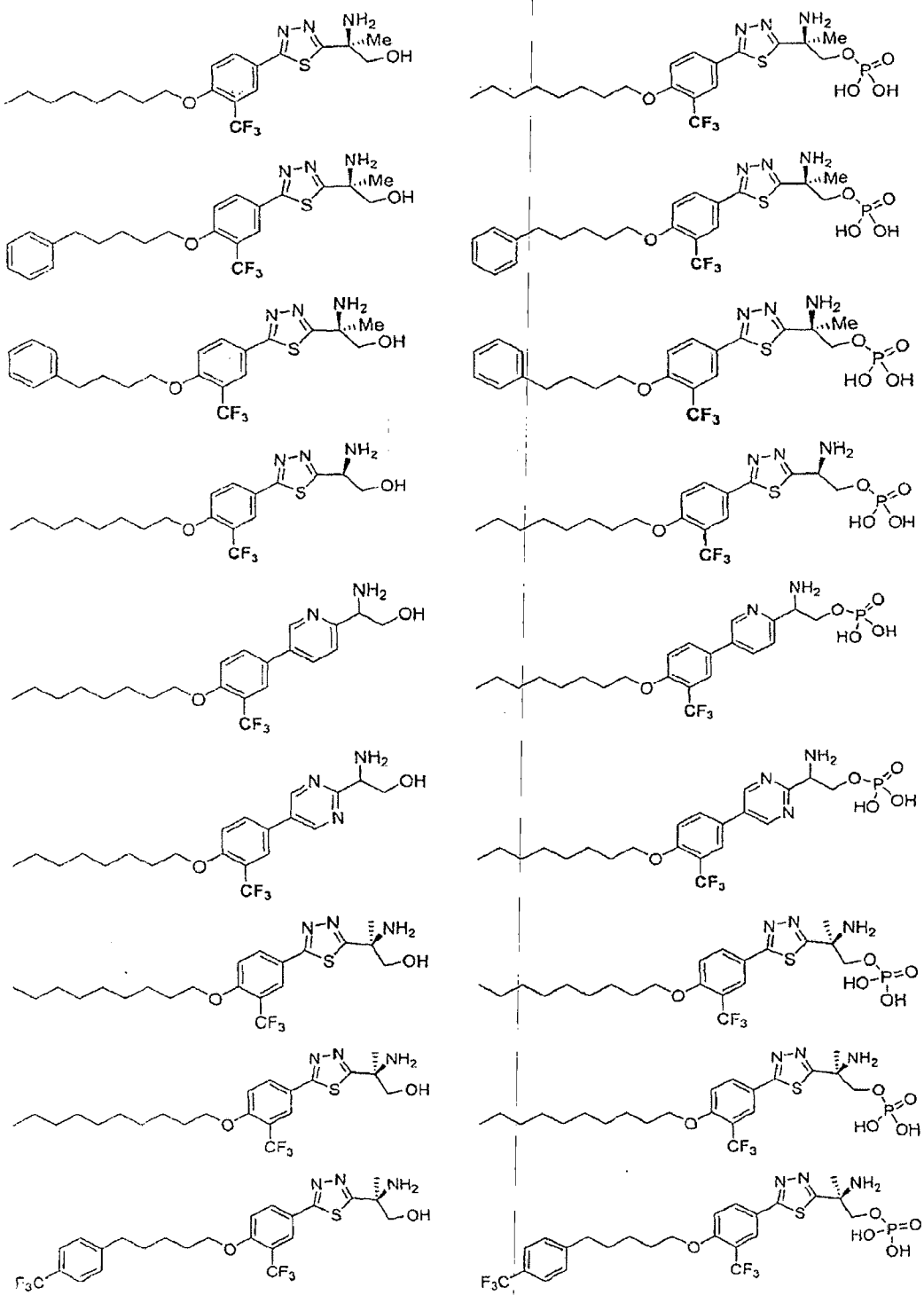


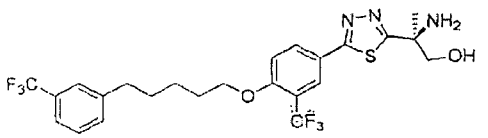


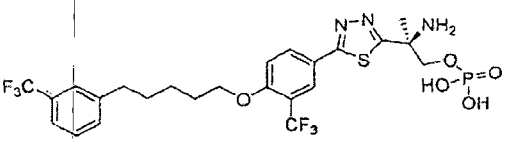


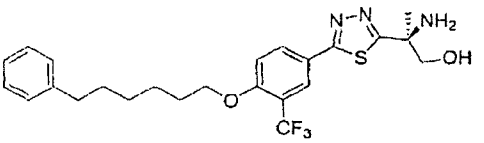


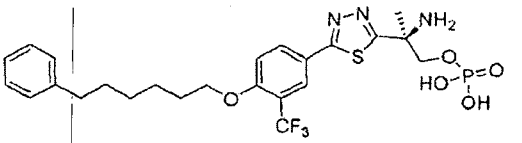
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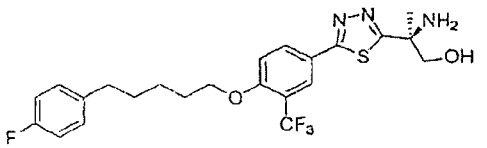


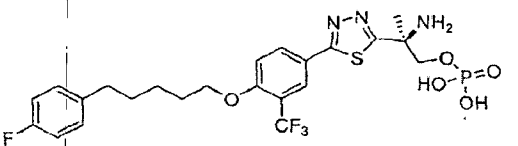


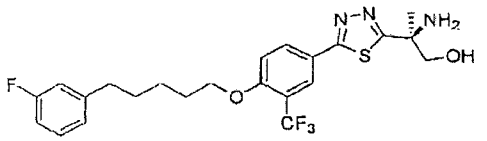


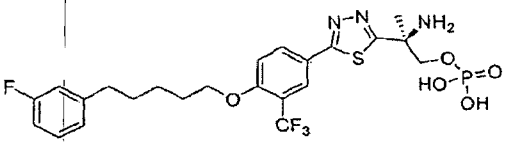


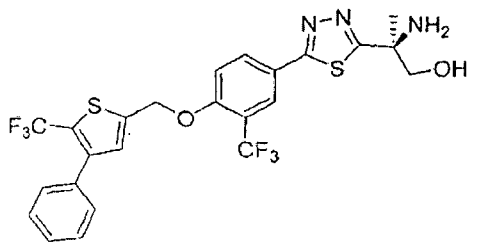


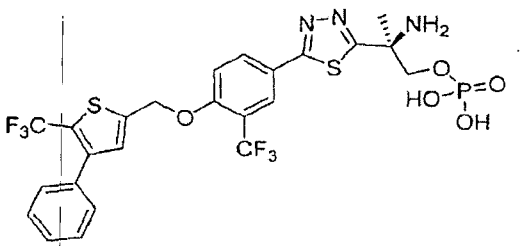


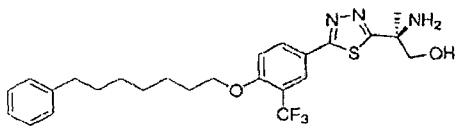


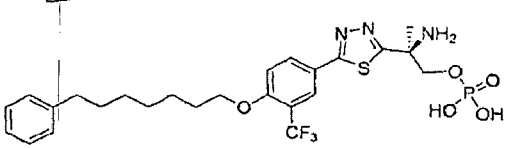


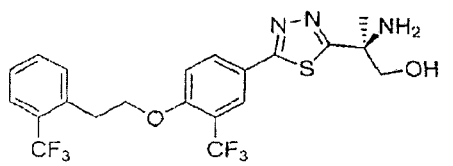


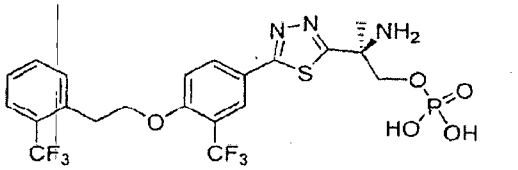


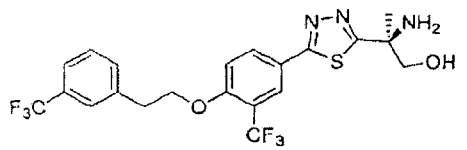


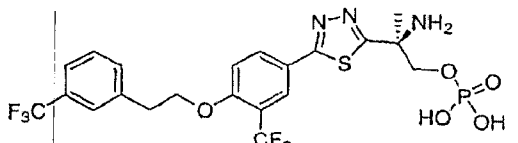


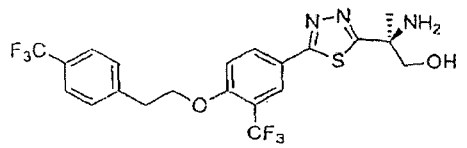


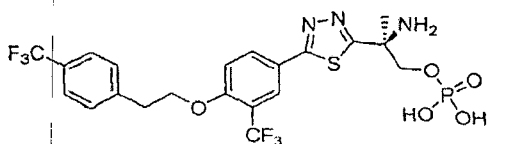


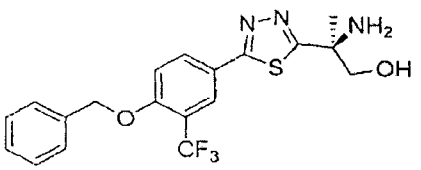
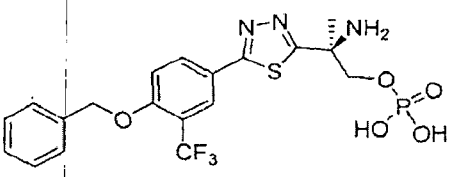
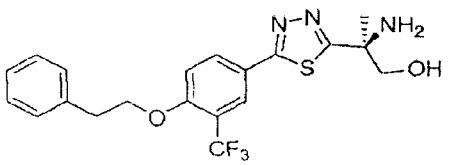
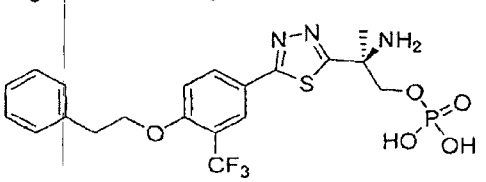
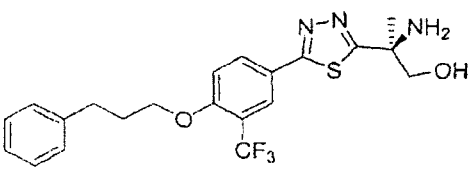
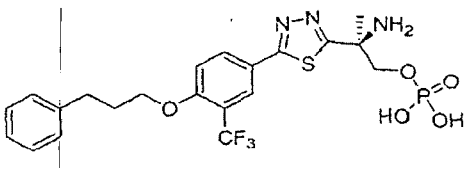
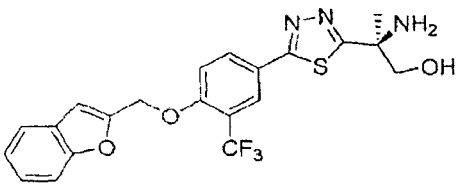
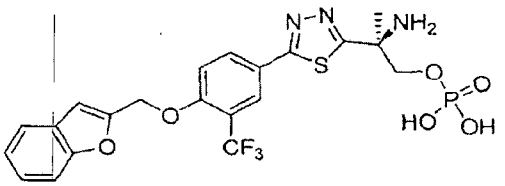
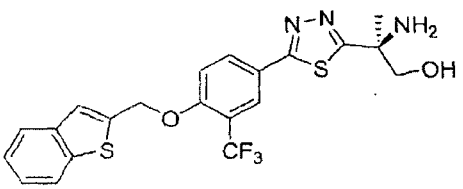
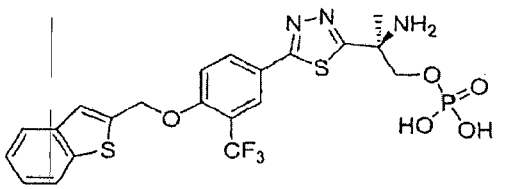
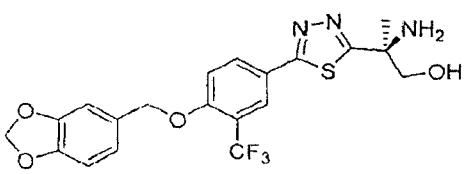
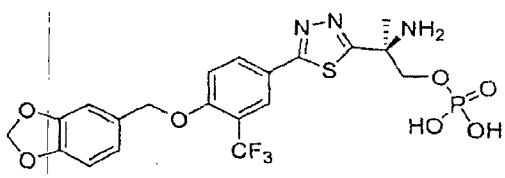
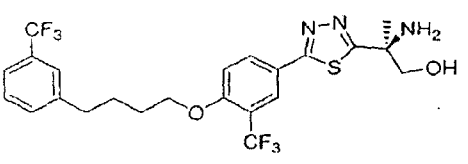
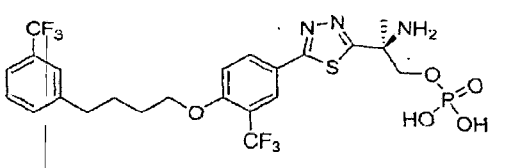
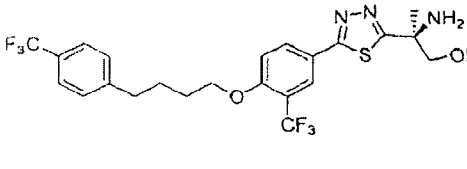
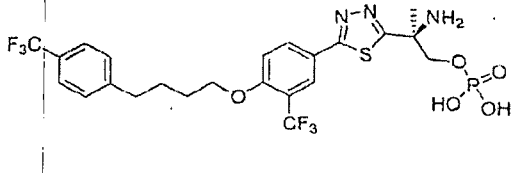




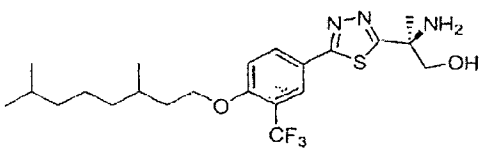
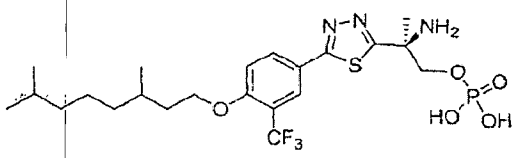
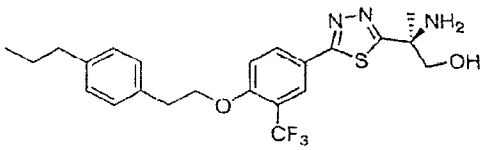
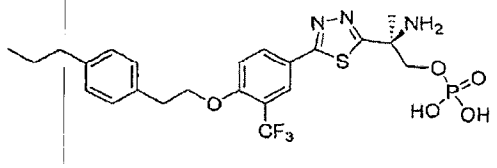
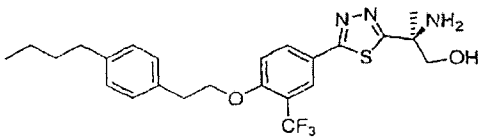
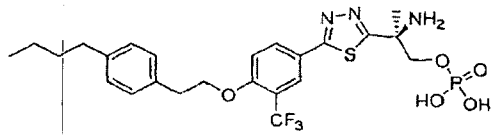
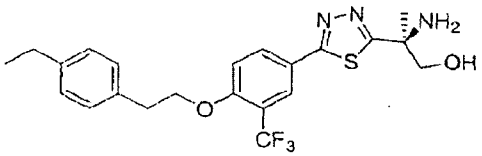
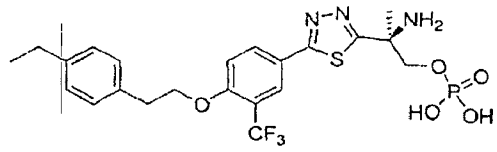
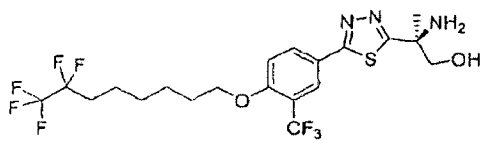
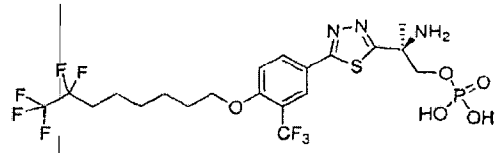
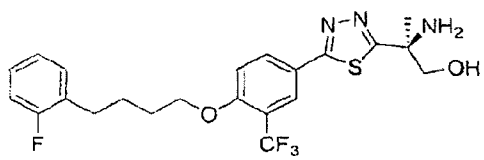
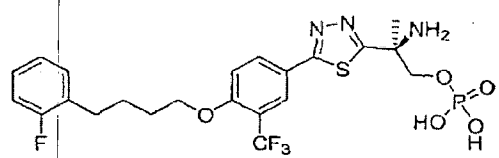
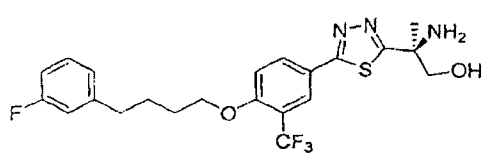
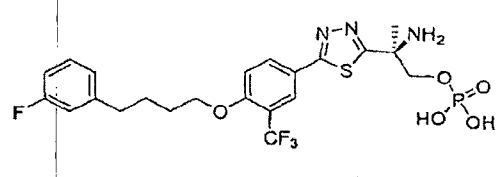
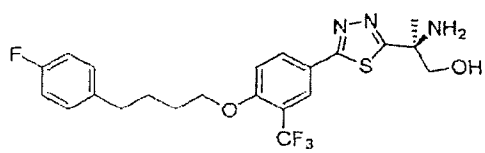
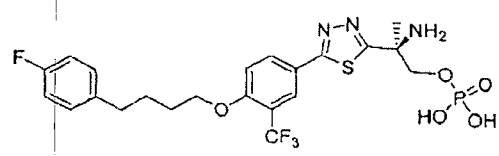
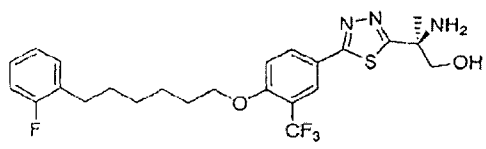
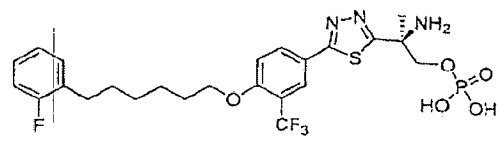




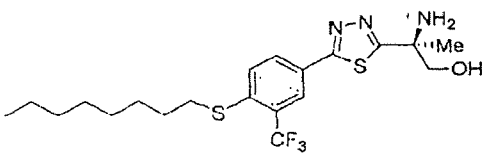


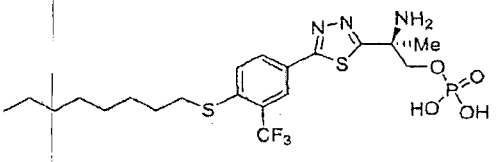

















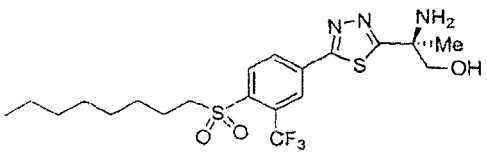
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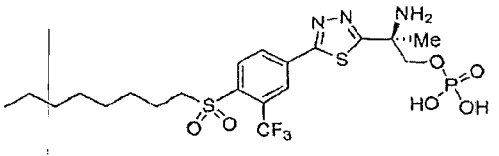



















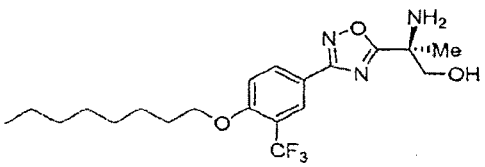
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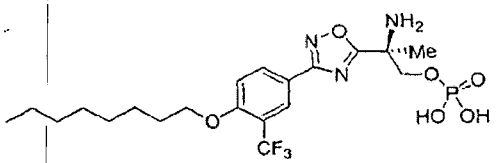


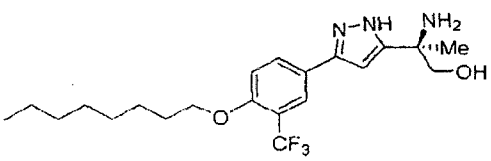


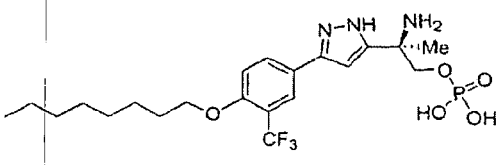


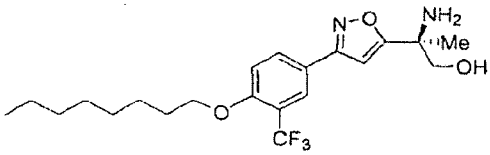


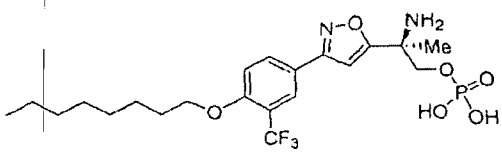


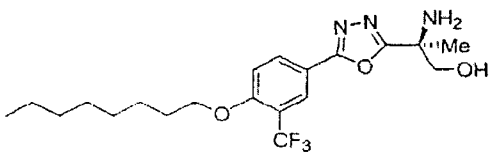


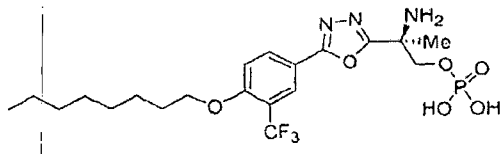


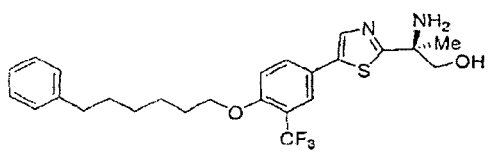


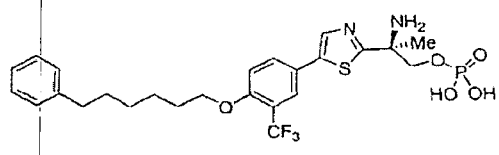


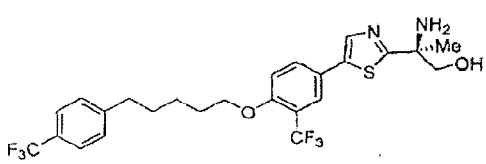


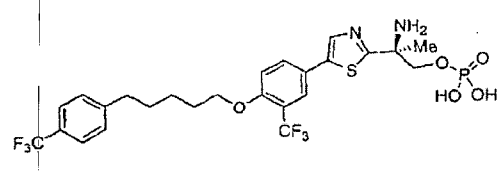


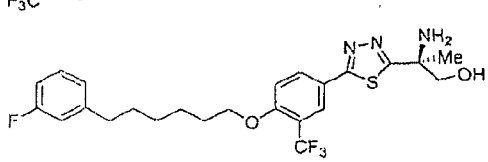


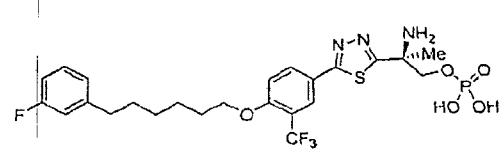


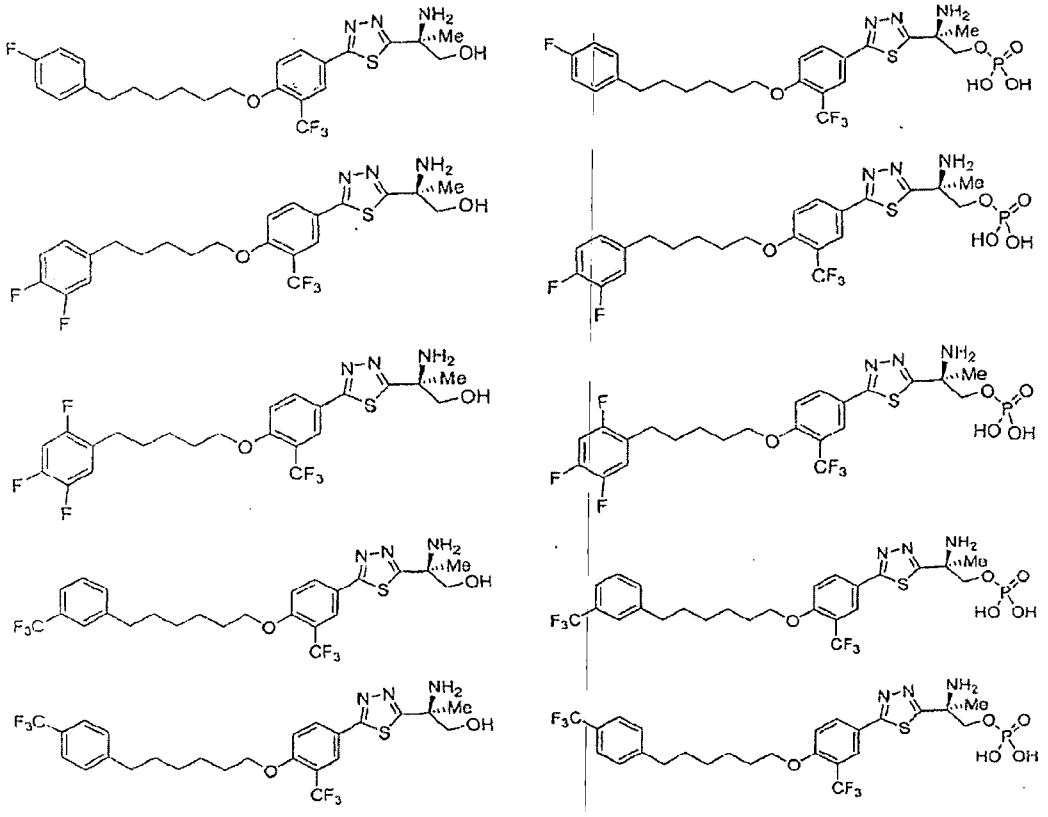






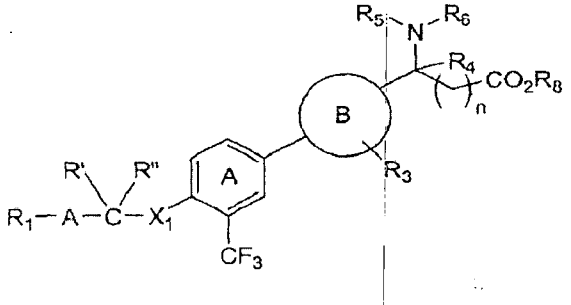






así como sales farmacéuticamente aceptables, derivados de fosfato, simuladores de fosfato, o análogos de precursor de fosfato de los mismos.

En algunos aspectos, la presente invención está dirigida a un compuesto de la fórmula III:



III

o una sal farmacéuticamente aceptable del mismo, en donde:

R_1 es hidrógeno, halógeno, ciano, alquilo, arilo, heteroarilo, cicloalquilo, heterocicloalquilo, aralquilo, heteroalquilo, -O-alquilo, -O-arilo, -O-heteroarilo, -S-alquilo, alquileno-O-alquilo, alquileno-CO_2H, alquileno-CO_2alquilo, alquiloSO_2, alquilensulfonilo, alquileno-CO-amino, alquileno-CO-alquilamino, alquileno-CO-dialquilamino, alquileno-NH-CO_2H, alquileno-NH-CO_2alquilo -CO_2alquilo, -OH, -C(O)-alquilo, -C(O)O-alquilo, -$CONH_2$, -CO-alquilamino, -CO-dialquilamino, amino, alquilamino, o dialquilamino, cualquiera de los cuales puede ser opcionalmente sustituido en carbono con 1, 2 ó 3 grupos seleccionados de halógeno, alquilo, halogenoalquilo, -CF_3, -CN, -OH, o -O-alquilo;

A es alquileno(C_1-C_{20}), alquenileno(C_2-C_{20}), o alquinileno(C_2-C_{20}), cada uno de los cuales puede ser opcionalmente sustituido en carbono con 1, 2 ó 3 grupos seleccionados de OH, CO_2H, CO_2alquilo, halógeno, amino, alquilamino, dialquilamino, -O-alquilo, alquileno-O-alquilo, alquileno-OH, o alquileno-CO_2H;

X_1 es un enlace o es CH_2, O, -CH_2O-, S, -S(O), -$S(O)_2$, -C(O)-, -C(O)O-, OrNR_x, en donde R_x es H o alquilo(C_1-C_6);

R' y R" son cada uno independientemente hidrógeno, halógeno, alquilo opcionalmente sustituido en carbono con halógeno, alquilo, o tomados junto al carbono al cual están unidos forman C=O o un anillo de 3, 4, 5 ó 6 miembros, que contiene opcionalmente 1 ó 2 heteroátomos seleccionados de O NH, N-alquilo, SO, o SO_2, cualquiera de los cuales puede ser

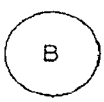
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opcionalmente sustituido en carbono con alquilo o halógeno;

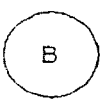
R_3 está ausente, hidrógeno, halógeno, ciano, alquilo, arilo, heteroarilo, cicloalquilo, heterocicloalquilo, aralquilo, heteroalquilo, -O-alquilo, -O-arilo, -O-heteroarilo, aralcoxi, heteroaralcoxi, -S-alquilo, alquileno-O-alquilo, alquileno-CO_2H, alquileno-CO_2alquilo, alquiloSO_2, alquilensulfonilo, alquileno-CO-amino, alquileno-CO-alquilamino, alquileno-CO-dialquilamino, alquileno-NH-CO_2H, alquileno-NH-CO_2alquilo -CO_2alquilo, -OH, -C(O)-alquilo, -C(O)O-alquilo, -$CONH_2$, -CO-alquilamino, -CO-dialquilamino, amino, alquilamino y dialquilamino, cualquiera de los cuales puede ser opcionalmente sustituido en carbono con 1, 2 ó 3 grupos seleccionados de halógeno, alquilo, OH, o -O-alquilo;



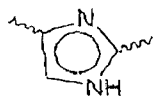
es fenilo o piridilo;



es arilo, heteroarilo, heterociclo, o cicloalquilo, cualquiera de los cuales puede ser opcionalmente sustituido en carbono con 1, 2 ó 3 grupos seleccionados de halógeno, alquilo, O-alquilo, CO_2H, CO_2alquilo, halógeno, amino; alquilamino, dialquilamino. -O-alquilo, alquileno-O-alquilo, alquileno-OH, o alquileno-CO_2H, siempre que



no sea



;

R_4 es hidrógeno, ciano, alquilo, arilo, heteroarilo, alquileno-O-alquilo, alquileno-OH, arilo, alquileno-O-alquilo, $-CO_2H$, $-CO_2$-alquilo, alquileno-CO_2H, o alquileno-CO_2-alquilo, alquileno-OC(O)R en donde R es hidrógeno o alquilo; cicloalquilo, heterocicloalquilo, alquileno-NH_2, alquileno-alquilamino, o alquileno-dialquilarnino, cualquiera de los cuales puede ser opcionalmente sustituido en carbono con 1, 2 ó 3 grupos seleccionados de OH, CO_2H, CO_2alquilo, halógeno, amino, alquilamino, dialquilo amino, -O-alquilo, alquileno-O-alquilo, alquileno-OH, o alquileno-CO_2H;

R_5 y R_6 se seleccionan cada uno independientemente del grupo que consiste de hidrógeno, alquilo, alquileno-OH, arilo, alquileno-O-alquilo, $-CO_2H$, CO_2-alquilo, alquileno- OC(O)alquilo, cicloalquilo, heterociclo, -C(O)-alquilo, -C(O)-arilo, C(O)-aralquilo, -C(O)- Oalquilo, -C(O)-Oarilo, -C(O)-Oaralquilo, alquileno-amino, alquileno-alquilamino, y alquileno-dialquilamino, cualquiera de los cuales puede ser opcionalmente sustituido en carbono con halógeno, alquilo, hidroxilo, CO_2H, CO_2alquilo o alcoxi; o

R_5 y R_6, junto con el nitrógeno al cual están unidos, pueden formar un anillo saturado o insaturado de 3, 4, 5 ó 6 miembros, que contiene opcionalmente 1 ó 2 heteroátomos adicionales seleccionados de O, S, NH, o N-alquilo, y opcionalmente sustituido en carbono con halógeno, alquilo, hidroxilo o alcoxi;

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R_8 es hidrógeno, alquilo o arilo; y

n es 0, 1 ó 2.

En algunas modalidades, R_1 es arilo o heteroarilo, opcionalmente sustituido con 1, 2 ó 3 grupos seleccionados de halógeno, alquilo, halogenoalquilo, -arilo, $-CF_3$, -CN, -OH, o -O-alquilo. En algunas modalidades, R_1 es arilo, v.gr., fenilo, opcionalmente sustituido con 1 ó 2 grupos seleccionados de $-CF_3$, -CN, -OMe, -Cl o -F. En algunas modalidades, R_1 es heteroarilo, v.gr., tiofeno o benzotiofeno, opcionalmente sustituido con 1 ó 2 grupos seleccionados de fenilo, $-CF_3$, -CN, -OMe, -Cl o -F. En algunas modalidades, R_1 es hidrógeno. En otras modalidades, R_1 es fenilo. En algunas modalidades, R_1 es piridilo. En otras modalidades, R_1 es tiofenilo. En otras modalidades adicionales, R_1 es ciclohexilo. En algunas modalidades, R_1 es ciclopentilo.

En algunas modalidades, A es un alquileno de C_1-C_{10}. En algunas modalidades, A es un alquileno de C_1-C_{10} ramificado. En otras modalidades, A es n-octilo. En otras modalidades, A es n-heptilo. En otras modalidades, A es n-hexilo. En algunas modalidades, A es un alquileno de C_1-C_5. En algunas modalidades, A es n-pentilo. En otras modalidades, A es n-butilo. En otras modalidades adicionales, A es n-propilo. En otras modalidades, A es etilo. En otras modalidades adicionales, A es metilo.

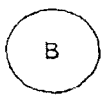
En algunas modalidades, X_1 es O. En otras modalidades, X_1 es S. En otras modalidades adicionales, X_1 es SO_2. En algunas modalidades, X_1 es CH_2. En otras modalidades, X_1 es C=O. En otras modalidades adicionales,

CH_2O, en donde ya sea el oxígeno o el carbono puede ser unido a



En algunas modalidades, R' es hidrógeno. En otras modalidades, R' es metilo. En algunas modalidades, R" es hidrógeno. En otras modalidades, R" es metilo. En algunas modalidades, R' y R" tomados junto con el carbono al cual están unidos, es C=O, con la condición de que sólo uno de X_1 o R' y R" tomados junto con el carbono pueden formar C=O.

En algunas modalidades, R_3 está ausente. Por ejemplo, en el caso de compuestos en donde



es



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R_3 se consideraría ausente, poque no hay sustituyentes en el anillo. En otras modalidades, R_3 es halógeno.

En algunas modalidades, R_4 es hidrógeno. En otras modalidades, R_4 es an alquilo, v.gr., un alquilo de C_1-C_4. Por ejemplo, en algunas modalidades, R_4 es metilo. En algunas modalidades, R_4 es hidroximetilo.

En algunas modalidades, R_5 es hidrógeno. En algunas modalidades, R_6 es hidrógeno. En algunas modalidades, R_5 es an alquilo,

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v.gr., un alquilo de C_1-C_4. En algunas modalidades, R_6 es an alquilo, v.gr., un alquilo de C_1-C_4.

En algunas modalidades,

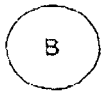


es fenilo. En otras modalidades,



es piridilo.

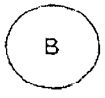
En algunas modalidades,



es



En algunas modalidades,

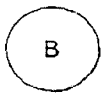


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En algunas modalidades,

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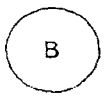


es



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En algunas modalidades,

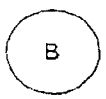


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En algunas modalidades,



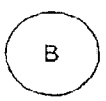
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es



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En algunas modalidades,



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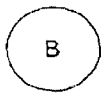
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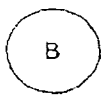
En algunas modalidades,



es



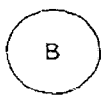
En algunas modalidades,



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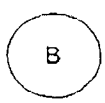
En algunas modalidades,



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En algunas modalidades,

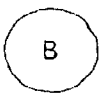


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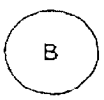
En algunas modalidades,



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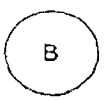
En algunas modalidades,



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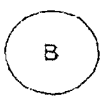
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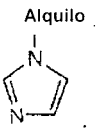


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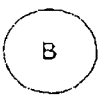


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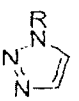
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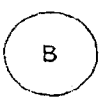
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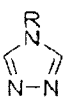
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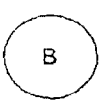
En algunas modalidades,



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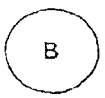
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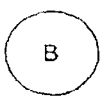


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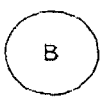


En cada una de las estructuras anteriores, R puede ser hidrógeno o alquilo.

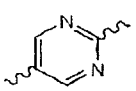
En algunas modalidades,



es piridilo. En algunas modalidades,

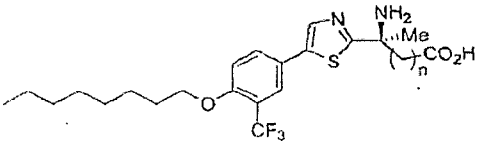
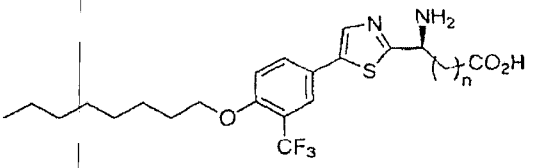
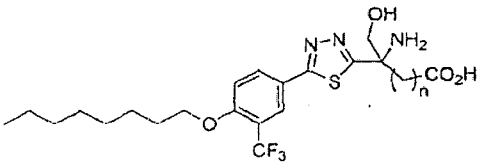
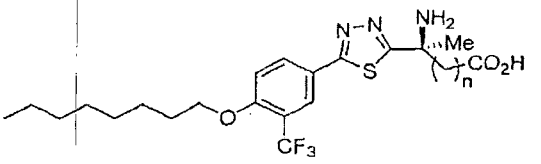
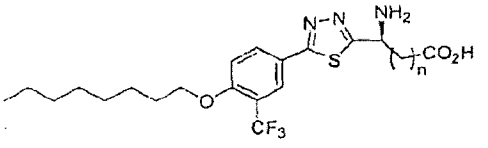
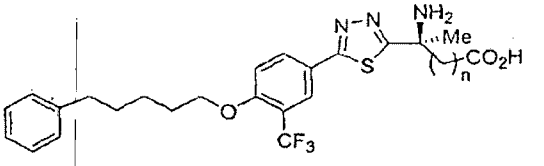
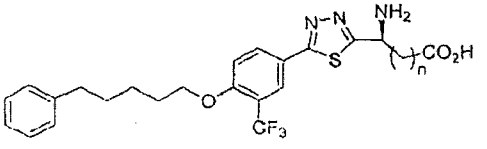
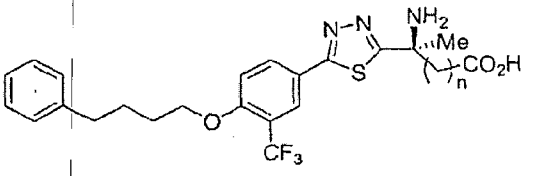
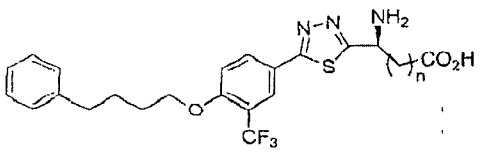
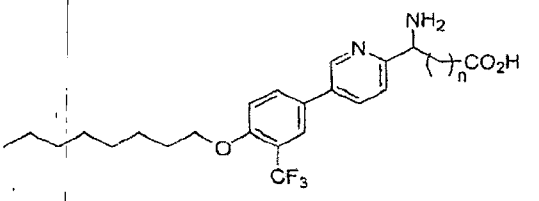
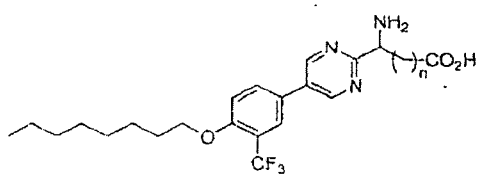


es



en donde "∿∿∿" indica los puntos de unión del anillo B al resto del compuesto.

En algunas modalidades, los compuestos de la presente invención incluyen los compuestos listados en el siguiente cuadro:

en donde n para cada compuesto es 0, 1 ó 2, así como sales farmacéuticamente aceptables, derivados de fosfato, simuladores de fosfato, o análogos de precursor de fosfato de los mismos.

Los compuestos de la presente invención incluyen los siguientes compuestos:

(*S*)-2-Amino-2-(5-(4-(octiloxi)-3-(trifluorometil)fenil)tiazol-2-

il)propan-1-ol;

2-Amino-2-(5-(4-(octiloxi)-3-(trifluorometil)fenil)tiazol-2-il)propano-1,3-diol;

(*S*)-2-Amino-2-(5-(4-(octiloxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol;

(*S*)-2-Amino-2-(5-(4-(5-fenilpentiloxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol;

(*S*)-2-Amino-2-(5-(4-(4-fenilbutoxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol;

(*S*)-2-Amino-2-(5-(4-(noniloxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol;

(*S*)-2-Amino-2-(5-(4-(deciloxi)-3(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol;

(*S*)-2-Ammo-2-(5-(3-(trifluorometil)-4-(5-(4-(trifluorometil)fenil)-pentiloxi)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol;

(*S*)-2-Amino-2-(5-(3-(trifluorometil)-4-(5-(3-(trifluorometil)fenil)pentiloxi)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol;

(*S*)-2-Amino-2-(5-(4-(6-fenilhexiloxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol;

(*S*)-2-Amino-2-(5-(4-(5-(4-fluorofenil)pentiloxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol;

(*S*)-2-Amino-2-(5-(4-(5-(3-fluorofenil)pentiloxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol;

(*S*)-2-Amino-2-(5-(4-((4-fenil-5-(trifluorometil)tiofen-2-il)metoxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol;

(*S*)-2-Amino-2-(5-(4-(7-fenilheptiloxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol;

(*S*)-2-Amino-2-(5-(3-(trifluorometil)-4-(2-(trifluorometil)fenetoxi)fenil)-1,3,4- tiadiazol-2-il)propan-1-ol;

(*S*)-2-Amino-2-(5-(3-(txifluorometil)-4-(3-(trifluorometil)fenetoxi)fenil)-1,3,4- tiadiazol-2-il)propan-1-ol;

(*S*)-2-Amino-2-(5-(3-(trifluorometil)-4-(4-(trifluorometil)fenetoxi)fenil)-1,3,4- tiadiazol-2-il)propan-1-ol;

(*S*)-2-Amino-2-(5-(4-(benziloxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol;

(*S*)-2-Amino-2-(5-(4-fenetoxi-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol;

(*S*)-2-Amino-2-(5-(4-(3-fenilpropoxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol;

(*S*)-2-Amino-2-(5-(4-(benzofuran-2-ilmetoxi)-3-(trifluorometil)fenil)-1,3,4- tiadiazol-2-il)propan-1-ol;

(*S*)-2-Amino-2-(5-(4-(benzo[*b*]tiofen-2-ilmetoxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol;

(*S*)-2-Amino-2-(5-(4-(benzo[*d*][1,3]dioxol-5-ilmetoxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol;

(*S*)-2-Amino-2-(5-(3-(trifluorometil)-4-(4-(3-

(trifluorometil)fenil)butoxi)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol;

(*S*)-2-Amino-2-(5-(3-(trifluorometil)-4-(4-(4-(trifluorometil)fenil)butoxi)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol;

(2*S*)-2-Amino-2-(5-(4-(3,7-dimetiloctiloxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol;

(*S*)-2-Amino-2-(5-(4-(4-propilfenetoxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol;

(*S*)-2-Amino-2-(5-(4-(4-butilfenetoxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol;

(*S*)-2-Amino-2-(5-(4-(4-etilfenetoxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol;

(*S*)-2-Amino-2-(5-(4-(7,7,8,8,8-pentafluorooctiloxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol;

(*S*)-2-Amino-2-(5-(4-(4-(2-fluorofenil)butoxi)-3-(trifluorometil)fenil)-1,3,4- tiadiazol-2-il)propan-1-ol;

(*S*)-2-Amino-2-(5-(4-(4-(3-fluorofenil)butoxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol;

(*S*)-2-Amino-2-(5-(4-(4-(4-fluorofenil)butoxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol;

(*S*)-2-Amino-2-(5-(4-(6-(2-fluorofenil)hexiloxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol;

(*S*)-2-Amino-2-(5-(4-(6-(3-fluorofenil)hexiloxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol;

(*S*)-2-Amino-2-(5-(4-(6-(4-fluorofenil)hexiloxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol;

(*S*)-2-Amino-2-(5-(4-(5-(3,4-difluorofenil)pentiloxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol;

(*S*)-2-Amino-2-(5-(3-(trifluorometil)-4-(5-(2,4,5-trifluorofenil)pentiloxi)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol;

(*S*)-2-Amino-2-(5-(3-(trifluorometil)-4-(6-(3-(trifluorometil)fenil)hexiloxi)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol;

(*S*)-2-Amino-2-(5-(3-(trifluorometil)-4-(6-(4-(trifluorometil)fenil)hexiloxi)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol;

(*S*)-2-Amino-2-(5-(4-(octiltio)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol;

(*S*)-2-Amino-2-(5-(4-(octilsulfonil)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol;

(*S*)-2-Amino-2-(3-(4-(octiloxi)-3-(trifluorometil)fenil)-1,2,4-oxadiazol-5-il)propan-1-ol;

(*R*)-2-Amino-2-(5-(4-(octiloxi)-3-(trifluorometil)fenil)-1H-pirazol-3-il)propan-1-ol;

(*S*)-2-Amino-2-(3-(4-(octiloxi)-3-(trifluorometil)fenil)isoxazol-5-il)propan-1-ol;

(*S*)-2-Amino-2-(5-(4-(octiloxi)-3-(trifluorometil)fenil)-1,3,4-oxadiazol-2-il)propan-1-ol;

(*S*)-2-Amino-2-(5-(4-(6-fenilhexiloxi)-3-(trifluorometil)fenil)tiazol-2-

il)propan-1-ol;

(*S*)-2-Amino-2-(5-(3-(trifluorometil)-4-(5-(4-(trifluorometil)fenil)pentiloxi)fenil)tiazol-2-il)propan-1-ol;

y sales farmacéuticamente aceptables, derivados de fosfato, simuladores de fosfato, y análogos de precursor de fosfato de los mismos.

Los compuestos de la presente invención además incluyen los siguientes compuestos:

Fosfato diácido de (*S*)-2-amino-2-(5-(4-(octiloxi)-3-(trifluorometil)fenil)tiazol-2-il)propilo;

Fosfato diácido de (*S*)-2-amino-2-(5-(4-(octiloxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propilo;

Fosfato diácido de (*S*)-2-amino-2-(5-(4-(5-fenilpentiloxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propilo;

Fosfato diácido de (*S*)-2-amino-2-(5-(4-(4-fenilbutoxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propilo;

Fosfato diácido de (*S*)-2-amino-2-(5-(4-(octiltio)-3-(trifluorometil)fenil)-1$_5$3,4-tiadiazol-2-il)propil dihidrógeno fosfato;

Fosfato diácido de (*S*)-2-amino-2-(5-(4-(noniloxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propilo;

Fosfato diácido de (*S*)-2-amino-2-(5-(3-(trifluorometil)-4-(5-(3-(trifluorometil)fenil)pentiloxi)fenil)-1,3,4-tiadiazol-2-il)propilo;

Fosfato diácido de (*S*)-2-amino-2-(5-(3-(trifluorometil)-4-(5-(4-(trifluorometil)fenil)pentiloxi)fenil)-1,3,4-tiadiazol-2-il)propilo;

Fosfato diácido de (*S*)-2-amino-2-(5-(4-((4-fenil-5-(trifluorometil)tiofen-2-il)metoxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propilo;

Fosfato diácido de (*S*)-2-amino-2-(5-(4-(6-fenilhexiloxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propilo;

Fosfato diácido de (*S*)-2-amino-2-(5-(4-(5-(3-fluorofenil)pentiloxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propilo;

Fosfato diácido de (*S*)-2-amino-2-(5-(4-(5-(4-fluorofenil)pentiloxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propilo;

Fosfato diácido de (*S*)-2-amino-2-(5-(3-(trifluorometil)-4-(4-(3-(trifluorometil)fenil)butoxi)fenil)-1,3,4-tiadiazol-2-il)propilo;

Fosfato diácido de (*S*)-2-amino-2-(5-(4-(4-(4-fluorofenil)butoxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propilo;

Fosfato diácido de (*S*)-2-amino-2-(5-(4-(6-(3-fluorofenil)hexiloxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propilo;

Fosfato diácido de (*S*)-2-amino-2-(5-(4-(6-(4-fluorofenil)hexiloxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propilo;

Fosfato diácido de (*S*)-2-Amino-2-(5-(4-(5-(3,4-difluorofenil)pentiloxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propilo;

Fosfato diácido de (*S*)-2-amino-2-(5-(3-(trifluorometil)-4-(5-(2,4,5-trifluorofenil)pentiloxi)fenil)-1,3,4-tiadiazol-2-il)propilo;

Fosfato diácido de (*S*)-2-amino-2-(3-(4-(octiloxi)-3-(trifluorometil)fenil)-1,2,4-oxadiazol-5-il)propilo;

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Fosfato diácido de (*R*)-2-amino-2-(3-(4-(octiloxi)-3-(trifluorometil)fenil)-1H-pirazol-5-il)propilo;

Fosfato diácido de (*S*)-2-amino-2-(3-(4-(octiloxi)-3-(trifluorometil)fenil)isoxazol-5-il)propilo;

Fosfato diácido de (*S*)-2-amino-2-(5-(4-(octiloxi)-3-(trifluorometil)fenil)-1,3,4-oxadiazol-2-il)propilo;

Fosfato diácido de (*S*)-2-amino-2-(5-(4-(6-fenilhexiloxi)-3-(trifluorometil)fenil)tiazol-2-il)propilo; y

Fosfato diácido de (*S*)-2-amino-2-(5-(3-(trifluorometil)-4-(5-(4-(trifluorometil)fenil)pentiloxi)fenil)tiazol-2-il)propilo.

Actividad biológica de los compuestos de la Invención

Prueba de linfopenia

Algunos de los compuestos descritos aquí se evaluaron para la capacidad para inducir linfopenia en ratones. Ratones C57B1/6 machos se dividieron en dos grupos de tres. Un grupo de control recibió el vehículo de 3% de BSA únicamente. Los otros dos grupos recibieron una sola dosis ya sea de una dosis especificada de compuesto de prueba en vehículo administrado por vía oral (PO) y por vía intravenosa (IV). Después de 6 horas, los ratones fueron anestesiados con isoflurano y aproximadamente 250 μL de sangre se removió del seno retroorbital y se recolectó en un microcontenedor de EDTA, se mezcló con un anticoagulante y se colocó sobre una mesa inclinada hasta que se completó el análisis de conteo de sangre (CBC). La

administración oral (10 mg/k) de esos compuestos indujo linfopenia incrementada versus el vehículo.

Una dosis oral de 10 mg/kg de (*S*)-2-amino-2-(5-(4-(octiloxi)-3-(trifluorometil)fenil)tiazol-2-il)propan-1-ol produjo una linfopenia de 75% en esta prueba.

Una dosis de 10 mg/kg de (*S*)-2-amino-2-(5-(4-(octiloxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol produjo una linfopenia de 77% en esta prueba.

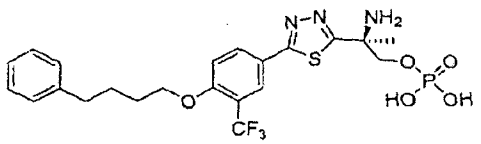
Unión a receptores S1P-1 o S1P-3

En ciertas modalidades, los compuestos de la invención fueron selectivos para el receptor S1P-1 en comparación con uno o más de los receptores S1P. Por ejemplo, un conjunto de compuestos incluye compuestos que selectivos para el receptor S1P-1 en relación con el receptor S1P-3. Los compuestos selectivos para el receptor S1P-1 pueden ser agonistas del receptor S1P-1, agonistas significativamente más débiles de uno o más de otros receptores y/o antagonistas de uno o más de otros receptores. Un compuesto es "selectivo" para el receptor S1P-1 en relación con un segundo receptor, si la CE_{50} del compuesto para el segundo receptor es por lo menos dos veces mayor que la CE_{50} para el receptor S1P-1. La CE_{50} de un compuesto se determina usando la prueba de unión a ^{35}S-GTPγS, como se describe en WO 03/061567, cuyo contenido se incorpora aquí por referencia en su totalidad. Además o alternativamente, un compuesto es "selectivo" para

el receptor S1P-1 en relación con un segundo receptor, si la CI_{50} del compuesto para el segundo receptor es por lo menos dos veces mayor que la CI_{50} para el receptor S1P-1. La CI_{50} de un compuesto se determina usando la prueba de unión a [^{33}P]1-fosfato de esfingosina, como se describe en Davis, M.D. et al., Sphingosine 1-Phosphate Analogs as Receptor Antagonists. *J. Biol. Chem.* (2005) 280:9833-9841, cuyo contenido se incorpora aquí por referencia en su totalidad.

Los términos "agonista" o agonista de receptor S1P-1" como se usa aquí incluye los compuestos descritos aquí que se unen a y/o agonizan el receptor S1P-1. En una modalidad, los agonistas de receptor S1P tienen una CI_{50} para el receptor S1P-1 de aproximadamente 100 nM – 0.25 nM, aproximadamente 50 nM – 0.25 nM, aproximadamente 25 nM – 0.5 nM, aproximadamente 100 nM o menor, aproximadamente 75 nM o menor, aproximadamente 50 nM o menor, aproximadamente 40 nM o menor, aproximadamente 30 nM o menor, aproximadamente 20 nM o menor, aproximadamente 10 nM o menor, aproximadamente 5 nM o menor, aproximadamente 1 nM o menor, aproximadamente 0.5 nM o menor, o aproximadamente 0.25 nM o menor. La CI_{50} de los compuestos para el receptor S1P-1 se puede medir usando las pruebas de unión descritas en el ejemplo 13 o aquellas descritas en WO 03/061567. Los compuestos de la invención generalmente tienen una CI_{50} en el intervalo de 100 pM (picomolar) a 100 M.

Por ejemplo,



tuvo una CI_{50} 3.23nM.

Se pretende que los intervalos intermedios para los valores mencionados anteriormente también sean parte de esta invención. Por ejemplo, se pretende que sean incluidos los intervalos que usan una combinación de cualquiera de los valores mencionados anteriormente como límites superior y/o inferior.

En una modalidad adicional, el agonista de receptor S1P tiene un valor de CI_{50} para el receptor S1P-3 de aproximadamente 10 nM – 10,000 nM, aproximadamente 100 nM – 5000 nM, aproximadamente 10 nM – 3000 nM, aproximadamente 10 nM o mayor, aproximadamente 20 nM o mayor, aproximadamente 40 nM o mayor, aproximadamente 50 nM o mayor, aproximadamente 75 nM o mayor, o aproximadamente 100 nM o mayor. En otra modalidad, el compuesto S1P de la invención se une al receptor S1P-3 con una CI_{50} de 1000 nM o mayor, 2000 nM o mayor, 3000 nM o mayor, 5000 nM o mayor, 10,000 nM o mayor. La CI_{50} para el receptor S1P-3 se pueden medir usando las pruebas de unión descritas aquí o aquellas descritas en el documento WO 03/061567.

Además, se entenderá que los intervalos intermedios a los valores mencionados anteriormente también se pretende que sea parte de esta invención. Por ejemplo, se pretende que sean incluidos los intervalos que

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usan una combinación de cualquiera de los valores mencionados anteriormente como límites superior y/o inferior.

En otra modalidad, los agonistas de receptor S1P descritos aquí tienen un valor de CI_{50} para el receptor S1P-1 que es aproximadamente 5 veces más bajo, aproximadamente 10 veces más bajo, aproximadamente 20 veces más bajo, aproximadamente 50 veces más bajo, aproximadamente 10 veces más bajo, aproximadamente 200 veces más bajo, aproximadamente 500 veces más bajo o aproximadamente 1000 veces más bajo que el valor de CI_{50} del receptor S1P-3.

Se pretende que los intervalos intermedios a los valores mencionados anteriormente también sean parte de esta invención. Por ejemplo, se pretende que sean incluidos los intervalos que usan una combinación de cualquiera de los valores mencionados anteriormente como límites superior y/o inferior.

La capacidad de algunos compuestos descritos aquí para unirse al receptor S1P-1 o S1P-3 también se probó como sigue.

Para la preparación de membrana, el ADN de plásmido fue transfectado a células HEK 293 T usando el protocolo de transfección de FuGENE 6 (públicamente disponible de Roche). En breve, monocapas subconfluentes de células HEK 293 T fueron transfectadas con la mezcla de ADN que contenía FuGENE 6 (usando una relación de 1:3). Las placas que contenían las células después se colocaron en una incubadora de cultivo de tejido (5% CO_2, 37°C). Las células se cosecharon 48 horas después de la

adición del ADN raspando en regulador de PH de HME (en mM: 20 HEPES, 5 $MgCl_2$, 1 EDTA, pH 7.4, 1mM PMSF) que contenía 10% de sacarosa sobre hielo, y se alteró usando un homogenizador de Dounce. Después de la centrifugación a 800 x g, el sobrenadante se diluyó con HME sin sacarosa y se centrifugó a 17,000 x g durante 1 hora. Esta pastilla de membrana cruda se resuspendió en HME con sacarosa, se formaron alícuotas con ella y se congeló instantáneamente por inmersión en nitrógeno líquido. Las membranas se almacenaron a -70°C. La concentración de proteína se determinó espectroscópicamente por el método de proteína de Bradford.

Para la prueba de unión, [^{33}P]1-fosfato de esfingosina (obtenido de American Radiolabeled Chemicals, Inc) se añadió a membranas en 200µl de placas de 96 pozos con concentraciones de prueba de 2.5 mM [^{33}P]1-fosfato de esfingosina, 4 mg/ml BSA, 50 mM HEPES, pH 7.5, 100 mM NaCl, 5 mM MgCl2, y 5 µg de proteína. La unión se realizó durante 60 minutos a temperatura ambiente con mezclado suave y se determinó recolectando las membranas sobre placas de filtro de GF/B. Después de secarse las placas de filtro durante 10 minutos, 50 µl de Microscint 40 se añadió a cada pozo y el radionúclido unido al filtro se midió en un contador Packard Top Count. La unión no específica se definió como la cantidad de radioactividad que quedó en presencia de exceso de S1P no marcado.

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Protocolo de prueba de GTPgS

Preparación de membrana

Para preparaciones de membrana se realizaron todos los pasos a 4°C. Células de hepatoma de rata que expresaron establemente el receptor S1P1 humano o células de leucemia basofílica de rata (RBL) que expresaron receptores S1P3 humanos establemente se hicieron crecer a 80% de confluencia antes de ser cosechadas en solución salina regulada en su pH con 10 ml Phospho (PBS) y centrifugadas a 1200 rpm durante 5 minutos. Después de la remoción del sobrenadante, la pastilla se resuspendió y las células se homogeneizaron dentro de un mezclador de Waring de vidrio para 2 ráfagas de 15 segundos en 200 mililitros de regulador de pH (50mM HEPES, 1 mM de leupeptin, 25 ug/ml de bacitracin, 1 mM de EDTA, 1 mM de PMSF, 2 uM de pepstatin A). El mezclador se colocó dentro de hielo durante 5 minutos después de cada ráfaga y 10-40 minutos después de la ráfaga final para dejar que la espuma se diS1Para. El material después se hizo girar a 500 g durante 20 minutos y el sobrenadante se hizo girar durante 36 minutos a 48,000 g. La pastilla se resuspendió en el mismo regulador de pH que antes pero sin PMSF y pepstatin A. El material después se forzó a través de una aguja de 0.6 mm, llenada hasta el volumen requerido (usualmente x4 el volumen de la pastilla de células original), se formaron alícuotas con el mismo y se almacenó bajo congelamiento a -80°C.

Prueba de GTPgS

Hepatoma de rata S1P1 humano o membrana RBL que expresan S1P3 (1.5 ug/pozo) se adhirieron a esferas de SPA revestidas con WGA (0.125 mg/pozo) en un regulador de pH de prueba (HEPES 20 mM, $MgCl_2$ 3 mM, NaCl 100 mM y pH ajustado a 7.4 usando KIH 5M, GDP 10 uM FAC y saponina 80 ug/pozo FAC también se añadió.

Después de 30 minutos de preacoplamiento a 4°C la suspensión de esferas y membrana se suministró a una placa de pozos Greiner de polipropileno de LV384 (ul/pozo), que contenía 0.1ul de compuesto de prueba o S1P. 5 ul/pozo [^{35}S]-GTP□S (concentración final de radioligando de 0.5 nM) hecha en regulador de pH de prueba se añadió después a las placas. El cóctel de prueba final (10.1 ul) se centrifugó a 1000 rpm durante 5 minutos y después se leyó inmediatamente en un Viewlux.

Todos los compuestos de prueba se disolvieron en DMSO a una concentración de 10 mM y se prepararon en 100% de DMSO usando un paso de dilución de 1 en 4 para proveer curvas de respuesta a la dosis de 11 puntos. Las diluciones fueron transferidas a las placas de prueba asegurándose que la concentración de DMSO fuera constante a través de la placa para todas las pruebas.

Todos los datos se normalizaron a la media de pozos de control 16 alto y 16 bajo en cada placa. Después se aplicó un ajuste de prueba de cuatro parámetros.

La sal de ácido trifluoroacético de fosfato diácido de (*S*)-2-amino-

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2-(5-(4-(octiloxi)-3-(trifluorometil)fenil)tiazol-2-il)propilo tuvo una pCE50 de 8.5 en la prueba de S1P1 y pCE50 de 6.1 en la prueba de S1P3.

La sal de trifluoroacético de fosfato diácido de (*S*)-2-amino-2-(5-(4-(octiloxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propilo tuvo una pCE50 de 9.2 en la prueba de S1P1 y pCE50 de 6.1 en la prueba de S1P3.

Métodos para usar compuestos de la invención

Se ha determinado que los compuestos de la invención son útiles en el tratamiento de trastornos asociados con sfingosina 1-fosfato. Por consiguiente, en una modalidad, la invención se refiere a un método para tratar a un sujeto que padece un trastorno asociado con 1-fosfato de esfingosina, que comprende administrar a un sujeto una cantidad efectiva de un compuesto de la invención; es decir, un compuesto de la fórmula I o compuestos de otra manera descritos aquí, de tal manera que el sujeto es tratado para un trastorno asociado con 1-fosfato de esfingosina.

El término "trastorno asociado con 1-fosfato de esfingosina" incluye trastornos, enfermedades o condiciones que están asociados con o son causados por una falta de regulación en la función y/o señalización de receptor S1P o función de ligando de receptor S1P. El término también incluye enfermedades, trastornos o condiciones que se pueden tratar administrando a un sujeto una cantidad efectiva de un agonista de receptor de 1-fosfato de esfingosina. Dichos receptores incluyen trastornos que están asociados con una respuesta inmune apropiada y condiciones asociadas con una respuesta

inmune sobrereactiva, v.gr., enfermedades autoinmunes. En algunas modalidades, trastornos asociados con 1-fosfato de esfingosina incluyen enfermedades autoinmunes. En otras modalidades, trastornos relacionados con 1-fosfato de esfingosina incluyen inflamación. En otras modalidades, trastornos asociados con 1-fosfato de esfingosina incluyen rechazo de trasplante. En otras modalidades más, los trastornos asociados con 1-fosfato de esfingosina incluyen síndrome de insuficiencia respiratoria en adultos (ARDS). En otras modalidades, los trastornos asociados con 1-fosfato de esfingosina incluyen asma. En otras modalidades más, los trastornos asociados con 1-fosfato de esfingosina incluyen cualquier combinación de los trastornos listados aquí.

"Tratamiento", o "tratar" como se usa aquí, se define como la aplicación o administración de un agente terapéutico tal como un compuesto de la fórmula I a un sujeto que tiene un trastorno asociado con 1-fosfato de esfingosina como se describe aquí, con el propósito de curar, cicatrizar, aliviar, retardar, sanar, alterar, remediar, mitigar, mejorar o afectar la enfermedad o trastorno, o síntomas de la enfermedad o trastorno. El término "tratamiento" o "tratar" también se usa aquí en el contexto de administrar agentes profilácticamente.

En algunas modalidades, la eficacia de los compuestos de la presente invención se puede medir comparando un valor, nivel, aspecto, característica, propiedad, etc., con un "control adecuado". Un "control adecuado" es cualquier control o estándar conocido por un experto en la

técnica útil para propósitos de comparación, etc. En una modalidad, un "control adecuado" es un valor, nivel, aspecto, característica, propiedad, etc., determinado antes de administrar una composición de la presente invención. Por ejemplo, la respuesta inmune, etc., se puede determinar antes de introducir un compuesto de la invención en una célula o sujeto. En otra modalidad, un "control adecuado" es un valor, nivel, aspecto, característica, propiedad, etc., determinado en una célula u organismo, v.gr., una célula u organismo de control o normal, que presenta, por ejemplo, rasgos normales. En otra modalidad más, un "control adecuado" es un valor, nivel, aspecto, característica, propiedad, etc., predefinido. Por ejemplo, un "control adecuado" puede ser un nivel predefinido de unión a un receptor S1P especificado.

Una modalidad adicional de la invención se refiere a un método para tratar a un sujeto que padece un trastorno asociado con 1-fosfato de esfingosina, que comprende administrar a un sujeto un compuesto, de tal manera que el sujeto sea tratado para un trastorno asociado con 1-fosfato de esfingosina por un compuesto de la invención; es decir, un compuesto de la fórmula I o compuestos de otra manera descritos aquí.

La presente invención también está dirigida a un método para tratar selectivamente un trastorno asociado con 1-fosfato de esfingosina, que comprende administrar a un sujeto una cantidad efectiva de un compuesto de la invención, v.gr., compuesto de cualquiera de las fórmulas I-VIII o compuestos de otra manera descritos aquí, de tal manera que el sujeto sea selectivamente tratado para trastorno asociado con 1-fosfato de esfingosina.

En ciertas modalidades, el trastorno asociado con 1-fosfato de esfingosina es un trastorno asociado con 1-fosfato de esfingosina-(1). En una modalidad particular, el trastorno asociado con 1-fosfato de esfingosina-(1) es selectivamente tratado en comparación con un trastorno asociado con 1-fosfato de esfingosina-(3).

Otra modalidad de la invención es un método para tratar selectivamente un trastorno asociado con 1-fosfato de esfingosina, que comprende administrar a un sujeto un compuesto, de tal manera que el sujeto sea tratado selectivamente para un trastorno asociado con 1-fosfato de esfingosina por un compuesto de la invención, v.gr., compuestos de cualquiera de las fórmulas I-VIII o compuestos de otra manera descritos aquí. En ciertas modalidades, el trastorno asociado con 1-fosfato de esfingosina es un trastorno asociado con 1-fosfato de esfingosina-(1). En una modalidad particular, el trastorno asociado con 1-fosfato de esfingosina-(1) es tratado selectivamente en comparación con un trastorno asociado con 1-fosfato de esfingosina-(3).

En otra modalidad, la presente invención provee un método para tratar una condición asociada con un sistema inmunológico activado. Dichas enfermedades o trastornos incluyen esclerosis múltiple así como rechazo de órganos, tejidos o células trasplantados; enfermedades de injerto-*versus*-hospedero ocasionadas por trasplante; síndromes autoinmunes incluyendo artritis reumatoide; lupus eritematoso sistémico; síndrome de antifosfolípidos; tiroiditis de Hashimoto; tiroiditis linfocítica; miastenia grave; diabetes de tipo I;

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uveítis; episcleritis; escleritis; enfermedad de Kawasaki, uveo-retinitis; uveítis posterior; uveítis asociada con enfermedad de Behcet; síndrome de uveomeningitis; encefalomelitis alérgica; vasculopatía de aloinjerto crónica; enfermedades autoinmunes postinfecciosas incluyendo fiebre reumática y glomerulonefritis postinfecciosa; enfermedades de la piel inflamatorias e hiperploriferativas; soriasis; artritis psoriática; dermatitis atópica; miopatía; miositis; osteomielitis; dermatitis de contacto; dermatitis eczematosa; dermatitis ceborréica; liquen plano; pénfigo; pénfigo ampuloso; epidermólisis ampollosa; urticaria; angioedema; vasculitis; eritema; eosinofilia cutáneo; acné; escleroderma; alopecia areata; queratoconjutivitis; conjuntivitis vernal; queratitis; queratitis herpética; distrofia epitelial de la córnea; leucoma de la córnea; pénfigo ocular; úlcera de Mooren; queratitis ulcerativa; escleritis; oftalmopatía de Grave; síndrome de Vogt-Koyanagi-Harada; sarcoidosis; alergias en polen; enfermedad de vías aéreas obstructivas reversible; asma bronquial; asma alérgica; asma intrínseca; asma extrínseca; asma por polvo; asma crónica o por invertebrados; asma final e hiperrespuestas de vías aéreas; bronquiolitis; bronquitis; endometriosis; orquitis, úlceras gástricas; enfermedades intestinales isquémicas; enfermedades intestinales inflamatorias; enterocolitis necrosante; lesiones intestinales asociadas con quemaduras térmicas; enfermedades celiacas; proctitis; gastroenteritis eosinofílica; mastocitosis; enfermedad de Crohn; colitis ulcerativa; daño vascular causado por enfermedades isquémicas y trombosis; aterosclerosis; corazón graso; miocarditis; infarto cardiaco; síndrome aortitis; caquexia debido

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a enfermedad viral; trombosis vascular; migraña; rinitis; eczema; nefritis intersticial; neuropatía inducida por IgA; síndrome de Goodpasture; síndrome hemolítico-urémico; neuropatía diabética; glomeruloesclerosis; glomerulonefritis; nefritis tubulointersticial; cistitis intersticial; miositis múltiple; síndrome de Guillain-Barre; enfermedad de Meniere; polineuritis; neuritis múltiple; mielitis; mononeuritis; radiculopatía; hipertiroidismo; enfermedad de Basedow; tirotoxicosis; aplasia de glóbulos rojos pura; anemia aplástica; anemia hipoplástica; púrpura trombocitopénica idiopática; anemia hemolítica autoimune; trombocitopenia autoinmune; agranulocitosis; anemia perniciosa; anemia megaloblástica; aneritroplasia; osteoporosis; pulmón fibroide; neumonía intersticial idiopática; dermatomiositis; leucoderma vulgar; ictiosis vulgar; sensibilidad fotoalérgica; linfoma de células T cutáneas; poliarteritis nodosa; corea de Huntington; corea de Sydenham; miocardosis; miocarditis; escleroderma; granuloma de Wegener; síndrome de Sjogren; adiposis; fascitis eosinofílica; lesiones de las encías, periodoncio, hueso alveolar, sustancia ósea dental; alopecia de patrón masculino o alopecia senil; distrofia muscular; pioderma; síndrome de Sezary; hipofisitis; insuficiencia adrenal crónica; enfermedad de Addison; lesión de isquemi-reperfusión de órganos que ocurre bajo conservación; choque endotóxico; colitis seudomembranosa; colitis causada por fármacos o radiación; insuficiencia renal aguda isquémica; insuficiencia renal crónica; cáncer sólido de pulmón; malignidad de origen linfoide; leucemias linfocíticas agudas o crónicas; linfoma; soriasis; enfisema pulmonar; cataratas; siderosis; retinitis pigmentosa; degeneración macular

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senil; cicatrización vítrea; quemadura alcalina de la córnea; eritema por dermatitis; dermatitis bullosa; dermatitis cementante; gingivitis; periodontitis; sepsis; pancreatitis; enfermedad de arteria periférica; carcinogénesis; tumores de cáncer sólido; metástasis de carcinoma; hipobaropatía; hepatitis autoinmune; cirrosis biliar primaria; colangitis esclerosante; resección de hígado parcial; necrosis de hígado agudo; cirrosis; cirrosis alcohólica; insuficiencia hepática; insuficiencia hepática fulminante; insuficiencia hepática de inicio tardío; insuficiencia hepática "aguda sobre crónica".

Como se usa aquí, el término "sujeto" incluye animales de sangre caliente, v.gr., mamíferos, incluyendo humanos, gatos, perros, caballos, osos, leones, tigres, hurones, conejos, ratones, vacas, ovejas, cerdos, etc. En una modalidad particular, el sujeto es un primate. En una modalidad específica, el primate es un humano.

Como se usa aquí, el término "administrar" a un sujeto incluye suministrar, proveer o aplicar un compuesto de la invención en una formulación farmacéutica (como se describe aquí), a un sujeto por cualquier vía adecuada para suministro del compuesto al lugar deseado en el sujeto, incluyendo suministro ya sea por la vía parenteral u oral, inyección intramuscular, inyección subcutánea/intradérmica, inyección intravenosa, administración bucal, suministro tópico, suministro transdérmico y administración por la vía rectal, colónica, vaginal, intranasal o tracto respiratorio.

Como se usa aquí, el término "cantidad efectiva" incluye una

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cantidad efectiva, a dosis y durante períodos necesarios para lograr el resultado deseado, v.gr., suficiente para tratar la condición en un sujeto. Una cantidad efectiva de un compuesto de la invención, como se define aquí, puede variar de acuerdo con factores tales como el estado de enfermedad, edad y peso del sujeto, y la capacidad del compuesto para inducir una respuesta deseada en el sujeto. Los regímenes de dosis se pueden ajustar para proveer la respuesta terapéutica óptima. Una cantidad efectiva es también en la cual cualesquiera efectos tóxicos o perjudiciales (v.gr., efectos colaterales) del compuesto son compensados por los efectos terapéuticamente benéficos.

Una cantidad terapéuticamente efectiva de un compuesto de la invención (es decir, una dosis efectiva) puede variar de aproximadamente 0.001 a 30 mg/kg de peso corporal, por ejemplo, de aproximadamente 0.01 a 25 mg/kg de peso corporal, por ejemplo, aproximadamente 0.1 a 20 mg/kg de peso corporal. Cabe entender que todos los valores e intervalos entre aquellos listados se pretende que sean abarcados por la presente invención. El experto en la técnica apreciará que ciertos factores pueden influir en la dosis requerida para tratar efectivamente a un sujeto, incluyendo pero sin limitarse a la severidad de la enfermedad o trastorno, tratamientos previos, la salud general y/o edad del sujeto y otras enfermedades presentes. Más aún, el tratamiento de un sujeto con una cantidad terapéuticamente efectiva de un compuesto de la invención puede incluir un ligero tratamiento o, por ejemplo, puede incluir una serie de tratamientos. También se apreciará que la dosis efectiva del

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compuesto usado para tratamiento puede incrementar o disminuir durante el curso de un tratamiento particular.

Los métodos de la invención además incluyen administrar a un sujeto una cantidad efectiva de un compuesto de la invención en combinación con otro compuesto farmacéuticamente activo conocido para tratar la enfermedad o condición, v.gr., un agente inmunomodulador o un agente antiinflamatorio. Compuestos farmacéuticamente activos que se pueden usar dependen de la condición que se ha de tratar, pero incluyen como ejemplos ciclosporina, rapamicina, FK506, metotrexato, etanercept, infliximab, adalimumab, agentes antiinflamatorios no esteroideos, inhibidores de ciclooxigenasa-2, tales como celecoxib y refecoxib, y costicosteroides. Otros compuestos adecuados se pueden encontrar en Harrison's Principles of Internal Medicine, Trigésimo primera edición, Eds. T. R. Harrison et al. McGraw-Hill N. Y., N. Y.; y Physicians Desk Reference 50ª. edición, 1997, Oradell New Jersey, Medical Economics Co., cuyo contenido completo se incorpora expresamente aquí por referencia. El compuesto de la invención y el compuesto farmacéuticamente activo adicional se pueden administrar al sujeto en la misma composición farmacéutica o en diferentes composiciones farmacéuticas (al mismo tiempo o en tiempos diferentes).

Composiciones farmacéuticas que comprenden compuestos de la invención

La presente invención provee formulaciones y composiciones

farmacéuticamente aceptables que comprenden uno o más compuestos de la invención; es decir, compuestos de la fórmula I o compuestos descritos de otra manera aquí. En ciertas modalidades, el compuesto de la invención está presente en la formulación en una cantidad terapéuticamente efectiva; es decir, una cantidad efectiva para tratar trastorno asociado con 1-fosfato de esfingosina.

Por consiguiente, en una modalidad, la invención se refiere a una composición farmacéutica que comprende una cantidad terapéuticamente efectiva de un compuesto de la invención; es decir, compuestos de la fórmula I o compuestos de otra manera descritos aquí, y un vehículo farmacéuticamente aceptable.

En otra modalidad, la invención está dirigida a una composición farmacéutica empacada que comprende un contenedor que contiene una cantidad terapéuticamente efectiva de un compuesto de la invención, es decir, compuestos de la fórmula I o compuestos de otra manera descritos aquí; e instrucciones para usar el compuesto para tratar un trastorno asociado con 1-fosfato de esfingosina en un sujeto.

El término "contenedlo" incluye cualquier receptáculo para contener la composición farmacéutica. Por ejemplo, en una modalidad, el contenedor es el empaque que contiene la composición farmacéutica. En otras modalidades, el contenedor no es el empaque que contiene la composición farmacéutica, es decir, el contenedor es un receptáculo, tal como una caja o frasco que contiene la composición farmacéutica empacada o

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composición farmacéutica no empacada y las instrucciones para el uso de la composición farmacéutica. Más aún, las técnicas de empaque son bien conocidas en la técnica. Cabe entender que las instrucciones para usar la composición farmacéutica pueden ser contenidas en el empaque que contiene la composición farmacéutica, y como tales las instrucciones forman una relación funcional incrementada al producto empacado. Sin embargo, cabe entender que las instrucciones pueden contener información relacionada con la capacidad del compuesto para realizar su función destinada, v.gr., tratar, prevenir o reducir un trastorno asociado con 1-fosfato de esfingosina en un sujeto.

Otra modalidad de la invención se refiere a una composición farmacéutica empacada que comprende un contenedor que contiene una cantidad terapéuticamente efectiva de un compuesto de la invención; es decir, un compuesto de la fórmula I o compuestos de otra manera descritos aquí, e instrucciones para usar el compuesto para tratar selectivamente un trastorno asociado a 1-fosfato de esfingosina en un sujeto.

Dichas formulaciones farmacéuticamente aceptables típicamente incluyen uno o más compuestos de la invención así como uno o más vehículos y/o excipientes farmacéuticamente aceptables. Como se usa aquí "vehículo farmacéuticamente aceptable" incluye cualquiera y todos los solventes, medios de dispersión, revestimientos, agentes antibacterianos y antimicóticos, agentes isotónicos y retardadores de absorción, y similares que son fisiológicamente compatibles. El uso de dichos medios y agentes para

sustancias farmacéuticamente activas es bien conocido en la técnica. Excepto hasta donde cualquier medio o agente convencional es incompatible con los compuestos de la invención, el uso de los mismos en las composiciones farmacéuticas se contempla.

Compuestos farmacéuticamente activos complementarios conocidos para tratar trasplante o enfermedad autoinmune, es decir, agentes inmunomoduladores y agentes antiinflamatorios, como se describió anteriormente, también se pueden incorporar en las composiciones de la invención. Compuestos farmacéuticamente activos adecuados que se pueden usar se pueden encontrar en Principles of Internal Medicine de Harrison.

Una composición farmacéutica de la invención se formula para ser compatible con la vía de administración destinada. Ejemplos de vías de administración incluyen administración parenteral, v.gr., intravenosa, intradérmica, subcutánea, oral (v.gr., inhalación), transdérmica (tópica), transmucosa y rectal. Soluciones o suspensiones usadas para aplicación parenteral, intradérmica o subcutánea pueden incluir los siguientes componentes: un diluyente estéril tal como agua para inyección, solución salina, aceites fijos, polietilenglicoles, glicerina, propilenglicol u otros solventes sintéticos; agentes antibacterianos tales como alcohol bencílico o metil parabenos; antioxidantes tales como ácido sórbico o bisulfito de sodio; agentes quelatadores tales como etilendiamintetraacético; reguladores de pH tales como acetatos, citratos o fosfatos y agentes para el ajuste de tonicidad tales como cloruro de sodio o dextrosa. El pH se puede ajustar con ácidos o

bases, tales como ácido clorhídrico o hidróxido de sodio. La preparación parenteral se puede contener en ampolletas, jeringas desechables o frascos de dosis múltiples hechos de vidrio o plástico.

Las composiciones farmacéuticas adecuadas para inyección incluyen soluciones acuosas estériles (en donde son solubles en agua) o dispersiones, o polvos estériles para la preparación extemporánea de soluciones o dispersiones inyectables estériles. Para administración intravenosa, los vehículos adecuados incluyen solución salina fisiológica, agua bacteriostática, Cremophor E1™ (BASF, Parsippany, N.J.) o solución salina regulada en su pH con fosfato (PBS). En todos los casos, la composición farmacéutica debe ser estéril y debe ser fluida al grado que pueda aplicarse fácilmente con jeringa. También debe ser estable bajo las condiciones de fabricación y almacenamiento y se debe conservar contra la acción contaminante de microorganismos tales como bacterias y hongos. El vehículo puede ser un solvente o medio de dispersión que contiene, por ejemplo, agua, etanol, poliol (por ejemplo, glicerol, propilenglicol y polietilenglicol líquido, y similares) y mezclas adecuadas de los mismos. La fluidez apropiada se puede mantener, por ejemplo, mediante el uso de un revestimiento tal como lecitina, mediante el mantenimiento del tamaño de partícula requerido en el caso de dispersión y mediante el uso de agentes tensioactivos. La prevención de la acción de microorganismos se puede lograr por varios agentes antibacterianos y antimicóticos, por ejemplo, parabenos, clorobutanol, fenol, ácido ascórbico, timerosal y similares. En muchos casos, será preferible incluir

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agentes isotónicos, por ejemplo, azúcares, polialcoholes tales como manitol, sorbitol o cloruro de sodio en la composición. La absorción prolongada de las composiciones inyectables se puede llevar a cabo incluyendo en la composición un agente que retarde la absorción, por ejemplo, monoestearato de aluminio y gelatina.

Soluciones inyectables estériles se pueden preparar incorporando el compuesto de la invención en la cantidad requerida en un solvente apropiado con una combinación de los ingredientes anteriormente enumerados, según sea necesario, seguido por esterilización filtrada.

Generalmente, las dispersiones se preparan incorporando el compuesto en un vehículo estéril que contiene un medio de dispersión básico y los otros ingredientes requeridos de aquellos enumerados anteriormente. En el caso de polvos estériles para la preparación de soluciones inyectables estériles, los métodos de preparación preferidos son secado bajo vacío y secado bajo congelamiento que produce un polvo del compuesto más cualquier ingrediente deseado adicional de una solución previamente filtrada en forma estéril del mismo.

Las composiciones orales generalmente incluyen un diluyente inerte o un vehículo digerible. Pueden ser contenidas en cápsulas de gelatina o comprimidas en tabletas. Para propósitos de administración terapéutica oral, el compuesto de la invención se puede incorporar con excipientes y usar en forma de tabletas, trociscos o cápsulas. Las composiciones orales pueden incluir también un revestimiento entérico. Las composiciones orales también

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se pueden preparar usando un fluido para usarse como enjuague bucal, en donde el compuesto en el vehículo líquido se aplica oralmente y con el mismo se pueden hacer gárgaras y expectorar e ingerirse. Agentes de unión farmacéuticamente compatibles y/o materiales adyuvantes se pueden incluir como parte de la composición. Las tabletas, píldoras, cápsulas, trociscos y similares pueden contener cualquiera de los siguientes ingredientes, o compuestos de naturaleza similar: un aglutinante tal como celulosa microcristalina, goma tragacanto o gelatina; un excipiente tal como almidón o lactosa, un agente desintegrante tal como ácido algínico, Primogel, o almidón de maíz; un lubricante tal como estearato de magnesio o Sterotes; un resbalante tal como dióxido de silicio coloidal; un agente edulcorante tal como sacarosa o sacarina; o un agente saborizante tal como menta, silicato de metilo o saborizante de naranja.

Para administrarse por inhalación, los compuestos de la invención se suministran en forma de una aspersión en aerosol desde un contenedor presurizado o despachador que contiene un propelente adecuado, v.gr., un gas tal como dióxido de carbono o un nebulizador.

La administración sistémica también puede ser por medios transmucosa o transdérmico. Para administración transmucosa o transdérmica, penetrantes apropiados para atravesar la barrera se usan en la formulación. Dichos penetrantes son generalmente conocidos en la técnica e incluyen, por ejemplo, administración transmucosa, detergentes, sales biliares, y derivados de ácido fusídico. La administración transmucosa se puede lograr

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a través del uso de aspersiones nasales o supositorios. Para administración transdérmica, los compuestos de la invención se formulan en pomadas, ungüentos, geles o cremas tales como se conocen generalmente en la técnica.

Las composiciones farmacéuticas de la presente también se pueden preparar en forma de supositorios (v.gr., con bases de supositorio convencionales tales como manteca de cacao y otros glicéridos) o enemas de retención para suministro rectal.

En una modalidad, los compuestos se preparan con vehículos que protegerán a los compuestos contra eliminación rápida del cuerpo, tales como una formulación de relación controlada, incluyendo implantes y sistemas de suministro microencapsulados. Se pueden usar polímeros biodegradables, biocompatibles, tales como etileno-acetato de vinilo, polianhídridos, ácido poliglicólico, colágeno, poliotoésteres y ácido poliláctico. Los métodos para la preparación de dichas formulaciones serán evidentes para los expertos en la técnica. Los materiales también se pueden obtener comercialmente de Alza Corporation y Nova Pharmaceuticals, Inc. Las suspensiones liposomales también se pueden usar como vehículos farmacéuticamente aceptables. Estas se pueden preparar de conformidad con métodos conocidos por los expertos en la técnica, por ejemplo, como se describe en la patente de E.U.A. No. 4,522,811, patente de E.U.A. No. 5,455,044 y patente de E.U.A. No. 5,576,018, y patente de E.U.A. No. 4,883,666, cuyo contenido se incorpora aquí por referencia.

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Los compuestos de la invención también se incorporan en composiciones farmacéuticas que permiten el suministro sostenido de los compuestos a un sujeto durante un período de por lo menos algunas semanas a un mes o más. Dichas formulaciones se describen en la solicitud del PCT publicada No. WO 02/74247, incorporada aquí por referencia.

Es especialmente ventajoso formular composiciones orales o parenterales en forma de unidad de dosis para facilidad de administración y uniformidad de dosis. La forma de unidad de dosis como se usa aquí se refiere a unidades físicamente discretas adecuadas como dosis unitarias del sujeto que ha de ser tratado; cada unidad contiene una cantidad predeterminada de un compuesto de la invención calculada para producir el efecto terapéutico deseado en asociación con el vehículo farmacéutico requerido. La especificación para las formas de dosis unitaria de la invención son determinadas por y dependen directamente de las características únicas del compuesto y el efecto terapéutico particular que se ha de lograr y las limitaciones inherentes en la técnica de combinar dichos compuestos para el tratamiento de individuos.

Esta invención se ilustra además mediante los siguientes ejemplos, que no deben considerarse limitantes. El contenido de todas las referencias, patentes, solicitudes de patente citadas a lo largo de la solicitud se incorporan aquí por referencia. Cabe entender que el uso de los compuestos aquí descritos está dentro del alcance de la presente invención y se pretende que sean abarcados por la presente invención y sean

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incorporados expresamente aquí para todos los propósitos.

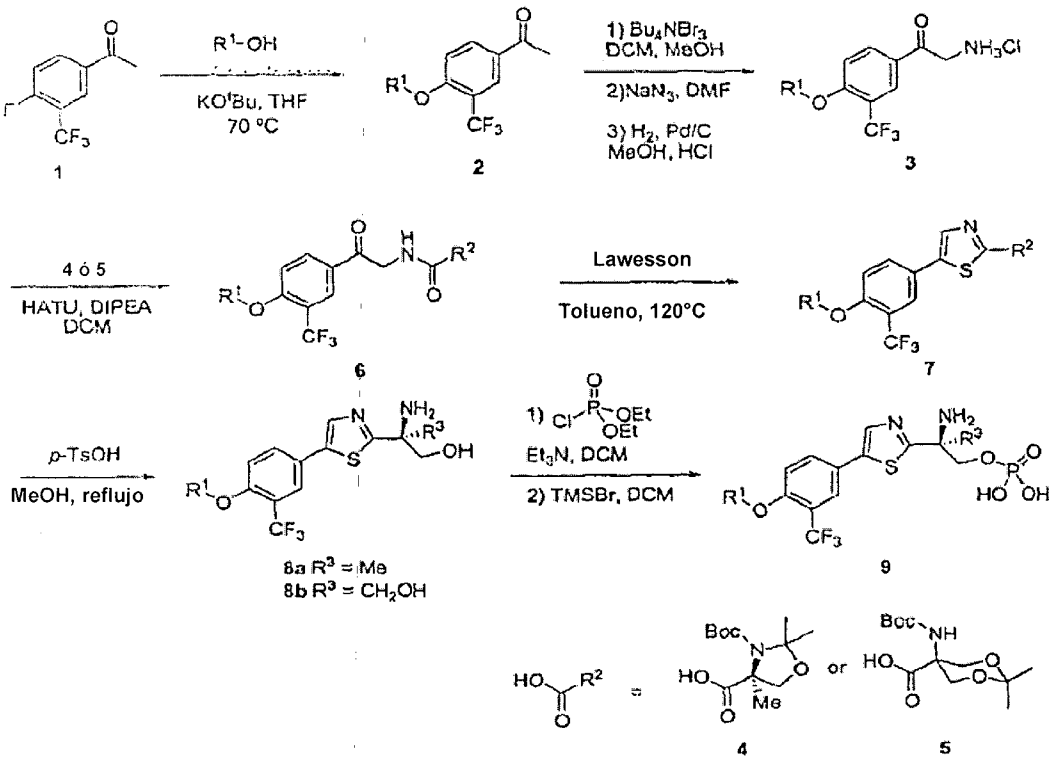
EJEMPLOS

Enfoque general a la síntesis de tiazoles 2,5-disustituidos

La síntesis de tiazoles 2,5-sustituidos se describe en el esquema 1. La reacción de alcohol R^1-OH en donde alquilo, aralquilo, heteroarilo, heterociclo o cicloalquilo de R^1 con 4-fluoroacetofenona sustituida 1 dieron el intermediario de éter-acetofenona 2. El intermediario de éter-acetofenona 2 después se convirtió a la bromo-acetofenona correspondiente usando Bu_4NBr_3, que, bajo reacción con NaN3, dio el intermediario de azido-acetofenona. La hidrogenación del intermediario de azido-acetofenona dio amina 3, seguido por acoplamiento con aminoácido ortogonalmente protegido 4 o ácido aminodiol-carboxílico 5 dio amida 6. Como se señaló, el compuesto 4 se sintetizó a partir de ácido (*S*)-2-(*ter*-butoxicarbonilamino)-3-hidroxi-2-metilpropanoico en tres pasos con un rendimiento global de 52-64%. Una síntesis de ácido (*R*)-3-(*ter*-butoxicarbonil)-2,2,4-trimetiloxazolidin-4-carboxílico se describe en Clemens, J. J.; Davis, M. D.; Lynch, K. R.; Macdonald, T. L. *Bioorg. Med. Chem. Lett.* 2005, *15*, 3568-3572. El compuesto 5 se sintetizó a partir de 2-amino-2-(hidroximetil)propano-1,3-diol en cinco pasos con un rendimiento global de 30%, también se describe en Clemens, J. J.; Davis, M. D.; Lynch, K. R.; Macdonald, T. L. *Bioorg. Med. Chem. Lett.* 2005, *15*, 3568-3572. Bajo condiciones usando reactivo de

Lawesson, la amida 6 se convirtió a tiazol 7 con buen rendimiento. La remoción de los grupos protectores dio el alcohol final 8, que, bajo reacción con clorofosfato de dietilo y desprotección subsecuente con TMSBr, dio el fosfato 9.

ESQUEMA 1

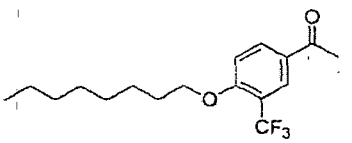


Protocolo general para la síntesis de acetofenonas sustituidas (síntesis de éter de Williamson (2)

A una solución del alcohol deseado (1.0 equivalente) en THF seco bajo atmósfera de nitrógeno se añadió KO^{t}Bu (ya sea solución 1.0 M en

THF o sólido, 1.1 equivalentes). La mezcla de reacción se calentó a 60-70°C durante 10 minutos, después se añadió 4-flouroacetofenona sustituida 1 (1.0 equivalentes). La reacción después se agitó durante 1 a 3 horas antes de enfriarse a temperatura ambiente (T.A.). El solvente se removió bajo vacío. El producto se purificó por cromatografía en columna de gel de sílice usando el sistema Combi-Flash (Hex:EtOAc).

1-(4-(Octiloxi)-3-(trifluorometil)fenil)etanona (2)



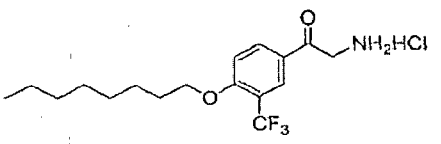
El producto se purificó por cromatografía en columna de gel de sílice usando el sistema Combi-Flash (Hex:EtOAc) como sólido blanco en 60% (1.20 g).

CCD (1:5 EtOAc:Hex), R_f= 0.4;

^{1}H RMN (400 MHz, $CDCl_3$) δ 8.18 (d, 1H, J= 2.0 Hz), 8.10 (dd, 1H, J= 8.8 Hz, J = 2.3 Hz), 7.02 (d, 1H, J= 8.8 Hz), 4.12 (t, 2H, J= 6.4 Hz), 2.58 (m, 3H), 1.80-1.89 (m, 2H), 1.42-1.54 (m, 2H), 1.22-1.40 (m, 8H), 0.89 (t, 3H, J= 6.7 Hz).

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Clorhidrato de 2-amino-1-(4-(octiloxi)-3-(trifluorometil)fenil)-etanona (3)



A una solución de la acetofenona sustituida 2 (390 mg, 1.0 equivalentes) en CH_2Cl_2 seco CH_2Cl_2 (9 ml) bajo atmósfera de nitrógeno se añadió Bu_4NBr_3 (0.60 g, 1.0 equiv). A la solución se añadió MeOH anhidro (1.0 ml). La mezcla de reacción se agitó a temperatura ambiente durante la noche. El solvente se removió bajo vacío, y el producto de bromo-acetofenona se usó como tal en el siguiente paso.

CCD (4:1, Hex/EtOAc), R_f= 0.6.

A la bromo-acetofenona deseada (del último paso, 1.0 equivalentes), en DMF (10 ml) se añadió NaN_3 (0.24 g, 3.0 equiv). La mezcla resultante se agitó después en DMF durante 1 hora. La mezcla de reacción *se diluyó* con EtOAc (50 ml) y se lavó con H_2O (2 x 50). El solvente se removió bajo vacío y el producto se purificó por cromatografía en columna de gel de sílice usando el sistema Combi-Flash (Hex:EtOAc) para dar el producto de azido-acetofenona como un sólido blanco con un rendimiento de 99% (0.44 g).

CCD (4:1, Hex/EtOAc), R_f = 0.4.

A una solución de la azido-acetofenona (0.44 g, 1.0 equivalentes) en MeOH (10 ml) se añadió HCl concentrado (1.5 ml), y 10% de Pd/C (44 mg). La mezcla de reacción se agitó bajo una atmósfera de H_2 (g)

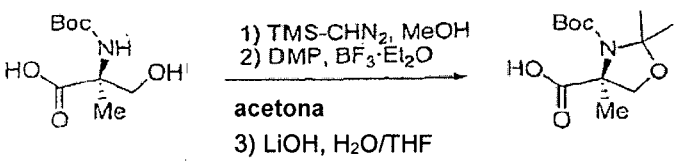
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durante 2 horas. La mezcla de reacción se filtró después a través de una capa delgada de Celite y el solvente se removió bajo vacío. La amino-acetofenona 3 se obtuvo como un sólido blanco en rendimiento cuantitativo (0.46 mg) con 90% de pureza.

CCD (1:5 EtOAc:Hex), R_f= 0.4;

^{1}H RMN (400 MHz, $CDCl_3$) δ 8.18 (d, 1H, J= 2.0 Hz), 8.10 (dd, 1H, J= 8.8 Hz, J= 2.3 Hz), 7.02 (d, 1H, J= 8.8 Hz), 4.52 (s, 2H). 4.12 (t, 2H, J= 6.4 Hz), 1.80-1.89 (m, 2H), 1.42-1.54 (m, 2H), 1.22-1.40 (m, 8H), 0.89 (t, 3H, J= 6.7 Hz).

Acido (*R*)-3-(*ter*-butoxicarbonil)-2,2,4-trimetiloxazolidin-4-carboxílico (4)



A una solución del ácido (*S*)-2-(*ter*-butoxicarbonilamino)-3-hidroxi-2-metilpropanoico (5.0 g, 1.0 equivalentes) en CH_2Cl_2/MeOH (4:1, 50 ml) a 0°C se añadió a solución de TMS-CHN_2 (2.0 M en éter dietílico o hexanos, 12.5 ml, 1.1 equivalentes) gota a gota hasta que la solución incolora se volvió de color amarillo claro. La mezcla de reacción se agitó durante 20 minutos, después una pocas gotas de ácido acético se añadieron para extinguir la última TMS-CHN_2 sin reaccionar (la solución se volvió incolora a

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partir de amarillo claro). El solvente se removió bajo vacío.

CCD (2:1, Hex/EtOAc), R_f= 0.4.

El residuo se disolvió en acetona (30 ml). A la solución resultante se añadió después 2,2-dimetoxipropano (DMP) (15 ml). A la mezcla se añadió $BF_3 \cdot OEt_2$ (2 ml) gota a gota y la solución se agitó a T.A. durante 4-18 horas. El solvente se removió bajo vacío y el producto se purificó por cromatografía en columna de gel de sílice usando el sistema Combi-Flash (Hex:EtOAc).

CCD (3:1, Hex/EtOAc), R_f= 0.6;

^{1}H RMN (400 MHz, $CDCl_3$) δ 4.06-4.12 (m, 1H), 3.73-3.83 (m, 4H), 1.55-1.64 (m, 9H), 1.48 (br s, 3H), 1.41 (br s, 6H).

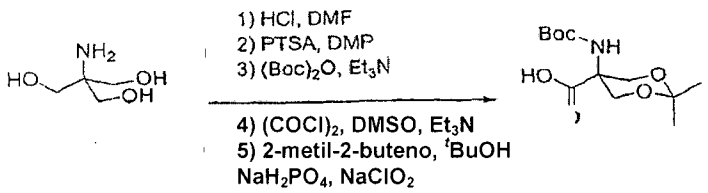
El residuo purificado se disolvió en THF (40 ml) y a la solución se añadió LiOH (1.15 g, 1.20 equiv) en H_2O (20 ml). La solución se calentó a reflujo durante 6-18 horas, después se concentró bajo vacío para remover la mayor parte de THF. La solución se diluyó con H_2O (150 ml) y se lavó con Et_2O (2 x 150 ml). La capa acuosa se enfrió a 0°C después se acidificó a pH de aproximadamente 3 usando HCl concentrado, después se extrajo con EtOAc (2 x 200 ml). Las capas de EtOAc se combinaron, se secaron ($MgSO_4$), se filtraron y el solvente se removió bajo vacío para dar carboxilato 4 como un sólido blanco con un rendimiento de 52-64% (3.78 g).

CCD (1:1 EtOAc:Hex), R_f= 0.2;

^{1}H RMN (400 MHz, $CDCl_3$) δ (rotámeros) 4.47 (br d, 0.5H, J= 8.8 Hz), 4.17 (br d, 0.5H, J= 8.8 Hz), 3.85 (br d, 0.5H, J= 8.8 Hz), 3.78 (br d, 0.5H, J= 8.8 Hz), 1.38-1.67 (m, 18H).

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Acido 5-(*ter*-butoxicarbonilamino)-1,2-dimetil-1,3-dioxano-5-carboxílico (5)



A una solución del 2-amino-2-(hidroximetil)propano-1,3-diol (2.0 g, 1.0 equivalentes) en DMF (20 ml) a T.A. se añadió HCl 1M (16.5 ml, 1.0 equiv.) en éter dietílico. La mezcla resultante se agitó durante 20 minutos, después se añadieron ácido *para*-toluensulfónico (PTSA) (157 mg, 0.05 equivalentes) y 2,2-dimetoxipropano (2.23 ml, 1.1 equivalentes). La mezcla de reacción se agitó durante 24 horas, después Et_3N (3.0 equivalente, 6.90 ml) y $(Boc)_2O$ (1.0 equiv, 3.60 g) se añadieron y la mezcla se agitó durante la noche. La mezcla de reacción se diluyó con EtOAc (50 ml) y se lavó con H_2O (2 x 50 ml). El solvente se removió bajo vacío y el producto se purificó por cromatografía en columna de gel de sílice usando el sistema Combi-Flash (Hex:EtOAc) como un sólido blanco con un rendimiento de 58% (2.49 g).

CCD (2:1, Hex/EtOAc), R_f= 0.3;

^{1}H RMN (400 MHz, $CDCl_3$) δ 5.33 (br s, 1H), 4.27 (br s, 1H), 3.79-3.84 (m, 4H), 3.72 (d, 2H, J= 6.4 Hz), 1.46 (s, 12H), 1.44 (s, 3H).

A una solución de cloruro de oxalilo (2.0 M en CH_2Cl_2, 5.74 ml, 3.0 equivalentes) en CH_2Cl_2 seco (10 ml) a –78°C se añadió DMSO (1.36 ml, 5.0 equivalentes). La mezcla resultante se agitó durante 15 minutos, después

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una solución del alcohol deseado (del último paso, 1.0 g) en CH_2Cl_2 seco (10 ml) se añadió gota a gota. La mezcla se agitó durante 2 horas, después se añadió Et_3N (5.33 ml, 10 equivalentes). La mezcla de reacción se agitó durante 10 minutos, posteriormente el baño de enfriamiento se removió y la mezcla se dejó calentar a T.A. La mezcla de reacción se diluyó después con EtOAc (50 ml) y se lavó con 10% de NH_4Cl (2 x 50 ml). La capa orgánica se secó sobre $MgSO_4$, se filtró, y el solvente se removió bajo vacío para dar el intermediario de aldehído como un sólido blanco con un rendimiento de >99% (1.00 g). Para condiciones de oxidación de Swern más detalladas véase: a) Blaskovich, M. A.; Evindar, G.; Rose, N. G. W.; Wilkinson, S.; Luo, Y.; Lajoie, G. A. *J. Org. Chem.* 1998, *63*, 3631-3646. y b) Rose, N. G. W.; Blaskovich, M. A.; Evindar, G.; Wilkinson, S.; Luo, Y.; Fishlock, D.; Reid, C; Lajoie, G. A. *Organic Syntheses* 2002, *79*, 216-227.

CCD (2:1, Hex/EtOAc), R_f= 0.7;

^{1}H RMN (400 MHz, $CDCl_3$) δ 9.63 (s, 1H), 5.55 (br s, 1H), 4.07 (d, 2H, J= 12.0 Hz), 3.95 (d, 2H, J= 12.0 Hz), 1.47 (s, 18H).

A una solución del aldehído (del último paso, 1.0 g) en *t*-BuOH (20 ml) y 2-metil-2-buteno (10 ml) a temperatura ambiente se añadió una solución de NaH_2PO_4 (1.06 g, 2.0 equivalentes), y $NaClO_2$ (1.40 g, 4.0 equivalentes) en H_2O (10 ml). La reacción se agitó durante 3 horas y después se diluyó con H_2O (10 ml). La mezcla se extrajo con EtOAc (30 ml). La capa orgánica se secó sobre $MgSO_4$, se filtró, y el solvente se removió bajo vacío para dar carboxilato 5 como un sólido blanco con un rendimiento de 52% (550

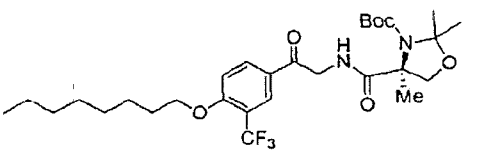
304

mg). Para un procedimiento más detallado de oxidación de aldehído a carboxilato véase: Tailor, R. E.; Galvin, G. M.; Hilfiker, K. A.; Chen, Y. *J. Org. Chem.* 1998, *63*, 9580-9583.

CCD (1:1 EtOAc:Hex), R_f= 0.2;

^{1}H RMN (400 MHz, $CDCl_3$) δ 5.50 (br s, 1H), 4.18 (d, 2H, J= 11.8 Hz), 4.10 (d, 2H, J= 11.8 Hz), 1.47 (br s, 18H).

2,2,4-Trimetil-4-(2-(4-(octiloxi)-3-(trifluorometil)fenil)-2-oxoetilcarbamoil)oxazolidin-3-carboxilato de (*R*)-*ter*-butilo (6)



A una solución de ácido oxazolidin-4-carboxílico protegido 4 (176 mg, 1 equivalentes), HATU (310 mg, 1.2 equivalentes), y DIEA (1.2 ml, 10 equivalentes) en CH_2Cl_2/DMF (1:1, 10 ml) se añadió amino-acetofenona 3 (250 mg, 1.0 equivalentes). La mezcla resultante se agitó a temperatura ambiente durante la noche. La mezcla de reacción se diluyó con EtOAc (50 ml) y se lavó con 10% de NH_4Cl (2 x 50 ml) y NaCl saturado (1 x 50 ml). El solvente se removió bajo vacío y el producto se obtuvo por cromatografía en columna de gel de sílice usando el sistema Combi-Flash (Hex:EtOAc), como un sólido blanco con un rendimiento de 40% (185 mg).

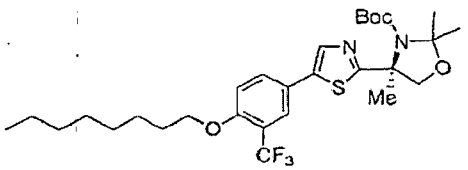
CCD (1:2 EtOAc:Hex), R_f= 0.3;

EM (ESI, M+Na) = 572.99;

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^{1}H RMN (400 MHz, $CDCl_3$) δ 8.21 (s, 1H), 8.11 (d, 1H, J= 8.4 Hz), 7.05 (d, 1H, J= 8.4 Hz), 4.62-4.79 (m, 2H), 4.13 (t, 2H, J= 6.4 Hz), 3.28 (br s, 1H), 1.22-1.90 (m, 30H), 0.89 (t, 3H, J= 6.4 Hz).

2,2,4-Trimetil-4-(5-(4-(octiloxi)-3-(trifluorometil)fenil)tiazol-2-il)oxazolidin-3-carboxilato de (*R*)-*ter*-butilo (7)



Una suspensión de oxazolidin-amida protegida 6 (180 mg, 1.0 equivalentes) y reactivo de Lawesson (390 mg, 3.0 equivalentes) en tolueno (5 ml) se selló y se calentó a 100°C durante 1 hora. Después de enfriarse a temperatura ambiente, la mezcla de reacción se purificó por cromatografía en columna de gel de sílice usando el sistema Combi-Flash (Hex;EtOAc) como un aceite incoloro espeso con un rendimiento de 67% (120 mg).

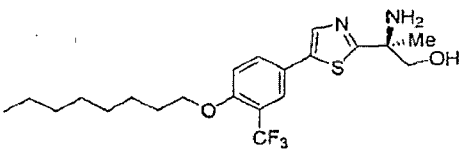
CCD (1:2 EtOAc:Hex), R_f = 0.8;

EM (ESI, $M+H^+$) = 571.11;

^{1}H RMN (400 MHz, $CDCl_3$) δ 7.73 (br s, 1H), 7.70 (s, 1H), 7.61 (d, 1H, J= 6.8 Hz), 7.01 (d, 1H, J= 6.8 Hz), 3.96-4.28 (m, 4H), 1.21-1.99 (m, 30H), 0.89 (t, 3H, J= 7.6 Hz).

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(*S*)-2-Amino-2-(5-(4-(octiloxi)-3-(trifluorometil)fenil)tiazol-2-il)-propan-1-ol (8a)

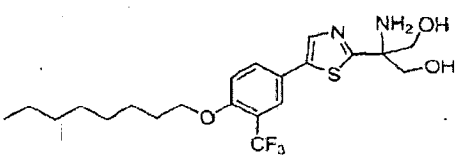


Una solución de tiazol 7 (120 mg) y ácido *para*-toluensulfónico (PTSA, 400 mg, 10 equivalentes) en MeOH (6 ml) se puso a reflujo durante 6 horas. El solvente se removió bajo vacío y el producto se purificó por CLAR preparativa de fase inversa, después se liofilizó a sequedad para obtener la sal de trifluoroacetato del producto como un sólido blanco con un rendimiento de 79% (90.5 mg).

EM (ESI, $M+H^+$) = 431.01;

^{1}H RMN (400 MHz, DMSO-d_6) δ 8.27 (s, 1H), 7.88 (dd, 1H, J= 8.8 Hz, J = 2.4 Hz), 7.85 (d, 1H, J= 2.4 Hz), 7.34 (d, 1H, J= 8.4 Hz), 5.77 (br s, 1H), 4.14 (t, 2H, J= 6.4 Hz), 3.76 (dd, 1H, J= 11.2, Hz, J= 1.2 Hz), 3.66 (dd, 1H, J= 11.2 Hz, J= 1.2 Hz), 1.73 (q, 2H, J= 6.8 Hz), 1.58 (s, 3H), 1.36-1.48 (m, 2H), 1.20-1.36 (m, 8H), 0.85 (t, 3H, J= 6.4 Hz).

2-Amino-2-(5-(4-(octiloxi)-3-(trifluorometil)fenil)tiazol-2-il)propano-1,3-diol (8b)



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El diol 8b se preparó a partir del carboxilato 5 y amino-acetofenona 3 de manera análoga al tiazol 8a con un rendimiento de 35% en tres pasos.

EM (ESI, $M+H^+$) = 447.01;

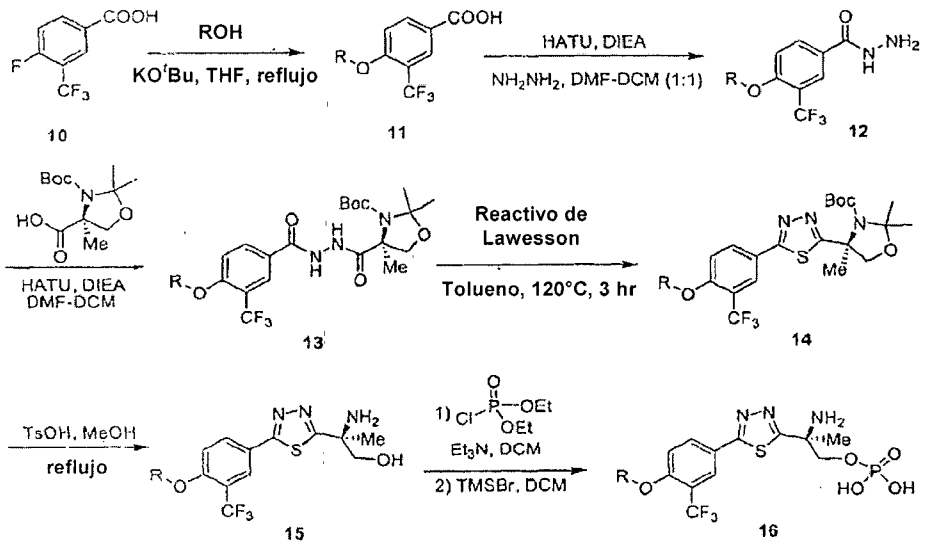
^{1}H RMN (400 MHz, DMSO-d_6) δ 8.27 (s, 1H), 7.87 (dd, 1H, J = 8.8 Hz, J= 2.4 Hz), 7.84 (d, 1H, J= 2.4 Hz), 7.32 (d, 1H, J= 8.4 Hz), 5.71 (br s, 1H), 4.13 (t, 2H, J= 6.4 Hz), 3.71-3.85 (m, 4H), 1.72 (q, 2H, J= 6.4 Hz), 1.36-1.46 (m, 2H), 1.19-1.35 (m, 8H), 0.84 (t, 3H, J= 6.4 Hz).

Enfoque general a la síntesis de 1,3,4-tiadiazoles 2,5-disustituidos

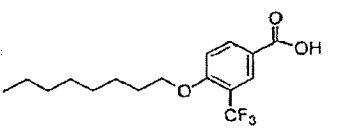
La síntesis de tiadiazoles 2,5-sustituidos se describe en el esquema 2. La reacción de alcohol ROH con ácido 4-fluorobezoico sustituido 10 dio el intermediate de éter-benzoato 11. El intermediate de éter-benzoato 11 después se acopló con hidrazina para dar benzohidrazida 13. La reacción de benzohidrazida 13 con aminoácido ortogonalmente protegido 4 usando hexafluorofosfato de N,N,N',N'-tetrametil-O-(7-azabenzotriazol-1-il)uronio (HATU) seguido por ciclización con Reactivo de Lawesson dio tiadiazol 14 con buen rendimiento. La remoción de los grupos protectores dio alcohol 15 final. El alcohol 15 después se convirtió al fosfato corresponding como se reporta en el esquema 1.

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ESQUEMA 2



Acido 4-(octiloxi)-3-(trifluorometil)benzoico (11a)

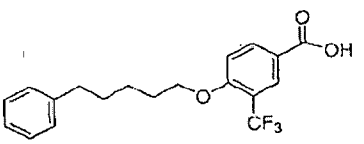


A una solución de 1-octanol (315 µl, 2.0 mmoles) en THF anhidro (5 ml) se añadió *t*-butóxido de potasio (5 ml, solución 1M en THF). La mezcla se calentó a 70°C durante 15 min, después se enfrió a temperatura ambiente. Se añadió ácido 4-fluoro-3-trifluorometilbenzoico (10) (417 mg, 2.0 mmoles) en THF (5 ml) y el producto resultante se calentó a 75°C durante la noche. Después de enfriarse a temperatura ambiente, la mezcla de reacción se diluyó con acetato de etilo y se lavó con agua. La capa acuosa se acidificó a un pH de aproximadamente 3 con HCl (2M) y se extrajo con acetato de etilo. Las

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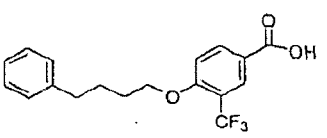
capas orgánicas combinadas se lavaron con salmuera, se secaron sobre Na_2SO_4 y se concentraron bajo vacío para dar el compuesto del título (632 mg, pureza por CLAR > 95%), que se usó para la siguiente reacción sin purificación adicional. El tiempo de retención de CLAR sobre una columna C8(2) (30 x 3.00 mm, 3 µ) fue de 3.28 min con gradiente de 50-98% de acetonitrilo-H_2O (0.1% de ácido trifluoroacético (TFA)) en 3.5 min como fase móvil.

Acido 4-(5-fenilpentiloxi)-3-(trifluorometil)benzoico (11b)



El compuesto del título se preparó de manera análoga al ácido 4-(octiloxi)-3-(trifluorometil)benzoico (11a) con un rendimiento de >95%. El tiempo de retención de CLAR sobre una columna C8(2) (30 x 3.00 mm, 3 µ) fue de 3.31 min con gradiente de 20-98% de acetonitrilo-H_2O (0.1% de TFA) en 3.5 min como fase móvil.

Acido 4-(4-fenilbutoxi)-3-(trifluorometil)benzoico (11c)

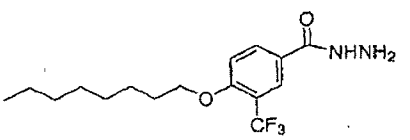


El compuesto del título se preparó de manera análoga al ácido 4-

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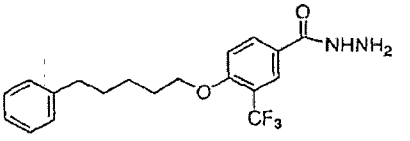
(octiloxi)-3-(trifluorometil)benzoico (11a) con un rendimiento de >95%. El tiempo de retención de CLAR sobre una columna C8(2) (30 x 3.00 mm, 3 µ) fue de 3.14 min con gradiente de 20-98% de acetonitrilo-H_2O (0.1% de TFA) en 3.5 min como fase móvil.

4-(Octiloxi)-3-(trifluorometil)benzohidrazida (12a)



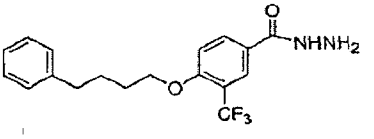
Acido 4-(octiloxi)-3-(trifluorometil)benzoico (11a) (632 mg, crudo, aproximadamente 1.89 mmoles) se agitó con HATU (905 mg) y DIEA (1.7 ml) en CH_2Cl_2-DMF (10 ml, 4:1) durante 10 min seguido por la adición de hidrazina (297 µl) gota a gota. La mezcla de reacción se agitó continuamente durante otra hora, después se diluyó con acetato de etilo (30 ml) y se lavó con agua (10 ml) y salmuera (3 x 15 ml). La capa orgánica se secó sobre Na_2SO_4 y se concentró bajo vacío para dar el compuesto del título (661 mg, pureza por CLAR > 90%), que se usó para la siguiente reacción sin purificación adicional. EM (ESI): 333.08 (MH^+); el tiempo de retención de CLAR sobre una columna C8(2) (30 x 3.00 mm, 3 µ) fue de 1.61 min con gradiente de 50-98% de acetonitrilo-H_2O (0.1% de TFA) en 3.5 min como fase móvil.

4-(5-Fenilpentiloxi)-3-(trifluorometil)benzohidrazida (12b)



El compuesto del título se preparó de manera análoga a la 4-(octiloxi)-3-(trifluorometil)-benzo-hidrazida (12a) con un rendimiento de >95%. EM (ESI): 367.14 (MH^+); tiempo de retención de CLAR sobre una columna C8(2) (30 x 3.00 mm, 3 µ) fue de 2.44 min con gradiente de 20-98% de acetonitrilo-H_2O (0.1% de TFA) en 3.5 min como fase móvil.

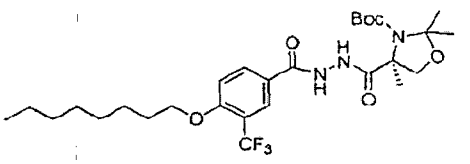
4-(4-Fenilbutoxi)-3-(trifluorometil)benzohidrazida (12c)



El compuesto del título se preparó de manera análoga a la 4-(octiloxi)-3-(trifluorometil)-benzo-hidrazida (12a) con un rendimiento de >95%. EM (ESI): 353.11 (MH^+); el tiempo de retención de CLAR sobre una columna C8(2) (30 x 3.00 mm, 3 µ) fue de 2.30 min con gradiente de 20-98% de acetonitrilo-H_2O (0.1% de TFA) en 3.5 min como fase móvil.

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2,2,4-Trimetil-4-(2-(4-(octiloxi)-3-(trifluorometil)benzoil)-hidrazina-carbonil)oxazolidin-3-carboxilato de (S)-*ter*-butilo (13a)



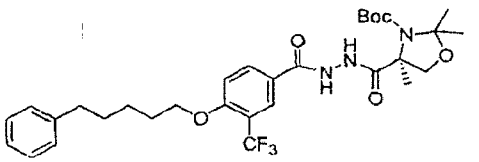
Acido (*R*)-3-(*ter*-butoxicarbonil)-2,2,4-trimetiloxazolidin-4-carboxílico (4) (210 mg, 0.81 mmoles) se agitó con HATU (372 mg, 0.98 mmoles) y diisopropiletilamina (DIEA) (0.705 ml, 4.1 mmoles) en CH_2Cl_2-DMF (2:1, 6 ml) durante 10 min seguido por la adición de 4-(octiloxi)-3-(trifluorometil)benzohidrazida (12a) (270 mg, 0.81 mmoles) en CH_2Cl_2 (2 ml). La reacción se agitó a temperatura ambiente durante 1 hora y después se concentró bajo vacío. El residuo se diluyó con acetato de etilo (20 ml) y se lavó con agua (5 ml), salmuera (2 x 10 ml) y se secó sobre Na_2SO_4. La capa orgánica se concentró bajo vacío y se sometió a cromatografía sobre una columna de gel de sílice (acetato de etilo-hexano, 0-33%, como eluyente) para dar el compuesto del título (428 mg, 82% de rendimiento).

EM (ESI): 573.84 (MH^+);

^{1}H RMN (400 MHz, $CDCl_3$) δ 9.43 (br, 2H), 8.06 (d, 1H, J= 2.0 Hz), 7.94 (dd, 1H, J= 8.8 Hz, J= 2.0 Hz), 6.96 (d, 1H, J= 8.8 Hz), 4.52 (br, 1H), 4.07 (t, 2H, J= 6.4 Hz), 3.76 (br, 1H), 1.82 (m, 2H), 1.67 (s, 6H), 1.57 (s, 3H), 1.51 (s, 9H), 1.51-1.43 (m, 4H), 1.38-1.24 (m, 6H), 0.88 (t, 3H, J= 7.2 Hz).

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2,2,4-Trimetil-4-(2-(4-(5-fenilpentiloxi)-3-(trifluorometil)-benzoil)-hidrazincarbonil)oxazolidin-3-carboxilato de (*S*)-*ter*-butilo (13b)

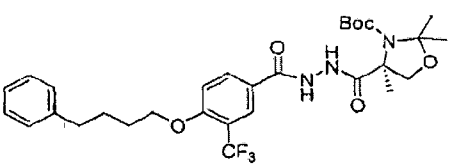


El compuesto del título se preparó de manera análoga al 2,2,4-trimetil-4-(2-(4-(octiloxi)-3-(trifluorometil)benzoil)-hidrazincarbonil)oxazolidin-3-carboxilato de (*S*)-*ter*-butilo (13a) en 95% de rendimiento.

EM (ESI): 607.81 (MH^+);

^{1}H RMN (400 MHz, $CDCl_3$) δ 9.94 (br, 1H), 9.04 (br, 1H), 8.05 (d, 1H, J= 2.4 Hz), 7.93 (dd, 1H, J= 8.8 Hz, J= 2.4 Hz), 7.29-7.25 (m, 2H), 7.18-7.15 (m, 3H), 6.97 (d, 1H, J= 8.8 Hz), 4.55 (br, 1H), 4.07 (t, 2H, J= 6.4 Hz), 3.77 (br, 1H), 2.64 (d, 2H, J= 7.6 Hz), 1.86 (m, 2H), 1.73-1.65 (m, 9H), 1.58-1.52 (m, 13 H).

2,2,4-Trimetil-4-(2-(4-(4-fenilbutoxi)-3-(trifluorometil)benzoil)-hidrazincarbonil)oxazolidin-3-carboxilato de (*S*)-*ter*-butilo (13c)



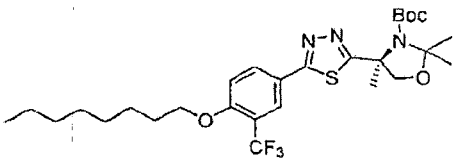
El compuesto del título se preparó de manera análoga al 2,2,4-trimetil-4-(2-(4-(octiloxi)-3-(trifluorometil)benzoil)-hidrazincarbonil)oxazolidin-3-carboxilato de (S)-*ter*-butilo (13a) en 97% de rendimiento.

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EM (ESI): 593.87 (MH^+);

^{1}H RMN (400 MHz, $CDCl_3$) δ 9.94 (br, 1H), 8.79 (br s, 1H), 8.05 (d, 1H, J= 2.4 Hz), 7.93 (dd, 1H, J= 8.8 Hz, J= 2.4 Hz), 7.30-7.25 (m, 2H), 7.20-7.16 (m, 3H), 6.98 (d, 1H, J= 8.8 Hz), 4.55 (br, 1H), 4.10 (t, 2H, J= 6.4 Hz), 3.78 (br s, 1H), 2.69 (d, 2H, J= 7.6 Hz), 1.86 (m, 4H), 1.68 (s, 6H), 1.58 (s, 3H), 1.52 (s, 9H).

2,2,4-Trimetil-4-(5-(4-(octiloxi)-3-(trfluorometil)fenil)-1,3,4-tiadiazol-2-il)oxazolidin-3-carboxilato de (*R*)-ter-butilo (14a)



Una solución de 2,2,4-trimetil-4-(2-(4-(octiloxi)-3-(trifluorometil-benzoil)hidrazincarbonil)oxazolidin-3-carboxilato de (*S*)-*ter*-butilo (13a) (228 mg, 0.39 mmolesl) en tolueno (5 ml) se trató con reactivo de Lawesson (473 mg, 1.17 mmoles) a 85°C durante 2 horas. La reacción se enfrió a temperatura ambiente y el sobrenadante se sometió a cromatografía sobre una columna de gel de sílice eluída con acetato de etilo-hexano (0-30%, v/v) para dar el compuesto del título (156 mg, 70% de rendimiento).

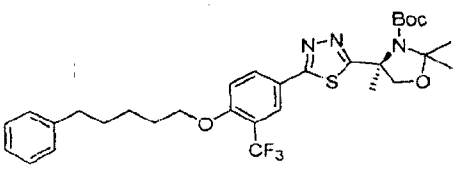
EM (ESI): 572.17 (MH^+),

^{1}H RMN (400 MHz, $CDCl_3$) δ 8.10 (d, 1H, J= 8.8 Hz), 8.08 (d, 1H, J= 6.8 Hz), 7.06 (d, 1H, J= 8.0 Hz), 4.41 (d, 1H, J= 8.0 Hz), 4.18 (d, 1H, J= 9.6 Hz), 4.13-4.07 (m, 3H), 2.00 (s, 3H), 1.85 (m, 2H), 1.78 (s, 3H), 1.68 (m, 4H),

315

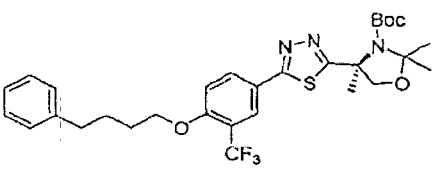
1.51 (s, 3H), 1.47 (m, 2H), 1.39-1.28 (m, 13H), 0.89 (t, 3H, J= 7.2 Hz).

2,2,4-Trimetil-4-(5-(4-(5-fenilpentiloxi)-3-(trifluorometil)-fenil)-1,3,4-tiadiazol-2-il)oxazolidin-3-carboxilato de (*R*)-ter-butilo (14b)



El compuesto del título se preparó de manera análoga al 2,2,4-trimetil-4-(5-(4-(octiloxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)oxazolidin-3-carboxilato de (*R*)-*ter*-butilo (14a) en 80% de rendimiento. EM (ESI): 606.19 (MH^+), el tiempo de retención de CLAR sobre una columna C8(2) (30 x 3.00 mm, 3 µ) fue de 3.78 min con gradiente de 50-98% de acetonitrilo-H_2O (0.1% de TFA) en 3.5 min como fase móvil.

2,2,4-Trimetil-4-(5-(4-(4-fenilbutoxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)oxazolidin-3-carboxilato de (*R*)-ter-butilo (14c)

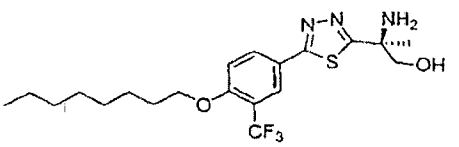


El compuesto del título se preparó de manera análoga al 2,2,4-trimetil-4-(5-(4-(octiloxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)oxazolidin-3-carboxilato de (*R*)-*ter*-butilo (14a) en 75% de rendimiento. EM (ESI): 592.14 (MH^+), el tiempo de retención de CLAR sobre una columna C8(2) (30 x 3.00

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mm, 3 µ) fue de 3.55 min con gradiente de 50-98% de acetonitrilo-H_2O (0.1% de TFA) en 3.5 min como fase móvil

(*S*)-2-Amino-2-(5-(4-(octiloxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol (15a)

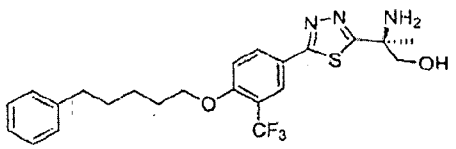


Una solución de 2,2,4-trimetil-4-(2-(4-(octiloxi)-3-(trifluorometil)-benzoil)hidrazincarbonil)oxazolidin-3-carboxilato de (*S*)-*ter*-butilo (14a) (156 mg, 0.27 mmoles) en metanol (5 ml) se trató ácido *p*-toluensulfónico monohidratado (259 mg, 1.36 mmoles) a 70°C durante 2 horas. La mezcla de reacción se enfrió después a temperatura ambiente y se purificó por CLAR prep. sobre una columna C8(2) ((Luna, 5µ, 100 x 21.10 mm) con acetonitrilo-H_2O (0.1% de TFA) como fase móvil y gradiente de 30-98% en 20 min. El compuesto del título se obtuvo como la sal de bis-TFA (36 mg, 20%).

EM (ESI): 432.00 (MH^+);

^{1}H RMN (400 MHz, DMSO-d_6) δ 8.21 (dd, 1H, J= 2.0 Hz, J= 8.8 Hz), 8.15 (d, 1H, J= 2.0 Hz), 8.09 (br s, 2H), 7.45 (d, 1H, J- 8.8 Hz), 5.96 (t, 1H, J= 4.8 Hz), 4.21 (t, 2H, J= 6.4 Hz), 3.81 (dd, 1H, J= 11.2 Hz, J= 5.2 Hz), 3.73 (dd, 1H, J= 11.2 Hz, J= 5.2 Hz), 1.76 (m, 2H), 1.66 (s, 3H), 1.44 (m, 2H), 1.28 (m, 8H), 0.86 (t, 3H, J= 6.8 Hz).

(*S*)-2-Amino-2-(5-(4-(5-fenilpentiloxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol (15b)

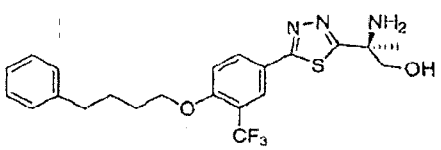


El compuesto del título se preparó de manera análoga al (*S*)-2-amino-2-(5-(4-(octiloxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol (15a) en 67% de rendimiento.

EM (ESI): 466.05 (MH^+);

^{1}H RMN (400 MHz, DMSO-d_6) δ 8.87 (br s, 2H), 8.22 (dd, 1H, J = 8.8 Hz, J= 2.0 Hz), 8.16 (d, 1H, J= 2.0 Hz), 7.45 (d, 1H, J= 8.8 Hz), 7.26 (t, 2H, J= 7.6 Hz), 7.20-7.14 (m, 3H), 6.10 (br, 1H), 4.22 (t, 2H, J= 6.4 Hz), 3.83 (d, 1H, J= 11.2 Hz), 3.77 (d, 1H, J= 11.2Hz), 2.59 (t, 2H, J= 7.2 Hz), 1.80 (m, 2H), 1.70 (s, 3H), 1.46 (m, 2H), 1.46 (m, 2H).

(*S*)-2-Amino-2-(5-(4-(4-fenilbutoxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol (15c)



El compuesto del título se preparó de manera análoga al (*S*)-2-amino-2-(5-(4-(octiloxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol (15a) en 70% de rendimiento.

EM (ESI): 452.06 (MH^+);

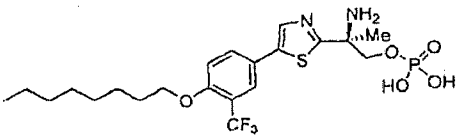
^{1}H RMN (400 MHz, DMSO-d_6) δ 8.60 (br s, 2H), 8.23 (dd, 1H, J = 8.8 Hz, J= 2.4 Hz), 8.16 (d, 1H, J= 2.4 Hz), 7.45 (d, 1H, J= 8.8 Hz), 7.28 (t, 2H, J= 7.2 Hz), 7.21-7.15 (m, 3H), 4.25, 4.22 (t, 2H, J= 5.6 Hz), 3.82 (d, 1H, J= 9.6 Hz), 3.75 (d, 1H, J= 9.6 Hz), 2.65 (t, 2H, J= 7.2 Hz), 1.80-172 (m, 4H), 1.68 (s, 3H).

Método general para síntesis de fosfato

La estrategia de síntesis para la síntesis de fosfatos deseada se ilustra en el esquema 1 anterior. A una solución de aminoalcohol no protegido (1.0 equiv) en CH_2Cl_2 seco a temperatura ambiente se añadió exceso de clorofosfato de dietilo (10.0 equiv) y trietilamina (20.0 equivalentes) y la reacción se agitó durante 12-18 horas. La reacción se monitoreó por CL-EM. La mezcla de reacción cruda después se evaporó a sequedad bajo vacío. El intermediario de fosfo-diéster obtenido se hizo reaccionar con exceso de bromotrimetilsilano (10.0-20.0 equiv) en CH_2Cl_2 seco a temperatura ambiente durante un periodo de 6-10 horas para dar el fosfato final que se purificó por CLAR preparativa de fase inversa después de la evaporación del solvente y exceso de reactivo.

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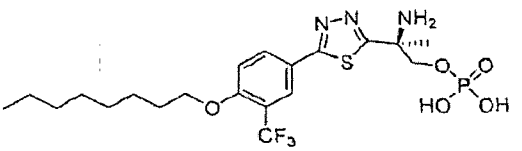
Fosfato diácido de (*S*)-2-amino-2-(5-(4-(octiloxi)-3-(trifluorometil)fenil)tiazol-2-il)propilo (9a)



El producto se obtuvo como un sólido blanco en 28% (10 mg) de rendimiento a partir del precursor de alcohol.

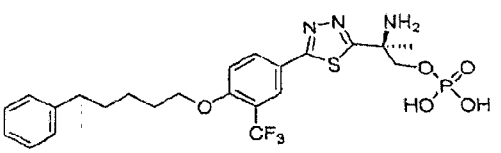
EM (ESI, $M+H^+$) = 511.1.

Fosfato diácido de (*S*)-2-amino-2-(5-(4-(octiloxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propilo (16a)



EM (ESI): 511.98 (MH^+), el tiempo de retención de CLAR sobre una columna C8(2) (30 x 3.00 mm, 3 µ) fue de 1.88 min con gradiente de 40-98% de acetonitrilo-H_2O (0.1% de TFA) en 3.5 min como fase móvil.

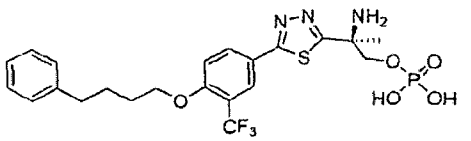
Fosfato diácido de (*S*)-2-amino-2-(5-(4-(5-fenilpentiloxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propilo (16b)



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EM (ESI): 546.01 (MH^+), el tiempo de retención de CLAR sobre una columna C8(2) (30 x 3.00 mm, 3 µ) fue de 2.06 min con gradiente de 30-98% de acetonitrilo-H_2O (0.1% de TFA) en 3.5 min como fase móvil.

Fosfato diácido de (*S*)-2-amino-2-(5-(4-(4-fenilbutoxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propilo (16c)



EM (ESI): 532.01 (MH^+), el tiempo de retención de CLAR sobre una columna C8(2) (30 x 3.00 mm, 3 µ) fue de 1.96 min con gradiente de 30-98% de acetonitrilo-H_2O (0.1% de TFA) en 3.5 min como fase móvil.

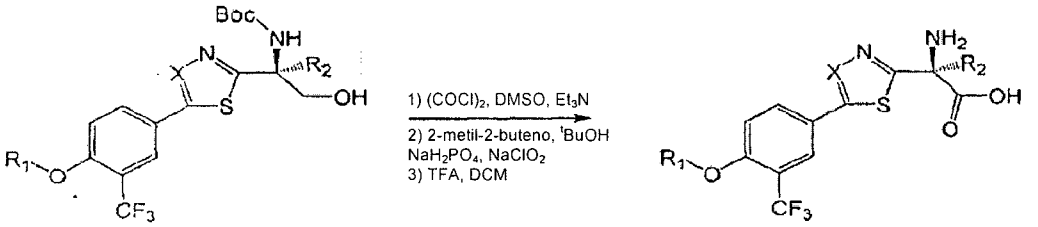
Enfoque general a síntesis de compuestos de la fórmula III

La síntesis de compuestos de la fórmula III se describe en el esquema 3. La síntesis de compuestos 1a y 1b en la estrategia A y compuesto 3 en estrategia B se describieron en los esquemas 1 y 2. La oxidación de los compuestos 1a y 1b en la estrategia A seguido por desprotección dio los compuestos 2a y 2b. En la estrategia B, el acoplamiento de la amina libre en el compuesto 3 con el aminoácido protegido deseado dio compuesto 4 que con ciclización bajo condiciones de reactivo de Lawesson dio el azol deseado 5. La remoción de los grupos protectores dio el carboxilato final 6.

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ESQUEMA 3

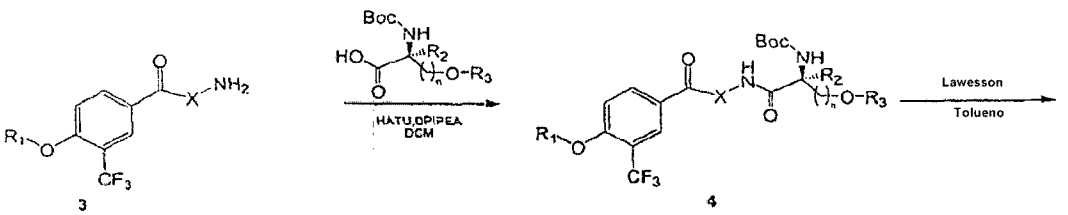
Estrategia A:

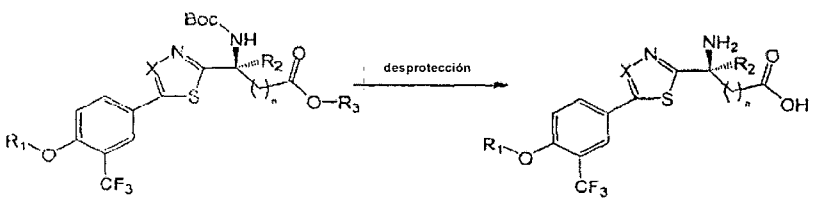


1a R_2 = H
1b R_2 = Me

2a R_2 = H
2b R_2 = Me

Estrategia B:





6a R_2 = H
6b R_2 = Me
6c R_2 = CH_2OH

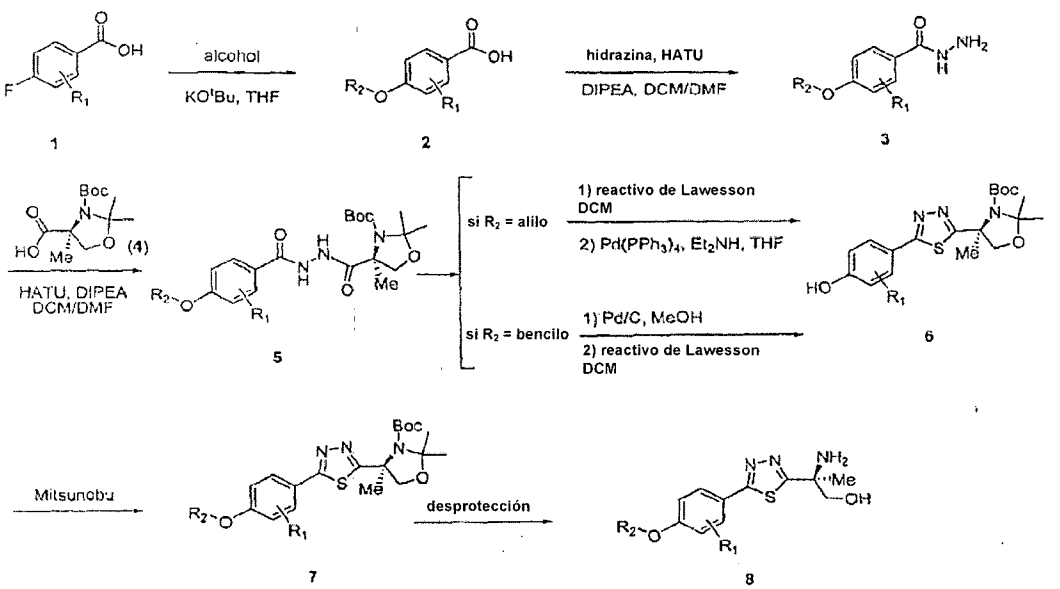
Enfoque general a síntesis de éter-fenil-tiadiazoles

La síntesis de fenil-tiazoles se describe en el esquema 4. La reacción de alcohol bencílico o alílico con ácido 4-fluorobenzoico sustituido 1

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dio el éter-benzoato sustituido 2. El éter-benzoato sustituido 2 después se acopló con hidrazina para dar benzohidrazida 3. La reacción de benzohidrazida 3 con aminoácido ortogonalmente protegido 4 bajo condiciones de HATU seguido por ciclización y desprotección (o viceversa) dio fenol 6 con buen rendimiento. La reacción de Mitsunobu de fenol 6 con el alcohol deseado seguido por desprotección dio el compuesto final deseado 8. La reacción del alcohol 8 con clorofosfato de dietilo seguido por desprotección con TMSBr dio el fosfato correspondiente.

ESQUEMA 4

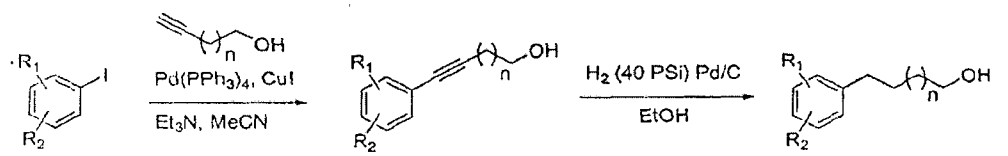


Procedimiento general para la preparación de alcoholes fenílicos sustituidos

Varios alcoholes de materiales de partida para la reacción de

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Mitsunobu se prepararon como se describe a continuación



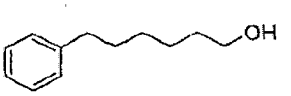
Procedimiento general para acoplamiento cruzado de Sonogashira

A una mezcla de 4-yodobenceno sustituido (1.0 equiv), $Pd(PPh_3)_4$ (0.02 equiv) y CuI (0.04 equiv) en MeCN se añadió el alquinol (1.5 equiv) y Et_3N (1.5 equiv). La mezcla de reacción se agitó durante 2-16 horas a reflujo, después el solvente se removió bajo vacío. El producto crudo se purificó por cromatografía en columna de gel de sílice usando el sistema Combi-Flash (HexrEtOAc) según era necesario.

Método general para hidrogenación de alquino

El alquino deseado se disuelve en etanol y se añade una mezcla heterogénea de paladio sobre carbón. La reacción se agita durante 2 horas bajo 2.81 kg/cm^2 de H_2. La filtración a través de celite y la remoción del solvente bajo vacío da el producto deseado.

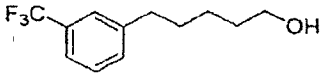
6-Fenilhexan-1-ol



El compuesto del título se preparó a partir de 6-fenilhex-5-in-1-ol con un rendimiento de 70% (241 mg).

^{1}H RMN (400 MHz, $CDCl_3$) δ 7.18-7.27 (m, 2H), 7.16-7.18 (m, 3H) 3.63 (t, 2H, J = 6.4 Hz), 2.61 (t, 2H, J= 8.0 Hz), 1.56-1.69 (m, 4H), 1.37-1.40 (m, 5H).

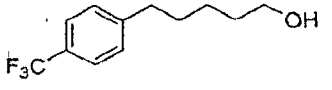
5-(3-(Trifluorometil)fenil)pentan-1-ol



El compuesto del título se preparó a partir de 5-(3-(trifluorometil)fenil)pent-4-in-1-ol con un rendimiento de 85% (241 mg).

^{1}H RMN (400 MHz, $CDCl_3$) δ 7.36-7.42 (m, 4H), 3.65 (t, 2H, J= 6.8 Hz), 2.68 (t, 2H, J= 6.0 Hz), 1.59-1.68 (m, 4H), 1.37-1.44 (m, 3H).

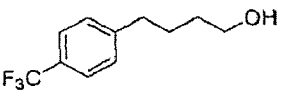
5-(4-(Trifluorometil)fenil)pentan-1-ol



El compuesto del título se preparó a partir de 5-(4-(trifluorometil)fenil)pent-4-in-1-ol con un rendimiento de 60% (140 mg).

^{1}H RMN (400 MHz, $CDCl_3$) δ 7.52 (d, 2H, J= 8.4 Hz), 7.27 (d, 2H, J= 7.3 Hz), 3.64 (t, 2H, J= 6.8 Hz), 2.68 (t, 2H, J= 8.0 Hz), 1.57-1.70 (m, 4H), 1.39-1.45 (m, 3H).

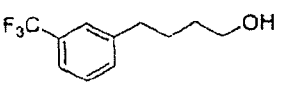
4-(4-(Trifluorometil)fenil)butan-1-ol



El compuesto del título se preparó a partir de 4-(4-(trifluorometil)fenil)but-3-in-1-ol con un rendimiento de 28% (183 mg).

^{1}H RMN (400 MHz, $CDCl_3$) δ 7.53 (d, 2H, J= 8.0 Hz), 7.29 (d, 2H, J= 1.6 Hz), 3.67 (t, 2H, J= 6.4 Hz), 2.71 (t, 2H, J= 7.6 Hz), 1.69-1.76 (m, 2H), 1.59-1.64 (m, 3H).

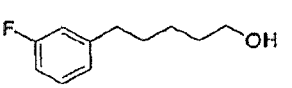
4-(3-(Trifluorometil)fenil)butan-1-ol



El compuesto del título se preparó a partir de 4-(3-(trifluorometil)fenil)but-3-in-1-ol con un rendimiento de 70% (453 mg).

^{1}H RMN (400 MHz, $CDCl_3$) δ 7.26-7.67 (m, 4H), 3.67 (t, 2H, J= 6.4 Hz), 2.70 (t, 2H, J= 6.4 Hz), 1.71-1.92 (m, 2H), 1.57-1.70 (m, 3H).

5-(3-Fluorofenil)pentan-1-ol



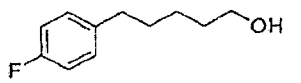
El compuesto del título se preparó a partir de 5-(3-fluorofenil)pent-4-in-1-ol con un rendimiento de 73% (405 mg).

^{1}H RMN (400 MHz, $CDCl_3$) δ 7.19-7.26 (m, 1H), 6.94 (d, 1H, J=

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7.6 Hz), 6.84-6.88 (m, 2H), 3.64 (t, 2H, J= 6.8 Hz), 2.62 (t, 2H, J= 7.6 Hz), 1.56-1.69 (m, 4H), 1.36-1.46 (m, 5H).

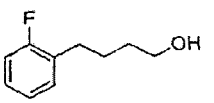
5-(4-Fluorofenil)pentan-1-ol



El compuesto del título se preparó a partir de 5-(4-fluorofenil)pent-4-in-1-ol con un rendimiento de 60% (325 mg).

^{1}H RMN (400 MHz, $CDCl_3$) δ 7.10-7.13 (m, 2H), 6.93-6.97 (m, 2H), 3.64 (t, 2H, J= 6.8 Hz), 2.59 (t, 2H, J= 7.2 Hz), 1.56-1.66 (m, 5H), 1.37-1.43 (m, 4H).

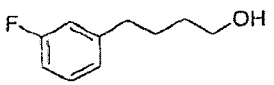
4-(2-Fluorofenil)butan-1-ol



El compuesto del título se preparó a partir de 4-(2-fluorofenil)but-3-in-1-ol con un rendimiento de 50% (246 mg).

^{1}H RMN (400 MHz, $CDCl_3$) δ 7.13-7.25 (m, 2H), 6.97-7.03 (m, 2H), 3.66 (t, 2H, J= 6.0 Hz), 2.68 (t, 2H, J = 6.8 Hz), 1.59-1.73 (m. 4H), 1.37 (br s, 1H).

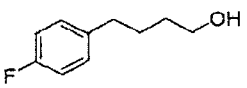
4-(3-Fluorofenil)butan-1-ol



El compuesto del título se preparó a partir de 4-(3-fluorofenil)but-3-in-1-ol con un rendimiento de 60% (295 mg).

^{1}H RMN (400 MHz, $CDCl_3$) δ 7.19-7.29 (m, 1H), 6.95 (d, 1H, J = 7.2 Hz), 6.83-6.89 (m, 2H), 3.66 (t, 2H, J= 6.4 Hz), 2.64 (t, 2H, J= 7.6 Hz), 1.56-1.74 (m, 4H), 1.39 (br s, 1H).

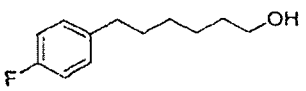
4-(4-Fluorofenil)butan-1-ol



El compuesto del título se preparó a partir de 4-(4-fluorofenil)but-3-in-1-ol con un rendimiento de 47% (233 mg).

^{1}H RMN (400 MHz, $CDCl_3$) δ 7.10-7.15 (m, 2H), 6.93-6.98 (m, 2H), 3.66 (t, 2H, J= 6.4 Hz), 2.61 (t, 2H, J= 7.6 Hz), 1.56-1.72 (m, 4H), 1.35 (s, 1H).

6-(4-Fluorofenil)hexan-1-ol

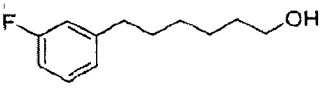


El compuesto del título se preparó a partir de 6-(4-fluorofenil)hex-5-in-1-ol con un rendimiento de 17% (95 mg).

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^{1}H RMN (400 MHz, $CDCl_3$) δ 7.15-7.18 (m, 2H), 6.98-7.07 (m, 2H), 3.65 (t, 2H, 6.8 Hz), 2.65 (t, 2H, J= 7.6 Hz), 1.57-1.65 (m, 4H), 1.38-1.42 (m,4H), 1.31 (s, 1H).

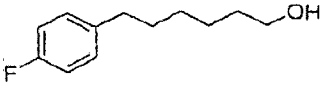
6-(3-fluorofenil)hexan-1-ol



El compuesto del título se preparó a partir de 6-(3-(trifluorometil)fenil)hex-5-in-1-ol con un rendimiento de 17% (100 mg).

^{1}H RMN (400 MHz, $CDCl_3$) δ 7.19-7.25 (m, 1H), 6.93 (d, 1H, J= 8.0 Hz), 6.83-6.88 (m, 2H), 3.63 (t, 2H, J= 6.4 Hz), 2.60 (t, 2H, J= 7.6 Hz), 1.53-1.66 (m, 4H), 1.31-1.43 (m, 5H)

6-(4-fluorofenil)hexan-1-ol

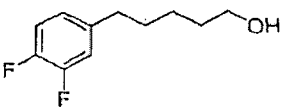


El compuesto del título se preparó a partir de 6-(3-(trifluorometil)fenil)hex-5-in-1-ol con un rendimiento de 27% (162 mg).

^{1}H RMN (400 MHz, $CDCl_3$) δ 7.19-7.27 (m, 1H), 7.09-7.13 (m, 1H), 6.92-7.04 (m, 2H), 3.63 (t, 2H, J= 6.4 Hz), 2.57 (t, 2H, J= 7.6 Hz), 1.49-1.66 (m, 5H), 1.34-1.42 (m, 4H).

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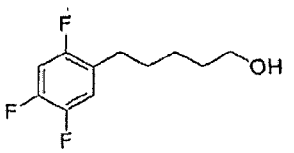
5-(3,4-difluorofenil)pentan-1-ol



El compuesto del título se preparó a partir de 6-(3-(trifluorometil)fenil)hex-5-in-1-ol con un rendimiento de 67% (404 mg).

^{1}H RMN (400 MHz, $CDCl_3$) δ 6.93-7.05 (m, 2H), 6.84-6.87 (m, 1H), 3.64 (t, 2H, J= 6.8 Hz), 2.58 (t, 2H, J= 7.6 Hz), 1.56-1.66 (m, 4H), 1.35-1.43 (m, 3H).

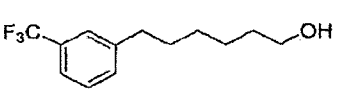
5-(2,4,5-trifluorofenil)pentan-1-ol



El compuesto del título se preparó a partir de 6-(3-(trifluorometil)fenil)hex-5-in-1-ol con un rendimiento de 57% (0.376 g).

^{1}H RMN (400 MHz, $CDCl_3$) δ 6.96-7.01 (m, 1H), 6.83-6.89 (m, 1H), 3.64 (t, 2H, J=6.8 Hz), 2.59 (t, 2H, J=7.2 Hz), 1.56-1.65 (m, 4H), 1.34-1.44 (m, 3H)

6-(3-(trifluorometil)fenil)hexan-1-ol

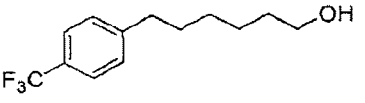


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El compuesto del título se preparó a partir de 6-(3-(trifluorometil)fenil)hex-5-in-1-ol con un rendimiento de 50% (362 mg).

^{1}H RMN (400 MHz, $CDCl_3$) δ 7.33-7.44 (m, 4H), 3.64 (t, 2H, J= 6.8 Hz), 2.67 (t, 2H, J= 7.2 Hz), 1.54-1.69 (m, 4H), 1.24-1.44 (m, 5H).

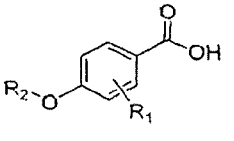
6-(4-(trifluorometil)fenil)hexan1-ol



El compuesto del título se preparó a partir de 6-(4-(trifluorometil)fenil)hex-5-in-1-ol con un rendimiento de 72% (534 mg).

^{1}H RMN (400 MHz, $CDCl_3$) δ 7.52 (d, 2H, J= 8.0 Hz), 7.27 (d, 2H, J = 8.0 Hz), 3.64 (t, 2H, J= 6.4 Hz), 2.66 (t, 2H, J= 7.2 Hz), 1.53-1.68 (m, 4H), 1.35-1.42 (m, 5H).

Protocolo general para la síntesis de ácido 4-(aliloxi)benzoico sustituido (2)

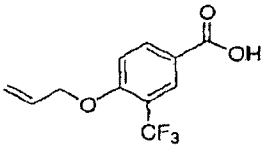


A una solución del alcohol deseado (1.05 equiv) en THF anhidro se añadió butilóxido de potasio (2.05 equiv). La mezcla se calentó a 65°C durante 10 minutos después se añadió ácido 4-fluorobenzoico sustituido (1)

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(1.00 equiv) en THF. La solución resultante se calentó a 65°C durante 1 a 3 horas. Después de enfriarse a temperatura ambiente, la reacción se diluyó con acetato de etilo y se lavó con 10% de $KHSO_4$ o HCl 1N (1x), y NaCl saturado (1x). La capa orgánica se secó sobre $MgSO_4$, se filtró, y el solvente se removió bajo vacío para dar el intermediario 2.

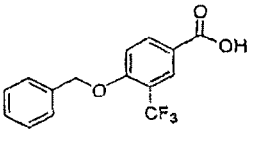
Acido 4-(aliloxi)-3-(trifluorometil)benzoico (2a)



El compuesto del título se preparó a partir de ácido 4-fluoro-3-(trifiuorometil)benzoico (1a) con un rendimiento de >99% (5.65 g). El tiempo de retención de CLAR sobre una columna C8(2) (30 x 3.00 mm, 3 µ) fue de 2.53 min con gradiente de 20-98% de acetonitrilo-H_2O (0.1% de TFA) en 4.0 min como fase móvil.

^{1}H RMN (400 MHz, DMSO-d_6) δ 13.10 (br s, 1H), 8.15 (dd, 1H, J= 8.8 Hz, J= 2.4 Hz), 8.08 (d, 1H, J= 2.4 Hz), 7.35 (d, 1H, J= 8.8 Hz), 5.95-6.80 (m, 1H), 5.38-5.45 (m, 1H), 5.26-5.32 (m, 1H), 4.77-4.82 (m, 2H).

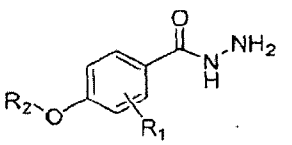
Acido 4-(benciloxi)-3-(trifluorometil)benzoico (2b)



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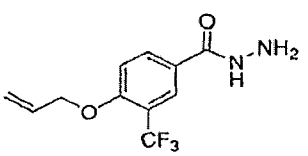
El compuesto del título se preparó a partir de ácido 4-fluoro-3-(trifluorometil)benzoico (1a) con un rendimiento de >99% (7.22 g).

Protocolo general para la síntesis de benzohidrazida sustituida (3)



Acido benzoico 2 (1.0 equiv) se agitó con HATU (1.1 equiv) y DIEA (3.0 equiv) en DCM-DMF (2:1) durante 20 minutos. La solución se añadió después a una solución de hidrazina monohidratada (3.0-5.0) en DCM-DMF (2:1). La mezcla de reacción se agitó a t.a. durante 1 hora, después se diluyó con acetato de etilo y se lavó con 10% de NH_4Cl (2x) y NaCl saturado (1x). La capa orgánica se secó sobre $MgSO_4$, se filtró, y el solvente se removió bajo vacío para dar benzohidrazida 3.

4-(Aliloxi)-3-(trifluorometil)benzohidrazida (3a)



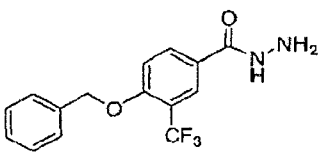
El compuesto del título se preparó a partir de ácido 4-(aliloxi)-3-(trifluorometil)benzoico (1a) con un rendimiento de >99% (6.00 g). El tiempo de retención de CLAR sobre una columna C8(2) (30 x 3.00 mm, 3 µ) fue de

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1.79 min con gradiente de 20-98% de acetonitrilo-H_2O (0.1% de TFA) en 4.0 min como fase móvil.

EM (ESI, $M+H^+$) = 261.09

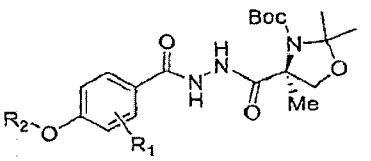
4-(Benciloxi)-3-(trifluorometil)benzohidrazida (3b)



El compuesto del título se preparó a partir de ácido 4-(benciloxi)-3-(trifluorometil)benzoico 2b con un rendimiento de >99% (14.7 g).

EM (ESI, $M+H^+$) = 311.1.

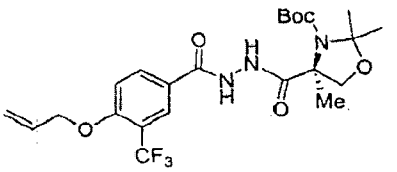
Protocolo general para la síntesis de acil-benzohidrazida (5)



Acido (*R*)-3-(*ter*-butoxicarbonil)-2,2,4-trimetiloxazolidin-4-carboxílico 4 (1.0 equiv) se agitó con HATU (1.1 equiv) y DIEA (3.0 equiv) en DCM-DMF (2:1) durante 10 min seguido por la adición de benzohidrazida sustituida 3 (1.0 equiv). La mezcla de reacción se agitó a t.a. durante 1 hora, después se diluyó con acetato de etilo y se lavó con 10% de NH4Cl (2x) y NaCl saturado (1x). La capa orgánica se secó sobre $MgSO_4$, se filtró, y el solvente se removió bajo vacío para dar acil-benzohidrazida 5.

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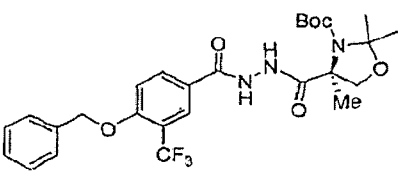
4-(2-(4-(Aliloxi)-3-(trifluorometil)benzoil)hidrazincarbonil)-2,2,4-trimetiloxazolïdin-3-carboxilato de (*R*)-*ter*-butilo (5a)



El compuesto del título se preparó a partir de 4-(aliloxi)-3-(trifluorometil)benzohidrazida 3a con un rendimiento de >99% (11.51 g). El tiempo de retención de CLAR sobre una columna C8(2) (30 x 3.00 mm, 3 µ) fue de 2.92 min con gradiente de 20-98% de acetonitrilo-H_2O (0.1% de TFA) en 4.0 min como fase móvil.

EM (ESI, $M+Na^+$) = 524.1

4-(2-(4-(Benciloxi)-3-(trifluorometil)benzoil)hidrazincarbonil)-2,2,4-trimetiloxazolidin-3-carboxilato de (*R*)-*ter*-butilo (5b)

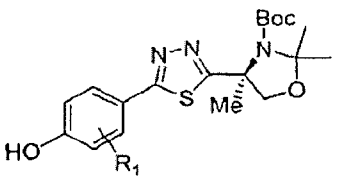


El compuesto del título se preparó a partir de 4-(benciloxi)-3-(trifluorometil)benzohidrazida 3b con un rendimiento de 83% (13.1 g).

EM (ESI, $M+Na^+$) = 574.1; CCD (2:1, Hex/EtOAc), R_f= 0.34.

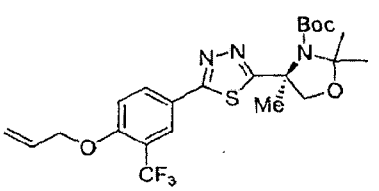
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Protocolo general para la síntesis de fenil-tiadiazol a partir de precursor de alilo protegido (6)



Una solución de acil-benzohidrazida protegida con alilo 5a (1.0 equiv) en DCM se trató con reactivo de Lawesson (1.0 equiv) a 50°C durante la noche. La reacción se enfrió a temperatura ambiente y el sobrenadante se sometió a cromatografía sobre una columna de gel de sílice eluida con acetato de etilo en hexanos (0-40%, v/v) para dar fenil-tiadiazol. Una solución de fenil-tiadiazol (1.0 equiv) y Et_2NH (1.5 equiv) en THF se trató con $Pd(PPh_3)_4$ (0.02 a 0.05 equiv) a t.a. durante 1-3 horas. El solvente se removió bajo vacío y el producto se purificó por cromatografía en columna de gel de sílice usando el sistema Combi-Flash (Hex.EtOAc).

4-(5-(4-(Aliloxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)-2,2,4-trimetiloxazolidin-3-carboxilato de (*R*)-*ter*-butilo



El compuesto del título se preparó a partir de acil-benzohidrazida 5a con un rendimiento de 88% (8.35 g). El tiempo de retención de CLAR sobre

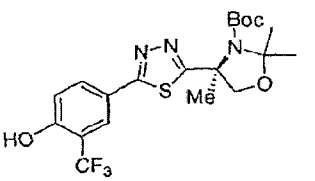
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una columna C8(2) (30 x 3.00 mm, 3 µ) fue de 2.84 min con gradiente de 50-98% de acetonitrilo-H_2O (0.1% de TFA) en 4.0 min como fase móvil.

EM (ESI, $M+H^+$) = 500.0;

^1H RMN (400 MHz, DMSO-d_6) δ 8.13-8.24 (m, 2H), 7.42 (d, 1H, J= 8.4 Hz), 5.98-6.10 (m, 1H), 5.40-5.50 (m, 1H), 5.25-5.34 (m, 1H), 4.80-4.84 (m, 2H), 4.10-4.40 (m, 2H), 1.88 (s, 3H), 1.66 (s, 3H), 1.56 (s, 3H), 1.41 (s, 3H), 1.18 (s, 6H).

4-(5-(4-Hidroxi-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)-2,2,4-trimetiloxazolidin-3-carboxilato de (*R*)-*ter*-butilo (6a)



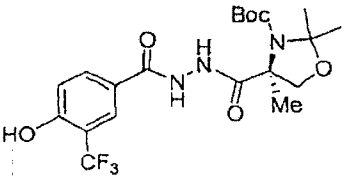
El compuesto del título se preparó a partir de fenil-tiadiazol protegido con alilo 6a en un rendimiento 64% (4.86 g). El tiempo de retención de CLAR sobre una columna C8(2) (30 x 3.00 mm, 3 µ) fue de 2.06 min con gradiente de 50-98% de acetonitrilo-H_2O (0.1% de TFA) en 4.0 min como fase móvil.

EM (ESI, $MH+H^+$) = 460.0;

^1H RMN (400 MHz, DMSO-d_6) δ 11.40 (s, 1H), 8.00-8.10 (m, 2H), 7.18 (d, 1H, J= 8.8 Hz), 4.07-4.21 (m, 2H), 1.88 (s, 3H), 1.67 (s, 3H), 1.57 (s, 3H), 1.42 (s, 3H), 1.19 (s, 6H).

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4-(2-(4-Hidroxi-3-(trifluorometil)benzoil)hidrazincarbonil)-2,2,4-trimetiloxazolidin-3-carboxilato de (*R*)-*ter*-butilo (5c)

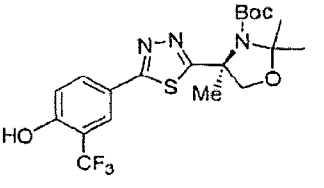


Una solución de acil-benzohidrazida protegida con bencilo 5b (1.0 equiv) en MeOH se sometió a hidrogenación en presencia de Pd/C (10% en peso) durante 1 hr. La mezcla de reacción se filtró a través de celite y se concentró para dar compuesto 5c (6.86 g, 99% de rendimiento).

EM (ESI, $M+Na^+$): 484.0; CCD (2:1, Hex/EtOAc), R_f= 0.20;

^{1}H RMN (400 MHz, CD_3OD) δ 8.11 (s, 1H), 7.95 (d, 1H, J= 8.8 Hz), 7.01 (d, 1H, J= 8.8 Hz), 4.28 (br s, 1H), 3.91 (br s, 1H), 1.69 (s, 3H), 1.64 (s, 3H), 1.58 (s, 3H), 1.49 (s, 9H).

4-(5-(4-Hidroxi-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)-2,2,4-trimetiloxazolidin-3-carboxilato de (*R*)-*ter*-butilo (6a)



El fenil-tiazol 6a se preparó mediante dos diferentes protocolos (A y B) a partir de 5c:

Protocolo A:

Una solución de acil-benzohidrazida 5c (1 equiv) en DCM se trató con reactivo de Lawesson (3.0 equiv) a 50°C durante la noche. La reacción se enfrió a temperatura ambiente y el sobrenadante se sometió a cromatografía sobre una columna de gel de sílice eluida con acetato de etilo en hexanos (0-40%, v/v) para dar fenil-tiadiazol 6 con un rendimiento de 37% (670 mg).

Protocolo B:

Una solución de acil-benzohidrazida 5c (1 equiv) en DCM se añadió anhídido de acetilo (1.1 equiv) y piridina (1.1 equiv). La mezcla se agitó a t.a. durante 4 hr. El solvente se removió bajo vacío y el residuo se disolvió en acetato de etilo, se lavó con salmuera (3x), se secó sobre $MgSO_4$ y se concentró para dar 5c acilado crudo en rendimiento cuantitativo (5.46 g).

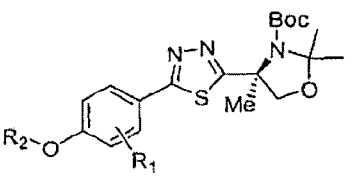
CCD (4:1, Hex/EtOAc), R_f= 0.40; EM (ESI, $M+H^+$) = 504.1.

A una solución del intermediario 5c acilado (1.0 equiv) en tolueno se añadió reactivo de Lawesson (1.1 equiv). La mezcla se calentó a 85°C durante 3 hr. La reacción se enfrió a temperatura ambiente y el sobrenadante se sometió a cromatografía sobre una columna de gel de sílice eluida con acetato de etilo en hexanos (15%-30%, v/v) para dar 6ª acilado con un rendimiento de 82% (5.1 g).

EM (ESI, $M+H^+$) = 502.0.

6a acilado se disolvió en una mezla de metanol y $NaHCO_3$ saturado (2:1, v/v) y se agitó a t.a. durante la noche. El metanol se removió y la fase acuosa se extrajo con acetato de etilo (3x). La fase orgánica combinada se lavó con salmuera, se secó sobre $MgSO_4$ y se concentró para dar 6a con un rendimiento de 76% (3.1 g).

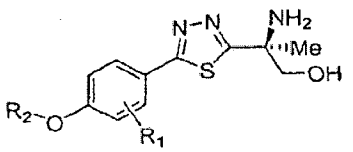
Protocolo general para reacción de Mitsunobu (7)



A una suspensión de trifenilfosfino, enlace de polímero [3 mmoles/g de carga] (1.2-6.0 equiv) en DCM o PPh_3 (1.0 equiv) en DCM o THF, se añadió un fenol 6 (1.0 equiv) y el alcohol deseado (1.0 equiv). La reacción se enfrió después a 0°C en un baño de hielo y se añadió azodicarboxilato de diisopropilo (DIAD) (1.0 equiv). La reacción después se dejó calentar a t.a. y se agitó durante 4-12 horas. La mezcla de reacción se filtró y el filtrado se concentró bajo presión reducida para dar un producto crudo, que se recorgió para el siguiente paso sin ninguna purificación adicional.

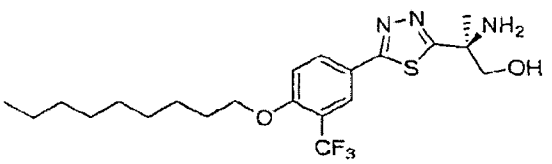
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Protocolo general para una desprotección en un crisol tanto de Boc como de oxazolidina (8)



A una solución de compuesto 8 en DCM se añadió TFA (10-50% v/v) y 1% de anisol o triisopropilsilano (TIPS) como depurador. La mezcla de reacción se dejó agitar a t.a. durante 0.5-2 horas, se secó bajo vacío y se sometió directamente a purificación por CLAR prep.. El producto se purificó por CLAR prep. sobre una columna C8(2) ((Luna, 5 µ, 100 x 21.10 mm) con acetonitrilo-H_2O (0.1% de TFA) como fase móvil y gradiente de 30-98% durante 20 min.

(*S*)-2-Amino-2-(5-(4-(noniloxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol (8a)



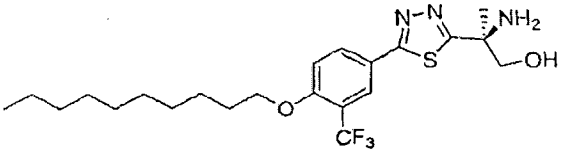
El compuesto del título se preparó a partir de fenil-tiadiazol protegido 6a con un rendimiento de 90% (579 mg). El tiempo de retención de CLAR sobre una columna C8(2) (30 x 50 mm, 3 µl) fue de 1.68 min con gradiente de 50-98% de acetonitrilo-H_2O (0.1% de TFA) en 3.5 min como fase móvil.

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EM (ESI, $M+H^+$) = 446.2;

^{1}H RMN (400 MHz, DMSO-d_6) δ 8.21 (dd, 1H, J= 9.0 Hz, J= 2.0 Hz), 8.15 (d, 1H, J= 2.0 Hz), 7.45 (d, 1H, J= 8.4), 4.21 (t, 2H, J= 6.2 Hz), 3.74-3.85 (m, 3H), 1.68-1.77 (m, 5H), 1.25-1.45 (m, 12H), 0.849 (t, 3H, J= 6.4).

(*S*)-2-Amino-2-(5-(4-(deciloxi)-3(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol (8b)



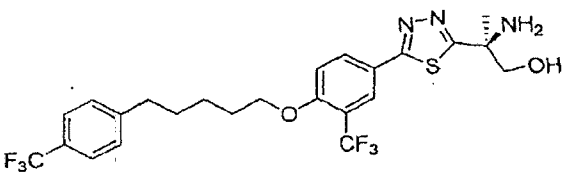
El compuesto del título se preparó a partir de fenil-tiadiazol protegido 6a con un rendimiento de 50% (208 mg). El tiempo de retención de CLAR sobre una columna C8(2) (30 x 50 mm, 3 µl) fue de 1.95 min con gradiente de 50-98% de acetonitrilo-H_2O (0.1% de TFA) en 3.5 min como fase móvil.

EM (ESI, $MH+H^+$) = 460.2;

^{1}H RMN (400 MHz, DMSO-d_6) δ 8.2 (d, 1H, J= 8.8 Hz), 8.15 (s, 1H), 7.44 (d, 1H, J= 8.8 Hz), 4.21 (t, 2H, J= 4.8 Hz), 3.74-3.78 (m, 3H), 1.75 (t, 3H, J = 6.8 Hz), 1.65 (s, 3H), 1.25-1.43 (m, 14H), 0.83-0.86 (m, 3H).

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(*S*)-2-Amino-2-(5-(3-(trifluorometil)-4-(5-(4-(trifluorometil)fenil)pentiloxi)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol (8c)

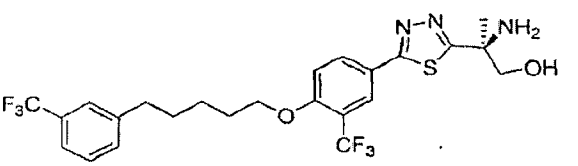


El compuesto del título se preparó a partir de fenil-tiadiazol protegido 6a con un rendimiento de 20% (149 mg). El tiempo de retención de CLAR sobre una columna C8(2) (30 x 50 mm, 3 µl) fue de 1.66 min con gradiente de 50-98% de acetonitrilo-H_2O (0.1% de TFA) en 3.5 min como fase móvil.

EM (ESI, $M+H^+$) = 534.1;

^{1}H RMN (400 MHz, DMSO-d_6) δ 8.87 (br s, 2H), 8.22 (d, 1H, J= 8 Hz), 8.16 (s, 1H), 7.44-7.55 (m, 5H), 4.22 (t, 2H, J= 6 Hz), 3.77-3.83 (m, 3H), 2.71 (t, 2H, J= 7.6 Hz), 1.68-1.82 (m, 7H), 1.46-1.48 (m, 2H).

(*S*)-2-Amino-2-(5-(3-(triflnorometil)-4-(5-(3-(trifluorometil)fenil)pentiloxi)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol (8d)



El compuesto del título se preparó a partir de fenil-tiadiazol protegido 6a con un rendimiento de 50% (379 mg). El tiempo de retención de CLAR sobre una columna C8(2) (30 x 50 mm, 3 µl) fue de 2.52 min con

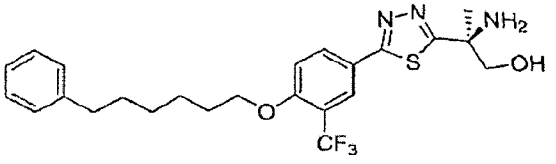
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gradiente de 30-98% de acetonitrilo-H_2O (0.1% de TFA) en 3.5 min como fase móvil.

EM (ESI, $M+H^+$) = 534.1;

^1H RMN (400 MHz, DMSO-d_6) δ 8.22 (d, 1H, J= 8 Hz), 8.15 (d, 1H, J= 2.0 Hz), 7.43-7.55 (m, 4H), 7.44 (d, 1H, J= 8.8 Hz), 4.22 (t, 2H, J= 6.0 Hz), 3.75-3.80 (m, 3H), 2.70 (t, 2H; J= 7.6 Hz), 1.78-1.82 (m, 2H), 1.67-1.70 (m, 5H), 1.45-1.47 (m, 2H).

(*S*)-2-Amino-2-(5-(4-(6-fenilhexiloxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol (8e)

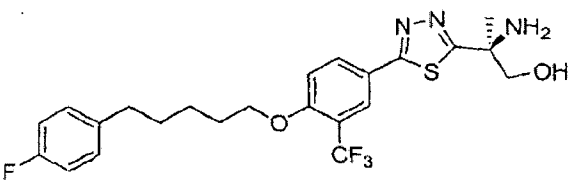


El compuesto del título se preparó a partir de fenil-tiadiazol protegido 6a con un rendimiento de 40% (271 mg). El tiempo de retención de CLAR sobre una columna C8(2) (30 x 50 mm, 3 µl) fue de 2.48 min con gradiente de 30-98% de acetonitrilo-H_2O (0.1% de TFA) en 3.5 min como fase móvil.

EM (ESI, $M+H^+$) = 480.1;

^1H RMN (400 MHz, DMSO-d_6) δ 8.21 (d, 1H, J= 9.6 Hz), 8.16 (s, 1H), 7.44 (d, 1H, J= 8.8 Hz), 7.13-7.27 (m, 5H), 4.21 (t, 2H, J= 6.4 Hz), 3.74-3.84 (m, 3H), 2.57 (t, 2H, J= 7.6 Hz), 1.69-1.79 (m, 5H), 1.55-1.62 (m, 2H), 1.44-1.51 (m, 2H), 1.33-1.39 (m, 2H).

(*S*)-2-Amino-2-(5-(4-(5-(4-fluorofenil)pentiloxi)-3-(trifluorometil)-fenil)-1,3,4-tiadiazol-2-il)propan-1-ol (8f)

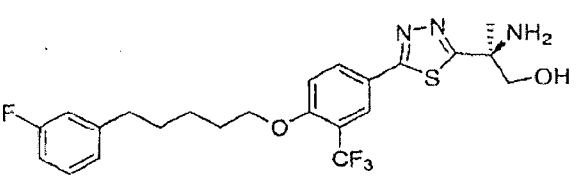


El compuesto del título se preparó a partir de fenil-tiadiazol protegido 6a con un rendimiento de 25% (155 mg). El tiempo de retención de CLAR sobre una columna C8(2) (30x50 mm, 3 µl) fue de 1.92 min con gradiente de 40-98% de acetonitrilo-H_2O (0.1% de TFA) en 3.5 min como fase móvil.

EM (ESI, $M+H^+$) = 484.1;

^{1}H RMN (400 MHz, DMSO-d_6) δ 8.19 (d, 1H, J= 9.6 Hz), 8.13 (s, 1H), 7.43 (d, 1H, J= 8.8 Hz), 7.19-7.22 (m, 2H), 7.03-7.08 (m, 2H), 4.20 (t, 2H, J= 6.0 Hz), 3.74-3.79 (m, 3H), 2.57 (t, 2H, J= 7.6 Hz), 1.76-1.79 (m, 2H), 1.60-1.67 (m, 5H), 1.42-1.45 (m, 2H).

(*S*)-2-Amino-2-(5-(4-(5-(3-fluorofenil)pentiloxi)-3-(trifluorometil) fenil)-1,3,4-tiadiazol-2-il)propan-1-ol (8g)



El compuesto del título se preparó a partir de fenil-tiadiazol

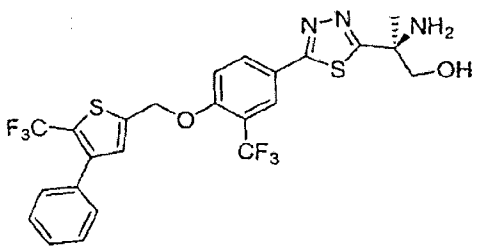
345

protegido 6a con un rendimiento de 35% (304 mg). El tiempo de retención de CLAR sobre una columna C8(2) (30 x 50 mm, 3 µl) fue de 2.71 min con gradiente de 20-95% de acetonitrilo-H_2O (0.1% de TFA) en 3.5 min como fase móvil.

EM (ESI, $M+H^+$) = 484.1;

^{1}H RMN (400 MHz, DMSO-d_6) δ 8.21 (dd, 1H, J= 8.4 Hz, J = 2.0 Hz), 8.15 (s, 1H), 7.44 (d, 1H, J= 8.8 Hz), 7.26-7.31 (m. 1H), 6.94-7.09 (m, 3H), 4.21 (t, 2H, J= 6.0 Hz), 3.74-3.83 (m, 3H), 2.61 (t, 2H, J= 7.6 Hz), 1.75-1.82 (m, 2H), 1.60-1.68 (m, 5H), 1.38-1.48 (m, 4H).

(*S*)-2-Amino-2-(5-(4-((4-fenil-5-(trifluorometil)tiofen-2-il)metoxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol (8h)



El compuesto del título se preparó a partir de 4-(5-(4-hidroxi-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)-2,2,4-trimetioxiazolidin-3-carboxilato 6a con un rendimiento de 38% (254 mg). El tiempo de retención de CLAR sobre una columna Synergi-Max RP (2 x 20 mm, 2 µl) fue de 1.47 min con gradiente de 30-99% de acetonitrilo-H_2O (0.1% de TFA) en 2 min como fase móvil.

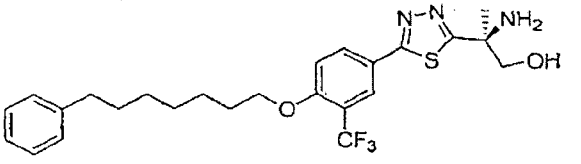
EM (ESI, $M+H^+$) = 560.0;

^{1}H RMN (400 MHz, DMSO-d_6) δ 8.88 (br s, 2H), 8.31 (dd, 1H, J=

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9.2 Hz, J= 2.4 Hz), 8.23 (d, 1H, J= 2.0 Hz), 7.44-7.51 (m, 6H), 6.11 (s, 1H), 5.72 (s, 2H), 3.79-3.85 (m, 3H), 1.72 (s, 3H).

(*S*)-2-Amino-2-(5-(4-(7-fenilheptiloxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol (8i)



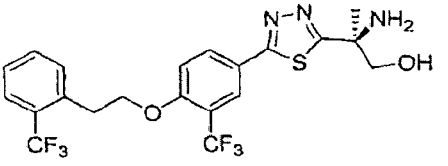
El compuesto del título se preparó a partir de 4-(5-(4-hidroxi-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)-2,2,4-trimetioxiazolidin-3-carboxilato 6a con un rendimiento de 50% (306 mg). El tiempo de retención de CLAR sobre una columna Synergi-Max RP (2 x 20 mm, 2 µl) fue de 1.32 min con gradiente de 40-99% de acetonitrilo-H_2O (0.1% de TFA) en 2 min como fase móvil.

EM (ESI, $M+H^+$) = 494.2;

^1H RMN (400 MHz, DMSO-d_6) δ 8.87 (br s, 2H), 8.22 (dd, 1H, J= 8.8, J= 2.4), 8.16 (d, 1H, J= 2.0 Hz), 7.45 (d, 1H, J= 8.4 Hz), 7.24-7.25 (m, 4H), 7.13-7.17 (m, 2H), 7.04 (s, 1H), 4.21 (t, 2H, J= 6.0 Hz), 3.78-3.85 (m, 3H), 2.56 (t. 2H, J= 7.6 Hz), 1.67-1.78 (m, 4H), 1.53-1.61 (m, 2H), 1.27-1.47 (m, 5H).

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(*S*)-2-Amino-2-(5-(3-(trifluorometil)-4-(2-(trifluorometil)fenetoxi) fenil)-1,3,4-tiadiazol-2-il)propan-1-ol (8j)

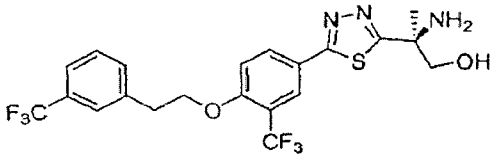


El compuesto del título se preparó a partir de 4-(5-(4-hidroxi-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)-2,2,4-trimetioxiazolidin-3-carboxilato 6a con un rendimiento de 58% (35 mg). El tiempo de retención de CLAR sobre una columna Synergi-Max RP (2 x 20 mm, 2 µl) fue de 0.70 min con gradiente de 40-99% de acetonitrilo-H_2O (0.1% de TFA) en 2 min como fase móvil.

EM (ESI, $M+H^+$) = 492.0;

^1H RMN (400 MHz, DMSO-d_6) δ 8.79 (br s, 2H), 8.22 (dd, 1H, J= 9.0 Hz, J= 2.0 Hz), 8.15 (d, 1H, J= 2.4 Hz), 7.73 (d, 1H, J= 8 Hz), 7.45-7.52 (m, 4H), 4.49 (t, 2H, J= 6.4 Hz), 3.75-3.85 (m, 3H), 3.28 (t, 2H, J= 6.4 Hz), 1.70 (s, 3H).

(*S*)-2-Amino-2-(5-(3-(trifluorometil)-4-(3-(trifluorometil) fenetoxi)fenil)-1,3.4-tiadiazol-2-il)propan-1-ol (8k)



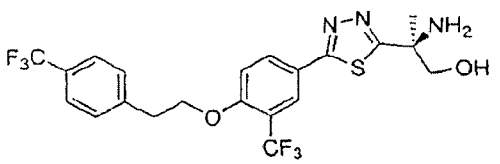
El compuesto del título se preparó a partir de 4-(5-(4-hidroxi-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)-2,2,4-trimetioxiazolidin-3-carboxilato 6a

con un rendimiento de 51% (30.7 mg). El tiempo de retención de CLAR sobre una columna Synergi-Max RP (2 x 20 mm, 2 µl) fue de 0.68 min con gradiente de 40-99% de acetonitrilo-H_2O (0.1% de TFA) en 2 min como fase móvil.

EM (ESI, $M+H^+$) = 491.9;

^1H RMN (400 MHz, DMSO-d_6) δ 8.88 (br s, 2H), 8.21 (dd, 1H, J= 8.6 Hz, J= 2.0 Hz), 8.14 (d, 1H, J= 2.4 Hz), 7.49-7.70 (m, 5H), 4.48 (t, 2H, J= 6.4 Hz), 3.77-3.85 (m, 3H), 3.20 (t, 2H, J= 6.0 Hz), 1.71 (s, 3H).

(*S*)-2-Amino-2-(5-(3-(trifluorometil)-4-(4-(trifluorometil)fenetoxi) fenil)-1,3,4-tiadiazol-2-il)propan-1-ol (8l)

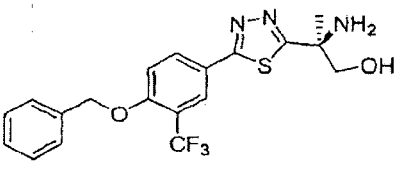


El compuesto del título se preparó a partir de 4-(5-(4-hidroxi-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)-2,2,4-trimetioxiazolidin-3-carboxilato 6a con un rendimiento de 64% (39 mg). El tiempo de retención de CLAR sobre una columna Synergi-Max RP (2 x 20 mm, 2 µl) fue de 0.77 min con gradiente de 50-98% acetomtrile-H_2O (0.1% de TFA) en 2 min como fase móvil.

EM (ESI, $M+H^+$) = 491.9;

^1H RMN (400 MHz, DMSO-d_6) δ 8.91 (br s, 2H), 8.22 (dd, 1H, J= 9.0 Hz, J= 2.0 Hz), 8.15 (d, 1H, J= 2.4 Hz), 7.44-7.68 (m, 5H), 4.49 (t, 2H, J= 6.0 Hz), 3.74-3.86 (m, 3H), 3.20 (t, 2H, J= 6.4 Hz), 1.71 (s, 3H).

(*S*)-2-Amino-2-(5-(4-(benciloxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol (8m)

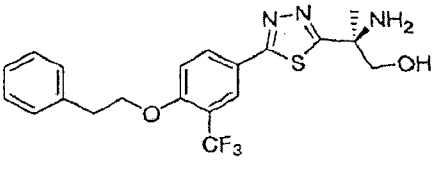


El compuesto del título se preparó a partir de 4-(5-(4-hidroxi-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)-2,2,4-trimetioxiazolidin-3-carboxilato 6a con un rendimiento de 19% (10 mg). El tiempo de retención de CLAR sobre una columna Synergi-Max RP (2 x 20 mm, 2 µl) fue de 1.37 min con gradiente de 20-95% de acetonitrilo-H_2O (0.1% de TFA) en 2 min como fase móvil.

EM (ESI, $M+H^+$) = 409.9;

^1H RMN (400 MHz, CD_3OD) δ 8.25 (d, 1H, J= 2.4 Hz), 8.16 (dd, 1H, J= 8.4 Hz, J= 2.4 Hz), 7.32-7.48 (m, 6H), 5.34 (s, 2H), 3.89-3.96 (m, 2H, 1.83 (s, 3H).

(*S*)-2-Amino-2-(5-(4-fenetoxi-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol (8n)



El compuesto del título se preparó a partir de 4-(5-(4-hidroxi-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)-2,2,4-trimetioxiazolidin-3-carboxilato 6a con un rendimiento de 12% (6.2 mg). El tiempo de retención de CLAR sobre

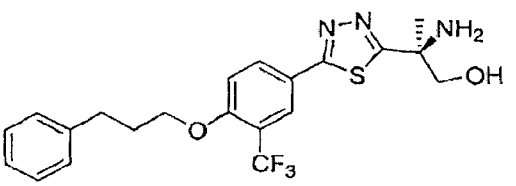
350

una columna Synergi-Max RP (2 x 20 mm, 2 µl) fue de 1.45 min con gradiente de 20-95% de acetonitrilo-H_2O (0.1% de TFA) en 2 min como fase móvil.

EM (ESI, $M+H^+$) = 423.9;

^1H RMN (400 MHz, CD_3OD) δ 8.25 (d, 1H, J= 2.4 Hz), 8.16 (dd, 1H, J= 8.4 Hz, J= 2.4 Hz), 7.26-7.35 (m, 6H), 4.40 (t, 2H, J= 6.8 Hz), 3.89-3.96 (m, 2H), 3.14 (t, 2H, J= 6.8 Hz), 1.82 (s, 3H).

(*S*)-2-Amino-2-(5-(4-(3-fenilpropoxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol (8o)



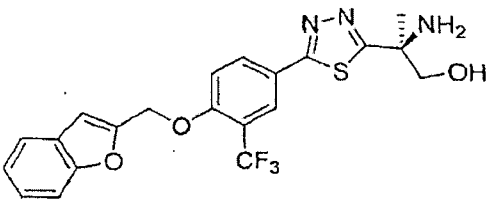
El compuesto del título se preparó a partir de 4-(5-(4-hidroxi-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)-2,2,4-trimetioxiazolidin-3-carboxilato 6a con un rendimiento de 12% (6.0 mg). El tiempo de retención de CLAR sobre una columna Synergi-Max RP (2 x 20 mm, 2 µl) fue de 1.26 min con gradiente de 30-99% de acetonitrilo-H_2O (0.1% de TFA) en 2 min como fase móvil.

EM (ESI, $M+H^+$) = 437.9;

^1H RMN (400 MHz, CD_3OD) δ 8.25 (d, 1H, J= 2.4 Hz), 8.16 (dd, 1H, J= 8.4 Hz, J= 2.4 Hz), 7.16-7.31 (m, 6H), 4.16 (t, 2H, J = 6.0 Hz), 3.89-3,96 (m, 2H), 2.85 (t, 2H, J= 7.6 Hz), 2.13-2.17 (m, 2H), 1.83 (s, 3H).

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(*S*)-2-Amino-2-(5-(4-(benzofuran-2-ilmetoxi)-3-(trifluorometil) fenil)-1,3,4-tiadiazol-2-il)propan-1-ol (8p)

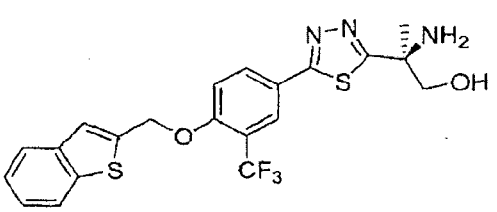


El compuesto del título se preparó a partir de 4-(5-(4-hidroxi-3-(trifluorometil)fenil)-1,3.4-tiadiazol-2-il)-2,2,4-trimetioxiazolidin-3-carboxilato 6a con un rendimiento de 29% (16 mg). El tiempo de retención de CLAR sobre una columna C8(2) (30 x 50 mm, 3 µl) fue de 2.12 min con gradiente de 20-98% de acetonitrilo-H_2O (0.1% de TFA) en 2 min como fase móvil.

EM (ESI, $M+H^+$) = 450.0;

^{1}H RMN (400 MHz, DMSO-d_6) δ 8.85 (br s, 2H), 8.28 (dd, 1H, J= 8.4 Hz, J= 2.4 Hz), 8.20 (d, 1H, J= 2.0 Hz), 7.89-7.74 (m, 3H), 7.25-7.37 (m, 2H), 6.97-7.23 (m, 1H), 5.59 (s, 3H), 3.75-3.85 (m, 3H), 1.71 (s, 3H).

(*S*)-2-Amino-2-(5-(4-(benzo[*b*]tiofen-2-ilmetoxi)-3-(trifluorometil) fenil)-1,3,4-tiadiazol-2-il)propan-1-ol (8q)



El compuesto del título se preparó a partir de 4-(5-(4-hidroxi-3-

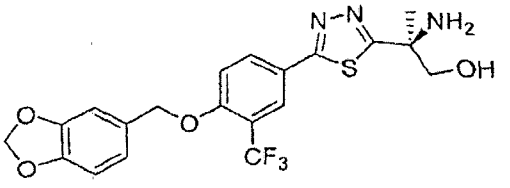
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(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)-2,2,4-trimetioxiazolidin-3- carboxilato 6a con un rendimiento de 16% (9 mg). El tiempo de retención de CLAR sobre una columna Synergi-Max RP (2 x 20 mm, 2 µl) fue de 1.49 min con gradiente de 20-95% de acetonitrilo-H_2O (0.1% de TFA) en 2 min como fase móvil.

EM (ESI, $M+H^+$) = 465.9;

^{1}H RMN (400 MHz, DMSO-d_6) δ 8.82 (br s, 2H), 8.28 (dd, 1H, J= 8.6 Hz, J= 2.0 Hz), 8.19 (d, 1H, J= 2.4 Hz), 8.02-8.04 (m, 1H), 7.91-7.93 (m, 1H), 7.74 (d, 1H, J= 8.8 Hz), 7.40-7.46 (m, 2H), 6.95-7.21 (m, 1H), 5.66 (s, 2H), 3.75-3.85 (m, 3H), 1.70 (s, 3H).

(*S*)-2-Amino-2-(5-(4-(benzo[*d*][1,3]dioxol-5-ilmetoxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol (8r)



El compuesto del título se preparó a partir de 4-(5-(4-hidroxi-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)-2,2,4-trimetioxiazolidin-3-carboxilato 6a con un rendimiento de 41% (232 mg). El tiempo de retención de CLAR sobre una columna Synergi-Max RP (2 x 20 mm, 2 µl) fue de 1.38 min con gradiente de 20-95% de acetonitrilo-H_2O (0.1% de TFA) en 2 min como fase móvil.

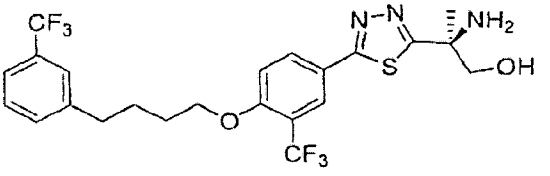
EM (ESI, $M+H^+$) = 453.9;

^{1}H RMN (400 MHz, DMSO-d_6) δ 8.87 (br s, 2H), 8.26 (dd, 1H, J=

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9.2 Hz, J= 2.4 Hz), 8.19 (d, 1H, J= 2.4 Hz), 7.58 (d, 1H, J= 8.8 Hz), 6.87-7.12 (m, 3H), 6.07 (s, 2H), 5.34 (s, 2H), 3.76-3.85 (m, 2H), 1.71 (s, 3H).

(S)-2-Amino-2-(5-(3-(trifluorometil)-4-(4-(3-(trifluorometil) fenil)butoxi)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol (8s)

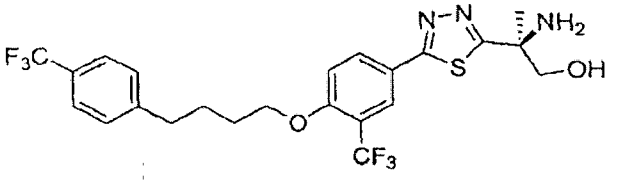


El compuesto del título se preparó a partir de 4-(5-(4-hidroxi-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)-2,2,4-trimetioxiazolidin-3-carboxilato 6a con un rendimiento de 29% (184 mg). El tiempo de retención de CLAR sobre una columna Synergi-Max RP (2 x 20 mm, 2 µl) fue de 1.67 min con gradiente de 20-95% de acetonitrilo-H_2O (0.1% de TFA) en 2 min como fase móvil.

EM (ESI, $M+H^+$) = 519.9;

^1H RMN (400 MHz, CD_3OD) δ 8.22 (d, 1H, J= 2.4 Hz), 8.16 (dd, 1H, J= 8.6 Hz, J= 2.4 Hz), 7.56 (d, 2H, J = 8.4 Hz), 7.4 (d, 2H, J= 8.0 Hz), 7.33 (d, 1H, J= 8.8 Hz), 4.23 (t, 2H, J= 5.2 Hz), 3.92-4.00 (m, 2H), 2.80 (t, 2H, J= 6.8 Hz), 1.88-1.92 (m, 4H), 1.84 (s, 3H).

(*S*)-2-Amino-2-(5-(3-(trifluorometil)-4-(4-(4-(trifluorometil)fenil) butoxi)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol (8t)

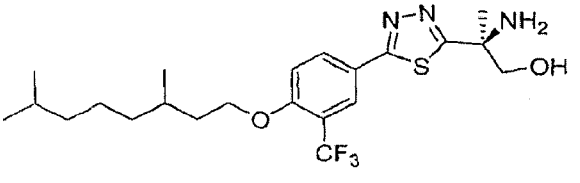


El compuesto del título se preparó a partir de 4-(5-(4-hidroxi-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)-2,2,4-trimetioxiazolidin-3-carboxilato 6a con un rendimiento de 12% (7.8 mg). El tiempo de retención de CLAR sobre una columna Synergi-Max RP (2 x 20 mm, 2 µl) fue de 1.64 min con gradiente de 20-95% de acetonitrilo-H_2O (0.1% de TFA) en 2 min como fase móvil.

EM (ESI, $M+H^+$) = 519.9;

^{1}H RMN (400 MHz, CD_3OD) δ 8.22 (d, 1H, J= 2.0 Hz), 8.16 (dd, 1H, J= 8.6 Hz, J= 2.0 Hz), 7.46-7.51 (m, 4H), 7.34 (d, 1H, J= 9.2 Hz), 4.24 (s, 2H), 3.90-3.98 (m, 2H), 2.80 (t, 2H, J= 6.8 Hz), 1.88-1.91 (m, 4H), 1.83 (s, 3H).

(2*S*)-2-Amino-2-(5-(4-(3,7-dimetiloctiloxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol (8u)



El compuesto del título se preparó a partir de 4-(5-(4-hidroxi-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)-2,2,4-trimetioxiazolidin-3-carboxilato 6a con un rendimiento de 41% (19 mg). El tiempo de retención de CLAR sobre

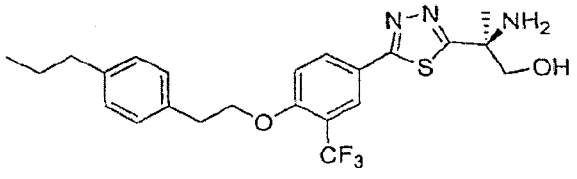
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una columna Synergi-Max RP (2 x 20 mm, 2 µl) fue de 1.79 min con gradiente de 50-98% de acetonitrilo-H_2O (0.1% de TFA) en 2 min como fase móvil.

EM (ESI, $M+H^+$) = 460.0;

^1H RMN (400 MHz, CD_3OD) δ 8.21 (d, 1H, J= 2.4 Hz), 8.17 (dd, 1H, J= 8.8 Hz, J= 2.4 Hz), 7.36 (d, 1H, J = 8.4 Hz), 4.86 (s, 5H), 4.22-4.27 (m, 2H), 3.90-3.98 (m, 2H), 1.87-1.90 (m, 1H), 1.83 (s, 3H), 1.74-1.78 (m, 1H), 1.61-1.65 (m, 1H), 1.50-1.55 (m, 1H), 1.30-1.40 (m, 3H), 1.16-1.22 (m, 3H), 0.97 (d, 3H, J= 6.4 Hz), 0.88 (d, 6H, J= 6.8 Hz)

(*S*)-2-Amino-2-(5-(4-(4-propilfenetoxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol (8v)



El compuesto del título se preparó a partir de 4-(5-(4-hidroxi-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)-2,2,4-trimetioxiazolidin-3-carboxilato 6a con un rendimiento de 47% (27 mg). El tiempo de retención de CLAR sobre una columna Synergi-Max RP (2 x 20 mm, 2 µl) fue de 1.66 min con gradiente de 50-98% de acetonitrilo-H_2O (0.1% de TFA) en 2 min como fase móvil.

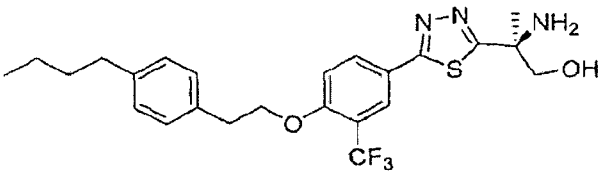
EM (ESI, $M+H^+$) = 466.0;

^1H RMN (400 MHz, CD_3OD) δ 8.20 (d, 1H, J= 1.6 Hz), 8.13 (dd, 1H, J= 8.8 Hz, J= 2.4 Hz), 7.32 (d, 1H, J = 8.8 Hz), 7.22 (d, 2H, J= 8.4 Hz), 7.10 (d, 2H, J= 8.4 Hz), 4.44 (t, 2H, J= 6.6 Hz), 3.90-3.98 (m, 2H), 3.10 (t, 2H,

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J= 6.6 Hz), 2.55 (t, 2H, J= 7.6 Hz), 1.83 (s, 3H), 1.58-1.64 (m, 2H), 1.25 (d, 5H, J= 6.4), 0.91 (t, 3H, J= 7.6).

(*S*)-2-Amino-2-(5-(4-(4-butilfenetoxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol (8w)

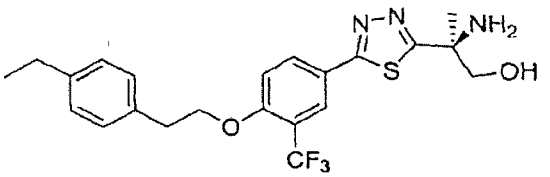


El compuesto del título se preparó a partir de 4-(5-(4-hidroxi-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)-2,2,4-trimetioxiazolidin-3-carboxilato 6a con un rendimiento de 38% (23 mg). El tiempo de retención de CLAR sobre una columna Synergi-Max RP (2 x 20 mm, 2 µl) fue de 1.73 min con gradiente de 20-95% de acetonitrilo-H_2O (0.1% de TFA) en 2 min como fase móvil.

EM (ESI, $M+H^+$) = 479.9;

^{1}H RMN (400 MHz, CD_3OD) δ 8.20 (d, 1H, J= 1.6 Hz), 8.13 (dd, 1H, J= 2.4 Hz, J= 8.8 Hz), 7.32 (d, 1H, J = 8.8 Hz), 7.22 (d, 2H, J= 8 Hz), 7.10 (d, 2H, J= 8 Hz), 4.36 (t, 2H, J= 6.4), 3.90-3.98 (m, 2H), 3.10 (t, 2H, J= 6.8 Hz), 2.57 (t, 2H, J= 7.6 Hz), 1.83 (s, 3H), 1.53-1.61 (m, 2H), 1.31-1.36 (m, 2H), 0.917 (t, 3H, J= 7.2 Hz).

(*S*)-2-Amino-2-(5-(4-(4-etilfenetoxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol (8x)

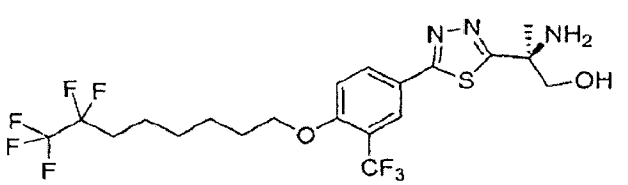


El compuesto del título se preparó a partir de 4-(5-(4-hidroxi-3-(trifluorotnetil)fenil)-1,3,4-tiadiazol-2-il)-2,2,4-trimetioxiazolidin-3-carboxilato 6a con un rendimiento de 63% (36 mg). El tiempo de retención de CLAR sobre una columna Synergi-Max RP (2 x 20 mm, 2 µl) fue de 1.59 min con gradiente de 20-95% de acetonitrilo-H_2O (0.1% de TFA) en 2 min como fase móvil.

EM (ESI, $M+H^+$) = 451.9;

^1H RMN (400 MHz, CD_3OD) δ 8.20 (d, 1H, J= 1.6 Hz), 8.14 (dd, 1H, J= 8.8 Hz, J= 2.4 Hz), 7.32 (d, 1H, J = 8.4 Hz), 7.23 (d, 2H, J- 8.4 Hz), 7.12 (d, 2H, J= 8.0 Hz), 4.36 (t, 2H, J= 6.8 Hz), 3.90-3.98 (m, 2H), 3.10 (t, 2H, J= 6.8 Hz), 2.55-2.65 (m, 2H), 1.83 (s, 3H), 1.20 (t, 3H, J= 7.6 Hz).

(*S*)-2-Amino-2-(5-(4-(7,7,8,8,8-pentafluorooctiloxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol (8y)



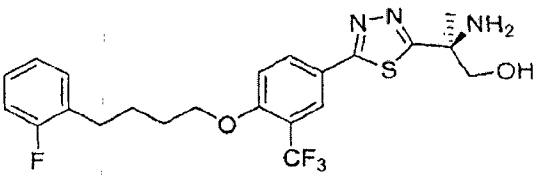
El compuesto del título se preparó a partir de 4-(5-(4-hidroxi-3-

(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)-2,2,4-trimetioxiazolidin-3-carboxilato 6a con un rendimiento de 35% (22 mg). El tiempo de retención de CLAR sobre una columna Synergi-Max RP (2 x 20 mm, 2 µl) fue de 1.68 min con gradiente de 20-95% de acetonitrilo-H_2O (0.1% de TFA) en 2 min como fase móvil.

EM (ESI, M+H+) - 522.0;

^{1}H RMN (400 MHz, CD_3OD) δ 8.21 (d, 1H, J= 2.4 Hz), 8.16 (dd, 1H, J= 8.6 Hz, J= 2.4 Hz), 7.34 (d, 1H, J = 9.2 Hz), 4.21 (t, 2H, J= 6.0 Hz), 3.90-3.96 (m, 2H), 2.05-2.19 (m, 2H), 1.84-1.91 (m, 2H), 1.81 (s, 3H), 1.48-1.67 (m, 6H).

(*S*)-2-Amino-2-(5-(4-(4-(2-fluorofenil)butoxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol (8z)



El compuesto del título se preparó a partir de 4-(5-(4-hidroxi-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)-2,2,-trimetioxiazolidin-3-carboxilato 6a con un rendimiento 8% (5 mg). El tiempo de retención de CLAR sobre una columna Synergi-Max RP (2 x 20 mm, 2 µl) fue de 1.59 min con gradiente de 20-95% de acetonitrilo-H_2O (0.1% de TFA) en 2 min como fase móvil.

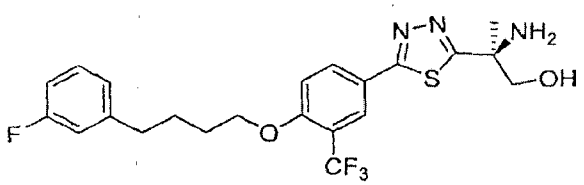
EM (ESI, $M+H^+$) = 469.9;

^{1}H RMN (400 MHz, CD_3OD) δ 8.21 (d, 1H, J= 1.6 Hz), 8.16 (dd, 1H, J= 8.4 Hz, J= 2.4 Hz), 7.34 (d, 1H, J= 8.4 Hz), 7.16-7.27 (m, 2H), 6.99-

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7.10 (m, 2H), 4.22 (t, 2H, J= 5.6 Hz), 3.90-3.97 (m, 2H), 2.74 (t, 2H, J= 7.2 Hz), 1.82-1.90 (m, 4H), 1.82 (s, 2H).

(*S*)-2-Amino-2-(5-(4-(4-(3-fluorofenil)butoxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol (8aa)



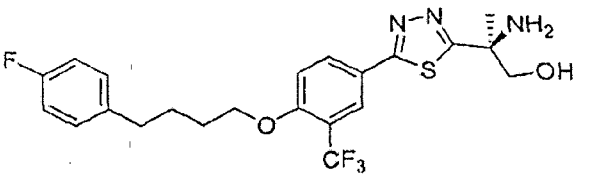
El compuesto del título se preparó a partir de 4-(5-(4-hidroxi-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)-2,2,4-trimetioxiazolidin-3-carboxilato 6a con un rendimiento de 16% (9 mg). El tiempo de retención de CLAR sobre una columna Synergi-Max RP (2 x 20 mm, 2 µl) fue de 1.60 min con gradiente de 20-95% de acetonitrilo-H_2O (0.1% de TFA) en 2 min como fase móvil.

EM (ESI, $M+H^+$) = 469.9;

^1H RMN (400 MHz, CD_3OD) δ 8.21 (d, 1H, J= 2.4 Hz), 8.16 (dd, 1H, J= 8.4 Hz, J= 2.4 Hz), 7.34 (d, 1H, J= 8.4 Hz), 7.23-7.29 (m, 1H), 7.02 (d, 1H, J= 5.0 Hz), 6.85-6.96 (m, 2H), 4.22, (t, 2H, J= 5.6 Hz), 3.91-3.97 (m, 2H), 2.70-2.74 (m, 2H), 1.83-1.88 (m, 4H), 1.83 (s, 3H).

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(*S*)-2-Amino-2-(5-(4-(4-(4-fluorofenil)butoxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol (8ab)

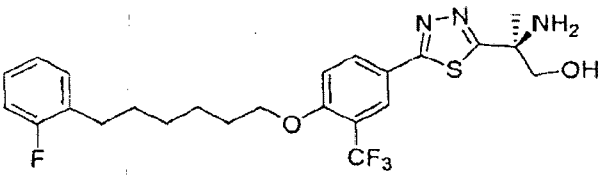


El compuesto del título se preparó a partir de 4-(5-(4-hidroxi-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)-2,2,4-trimetioxiazolidin-3-carboxilato 6ª con un rendimiento de 16% (9 mg). El tiempo de retención de CLAR sobre una columna Synergi-Max RP (2 x 20 mm, 2 µl) fue de 1.91 min con gradiente de 20-95% de acetonitrilo-H_2O (0.1% de TFA) en 2 min como fase móvil.

EM (ESI, $M+H^+$) = 469.9;

^{1}H RMN (400 MHz, CD_3OD) δ 8.21 (d, 1H, J= 2.4 Hz), 8.16 (dd, 1H, J= 8.6 Hz, J= 2.4 Hz), 7.34 (d, 1H, J= 8.0 Hz), 7.2 (m, 2H), 6.95-6.70 (m, 2H), 4.21 (t, 2H, J= 5.5 Hz), 3.90-3.98 (m, 2H), 2.69 (t, 2H, J= 6.8 Hz), 1.83-1.86 (m, 4H), 1.82 (s, 3H).

(*S*)-2-Amino-2-(5-(4-(6-(2-fluorofenil)hexiloxi)-3-(trifluorometil) fenil)-1,3,4-tiadiazol-2-il)propan-1-ol (8ac)



El compuesto del título se preparó a partir de 4-(5-(4-hidroxi-3-

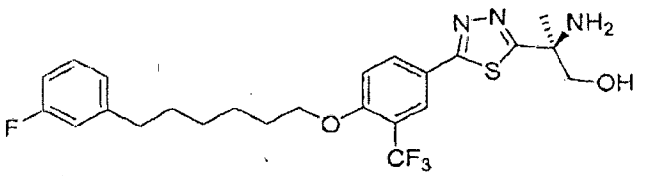
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(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)-2,2,4-trimetioxiazolidin-3-carboxilato 6a con un rendimiento de 15% (9 mg). El tiempo de retención de CLAR sobre una columna Synergi-Max RP (2 x 20 mm, 2 µl) fue de 1.73 min con gradiente de 20-95% de acetonitrilo-H_2O (0.1% de TFA) en 2 min como fase móvil.

EM (ESI, $M+H^+$) = 498.1;

^1H RMN (400 MHz, CD_3OD) δ 8.21 (d, 1H, J= 2.4 Hz), 8.16 (dd, 1H, J= 8.4 Hz, J= 2.4 Hz), 7.34 (d, 1H, J= 8.4 Hz), 7.14-7.23 (m, 2H), 6.87-7.07 (m, 2H), 4.19 (t, 2H, J= 6.0 Hz), 3.90-3.97 (m, 2H), 3.79 (s, 2H), 2.66 (t, 2H, J= 8.0 Hz), 1.83-1.88 (m, 1H), 1.82 (s, 3H), 1.53-1.69 (m, 3H), 1.41-1.47 (m, 2H), 1.25-1.27 (m, 3H).

(*S*)-2-Amino-2-(5-(4-(6-(3-fluorofenil)hexiloxi)-3-(trifluorometil) fenil)-1,3,4-tiadiazol-2-il)propan-1-ol (8ad)



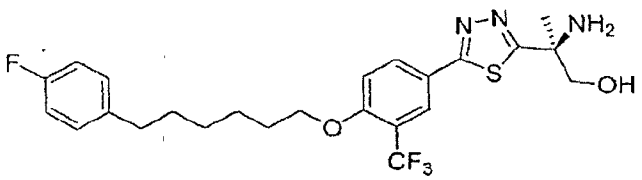
El compuesto del título se preparó a partir de acil-benzohidrazida desprotegida 5b con un rendimiento de 23% (11.3 mg). El tiempo de retención de CLAR sobre una columna Synergi-Max RP (2 x 20 mm, 2 µl) fue de 1.69 min con gradiente de 20-95% de acetonitrilo-H_2O (0.1% de TFA) en 2 min como fase móvil.

EM (ESI): 497.98 (MH^+);

^1H RMN (400 MHz, CD_3OD) δ 8.21 (d, 1H, J= 2.4 Hz), 8.16 (dd,

1H, J= 8.6 Hz, J= 2.4 Hz), 7.34 (d, 1H, J= 8.4 Hz), 7.20-7.24 (m, 1H), 6.98 (d, 1H, J= 7.6 Hz), 6.85-6.91 (m, 2H), 4.19 (t, 2H, J= 6.4 Hz), 3.90-3.96 (m, 2H), 2.64 (t, 1H, J= 7.6 Hz), 1.85-2.01 (m, 2H), 1.83 (s, 3H), 1.63-1.68 (m, 2H), 1.55-1.59 (m, 2H), 1.40-1.46 (m, 2H).

(*S*)-2-Amino-2-(5-(4-(6-(4-fluorofenil)hexiloxi)-3-(trifluorometil) fenil)-1,3,4-tiadiazol-2-il)propan-1-ol (8ae)



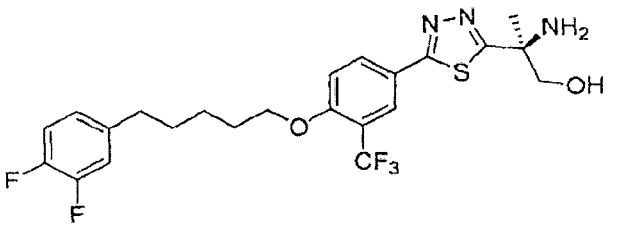
El compuesto del título se preparó a partir de acil-benzohidrazida desprotegida 5b con un rendimiento de 35% (17.4 mg). El tiempo de retención de CLAR sobre una columna Synergi-Max RP (2 x 20 mm, 2 µl) fue de 1.69 min con gradiente de 20-95% de acetonitrilo-H_2O (0.1% de TFA) en 2 min como fase móvil.

EM (ESI): 497.98 (MH^+);

^1H RMN (400 MHz, CD_3OD) δ 8.21 (d, 1H, J= 2.0 Hz), 8.16 (dd, 1H, J= 8.4 Hz, J= 2.0 Hz), 7.32 (d, 1H, J= 8.4 Hz), 7.14-7.17 (m, 2H), 6.92-6.96 (m, 2H), 4.18 (t, 2H, J= 6.4 Hz), 3.90-3.98 (m, 2H), 2.60 (t, 1H, J= 8.0 Hz), 1.85-2.01 (m, 2H), 1.83 (s, 3H), 1.60-1.68 (m, 2H), 1.52-1.58 (m, 2H), 1.38-1.44 (m, 2H).

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(*S*)-2-Amino-2-(5-(4-(5-(3,4-difluorofenil)pentiloxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol (8af)

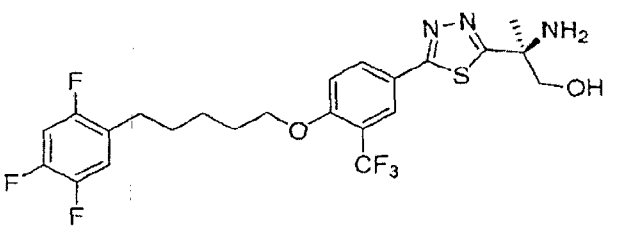


El compuesto del título se preparó a partir de acil-benzohidrazida desprotegida 5b en 44% (22.0 mg). El tiempo de retención de CLAR sobre una columna Synergi-Max RP (2 x 20 mm, 2 µl) fue de 1.46 min con gradiente de 30-99% de acetonitrilo-H_2O (0.1% de TFA) en 2 min como fase móvil.

EM (ESI): 501.86 (MH^+);

^{1}H RMN (400 MHz, CD_3OD) δ 8.21 (d, 1H, J= 2.4 Hz), 8.16 (dd, 1H, J= 8.4 Hz, J= 2.4 Hz), 7.34 (d, 1H, J= 8.4 Hz), 7.05-7.14 (m, 2H), 6.94-6.98 (m, 1H), 4.20 (t, 2H, J= 6.0 Hz), 3.89-3.96 (m, 2H), 2.64 (t, 2H, J= 7.2 Hz), 1.85-1.91 (m, 2H), 1.83 (s, 3H), 1.66-1.74 (m, 2H), 1.52-1.58 (m, 2H).

(*S*)-2-Amino-2-(5-(3-(trifluorometil)-4-(5-(2,4,5-trifluorofenil) pentiloxi)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol (8ag)



El compuesto del título se preparó a partir de acil-benzohidrazida

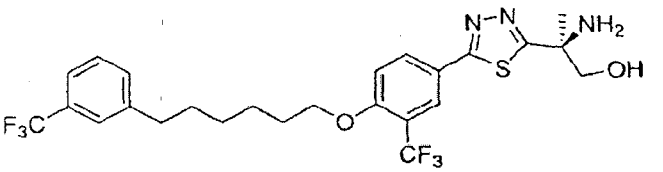
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desprotegida 5b en 28% (14.7 mg). El tiempo de retención de CLAR sobre una columna Synergi-Max RP (2 x 20 mm, 2 µl) fue de 1.69 min con gradiente de 20-95% de acetonitrilo-H_2O (0.1% de TFA) en 2 min como fase móvil.

EM (ESI): 497.98 (MH^+);

^1H RMN (400 MHz. CD_3OD) δ 8.21 (d, 1H, J=2 Hz), 8.16 (dd, 1H, J= 8.4 Hz, J= 2.0 Hz), 7.34 (d, 1H, J= 9.2 Hz), 7.14-7.21 (m, 1H), 7.02-7.08 (m, 1H), 4.20 (t, 2H, J= 6.0 Hz), 3.89-3.98 (m, 2H), 2.65 (t, 2H, J= 7.2 Hz), 1.83-1.90 (m, 5H), 1.65-1.71 (m, 2H), 1.53-1.59 (m, 2H).

(*S*)-2-Amino-2-(5-(3-(trifluorometil)-4-(6-(3-(trifluorometil) fenil)hexiloxi)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol (8ah)



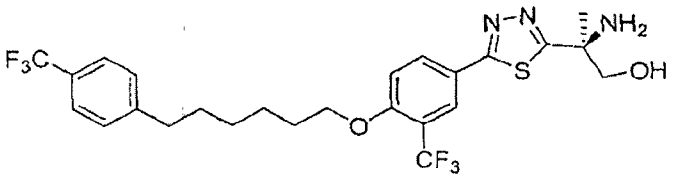
El compuesto del título se preparó a partir de acil-benzohidrazida desprotegida 5b en 60% (33.1 mg). El tiempo de retención de CLAR sobre una columna Synergi-Max RP (2 x 20 mm, 2 µl) fue de 1.73 min con gradiente de 20-95% de acetonitrilo-H_2O (0.1% de TFA) en 2 min como fase móvil.

EM (ESI): 548.00 (MH^+);

^1H RMN (400 MHz, CD_3OD) δ 8.21 (d, 1H, J= 1.6 Hz), 8.16 (dd, 1H, J= 8.4 Hz, J= 2.4 Hz), 7.44-7.46 (m, 4H), 7.33 (d, 1H, J= 8.4 Hz), 4.19 (t, 2H, J= 6.4 Hz), 3.90-3.99 (m, 2H), 2.71 (t, 2H, J= 7.6 Hz), 1.81-1.88 (m, 2H), 1.65-1.73 (m, 2H), 1.54-1.61 (m, 2H), 1.39-1.47 (m, 2H), 1.24-1.28 (m, 3H).

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(*S*)-2-Amino-2-(5-(3-(trifluorometil)-4-(6-(4-(trifluorometil) fenil)hexiloxi)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol (8ai)



El compuesto del título se preparó a partir de acil-benzohidrazida desprotegida 5b en 59% (32.0 mg). El tiempo de retención de CLAR sobre una columna Synergi-Max RP (2 x 20 mm, 2 µl) fue de 1.74 min con gradiente de 20-95% de acetonitrilo-H_2O (0.1% de TFA) en 2 min como fase móvil.

EM (ESI): 547.92 (MH^+);

^{1}H RMN (400 MHz, CD_3OD) δ 8.22 (d, 1H, J= 2.0 Hz), 8.16 (dd, 1H, J= 8.6 Hz, J= 2.0 Hz), 7.53 (d, 2H, J= 8.0 Hz), 7.32-7.37 (m, 3H), 4.19 (t, 2H, J= 6.4 Hz), 3.90-3.98 (m, 2H), 2.72 (t, 2H, J= 7.6 Hz), 1.81-1.88 (m, 2H), 1.66-1.73 (m, 2H), 1.54-1.61 (m, 2H), 1.41-1.47 (m, 2H), 1.24-1.27 (m, 3H).

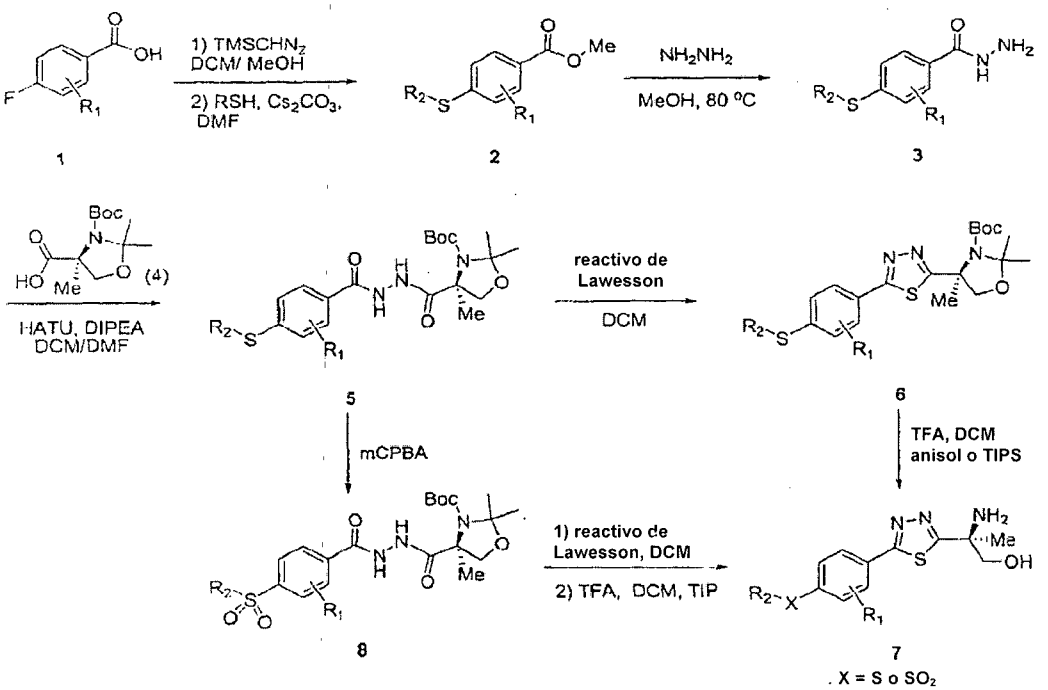
Enfoque general de la síntesis de tio-éter-fenil-tiadiazoles

La síntesis de tio-éter-fenil-tiazoles se describe en el esquema 5. El tratamiento de ácido 4-fluorobenzoico sustituido 1 con TMS-CHN_2 dio el éster metílico correspondiente bajo reacción con varios tioles dio el tio-éter sustituido 2. El tio-éter sustituido 2 después se condensó con hidrazina para dar benzohidrazida 3. La reacción de benzohidrazida 3 con aminoácido ortogonalmente protegido 4 bajo condiciones de HATU para dar acil-

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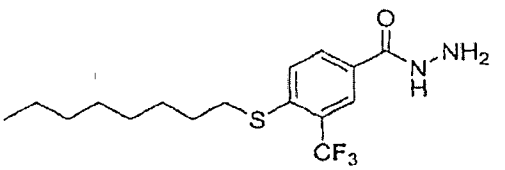
benzohidrazida 5 que bajo tratamiento con reactivo de Lawesson dio fenol 6 con buen rendimiento. La reacción de Mitsunobu de fenol 6 con alcohol deseado seguido por desprotección dio el compuesto final deseado 7. La acil-benzohidrazida 5 también se podriá oxidar con mCPBA para dar acil-benzohidrazida 8 antes de tratamiento con reactivo de Lawesson y desprotección. La reacción del alcohol 7 con clorofosfato de dietilo seguido por desprotección con TMSBr dio el fosfato correspondiente.

ESQUEMA 5



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4-(Octiltio)-3-(trifluorometil)benzohidrazida (3a)



A una solución de ácido 4-fluoro-3-(trifluorometil)benzoico 1a (1.04 g, 5 mmoles) en DCM/MeOH (4:1, 10 ml) a 0°C se añadió gota a gota una solución de $TMSCHN_2$ (2.0 M en éter, 2.6 ml, 5.1 mmoles). La mezcla de reacción se agitó a 0°C hasta que la solución incolora empezó a volverse amarillo claro y se mantuvo su color amarillo claro. La reacción se agitó durante 20 minutos adicionales, después se añadieron una pocas gotas de ácido acético para extinguir las últimas pocas gotas de $TMS\text{-}CHN_2$ (la solución se volvió incolora a partir de amarillo claro). El solvente se removió bajo vacío para dar un producto crudo que se usó directamente para el siguiente paso.

EM (ESI, $M+H^+$) = 223.0

A una solución del éster metílico crudo en DMF (5 ml) se añadió octano-1-tiol (0.87 ml, 5 mmoles) y Cs_2CO_3 (2.44 g, 7.5 mmoles). La mezcla de reacción se agitó a 60°C durante 1 hr, se concentró, se extinguió con NH_4Cl, se extrajo con EtOAc. Los compuestos orgánicos se secaron sobre Na_2SO_4, se concentraron bajo presión reducida para dejar el 4-(octiltio)-3-(trifluorometil)benzoato de metilo crudo 2a.

EM (ESI, $M+H^+$) = 349.0

El 4-(octiltio)-3-(trifluorometil)benzoato de metilo crudo se disolvió en 2 ml de MeOH y se trató con 2 ml de hidrazina hidratada. La

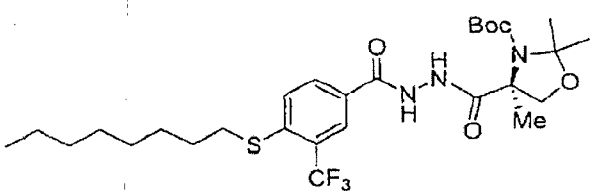
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mezcla de reacción se dejó agitar a 80°C durante 1 hora, se vació en agua con hielo. El sólido se filtró, se lavó con H_2O y se secó bajo vacío para proveer la 4-(octiltio)-3-(trifluorometil)benzohidrazida 3a como un sólido amarillo. El tiempo de retención de CLAR sobre una columna C18 (30 x 4.6 mm, 3.5 µ) fue de 2.69 min con gradiente de 10-95% de acetonitrilo-H_2O (0.1% de TFA) en 3.5 min como fase móvil.

EM (ESI, $M+H^+$) = 349.3;

^{1}H RMN (400 MHz, $CDCl_3$) δ 9.99 (s, 1H), 8.13 (d, 1H. J=1.6 Hz), 8.03 (dd, 1H, J= 8.2 Hz, J= 1.6 Hz), 7.67 (d, 1H, J= 8.8 Hz), 4.59 (s, 2H), 3.13 (t, 2H, J= 7.2 Hz), 1.61 (quintuplete, 2H, J= 6.8 Hz), 1.44-1.36 (m, 2H), 1.30-1.20 (m, 8H), 0.85 (t, 3H, J= 6.8 Hz).

2,2,4-Trimetil-4-(2-(4-(octiltio)-3-(trifluorometil)benzoil)hidrazina carbonil)oxazolidin-3-carboxilato de (*R*)-*ter*-butilo (5a)

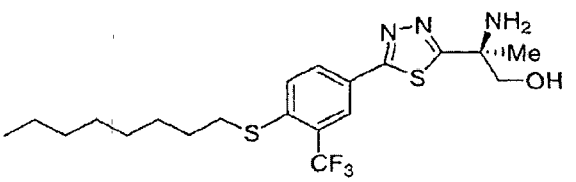


A una solución de ácido (R)-3-(ter-butoxicarbonil)-2,2,4-trimetiloxazolidin-4-carboxílico 4 (129.6 mg, 0.5 mmoles) en DMF (1 ml) se añadió HATU (209 mg, 0.55 moles) y DIPEA (0.436 ml, 2.5 mmoles). Después de agitarse a t.a. durante 10 min, la mezcla de reacción se trató con 4-(octiltio)-3-(trifluorometil)benzohidrazida 3a (174 mg, 0.5 mmoles) en THF (2

ml) y se dejó agitar durante la noche. Se añadió solución de $NaHCO_3$ acuosa y la mezcla se extrajo con EtOAc. La capa orgánica se lavó con salmuera, se secó sobre Na_2SO_4 anhidro, y se evaporó bajo presión reducida para dar un residuo, que se purificó por cromatografía en columna de SiO_2 (n-hexano/EtOAc =3:7) para dar 2,2,4-trimetil-4-(2-(4-(octiltio)-3-(trifluorometil)benzoil)hidrazinacarbonil)oxazolidin-3-carboxilato de (*R*)-*ter*-butilo 5a (247 mg, 84%). El tiempo de retención de CLAR sobre una columna C18 (30 x 4.6 mm, 3.5 µ) fue de 3.08 min con gradiente de 10-95% de acetonitrilo-H_2O (0.1% de TFA) en 3.5 min como fase móvil.

EM (ESI, $M+H^+$) = 590.5

(*S*)-2-Amino-2-(5-(4-(octiltio)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol (7a)

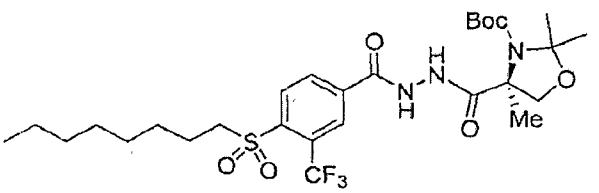


El producto del título se obtuvo con un rendimiento de 32% a partir de 2,2,4-trimetil-4-(2-(4-(octiltio)-3-(trifluorometil)benzoil)hidrazincarbonil) oxazolidin-3-carboxilato de (*R*)-*ter*-butilo 6a. El tiempo de retención de CLAR sobre una columna C18 (30 x 4.6 mm, 3.5 µ) fue de 2.46 min con gradiente de 10-95% de acetonitrilo-H_2O (0.1% de TFA) en 3.5 min como fase móvil.

EM (ESI, $M+H^+$) = 448.4.

^{1}H RMN (400 MHz, CD_3OD) δ 8.17 (s, 1H), 8.13 (d, 1H, J= 8.4 Hz), 7.75 (d, 1H, J= 8.4 Hz), 3.80 (AB, 1H, J_{AB} =11.2 Hz), 3.73 (AB, 1H, J_{AB} =11-2 Hz), 3.14 (t, 2H, J= 7.2 Hz), 1.67 (s, 3H), 1.61 (quintuplete, 2H, J= 6.8 Hz), 1.40-1.35 (m, 2H), 1.25-1.20 (m, 8H), 0.81 (t, 3H, J = 6.6 Hz).

2,2,4-Trimetil-4-(2-(4-(octilsulfonil)-3-(trifluorometil)benzoil) hidrazinacarbonil)oxazolidin-3-carboxilato de (*R*)-*ter*-butilo (8a)



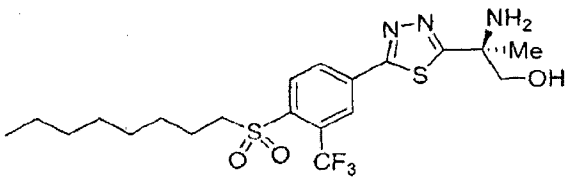
Una solución 2,2,4-trimetil-4-(2-(4-(octiltio)-3-(trifluorometil) benzoil)hidrazincarbonil)oxazolidin-3-carboxilato de (*R*)-*ter*-butilo 5a (123 mg, 0.21 mmoles) en DCM (10 ml) se trató con mCPBA (164 mg, 77%, 722 mmoles) a t.a. La mezcla de reacción se agitó a t.a. durante la noche, se extinguió con $NaHCO_3$ acuoso saturado, se extrajo con DCM. La capa orgánica se lavó con $NaHCO_3$ acuoso saturado (3X), se secó sobre Na_2SO_4 y se evaporó bajo presión reducida para dar un residuo, que se purificó por cromatografía en columna de SiO_2 (n-hexano/EtOAc =3:7) para dejar 2,2,4-trimetil-4-(2-(4-(octilsulfonil)-3-(trifluorometil)benzoil)hidrazincarbonil) oxazolidin-3-carboxilato de (*R*)-*ter*-butilo 8a (112 mg, 92%). El tiempo de retención de CLAR sobre una columna C18 (30 x 4.6 mm, 3.5 µ) fue de 3.27 min con gradiente de 10-95% de acetonitrilo-H_2O (0.1% de TFA) en 3.5 min

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como fase móvil.

EM (ESI, $M+H^+$) = 622.5.

(*S*)-2-Amino-2-(5-(4-(octilsulfonil)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol (7b)



El compuesto del título se preparó de conformidad con el procedimiento general a partir de 2,2,4-trimetil-4-(2-(4-(octilsulfonil)-3-(trifluorometil)benzoil)hidrazincarbonil)oxazolidin-3-carboxilato de (*R*)-*ter*-butilo 8a. El tiempo de retención de CLAR sobre una columna C18 (30 x 4.6 mm, 3.5 µ) fue de 2.11 min con gradiente de 10-95% de acetonitrilo-H_2O (0.1% de TFA) en 3.5 min como fase móvil.

EM (ESI, $M+H^+$) = 480.3;

^{1}H RMN (400 MHz, DMSO-d6) δ 8.56 (dd, 1H, J= 8.2 Hz, J= 1.6 Hz), 8.53 (d, 1H, J= 1.6 Hz), 8.38 (d, 1H, J= 8.8 Hz), 3.87 (AB, 1H, J_{AB} = 10.8 Hz), 3.80 (AB, 1H, J_{AB} = 10.8 Hz), 3.44 (t, 1H, J= 7.8 Hz), 1.68 (s, 3H), 1.66-1.60 (m, 2H), 1.37-1.31 (m, 2H), 1.25-1.16 (m, 8H), 0.83 (t, 3H, J= 7.2 Hz).

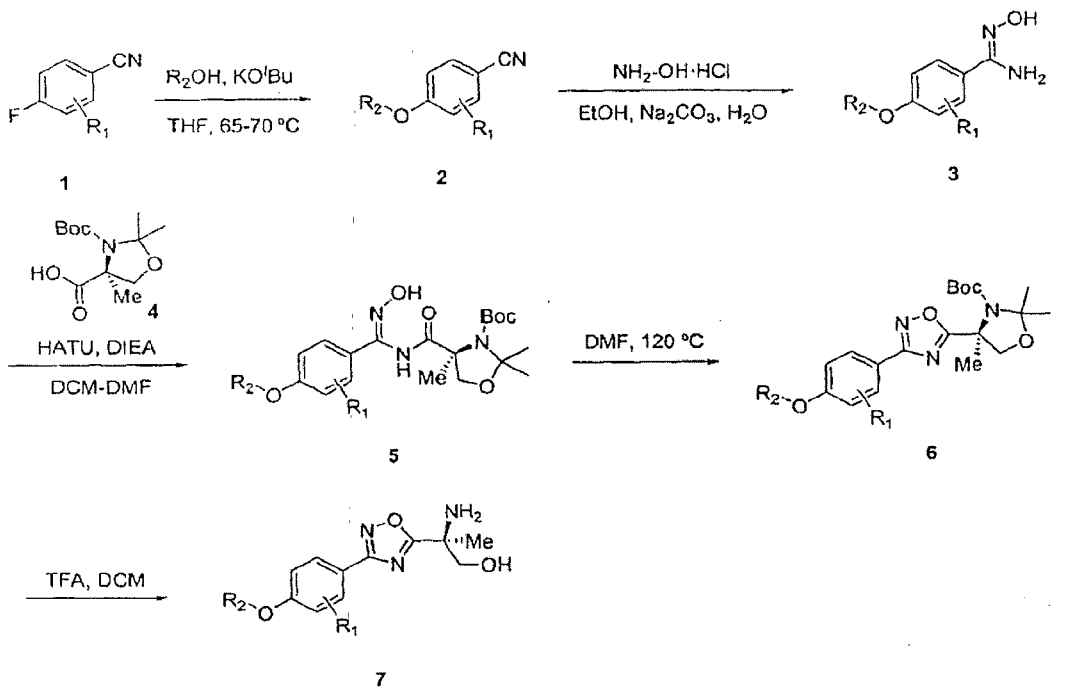
Enfoque general para la síntesis de fenil-oxadiazoles

La síntesis de fenil-oxadiazoles se describe en el esquema 6. La reacción del alcohol deseado con 4-fluorobenzonitrilo sustituido 1 dio el

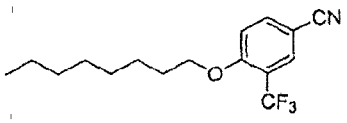
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benzonitrilo sustituido 2. El benzonitrilo sustituido 2 después se condensó con hidroxilamina para dar hidroxibenzimidamida 3. El acoplamiento del intermediario de hidroxiamidina 3 con aminoácido ortogonalmente protegido 4 bajo condiciones de HATU seguido por ciclización dio oxadiazol ortogonalmente protegido 6. El tratamiento del oxadiazol protegido 6 con TFA dio amino-alcohol final deseado 7.

ESQUEMA 6



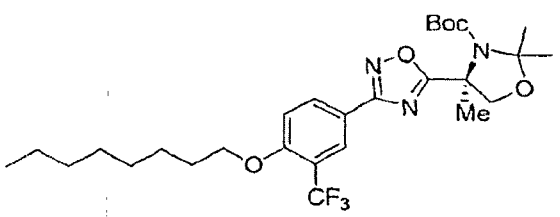
4-(Octiloxi)-3-(trifluorometil)benzonitrilo (2a)



El compuesto del título se preparó de manera análoga al compuesto 2 (Esquema 4) con un rendimiento de >95%.

^{1}H RMN (400 MHz, $CDCl_3$) δ 7.85 (d, 1H, J= 0.2 Hz), 7.77 (dd, 1H, J= 8.8 Hz, J= 2.0 Hz), 7.04 (d, 1H, J= 8.8 Hz), 4.11 (t, 2H, J= 5.6 Hz), 1.84 (m, 2H), 1.47 (m, 2H), 1.32 (m, 8H), 0.89 (t, 3H, J= 7.2 Hz).

2,2,4-Trimetil-4-(3-(4-(octiloxi)-3-(trifluorometil)fenil)-1,2,4-oxadiazol-5-il)oxazolidin-3-carboxilato de (*R*)-*ter*-butilo (6a)



Una suspensión de 4-(octiloxi)-3-(trifluorometil)benzonitrilo (600 mg, 1.0 equiv), NH_2OH•HCl (280 mg, 2.0 equiv), Na_2CO_3 (636 mg, 3.0 equiv) en etanol-agua (12 ml, 5:1) se puso a reflujo durante 3 hr. La reacción se condensó bajo vacío y el residuo se trató con agua seguido por extracción con acetato de etilo. La capa de acetato de etilo se lavó con NaCl saturado (1x), se secó sobre Na_2SO_4, y se condensó para dar el intermediario de hidroxiamindina (750 mg). Parte del intermediario (166 mg, 1.0 equiv) se trató

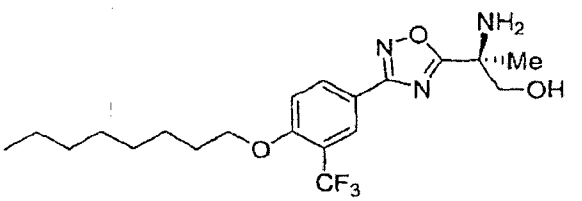
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con HATU (190 mg, 1.0 equiv), DIEA (260 µl, 3.0 equiv) y ácido (*R*)-3-(ter-butoxicarbonil)-2,2,4-trimetiloxazolidin-4-carboxílico (130 mg, 1.0 equiv) en DMF (1 ml) durante 1 hora. La reacción se diluyó con acetato de etilo y se lavó con agua seguido por NaCl saturado (1x), se secó sobre Na_2SO_4, y se condensó bajo vacío. El residuo se disolvió en DMF y se calentó a 120°C durante 2 horas. El tratamiento acuoso seguido por sistema de purificación Isco dio el compuesto del título con un rendimiento de 28% (70 mg) en tres pasos.

EM (ESI, $M+H^+$) = 558.1

^{1}H RMN (400 MHz, $CDCl_3$) δ 8.28 (d, 1H, J= 1.6 Hz), 8.18 (dd, 1H, J= 8.4 Hz, J= 1.6 Hz), 7.07 (d, 1H, J = 8.4 Hz), 4.23, 4.00 (AB, 2H, J= 9.2 Hz), 4.11 (t, 2H, J= 7.2 Hz), 1.92 (s, 3H), 1.84 (m, 2H), 1.76 (s, 3H), 1.70 (s, 3H), 1.51-1.46 (m, 4H), 1.25 (m, 9H), 1.25 (s, 6H), 0.89 (t, 3H, J= 7.2 Hz).

(*S*)-2-Amino-2-(3-(4-(octiloxi)-3-(trifluorometil)fenil)-1,2,4-oxadiazol-5-il)propan-1-ol (7a)



El compuesto del título se preparó de manera análoga al compuesto 8 (esquema 4) a partir del compuesto 7a.

EM (ESI, $M+H^+$) = 416.0;

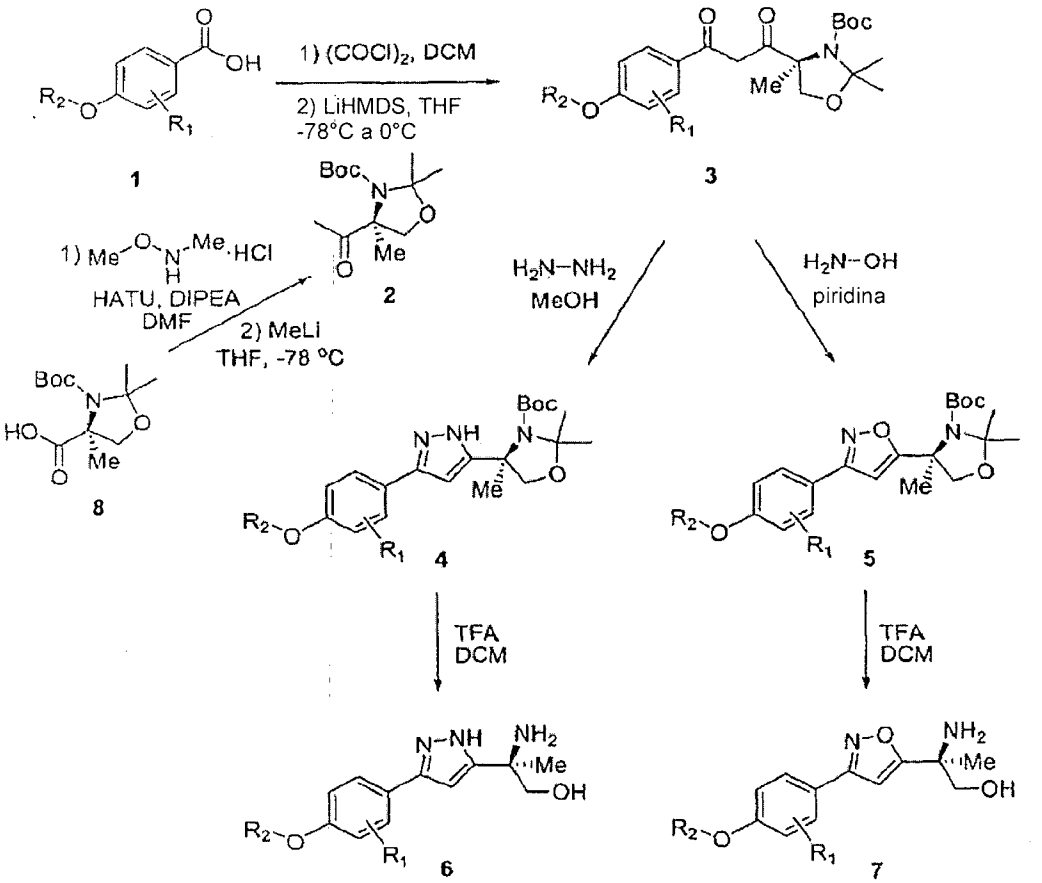
^{1}H RMN (400 MHz, CD_3OD) δ 8.28 (m 2H), 7.34 (d, 1H, J= 9.6 Hz), 4.19 (t, 2H, J = 5.6 Hz), 4.11, 3.89 (AB, 2H, J= 11.6 Hz), 1.84 (m, 2H), 1.77 (s, 3H), 1.53 (m, 2H), 1.40-1.32 (m, 8H), 0.91 (t, 3H, J= 7.2 Hz).

Enfoque general para la síntesis de fenil-isoxazoles y fenil-pirazoles

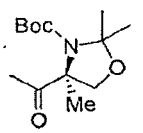
La síntesis de fenil-isoxazoles y fenil-pirazoles se describen en el Esquema 7. La reacción del ácido benzoico deseado con cloruro de oxalilo y atrapando el cloruro ácido con enolato de oxazolidin-cetona 2 dio 1,3-diona 3. La oxazolidin-cetona 2 se sintetizó a partir de oxazolidin-carboxilato 8 después de conversión de 8 a la amida Weinreb correspondiente seguido por la adición de metil-litio. La reacción de la 1,3-diona 3 con ya sea hidrazina o hidroxilamina seguido por desprotección dio el compuesto final deseado 6 y 7 respectivamente.

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ESQUEMA 7



4-Acetil-2,2,4-trimetiloxazolidin-3-carboxilato de (*R*)-*ter*-butilo (2)



A una solución de ácido (*R*)-3-(*ter*-butoxicarbonil)-2,2,4-trimetiloxazolidin-4-carboxílico 8 (2.6 g, 10 mmoles, 1.0 equiv) en DMF (25 ml) se añadió HATU (4.6 g, 12 mmoles, 1.2 equiv) y DPEA (8.7 ml, 50 mmoles,

5.0 equiv). La mezcla de reacción se agitó a t.a. durante 10 min y se trató con clorhidrato de N,O-dimetilhidroxilamina (2.9 g, 30 mmoles, 3.0 equiv), se agitó durante 2 días a t.a., se extinguió con $NaHCO_3$ medio saturado, se extrajo con EtOAc. Los compuestos orgánicos se secaron sobre Na_2SO_4, se concentraron para dar amida de Weinreb correspondiente con un rendimiento de 92% (2.78 g). El tiempo de retención de CLAR sobre una columna C18 (30 x 4.6 mm, 3.5 µ) fue de 2.20 min con gradiente de 10-95% de acetonitrilo-H_2O (0.1% de TFA) en 3.5 min como fase móvil.

EM (ESI, $M+H^+$) = 303.3.

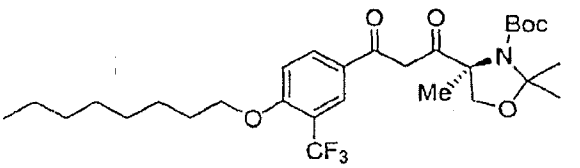
La amida de Weinreb correspondiente (2.78 g, 9.2 mmoles, 1.0 equiv) se disolvió en THF (50 ml), se enfrió a –78°C y se trató con una solución de MeLi 1.6 M (14.7 ml, 23 mmoles, 2.5 equiv) en éter gota a gota. Después de agitarse a -78°C durante 3 hr, la mezcla de reacción se dejó calentar a t.a., se extinguió con NH_4Cl acuoso saturado, se extrajo con EtOAc. Los compuestos orgánicos se secaron sobre Na_2SO_4, se concentraron bajo vacío para dar un aceite que se purificó por cromatografía en columna de gel de sílice (n-hexano/EtOAc = 85:15) para dar 4-acetil-2,2,4-trimetiloxazolidin-3-carboxilato de (*R*)-*ter*-butilo como un sólido blanco con un rendimiento de 82% (1.94 g). El tiempo de retención de CLAR sobre una columna C18 (30 x 4.6 mm, 3.5 µ) fue de 2.39 min con gradiente de 10-95% de acetonitrilo-H_2O (0.1% de TFA) en 3.5 min como fase móvil.

EM (ESI, $M+H^+$) = 258.4;

^1H RMN (400 MHz, $CDCl_3$) δ 3.95 (d, 1H, J= 9.6 Hz), 3.74 (d, 1H,

J= 9.6 Hz), 2.21 (s, 3H), 1.69 (s, 2H), 1.65-1.64 (m, 1H), 1.61 (s, 2H), 1.57-1.55 (m, 2H), 1.49 (s, 5H), 1.42 (s, 6H).

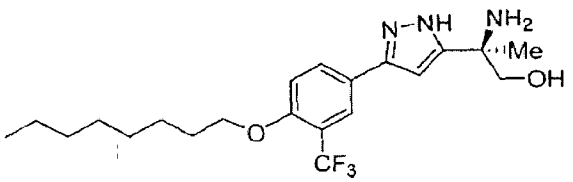
2,2,4-Trimetil-4-(3-(4-(octiloxi)-3-(trifluorometil)fenil)-3-oxo-propanoil)oxazolidin-3-carboxilato de (*S*)-*ter*-butilo (3a)



Acido 4-(octiloxi)-3-(trifluorometil)benzoico (460 mg, 1.0 equiv) se trató con cloruro de oxalilo (244 µl, 2.0 equiv) durante 30 min. La reacción se condensó y parte de este residuo (81 mg, 1.2 equiv) se disolvió en THF y se transfirió a una solución de 4-acetil-2,2,4-trimetiloxazolidin-3-carboxilato de (*S*)-*ter*-butilo (51 mg, 1.0 equiv) y LiHMDS 1.0M (0.72 ml, 3.0 equiv) en THF a –78°C. El producto resultante se agitó a 0°C durante 1 hora. La reacción se extinguió con NH_4Cl acuoso y se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera y se secó sobre Na_2SO_4 y se condensó bajo vacío. El residuo se purificó sobre una columna de gel de sílice con acetato de etilo-hexano (0-30%) como sistema de eluyente para dar el compuesto del título con un rendimiento de 39% (55 mg).

EM (ESI, $M+H^+$) = 557.9

(*R*)-2-Amino-2-(5-(4-(octiloxi)-3-(trifluorometil)fenil)-1*H*-pirazol-3-il)propan-1-ol (6a)



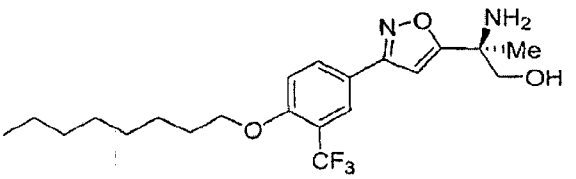
La solución de 2,2,4-trimetil-4-(3-(4-(octiloxi)-3-(trifluorometil)-fenil)-3-oxo-propanoil)oxazolidin-3-carboxilato de (*S*)-*ter*-butilo (27 mg, 0.05 mmoles, 1.0 equiv) e hidrazina monohidratada (2.7 µl, 0.055 mmoles, 1.1 equiv) en metanol (0.2 ml) se agitó a temperatura ambiente durante 2 horas. La reacción se condensó y el residuo se trató con 20% de TFA-DCM durante 30 min. Después de la remoción de la cantidad excesiva de TFA y DCM, el producto crudo se purificó por CLAR prep. y dio el compuesto del título como sal de mono-TFA (5.0 mg).

EM (ESI, $M+H^+$) = 414.0;

^{1}H RMN (400 MHz, CD_3OD) δ 7.81 (s, 1H), 7.76 (d, 1H, J= 9.2 Hz), 7.14 (d, 1H, J= 9.2 Hz), 6.56 (s, 1H), 4.03 (t, 2H, J= 6.0 Hz), 3.79, 3.67 (AB, 2H, J= 12.0 Hz), 1.76-1.69 (m, 2H), 1.59 (s, 3H), 1.46-1.38 (m, 2H), 1.32-1.16 (m, 8H), 0.81 (t, 3H, J= 7.2 Hz).

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(*S*)-2-Amino-2-(3-(4-(octiloxi)-3-(trifluorometil)fenil)isoxazol-5-il)propan-1-ol (7a)



La solución de 2,2,4-trimetil-4-(3-(4-(octiloxi)-3-(trifluorometil)-fenil)-3-oxo-propanoil)oxazolidin-3-carboxilato de (*S*)-*ter*-butilo (27 mg, 0.05 mmoles, 1.0 equiv) y clorhidrato de hidroxilamina (6.6 mg, 0.10 mmoles, 2.0 equiv) en piridina (0.5 ml) se agitó a 60°C durante 2 días. La reacción se condensó y el residuo se trató con 20% de TFA-DCM durante 30 min. Después de la remoción de la cantidad excesiva de TFA y DCM, el producto crudo se purificó por CLAR prep. y dio el compuesto del título como sal de mono-TFA (6.0 mg).

EM (ESI, $M+H^+$) = 415.0;

^1H RMN (400 MHz, CD_3OD) δ 8.06 (s, 1H), 8.04 (d, 1H, J= 9.6 Hz), 7.31 (d, 1H, J= 9.6 Hz), 7.03 (s, 1H), 4.16 (t, 2H, J= 6.0 Hz), 4.01, 3.83 (AB, 2H, J= 12.0 Hz), 1.87-1.80 (m, 2H), 1.75 (s, 3H), 1.56-1.47 (m,2H), 1.40-1.32 (m, 8H), 0.91 (t, 3H, J= 7.2 Hz).

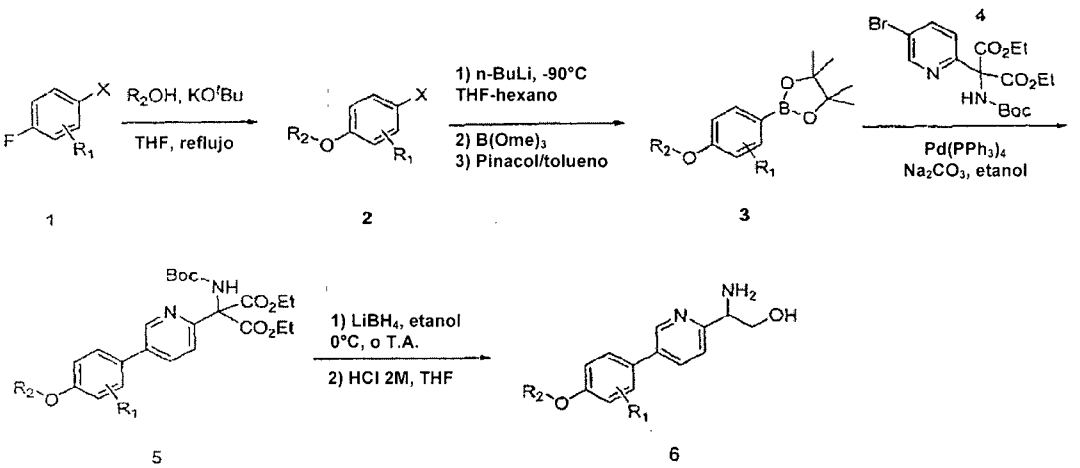
Enfoque general para la síntesis de análogos de fenil-piridina

La síntesis de análogos de fenil-piridina se describe en el esquema 8. La reacción del alcohol deseado con halógeno-benceno sustituido

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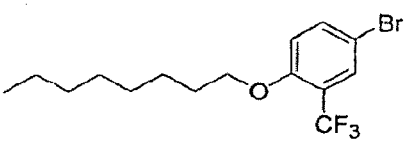
1 dio el halógeno-benceno-éter 2. El halógeno-benceno-éter 2 sustituido se trató después con n-butil-litio, $B(OMe)_3$, y pinacol respectivamente para dar éster 3. El acoplamiento cruzado de Suzuki del éster 3 con el compuesto 4 dio biarilo 5 que bajo reducción y desprotección dio el aminoalcohol 6.

ESQUEMA 8



1 2 3 4 5 6

4-Bromo-1-(octiloxi)-2-(trifluorometil)benceno (2a)



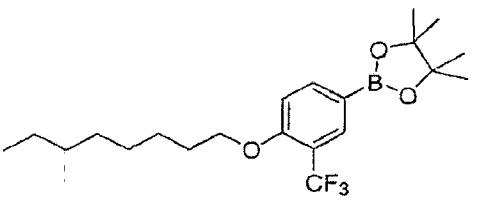
Usando 4-bromo-1-fluoro-2-(trifluorometil)benceno como material de partida, la sustitución de fluoro aromático estándar con *n*-octanol dio el compuesto del título con rendimiento cuantitativo.

^{1}H RMN (400 MHz, $CDCl_3$) δ 7.65 (δ, 1H, J= 2.4 Hz), 7.55 (dd,

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1H, J= 8.8 Hz, J= 2.4 Hz), 6.85 (d, 1H, J= 8.8 Hz), 4.01 (t, 2H, J= 6.4 Hz), 1.80 (m, 2H), 1.46 (rn, 2H), 1.32 (m, 8H), 0.90 (t, 2H, J= 5.6 Hz).

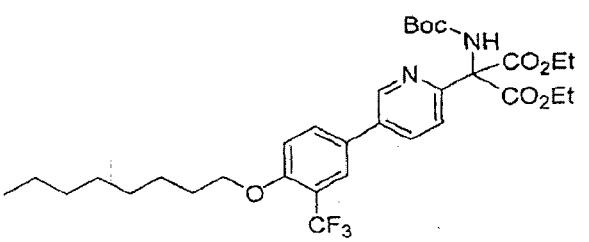
4,4,5,5-Tetrametil-2-(4-(octiloxi)-3-(trifluorometil)fenil)-1,3,2-dioxaborolano (3a)



Usando 4-bromo-1-(octiloxi)-2-(trifluorometil)benceno como material de partida, se preparó el compuesto del título usando un procedimiento de la literatura en un rendimiento de 96% (J. Am. Chem. Soc. 2004, *126*, 14316-14317).

^{1}H RMN (400 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.89 (dd, 1H, J= 8.4 Hz, J= 1.2 Hz), 6.95 (d, 1H, J= 8.4 Hz), 4.06 (t, 2H, J= 6.0 Hz), 1.81 (m, 2H), 1.47 (m, 2H), 1.36-1.28 (m, 8H), 0.88 (t, 2H, J= 7.2 Hz).

2-(*ter*-Butoxicarbonilamino)-2-(5-(4-(octiloxi)-3-(trifluorometil)-fenil)piridin-2-il)malonato de dietilo (5a)



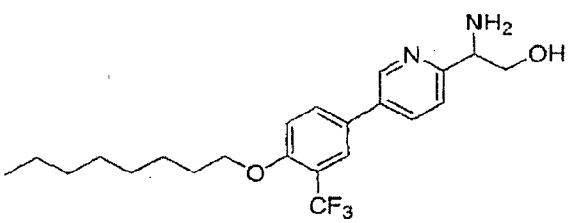
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La suspensión de 4,4,5,5-tetrametil-2-(4-(octiloxi)-3-(trifluorometil)fenil)-1,3,2-dioxaborolano 3a (136 mg, 0.34 mmoles, 1.5 equiv), 2-(5-bromopiridin-2-il)-2-(*ter*-butoxicarbonilamino)malonato de dietilo (98 mg, 0.23 mmoles, 1.0 equiv), $Pd(PPh_3)_4$ (26.3 mg, 0.023 mmoles, 0.1 equiv), y Na_2CO_3 (120 mg, 1.14 mmoles, 4.0 equiv) en etanol-H_2O se calentó a 80°C durante 1 hora. La mezcla de reacción se filtró y el filtrado se purificó por columna de gel de sílice para dar el compuesto del título con un rendimiento de 77% (110 mg).

EM (ESI, $M+H^+$) = 625.1;

^1H RMN (400 MHz, $CDCl_3$) δ 8.66 (s, 1H). 7.88 (s, 1H), 7.86 (dd, 1H, J= 8.4 Hz, J= 2.0 Hz), 7.75 (d, J= 2.5 Hz), 7.66 (d, 1H, J = 8.4 Hz), 7.08 (d, 1H, J= 8.4 Hz), 6.82 (s, 1H), 4.30 (m, 4H), 4.09 (t, 2H, J= 6.0 Hz), 1.84 (m, 2H), 1.46 (m, 11H), 1.28 (m, 14H), 0.90 (t, 3H, J= 7.2 Hz).

<u>2-Amino-2-(5-(4-(octiloxi)-3-(trifluorometil)fenil)piridin-2-il)etanl (6a)</u>



2-(*ter*-Butoxicarbonilamino)-2-(5-(4-(octiloxi)-3-(trifluorometil)-fenil)-piridin-2-il)malonato de dietilo 5a (110 mg, 0.176 mmoles, 1.0 equiv) en THF (2.0 ml) se añadió $LiBH_4$ (57 mg, 2.64 mmoles, 15.0 equiv) a 0°C,

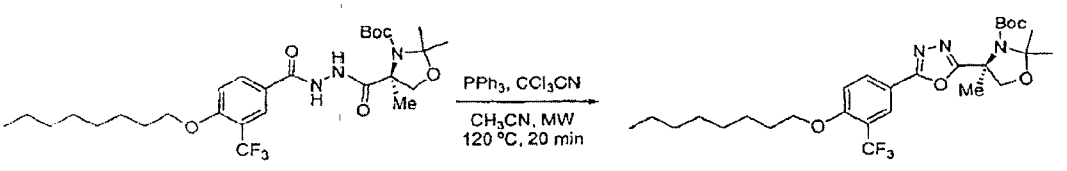
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seguido por la adición cuidadosa de etanol (0.8 ml). El producto resultante se calentó a temperatura ambiente durante 10 minutos. CL-EM indicó que la reacción se había completado. La reacción se terminó mediante la adición de agua. La extracción con acetato de etilo y la capa orgánica se lavó con salmuera y se secó sobre sulfato de sodio y se condensó. El residuo (producto de reducción crudo con descarboxilación significativa) se trató con HCl 2M en THF para dar el compuesto del título después de purificación por CLAR preparativa.

EM (ESI, $M+H^+$) = 411.1;

^{1}H RMN (400 MHz, DMSO-d_6) δ 8.95 (d, 1H, J= 2.4 Hz), 8.39 (s, 3H), 8.22 (dd, 1H, J = 8.4 Hz, J= 2.4 Hz), 8.01 (dd, 1H, J= 8.4 Hz, J= 2.0 Hz), 7.93 (d, 1H, J= 2.0 Hz), 7.60 (d, 1H, J= 8.4 Hz), 7.39 (d, 1H, J= 9.2 Hz), 5.48 (br, 1H), 4.48 (br, 1H), 4.17 (t, 2H, J = 6.0Hz), 3.86-3.72 (m, 2H), 1.75 (m, 2H), 1.44 (m, 2H), 1.29 (m, 8H), 0.86 (t, 3H, J= 6.8 Hz).

2,2,4-Trimetil-4-(5-(4-(octiloxi)-3-(trifluorometil)fenil)-1,3,4-oxadiazol-2-il)oxazolidin-3-carboxilato de (*R*)-*t*-butilo



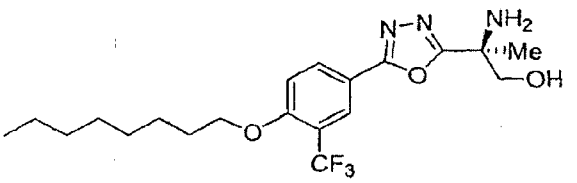
El compuesto del título se preparó a partir de 2,2,4-trimetil-4-(2-(4-(octiloxi)benzoil)hidrazincarbonil)oxazolidin-3-carboxilato de (*S*)-*t*-butilo usando un procedimiento publicado (Tet. Letters, 2006, 47, 105-108) con un

rendimiento de 85%.

EM (ESI, $M+H^+$) = 556.1;

^{1}H RMN (400 MHz, $CDCl_3$) δ 8.22 (d, 1H, J= 1.6 Hz), 8.14 (d, 1H, J= 8.8 Hz), 8.10 (dd, 1H, J= 8.8 Hz, J= 1.6 Hz), 4.22 (d, 1H, J= 8.8 Hz), 4.12 (t, 2H, J= 6.0 Hz), 4.01 (m, 1H), 1.94 (s, 3H), 1.85 (m, 2H), 1.76 (s, 3H), 1.72 (s, 3H), 1.51-1.46 (m, 4H), 1.22 (m, 7H), 1.25 (s, 6H), 0.89 (t, 3H, J= 7.2 Hz).

(*S*)-2-Amino-2-(5-(4-(octiloxi)-3-(trifluorometil)fenil)-1,3,4-oxadiazol-2-il)propan-1-ol



La desprotección estándar con 20% de TFA de 2,2,4-trimetil-4-(5-(4-(octiloxi)-3-(trifluorometil)fenil)-1,3,4-oxadi-azol-2-il)oxazolidin-3-carboxilato de (*R*)-*t*-butilo dio el compuesto del título con un rendimiento de 55%.

(ESI, $M+H^+$) = 416.0;

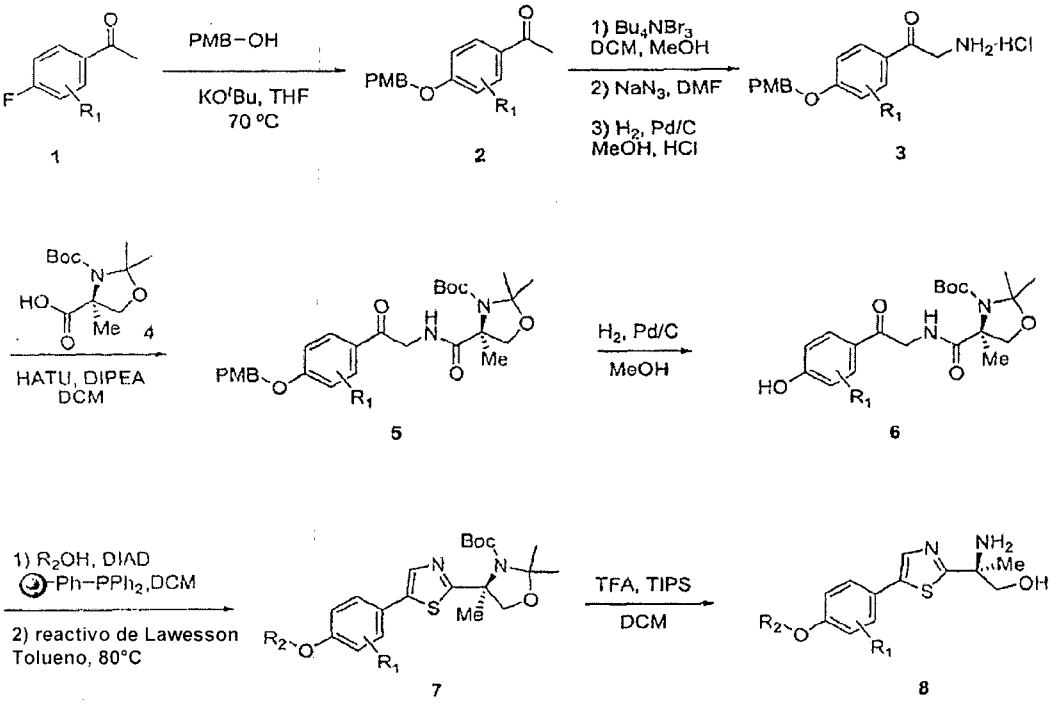
^{1}H RMN (400 MHz, CD_3OD) δ 8.18 (d, 1H, J= 8.8 Hz), 8.18 (s, 1H), 7.30 (d, 1H, J= 8.8 Hz), 4.12 (t, 2H, J = 6.0 Hz), 4.01, 3.79 (AB, 2H, J= 11.6 Hz), 1.74 (m, 2H), 1.68 (s, 3H), 1.43 (m, 2H), 1.31-1.19 (m, 8H), 0.81 (t, 3H, J= 2.8 Hz).

Enfoque general para la síntesis de éter-fenil-tiazoles

La síntesis de tiazoles 2,5-sustituidos se describe en el Esquema 9. La reacción del alcohol deseado, alcohol *para*-metoxibencílico (PMB-OH) con 4-fluoroacetofenona sustituida 1 dio el intermediario de acetofenona 2. El intermediario de acetofenona 2 después se convirtió a la bromo-acetofenona correspondente usando Bu_4NBr_3 que, bajo reacción con NaN_3, dio el intermediario de azido-acetofenona. La hidrogenación del intermediario de azido-acetofenona dio amina 3, seguido por acoplamiento con aminoácido ortogonalmente protegido 4 dio amida 5. La remoción del grupo PMB bajo hidrogenación dio fenol 6. La reacción de Mitsunobu del fenol 6 con el alcohol deseado seguido por formación de tiazol bajo condiciones de reactivo de Lawesson dio el intermediario 7 con buen rendimiento. La remoción del grupo protector a partir del intermediario 7 dio el amino-alcohol final 8.

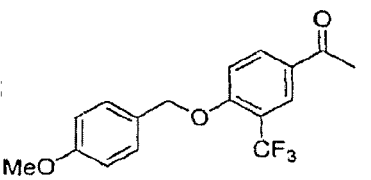
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ESQUEMA 9



Para el protocolo general para la síntesis de compuesto 2, 3, 4, y 5 refiérase al esquema 1.

1-(4-(4-Metoxibenciloxi)-3-(trifluorometil)fenil)etanona (2a)



Para el protocolo general para la síntesis de compuesto 2 refiérase al esquema 1. El producto se purificó por cromatografía en columna de gel de sílice usando el sistema Combi-Flash (Hex:EtOAc) como aceite incoloro en 90% (4.25 g). El tiempo de retención de CLAR sobre una columna

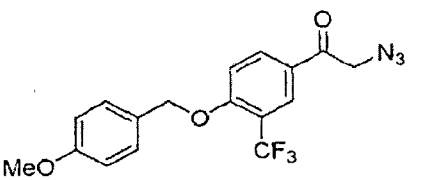
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C8(2) (30 x 3.00 mm, 3 μ) fue de 2.02 min con gradiente de 50-98% de acetonitrilo-H_2O (0.1% de TFA) en 4.0 min como fase móvil.

CCD (1:3 EtOAc:Hex), R_f= 0.4;

^{1}H RMN (400 MHz, $CDCl_3$) δ 8.20 (d, 1H, J= 1.6 Hz), 8.09 (dd, 1H, J= 8.8 Hz, J= 2.0 Hz), 7.35 (d, 2H, J= 8.4 Hz), 7.09 (d, 1H, J= 8.4 Hz), 6.93 (d, 2H, J= 8.4 Hz), 5.21 (s, 2H), 3.82 (s, 3H), 2.58 (s, 3H).

2-Azido-1-(4-(4-metoxibenciloxi)-3-(trifluorometil)fenil)etanona



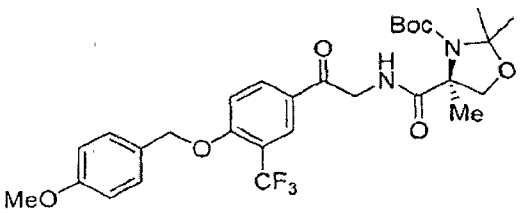
Para el protocolo general para la síntesis del intermediario azido refiérase al esquema 1. El producto se purificó por cromatografía en columna de gel de sílice usando el sistema Combi-Flash (Hex:EtOAc) como sólido amarillo con un rendimiento de 76% (3.64 g) a partir de acetofenona 2a. El tiempo de retención de CLAR sobre una columna C8(2) (30 x 3.00 mm, 3 μ) fue de 2.20 min con gradiente de 50-98% e acetonitrilo-H_2O (0.1% de TFA) en 4.0 min como fase móvil.

CCD (1:3 EtOAc:Hex), R_f= 0.3;

^{1}H RMN (400 MHz, $CDCl_3$) δ 8.15 (d, 1H, J= 2.0 Hz), 8.05 (dd, 1H, J= 8.8 Hz, J= 2.4 Hz), 7.33-7.36 (m, 2H), 7.12 (d, 1H, J= 8.8 Hz), 6.90-6.94 (m, 2H), 5.22 (s, 2H), 4.51 (s, 2H), 3.82 (s, 3H).

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4-(2-(4-(4-metoxibenciloxi)-3-(trifluorometil)fenil)-2-oxoetil-carbamoil)-2,2,4-trimetiloxazolidin-3-carboxilato de (*R*)-*ter*-butilo (5a)



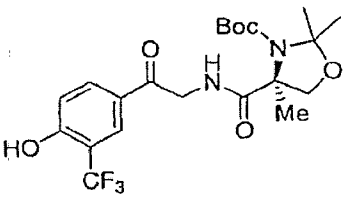
Para el protocolo general para la síntesis de compuesto 5 refiérase al esquema 1. La reacción se agitó a temperatura ambiente durante 2 horas. El producto se purificó por cromatografía en columna de gel de sílice usando el sistema Combi-Flash (Hex:EtOAc) como espuma amarilla con un rendimiento de 72% (2.44 g) a partir de amino-acetofenona 3a. El tiempo de retención de CLAR sobre una columna C8(2) (30 x 3.00 mm, 3 µ) fue de 2.51 min con gradiente de 50-98% de acetonitrilo-H_2O (0.1% de TFA) en 4.0 min como fase móvil.

CCD (1:1 EtOAc:Hex), R_f= 0.5;

^{1}H RMN (400 MHz, $CDCl_3$) δ 8.24 (br s, 1H), 8.09 (br d, 1H, J= 8.4 Hz), 7.32-7.39 (m, 2H), 7.12 (d, 1H, J = 8.4 Hz), 6.90-6.97 (m, 2H), 5.22 (s, 2H), 4.70 (t, 2H, J= 5.2 Hz), 4.30 (br s, 1H), 3.78-3.86 (m, 5H), 1.38-1.85 (m, 18H).

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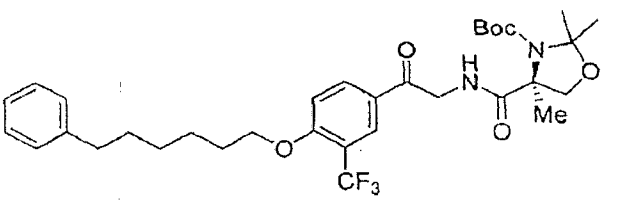
4-(2-(4-Hidroxi-3-(trifluorometil)fenil)-2-oxoetilcarbamoil)-2,2,4-trimetiloxazolidin-3-carboxilato de (*R*)-*ter*-butilo (6a)



A una solución de 4-(2-(4-(4-metoxibenciloxi)-3-(trifluorometil)fenil)-2-oxoetilcarbamoil)-2,2,4-trimetiloxazolidin-3-carboxilato de (*R*)-*ter*-butilo (4) (2.4 g, 4.1 mmoles, 1.0 equiv) en metanol (20 ml) se añadió 10% de Pd/C (240 mg). La mezcla de reacción se agitó durante 3 horas a t.a. bajo atmósfera de H_2 usando un balón de H_2, se filtró a través de celite y se concentró para dar 4-(2-(4-hidroxi-3-(trifluorometil)fenil)-2-oxoetilcarbamoil)-2,2,4-trimetiloxazolidin-3-carboxilato de (*R*)-*ter*-butilo (6a) como una espuma blanca con rendimiento cuantitativo. El tiempo de retención de CLAR sobre una columna C18 (30 x 4.6 mm, 3.5 µ) fue de 2.62 min con gradiente de 10-95% de acetonitrilo-H_2O (0.1% de TFA) en 3.5 min como fase móvil.

EM (ESI, $M+H^+$) = 461.4.

2,2,4-trimetil-4-(2-oxo-2-(4-(6-fenilhexiloxi)-3-(trifluorometil)fenil)etilcarbamoil)oxazolidin-3-carboxilato de (*R*)-*ter*-butilo

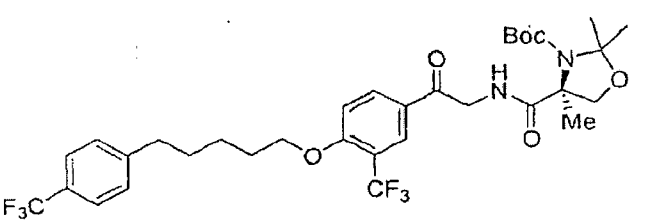


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A una solución de 4-(2-(4-hidroxi-3-(trifluorometil)fenil)-2-oxoetilcarbamoil)-2,2,4-trimetiloxazolidin-3-carboxilato de (*R*)-*ter*-butilo (114 mg, 0.25 mmoles, 1.0 equiv) y 6-fenilhexan-1-ol (45 mg, 0.25 mmoles, 1.0 equiv) en DCM (1 ml) se añadió enlace de polímero PPh_3 (125 mg, 0.75 mmoles, 3.0 equiv). La mezcla de reacción se agitó a t.a. durante 0.5 horas y se enfrió a 0°C. Una solución de DIAD (0.053 ml, 0.25 mmoles, 1.0 equiv) en DCM (0.5 ml) se añadió gota a gota a la mezcla de reacción. La mezcla de reacción se agitó a t.a. durante 2 horas, se filtró y se evaporó bajo presión reducida para dar un residuo, que se purificó por cromatografía en columna de SiO_2 (30-50% de EtOAc en hexanos) para dar 2,2,4-trimetil-4-(2-oxo-2-(4-(6-fenilhexiloxi)-3-(trifluorometil)fenil)etilcarbamoil)oxazolidin-3-carboxilato de (*R*)-*ter*-butilo con un rendimiento de 75% (155 mg). El tiempo de retención de CLAR sobre una columna C18 (30 x 4.6 mm, 3.5 µ) fue de 3.31 min con gradiente de 50-95% de acetonitrilo-H_2O (0.1% de TFA) en 3.5 min como fase móvil.

EM (ESI, $M+H^+$) = 621.6.

2,2,4-Trimetil-4-(2-oxo-2-(3-(trifluorometil)-4-(5-(4-(trifluorometil)fenil)pentiloxi)fenil)etilcarbamoil)oxazolidin-3-carboxilato de (*R*)-*ter*-butilo

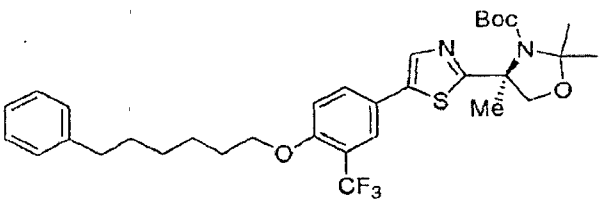


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El compuesto del título se preparó a partir de 4-(2-(4-hidroxi-3-(trifluorometil)fenil)-2-oxoetilcarbamoil)-2,2,4-trimetiloxazolidin-3-carboxilato de (*R*)-*ter*-butilo (0.25 mmoles, 1.0 equiv) y 5-(4-(trifluorometil)fenil)pentan-1-ol (0.25 mmoles, 1.0 equiv) de confomridad con el procedimiento general con un rendimiento de 31%. El tiempo de retención de CLAR sobre una columna C18 (30 x 4.6 mm, 3.5 μ) fue de 3.26 min con gradiente de 50-95% de acetonitrilo-H_2O (0.1% de TFA) en 3.5 min como fase móvil.

EM (ESI, $M+H^+$) = 675.6.

2,2,4-Trimetil-4-(5-(4-(6-fenilhexiloxi)-3-(trifluorometil)fenil)tiazol-2-il)oxazolidin-3-carboxilato de (*R*)-*ter*-butilo (7a)



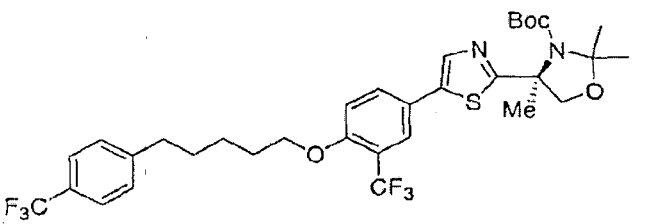
A una solución de 2,2,4-trimetil-4-(2-oxo-2-(4-(6-fenilhexiloxi)-3-(trifluorometil)fenil)etilcarbamoil)oxazolidin-3-carboxilato de (*R*)-*ter*-butilo (49 mg, 0.079 mmoles, 1.0 equiv) en tolueno (1 ml) se añadió reactivo de Lawesson (32 mg, 0.087 mmoles, 1.1 equiv). La mezcla de reacción se calentó a 80°C durante 3 hr. El producto crudo se purificó directamente por cromatografía en columna de SiO_2 (EtOAc/hexanos, 3:7) para dar 2,2,4-trimetil-4-(5-(4-(6-fenilhexiloxi)-3-(trifluorometil)fenil)tiazol-2-il)oxazolidin-3-carboxilato de (*R*)-*ter*-butilo. El tiempo de retención de CLAR sobre una

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columna C8(2) (30 x 50 mm, 3 µ) fue de 3.29 min con gradiente de 70-98% de acetonitrilo-H_2O (0.1% de TFA) en 3.5 min como fase móvil.

EM (ESI, $M+H^+$) = 619.0.

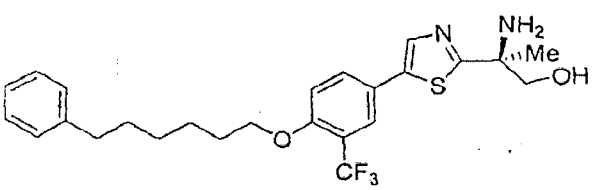
2,2,4-Trimetil-4-(5-(3-(trifluorometil)-4-(5-(4-(trifluorometil)fenil)pentiloxi)fenil)tiazol-2-il)oxazolidin-3-carboxilato de (*R*)-*ter*-butilo (7b)



El compuesto del título se preparó a partir de 2,2,4-trimetil-4-(2-oxo-2-(3-(trifluorometil)-4-(5-(4-(trifluorometil)fenil)pentiloxi)fenil)etilcarbarnoil)-oxazolidin-3-carboxilato de (*R*)-*ter*-butilo. El tiempo de retención de CLAR sobre una columna C8(2) (30 x 50 mm, 3 µ) fue de 3.29 min con gradiente de 70-98% de acetonitrilo-H_2O (0.1% de TFA) en 3.5 min como fase móvil.

EM (ESI, $M+H^+$) = 673.0.

(*S*)-2-Amino-2-(5-(4-(6-fenilhexiloxi)-3-(trifluorometil)fenil)tiazol-2-il)propan-1-ol (8a)



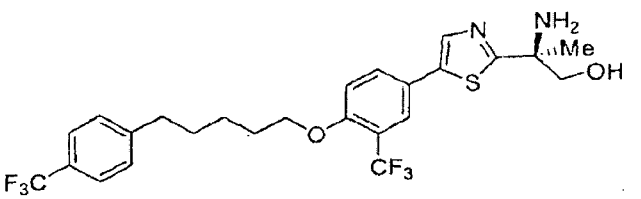
394

El compuesto del título se preparó a partir de 2,2,4-trimetil-4-(5-(4-(6-fenilhexiloxi)-3-(trifluorometil)fenil)tiazol-2-il)oxazolidin-3-carboxilato de (*R*)-*ter*-butilo. El tiempo de retención de CLAR sobre una columna C18 (30 x 4.6 mm, 3.5 µ) fue de 2.41 min con gradiente de 10-95% de acetonitrilo-H_2O (0.1% de TFA) en 3.5 min como fase móvil.

EM (ESI, $M+H^+$) = 479.4;

^1H RMN (400 MHz, $CDCl_3$) δ 7.76 (s, 1H), 7.65 (d, 1H, J= 2.0 Hz), 7.55 (dd, 1H, J= 8.8 Hz, J= 2.0 Hz), 7.28-7.23 (m, 2H), 7.18-7.15 (m, 3H), 6.96 (d, 1H, J= 9.2 Hz), 4.06-3.99 (m, 4H), 2.62 (t, 2H, J= 7.6 Hz), 1.85-1.78 (m, 5H), 1.69-1.62 (m, 2H), 1.56-1.50 (m, 2H), 1.44-1.38 (m, 2H).

(*S*)-2-Amino-2-(5-(3-(trifluorometil)-4-(5-(4-(trifluorometil)fenil) pentiloxi)fenil)tiazol-2-il)propan-1-ol (8b)



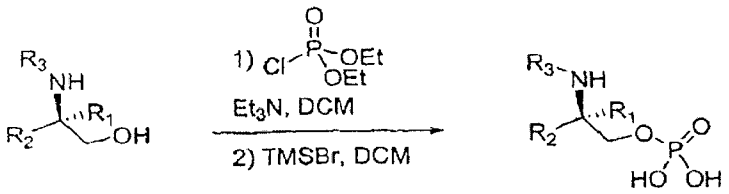
El compuesto del título se preparó a partir de 2,2,4-trimetil-4-(5-(3-(trifluorometil)-4-(5-(4-(trifluorometil)fenil)pentiloxi)fenil)tiazol-2-il)oxazolidin-3-carboxilato de (*R*)-*ter*-butilo. El tiempo de retención de CLAR sobre una columna C18 (30 x 4.6 mm, 3.5 µ) fue de 2.50 min con gradiente de 10-95% de acetonitrilo-H_2O (0.1% de TFA) en 3.5 min como fase móvil.

EM (ESI, $M+H^+$) = 533.4;

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^{1}H RMN (400 MHz, $CDCl_3$) δ 7.77 (s, 1H), 7.66 (d, 1H, J= 2.0 Hz), 7.56 (dd, 1H, J= 9.0 Hz, J= 2.4 Hz), 7.52 (d, 2H, J= 8.0 Hz), 7.28 (d, 2H, J= 8.0 Hz), 6.97 (d, 1H, J= 8.8 Hz), 4.07-4.03 (m, 4H), 2.70 (t, 2H, J= 7.8 Hz), 1.89-1.82 (m, 5H), 1.74-1.67 (m, 2H), 1.57-1.50 (m, 2H).

Método general para síntesis de fosfato

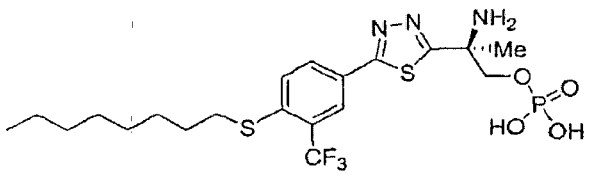


R_3 = H o grupo protector

La estrategia de síntesis para la síntesis de fosfatos deseados se ilustra anteriormente. A una solución de aminoalcohol no protegido (1.0 equiv) en CH_2Cl_2 seco a T.A. se añadió exceso de clorofosfato de dietilo (10.0 equiv) y trietilamina (20.0 equiv) y la reacción se agitó durante 12-18 horas. La reacción se monitoreó por CL-EM. La mezcla de reacción cruda después se evaporó a sequedad bajo vacío. El intermediario de fosfo-diéster obtenido se hizo reaccionar con exceso de bromotrimetilsilano (10.0-20.0 equiv) en CH_2Cl_2 seco a T.A. durante un periodo de 6-10 horas para dar el fosfato final que se purificó por CLAR preparativa de fase inversa después de la evaporación del solvente y exceso de reactivo.

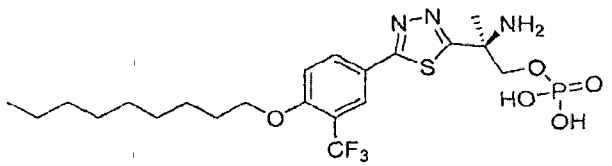
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Fosfato diácido de (*S*)-2-amino-2-(5-(4-(octiltio)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propilo (a)



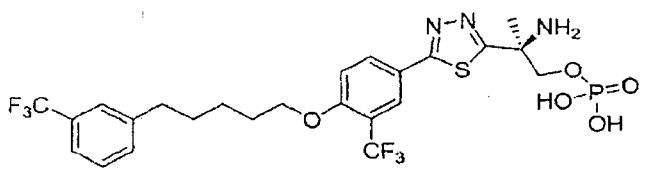
EM (ESI, $M+H^+$) = 528.0; el tiempo de retención de CLAR sobre una columna C8(2) (30 x 3.00 mm, 3 µ) fue de 2.27 min con gradiente de 30-98% de acetonitrilo-H_2O (0.1% de TFA) en 3.5 min como fase móvil.

Fosfato diácido de (*S*)-2-amino-2-(5-(4-(noniloxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propilo (b)



EM (ESI, $M+H^+$) = 526.0; el tiempo de retención de CLAR sobre una columna Synergi-Max RP (2 x 20 mm, 2 µl) fue de 1.51 min con gradiente de 30-99% de acetonitrilo-H_2O (0.1% de TFA) en 2 min como fase móvil.

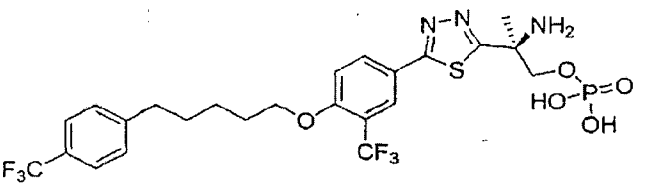
Fosfato diácido de (*S*)-2-amino-2-(5-(3-(trifluorometil)-4-(5-(3-(trifluorometil)fenil)-pentiloxi)fenil)-1,3,4-tiadiazol-2-il)propilo (c)



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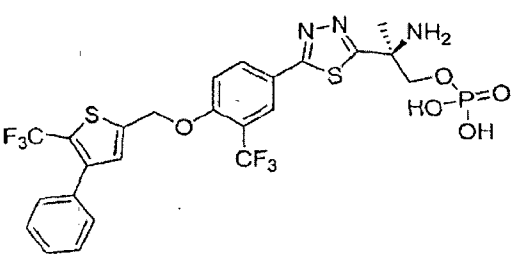
EM (ESI, $M+H^+$) = 614.0; el tiempo de retención de CLAR sobre una columna Synergi-Max RP (2 x 20 mm, 2 µl) fue de 1.44 min con gradiente de 30-99% de acetonitrilo-H_2O (0.1% de TFA) en 2 min como fase móvil.

Fosfato diácido de (*S*)-2-amino-2-(5-(3-(trifluorometil)-4-(5-(4-(trifluorometil)fenil)pentiloxi)fenil)-1,3,4-tiadiazol-2-il)propilo (d)



EM (ESI, $M+H^+$) = 614.0; el tiempo de retención de CLAR sobre una columna Synergi-Max RP (2 x 20 mm, 2 µl) fue de 1.44 min con gradiente de 30-99% de acetonitrilo-H_2O (0.1% de TFA) en 2 min como fase móvil.

Fosfato diácido de (*S*)-2-amino-2-(5-(4-((4-fenil-5-(trifluorometil)tiofen-2-il)metoxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propilo (e)

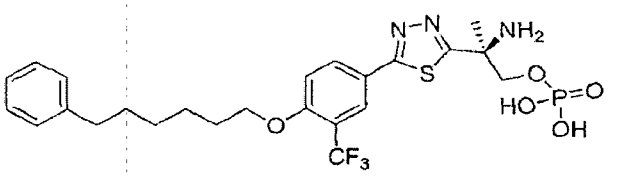


EM (ESI, $M+H^+$) = 639.8; el tiempo de retención de CLAR sobre una columna Synergi-Max RP (2 x 20 mm, 2 µl) fue de 1.37 min con gradiente

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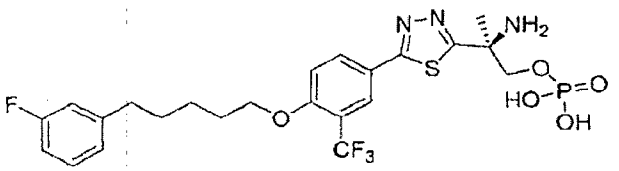
de 30-99% de acetonitrilo-H_2O (0.1% de TFA) en 2 min como fase móvil.

Fosfato diácido de (*S*)-2-amino-2-(5-(4-(6-fenilhexiloxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propilo (f)



EM (ESI, $M+H^+$) = 599.9; el tiempo de retención de CLAR sobre una columna Synergi-Max RP (2 x 20 mm, 2 µl) fue de 1.41 min con gradiente de 30-99% de acetonitrilo-H_2O (0.1% de TFA) en 2 min como fase móvil.

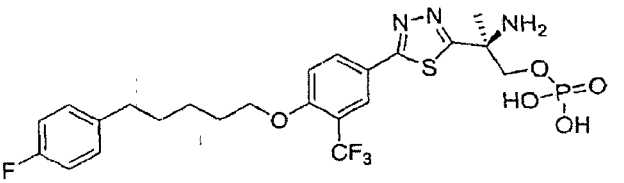
Fosfato diácido de (*S*)-2-amino-2-(5-(4-(5-(3-fluorofenil)pentiloxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propilo (g)



EM (ESI, $M+H^+$) = 563.9; el tiempo de retención de CLAR sobre una columna Synergi-Max RP (2 x 20 mm, 2 µl) fue de 1.53 min con gradiente de 20-95% de acetonitrilo-H_2O (0.1% de TFA) en 2 min como fase móvil.

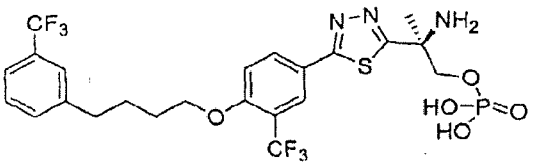
399

Fosfato diácido de (*S*)-2-amino-2-(5-(4-(5-(4-fluorofenil)pentiloxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propilo (h)



EM (ESI, $M+H^+$) = 593.9; el tiempo de retención de CLAR sobre una columna Synergi-Max RP (2 x 20 mm, 2 µl) fue de 1.57 min con gradiente de 20-95% de acetonitrilo-H_2O (0.1% de TFA) en 2 min como fase móvil.

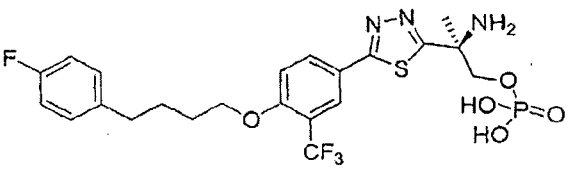
Fosfato diácido de (*S*)-2-amino-2-(5-(3-(trifluorometil)-4-(4-(3-(trifluorometil)fenil)butoxi)fenil)-1,3,4-tiadiazol-2-il)propilo (i)



EM (ESI, M+H*) = 599.9; el tiempo de retención de CLAR sobre una columna Synergi-Max RP (2 x 20 mm, 2 µl) fue de 2.03 min con gradiente de 20-95% de acetonitrilo-H_2O (0.1% de TFA) en 2 min como fase móvil.

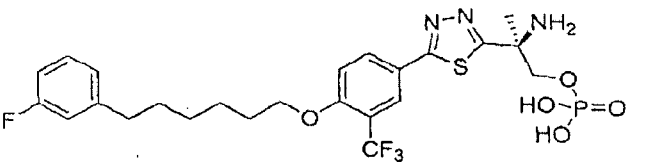
400

Fosfato diácido de (*S*)-2-amino-2-(5-(4-(4-(4-fluorofenil)butoxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propilo (j)



EM (ESI, M-HH$^+$) = 549.9; el tiempo de retención de CLAR sobre una columna Synergi-Max RP (2 x 20 mm, 2 µl) fue de 1.51 min con gradiente de 20-95% de acetonitrilo-H_2O (0.1% de TFA) en 2 min como fase móvil.

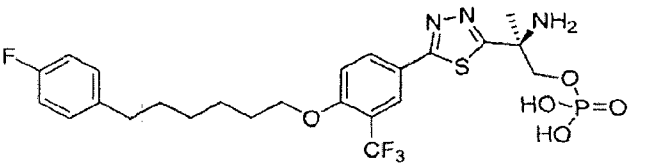
Fosfato diácido de (*S*)-2-amino-2-(5-(4-(6-(3-fluorofenil)hexiloxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propilo (k)



EM (ESI, M+H$^+$) = 577.9; el tiempo de retención de CLAR sobre una columna Synergi-Max RP (2 x 20 mm, 2 µl) fue de 1.65 min con gradiente de 20-95% de acetonitrilo-H_2O (0.1% de TFA) en 2 min como fase móvil.

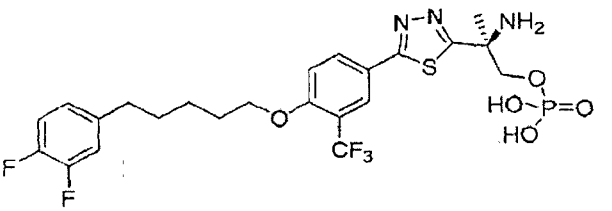
401

Fosfato diácido de (*S*)-2-amino-2-(5-(4-(6-(4-fluorofenil)hexiloxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propilo (l)



EM (ESI, $M+H^+$) = 578.0; el tiempo de retención de CLAR sobre una columna Synergi-Max RP (2 x 20 mm, 2 µl) fue de 1.63 min con gradiente de 20-95% de acetonitrilo-H_2O (0.1% de TFA) en 2 min como fase móvil.

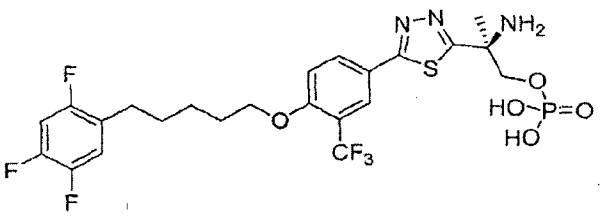
Fosfato diácido de (*S*)-2-amino-2-(5-(4-(5-(3,4-difluorofenil)pentiloxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propilo (m)



EM (ESI, $M+H^+$) = 582.0; el tiempo de retención de CLAR sobre una columna Synergi-Max RP (2 x 20 mm, 2 µl) fue de 1.58 min con gradiente de 20-95% de acetonitrilo-H_2O (0.1% de TFA) en 2 min como fase móvil.

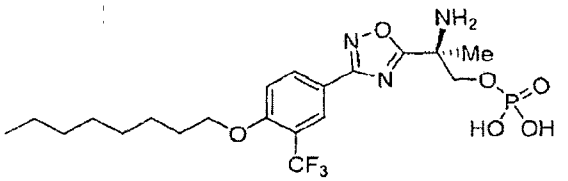
1402

Fosfato diácido de (*S*)-2-amino-2-(5-(3-(trifluorometil)-4-(5-(2,4,5-trifluorofenil)pentiloxi)fenil)-1,3,4-tiadiazol-2-il)propilo (n)



EM (ESI, $M+H^+$) = 599.9; el tiempo de retención de CLAR sobre una columna Synergi-Max RP (2 x 20 mm, 2 µl) fue de 1.59 min con gradiente de 20-95% acetonïtrile-H_2O (0.1% de TFA) en 2 min como fase móvil.

Fosfato diácido de (*S*)-2-amino-2-(3-(4-(octiloxi)-3-(trifluorometil)fenil)-1,2,4-oxadiazol-5-il)propilo (o)

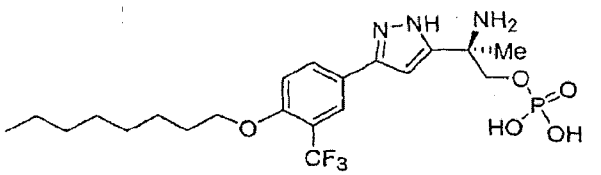


El producto del título se obtuvo de conformidad con el procedimiento general a partir de compuesto 7a (Esquema 6).

EM (ESI, $M+H^+$) = 496.0

403

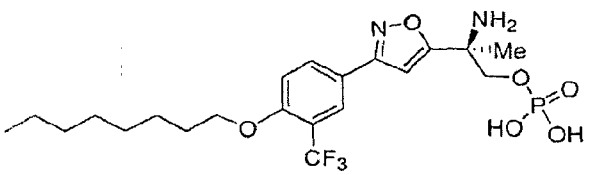
Fosfato diácido de (*R*)-2-amino-2-(3-(4-(octiloxi)-3-(trifluorometil)fenil)-1*H*-pirazol-5-il)propilo (p)



El producto del título se obtuvo de conformidad con el procedimiento general a partir de compuesto 3a (Esquema 7).

EM (ESI, $M+H^+$) = 494.1

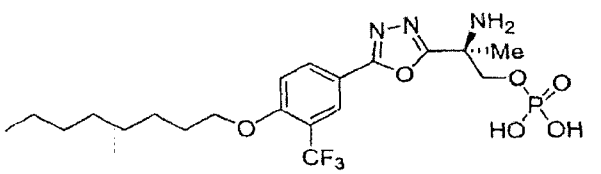
Fosfato diácido de (*S*)-2-amino-2-(3-(4-(octiloxi)-3-(trifluorometil)fenil)isoxazol-5-il)propilo (q)



El producto del título se obtuvo de conformidad con el procedimiento general a partir de compuesto 3a (Esquema 7).

EM (ESI, $M+H^+$) = 495.0

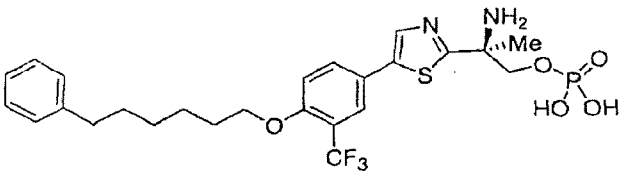
Fosfato diácido de (*S*)-2-amino-2-(5-(4-(octiloxi)-3-(trifluorometil) fenil)-1,3,4-oxadiazol-2-il)propilo (q)



El producto del título se obtuvo de conformidad con el procedimiento general a partir del amino-alcohol correspondiente.

EM (ESI, $M+H^+$) = 496.0

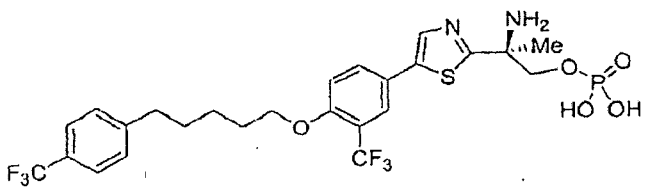
Fosfato diácido de (*S*)-2-amino-2-(5-(4-(6-fenilhexiloxi)-3-(trifluorometil)fenil)tiazol-2-il)propilo (r)



El compuesto del título se preparó a partir de (*S*)-2-amino-2-(5-(4-(6-fenilhexiloxi)-3-(trifluorometil)fenil)tiazol-2-il)propan-1-ol. El tiempo de retención de CLAR sobre una columna C18 (30 x 4.6 mm, 3.5 µ) fue de 2.48 min con gradiente de 10-95% acetonitrilo-H_2O (0.1% de TFA) en 3.5 min como fase móvil.

EM (ESI, $M+H^+$) = 559.5.

Fosfato diácido de (*S*)-2-amino-2-(5-(3-(trifluorometil)-4-(5-(4-(trifluorometil)fenil)pentiloxi) fenil)tiazol-2-il)propilo (s)



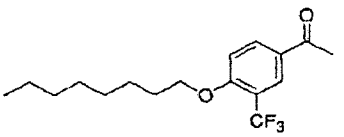
El compuesto del título se preparó a partir de (*S*)-2-amino-2-(5-(3-(trifluorometil)-4-(5-(4-(trifluorometil)fenil)pentiloxi)fenil)tiazol-2-il)propan-1-ol. El tiempo de retención de CLAR sobre una columna C18 (30 x 4.6 mm, 3.5 µ) fue de 2.53 min con gradiente de 10-95% de acetonitrilo-H_2O (0.1% de TFA) en 3.5 min como fase móvil.

EM (ESI, $M+H^+$) = 613.5.

Ejemplos de métodos específicos usados para hacer (*S*)-2-amino-2-(5-(4-(octiloxi)-3-(trifluorometil)fenil)tiazol-2-il)propan-1-ol y (*S*)-2-amino-2-(5-(4-(octiloxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol

Descripción 1

1-(4-(octiloxi)-3-(trifluorometil)fenil)etanona (D1)



1-octanol (2 ml), 1-[4-fluoro-3-(trifluorometil)fenil]etanona (2.62 g), *ter*-butóxido de potasio (14 ml, 1.0M) y tetrahidrofurano (30 ml) se calentaron a 65°C durante 3hr para producir el producto del título como un aceite pardusco (4.00 g). El producto se purificó por cromatografía en columna de gel de sílice usando el sistema Combi-Flash (Hex:EtOAc) como sólido blanco en 60% (1.20 g).

CCD (1:5 EtOAc:Hex), R_f= 0.4;

^{1}H RMN (400 MHz, $CDCl_3$) δ 8.18 (d, 1H, J= 2.0 Hz), 8.10 (dd, 1H, J= 8.8 Hz, J= 2.3 Hz), 7.02 (d, 1H, J= 8.8 Hz),4.12 (t, 2H, J= 6.4 Hz), 2.58 (m, 3H), 1.80-1.89 (m, 2H), 1.42-1.54 (m, 2H), 1.22-1.40 (m, 8H), 0.89 (t, 3H, J= 6.7 Hz).

Método alternativo de la descripción 1 (D1A)

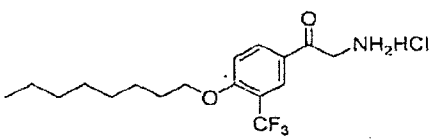
1-(4-(Octiloxi)-3-(trifluorometil)fenil)etanona (D1)

Una solución de n-octanol (13.3 g, 0.102 moles), en THF (224 ml) se trató con *t*-butóxido de potasio 1.0 M en THF (112 ml, 1.1 equiv) a temperatura ambiente y se calentó a 65°C. Después de 15 minutos, una solución de 1-[4-fluoro-3-(trifluorometil)fenil]etanona (21 g, 1.0 equiv) en THF (224 ml) se cargó lentamente durante 30 minutos. Se observó evolución vigorosa de gas durante la adición. La reacción se monitoreó por HPLC y se consideró completa después de 1.5 hr. La mezcla de reacción se enfrió a temperatura ambiente, se trató con 10% de ácido cítrico acuoso (250 ml), se extrajo con MTBE (2 x 500 ml), se secó y se concentró para dar el producto (31.99 g, 99.3%, 88.1% de AUC por CLAR). Esta reacción se repitió con una ligera modificación como se describió antes (reduciendo la cantidad de THF usada para disolver la acetofenona a 3 ml/g a partir de 10.7 ml/g con control mejorado de evolución de gas) en una escala de 100 g para dar 137.1 g, >100% de rendimiento). Los dos lotes se combinaron y se purificaron por cromatografía en columna usando gel de sílice (1 kg), se eluyeron con 10% de acetato de etilo: 90% de heptano para dar el producto del título (105 g, 75%

de rendimiento) como un aceite color amarillo pálido. Se recogieron las fracciones impuras y dieron 22.8 g (16.3% de rendimiento) del producto.

Descripción 2

Clorhidrato de 2-amino-1-(4-(octiloxi)-3-(trifluorometil)fenil)-etanona (D2)



A una solución de 1-(4-(octiloxi)-3-(trifluorometil)fenil)etanona (D1) (0.5 g, 1.0 equivalentes) en CH_2Cl_2/MeOH (4:1, 10 ml) se añadió Bu_4NBr_3 (0.76 g, 1.0 equiv). La mezcla de reacción se agitó a temperatura ambiente durante 3 horas. CCD (4:1, Hex/EtOAc), R_f= 0.6. El solvente se removió bajo vacío, y se volvió a disolver en DMF (10 ml). NaN_3 (0.31 g, 3.0 equiv) se añadió a la reacción y la mezcla resultante se agitó después a temperatura ambiente durante 2 hr. El solvente se removió bajo vacío y el producto se purificó por cromatografía en columna de gel de sílice usando el sistema Combi-Flash (Hex:EtOAc) para dar el producto de azido-acetofenona. CCD (4:1, Hex/EtOAc), R_f = 0.4. El residuo después se disolvió en HCl concentrado (1.0 ml) y MeOH (20 ml). Se añadió 10% de Pd/C (100 mg) y la mezcla se agitó bajo una atmósfera de H_2 (g) durante 3 horas. La mezcla de reacción se filtró después y se evaporó a sequedad para dar el producto del título como un sólido amarillo 98% (rendimiento de 570 mg). CCD (4:1, Hex/EtOAc), R_f= 0.6.

Método alternativo de la descripción 2 (D2A)

Clorhidrato de 2-amino-1-(4-(octiloxi)-3-(trifluorometil)fenil)-etanona (D2)

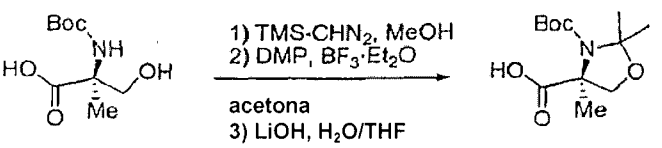
Un matraz de fondo redondo de 5 l se cargó con 1-(4-(octiloxi)-3-(trifluorometil)fenil)etanona (D1A) (128 g, 0.40 moles), diclorometano anhidro (3.2 l), tribromuro de tetrabutilamonio (175 g, 0.36 moles, 0.9 equiv), metanol (640 ml) y se agitó durante 1 hora a temperatura ambiente (18 a 23°C) y después se trató con bromuro de tetrabutilamonio adicional (20 g, 0.1 equiv) y se mantuvo durante cinco horas adicionales. La reacción se consideró completa por análisis de CCD (10% acetato de etilo en tolueno) y se concentró a un residuo. El residuo se purificó por cromatografía en columna usando gel de sílice (2.7 kg), se eluyó con 10% de acetato de etilo: 90% de heptano para dar un sólido espumoso (128 g, 80% de rendimiento). Un matraz de fondo redondo de 3 litros se cargó con una solución del sólido espumoso (128 g, 0.32 moles) en acetonitrilo (1 l) y diformilamida de sodio (36.9 g, 0.38 moles, 1.2 equiv), y se calentó a 65°C durante 2 horas. La reacción se probó por CCD y pareció ser aproximadamente 50% completa. La reacción se dejó continuar durante 10 horas adicionales, punto en el cual se encontró que estaba completa por CCD. La mezcla se enfrió a temperatura ambiente (18 a 23°C) y se cargó con MTBE (1 l), se agitó durante 15 minutos, se filtró, los sólidos se lavaron dos veces con MTBE (2 x 250 ml). Los filtrados se combinaron y se concentraron a un aceite espeso. El aceite se recogió en el alcohol reactivo (1.1 l), se cargó con HCl 10 N (100 ml) y se calentó a 70°C y

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se mantuvo durante 3 horas, punto en el cual CCD indicó que la reacción estaba completa. La mezcla se enfrió a 40-50°C y SE transfirió a un evaporador giratorio y el etanol se removió y se azeotropó tres veces con tolueno (3 x 1 l) para dar el producto del título (149 g, rendimiento cuantitativo) como aceite gomoso.

Descripción 3

Acido (*R*)-3-(*ter*-butoxicarbonil)-2,2,4-trimetiloxazolidin-4-carboxílico (D3)



A una solución del ácido (*S*)2-(*ter*-butoxicarbonilamino)-3-hidroxi-2-metilpropanoico (5.0 g, 1.0 equiv) en CH_2Cl_2/MeOH (4:1, 50 ml) a 0°C se añadió una solución de TMS-CHN_2 (2.0 M en éter dietílico o hexanos, 12.5 ml, 1.1 equiv) gota a gota hasta que la solución incolora se volvió a color amarillo claro. La mezcla de reacción se agitó durante 20 minutos a 0°C, después se añadieron una pocas gotas de ácido acético para extinguir el último TMS-CHN_2 sin reaccionar (la solución se volvió incolora a partir de amarillo claro). El solvente se removió bajo vacío. CCD (2:1, Hex/EtOAc), R_f= 0.4.

El residuo se disolvió en acetona (30 ml), 2,2-dimetoxipropano (DMP) (12 ml) y BF_3•OEt_2 (2 ml). La solución se agitó a T.A. durante 4 horas. El solvente se removió bajo vacío y el producto se purificó por cromatografía

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en columna de gel de sílice usando el sistema Combi-Flash (Hex:EtOAc).

CCD (3:1, Hex/EtOAc), R_f= 0.6;

^{1}H RMN (400 MHz, $CDCl_3$) δ 4.06-4.12 (m, 1H), 3.73-3.83 (m, 4H), 1.55-1.64 (m, 9H), 1.48 (br s, 3H), 1.41 (br s, 6H).

El residuo purificado se disolvió en THF (40 ml) y a la solución se añadió LiOH (1.15 g, 1.20 equiv) en H_2O (20 ml). La solución se calentó a reflujo durante 6 horas después se agitó durante la noche, después se concentró bajo vacío para remover la mayor parte de THF. La solución se diluyó con H_2O (150 ml) y se lavó con Et_2O (2 x 150 ml). La capa acuosa se enfrió a 0°C después se acidificó a un pH de 2 usando HCl concentrado, después se extrajo con EtOAc (2 x 200 ml). Las capas de EtOAc se combinaron, se secaron ($MgSO_4$), se filtraron y el solvente se removió bajo vacío para dar el compuesto del título de carboxilato como un sólido blanco con un rendimiento de 64% (3.78 g).

CCD (1:1 EtOAc:Hex), R_f= 0.2;

^{1}H RMN (400 MHz, $CDCl_3$) δ (rotámeros) 4.47 (br d, 0.5H, J= 8.8 Hz), 4.17 (br d, 0.5H, J = 8.8 Hz), 3.85 (br d, 0.5H, J= 8.8 Hz), 3.78 (br d, 0.5H, J= 8.8 Hz), 1.38-1.67 (m, 18H).

Método alternativo de la descripción 3 (D3A)

Acido (*R*)-3-(*ter*-butoxicarbonil)-2,2,4-trimetiloxazolidin-4-carboxílico (D3)

Un matraz de fondo redondo de 22 l se hizo inerte y se cargó con

ácido (*S*)-2-(*ter*-butoxicarbonilamino)-3-hidroxi-2-metilpropanoico (564 g, 2.57 moles), acetona (8.4 l) y se agitó. La mezcla se cargó lentamente con 1,8-diazabiciclo[5.4.0]undec-7-eno (770 ml, 5.1 moles, 2 equiv.). La adición fue exotérmica y la temperatura se mantuvo por abajo de 25°C. La mezcla se agitó durante 45 minutos a condiciones ambientales y después, cuidadosamente, se cargó con yodometano (320 ml, 5.1 moles, 2 equiv). La adición fue exotérmica y la temperatura se mantuvo por abajo de 25°C. La mezcla se dejó agitar durante la noche a temperatura ambiente (18 a 23°C). Después de 16 horas, CCD indicó que quedó material de partida . La reacción se cargó con yodometano (320 ml, 5.1 moles, 2 equiv), se calentó a 30°C durante 4 horas, y después se dejó agitar durante la noche a temperatura ambiente (18 a 23°C). Después de 16 horas, la prueba por CCD indicó que la reacción se completó. La mezcla de reacción se combinó con otra mezcla de reacción de una escala de 275 g. Las mezclas de reacción combinadas se concentraron bajo vacío a un residuo, se transfirieron en un reactor, se cargaron con agua (8.4 l), acetato de etilo (8.4 l), se mezcló completamente, las fases se separaron, la fase acuosa se extrajo una vez más con acetato de etilo (8.4 l), las fases orgánicas se combinaron, se lavaron con 5% p/v de ácido cítrico (900 ml), salmuera (1 l), se secaron con sulfato de magnesio, se filtraron sobre Celite, y se concentraron para dar un aceite (925 g, 104% de rendimiento). Un matraz de fondo redondo de 22 l se cargó con este producto crudo (925 g, 3.8 moles con base en la salida teórica del paso anterior), diclorometano (10 l), 2,2-dimetoxipropano (2.6 l), y se mezcló. n (200 ml, 1.62

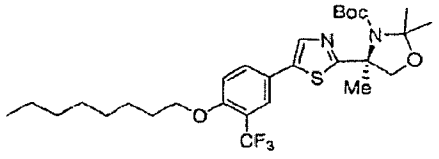
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moles, 0.42 equiv) en diclorometano (1.2 L) se cargó cuidadosamente durante 45 minutos. La solución oscura resultante se agitó durante la noche a temperatura ambiente (18 a 23°C). Después de 16 horas CCD indicó que la reacción se completó. La mezcla se extinguió lentamente con bicarbonato de sodio saturado (3.5 l) mientras se mantenía la temperatura por debajo de los 25°C. Una vez que la extinción se completó, la mezcla se agitó durante 30 minutos, las fases se separaron y la fase acuosa se extrajo con diclorometano (3.5 l), las fases orgánicas se combinaron, se lavaron con bicarbonato de sodio saturado (3 l), se concentraron para obtener compuesto como un aceite amarillo (1070 g, cuantitativo). Un matraz de fondo redondo de 22 l se cargó con hidróxido de litio monohidratado (482 g, 11.4 moles, 3 equiv), agua (2.3 l), metanol (2.1 l), una solución de aceite amarillo crudo (1046 g, con base en la salida teórica del paso anterior, 3.82 moles) en tetrahidrofurano (6.5 l). La mezcla se agitó durante 72 horas a temperatura ambiente (18 a 23°C). CCD indicó que la reacción se completó. La mezcla se concentró bajo vacío a 40°C, el residuo se cargó con agua (10 l), MTBE (6 l), se mezcló completamente y las fases se separaron. La fase orgánica se lavó con agua (4 l), las fases acuosas se combinaron, y se cargó ácido cítrico sólido en porciones hasta que se obtuvo un pH de 3. La fase acuosa se extrajo con acetato de etilo (2 x 10 l), las fases de acetato de etilo se combinaron, se lavaron con salmuera (7 l), se secaron con sulfato de magnesio, se filtraron sobre Celite, y se concentraron para dar el producto del título (770 g, rendimiento de 77.6%) como un sólido blanquecino

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Descripción 4

2,2,4-Trimetil-4-(5-(4-(octiloxi)-3-(trifluorometil)fenil)tiazol-2-il)oxazolidin-3-carboxilato de (*R*)-ter-butilo (D4)



A una solución de ácido (*R*)-3-(*ter*-Butoxicarbonil)-2,2,4-trimetiloxazolidin-4-carboxílico (D3) (100 mg, 1 equiv), HATU (220 mg, 1.5 equiv), y DIEA (0.67 ml, 10 equiv) en DCM (5 ml) se añadió clorhidrato de 2-amino-1-(4-(octiloxi)-3-(trifluorometil)fenil)etanona (D2) (142 mg, 1.0 equivalentes). El solvente se removió bajo vacío y el producto se purificó por cromatografía en columna de gel de sílice usando el sistema Combi-Flash (Hex:EtOAc). Esto dio por resultado un aceite espeso, incoloro que se disolvió en tolueno (5 ml) con reactivo de Lawesson (280 mg, 3 equiv). La mezcla resultante se calentó a 120°C durante 2 horas para producir el producto del título como un aceite incoloro con un rendimiento de 41% (90 mg).

CCD (1:2 EtOAc:Hex), R_f= 0.3;

EM (ESI, M+Na) = 572.99;

^{1}H RMN (400 MHz, $CDCl_3$) δ 8.21 (s, 1H), 8.11 (d, 1H, J= 8.4 Hz), 7.05 (d, 1H, J= 8.4 Hz), 4.62-4.79 (m, 2H), 4.13 (t, 2H, J= 6.4 Hz), 3.28 (br s, 1H), 1.22-1.90 (m, 30H), 0.89 (t, 3H, J= 6.4 Hz).

Método alternativo de la descripción 4 (D4A)

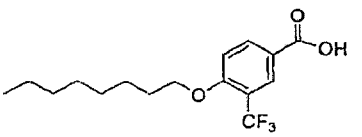
2,2,4-Trimetil-4-(5-(4-(octiloxi)-3-(trifluorometi])fenil)tiazol-2-il)oxazolidin-3-carboxilato de (*R*)-*ter*-butilo (D4)

Un matraz de fondo redondo de 5 l se cargó con HATU (147 g, 0.38 moles, 1.2 equiv), cloruro de metileno (600 ml), *N,N*-dimetilformamida (300 ml), diisopropiletilamina (83.5 g, 0.64 moles, 2 equiv) y la mezcla se enfrió a 10-15°C. Una solución de ácido (*R*)-3-(*ter*-butoxicarbonil)-2,2,4-trimetiloxazolidin-4-carboxílico (D3A) (83.7 g, 0.32 moles, 1 equiv) en cloruro de metileno (600 ml) se cargó durante un periodo de 30 minutos. La mezcla se calentó a temperatura ambiente (18 a 23°C) y se agitó durante 1 hora. Un matraz separado se cargó con solución de clorhidrato de 2-amino-1-(4-(octiloxi)-3-(trifluorometil)fenil)etanona (D2A) (149 g, 0.32 moles -|con base en producción teórica) en cloruro de metileno (1 l), *N,N*-dimetilformamida (400 ml) y diisopropiletilamina (125 g, 0.96 moles, 3 equiv). La solución del segundo matraz se cargó lentamente al primer matraz durante un periodo de 35 minutos. La solución café resultante se agitó durante 1 hora, punto en el cual el análisis de CCD indicó que la reacción se completó. La mezcla se transfirió a un evaporador giratorio y se concentró para remover el cloruro de metileno. La mezcla se transfirió una vez más al matraz de fondo redondo y se cargó con MTBE (3 l), 10% p/v de solución acuosa de cloruro de sodio (3 l), se agitó durante 10 minutos, las fases se separaron y la fase acuosa se extrajo una vez más con MTBE (1 l). Las fases orgánicas se combinaron, se lavaron dos veces con 10% p/v de solución acuosa de cloruro de sodio (2 x 1 l), se

secaron con sulfato de magnesio, y se concentraron a un residuo que se purificó por cromatografía en columna usando gel de sílice (1.3 kg), se eluyó con 5% de acetato de etilo: 95% de heptano a 30% de acetato de etilo: 70% de heptano para dar el producto como un aceite color amarillo (137.5 g, rendimiento de 74%). Un matraz de fondo redondo de 5 l se cargó con reactivo de Lawesson (116.2 g, 0.28 moles, 1.2 equiv), una solución del aceite de color amarillo (137 g, 0.239 moles) en tolueno (2 l). La suspensión resultante se calentó a 80°C, que después de 30 minutos se hizo una solución clara. La solución se mantuvo a 80°C durante otras 2 horas, punto en el cual CCD (25% acetato de etilo: 75% heptano) indicó que la reacción se completó. La mezcla de reacción se enfrió a temperatura ambiente (18 a 23°C), se cargó con solución saturada de bicarbonato de sodio (1 l), 10% p/v de cloruro de sodio (1 l), acetato de etilo (1 l), y se agitó durante 30 minutos. Las fases se separaron y la fase acuosa se extrajo una vez más con acetato de etilo (1 l). Las fases orgánicas se combinaron y se concentraron a un residuo. El residuo se purificó por cromatografía en columna usando gel de sílice (1.3 kg), se eluyó con 100% de heptano a 30% de acetato de etilo: 70% de heptano para dar el producto del título (91.1 g, rendimiento de 67%, 96.6% AUC por CLAR) como un aceite café.

Descripción 5

Acido 4-(octiloxi)-3-(trifluorometil)benzoico (D5)



1-octanol (315 µl, 2.0 mmoles), THF (5 ml), *t*-butóxido de potasio (5 ml, solución 1M en THF), ácido 4-fluoro-3-trifluorometilbenzoico (417 mg, 2.0 mmoles) se mezclaron y se calentaron a 75°C durante 3-4 hr. La mezcla de reacción se diluyó después con acetato de etilo y se lavó con agua. La capa acuosa se acidificó y se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera y se secó sobre Na_2SO_4 y se concentró para dar el compuesto del título (632 mg, pureza por CLAR > 95%), que se usó para la siguiente reacción sin purificación adicional. El tiempo de retención de CLAR sobre una columna C8(2) (30 x 3.00 mm, 3 µ) fue de 3.28 min con gradiente de 50-98% de acetonitrilo-H_2O (0.1% de ácido trifluoroacético (TFA)) en 3.5 min como fase móvil.

Método alternativo A de la descripción 5 (D5A)

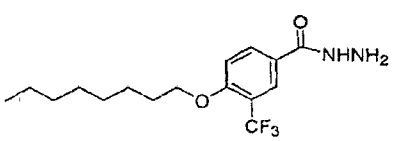
Acido 4-(octiloxi)-3-(trifluorometil)benzoico (D5)

Un matraz de fondo redondo de 12 l se hizo inerte y se cargó con 1-octanol (103 g, 0.793 moles, 1 equiv), THF (2 l), *ter*-butóxido de potasio 1M (2 l, 2.5 equiv) y se calentó a 65°C y se mantuvo durante 45 minutos. La reacción se cargó durante 1 hora con ácido 4-fluoro-3-trifluorometilbenzoico

(165 g, 0.793 moles) mientras se mantenía la temperatura a 64 a 67°C. Después de 2 horas, se muestreó la mezcla de reacción. La muestra se concentró, se extinguió en HCl 1 N, se extrajo con acetato de etilo, se removió el acetato de etilo, se diluyó con acetonitrilo y se inyectó a la CLAR. La reacción se completó. La mezcla de reacción se agitó durante la noche de 18 a 23°C. La mezcla se enfrió de 5 a 10°C y cuidadosamente se extinguió con agua (1.6 l). La extinción fue exotérmica y la temperatura se mantuvo a T<10°C. La mezcla resultante se concentró bajo vacío hasta que ya no se desprendió THF evidente. La mezcla acuosa resultante se acidificó a pH de 1 a 2 usando HCl 6 N (400 ml). La mezcla se extrajo con MTBE (2 x 2.5 l). Las fases de MTBE se combinaron, se lavaron con salmuera (2 l), se secaron con sulfato de magnesio, se filtraron sobre Celite, se concentraron para dar el producto del título (279 g, rendimiento de 111%, 95.6% AUC por CLAR) como un sólido color canela.

Descripción 6

4-(Octiloxi)-3-(trifluorometil)benzohidrazida (D6)



Acido 4-(octiloxi)-3-(trifluorometil)benzoico (D5) (600 mg, 1 equiv) se agitó con HATU (859 mg, 1.2 equiv) y DIEA (1.63 ml, 5 equiv) en CH_2Cl_2-DMF (10 ml, 4:1, 3 equivalentes) seguido por la adición de hidrazina (282 µl, 3

equiv). La mezcla de reacción se diluyó después con acetato de etilo y se lavó con agua y salmuera. La capa orgánica se secó sobre Na_2SO_4 y se concentró bajo vacío para dar el compuesto del título (661 mg). EM (ESI): 333.08 (MH^+)

Se hizo otro lote también usando D5 (32 mg, 1 equivalente), HATU (46 mg, 1.2 equivalentes), DIEA (87 µl, 5 equiv) en CH_2Cl_2-DMF (1.5 ml, 2:1) seguido por la adición de hidrazina (15 µl, 3 equiv).

Método alternativo de la descripción 6 (D6A)

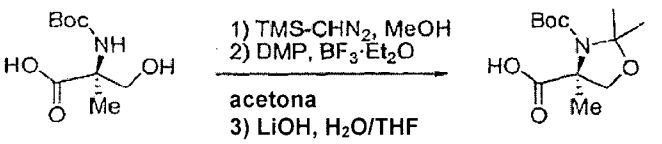
4-(Octiloxi)-3-(trifluorometil)benzohidrazida (D6)

Un matraz de fondo redondo de 3 cuellos de 5 litros se hizo inerte y se cargó con CDI (153 g, 0.94 moles, 1.2 equiv), ácido 4-(octiloxi)-3-(trifluorometil)benzoico (D5A) (250 g con base en la producción teórica del paso anterior, 0.78 moles), THF (2.5 l) y se agitó a 18 a 23°C durante 1 hora. Un matraz de fondo redondo de 12 l separado se hizo inerte y se cargó con hidrazina monohidratada (235 g, 4.71 moles, 6 equiv) y THF (1.2 l). Los contenidos del primer matraz se cargaron en el segundo matraz durante 1 hora. Durante la adición, la temperatura se mantuvo a T<25°C. Una vez que la adición se completó, la mezcla se agitó durante 2 horas a 18 a 23°C, punto en el cual CCD indicó que la reacción se completó. La mezcla se concentró bajo vacío a 35 a 40°C hasta que se obtuvo aproximadamente 10 a 15% del volumen original. Se cargaron agua (2 l) y salmuera (2 l) a la mezcla que después se extrajo con diclorometano (2 x 2.5 l). Hubo una pequeña emulsión durante cada extracción. Las fases orgánicas se combinaron, se lavaron con

salmuera (500 ml), se secaron con sulfato de magnesio, se filtraron sobre Celite, y se concentraron para dar el producto del título (247 g, rendimiento de 94%, 96% AUC por CLAR) como un sólido amarillo.

Descripción 7

Acido (*R*)-3-(*ter*-butoxicarbonil)-2,2,4-trimetiloxazolidin-4-carboxílico (D7)



A una solución del ácido (*S*)-2-(*ter*-butoxicarbonilarnino)-3-hidroxi-2-metilpropanoico (5.0 g, 1.0 equiv) en CH_2Cl_2/MeOH (4:1, 50 ml) se añadió una solución de TMS-CHN_2.

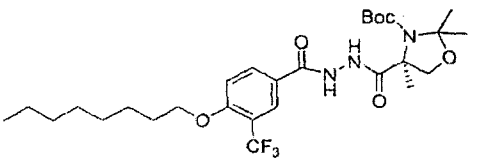
El residuo se disolvió en acetona (30 ml), 2,2-dimetoxipropano (DMP) (12 ml) y BF_3•OEt_2 (2 ml). La solución se agitó a T.A. durante 4 horas. El solvente se removió bajo vacío y el producto se purificó por cromatografía en columna de gel de sílice usando el sistema Isco (0-30% de HexrEtOAc) para dar el intermediario de éster oxazolinmetílico.

El residuo purificado se disolvió en H_2O-THF (1:4) y a la solución se añadió LiOH (1.16 g). La solución se calentó a reflujo durante la noche, se enfrió a temperatura ambiente y se condensó para remover la THF. El material acuoso se diluyó con H_2O (~100 ml), se acidificó a pH 2 con 10% de $KHSO_4$ y después se extrajo con EtOAc. Las capas orgánicas se secaron sobre

Na_2SO_4, y se condensaron para dar el compuesto del título con un rendimiento de 66% (3.29 g).

Descripción 8

2,2,4-trimetil-4-(2-(4-(octiloxi)-3-(trifluorometil)benzoil)-hidrazincarbonil)oxazolidin-3-carboxilato de (*S*)-*ter*-butilo (D8)



Acido (*R*)-3-(*ter*-butoxicarbonil)-2,2,4-trimetiloxazolidin-4-carboxílico (D7) (210 mg, 0.81 mmoles), HATU (372 mg, 0.98 mmoles), diisopropiletilamina (DIEA) (0.705 ml, 4.1 mmoles), CH_2Cl_2-DMF y 4-(octiloxi)-3-(trifluorometil)benzohidrazida (D6) (270 mg, 0.81 mmoles) se mezclaron juntos. La reacción se condensó, se diluyó con acetato de etilo, se lavó con agua y salmuera, y se condensó nuevamente. Se hizo otro lote usando este método con (D7) (0.1 mmoles), HATU (46 mg, 0.12 mmoles), DIEA (87 µl, 0.5 mmoles), CH_2Cl_2-DMF y 4-(octiloxi)-3-(trifluorometil)benzohidrazida (D6) (>6 mg, 0.1 mmol). Los lotes se sometieron a cromatografía y se combinaron para proveer el producto del título (428 mg).

EM (ESI): 573.84 (MH^+);

^1H RMN (400 MHz, $CDCl_3$) δ 9.43 (br, 2H), 8.06 (d, 1H, J= 2.0 Hz), 7.94 (dd, 1H, J= 8.8 Hz, J= 2.0 Hz), 6.96 (d, 1H, J= 8.8 Hz), 4.52 (br, 1H), 4.07 (t, 2H, J= 6.4 Hz), 3.76 (br, 1H), 1.82 (m, 2H), 1.67 (s, 6H), 1.57 (s, 3H),

1.51 (s, 9H), 1.51-1.43 (m, 4H), 1.38-1.24 (m, 6H), 0.88 (t, 3H, J= 7.2 Hz).

Método alternativo de la descripción 8 (D8A)

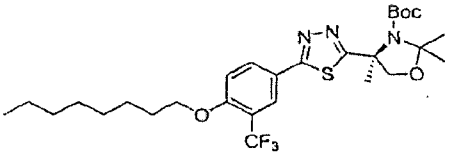
2,2,4-Trimetil-4-(2-(4-(octiloxi)-3-(trifluorometil)benzoil)-hidrazincarbonil)oxazolidin-3-carboxilato de (*S*)-*ter*-butilo (D8)

Un matraz de fondo redondo de 5 l se hizo inerte y se cargó con HATU (199 g, 0.52 moles, 1.2 equiv), *N,N*-dimetilformamida (380 ml), y se mezcló. Una solución de ácido (*R*)-3-(*ter*-butoxicarbonil)-2,2,4-trimetiloxazolidin-4-carboxílico (D3A) (133.1 g, 0.43 moles, 1 equiv), diclorometane (870 ml), y *N,N*-diisopropiletilamina (155 ml, 0.88 moles, 2 equiv) se cargó al matraz durante 15 minutos. La mezcla resultante se agitó a 18 a 23°C durante 1 hora. Una solución de benzohidrazida (D6) (145 g, 0.43 moles, 1 equiv) en diclorometano (1120 ml), y *N,N*-dimetilformamida (420 ml) se cargó durante 15 minutos, después se agitó a 18 a 23°C durante 1 hora. Después de 1 hora, CCD indicó que la reacción se completó. La mezcla se concentró, se dividió entre acetato de etilo (2.5 l) y agua (2.5 l). Las fases se separaron y la fase acuosa se extrajo una vez más con acetato de etilo (1 l). Las fases orgánicas se combinaron, se lavaron con 10% de p/v de cloruro de sodio (2 x 1 l), se secaron con sulfato de magnesio, se filtraron sobre Celite, y se concentraron bajo vacío para dar el producto crudo (367 g, rendimiento de 146%). El material crudo se purificó usando una columna de gel de sílice (2 kg) que se eluyó con 5 a 25% de acetato de etilo en heptano para dar el producto del título (270 g, rendimiento de 108%, 95.9% AUC por CLAR) como

un aceite amarillo.

Descripción 9

2,2,4-Trimetil-4-(5-(4-(octiloxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)oxazolidin-3-carboxilato de (*R*)-*ter*-butilo (D9)



Una solución de 2,2,4-trimetil-4-(2-(4-(octiloxi)-3-(trifluorometil)-benzoil)hidrazincarbonil)oxazolidin-3-carboxilato de (*S*)-*ter*-butilo (D8) (228 mg, 0.39 mmoles) en tolueno (5 ml) se trató con reactivo de Lawesson (321 mg, 0.79 mmoles). La reacción se sometió a cromatografía sobre una columna de gel de sílice eluida con acetato de etilo-hexano para dar el compuesto del título (~156 mg).

EM (ESI): 572.17 (MH^+),

^{1}H RMN (400 MHz, $CDCl_3$) δ 8.10 (d, 1H, J= 8.8 Hz), 8.08 (d, 1H, J= 6.8 Hz), 7.06 (d, 1H, J= 8.0 Hz), 4.41 (d, 1H, J= 8.0 Hz), 4.18 (d, 1H, J= 9.6 Hz), 4.13-4.07 (m, 3H), 2.00 (s, 3H), 1.85 (m, 2H), 1.78 (s, 3H), 1.68 (m, 4H), 1.51 (s, 3H), 1.47 (m, 2H), 1.39-1.28 (m, 13H), 0.89 (t, 3H, J= 1.1 Hz).

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Método alternativo de la descripción 9 (D9A)

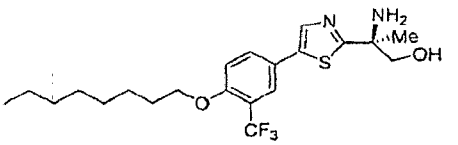
2,2,4-Trimetil-4-(5-(4-(octiloxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)oxazolidin-3-carboxilato de (*R*)-*ter*-butilo (D9)

Un matraz de fondo redondo de 12 l se hizo inerte y se cargó con reactivo de Lawesson (211.5 g, 0.52 moles, 1.2 equiv), una solución de 2,2,4-trimetil-4-(2-(4-(octiloxi)-3-(trifluorometil)benzoil)-hidrazincarbonil)oxazolidin-3-carboxilato de (*S*)-*ter*-butilo (D8A) (250 g -|con base en producción teórica, 0.43 moles) en tolueno (2.5 l), y la suspensión resultante se calentó a 80°C y se mantuvo durante 3 horas. CCD indicó que la reacción se completó. La mezcla se enfrió a 18-23°C, se cargó con solución saturada de $NaHCO_3$ (2 l), que fue ligeramente exotérmica. La fase acuosa se extrajo dos veces con acetato de etilo (2 l, 1.5 l), las fases orgánicas se combinaron, se concentraron, se disolvieron en diclorometano (500 ml), se cargaron con gel de sílice (500 g), se concentraron para remover diclorometano y se purificaron usando una columna de gel de sílice (2.5 kg) que se eluyó con 5% de acetato de etilo: 95% de heptano para dar el producto del título (185 g, rendimiento de 74%, 95% AUC por CLAR) como un aceite color amarillo.

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EJEMPLO 1

(*S*)-2-Amino-2-(5-(4-(octiloxi)-3-(trifluorometil)fenil)tiazol-2-il)propan-1-ol (E1)



2,2,4-Trimetil-4-(5-(4-(octiloxi)-3-(trifluorometil)fenil)tiazol-2-il)oxazolidin-3-carboxilato de (*R*)-*ter*-butilo (D4) (90 rng, 1 equiv) y ácido *para*-toluensulfónico (PTSA, 300 mg, 10 equiv) en MeOH (6 ml) se puso a reflujo durante 4 horas. El solvente se removió a partir de 2/3 de la mezcla de reacción y el producto se purificó por CLAR preparativa para dar el producto del título como la sal de trifluoroacetato (35 mg).

EM (ESI, $M+H^+$) = 431.01;

^{1}H RMN (400 MHz, DMSO-d_6) δ 8.27 (s, 1H), 7.88 (dd, 1H, J= 8.8 Hz, J= 2.4 Hz), 7.85 (d, 1H, J= 2.4 Hz), 7.34 (d, 1H, J= 8.4 Hz), 5.77 (br s, 1H), 4.14 (t, 2H, J= 6.4 Hz), 3.76 (dd, 1H, J= 11.2, Hz, J= 1.2 Hz), 3.66 (dd, 1H, J= 11.2 Hz, J = 1.2 Hz), 1.73 (q, 2H, J= 6.8 Hz), 1.58 (s, 3H), 1.36-1.48 (m, 2H), 1.20-1.36 (m, 8H), 0.85 (t, 3H, J = 6.4 Hz).

Método alternativo del ejemplo 1 (E1A)

(*S*)-2-Amino-2-(5-(4-(octiloxi)-3-(trifluorometil)fenil)tiazol-2-il)propan-1-ol (E1)

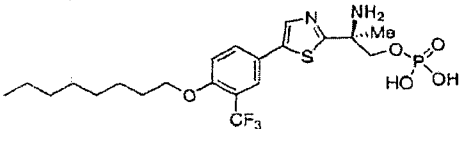
2,2,4-Trimetil-4-(5-(4-(octiloxi)-3-(trifluorometil)fenil)tiazol-2-

il)oxazolidin-3-carboxilato de (*R*)-*ter*-butilo (47 g, 82.35 mmoles), se hizo reaccionar con *p*-TSA (2 equiv) en metanol (470 ml) a reflujo durante 4 hr, punto en el cual CLAR indicó que la reacción se completó. La mezcla se enfrió a t.a., se concentró a un residuo, y se trituró con IPAc (235 ml). El sólido resultante se filtró, se lavó con IPAc (470 ml) para dar la sal de PPI-5325 *p*-TSA (45 g) como un sólido blanco. El sólido se convirtió a la base libre tratando con NaOH 6 N y DCM como un solvente.

Para formar una sal de clorhidrato de E1, la base libre (30 g, 69.84 mmoles) se recogió en HCl 4 M en dioxano (70 ml) y se agitó a t.a. durante 0.25 horas. El 1,4-dioxano se concentró a sequedad y el crudo se trituró con acetonitrilo (200 ml). La mezcla resultante se agitó durante 1 hr y se filtró el sólido blanco (23.3 g, 60%, ^{1}H-RMN fue consistente con la estructura).

EJEMPLO 2

Fosfato diácido de (*S*)-2-amino-2-(5-(4-(octiloxi)-3-(trifluorometil)fenil)tiazol-2-il)propilo (E2)



E1 (25 mg, 1.0 equiv), DCM (5 ml), clorofosfato de dietilo (85 µl, 10.0 equiv) y trietilamina (165 µl, 20.0 equiv) se agitaron durante la noche. El intermediario de fosfo-diéster obtenido se hizo reaccionar con exceso de bromotrimetilsilano en DCM durante 5 hr. El fosfato resultante se purificó por

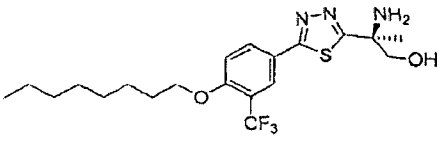
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CLAR preparativa como la sal de triflouroacetato (10 mg).

EM (ESI, $M+H^+$) = 511.1.

EJEMPLO 3

(*S*)-2-Amino-2-(5-(4-(octiloxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol (E3)



Una solución de 2,2,4-trimetil-4-(2-(4-(octiloxi)-3-(trifluorometil)-benzoil)hidrazincarbonil)oxazolidin-3-carboxilato de (*S*)-ter-butilo (D9) (156 mg, 0.27 mmoles) en metanol (10 ml) se trató con ácido *p*-toluensulfónico monohidratado (259 mg, 1.36 mmoles) a 70°C durante 3 horas. Dos terceras partes de la mezcla de reacción se purificaron por CLAR prep. sobre una columna C8(2) ((Luna, 5µ, 100 x 21.10 mm) con acetonitrilo-H_2O (0.1% de TFA) como fase móvil y gradiente 30-98% en 20 min. El compuesto del título se obtuvo como la sal de bis-TFA (24 mg).

EM (ESI): 432.00 (MH^+);

^{1}H RMN (400 MHz, DMSO-d_6) δ 8.21 (dd, 1H, J= 2.0 Hz, J= 8.8 Hz), 8.15 (d, 1H, J= 2.0 Hz), 8.09 (br s, 2H), 7.45 (d, 1H, J= 8.8 Hz), 5.96 (t, 1H, J= 4.8 Hz), 4.21 (t, 2H, J= 6.4 Hz), 3.81 (dd, 1H, J= 11.2 Hz, J= 5.2 Hz), 3.73 (dd, 1H, J= 11.2 Hz, J= 5.2 Hz), 1.76 (m, 2H), 1.66 (s, 3H), 1.44 (m, 2H), 1.28 (m, 8H), 0.86 (t, 3H, J = 6.8 Hz).

La tercera parte restante de la reacción se condensó y el residuo se re-disolvió en acetato de etilo y se lavó con $NaHCO_3$ acuoso, salmuera, se secó sobre salmuera y se condensó nuevamente para proveer producto crudo para usarse en el ejemplo 4.

Método alternativo del ejemplo 3 (E3A)

(*S*)-2-Amino-2-(5-(4-(octiloxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol (E3)

Un matraz de fondo redondo de 5 l se hizo inerte y se cargó con ácido *p*-toluensulfónico monohidratado (208 g, 1.09 moles, 5 equiv) y una solución de 2,2,4-trimetil-4-(5-(4-(octiloxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)oxazolidin-3-carboxilato de (*R*)-*ter*-butilo (125 g, 0.22 moles) en metanol (2.5 l), y se calentó a reflujo. Después de 1.5 hr CLAR indicó que la reacción estaba completa. El calor se apagó y la mezcla se dejó enfriar a temperatura ambiente (18 a 23°C) y se agitó durante 12 horas. La mezcla se concentró bajo vacío a un residuo para proveer el producto del título.

El residuo se recogió en dioxano (2 l), se cargó con HCl 4 M en dioxano (820 ml, 3.28 moles, 15 equiv), se calentó a 50°C durante 45 minutos, se enfrió a 18-23°C, se agitó durante 2 horas, se filtró sobre un filtro de vidrio fritado, se desplazó una vez con MTBE (300 ml), se suspendió una vez con MTBE (300 ml), y se secó en un filtro para dar un clorhidrato de E3 (72 g, humedecido con solvente).

Tres lotes del clorhidrato de E3 se sintetizados usando este

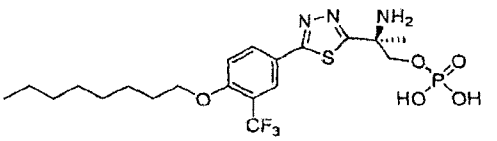
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método se combinaron (un total de 143 g, humedecido con solvente), se suspendieron dos veces en MTBE (750 ml, 500 ml), el solvente se filtró cada una de las veces, el material se transfirió a un horno de vacío y se secó durante la noche a temperatura ambiente (18 a 23°C).

^{1}H-RMN indicó presencia de dioxano (0.24% en peso). Secado adicional a una temperatura incrementada de 30 a 35°C durante 72 horas dio un clorhidrato (135 g, 98.6% AUC por CLAR) como un sólido blanco.

EJEMPLO 4

Fosfato diácido de (*S*)-2-amino-2-(5-(4-(octiloxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2- il)propilo (E4)



El producto crudo de E3 (30 mg, 0.069 mmoles) se añadió a clorofosfato de dietilo (100 µl, 0.69 mmoles) y trietilamina (194 µl, 1.39 mmoles) en DCM y se agitó durante aprox. 36 hr. La mezcla de reacción después se condensó y se trató con bromotrimetilsilano (0.3 ml) en DCM (5 ml) para proveer el compuesto del título (~2 mg).

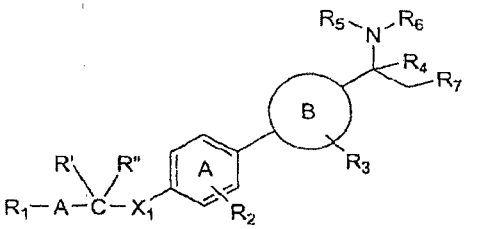
EM (ESI): 511.98 (MH^+),

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NOVEDAD DE LA INVENCION

REIVINDICACIONES

1.-Un compuesto de la fórmula I:



I

o una sal farmacéuticamente aceptable del mismo, en donde: R_1 es hidrógeno, halógeno, ciano, alquilo, arilo, heteroarilo, cicloalquilo, heterocicloalquilo, aralquilo, heteroalquilo, -O-alquilo, -O-arilo, -O-heteroarilo, -S-alquilo, alquileno-O-alquilo, alquileno-CO_2H, alquileno-CO_2alquilo, alquiloSO_2, alquilensulfonilo, alquileno-CO-amino, alquileno-CO-alquilamino, alquileno-CO-dialquilamino, alquileno-NH- CO_2H, alquileno-NH-CO_2alquilo-CO_2alquilo, -OH, -C(O)-alquilo, -C(O)O-alquilo, -$CONH_2$, -CO-alquilamino, -CO-dialquilamino, amino, alquilamino o dialquilamino, cualquiera de los cuales puede ser opcionalmente sustituido en carbono con 1, 2 ó 3 grupos seleccionados de halógeno, alquilo, halogenoalquilo, -CF_3, arilo, -CN, -OH, o -O-alquilo; A es alquileno(C_1-C_{20}), alquenileno(C_2-C_{20}), o alquinileno(C_2-C_{20}), cada uno de los cuales puede ser opcionalmente sustituido en carbono con 1, 2 ó 3 grupos seleccionados de OH, CO_2H, CO_2alquilo, halógeno, amino, alquilamino, dialquilamino, -O-alquilo, alquileno-O-alquilo, alquileno-OH, o

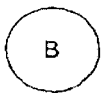
alquileno-CO_2H; X_1 es un enlace o es CH_2, O, -CH_2O-, S, -S(O), -$S(O)_2$, -C(O)-, -C(O)O-, o NR_x, en donde R_x es H o alquilo (C_1-C_6); R' y R" son cada uno independientemente hidrógeno, halógeno, alquilo opcionalmente sustituido en carbono con halógeno, alquilo, o tomados junto al carbono al cual están unidos forman C=O o un anillo de 3, 4, 5 ó 6 miembros, que contiene opcionalmente 1 ó 2 heteroátomos seleccionados de O NH, N-alquilo, SO o SO_2, cualquiera de los cuales puede ser opcionalmente sustituido en carbono con alquilo o halógeno; R_2 es ciano, alquilo, arilo, heteroarilo, cicloalquilo, heterocicloalquilo, aralquilo, heteroalquilo, -O-alquilo, -O-arilo, -O-heteroarilo, aralcoxi, heteroaralcoxi, -S-alquilo, alquileno-O-alquilo, alquileno-CO_2H, alquileno-CO_2alquilo, alquiloSO_2, alquilensulfonilo, alquileno-CO-amino, alquileno-CO-alquilamino, alquileno-CO-dialquilamino, alquileno-NH-CO_2H, alquileno-NH-CO_2alquilo -CO_2alquilo, -OH, -C(O)-alquilo, -C(O)O-alquilo, -$CONH_2$, -CO-alquilamino, -CO-dialquilamino, amino, alquilamino y dialquilamino, cualquiera de los cuales puede ser opcionalmente sustituido en carbono con 1, 2 ó 3 grupos seleccionados de halógeno, alquilo, OH, o -O-alquilo; R_3 está ausente, es hidrógeno, halógeno, ciano, alquilo, arilo, heteroarilo, cicloalquilo, heterocicloalquilo, aralquilo, heteroalquilo, -O-alquilo, -O-arilo, -O-heteroarilo, aralcoxi, heteroaralcoxi, -S-alquilo, alquileno-O-alquilo, alquileno-CO_2H, alquileno-CO_2alquilo, alquiloSO_2, alquiloensulfonilo, alquileno-CO-amino, alquileno-CO-alquilamino, alquileno-CO-dialquilamino, alquileno-NH-CO_2H, alquileno-NH-CO_2alquilo -CO_2alquilo, -OH, -C(O)-alquilo, -C(O)O-alquilo, -$CONH_2$, -CO-alquilamino, -CO-dialquilamino, amino,

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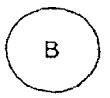
alquilamino y dialquilamino, cualquiera de los cuales puede ser opcionalmente sustituido en carbono con 1, 2 ó 3 grupos seleccionados de halógeno, alquilo, OH, o -O-alquilo;



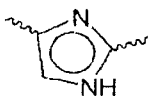
es fenilo o piridilo;



es arilo, heteroarilo, heterociclo o cicloalquilo, cualquiera de los cuales puede ser opcionalmente sustituido en carbono con 1, 2 ó 3 grupos seleccionados de halógeno, alquilo, O-alquilo, CO_2H, CO_2alquilo, halógeno, amino, alquilamino, dialquilamino, -O-alquilo, alquileno-O-alquilo, alquileno-OH, o alquileno-CO_2H, siempre que



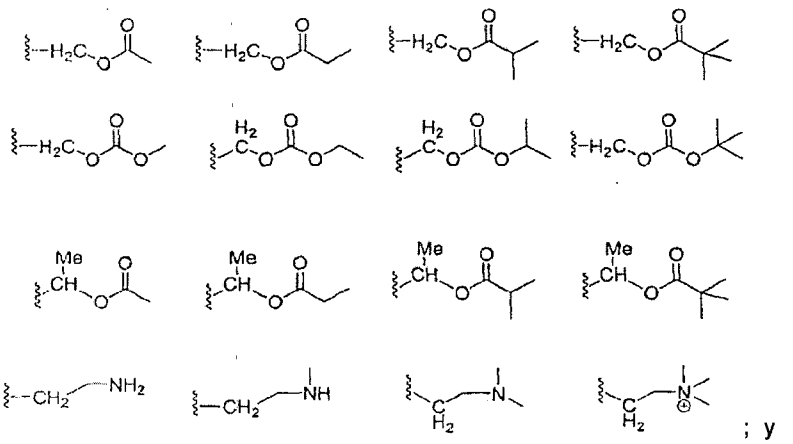
no sea



;

R_4 es hidrógeno, ciano, alquilo, arilo, heteroarilo, alquileno-O-alquilo, alquileno-OH, arilo, alquileno-O-alquilo, -CO_2H, -CO_2-alquilo, alquileno-CO_2H, o alquileno-CO_2-alquilo, alquileno-OC(O)R en donde R es hidrógeno o alquilo; cicloalquilo, heterocicloalquilo, alquileno-NH_2, alquileno-alquilamino, o alquileno-dialquilamino, cualquiera de los cuales puede ser opcionalmente

sustituido en carbono con 1, 2 ó 3 grupos seleccionados de OH, CO_2H, CO_2alquilo, halógeno, amino, alquilamino, dialquilamino, -O-alquilo, alquileno-O-alquilo, alquileno-OH, o alquileno-CO_2H; R_5 y R_6 se seleccionan cada uno independientemente del grupo que consiste de hidrógeno, alquilo, alquileno-OH, arilo, alquileno-O-alquilo, -CO_2H, CO_2-alquilo, alquileno- OC(O)alquilo, cicloalquilo, heterociclo, -C(O)-alquilo, -C(O)-arilo, C(O)-aralquilo, -C(O)-Oalquilo, -C(O)-Oarilo, -C(O)-Oaralquilo, alquileno-amino, alquileno-alquilamino, y alquileno-dialquilamino, cualquiera de los cuales puede ser opcionalmente sustituido en carbono con halógeno, alquilo, hidroxilo, CO_2H, CO_2alquilo o alcoxi; o R_5 y R_6, junto con el nitrógeno al cual están unidos, pueden formar un anillo saturado o insaturado de 3, 4, 5 ó 6 miembros, que contiene opcionalmente 1 ó 2 heteroátomos adicionales seleccionados de O, S, NH_5 o N-alquilo, y opcionalmente sustituido en carbono con halógeno, alquilo, hidroxilo, o alcoxi; R_7 se selecciona del grupo que consiste de -OH, -O-alquilo, alquileno-OH, -CO_2H, alquileno-CO_2H, -C(O)O-alquilo, -alquileno-CO_2-alquilo, -C(O)O-arilo, -CH_2=$CHCO_2H$, - CH_2=CHC(O)O-alquilo, -CH_2=CHC(O)O-arilo, -OPO_2R_p,R_{p2}, -$OPO_3R_{p1}R_{p2}$, -$CH_2PO_3R_{p1}R_{p2}$, -$OPO_2(S)R_{p1}R_{p2}$ y -C(Z')(Z")$PO_3R_{p1}R_{p2}$, cualquiera de los cuales puede ser opcionalmente sustituido en carbono con halógeno, alquilo, hidroxilo, carboxi o alcoxi; y en donde Z' es hidroxilo o halógeno; Z" es H o halógeno; R_{p1} y R_{p2} son cada uno independientemente hidrógeno, alquilo de C_1-C_6, arilo, o uno de los siguientes grupos:



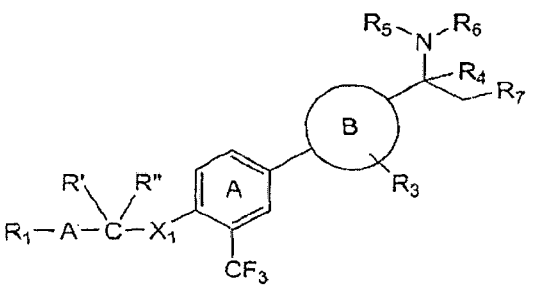
; y

Y es heterociclo o heteroarilo.

2.- El compuesto de conformidad con la reivindicación 1, caracterizado además porque R2 es alquilo sustituido con 1, 2 ó 3 grupos halógeno.

3.- El compuesto de conformidad con la reivindicación 1, caracterizado además porque R2 es trifluorometilo.

4.- Un compuesto de la fórmula II:



II

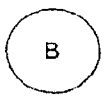
o una sal farmacéuticamente aceptable del mismo, en donde: R_1 es hidrógeno, halógeno, ciano, alquilo, arilo, heteroarilo, cicloalquilo, heterocicloalquilo, aralquilo, heteroalquilo, -O-alquilo, -O-arilo, -O-heteroarilo, -S-alquilo, alquileno-O-alquilo, alquileno-CO_2H, alquileno-CO_2alquilo,

alquiloSO_2, alquilensulfonilo, alquileno-CO-amino, alquileno-CO-alquilamino, alquileno-CO-dialquilamino, alquileno-NH-CO_2H, alquileno-NH-CO_2alquilo -CO_2alquilo, -OH, -C(O)-alquilo, -C(O)O-alquilo, -$CONH_2$, - CO-alquilamino, -CO-dialquilamino, amino, alquilamino, o dialquilamino, cualquiera de los cuales puede ser opcionalmente sustituido en carbono con 1, 2 ó 3 grupos seleccionados de halógeno, alquilo, halogenoalquilo, -CF_3, -CN, -OH, o -O-alquilo; A es alquileno (C_1-C_{20}), alquenileno (C_2-C_{20}), o alquinileno(C_2-C_{20}), cada uno de los cuales puede ser substituido en carbono con 1, 2 ó 3 grupos seleccionados de OH, CO_2H, CO_2alquilo, halógeno, amino, alquilamino, dialquilamino, -O-alquilo, alquileno-O-alquilo, alquileno-OH, o alquileno-CO_2H; X_1 es un enlace o es CH_2, O, -CH_2O-, S, -S(O), -$S(O)_2$, -C(O)-, -C(O)O-, o NR_x, en donde R_x es H o alquilo(C_1-C_6); R' y R" son cada uno independientemente hidrógeno, halógeno, alquilo opcionalmente sustituido en carbono con halógeno, alquilo, o tomados junto al carbono al cual están unidos forman C=O o un anillo de 3, 4, 5 ó 6 miembros, que contiene opcionalmente 1 ó 2 heteroátomos seleccionados de O NH, N-alquilo, SO o SO_2, cualquiera de los cuales puede ser opcionalmente sustituido en carbono con alquilo o halógeno; R_3 está ausente, es hidrógeno, halógeno, ciano, alquilo, arilo, heteroarilo, cicloalquilo, heterocicloalquilo, aralquilo, heteroalquilo, -O-alquilo, -O-arilo, -O-heteroarilo, aralcoxi, heteroaralcoxi, -S-alquilo, alquileno-O-alquilo, alquileno-CO_2H, alquileno-CO_2alquilo, alquiloSO_2. alquilensulfonilo, alquileno-CO-amino, alquileno-CO-alquilamino, alquileno-CO-dialquilamino, alquileno-NH-CO_2H, alquileno-NH-CO_2alquilo -CO_2alquilo, -

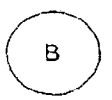
OH, -C(O)-alquilo, -C(O)O-alquilo, $-CONH_2$, -CO-alquilamino, -CO-dialquilamino, amino, alquilamino y dialquilamino, cualquiera de los cuales puede ser opcionalmente sustituido en carbono con 1, 2 ó 3 grupos seleccionados de halógeno, alquilo, OH, o -O-alquilo;



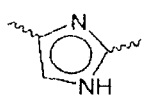
es fenilo o piridilo;



es arilo, heteroarilo, heterociclo o cicloalquilo, cualquiera de los cuales puede ser opcionalmente sustituido en carbono con 1, 2 ó 3 grupos seleccionados de halógeno, alquilo, O-alquilo, CO_2H, CO_2alquilo, halógeno, amino, alquilamino, dialquilamino, -O-alquilo, alquileno-O-alquilo, alquileno-OH, o alquileno-CO_2H, siempre que



no sea

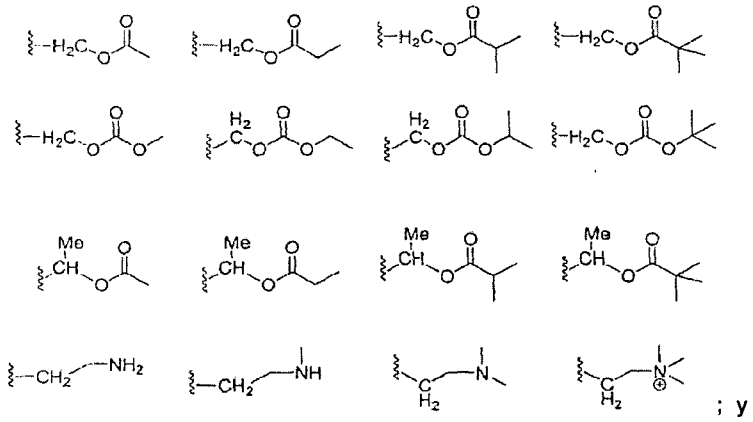


;

R_4 es hidrógeno, ciano, alquilo, arilo, heteroarilo, alquileno-O-alquilo, alquileno-OH, arilo, alquileno-O-alquilo, $-CO_2H$, $-CO_2$-alquilo, alquileno-CO_2H, o alquileno-CO_2-alquilo, alquileno-OC(O)R en donde R es hidrógeno o alquilo; cicloalquilo, heterocicloalquilo, alquileno-NH_2, alquileno-alquilamino, o

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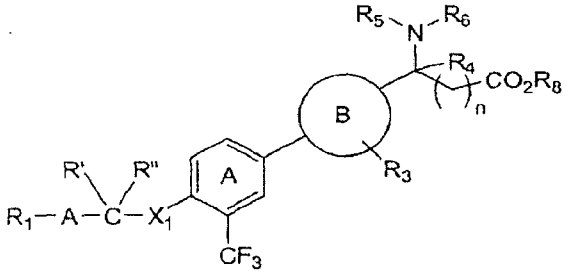
alquileno-dialquilamino, cualquiera de los cuales puede ser opcionalmente sustituido en carbono con 1, 2 ó 3 grupos seleccionados de OH, CO_2H, CO_2alquilo, halógeno, amino, alquilamino, dialquilamino, -O-alquilo, alquileno-O-alquilo, alquileno-OH, o alquileno-CO_2H; R_5 y R_6 se seleccionan cada uno independientemente del grupo que consiste de hidrógeno, alquilo, alquileno-OH, arilo, alquileno-O-alquilo, -CO_2H, CO_2-alquilo, alquileno- OC(O)alquilo, cicloalquilo, heterociclo, -C(O)-alquilo, -C(O)-arilo, C(O)-aralquilo, -C(O)-Oalquilo, -C(O)-Oarilo, -C(O)-Oaralquilo, alquileno-amino, alquileno-alquilamino, y alquileno-dialquilamino, cualquiera de los cuales puede ser opcionalmente sustituido en carbono con halógeno, alquilo, hidroxilo, CO_2H_5 CO_2alquilo o alcoxi; o; R_5 y R_6, junto con el nitrógeno al cual están unidos, pueden formar un anillo saturado o insaturado de 3, 4, 5 ó 6 miembros, que contiene opcionalmente 1 ó 2 heteroátomos adicionales seleccionados de O, S, NH, o N-alquilo, y opcionalmente sustituido en carbono con halógeno, alquilo, hidroxilo o alcoxi; R_7 se selecciona del grupo que consiste de -OH, -O-alquilo, -alquileno-OH, -CO_2H, -alquileno-CO_2H, -C(O)O-alquilo, -alquileno-CO_2-alquilo, -C(O)O-arilo, -CH_2=$CHCO_2H$, -CH_2=CHC(O)O-alquilo, -CH_2=CHC(O)O-arilo, -$OPO_2R_{p1}R_{p2}$, -$OPO_3R_{p1}R_{p2}$, -$CH_2PO_3R_{p1}R_{p2}$, -$OPO_2(S)R_{p1}R_{p2}$, y -$C(Z')(Z'')PO_3R_{p1}R_{p2}$, cualquiera de los cuales puede ser opcionalmente sustituido en carbono con halógeno, alquilo, hidroxilo, carboxi, o alcoxi; y en donde Z' es hidroxilo o halógeno; Z'' es H o halógeno; R_{p1} y R_{p2} son cada uno independientemente hidrógeno, alquilo de C_1-C_6, arilo, o uno de los siguientes grupos:



; y

Y es heterociclo o heteroarilo.

5.- Un compuesto de la fórmula III:



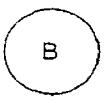
III

o una sal farmacéuticamente aceptable del mismo, en donde: R_1 es hidrógeno, halógeno, ciano, alquilo, arilo, heteroarilo, cicloalquilo, heterocicloalquilo, aralquilo, heteroalquilo, -O-alquilo, -O-arilo, -O-heteroarilo, -S-alquilo, alquileno-O-alquilo, alquileno-CO_2H, alquileno-CO_2alquilo, alquiloSO_2, alquilensulfonilo, alquileno-CO-amino, alquileno-CO-alquilamino, alquileno-CO-dialquilamino, alquileno-NH-CO_2H, alquileno-NH-CO_2alquilo -CO_2alquilo, -OH, -C(O)-alquilo, -C(O)O-alquilo, -$CONH_2$, -CO-alquilamino, -CO-dialquilamino, amino, alquilamino, o dialquilamino, cualquiera de los cuales puede ser opcionalmente sustituido en carbono con 1, 2 ó 3 grupos seleccionados de halógeno, alquilo, halogenoalquilo, -CF_3, -CN, -OH, o -O-

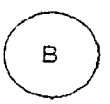
alquilo; A es alquileno(C_1-C_{20}), alquenileno(C_2-C_{20}), o alquinileno(C_2-C_{20}), cada uno de los cuales puede ser opcionalmente sustituido en carbono con 1, 2 ó 3 grupos seleccionados de OH, CO_2H, CO_2alquilo, halógeno, amino, alquilamino, dialquilamino, -O-alquilo, alquileno-O-alquilo, alquileno-OH, o alquileno-CO_2H; X_1 es un enlace o es CH_2, O, -CH_2O-, S, -S(O), -$S(O)_2$, -C(O)-, -C(O)O-, $OrNR_x$, en donde R_x es H o alquilo(C_1-C_6); R' y R" son cada uno independientemente hidrógeno, halógeno, alquilo opcionalmente sustituido en carbono con halógeno, alquilo, o tomados junto al carbono al cual están unidos forman C=O o un anillo de 3, 4, 5 ó 6 miembros, que contiene opcionalmente 1 ó 2 heteroátomos seleccionados de O NH, N-alquilo, SO, o SO_2, cualquiera de los cuales puede ser opcionalmente sustituido en carbono con alquilo o halógeno; R_3 está ausente, hidrógeno, halógeno, ciano, alquilo, arilo, heteroarilo, cicloalquilo, heterocicloalquilo, aralquilo, heteroalquilo, -O-alquilo, -O-arilo, -O-heteroarilo, aralcoxi, heteroaralcoxi, -S-alquilo, alquileno-O-alquilo, alquileno-CO_2H, alquileno-CO_2alquilo, alquiloSO_2, alquilensulfonilo, alquileno-CO-amino, alquileno-CO-alquilamino, alquileno-CO-dialquilamino, alquileno-NH-CO_2H, alquileno-NH-CO_2alquilo -CO_2alquilo, -OH, -C(O)-alquilo, -C(O)O-alquilo, -$CONH_2$, -CO-alquilamino, -CO-dialquilamino, amino, alquilamino y dialquilamino, cualquiera de los cuales puede ser opcionalmente sustituido en carbono con 1, 2 ó 3 grupos seleccionados de halógeno, alquilo, OH, o -O-alquilo;



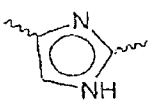
es fenilo o piridilo;



es arilo, heteroarilo, heterociclo, o cicloalquilo, cualquiera de los cuales puede ser opcionalmente sustituido en carbono con 1, 2 ó 3 grupos seleccionados de halógeno, alquilo, O-alquilo, CO_2H, CO_2alquilo, halógeno, amino; alquilamino, dialquilamino. -O-alquilo, alquileno-O-alquilo, alquileno-OH, o alquileno-CO_2H, siempre que



no sea



;

R_4 es hidrógeno, ciano, alquilo, arilo, heteroarilo, alquileno-O-alquilo, alquileno-OH, arilo, alquileno-O-alquilo, -CO_2H, -CO_2-alquilo, alquileno-CO_2H, o alquileno-CO_2-alquilo, alquileno-OC(O)R en donde R es hidrógeno o alquilo; cicloalquilo, heterocicloalquilo, alquileno-NH_2, alquileno-alquilamino, o alquileno-dialquilarnino, cualquiera de los cuales puede ser opcionalmente sustituido en carbono con 1, 2 ó 3 grupos seleccionados de OH, CO_2H, CO_2alquilo, halógeno, amino, alquilamino, dialquilo amino, -O-alquilo, alquileno-O-alquilo, alquileno-OH, o alquileno-CO_2H; R_5 y R_6 se seleccionan cada uno independientemente del grupo que consiste de hidrógeno, alquilo, alquileno-OH, arilo, alquileno-O-alquilo, -CO_2H, CO_2-alquilo, alquileno-

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OC(O)alquilo, cicloalquilo, heterociclo, -C(O)-alquilo, -C(O)-arilo, C(O)-aralquilo, -C(O)- Oalquilo, -C(O)-Oarilo, -C(O)-Oaralquilo, alquileno-amino, alquileno-alquilamino, y alquileno-dialquilamino, cualquiera de los cuales puede ser opcionalmente sustituido en carbono con halógeno, alquilo, hidroxilo, CO_2H, CO_2alquilo o alcoxi; o R_5 y R_6, junto con el nitrógeno al cual están unidos, pueden formar un anillo saturado o insaturado de 3, 4, 5 ó 6 miembros, que contiene opcionalmente 1 ó 2 heteroátomos adicionales seleccionados de O, S, NH, o N-alquilo, y opcionalmente sustituido en carbono con halógeno, alquilo, hidroxilo o alcoxi; R_8 es hidrógeno, alquilo o arilo; y n es 0, 1 ó 2.

6.- Un compuesto seleccionado del grupo que consiste de: (*S*)-2-Amino-2-(5-(4-(octiloxi)-3-(trifluorometil)fenil)tiazol-2-il)propan-1-ol; 2-Amino-2-(5-(4-(octiloxi)-3-(trifluorometil)fenil)tiazol-2-il)propano-1,3-diol; (*S*)-2-Amino-2-(5-(4-(octiloxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol; (*S*)-2-Amino-2-(5-(4-(5-fenilpentiloxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol; (*S*)-2-Amino-2-(5-(4-(4-fenilbutoxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol; (*S*)-2-Amino-2-(5-(4-(noniloxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol; (*S*)-2-Amino-2-(5-(4-(deciloxi)-3(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol; (*S*)-2-Ammo-2-(5-(3-(trifluorometil)-4-(5-(4-(trifluorometil)fenil)-pentiloxi)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol; (*S*)-2-Amino-2-(5-(3-(trifluorometil)-4-(5-(3-(trifluorometil)fenil)pentiloxi)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol; (*S*)-2-Amino-2-(5-(4-(6-fenilhexiloxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol;

(*S*)-2-Amino-2-(5-(4-(5-(4-fluorofenil)pentiloxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol; (*S*)-2-Amino-2-(5-(4-(5-(3-fluorofenil)pentiloxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol; (*S*)-2-Amino-2-(5-(4-((4-fenil-5-(trifluorometil)tiofen-2-il)metoxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol; (*S*)-2-Amino-2-(5-(4-(7-fenilheptiloxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol; (*S*)-2-Amino-2-(5-(3-(trifluorometil)-4-(2-(trifluorometil)fenetoxi)fenil)-1,3,4- tiadiazol-2-il)propan-1-ol; (*S*)-2-Amino-2-(5-(3-(txifluorometil)-4-(3-(trifluorometil)fenetoxi)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol; (*S*)-2-Amino-2-(5-(3-(trifluorometil)-4-(4-(trifluorometil)fenetoxi)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol; (*S*)-2-Amino-2-(5-(4-(benziloxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol; (*S*)-2-Amino-2-(5-(4-fenetoxi-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol; (*S*)-2-Amino-2-(5-(4-(3-fenilpropoxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol; (*S*)-2-Amino-2-(5-(4-(benzofuran-2-ilmetoxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol; (*S*)-2-Amino-2-(5-(4-(benzo[*b*]tiofen-2-ilmetoxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol; (*S*)-2-Amino-2-(5-(4-(benzo[*d*][1,3]dioxol-5-ilmetoxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol; (*S*)-2-Amino-2-(5-(3-(trifluorometil)-4-(4-(3-(trifluorometil)fenil)butoxi)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol; (*S*)-2-Amino-2-(5-(3-(trifluorometil)-4-(4-(4-(trifluorometil)fenil)butoxi)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol; (2*S*)-2-Amino-2-(5-(4-(3,7-dimetiloctiloxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol; (*S*)-2-Amino-2-(5-(4-(4-propilfenetoxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol; (*S*)-2-Amino-2-(5-(4-(4-

butilfenetoxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol; (*S*)-2-Amino-2-(5-(4-(4-etilfenetoxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol; (*S*)-2-Amino-2-(5-(4-(7,7,8,8,8-pentafluorooctiloxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol; (*S*)-2-Amino-2-(5-(4-(4-(2-fluorofenil)butoxi)-3-(trifluorometil)fenil)-1,3,4- tiadiazol-2-il)propan-1-ol; (*S*)-2-Amino-2-(5-(4-(4-(3-fluorofenil)butoxi)-3-(trifluiorometil)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol; (*S*)-2-Amino-2-(5-(4-(4-(4-fluorofenil)butoxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol; (*S*)-2-Amino-2-(5-(4-(6-(2-fluorofenil)hexiloxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol; (*S*)-2-Amino-2-(5-(4-(6-(3-fluorofenil)hexiloxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol; (*S*)-2-Amino-2-(5-(4-(6-(4-fluorofenil)hexiloxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol; (*S*)-2-Amino-2-(5-(4-(5-(3,4-difluorofenil)pentiloxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol; (*S*)-2-Amino-2-(5-(3-(trifluorometil)-4-(5-(2,4,5-trifluorofenil)pentiloxi)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol; (*S*)-2-Amino-2-(5-(3-(trifluorometil)-4-(6-(3-(trifluorometil)fenil)hexiloxi)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol; (*S*)-2-Amino-2-(5-(3-(trifluorometil)-4-(6-(4-(trifluorometil)fenil)hexiloxi)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol; (*S*)-2-Amino-2-(5-(4-(octiltio)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol; (*S*)-2-Amino-2-(5-(4-(octilsulfonil)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol; (*S*)-2-Amino-2-(3-(4-(octiloxi)-3-(trifluorometil)fenil)-1,2,4-oxadiazol-5-il)propan-1-ol; (*R*)-2-Amino-2-(5-(4-(octiloxi)-3-(trifluorometil)fenil)-1H-pirazol-3-il)propan-1-ol; (*S*)-2-Amino-2-(3-(4-(octiloxi)-3-(trifluorometil)fenil)isoxazol-5-il)propan-1-ol; (*S*)-2-Amino-2-(5-

(4-(octiloxi)-3-(trifluorometil)fenil)-1,3,4-oxadiazol-2-il)propan-1-ol; (*S*)-2-Amino-2-(5-(4-(6-fenilhexiloxi)-3-(trifluorometil)fenil)tiazol-2-il)propan-1-ol; (*S*)-2-Amino-2-(5-(3-(trifluorometil)-4-(5-(4-(trifluorometil)fenil)pentiloxi)fenil)tiazol-2-il)propan-1-ol; y sales farmacéuticamente aceptables, derivados de fosfato, simuladores de fosfato, y análogos de precursor de fosfato de los mismos.

7.- Un compuesto que es (*S*)-2-amino-2-(5-(4-(octiloxi)-3-(trifluorometil)fenil)tiazol-2-il)propan-1-ol o una sal farmacéuticamente aceptable, derivado de fosfato, simulador de fosfato o análogo de precursor de fosfato del mismo.

8.- Un compuesto que es fosfato diácido de (*S*)-2-amino-2-(5-(4-(octiloxi)-3-(trifluorometil)fenil)tiazol-2-il)propilo o una sal farmacéuticamente aceptable del mismo.

9.- Un compuesto que es (*S*)-2-amino-2-(5-(4-(octiloxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propan-1-ol o una sal farmacéuticamente aceptable, derivado de fosfato, simulador de fosfato o un análogo de precursor de fosfato del mismo.

10.- Un compuesto que es fosfato diácido de (S)-2-amino-2-(5-(4-(octiloxi)-3-(trifluorometil)fenil)-1,3,4-tiadiazol-2-il)propilo o una sal farmacéuticamente aceptable del mismo.

11.- El compuesto de conformidad con cualquiera de las reivindicaciones 1 a 10 o una sal farmacéuticamente aceptable, derivado de fosfato, simulador de fosfato o análogo de precursor de fosfato del mismo para usarse como una sustancia terapéutica.

12.- El compuesto de conformidad con cualquiera de las reivindicaciones 1 a 10 o una sal farmacéuticamente aceptable, derivado de fosfato, simulador de fosfato, o análogo de precursor de fosfato del mismo para usarse en el tratamiento de un trastorno asociado con esfingosina.

13.- El compuesto de conformidad con cualquiera de las reivindicaciones 1 a 10 o una sal farmacéuticamente aceptable, derivado de fosfato, simulador de fosfato, o análogo de precursor de fosfato del mismo para usarse en el tratamiento de esclerosis múltiple.

14.- El compuesto de conformidad con cualquiera de las reivindicaciones 1 a 10 o una sal farmacéuticamente aceptable, derivado de fosfato, simulador de fosfato, o análogo de precursor de fosfato del mismo para usarse en la fabricación de un medicamento para usarse en el tratamiento de un trastorno asociado con esfingosina.

15.- El compuesto de conformidad con cualquiera de las reivindicaciones 1 a 10 o una sal farmacéuticamente aceptable, derivado de fosfato, simulador de fosfato, o análogo de precursor de fosfato del mismo para usarse en la fabricación de un medicamento para el tratamiento de esclerosis múltiple.

16.- Un método de tratamiento de un trastorno asociado con 1-fosfato de esfingosina que comprende administrar a un sujeto una cantidad terapéuticamente efectiva de un compuesto de conformidad con cualquiera de las reivindicaciones 1 a 10 o una sal farmacéuticamente aceptable, derivado de fosfato, simulador de fosfato, o análogo de precursor de fosfato del mismo,

de tal manera que se trata el trastorno asociado con 1-fosfato de esfingosina.

17.- Una composición farmacéutica que comprende un compuesto de conformidad con cualquiera de las reivindicaciones 1 a 10 o una sal farmacéuticamente aceptable, derivado de fosfato, simulador de fosfato, o análogo de precursor de fosfato del mismo.

18.- Un procedimiento para la preparación de una composición farmacéutica de conformidad con la reivindicación 17.

19.- Un procedimiento para la preparación de un compuesto de conformidad con cualquiera de las reivindicaciones 1 a 10 o una sal farmacéuticamente aceptable, derivado de fosfato, simulador de fosfato, o análogo de precursor de fosfato del mismo.

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RESUMEN DE LA INVENCION

La invención provee compuestos de la fórmula I, su preparación, y su uso como agentes inmunosupresores farmacéuticamente activos para el tratamiento de trastornos autoinmunes, rechazo de trasplante de órganos, trastornos asociados con un sistema inmunológico activado, así como otros trastornos modulados por linfopenia o receptores de S1P.

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C07D 271/10 (2006.01)	*A61K 31/433* (2006.01)
C07D 277/28 (2006.01)	*A61K 31/44* (2006.01)
C07D 285/12 (2006.01)	*A61K 31/505* (2006.01)
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(72) Inventors; and

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(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.

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(54) Title: CHEMICAL COMPOUNDS

(57) Abstract: The invention provides compounds formula I, their preparation, and their use as pharmaceutically active immunosuppressive agents for the treatment of autoimmune disorders, organ transplant rejection, disorders associated with an activated immune system, as well as other disorders modulated by lymphopenia or SIP receptors.

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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2007/017282

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D213/38 C07D261/08 C07D271/10 C07D277/28 C07D285/12
C07D417/12 C07F9/6539 A61K31/425 A61K31/433 A61K31/44
A61K31/505 A61P37/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D C07F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2006/020951 A (PRAECIS PHARM INC [US]; SAHA ASHIS K [US]; KAVARANA MALCOLM J [US]; EV) 23 February 2006 (2006-02-23) claims 40-51; compounds 232-236	1-19
E	WO 2007/092190 A (PRAECIS PHARM INC [US]; DENG HONGFENG [US]; EVINDAR GHOTAS [US]; KAVAR) 16 August 2007 (2007-08-16) claims 56-62; compounds 358-399	1-19

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 January 2008	01/02/2008

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Beyss-Kahana, Ellen

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2007/017282

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 16 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers allsearchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search reportcovers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

[ ] The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2007/017282

450

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2006020951 A	23-02-2006	AU 2005272619 A1	23-02-2006
		CA 2576388 A1	23-02-2006
		EP 1781595 A1	09-05-2007
		KR 20070058455 A	08-06-2007
		US 2006135786 A1	22-06-2006
		US 2006223866 A1	05-10-2006
WO 2007092190 A	16-08-2007	NONE	

Industria y Comercio
SUPERINTENDENCIA

REQUISITOS MINIMOS PARA ADMISION A TRAMITE
PCT

PATENTE DE INVENCION [ ] MODELO DE UTILIDAD [ ]

- Indicación de que se solicita la concesión de una patente [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Descripción de la invención [ ]
- Dibujos de ser estos pertinentes [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

DISEÑO INDUSTRIAL [ ]

- Indicación de que se solicita el registro de Diseño Industrial [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Representación gráfica y fotográfica del Diseño Industrial o muestra del material que incorpora el diseño [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

ESQUEMA DE TRAZADO [ ]

- Indicación de que se solicita el registro de un Esquema de Trazado [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Representación gráfica del esquema trazado [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

Firma Responsable

Fecha_

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 09-008880- -00000-0000
Fecha: 2009-01-30 17:01:37 Dep: 2020 NUECREACION
Tra: 11 PATENTEIYII Eve: 378 FASENACIONALI
Act: 411 PRESENTACION Folios: 450

Carrera 13 No. 27-00 Piso 5, 7 y 10
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Bogotá, D.C., Colombia

REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Bogotá,
2020

Doctor(a)
OLARTE GARCIA CARLOS REYNALDO

REFERENCIA	Radicación No.	09 8880
	Solicitud internacional	PCT/US2007/017282
	Fecha inicio fase nacional	01/03/2009
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	3426

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 el poder debidamente otorgado, con el lleno de los requisitos exigidos por los artículos 63 y subsiguientes del Código de Procedimiento Civil. Adicionalmente, deberá presentar el documento que acredita la existencia y representación legal de la sociedad solicitante, cuando ésta fuere persona jurídica.

2. El solicitante debe presentar un nuevo titulo que permita identificar la materia de la cual trata la solicitud, ya que el titulo relacionado no se encuentra con la precisión necesaria para identificar claramente el objeto de la solicitud de patente. (Regla 4.3 PCT, Art 26-27 D-486, Circular única 5.2.9)

3. 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

Continua en la página siguiente...

REPUBLICA DE COLOMBIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Radicación No. 9 8880

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 20 MAR. 2009
adpall