SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 11-064157- -00000-0000
Fecha: 2011-05-24 16:41:17 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 159

Q.F

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
INVENTARIO

PCT

DELEGATURA DE PROPIEDAD INDUSTRIAL

DIRECCIÓN DE NUEVAS CREACIONES

11-64157

SOLICITUD DE PATENTE DE INVENCIÓN

TITULO: 3-AMINOCICLOPENTANCARBOXAMIDAS

SOLICITANTE: PFIZER INC

DIRECCIÓN: 235 East 42nd Street, New York, NY 10017, E. U. A.

APODERADO: CARLOS R. OLARTE

BOGOTÁ 24 de Mayo de 2011

P2011/000099

26-06-2011

OLARTEMOURE

OLARTE MOURE & ASOCIA

Industria y Comercio
SUPERINTENDENCIA

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PETITORIO - FORMULARIO ÚNICO DE SOLICITUD
PATENTE PCT
ENTRADA EN FASE NACIONAL **P2011/000099**

SOLICITUD DE:

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

[X] Capítulo I. [ ] Capítulo II.

(2) **SOLICITANTE (71)**	**Nombre:** PFIZER INC. **Dirección:** 235 East 42nd Street, New York, New York 10017 **Nacionalidad o Domicilio:** Estados Unidos **Lugar de Constitución:** Estados Unidos **Teléfono:** _____ **Fax:** _____ **E-mail:** _____	**IDENTIFICACIÓN** **C.C.** [ ] **NIT** [ ] **C.E.** [ ] **Otro** [ ] **Cual** _____ **Número** _____
REPRESENTANTE O APODERADO	**Nombre:** CARLOS R. OLARTE **Dirección:** Diagonal 34 No. 5-28 Bogotá, Colombia **Teléfono:** 601-7700 **Fax:** 601-7799 **E-mail:** office@olartemoure.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/IB2009/055232 Fecha Noviembre 20, 2009

Publicación Internacional No. WO 2010/061329 Fecha Junio 03, 2010

(6) **Título (54)** **3-AMINOCICLOPENTANCARBOXAMIDAS**

Clasificación Internacional (51) C07D 487/08; A61K 31/407; A61P 29/02; A61P 35/00.

Prioridad SI [X] NO [ ]	(33) País de Origen	(32) Fecha	(31) Número de Solicitud
	US	Noviembre 26, 2008	61/118.053

(9) **Comprobante de pago No.** 11- **Fecha** Mayo de 2011

(10) **ANEXOS**

- [x] Comprobante de pago de la tasa de presentación de la solicitud.
- [x] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- [x] Poderes, si fuere el caso. Adjunto copia simple. Ver Exp. Nº 09-081.255
- [x] Documento de cesión del inventor al solicitante o a su causante. Declaración bajo la Regla 417(ii) del PCT.
- [ ] 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.
- [x] De ser el caso, modificaciones efectuadas a la solicitud internacional.
- [x] Otros. Búsqueda Internacional

(11) **FIGURA CARACTERÍSTICA:**

(12) Solicito la concesión de la patente,

NOMBRE: CARLOS R. OLARTE FIRMA: _____

C.C. 79.782.747 Btá T.P. 74.295

LISTA DE INVENTORES

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Estados Unidos de América
Nacionalidad: Estadounidense

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

Industria y Comercio
SUPERINTENDENCIA

RECIBO DE CAJA

No. 11 - 0048925

Bogotá D.C., Mayo 20 de 2011 - 16:30:31

RECIBIDO DE : OLARTERAISBECK NI 830.122.370

*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR.PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	444403245	20/05/2011	4.568.000.00

*** Conceptos Pagados ***

CANT.	RENTISTICO	CONCEPTO	Vr.UNDITARIO	Vr.CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE INVENCION	571.000.00	571.000.00
				$571.000.00

SON: **QUINIENTOS SETENTA Y UN MIL PESOS MONEDA CORRIENTE***

Responsable: _____
****

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 11-064157- -00000-0000

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Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
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5

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

APOSTILLA EN PODER DE REPRESENTACIÓN DE

PFIZER INC.

Bilingüe inglés- español otorgado en Nueva York, Estados Unidos el 14 de julio de 2003 y firmado por J. Trevor Lumb, Vicepresidente de Pfizer Products Inc.

CERTIFICACION NOTARIAL

Bilingüe inglés- español, el 14 de julio de 2003 el suscrito notario Kenneth Greenwood certifica que J. Trevor Lumb, domiciliado en Nueva York ejercía funciones de Asistente General Consejero de Patentes la Compañía Pfizer Inc., con sede en Nueva York, Nueva York, Estados Unidos.

Firma del notario: Kenneth Greenwood

Sello notarial: certificado, verificado y autenticado en la Localidad de Egham en Surrey, 14 julio, 2003 por el Notario Kenneth Greenwood-Horne Engall & Freeman

Sello Notario Público en alto relieve rojo.

APOSTILLA

REINO UNIDO DE GRAN BRETAÑA E IRLANDA DEL NORTE

1. País :Reino Unido de Gran Bretaña e Irlanda del Norte
   Este documento Público
2. ha sido firmado por K. Greenwood
3. ejerce funciones de Notario Público
4. Lleva el sello de dicho Notario Público

CERTIFICADO

5. En Londres 6. El 17 de julio de 2003
7. Por el Secretario de Estado Principal de su Majestad para Asuntos exteriores y de la mancomunidad
8. No. G210434
9. Sello del Secretario de Estado Principal de su Majestad para Asuntos exteriores y de la mancomunidad
10. Firma de R. Bawden - Por Secretario de Estado

Si el documento se usa en un país que no es parte de la convención de la Haya del 5 de octubre 1961, debe presentarse en sección consular de la misión que representa el país.

Es traducción fiel del inglés, con copia archivo para confrontación. Bogotá 25 de julio-2003. Marlen Neira C.

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

OLARTERAISBECK
OLARTE RAISBECK & FRIERI, LTDA.
LEGAL & PROFESSIONAL SERVICES

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

www.olarteraisbeck.com

Power of Attorney

The undersigned,

domiciled in

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

Poder

El suscrito,

Pfizer Inc.

domiciliado en

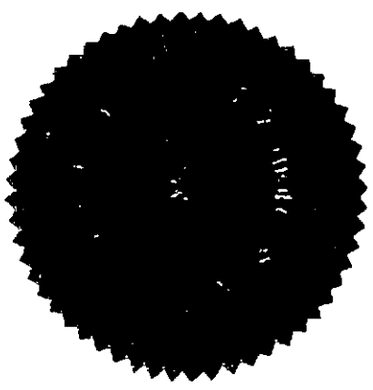
235 East 42nd Street, New York, NY 10017 USA

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

Signature/Firma: _____

Date/Fecha: July 14, 2003

City,Country/Ciudad,País: New York, USA



OLARTERAISBECK

OLARTE RAISBECK & FRIERI, LTDA.
LEGAL & PROFESSIONAL SERVICES

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FAX: +57-1 638-6201

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Notarial Certification

On this date,
July 14, 2003
The undersigned Notary Public certifies:

1. That J. Trevor Lumb

of legal age and domiciled in New York, USA
signed the foregoing document.

2. That the grantor has executed the foregoing document as Assistant General Patent Counsel of Pfizer Inc.

3. That Pfizer Inc.,
having its principal place of business located in New York, New York, U.S.A.
is duly incorporated, is currently in existence, and that the purposes for which the Power of Attorney is granted are within the scope of its corporate purposes.

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

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

Certificación Notarial

En esta fecha,

el Notario Público suscrito certifica:

1. Que
J. Trevor Lumb
mayor de edad y domiciliado
New York
suscribió el documento que antecede.

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

4. Que
con sede principal ubicada en

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

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

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

NOTARY PUBLIC (Signature):

EXECUTION
Certified Verified and Authenticated
In The Town Of Egham In Surrey
This 14th Day Of July 2003

KENNETH GREENWOOD
NOTARY PUBLIC
HORNE ENGALL AND FREEMAN

APOSTILLE

(Hague Convention of 5 October 1961 / Convention de La Haye du 5 octobre 1961)

UNITED KINGDOM OF GREAT BRITAIN AND NORTHERN IRELAND

1. Country: United Kingdom of Great Britain and Northern Ireland
   Pays: Royaume-Uni de Grande-Bretagne et d'Irlande du Nord

   This public document / Le présent acte public

2. Has been signed by / a été signé par **K Greenwood**

3. Acting in the capacity of / agissant en qualité de **Notary Public**

4. Bears the seal/stamp of / est revêtu du sceau/timbre de **The Said Notary Public**

5. at London/à Londres

   Certified/Attesté

6. the/le **17 July 2003**

7. by Her Majesty's Principal Secretary of State for Foreign and Commonwealth Affairs / par le Secrétaire d'Etat Principal de Sa Majesté aux Affaires Etrangères et du Commonwealth.

8. Number/sous No **G210434**

9. Stamp: / timbre:

10. Signature: **R. Bawden**

FOREIGN AND COMMONWEALTH OFFICE LONDON

For the Secretary of State / Pour le Secrétaire d'Etat

If this document is to be used in a country which is not party to the Hague Convention of 5 October 1961, it should be presented to the consular section of the mission representing that country.

PCT

Paper Copy (NOT for submission)

VIII-1-1	**Declaration: Identity of the Inventor** Declaration as to the identity of the inventor (Rules 4.17(i) and 51bis.1(a)(i))	in relation to this international application
	Name (LAST, First) Address	DEVRAJ, Rajesh Venkateswaran of Pfizer Global Research & Development 700 Chesterfield Parkway West Chesterfield, Missouri 63017 United States of America is the inventor of the subject matter for which protection is sought by way of this international application
	Name (LAST, First) Address	HUANG, Wei of Pfizer Global Research & Development 700 Chesterfield Parkway West Chesterfield, Missouri 63017 United States of America is the inventor of the subject matter for which protection is sought by way of this international application
	Name (LAST, First) Address	HUGHES, Robert Owen of Pfizer Global Research & Development 700 Chesterfield Parkway West Chesterfield, Missouri 63017 United States of America is the inventor of the subject matter for which protection is sought by way of this international application
	Name (LAST, First) Address	ROGIER JR., Donald Joseph of Pfizer Global Research & Development 700 Chesterfield Parkway West Chesterfield, Missouri 63017 United States of America is the inventor of the subject matter for which protection is sought by way of this international application
	Name (LAST, First) Address	TRUJILLO, John Isidro of Pfizer Global Research & Development 700 Chesterfield Parkway West Chesterfield, Missouri 63017 United States of America is the inventor of the subject matter for which protection is sought by way of this international application

PCT

Paper Copy (NOT for submission)

VIII-2-1	**Declaration: Entitlement to apply for and be granted a patent** Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent (Rules 4.17(ii) and 51bis.1(a)(ii)), in a case where the declaration under Rule 4.17(iv) is not appropriate: Name (LAST, First)	in relation to this international application PFIZER INC. is entitled to apply for and be granted a patent by virtue of the following:
VIII-2-1(iv)		an assignment from DEVRAJ, Rajesh Venkateswaran to Pfizer Products Inc., dated 07 July 2009 (07.07.2009)
VIII-2-1(iv)		an assignment from HUANG, Wei to Pfizer Products Inc., dated 07 July 2009 (07.07.2009)
VIII-2-1(iv)		an assignment from HUGHES, Robert Owen to Pfizer Products Inc., dated 07 July 2009 (07.07.2009)
VIII-2-1(iv)		an assignment from ROGIER JR., Donald Joseph to Pfizer Products Inc., dated 07 July 2009 (07.07.2009)
VIII-2-1(iv)		an assignment from TRUJILLO, John Isidro to Pfizer Products Inc., dated 07 July 2009 (07.07.2009)
VIII-2-1(iv)		an assignment from TURNER, Steve Ronald to Pfizer Products Inc., dated 07 July 2009 (07.07.2009)
VIII-2-1(iv)		an assignment from Pfizer Products Inc. to PFIZER INC., dated 14 October 2009 (14.10.2009)

PCT

Paper Copy (NOT for submission)

VIII-3-1	**Declaration: Entitlement to claim priority** Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application specified below, where the applicant is not the applicant who filed the earlier application or where the applicant's name has changed since the filing of the earlier application (Rules 4.17(iii) and 51bis.1(a)(iii)) Name	in relation to this international application PFIZER INC. is entitled to claim priority of earlier application No. 61/118,053 by virtue of the following:
VIII-3-1(iv)		an assignment from TRUJILLO, John Isidro to Pfizer Products Inc., dated 07 July 2009 (07.07.2009)
VIII-3-1(iv)		an assignment from TURNER, Steve Ronald to Pfizer Products Inc., dated 07 July 2009 (07.07.2009)
VIII-3-1(iv)		an assignment from Pfizer Products Inc. to PFIZER INC., dated 14 October 2009 (14.10.2009)
VIII-3-1(iv)		an assignment from DEVRAJ, Rajesh Venkateswaran to Pfizer Products Inc., dated 07 July 2009 (07.07.2009)
VIII-3-1(iv)		an assignment from HUANG, Wei to Pfizer Products Inc., dated 07 July 2009 (07.07.2009)
VIII-3-1(iv)		an assignment from HUGHES, Robert Owen to Pfizer Products Inc., dated 07 July 2009 (07.07.2009)
VIII-3-1(iv)		an assignment from ROGIER JR., Donald Joseph to Pfizer Products Inc., dated 07 July 2009 (07.07.2009)

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

(19) World Intellectual Property Organization
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3 June 2010 (03.06.2010)

PCT

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WO 2010/061329 A1

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C07D 487/08 (2006.01) *A61P 29/02* (2006.01)
A61K 31/407 (2006.01) *A61P 35/00* (2006.01)

(21) International Application Number:
PCT/IB2009/055232

(22) International Filing Date:
20 November 2009 (20.11.2009)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/118,053 26 November 2008 (26.11.2008) US

(71) Applicant *(for all designated States except US)*: **PFIZER INC.** [US/US]; 235 East 42nd Street, New York, New York 10017 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **DEVRAJ, Rajesh Venkateswaran** [IN/US]; Pfizer Global Research & Development, 700 Chesterfield Parkway West, Chesterfield, Missouri 63017 (US). **HUANG, Wei** [US/US]; Pfizer Global Research & Development, 700 Chesterfield Parkway West, Chesterfield, Missouri 63017 (US). **HUGHES, Robert Owen** [GB/US]; Pfizer Global Research & Development, 700 Chesterfield Parkway West, Chesterfield, Missouri 63017 (US). **ROGIER JR., Donald Joseph** [US/US]; Pfizer Global Research & Development, 700 Chesterfield Parkway West, Chesterfield, Missouri 63017 (US). **TRUJILLO, John Isidro** [US/US]; Pfizer Global Research & Development, 700 Chesterfield Parkway West, Chesterfield, Missouri 63017 (US). **TURNER, Steve Ronald** [US/US]; Pfizer Global Research & Development, 700 Chesterfield Parkway West, Chesterfield, Missouri 63017 (US).

(74) Agents: **BENSON, Gregg C.** et al.; Pfizer Inc. Eastern Point Road, MS 9114, Groton, Connecticut 06340 (US).

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

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

Declarations under Rule 4.17:

— *as to the identity of the inventor (Rule 4.17(i))*

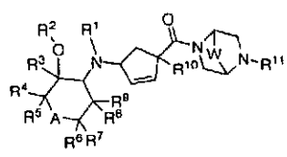
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

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

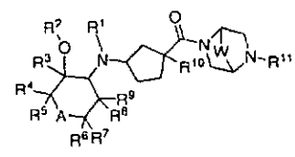
Published:

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

(54) Title: 3-AMINOCYCLOPENTANECARBOXAMIDES AS CHEMOKINE RECEPTOR MODULATORS



I(a)



I(b)

(57) Abstract: There is provided a compound of Formula I(a) or I(b) or a pharmaceutically acceptable salt thereof, wherein the various substitutents are defined herein.

WO 2010/061329 A1

3-AMINOCYCLOPENTANECARBOXAMIDES AS CHEMOKINE RECEPTOR MODULATORS

This application claims benefit of U.S. provisional Application No. 61/118,053 filed on November 26, 2008.

FIELD OF THE INVENTION

The present invention relates to compounds that modulate the activity of chemokine receptors, such as CCR2 and CCR5. The compounds can be used, for example, to treat diseases associated with chemokine receptor expression or activity.

BACKGROUND OF THE INVENTION

The migration and transport of leukocytes from blood vessels into diseased tissues is involved in the initiation of normal disease-fighting inflammatory responses. The process, also known as leukocyte recruitment, is also related to the onset and progression of inflammatory and autoimmune diseases. The resulting pathology of these diseases derives from the attack of the body's immune system defenses on normal tissues. Accordingly, preventing and blocking leukocyte recruitment to target tissues in inflammatory, autoimmune disease and cancer would be an effective approach to therapeutic intervention.

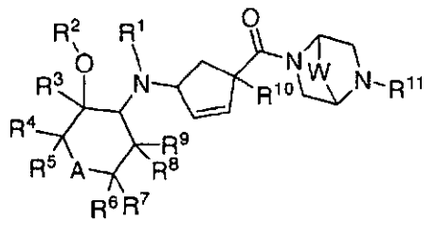
The infiltration of monocytes/macrophages into sites of inflammation is related to proteins, such as monocyte chemoattractant protein-1 (MCP-1, CCL2). Macrophages produce chemokines, such as macrophage inflammatory protein-1-beta (MIP-1β, CCL4). Such proteins interacts with chemokine receptors, for example, CCR2 and CCR5. Modulation, such as antagonism or inhibition, of CCR2 or CCR5 would be helpful to treat a wide range of diseases.

The identification of compounds that modulate the activity of chemokine receptors represents a desirable drug design approach to develop pharmacological agents for the treatment of diseases associated with chemokine

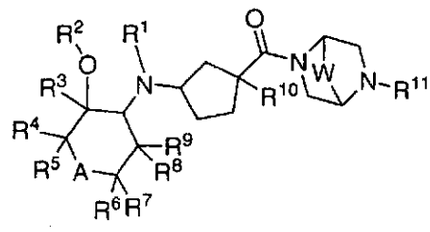
receptor activity. The compounds of the present invention help fulfill these and other needs.

SUMMARY OF THE INVENTION

In an embodiment of the present invention, there is provided a compound of Formula I(a) or I(b):



I(a)



I(b)

or a pharmaceutically acceptable salt thereof, wherein:

A is O or CF_2;

W is $CR^{13}R^{14}$, C(O), $CHOR^{15}$, CHF, CF_2, O or S

R^1 is H or C_{1-6} alkyl optionally substituted by 1-3 substituents selected from halo, OH, CO_2H, CO_2-(C_{1-6} alkyl), or C_{1-3} alkoxy;

R^2 and R^3 are each, independently, H, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, halo, (C_3-C_6)cycloalkyl, CN, OH, CO_2R, $OCOR^{12}$; wherein said (C_1-C_6)alkyl is optionally substituted with one or more substituents selected from F, (C_1-C_3) alkoxy, OH, CN or CO_2R^{12};

R^8 and R^9 are each, independently, H, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_3-C_6)cycloalkyl, (C_3-C_6)cycloalkyloxy, CN, OH, CO_2R, $OCOR^{12}$; wherein said (C_1-

C_6)alkyl is optionally substituted with one or more substituents selected from F, (C_1-C_3)alkoxy, OH, CN or CO_2R^{12};

R^2 and R^9, taken together may form a 5-8 membered ring;

R^4 and R^7, taken together may form a 5-8 membered ring.

R^4 and R^5 are each, independently, H, CN, (C_1-C_6)alkyl, halo, (C_1-C_3) alkoxy, (C_1-C_3)haloalkoxy, (C_3-C_6)cycloalkyl, OH, CO_2R^{12}, $OCOR^{12}$, wherein said (C_1-C_6)alkyl is optionally substituted with one or more substituents selected from F, (C_1-C_3) alkoxy, OH or CO_2R^{12};

R^6 and R^7 are each, independently, H, CN, (C_1-C_6)alkyl, halo, (C_1-C_3)alkoxy, (C_1-C_3)haloalkoxy, (C_3-C_6)cycloalkyl, OH, CO_2R^{12}, $OCOR^{12}$, wherein said (C_1-C_6)alkyl is optionally substituted with one or more substituents selected from F, (C_1-C_3)alkoxy, OH or CO_2R^{12};

or R^2 and R^3 together with the carbon atom to which they are attached form a 3-7 membered spirocyclyl group;

or R^4 and R^5 together with the carbon atom to which they are attached form a 4-7 membered spirocyclyl group;

or R^3 and R^4 together with the C atoms to which they are attached form a fused 3-7 membered cycloalkyl group or 3-7 membered heterocycloalkyl group;

R^{10} is (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)hydroxyalkyl, (C_1-C_6)alkoxy, (C_3-C_6)cycloalkyl, hydroxy(C_3-C_6)cycloalkyl, (C_1-C_6)alkoxy cycloalkyl, OH, (C_1-C_5)heterocyclyl, amino, aryl or CN,

R^{11} is aryl or heteroaryl, said R^{11} optionally, independently substituted by one or more $(C_1\text{-}C_6)$ alkyl, halo, $(C_1.C_6)$haloalky $(C_1\text{-}C_6)$alkoxy, OH, amino, $C(O)NH_2$, NH_2SO_2, SF_5,or CN;

R^{12} is H, $(C_1\text{-}C_4)$alkyl, or $(C_3\text{-}C_6)$cycloalkyl;

R^{13} is H, halo, $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkoxy,or OH;

R^{14} is H, halo, $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkoxy or OH; and

R^{15} is H ,$(C_1\text{-}C_6)$alkyl or $(C_3\text{-}C_6)$cycloalkyl.

DETAILED DESCRIPTION OF THE INVENTION

These inventions are not limited to the embodiments described in this specification, and may be modified.

A. Definitions

For the following defined terms, these definitions shall be applied, unless a different definition is given in the claims or elsewhere in this specification.

The term aryl groups is intended to include aromatic carbocylic groups such as phenyl, biphenylyl, indenyl, naphthyl as well as aromatic carbocycles fued to a heterocycle such as benzothienyl, benzofuranyl, indolyl, quinolinyl, benzothiazole, benzooxazole, benzimidazole, isoquinolinyl, isoindolyl, benzotriazole, indazole, and acridinyl.

The term heteroaryl includes mono- and poly-cyclic aromatic rings containing from 3 to 20, or from 4 to 10 ring atoms, at least one of which is a heteroatom such as oxygen, sulphur, phosphorus or nitrogen. Examples of such groups include furyl, thienyl, pyrrolyl, imidazolyl, triazolyl, thiazolyl, tetrazolyl, oxazolyl, isoxazolyl, pyrazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl,

quinolinyl, iosquinolinyl, quinoxalinyl, benzthiazolyl, benzoxazolyl, benzothienyl or benzofuryl.

The term "cycloalkyl," refer to cyclized hydrocarbons (mono and polycyclic) such as cyclized alkyl, alkenyl, or alkynyl groups. In some embodiments, the cycloalkyl group is C_{3-14}, C_{3-10}, C_{3-8}, C_{3-7}, C_{3-6}, or C_{3-5}. In some embodiments, cycloalkyl moieties each have from 3 to 14, from 3 to 10, or from 3 to 6 ring-forming carbon atoms. In some embodiments, the cycloalkyl group has 0, 1 or 2 double or triple bonds. Examples of cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclopentenyl, etc. In the present application, cycloalkyl is also intended to include bridged cyclic hydrocarbons such as adamantyl groups and the like.

Heterocycles are carbocyclic rings (mono or polycyclic) which include one or more heteroatoms such as nitrogen, oxygen or sulfur in the ring. In some embodiments, the heterocycle contains 3 to 8 ring members. In some embodiments, the heterocycle contains 3 to 6 ring members. In some embodiments, the heterocycle contains 1, 2 or 3 heteroatoms. Heterocycles can be saturated or unsaturated. In some embodiments, heterocycles contain 0, 1 or 2 double bonds or triple bonds. Ring-forming carbon atoms and heteroatoms can also bear oxo or sulfide substituents (such as, CO, CS, SO, SO_2, NO, and the like.). Examples of heterocycles include tetrahydrofuranyl, tetrahydrothiophenyl, morpholino, thiomorpholino, azetidinyl, pyrrolidinyl, piperazinyl, piperidinyl, pyrane, dioxane, and thiazolidinyl.

Monosubstituted aryl refers to an aryl group having one substituent. Polysubstituted aryl refers to aryl having 2 or more substitutents (such as 2-4 substituents). Monosubstituted heteroaryl refers to a heteroaryl group having one substituent. Polysubstituted heteroaryl refers to heteroaryl having 2 or more substitutents (such as 2-4 substituents). Monosubstituted cycloalkyl (or carbocycle) refers to a cycloalkyl group having one substituent. Polysubstituted cycloalkyl (or carbocycle) refers to cycloalkyl having 2 or more substitutents (such as 2-4 substituents). Monosubstituted heterocycle refers to a heterocycle

having one substituent. Polysubstituted heterocycle refers to heterocycle having 2 or more substitutents (such as 2-4 substituents).

The term halo, by itself or as part of another substituent, means, unless otherwise stated, a fluorine, chlorine, bromine, or iodine. Similarly, terms such as haloalkyl, are meant to include monohaloalkyl and polyhaloalkyl. For example, the term haloalkyl, such as halo(C_1-C_4)alkyl, is meant to include trifluoromethyl, 2,2,2-trifluoroethyl, 4-chlorobutyl, 3-bromopropyl, and the like.

The term alkyl when used either alone or as a suffix includes straight chain and branched structures such as primary alkyl groups, secondary alkyl groups and tertiary alkyl groups. These groups may contain up to 15, or up to 8, or up to 4 carbon atoms. In some embodiments, the alkyl group is C_{1-10}, C_{1-8}, C_{1-6}, C_{1-5}, C_{1-4}, or C_{1-3}. Examples of alkyl radicals include groups such as methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, isobutyl, and sec-butyl. Similarly the terms alkenyl and alkynyl refer to unsaturated straight or branched structures containing for example from 2 to 12, or from 2 to 6 carbon atoms. In some embodiments, the alkenyl or alkynyl group is C_{2-10}, C_{2-8}, C_{2-6}, C_{2-5}, C_{2-4}, or C_{2-3}. Examples of alkenyl and alkynyl groups include vinyl, 2-propenyl, crotyl, 2-isopentenyl, 2-(butadienyl), 2,4-pentadienyl, 3-(1,4-pentadienyl), ethynyl, 1- and 3-propynyl, 3-butynyl, and the higher homologs and isomers.

The term "carrier" describes an ingredient other than a compound. Carriers may be pharmaceutically acceptable material or vehicle. Examples include liquid or solid filler, diluent, excipient, solvent or encapsulating material.

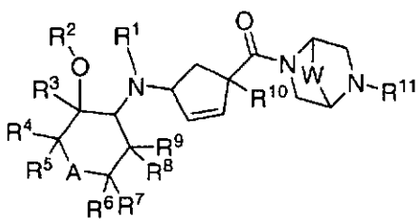
The phrase "contacting a chemokine receptor" means *in vivo*, *ex vivo*, or *in vitro* contact is made with a chemokine receptor and includes administration of a compound or salt of the present invention to a subject having a chemokine receptor, as well as, for example, introducing a compound or salt of the invention into a sample containing a cellular, unpurified, or purified preparation containing a chemokine receptor. For example, contacting includes interactions between the compound and the receptor, such as binding.

The term "subject" refers to any animal, including mammals, such as mice, rats, other rodents, rabbits, dogs, cats, pigs, cattle, sheep, horses, primates, or humans.

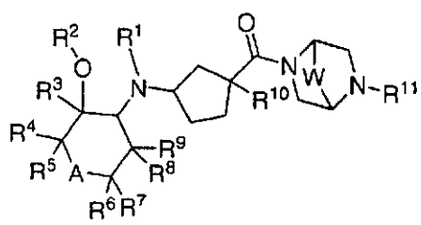
The term "treating" (and corresponding terms "treat" and "treatment") includes palliative, restorative, or preventative ("prophylactic") treating of a subject. The term "palliative treating" refers to treatment that eases or reduces the effect or intensity of a condition in a subject without curing the condition. The term "preventative treating" (and the corresponding term "prophylactic treating") refers to treatment that prevents the occurrence of a condition in a subject. The term "restorative treating" ("curative") refers to treatment that halts the progression of, reduces the pathologic manifestations of, or entirely eliminates a condition in a subject. Treating can be done with a therapeutically effective amount of compound, salt or composition that elicits the biological or medicinal response of a tissue, system or subject that is being sought by an individual such as a researcher, doctor, veterinarian, or clinician.

B. Compounds

In an embodiment of the present invention, there is provided a compound of I(a) or I(b):



I(a)



I(b)

or a pharmaceutically acceptable salt thereof, wherein:

A is O or CF_2;

W is $CR^{13}R^{14}$, C(O), $CHOR^{15}$, CHF, CF_2, O or S

R^1 is H or C_{1-6} alkyl optionally substituted by 1-3 substituents selected from halo, OH, CO_2H, CO_2-(C_{1-6} alkyl), or C_{1-3} alkoxy;

R^2 and R^3 are each, independently, H, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, halo, (C_3-C_6)cycloalkyl, CN, OH, CO_2R, $OCOR^{12}$; wherein said (C_1-C_6)alkyl is optionally substituted with one or more substituents selected from F, (C_1-C_3)alkoxy, OH, CN or CO_2R^{12};

R^8 and R^9 are each, independently, H, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_3-C_6)cycloalkyl, CN, OH, CO_2R, $OCOR^{12}$; wherein said (C_1-C_6)alkyl is optionally substituted with one or more substituents selected from F, (C_1-C_3)alkoxy, OH, CN or CO_2R^{12};

R^2 and R^9, taken together may form a 5-8 membered ring;

R^4 and R^7, taken together may form a 5-8 membered ring.

R^4 and R^5 are each, independently, H, CN, (C_1-C_6)alkyl, halo, (C_1-C_3)alkoxy, (C_1-C_3)haloalkoxy, (C_3-C_6) cycloalkyl, OH, CO_2R^{12}, $OCOR^{12}$, wherein said (C_1-C_6)alkyl is optionally substituted with one or more substituents selected from F, C_{1-3} alkoxy, OH or CO_2R^{12};

R^6 and R^7 are each, independently, H, CN, (C_1-C_6)alkyl, halo, (C_1-C_3)alkoxy, (C_1-C_3)haloalkoxy, (C_3-C_6)cycloalkyl, OH, CO_2R^{12}, $OCOR^{12}$, wherein said (C_1-C_6)alkyl is optionally substituted with one or more substituents selected from F, (C_1-C_3) alkoxy, OH or CO_2R^{12};

or R^2 and R^3 together with the carbon atom to which they are attached form a 3-7 membered spirocyclyl group;

or R^4 and R^5 together with the carbon atom to which they are attached form a 3-7 membered spirocyclyl group;

or R^3 and R^4 together with the C atoms to which they are attached form a fused 3-7 membered cycloalkyl group or 3-7 membered heterocycloalkyl group;

R^{10} is $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$haloalkyl, $(C_1\text{-}C_6)$hydroxyalkyl, $(C_1\text{-}C_6)$alkoxy, $(C_3\text{-}C_6)$cycloalkyl, hydroxy$(C_3\text{-}C_6)$cycloalkyl, alkoxy cycloalkyl, OH, $(C_1\text{-}C_5)$heterocyclyl, amino, aryl or CN,

R^{11} is aryl or heteroaryl, said R^{11} optionally, independently substituted by one or more $(C_1\text{-}C_6)$ alkyl, halo, (C_1C_6)haloalky $(C_1\text{-}C_6)$alkoxy, OH, amino, $C(O)NH_2$, NH_2SO_2, SF_5,or CN;

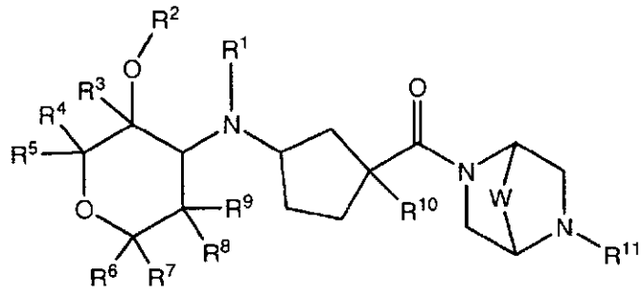
R^{12} is H, $(C_1\text{-}C_4)$alkyl, or $(C_3\text{-}C_6)$cycloalkyl;

R^{13} is H, halo, $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkoxy,or OH;

R^{14} is H, halo, $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkoxy or OH; and

R^{15} is H, $(C_1\text{-}C_6)$alkyl or $(C_3\text{-}C_6)$cycloalkyl.

In another embodiment of the present invention, there is provided a compound of Formula II:



(II)

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is H, $(C_1\text{-}C_6)$alkyl or cyclopropyl, said $(C_1\text{-}C_6)$alkyl optionally substituted by halo, CN, C(O)OH or OH;

R^2 is $(C_1\text{-}C_6)$alkyl $(C_1\text{-}C_6)$haloalkyl or $(C_3\text{-}C_6)$cycloalkyl;

R^3 R^4, R^5, R^6, R^7, R^8 and R^9 are independently H, $(C_1\text{-}C_4)$ alkyl, CN, halo or amino;

R^{10} is $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$haloalkyl, $(C_1\text{-}C_6)$hydroxyalkyl, $(C_1\text{-}C_6)$alkoxy, $(C_3\text{-}C_6)$cycloalkyl, hydroxy$(C_3\text{-}C_6)$cycloalkyl, alkoxy $(C_3\text{-}C_6)$cycloalkyl, OH, $(C_1\text{-}C_5)$heterocyclyl, amino, aryl or CN;

R^{11} is aryl or heteroaryl, said R^{11} optionally, independently substituted by one or more $(C_1\text{-}C_6)$ alkyl, halo, $(C_1\text{-}C_6)$haloalky $(C_1\text{-}C_6)$alkoxy, OH, amino, $C(O)NH_2$, NH_2SO_2, SF_5 or CN;

W is $CR^{13}R^{14}$, C(O), $CHOR^{15}$, CHF, CF_2, O or S;

R^{13} and R^{14} are independently H, halo, $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkoxy,or OH; and

R^{15} is H, $(C_1\text{-}C_6)$alkyl or $(C_3\text{-}C_6)$cycloalkyl.

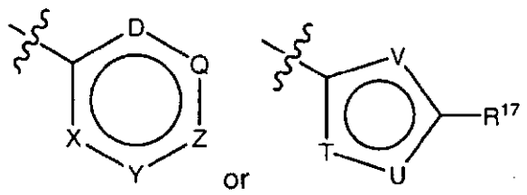
In another embodiment, there is provided a compound of Formula II, or a pharmaceutically acceptable salt thereof, wherein:

R^1 is H or $(C_1\text{-}C_6)$alkyl

R^2 is $(C_1\text{-}C_6)$alkyl or $(C_1\text{-}C_6)$haloalkyl

R^3, R^4, R^5, R^6, R^7, R^8 and R^9 are each H;

R^{11} is



wherein X, Y, Z, Q and D are independently N or CR^{16}, and wherein 0, 1, 2 or 3 of X, Y, Z, Q and D are N; and

wherein T, U and V are independently selected from CH, N, S, or O, provided that T and U are not both simultaneously O or S;

each R^{16} is independently H, halo, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$haloalkyl, $(C_1\text{-}C_6)$alkoxy or CN;

R^{17} is H, $(C_1\text{-}C_6)$alky, $(C_1\text{-}C_6)$haloalky, or $(C_1\text{-}C_6)$alkoxy; and

W is $CR^{13}R^{14}$, C(O), $CHOR^{15}$, CHF or CF_2.

In some embodiments of the compound of Formula II, or a pharmaceutically acceptable salt thereof, R^2 is methyl.

In some embodiments of the compound of Formula II, or a pharmaceutically acceptable salt thereof,

R^1 is H, $(C_1\text{-}C_6)$alkyl or cyclopropyl, said $(C_1\text{-}C_6)$alkyl optionally substituted by halo, CN, C(O)OH or OH;

R^2 is methyl;

R^3 R^4, R^5, R^6, R^7, R^8 and R^9 are independently H, $C_1\text{-}C_4$ alkyl, CN, halo or amino;

R^{10} is $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$haloalkyl, $(C_1\text{-}C_6)$hydroxyalkyl, $(C_1\text{-}C_6)$alkoxy, $(C_3\text{-}C_6)$cycloalkyl, hydroxy$(C_3\text{-}C_6)$cycloalkyl, alkoxy $(C_3\text{-}C_6)$cycloalkyl, OH, $(C_1\text{-}C_5)$heterocyclyl, amino, aryl or CN;

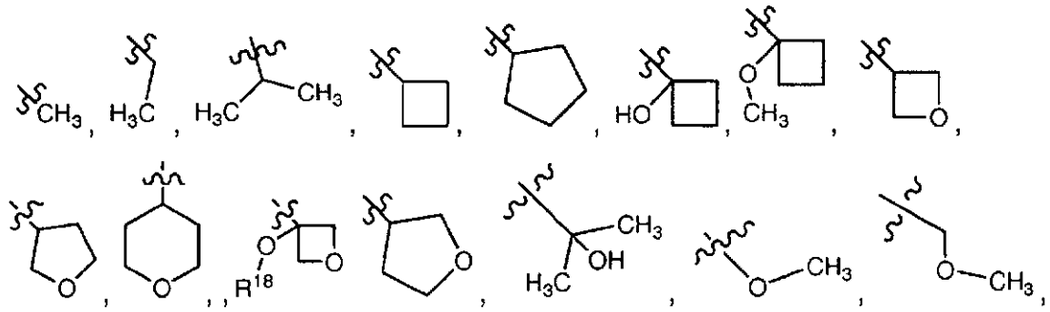
R^{11} is aryl or heteroaryl, said R^{11} optionally, independently substituted by one or more $(C_1\text{-}C_6)$ alkyl, halo, $(C_1\text{-}C_6)$haloalky $(C_1\text{-}C_6)$alkoxy, OH, amino, $C(O)NH_2$, NH_2SO_2, SF_5 or CN;

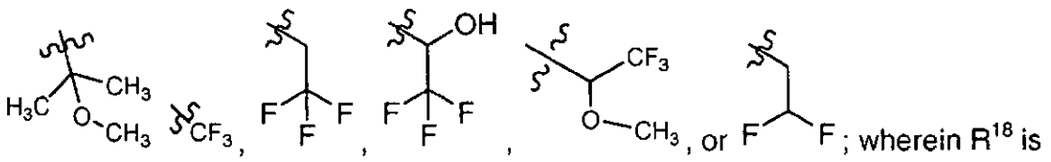
W is $CR^{13}R^{14}$, C(O), $CHOR^{15}$, CHF, CF_2, O or S;

R^{13} and R^{14} are independently H halo, $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkoxy,or OH; and

R^{15} is H, $(C_1\text{-}C_6)$alkyl or $(C_3\text{-}C_6)$cycloalkyl.

In some embodiments of the compound of Formula II, or a pharmaceutically acceptable salt thereof, R^{10} is




; wherein R^{18} is H or $(C_1\text{-}C_6)$alkyl

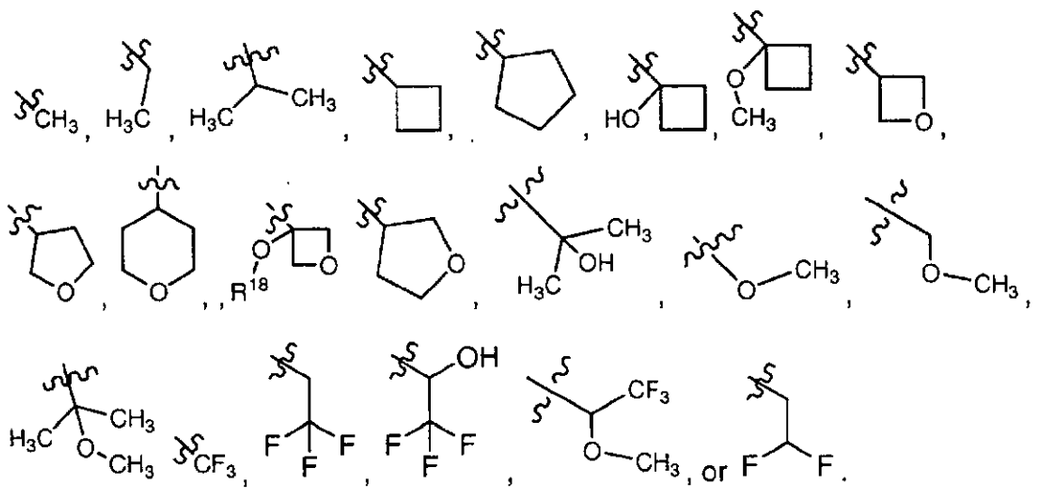
In some embodiments of the compound of Formula II, or a pharmaceutically acceptable salt thereof,

R^1 is H, $(C_1\text{-}C_6)$alkyl or cyclopropyl, said $(C_1\text{-}C_6)$alkyl optionally substituted by halo, CN, C(O)OH or OH;

R^2 is methyl;

R^3 R^4, R^5, R^6, R^7, R^8 and R^9 are independently H, $C_1\text{-}C_4$ alkyl, CN, halo or amino;

R^{10} is



R^{11} is aryl or heteroaryl, said R^{11} optionally, independently substituted by one or more $(C_1\text{-}C_6)$ alkyl, halo, (C_1C_6)haloalky $(C_1\text{-}C_6)$alkoxy, OH, amino, $C(O)NH_2$, NH_2SO_2, SF_5 or CN;

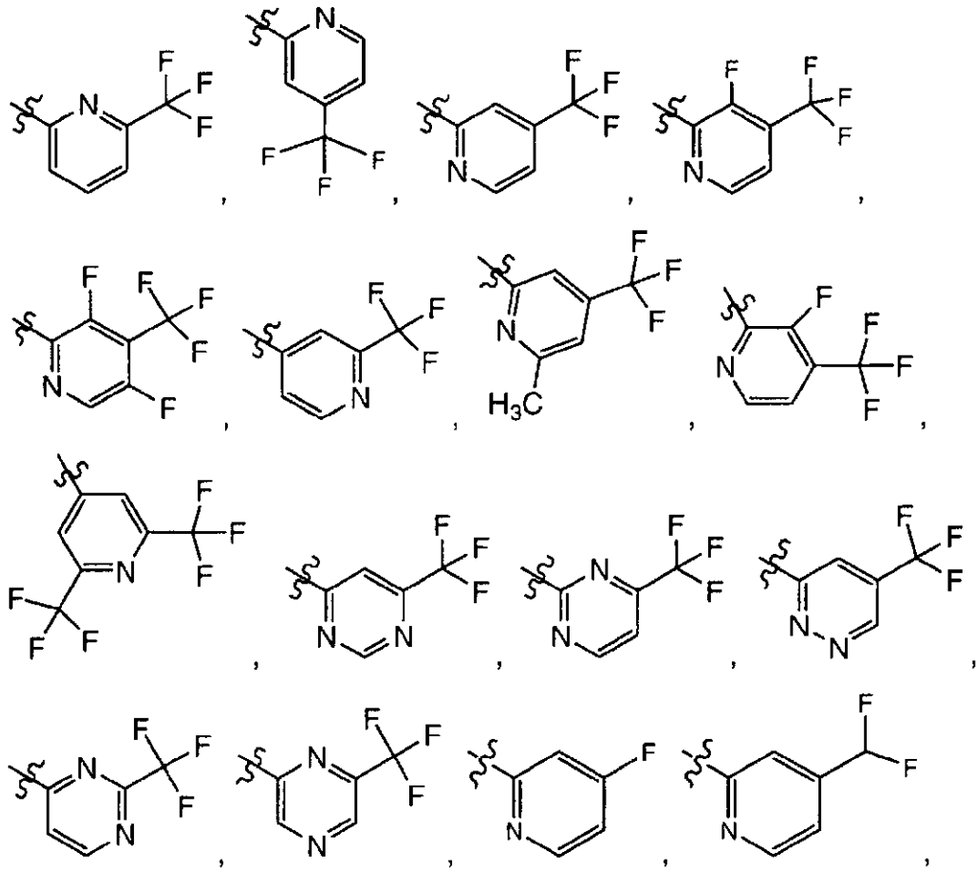
W is $CR^{13}R^{14}$, C(O), $CHOR^{15}$, CHF, CF_2, O or S;

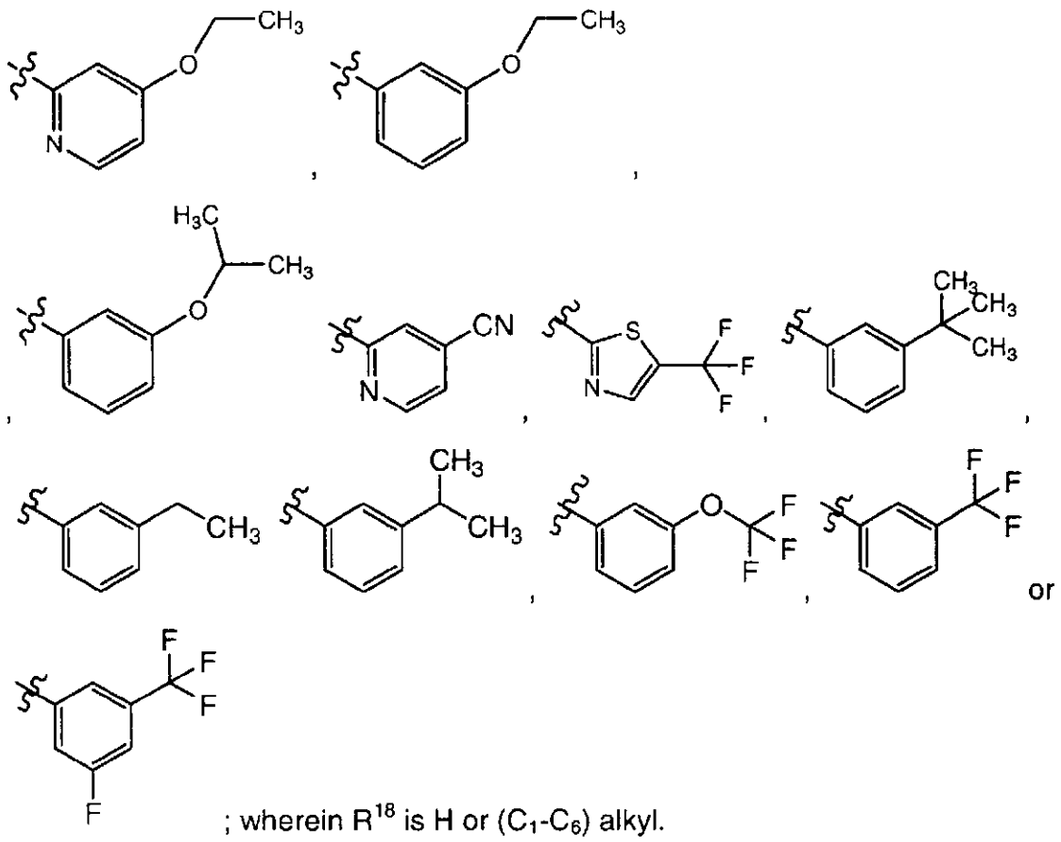
R^{13} and R^{14} are independently H halo, $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkoxy,or OH;

R^{15} is H, $(C_1\text{-}C_6)$alkyl or $(C_3\text{-}C_6)$cycloalkyl; and

R^{18} is H or $(C_1\text{-}C_6)$alkyl.

In some embodiments of the present invention, there is provided a compound of Formula II, or a pharmaceutically acceptable salt thereof, wherein R^{11} is





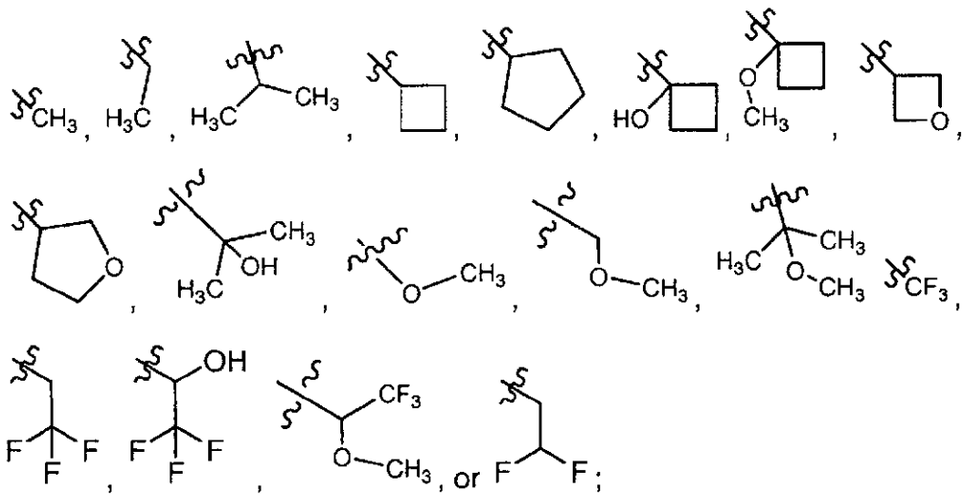
; wherein R^{18} is H or (C_1-C_6) alkyl.

In some embodiments of the present invention, there is provided a compound of Formula II, or a pharmaceutically acceptable salt thereof, wherein R^1 is H, (C_1-C_6)alkyl or cyclopropyl, said (C_1-C_6)alkyl optionally substituted by halo, CN, C(O)OH or OH;

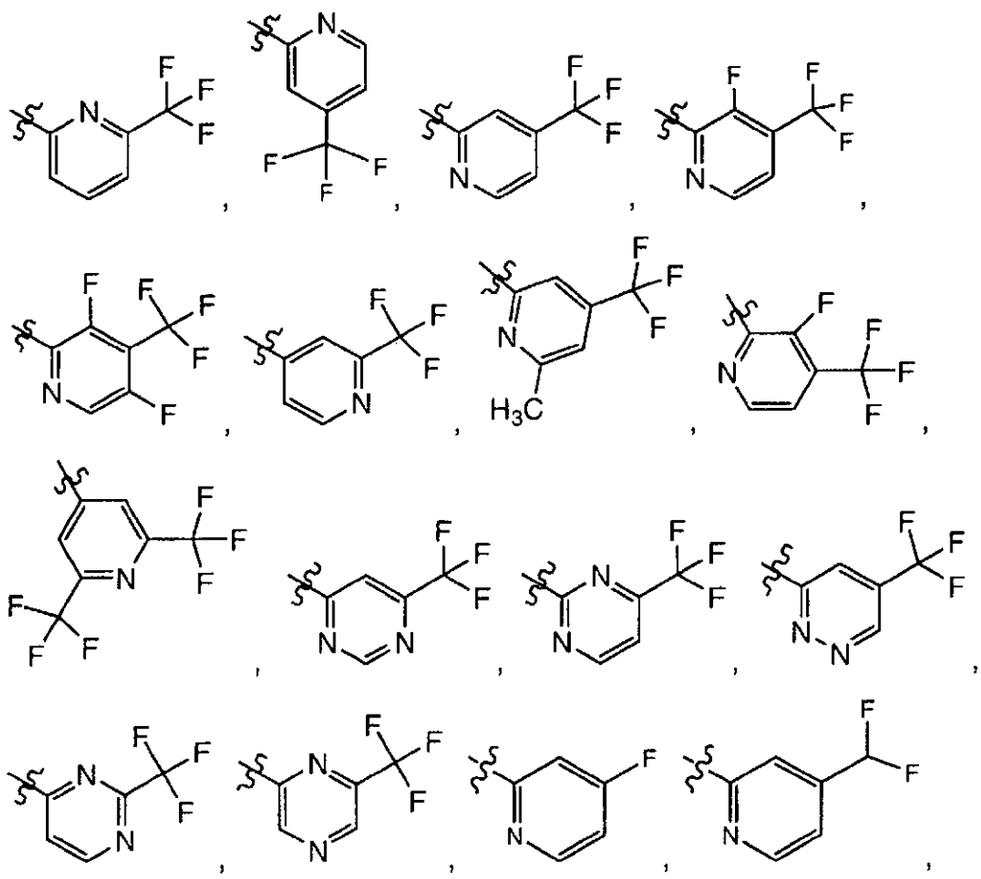
R^2 is methyl;

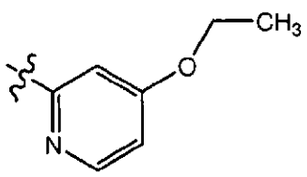
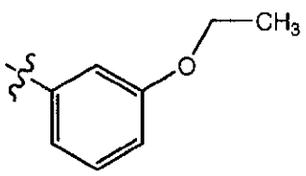
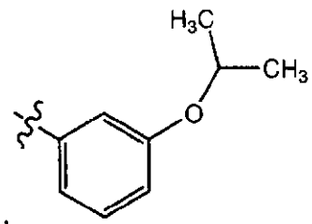
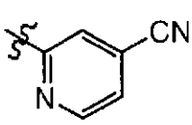
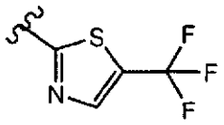
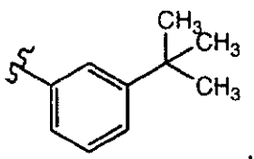
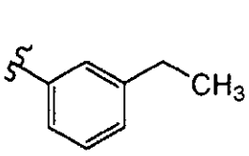
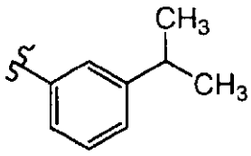
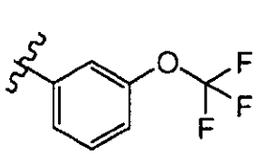
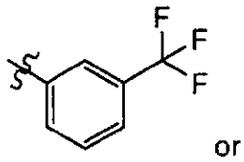
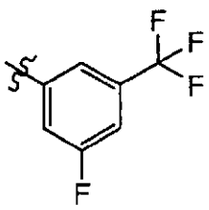
R^3 R^4, R^5, R^6, R^7, R^8 and R^9 are independently H, C_1-C_4 alkyl, CN, halo or amino;

R^{10} is



R^{11} is



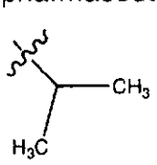
; wherein R^{18} is H or (C_1-C_6) alkyl;

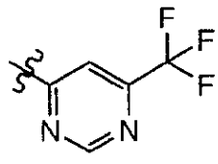
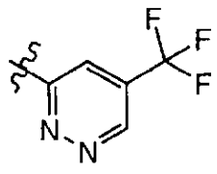
W is $CR^{13}R^{14}$, C(O), $CHOR^{15}$, CHF, CF_2, O or S;

R^{13} and R^{14} are independently H halo, (C_1-C_4)alkyl, (C_1-C_4)alkoxy,or OH; and

R^{15} is H, (C_1-C_6)alkyl or (C_3-C_6)cycloalkyl.

In some embodiments, there is provided a compound of Formula II, or pharmaceutically acceptable salt thereof, wherein R^{10} is


, or  and

R^{11} is  , or  .

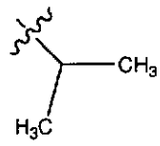
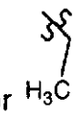
In some embodiments, there is provided a compound of Formula II, or pharmaceutically acceptable salt thereof, wherein

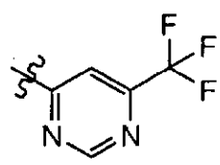
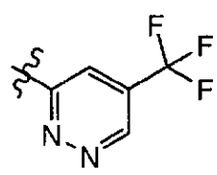
R^1 is H;

R^2 is methyl;

R^3 R^4, R^5, R^6, R^7, R^8 and R^9 are each H;

R^{10} is

 , or  ;

R^{11} is  , or  ; and

W is CH_2.

In another embodiment, there is provideded compound, or pharmaceutically acceptable salt thereof, selected from the group consisting of: 1,5-anhydro-2,3-dideoxy-3-{[(1R,3S)-3-ethyl-3-({(1S,4S)-5-[4-(trifluoromethyl)pyridin-2-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methyl-D-erythro-pentitol;

1,5-anhydro-2,3-dideoxy-3-{[(1R,3S)-3-ethyl-3-({(1S,4S)-5-[4-(trifluoromethyl)pyrimidin-2-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methyl-D-erythro-pentitol;
1,5-anhydro-2,3-dideoxy-3-{[(1R,3S)-3-ethyl-3-({(1S,4S)-5-[6-(trifluoromethyl)pyrimidin-4-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methyl-D-erythro-pentitol;
1,5-anhydro-2,3-dideoxy-3-{[(1R,3S)-3-ethyl-3-({(1S,4S)-5-[6-(trifluoromethyl)pyrazin-2-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methyl-D-erythro-pentitol;
1,5-anhydro-2,3-dideoxy-3-{[(1R,3S)-3-ethyl-3-({(1S,4S)-5-[2-(trifluoromethyl)pyrimidin-4-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methyl-D-erythro-pentitol;
1,5-anhydro-2,3-dideoxy-3-{[(1R,3S)-3-ethyl-3-({(1S,4S)-5-[6-(trifluoromethyl)pyridin-2-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methyl-D-erythro-pentitol;
1,5-anhydro-2,3-dideoxy-3-{[(1R,3S)-3-ethyl-3-({(1S,4S)-5-[2-(trifluoromethyl)pyridin-4-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methyl-D-erythro-pentitol;
1,5-anhydro-2,3-dideoxy-3-{[(1R,3S)-3-ethyl-3-({(1S,4S)-5-[3-fluoro-4-(trifluoromethyl)pyridin-2-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methyl-D-erythro-pentitol;
1,5-anhydro-2,3-dideoxy-3-{[(1R,3S)-3-methyl-3-({(1S,4S)-5-[4-(trifluoromethyl)pyridin-2-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methyl-D-erythro-pentitol;
1,5-anhydro-2,3-dideoxy-3-{[(1R,3S)-3-methyl-3-({(1S,4S)-5-[6-(trifluoromethyl)pyrazin-2-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methyl-D-erythro-pentitol;
1,5-anhydro-2,3-dideoxy-3-{[(1R,3S)-3-isopropyl-3-({(1S,4S)-5-[4-(trifluoromethyl)pyridin-2-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methyl-D-erythro-pentitol;

1,5-anhydro-2,3-dideoxy-3-{[(1R,3S)-3-isopropyl-3-({(1S,4S)-5-[4-(trifluoromethyl)pyrimidin-2-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methyl-D-erythro-pentitol;
1,5-anhydro-2,3-dideoxy-3-{[(1R,3S)-3-isopropyl-3-({(1S,4S)-5-[6-(trifluoromethyl)pyrimidin-4-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methyl-D-erythro-pentitol;
1,5-anhydro-2,3-dideoxy-3-{[(1R,3S)-3-isopropyl-3-({(1S,4S)-5-[6-(trifluoromethyl)pyrazin-2-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methyl-D-erythro-pentitol;
1,5-anhydro-2,3-dideoxy-3-{[(1R,3S)-3-isopropyl-3-({(1S,4S)-5-[2-(trifluoromethyl)pyrimidin-4-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methyl-D-erythro-pentitol;
1,5-anhydro-2,3-dideoxy-3-{[(1R,3S)-3-isopropyl-3-({(1S,4S)-5-[6-(trifluoromethyl)pyridin-2-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methyl-D-erythro-pentitol;
1,5-anhydro-2,3-dideoxy-3-{[(1R,3S)-3-isopropyl-3-({(1S,4S)-5-[2-(trifluoromethyl)pyridin-4-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methyl-D-erythro-pentitol;
1,5-anhydro-2,3-dideoxy-3-{[(1R,3S)-3-isopropyl-3-({(1S,4S)-5-[5-(trifluoromethyl)pyridazin-3-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methyl-D-erythro-pentitol;
1,5-anhydro-3-{[(1R,3S)-3-isopropyl-3-({(1S,4S)-5-[2,6-bis(trifluoromethyl)pyridin-4-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)-3-isopropylcyclopentyl]amino}-2,3-dideoxy-4-O-methyl-D-erythro-pentitol;
1,5-anhydro-2,3-dideoxy-3-{[(1R,3S)-3-({(1S,4S)-5-[3-fluoro-4-(trifluoromethyl)pyridin-2-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)-3-isopropylcyclopentyl]amino}-4-O-methyl-D-erythro-pentitol;
1,5-anhydro-2,3-dideoxy-3-{[(1R,3S)-3-isopropyl-3-({(1S,4S)-5-[6-methyl-4-(trifluoromethyl)pyridin-2-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methyl-D-erythro-pentitol;

1,5-anhydro-2,3-dideoxy-3-{[(1R,3S)-3-isopropyl-3-({(1S,4S)-5-[3-(trifluoromethyl)phenyl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methyl-D-erythro-pentitol;
1,5-anhydro-2,3-dideoxy-3-{[(1R,3S)-3-({(1S,4S)-5-[3-fluoro-5-(trifluoromethyl)phenyl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)-3-isopropylcyclopentyl]amino}-4-O-methyl-D-erythro-pentitol;
1,5-anhydro-2,3-dideoxy-3-{[(1R,3S)-3-(2,2-difluoroethyl)-3-({(1S,4S)-5-[6-(trifluoromethyl)pyrimidin-4-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methyl-D-erythro-pentitol;
1,5-anhydro-2,3-dideoxy-3-{[(1R,3S)-3-(2,2-difluoroethyl)-3-({(1S,4S)-5-[4-(trifluoromethyl)pyridin-2-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methyl-D-erythro-pentitol;
1,5-anhydro-2,3-dideoxy-3-{[(1R,3S)-3-(2,2-difluoroethyl)-3-({(1S,4S)-5-[2-(trifluoromethyl)pyridin-4-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methyl-D-erythro-pentitol;
1,5-anhydro-2,3-dideoxy-3-{[(1R,3S)-3-(2,2-difluoroethyl)-3-({(1S,4S)-5-[4-(trifluoromethyl)pyrimidin-2-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methyl-D-erythro-pentitol
1,5-anhydro-2,3-dideoxy-3-{[(1R,3S)-3-(2,2-difluoroethyl)-3-({(1S,4S)-5-[6-(trifluoromethyl)pyridin-2-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methyl-D-erythro-pentitol;
1,5-anhydro-2,3-dideoxy-3-{[(1R,3S)-3-(2,2-difluoroethyl)-3-({(1S,4S)-5-[6-(trifluoromethyl)pyrazin-2-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methyl-D-erythro-pentitol;
1,5-anhydro-2,3-dideoxy-3-{[(1R,3S)-3-(2,2-difluoroethyl)-3-({(1S,4S)-5-[2-(trifluoromethyl)pyrimidin-4-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methyl-D-erythro-pentitol;
1,5-anhydro-2,3-dideoxy-3-{[(1R,3S)-3-(2,2-difluoroethyl)-3-({(1S,4S)-5-[5-(trifluoromethyl)pyridazin-3-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methyl-D-erythro-pentitol;

1,5-anhydro-2,3-dideoxy-4-O-methyl-3-{[(1R,3S)-3-(2,2,2-trifluoroethyl)-3-({(1S,4S)-5-[6-(trifluoromethyl)pyrimidin-4-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-D-erythro-pentitol;

1,5-anhydro-2,3-dideoxy-4-O-methyl-3-{[(1R,3S)-3-(2,2,2-trifluoroethyl)-3-({(1S,4S)-5-[4-(trifluoromethyl)pyridin-2-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-D-erythro-pentit;

1,5-anhydro-2,3-dideoxy-4-O-methyl-3-{[(1R,3S)-3-(2,2,2-trifluoroethyl)-3-({(1S,4S)-5-[2-(trifluoromethyl)pyridin-4-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-D-erythro-pentitol;

1,5-anhydro-2,3-dideoxy-4-O-methyl-3-{[(1R,3S)-3-(2,2,2-trifluoroethyl)-3-({(1S,4S)-5-[4-(trifluoromethyl)pyrimidin-2-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-D-erythro-pentitol;

1,5-anhydro-2,3-dideoxy-4-O-methyl-3-{[(1R,3S)-3-(2,2,2-trifluoroethyl)-3-({(1S,4S)-5-[6-(trifluoromethyl)pyridin-2-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-D-erythro-pentitol;

1,5-anhydro-2,3-dideoxy-4-O-methyl-3-{[(1R,3S)-3-(2,2,2-trifluoroethyl)-3-({(1S,4S)-5-[6-(trifluoromethyl)pyrazin-2-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-D-erythro-pentitol;

1,5-anhydro-2,3-dideoxy-4-O-methyl-3-{[(1R,3S)-3-(2,2,2-trifluoroethyl)-3-({(1S,4S)-5-[2-(trifluoromethyl)pyrimidin-4-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-D-erythro-pentitol

1,5-anhydro-2,3-dideoxy-4-O-methyl-3-{[(1R,3S)-3-(2,2,2-trifluoroethyl)-3-({(1S,4S)-5-[5-(trifluoromethyl)pyridazin-3-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-D-erythro-pentitol;

1,5-anhydro-2,3-dideoxy-3-{[(1S,4S)-4-isopropyll-4-({(1S,4S)-5-[4-(trifluoromethyl)pyridin-2-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopent-2-en-1-yl]amino}-4-O-methyl-D-erythro-pentitol;

1,5-anhydro-2,3-dideoxy-3-{[(1S,4S)-4-isopropyll-4-({(1S,4S)-5-[4-(trifluoromethyl)pyrimidin-2-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopent-2-en-1-yl]amino}-4-O-methyl-D-erythro-pentitol;

1,5-anhydro-2,3-dideoxy-3-{[(1S,4S)-4-isopropyll-4-({(1S,4S)-5-[6-(trifluoromethyl)pyridin-2-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopent-2-en-1-yl]amino}-4-O-methyl-D-erythro-pentitol;

1,5-anhydro-2,3-dideoxy-3-{[(1S,4S)-4-isopropyll-4-({(1S,4S)-5-[6-(trifluoromethyl)pyrazin-2-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopent-2-en-1-yl]amino}-4-O-methyl-D-erythro-pentitol;

1,5-anhydro-3-{[(1R,3S)-3-{[(1S,4S)-5-(tert-butoxycarbonyl)-2,5-diazabicyclo[2.2.1]hept-2-yl]carbonyl}-3-ethylcyclopentyl]amino}-2,3-dideoxy-4-O-methyl-D-erythro-pentitol;

1,5-anhydro-3-{[(1R,3S)-3-{[(1S,4S)-5-(tert-butoxycarbonyl)-2,5-diazabicyclo[2.2.1]hept-2-yl]carbonyl}-3-(2,2,2-trifluoroethyl)cyclopentyl]amino}-2,3-dideoxy-4-O-methyl-D-erythro-pentitol;

1,5-Anhydro-2,3-dideoxy-3-{[(1R,3S)-3-(1-hydroxycyclobutyl)-3-({(1S,4S)-5-[6-(trifluoromethyl)pyridin-2-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methyl-D-erythro-pentitol;

1,5-Anhydro-2,3-dideoxy-3-{[(1R,3S)-3-(1-hydroxycyclobutyl)-3-({(1S,4S)-5-[4-(trifluoromethyl)pyridin-2-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methyl-D-erythro-pentitol;

1,5-Anhydro-2,3-dideoxy-3-{[(1R,3S)-3-(1-hydroxycyclobutyl)-3-({(1S,4S)-5-[4-(trifluoromethyl)pyrimidin-2-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methyl-D-erythro-pentitol;

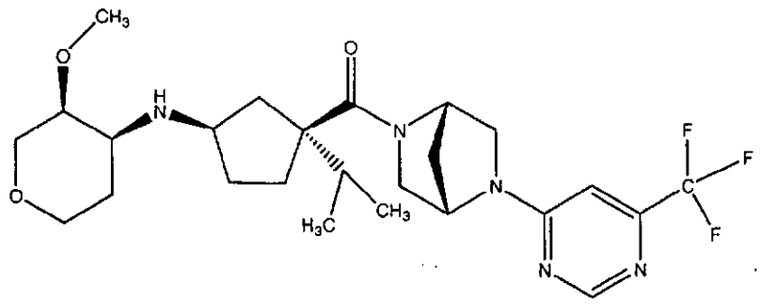
1,5-Anhydro-2,3-dideoxy-3-{[(1R,3S)-3-(1-hydroxycyclobutyl)-3-({(1S,4S)-5-[2-(trifluoromethyl)pyrimidin-4-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methyl-D-erythro-pentitol

1,5-anhydro-2,3-dideoxy-3-{[(1R,3S)-3-(1-hydroxycyclobutyl)-3-({(1S,4S)-5-[6-(trifluoromethyl)pyrimidin-4-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methyl-D-erythro-pentitol;

1,5-Anhydro-2,3-dideoxy-3-{[(1R,3S)-3-(1-hydroxycyclobutyl)-3-({(1S,4S)-5-[6-(trifluoromethyl)pyrazin-2-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methyl-D-erythro-pentitol;

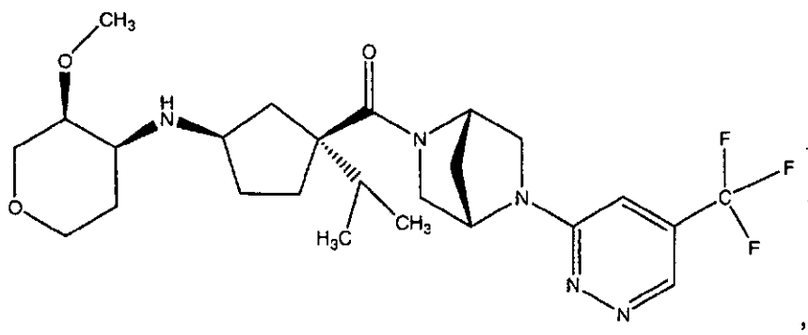
1,5-Anhydro-2,3-dideoxy-3-{[(1R,3S)-3-(1-hydroxycyclobutyl)-3-({(1S,4S)-5-[2-(trifluoromethyl)pyridin-4-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methyl-D-erythro-pentitol;
1,5-Anhydro-2,3-dideoxy-3-{[3-(1-hydroxy-1-methylethyl)-3-({5-[4-(trifluoromethyl)pyridin-2-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methylpentitol;
1,5-Anhydro-2,3-dideoxy-3-{[3-(1-hydroxy-1-methylethyl)-3-({5-[6-(trifluoromethyl)pyrimidin-4-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methylpentitol;
1,5-Anhydro-2,3-dideoxy-3-{[3-(1-hydroxy-1-methylethyl)-3-({5-[4-(trifluoromethyl)pyrimidin-2-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methylpentitol;
1,5-Anhydro-2,3-dideoxy-3-{[3-(1-hydroxy-1-methylethyl)-3-({5-[5-(trifluoromethyl)pyridazin-3-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methylpentitol;
1,5-Anhydro-2,3-dideoxy-3-{[3-(1-hydroxy-1-methylethyl)-3-({5-[2-(trifluoromethyl)pyrimidin-4-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methylpentitol;
1,5-Anhydro-2,3-dideoxy-3-{[3-(1-hydroxy-1-methylethyl)-3-({5-[6-(trifluoromethyl)pyridin-2-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methylpentitol;
1,5-Anhydro-2,3-dideoxy-3-{[3-(1-hydroxy-1-methylethyl)-3-({5-[2-(trifluoromethyl)pyridin-4-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methylpentitol; and
1,5-Anhydro-2,3-dideoxy-3-{[3-(1-hydroxy-1-methylethyl)-3-({5-[6-(trifluoromethyl)pyrazin-2-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methylpentitol.

In another embodiment, there is provided a compound of formula:



, or a pharmaceutically acceptable salt thereof..

In another embodiment, there is provided a compound of formula



, or a pharmaceutically acceptable salt thereof.

In another embodiment of the present invention, there is provided a composition comprising a compound of Formula I or II, or a pharmaceutically acceptable salt thereof, and a carrier.

In another embodiment, there is provided a method of treating a disease associated with expression or activity of a chemokine receptor in a patient comprising administering to said patient a compound of Formula I or II, or a pharmaceutically acceptable salt thereof.

In one embodiment of the method, said chemokine receptor is CCR2 or CCR5.

In another embodiment of the method, the disease is rheumatoid arthritis, atherosclerosis, lupus, multiple sclerosis, pain, transplant rejection, diabetes, diabetic nephropathy, diabetic conditions, liver fibrosis, viral disease, cancer, asthma, seasonal and perennial allergic rhinitis, sinusitis, conjunctivitis, age-related macular degeneration, food allergy, scombroid poisoning, psoriasis, undifferentiated spondyloarthropy, gout, urticaria, pruritus, eczema, inflammatory bowel disease, thrombotic disease, otitis media, fibrosis, liver cirrhosis, cardiac disease, Alzheimer's disease, sepsis, restenosis, Crohn's disease, ulcerative colitis, irritable bowel syndrome, hypersensitivity lung diseases, drug-induced pulmonary fibrosis, chronic obstructive pulmonary disease, arthritis, nephritis, atopic dermatitis, stroke, acute nerve injury, sarcoidosis, hepatitis, endometriosis, neuropathic pain, hypersensitivity pneumonitis, eosinophilic pneumonias, delayed-type hypersensitivity, interstitial lung disease, eye disorders or obesity.

In anther embodiment of the present invention, there is provided the use of a compound of Formula I or II, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of rheumatoid arthritis, atherosclerosis, lupus, multiple sclerosis, pain, transplant rejection, diabetes, diabetic nephropathy, diabetic conditions, liver fibrosis, viral disease, cancer, asthma, seasonal and perennial allergic rhinitis, sinusitis, conjunctivitis, age-related macular degeneration, food allergy, scombroid poisoning, psoriasis, undifferentiated spondyloarthropy, gout, urticaria, pruritus, eczema, inflammatory bowel disease, thrombotic disease, otitis media, fibrosis, liver cirrhosis, cardiac disease, Alzheimer's disease, sepsis, restenosis, Crohn's disease, ulcerative colitis, irritable bowel syndrome, hypersensitivity lung diseases, drug-induced pulmonary fibrosis, chronic obstructive pulmonary disease, arthritis, nephritis, atopic dermatitis, stroke, acute nerve injury, sarcoidosis, hepatitis, endometriosis, neuropathic pain, hypersensitivity pneumonitis, eosinophilic pneumonias, delayed-type hypersensitivity, interstitial lung disease, eye disorders or obesity.

In another embodiment, the present invention relates to a combination for treating a CCR2 or CCR2/CCR5 mediated disease, disorder or condition, said combination comprising a compound of Formula I or II as defined above, or a pharmaceutically acceptable salt thereof, and one or more additional therapeutic agents.

In another embodiment, the present invention relates to a compound of formula I or II as defined above, or a pharmaceutically acceptable salt thereof, as defined above, for use as a medicament.

In another embodiment, the present invention is directed to a method of treating a CCR2 or CCR2/CCR5 mediated disease, disorder or condition in a subject in need of such treatment, by administering a therapeutically effective amount of a compound of Formula I or II as defined above, or a pharmaceutically acceptable salt or solvate thereof to said subject.

In another embodiment, the present invention is directed to a compound of Formula I or II as defined above, or a pharmaceutically acceptable salt thereof, for use in treating a CCR2 or CCR2/CCR5 mediated disease, disorder or condition.

In another embodiment, the present invention is directed to the use of a compound of Formula I or II as defined above, or a pharmaceutically acceptable salt or solvate thereof, for the manufacture of a medicament for treating a CCR2 or CCR2/CCR5 mediated disease, disorder or condition.

Salts of compounds of the invention can include the acid addition salts or base addition salts (including disalts) thereof. The salts can be pharmaceutically acceptable.

Suitable acid addition salts are formed from acids which form non-toxic salts. Examples include the acetate, aspartate, benzoate, besylate, bicarbonate/carbonate, bisulphate/sulphate, borate, camsylate, citrate, edisylate,

esylate, formate, fumarate, gluceptate, gluconate, glucuronate, hexafluorophosphate, hibenzate, hydrochloride/chloride, hydrobromide/bromide, hydroiodide/iodide, isethionate, lactate, malate, maleate, malonate, mesylate, methylsulphate, naphthylate, 2-napsylate, nicotinate, nitrate, orotate, oxalate, palmitate, pamoate, phosphate/hydrogen phosphate/dihydrogen phosphate, saccharate, stearate, succinate, tartrate, tosylate and trifluoroacetate salts. Suitable base salts are formed from bases which form non-toxic salts. Examples include the aluminium, arginine, benzathine, calcium, choline, diethylamine, diolamine, glycine, lysine, magnesium, meglumine, olamine, potassium, sodium, tromethamine and zinc salts.

Hemisalts of acids and bases may also be formed, for example, hemisulphate and hemicalcium salts.

For a review on suitable salts, see "Handbook of Pharmaceutical Salts: Properties, Selection, and Use" by Stahl and Wermuth (Wiley-VCH, Weinheim, Germany, 2002).

A salt may be readily prepared by mixing together solutions of compounds of the present invention and the desired acid or base, as appropriate. The salt may precipitate from solution and be collected by filtration or may be recovered by evaporation of the solvent. The degree of ionization in the salt may vary from completely ionized to almost non-ionized.

The compounds of the present invention may be administered as prodrugs. Thus, certain derivatives which may have little or no pharmacological activity themselves can, when administered into or onto the body, be converted into compounds of the present invention having the desired activity, for example, by hydrolytic cleavage. Such derivatives are referred to as 'prodrugs'. Further information on the use of prodrugs may be found in 'Pro-drugs as Novel Delivery Systems, Vol. 14, ACS Symposium Series (T Higuchi and W Stella) and 'Bioreversible Carriers in Drug Design', Pergamon Press, 1987 (ed. E B Roche, American Pharmaceutical Association).

Prodrugs can, for example, be produced by replacing appropriate functionalities present in the compounds of the present invention with certain moieties known to those skilled in the art as 'pro-moieties' as described, for example, in "Design of Prodrugs" by H Bundgaard (Elsevier, 1985).

Some examples of such prodrugs include:

(i) where the compound contains an alcohol functionality (-OH), an ether thereof, for example, replacement of the hydrogen with (C_1-C_6)alkanoyloxymethyl; and

(ii) where the compound contains a secondary amino functionality , an amide thereof, for example, replacement of hydrogen with (C_1-C_{10})alkanoyl.

All isomers, such as stereoisomers, geometric (*cis*/*trans* or Z/E) isomers and tautomeric forms of the compounds or salts are included in the scope of the present invention, including compounds or salts having more than one type of isomerism, and mixtures of one or more thereof.

Also included are acid addition or base salts wherein the counterion is optically active, for example, D-lactate or L-lysine, or racemic, for example, DL-tartrate or DL-arginine.

Isomers may be separated by conventional techniques well known to those skilled in the art.

The present invention includes isotopically-labelled compounds of the invention wherein one or more atoms are replaced by atoms having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number usually found in nature.

Isotopically-labeled compounds of the invention can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the accompanying Examples and Preparations using an appropriate isotopically-labelled reagent in place of the non-labeled reagent previously employed.

For the treatment of the conditions referred to below, the compounds of the present invention can be administered. Salts of the compounds of the present invention could also be used.

C. Compositions

Compounds or salts of the present invention could be part of a composition. Compositions can also include one or more compounds or salts of the present invention. The composition can also include an enantiomeric excess of one or more compounds of the present invention. Other pharmacologically active substances and carriers can be included in the composition.

One embodiment is a composition comprising a compound of Formula I or II, or a salt thereof. Another embodiment is a composition comprising a compound of Formula I or II, or a salt thereof and a carrier.

For example, the carrier can be an excipient. The choice of excipient will to a large extent depend on factors such as the particular mode of administration, the effect of the excipient on solubility and stability, and the nature of the dosage form.

The composition can be a solid, a liquid, or both, and may be formulated with the compound as a unit-dose composition, for example, a tablet, which can contain from 0.05% to 95% by weight of the active compounds. Compounds or salts of the present invention may be coupled with suitable polymers as targetable drug carriers.

D. Methods

In some embodiments, compounds of the invention can be used in methods that modulate activity of one or more chemokine receptors. Accordingly, the invention includes methods comprising contacting a chemokine receptor with a compound of Formula I or II, or a salt thereof. In some embodiments, the chemokine receptor is CCR2. In other embodiments, the chemokine receptor is CCR5. In other embodiments, the invention includes methods of modulating a chemokine receptor by contacting the receptor with any one or more of the compounds or compositions described herein. In some embodiments, compounds of the present invention can act as inhibitors or antagonist of chemokine receptors. In further embodiments, the compounds of

the invention can be used to modulate activity of a chemokine receptor in an individual in need of modulation of the receptor by administering a modulating amount of a compound of Formula I or II, or a slat thereof.

Chemokine receptors to which the present compounds bind and/or modulate include any chemokine receptor. In some embodiments, the chemokine receptor belongs to the CC family of chemokine receptors including, for example, CCR1, CCR2, CCR3, CCR4, CCR5, CCR6, CCR7, CCR8, and CCR10. In some embodiments, the chemokine receptor is CCR2 or CCR5. In other embodiments, the chemokine receptor is CCR2. In some embodiments, the chemokine receptor is CCR5. In some embodiments, the chemokine receptor binds and/or modulates both CCR2 and CCR5.

The compounds of the invention can be selective, that is a compound binds to or inhibits a chemokine receptor with greater affinity or potency, respectively, compared to at least one other chemokine receptor.

Compounds of the invention can be dual inhibitors or binders of CCR2 and CCR5, meaning that the compounds of the invention can bind to or inhibit both CCR2 and CCR5 with greater affinity or potency, respectively, than for other chemokine receptors such as CCR1, CCR3, CCR4, CCR6, CCR7, CCR8, and CCR10. In some embodiments, the compounds of the invention have binding or inhibition selectivity for CCR2 and CCR5 over any other chemokine receptor. Binding affinity and inhibitor potency can be measured according to routine methods in the art, such as according to the assays provided herein.

The present invention further provides methods of treating a chemokine receptor-associated disease or disorder in an individual (e.g., patient) by administering to the individual in need of such treatment a therapeutically effective amount or dose of a compound of the present invention or a pharmaceutical composition thereof. In other embodiments, the invention includes method of treating a condition mediated by chemokine receptor activity in a subject comprising administering to the subject a compound of Formula I or II, or a pharmaceutically acceptable salt thereof.

A chemokine receptor-associated disease or condition can include any disease, disorder or condition that is directly or indirectly linked to expression or activity of the chemokine receptor. A chemokine receptor-associated disease or condition can also include any disease, disorder or condition that can be prevented, ameliorated, or cured by modulating chemokine receptor activity. A chemokine receptor-associated disease can further include any disease, disorder or condition that is characterized by binding of an infectious agent such as a virus or viral protein with a chemokine receptor. In some embodiments, the chemokine receptor-associated disease is a CCR5-associated disease such as HIV infection.

Examples of a condition mediated by chemokine receptor include inflammation, inflammatory diseases, immune disorders, pains, cancers, or viral infections.

Examples of a condition mediated by chemokine receptor include inflammation, inflammatory diseases, immune disorders, pains, cancers, or viral infections.

Examples of inflammatory diseases include diseases believed to have an inflammatory component such as asthma, seasonal and perennial allergic rhinitis, sinusitis, conjunctivitis, age-related macular degeneration, food allergy, scombroid poisoning, psoriasis, undifferentiated spondyloarthropy, juvenile-onset spondyloarthritis, gout, urticaria, pruritus, eczema, inflammatory bowel disease, thrombotic disease, otitis media, fibrosis, liver fibrosis, liver cirrhosis, cardiac disease, Alzheimer's disease, sepsis, restenosis, atherosclerosis, multiple sclerosis, Crohn's disease, ulcerative colitis, irritable bowel syndrome, inflammatory bowel disease, hypersensitivity lung diseases, drug-induced pulmonary fibrosis, chronic obstructive pulmonary disease (COPD), arthritis, nephritis, ulcerative colitis, atopic dermatitis, stroke, acute nerve injury, sarcoidosis, hepatitis, endometriosis, neuropathic pain, hypersensitivity pneumonitis, eosinophilic pneumonias, delayed-type hypersensitivity, interstitial lung disease (ILD) (e.g., idiopathic pulmonary fibrosis, or ILD associated with rheumatoid arthritis, systemic lupus erythematosus, ankylosing spondylitis,

systemic sclerosis, Sjogren's syndrome, polymyositis or dermatomyositis, eye disorders (e.g., retinal neurodegeneration, choroidal neovascularization, etc.) and the like.

Example immune disorders include rheumatoid arthritis, psoriatic arthritis, systemic lupus erythematosus, myastenia gravis, juvenile onset diabetes; glomerulonephritis, autoimmune throiditis, organ transplant rejection including allograft rejection and graft-versus-host disease.

Examples of pain include nociceptive and neuropathic pain. The pain can be acute or chronic. Pain includes cutaneous pain, somatic pain, visceral pain, and phantom limb pain. Pain also includes fibromyalgia, rheumatoid arthritis pain, osteoarthritis pain, and pain associated with the other diseases and conditions detailed herein.

Example cancers include breast cancer, ovarian cancer, multiple myeloma and the like that are characterized by infiltration of macrophages (e.g., tumor associated macrophages, TAMs) into tumors or diseased tissues.

Example viral infections include influenza, avian influenza, herpes infection, HIV infection or AIDS.

Further inflammatory or immune diseases treatable by administration of a compound of the present invention include, for example, autoimmune nephritis, lupus nephritis, Goodpasture's syndrome nephritis and Wegeners granulomatosis nephritis, lupus erythematosus, Goodpasture's syndrome and Wegeners granulomatosis.

Examples of diabetic conditions include diabetes, insulin resistance, diabetic neuropathy, diabetic nephropathy, diabetic retinopathy, cataracts, hyperglycemia, hypercholesterolemia, hypertension, hyperinsulinemia, hyperlipidemia, atherosclerosis, tissue ischemia, diabetic cardiomyopathy, diabetic microangiopathy ,diabetic macroangiopathy and foot ulcers. Included in the treatment of diabetes is the prevention or attenuation of long term conditions such as neuropathy, nephropathy, retinopathy or cataracts.

In some embodiments, the condition to be treated is rheumatoid arthritis, atherosclerosis, lupus, multiple sclerosis, neuropathic pain, transplant rejection, diabetes, diabetic nephropathy, diabetic conditions, or obesity.

In some embodiments, the condition is rheumatoid arthritis.

In some embodiments, the condition is diabetes.

In some embodiments, the condition is diabetic nephropathy.

In some embodiments, the condition is liver fibrosis.

In some embodiments, the condition is osteoarthritis pain.

In some embodiments, the condition is breast cancer, ovarian cancer or multiple myeloma.

In some embodiments, the condition is HIV infection.

E. Dosage and Administration

Pharmaceutical Formulations and Dosage Forms

When employed as pharmaceuticals, the compounds of Formula I or II can be administered in the form of pharmaceutical compositions. These compositions can be prepared in a manner well known in the pharmaceutical art, and can be administered by a variety of routes depending upon whether local or systemic treatment is desired and upon the area to be treated. Administration can be topical (including ophthalmic and to mucous membranes including intranasal, vaginal and rectal delivery), pulmonary (e.g., by inhalation or insufflation of powders or aerosols, including by nebulizer; intratracheal, intranasal, epidermal and transdermal), oral or parenteral. Parenteral administration includes intravenous, intraarterial, subcutaneous, intraperitoneal intramuscular or injection or infusion; or intracranial, e.g., intrathecal or intraventricular, administration. Parenteral administration can be in the form of a single bolus dose, or can be, for example, by a continuous perfusion pump. Pharmaceutical compositions and formulations for topical administration can include transdermal patches, ointments, lotions, creams, gels, drops, suppositories, sprays, liquids and powders. Conventional pharmaceutical carriers, aqueous, powder or oily bases, thickeners and the like may be

necessary or desirable. Coated condoms, gloves and the like may also be useful.

This invention also includes pharmaceutical compositions which contain, as the active ingredient, one or more of the compounds of Formula I or II above in combination with one or more pharmaceutically acceptable carriers. In making the compositions of the invention, the active ingredient is typically mixed with an excipient, diluted by an excipient or enclosed within such a carrier in the form of, for example, a capsule, sachet, paper, or other container. When the excipient serves as a diluent, it can be a solid, semi-solid, or liquid material, which acts as a vehicle, carrier or medium for the active ingredient. Thus, the compositions can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium), ointments containing, for example, up to 10% by weight of the active compound, soft and hard gelatin capsules, suppositories, sterile injectable solutions, and sterile packaged powders.

In preparing a formulation, the active compound can be milled to provide the appropriate particle size prior to combining with the other ingredients. If the active compound is substantially insoluble, it can be milled to a particle size of less than 200 mesh. If the active compound is substantially water soluble, the particle size can be adjusted by milling to provide a substantially uniform distribution in the formulation, e.g. about 40 mesh.

Some examples of suitable excipients include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, water, syrup, and methyl cellulose. The formulations can additionally include: lubricating agents such as talc, magnesium stearate, and mineral oil; wetting agents; emulsifying and suspending agents; preserving agents such as methyl- and propylhydroxy-benzoates; sweetening agents; and flavoring agents. The compositions of the invention can be formulated so as to provide quick, sustained or delayed release of the active

ingredient after administration to the patient by employing procedures known in the art.

The compositions can be formulated in a unit dosage form, each dosage containing from about 5 to about 1000 mg (1 g), more usually about 100 to about 500 mg, of the active ingredient. The term "unit dosage forms" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient.

In some embodiments, the compounds or compositions of the invention contain from about 5 to about 50 mg of the active ingredient. One having ordinary skill in the art will appreciate that this embodies compounds or compositions containing from about 5 to about 10, from about 10 to about 15, from about 15 to about 20, from about 20 to about 25, from about 25 to about 30, from about 30 to about 35, from about 35 to about 40, from about 40 to about 45, or from about 45 to about 50 mg of the active ingredient. In another embodiment, the dose can be 35-45 mg.

In some embodiments, the compounds or compositions of the invention contain from about 50 to about 500 mg of the active ingredient. One having ordinary skill in the art will appreciate that this embodies compounds or compositions containing from about 50 to about 75, from about 75 to about 100, from about 100 to about 125, from about 125 to about 150, from about 150 to about 175, from about 175 to about 200, from about 200 to about 225, from about 225 to about 250, from about 250 to about 275, from about 275 to about 300, from about 300 to about 325, from about 325 to about 350, from about 350 to about 375, from about 375 to about 400, from about 400 to about 425, from about 425 to about 450, from about 450 to about 475, or from about 475 to about 500 mg of the active ingredient.

In some embodiments, the compounds or compositions of the invention contain from about 500 to about 1000 mg of the active ingredient. One having ordinary skill in the art will appreciate that this embodies compounds or

compositions containing from about 500 to about 550, from about 550 to about 600, from about 600 to about 650, from about 650 to about 700, from about 700 to about 750, from about 750 to about 800, from about 800 to about 850, from about 850 to about 900, from about 900 to about 950, or from about 950 to about 1000 mg of the active ingredient.

The active compound can be effective over a wide dosage range and is generally administered in a pharmaceutically effective amount. It will be understood, however, that the amount of the compound actually administered will usually be determined by a physician, according to the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual compound administered, the age, weight, and response of the individual patient, the severity of the patient's symptoms, and the like.

For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical excipient to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention. When referring to these preformulation compositions as homogeneous, the active ingredient is typically dispersed evenly throughout the composition so that the composition can be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation is then subdivided into unit dosage forms of the type described above containing from, for example, 0.1 to about 1000 mg of the active ingredient of the present invention.

The tablets or pills of the present invention can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permit the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric

acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol, and cellulose acetate.

The liquid forms in which the compounds and compositions of the present invention can be incorporated for administration orally or by injection include aqueous solutions, suitably flavored syrups, aqueous or oil suspensions, and flavored emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil, or peanut oil, as well as elixirs and similar pharmaceutical vehicles.

Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. The liquid or solid compositions may contain suitable pharmaceutically acceptable excipients as described supra. In some embodiments, the compositions are administered by the oral or nasal respiratory route for local or systemic effect. Compositions in can be nebulized by use of inert gases. Nebulized solutions may be breathed directly from the nebulizing device or the nebulizing device can be attached to a face masks tent, or intermittent positive pressure breathing machine. Solution, suspension, or powder compositions can be administered orally or nasally from devices which deliver the formulation in an appropriate manner.

The amount of compound or composition administered to a patient will vary depending upon what is being administered, the purpose of the administration, such as prophylaxis or therapy, the state of the patient, the manner of administration, and the like. In therapeutic applications, compositions can be administered to a patient already suffering from a disease in an amount sufficient to cure or at least partially arrest the symptoms of the disease and its complications. Effective doses will depend on the disease condition being treated as well as by the judgment of the attending clinician depending upon factors such as the severity of the disease, the age, weight and general condition of the patient, and the like.

The compositions administered to a patient can be in the form of pharmaceutical compositions described above. These compositions can be sterilized by conventional sterilization techniques, or may be sterile filtered.

Aqueous solutions can be packaged for use as is, or lyophilized, the lyophilized preparation being combined with a sterile aqueous carrier prior to administration. The pH of the compound preparations typically will be between 3 and 11, or from 5 to 9, or from 7 to 8. It will be understood that use of certain of the foregoing excipients, carriers, or stabilizers will result in the formation of pharmaceutical salts.

The therapeutic dosage of the compounds of the present invention can vary according to, for example, the particular use for which the treatment is made, the manner of administration of the compound, the health and condition of the patient, and the judgment of the prescribing physician. The proportion or concentration of a compound of the invention in a pharmaceutical composition can vary depending upon a number of factors including dosage, chemical characteristics (e.g., hydrophobicity), and the route of administration. For example, the compounds of the invention can be provided in an aqueous physiological buffer solution containing about 0.1 to about 10% w/v of the compound for parenteral adminstration. Some typical dose ranges are from about 1 µg/kg to about 1 g/kg of body weight per day. In some embodiments, the dose range is from about 0.01 mg/kg to about 100 mg/kg of body weight per day. The dosage is likely to depend on such variables as the type and extent of progression of the disease or disorder, the overall health status of the particular patient, the relative biological efficacy of the compound selected, formulation of the excipient, and its route of administration. Effective doses can be extrapolated from dose-response curves derived from *in vitro* or animal model test systems.

The compounds of the invention can also be formulated in combination with one or more additional active ingredients which can include any pharmaceutical agent such as antibodies, immune suppressants, anti-inflammatory agents, chemotherapeutics, lipid lowering agents, HDL elevating agents, insulin secretagogues or sensitizers, drugs used for the treatment of rheumatoid arthritis and the like.

Rheumatoid Arthritis (RA) Treatment Regimen

Rheumatoid arthritis (RA) patients, treated aggressively with disease modifying agents (methotrexate, antimalarials, gold, penicillamine, sulfasalazine, dapsone, leflunamide, or biologicals), can achieve varying degrees of disease control, including complete remissions. These clinical responses are associated with improvement in standardized scores of disease activity, specifically the ACR criteria which includes: pain, function, number of tender joints, number of swollen joints, patient global assessment, physician global assessment, laboratory measures of inflammation (CRP and ESR), and radiologic assessment of joint structural damage. Current disease-modifying drugs (DMARDs) require continued administration to maintain optimal benefit. Chronic dosing of these agents is associated with significant toxicity and host defense compromise. Additionally, patients often become refractory to a particular therapy and require an alternative regimen. For these reasons, a novel, effective therapy which allows withdrawal of standard DMARDs would be a clinically important advance.

Patients with significant response to anti-TNF therapies (infliximab, etanercept, adalimumab), anti- IL-1 therapy (kinaret) or other disease modifying anti-rheumatic drugs (DMARDs) including but not limited to methotrexate, cyclosporine, gold salts, antimalarials, penicillamine or leflunamide; who have achieved clinical remission of disease can be treated with a substance that inhibits expression and/or activity of CCR2 including, for example, nucleic acids (e.g., antisense or siRNA molecules), proteins (e.g., anti-CCR2 antibodies), small molecule inhibitors (e.g., the compounds disclosed herein and other chemokine receptor inhibitors known in the art).

In some embodiments, the substance that inhibits expression and/or activity of CCR2 is a small molecule CCR2 inhibitor (or antagonist). The CCR2 antagonist can be dosed orally q.d. or b.i.d at a dose not to exceed about 500 mgs a day. The patients can be withdrawn from or have a decrease in the dosage of their current therapy and would be maintained on treatment with the CCR2 antagonist. Treating patients with a combination of CCR2 antagonist and their current therapy can be carried out for, for example, about one to about two

days, before discontinuing or dose reducing the DMARD and continuing on CCR2 antagonist.

Advantages of substituting traditional DMARDS with CCR2 antagonists are numerous. Traditional DMARDs have serious cumulative dose-limiting side effects, the most common being damage to the liver, as well as immunosuppressive actions. CCR2 antagonism is expected to have an improved long-term safety profile and will not have similar immunosuppressive liabilities associated with traditional DMARDs. Additionally, the half-life of the biologicals is typically days or weeks, which is an issue when dealing with adverse reactions. The half-life of an orally bioavailable CCR2 antagonist is expected to be on the order of hours so the risk of continued exposure to the drug after an adverse event is very minimal as compared to biological agents. Also, the current biologic agents (infliximab, etanercept, adalimumab, kinaret) are typically given either i.v. or s.c., requiring doctor's administration or patient self-injection. This leads to the possibility of infusion reaction or injection site reactions. These are avoidable using an orally administered CCR2 antagonist.

Diabetes and Insulin Resistance Treatment Regimen

Type 2 diabetes is one of the leading causes of morbidity and mortality in western societies. In the vast majority of patients, the disease is characterized by pancreatic beta-cell dysfunction accompanied by insulin resistance in the liver and in peripheral tissues. Based on the primary mechanisms that are associated with disease, two general classes of oral therapies are available to treat type 2 diabetes: insulin secretagogues (sulfonylureas such as glyburide) and insulin sensitizers (metformin and thiazolidinediones such as rosiglitazone). Combination therapy that addresses both mechanisms has been shown to manage the metabolic defects of this disease and in many instances can be shown to ameliorate the need for exogenous insulin administration. However, with time, insulin resistance often progresses, leading to the need for further insulin supplementation. In addition, a prediabetic state, referred to as the metabolic syndrome, has been demonstrated to be characterized by impaired

glucose tolerance, particularly in association with obesity. The majority of patients who develop type 2 diabetes begin by developing insulin resistance, with the hyperglycemia occurring when these patients can no longer sustain the degree of hyperinsulinemia necessary to prevent loss of glucose homeostasis. The onset of the insulin resistance component is highly predictive of disease onset and is associated with an increase in the risk of developing type 2 diabetes, hypertension and coronary heart disease.

One of the strongest correlates of impaired glucose tolerance and of the progression from an insulin resistant state to type 2 diabetes is the presence of central obesity. Most patients with type 2 diabetes are obese and obesity itself is associated with insulin resistance. It is clear that central adiposity is a major risk factor for the development of insulin resistance leading to type 2 diabetes, suggesting that signals from visceral fat contribute to the development of insulin resistant and progression to disease. In addition to the secreted protein factors, obesity induces a cellular inflammatory response in which bone-marrow derived macrophages accumulate in adipose depots, becoming adipose tissue macrophages. Adipose tissue macrophages accumulate in adipose tissue in proportion to measures of adiposity. Tissue infiltrating macrophages are a source of many of the inflammatory cytokines that have been demonstrated to induce insulin resistance in adipocytes.

Adipose tissue produces MCP-1 in proportion to adiposity, suggesting that its activity by signaling through CCR2 also might play an important role in the accumulation of macrophages in adipose tissue. It is unknown whether the MCP-1/CCR2 interaction is directly responsible for monocyte recruitment to adipose tissue, whether reduced recruitment of macrophages to adipose tissue in humans will directly lead to the reduced production of proinflammatory molecules and whether the proinflammatory molecule production is directly linked to insulin resistance.

Patients who demonstrate insulin resistance, either prediabetic (normoglycemic) or diabetic (hyperglycemic), could be treated with a substance that inhibits the expression and/or activity of CCR2 including, for example,

nucleic acids (e.g., antisense or siRNA molecules), proteins (e.g., anti-CCR2 antibodies), small molecule inhibitors (e.g., the compounds disclosed herein and other chemokine receptor inhibitors known in the art). In some embodiments, the substance that inhibits expression and/or activity of CCR2 is a small molecule CCR2 inhibitor (or antagonist). The CCR2 antagonist can be dosed orally q.d. or b.i.d. The patients can be withdrawn from or have a decrease in the dosage of their current therapy and would be maintained on treatment with the CCR2 antagonist. Alternately CCR2 antagonist treatment may be used to supplement their current therapy to enhance its effectiveness or to prevent progression to further insulin dependence.

Advantages of substituting or supplementing traditional agents with CCR2 antagonists are numerous. Such agents may be useful, for example, to preclude progression from a prediabetic, insulin resistant state to a diabetic state. Such agents may reduce or replace the need for the use of insulin sensitizers, with their attendant toxicities. Such agents may also reduce the need for, or prolong the period until, exogenous insulin supplementation is required.

Atherosclerosis Treatment Regimen

Atherosclerosis is a condition characterized by the deposition of fatty substances in arterial walls. Plaque encompasses such deposits of fatty substances, cholesterol, cellular waste products, calcium and other substances that build up in the inner lining of an artery. Plaques can grow large enough to significantly reduce the blood's flow through an artery. However, more significant damage occurs when the plaque becomes unstable and ruptures. Plaques that rupture cause blood clots to form that can block blood flow or break off and travel to other parts of the body. If the clot blocks a blood vessel that feeds the heart, it causes a heart attack. If it blocks a blood vessel that feeds the brain, it causes a stroke. Atherosclerosis is a slow, complex disease that typically starts in childhood and often progresses as people grow older.

A high level of cholesterol in the blood is a major risk factor for coronary heart disease. Based on cholesterol as a primary composition of plaque, the

advance of plaque formation has been managed by the reduction of circulating cholesterol or by elevation of cholesterol-carrying high density lipoproteins (HDL). Circulating cholesterol can be reduced, for example, by inhibiting its synthesis in the liver using or by reducing update from food. Such medicaments that act through these mechanism may include medicines that are used to lower high cholesterol levels: bile acid absorbers, lipoprotein synthesis inhibitors, cholesterol synthesis inhibitors and fibric acid derivatives. Circulating HDL can additionally be elevated by administration of, for example, probuchol or high doses of niacin. Therapy that addresses multiple mechanisms has been shown to slow disease progression and progression to plaque rupture.

Atherosclerosis is typically accompanied by a cellular inflammatory response in which bone-marrow derived macrophages accumulate in fatty streaks along the vessel wall, becoming foam cells. Foam cells are a source of many of the inflammatory cytokines that have been demonstrated to induce plaque progression and of the enzymes that can promote plaque destabilization. Atherosclerotic tissue also produces MCP-1, suggesting that its activity by signaling through CCR2 also might play an important role in the accumulation of macrophages as foam cells in plaques. CCR2-/- mice have been demonstrated to have significantly reduced macrophages in fatty streaks generated as a result of high fat diet or genetic alteration in lipid metabolism.

Patients who demonstrate high circulating cholesterol, low HDL, or elevated circulating CRP or present with vessel wall plaque by imaging, or any other evidence of the presence of atherosclerosis could be treated with a substance that inhibits the expression and/or activity of CCR2 including, for example, nucleic acids (e.g., antisense or siRNA molecules), proteins (e.g., anti-CCR2 antibodies), small molecule inhibitors (e.g., the compounds disclosed herein and other chemokine receptor inhibitors known in the art). In some embodiments, the substance that inhibits expression and/or activity of CCR2 is a small molecule CCR2 inhibitor (or antagonist) such as a compound of the invention. The CCR2 antagonist can be dosed orally q.d. or b.i.d at a dose not to exceed about 500 mgs a day. The patients can be withdrawn from or have a

decrease in the dosage of their current therapy and would be maintained on treatment with the CCR2 antagonist. Alternately CCR2 antagonist treatment may be used to supplement their current therapy to enhance its effectiveness in, for example, preventing plaque progression, stabilizing plaque that has already formed or inducing plaque regression.

Advantages of substituting or supplementing traditional agents with CCR2 antagonists are numerous. Such agents may be useful, for example, to preclude progression of the plaque to a stage of instability with its associated risk of plaque rupture. Such agents may reduce or replace the need for the use of cholesterol modifying drugs or HDL elevating drugs, with their attendant toxicities including, but not limited to, flushing, liver damage and muscle damage such as myopathy. Such agents may also reduce the need for, or prolong the period until, surgery is required to open the vessel wall or until use of anticoagulants is required to limit damage due to potential plaque rupture.

Labeled Compounds and Assay Methods

Another aspect of the present invention relates to fluorescent dye, spin lable, heavy metal or radio-labeled compounds of Formula I that would be useful not only in imaging but also in assays, both *in vitro* and *in vivo*, for localizing and quantitating the chemokine receptor in tissue samples, including human, and for identifying chemokine receptor ligands by inhibition binding of a labeled compound. Accordingly, the present invention includes chemokine receptor assays that contain such labeled compounds.

The present invention further includes isotopically-labeled compounds of Formula I. An "isotopically" or "radio-labeled" compound is a compound of the invention where one or more atoms are replaced or substituted by an atom having an atomic mass or mass number different from the atomic mass or mass number typically found in nature (i.e., naturally occurring). Suitable radionuclides that may be incorporated in compounds of the present invention include but are not limited to ^{2}H, ^{3}H (also written as T for tritium), ^{11}C, ^{13}C, ^{14}C, ^{13}N, ^{15}N, ^{15}O, ^{17}O, ^{18}O, ^{18}F, ^{35}S, ^{36}Cl, ^{82}Br, ^{75}Br, ^{76}Br, ^{77}Br, ^{123}I, ^{124}I, ^{125}I and ^{131}I. The radionuclide

that is incorporated in the instant radio-labeled compounds will depend on the specific application of that radio-labeled compound. For example, for *in vitro* chemokine receptor labeling and competition assays, compounds that incorporate ^{3}H, ^{14}C, ^{82}Br, ^{125}I , ^{131}I, or ^{35}S will generally be most useful. For radio-imaging applications ^{11}C, ^{18}F, ^{125}I, ^{123}I, ^{124}I, ^{131}I, ^{75}Br, ^{76}Br or ^{77}Br will generally be most useful.

It is understood that a "radio-labeled " or "labeled compound" is a compound that has incorporated at least one radionuclide. In some embodiments the radionuclide is selected from the group consisting of ^{3}H, ^{14}C, ^{125}I , ^{35}S and ^{82}Br.

Synthetic methods for incorporating radio-isotopes into organic compounds are applicable to compounds of the invention and are well known in the art. A radio-labeled compound of the invention can be used in a screening assay to identify/evaluate compounds. In general terms, a newly synthesized or identified compound (i.e., test compound) can be evaluated for its ability to reduce binding of the radio-labeled compound of the invention to the chemokine receptor. Accordingly, the ability of a test compound to compete with the radio-labeled compound for binding to the chemokine receptor directly correlates to its binding affinity.

Kits

The present invention also includes pharmaceutical kits useful, for example, in the treatment or prevention of chemokine-associated diseases which include one or more containers containing a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula I. Such kits can further include, if desired, one or more of various conventional pharmaceutical kit components, such as, for example, containers with one or more pharmaceutically acceptable carriers, additional containers, etc., as will be readily apparent to those skilled in the art. Instructions, either as inserts or as labels, indicating quantities of the components to be administered, guidelines for

administration, and/or guidelines for mixing the components, can also be included in the kit.

Combination

The compounds or salts of the invention, or mixtures thereof, may be administered in combination with one or more other therapeutic agents, such as a drug. The compound of the present invention or salt thereof may be administered at the same time or different time as one or more other therapeutic agents.

For example, "in combination" includes: simultaneous administration of a combination of compound or salt of the invention and a therapeutic agent to a subject, when such components are formulated together into a single dosage form which releases said components at substantially the same time to said subject; substantially simultaneous administration of a combination of compound or salt of the invention and a therapeutic agent to a subject in need of treatment, when such components are formulated apart from each other into separate dosage forms which are taken at substantially the same time by said subject, whereupon said components are released at substantially the same time to said subject; sequential administration of a combination of compound or salt of the invention and a therapeutic agent to a subject, when such components are formulated apart from each other into separate dosage forms which are taken at consecutive times by said subject with a significant time interval between each administration, whereupon said components are released at substantially different times to said subject; and sequential administration of such combination of compound or salt of the invention and a therapeutic agent to a subject, when such components are formulated together into a single dosage form which releases said components in a controlled manner whereupon they are concurrently, consecutively, and/or overlappingly administered at the same and/or different times by said subject, where each part may be administered by either the same or different route.

One or more additional pharmaceutical agents such as, for example, antibodies, anti-inflammatory agents, immunosuppressants, chemotherapeutics can be used in combination with the compounds of the present invention for treatment of chemokine receptor-associated diseases, disorders or conditions.

One or more additional pharmaceutical agents such as, for example, anti-viral agents, antibodies, anti-inflammatory agents, insulin secretagogues and sensitizers, serum lipid and lipid-carrier modulating agents, and/or immunosuppressants can be used in combination with the compounds of the present invention for treatment of chemokine receptor-associated diseases, disorders or conditions. The agents can be combined with the present compounds in a single or continuous dosage form, or the agents can be administered simultaneously or sequentially as separate dosage forms.

Suitable antiviral agents contemplated for use in combination with the compounds of the present invention can comprise nucleoside and nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors and other antiviral drugs.

Suitable antiviral agents contemplated for use in combination with the compounds of the present invention can comprise nucleoside and nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors, entry inhibitors, fusion inhibitors, maturation inhibitors, and other antiviral drugs.

Example suitable NRTIs include zidovudine (AZT); didanosine (ddI); zalcitabine (ddC); stavudine (d4T); lamivudine (3TC); abacavir (1592U89); adefovir dipivoxil [bis(POM)-PMEA]; lobucavir (BMS-180194); BCH-10652; emitricitabine [(-)-FTC]; beta-L-FD4 (also called beta-L-D4C and named beta-L-2', 3'-dicleoxy-5-fluoro-cytidene); DAPD, ((-)-beta-D-2,6,-diamino-purine dioxolane); and lodenosine (FddA).

Typical suitable NNRTIs include nevirapine (BI-RG-587); delaviradine (BHAP, U-90152); efavirenz (DMP-266); PNU-142721; AG-1549; MKC-442 (1-(ethoxy-methyl)-5-(1-methylethyl)-6-(phenylmethyl)-(2,4(1H,3H)-pyrimidi nedione); and (+)-calanolide A (NSC-675451) and B.

Typical suitable protease inhibitors include saquinavir (Ro 31-8959); ritonavir (ABT-538); indinavir (MK-639); nelfnavir (AG-1343); amprenavir (141W94); lasinavir (BMS-234475); DMP-450; BMS-2322623; ABT-378; and AG-1 549.

Other antiviral agents include hydroxyurea, ribavirin, IL-2, IL-12, pentafuside, enfuvirtide, C-34, the cyclotriazadisulfonamide CADA, PA-457 and Yissum Project No.11607.

In some embodiments, anti-inflammatory or analgesic agents contemplated for use in combination with the compounds of the present invention can comprise, for example, an opiate agonist, a lipoxygenase inhibitor such as an inhibitor of 5-lipoxygenase, a cyclooxygenase inhibitor such as a cyclooxygenase-2 inhibitor, an interleukin inhibitor such as an interleukin-1 inhibitor, a TNF inhibitor such as infliximab, etanercept, or adalimumab an NNMA antagonist, an inhibitor of nitric oxide or an inhibitor of the synthesis of nitric oxide, a non-steroidal antiinflammatory agent, or a cytokine-suppressing antiinflammatory agent, for example, such as acetaminophen, aspirin, codeine, fentanyl, ibuprofen, indomethacin, ketodolac, morphine, naproxen, phenacetin, piroxicam, a steroidal analgesic, sufentanyl, sunlindac, tenidap, and the like. Similarly, the instant compounds can be administered with a pain reliever; a potentiator such as caffeine, an H2-antagonist, simethicone, aluminum or magnesium hydroxide; a decongestant such as phenylephrine, phenylpropanolamine, pseudophedrine, oxymetazoline, ephinephrine, naphazoline, xylometazoline, propylhexedfine, or levo-desoxyephedrine; an antfitussive such as codeine, hydrocodone, caramiphen, carbetapentane, or dextramethorphan; a diuretic; and a sedating or non-sedating antihistamine.

In some embodiments, pharmaceutical agents contemplated for use in combination with the compounds of the present invention can comprise but are not limited to (a) VLA-4 antagonists such as those described in US 5,510,332, W095/15973, W096/01644, W096/06108, W096/20216, W096/229661, W096/31206, W096/4078, W097/030941, W097/022897 WO 98/426567 W098/53814, W098/53817, W098/538185, W098/54207, and W098/58902; (b)

steroids such as beclornethasone, methylpi-ednisolone, betarnethasone, prednisone, dexamethasone, and hydrocortisone; (c) immunosuppressants such as cyclosporin, tacrolimus, raparnycin and other FK506 type immunosuppressants; (d) antihistamines (HI-histamine antagonists) such as bromopheniramine, chlorpheniramine, dexchlorpheniramine, triprolidine, clemastine, diphenhydramine, diphenylpyraline, tripelennamine, hydroxyzine, methdilazine, promethazine, trimeprazine, azatadine, cyproheptadine, antazoline, pheniramine pyrilarnine, asternizole, terfenadine, loratadine, cetirizine, fexofenadine, desearboethoxyloratadine, and the like; (e) non-steroidal anti-asthmatics such as terbutaline, metaproterenol, fenoterol, isoethaiine, albuterol, bitolterol, pirbuterol, theophylline, cromolyn sodium, atropine, ipratropium bromide, leukotriene antagonists (e.g., zafirlukast, montelukast, pranlukast, iralukast, pobilukast, SKB-106,203), leukotriene biosynthesis inhibitors (e.g., zileuton, BAY-1005); (f) nonsteroidal antiinflammatory agents (NSAIDs) such as propionic acid derivatives (e.g., alminoprofen, benoxaprofen, bucloxic acid, carprofen, fenbufen, fenoprofen, fluprofen, flurbiprofen, ibuprofen, indoprofen, ketoprofen, miroprofen, naproxen, oxaprozin, pirprofen, pranoprofen, suprofen, tiaprofenic acid, and tioxaprofen), acetic acid derivatives (e.g., indomethacin, acernetacin, alclofenac, clidanac, diclofenac, fenclofenac, fenclozic acid, fentiazac, furofenac, ibufenac, isoxepac, oxpinac, sulindac, tiopinac, tolmetin, zidometacin, and zomepirac), fenarnic acid derivatives (flufenarnic acid, meclofenamic acid, rnefenamic acid, niflumic acid and tolfenarnic acid), biphenylcarboxylic acid derivatives (diflunisal and flufenisal), oxicarns (isoxicarn, piroxicam, sudoxicam and tenoxican), salicylates (acetyl salicylic acid, sulfasalazine) and the pyrazolones (apazone, bezpiperylon, feprazone, mofebutazone, oxyphenbutazone, phenylbutazone); (g) cyclooxygenase-2 (COX-2) inhibitors; (h) inhibitors of phosphodiesterase type IV (PDE-IV); (i) other antagonists of the chemokine receptors, especially CXCR-4, CCR1, CCR2, CCR3 and CCR5 ; (j) cholesterol lowering agents such as HMG-CoA reductase inhibitors (lovastatin, sirrivastatin and pravastatin, fluvastatin, atorvastatin, and other statins), sequestrants (cholestyramine and colestipol), nicotinic acid,

fenofibric acid derivatives (gemfibrozil, clofibrat, fenofibrate and benzafibrate), and probucol; (k) anti-inflammatory biologic agents such as anti-TNF therapies, anti-IL-1 receptor, CTLA-4Ig, anti-CD20, and anti-VLA4 antibodies; (l) anti-diabetic agents such as insulin, sulfonylureas, biguanides (metformin), U.-glucosidase inhibitors (acarbose) and orlitazones (troglitazone and pioglitazone); (m) preparations of interferon beta (interferon beta- Io., interferon beta-1 P); (n) other compounds such as aminosalicylic acids, antimetabolites such as azathioprine and 6-mercaptopurine, and cytotoxic cancer chemotherapeutic agents. The weight ratio of the compound of the compound of the present invention to the second active ingredient may be varied and will depend upon the effective dose of each ingredient. .

For example, a CCR2 and/or CCR5 antagonist can be used in combination with an anti-inflammatory pharmaceutical agent in the treatment of inflammation, metabolic disease, autoimmune disease, pain, cancer or viral infection to improve the treatment response as compared to the response to the therapeutic agent alone, without exacerbation of its toxic effects. Additive or synergistic effects are desirable outcomes of combining a CCR2 and/or CCR5 antagonist of the present invention with an additional agent. Furthermore, resistance of cancer cells to agents such as dexamethasone can be reversible upon treatment with a CCR2 and/or CCR5 antagonist of the present invention.

F. Use in the Preparation of a Composition or Medicament

In one embodiment, the present invention comprises methods for the preparation of a composition or medicament comprising the compounds or salts of the present invention for use in treating condition mediated by chemokine receptors.

In another embodiment, the invention comprises the use of one or more compounds or salts of the present invention in the preparation of a composition or a medicament for inflammation, inflammatory disease, immune disorder, pain, cancer, or viral infection.

The present invention also includes the use of one or more compounds or salts of the present invention for preparation of a composition or a medicament for treating one or more conditions detailed in the Methods section.

G. Schemes

The compounds of the present invention may be prepared using the methods illustrated in the general synthetic schemes and experimental procedures detailed below. The reactions of the synthetic methods herein are carried out in suitable solvents which may be readily selected by one skilled in the art of organic synthesis, said suitable solvents generally being any solvent which is substantially nonreactive with the starting materials (reactants), the intermediates, or products at the temperatures at which the reactions are carried out. A given reaction may be carried out in one solvent or a mixture of more than one solvent. Depending on the particular reaction step, suitable solvents for a particular reaction step may be selected.

Preparation of compounds of the invention can involve the protection and deprotection of various chemical groups. The need for protection and deprotection, and the selection of appropriate protecting groups can be readily determined by one skilled in the art. The chemistry of protecting groups can be found, for example, in T.W. Greene and P.G.M. Wuts, *Protective Groups in Organic Synthesis*, 3rd. Ed., Wiley & Sons, Inc., New York (1999), which is incorporated herein by reference in its entirety.

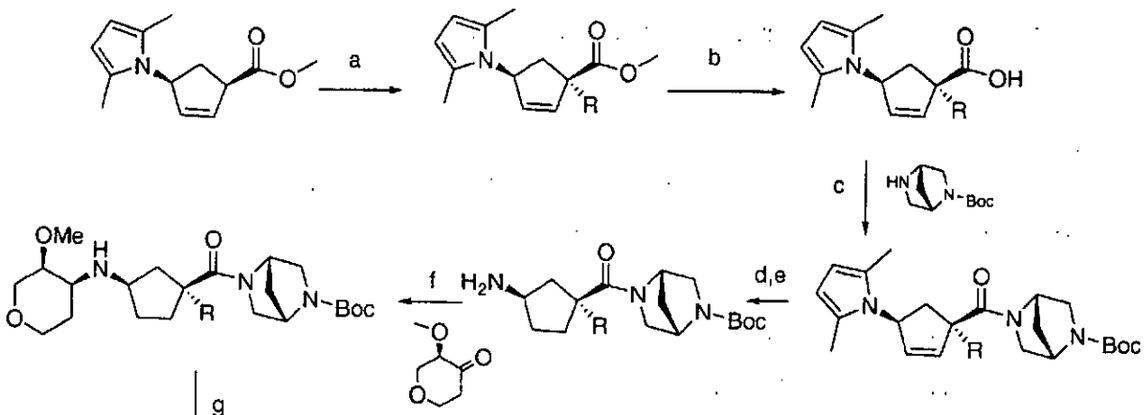
Reactions can be monitored according to any suitable method known in the art. For example, product formation can be monitored by spectroscopic means, such as nuclear magnetic resonance spectroscopy (*e.g.*, ^{1}H or ^{13}C) infrared spectroscopy, spectrophotometry (*e.g.*, UV-visible), or mass spectrometry, or by chromatography such as high performance liquid chromatography (HPLC) or thin layer chromatography.

The starting materials used herein are either commercially available or may be prepared by routine synthetic methods.

The general synthetic schemes are presented for purposes of illustration and are not intended to be limiting.

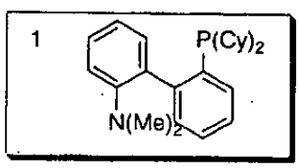
Scheme 1 Preparation of Examples 1- 23

Scheme1

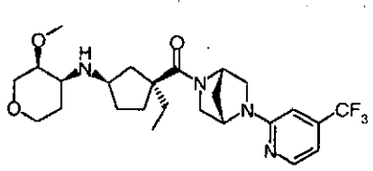


a) LDA or NaHMDS, R-X, THF; b) 2.5N NaOH, MeOH; c) 2.2.1-Boc, DMF, DIPEA, Bop; d) H_2NOH^*HCl, MeOH, $NH_2OH(aq)$; e) 5% Pd/C, MeOH, 50 psi H_2; f) pyranone, DCM, $Na(OAc)_3BH$; g) 4N HCl/1,4-dioxane; h) cond a or cond b or cond c or cond d

cond a = Ar-X, DMSO, Et_3N, 120 °C
cond b = Ar-X, Cs_2CO_3, XantPhos, $Pd_2(dba)_3$, dioxane, DMSO
cond c = Ar-X, 1,4-dioxane, Et_3N, 100 °C
cond d = Ar-X, NaOtBu, catalyst 1, $Pd_2(dba)_3$, dioxane, DMSO

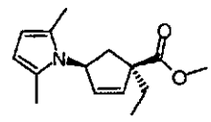


Example 1



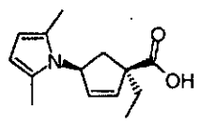
1,5-anhydro-2,3-dideoxy-3-{[(1R,3S)-3-ethyl-3-({(1S,4S)-5-[4-(trifluoromethyl)pyridin-2-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methyl-D-erythro-pentitol

Step 1: Preparation of methyl (1R,4S)-4-(2,5-dimethyl-1H-pyrrol-1-yl)-1-ethylcyclopent-2-ene-1-carboxylate



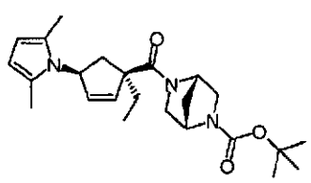
A -40ºC solution of 2M (in THF/ethylbenzene/heptane) LDA (68ml, 138mmol) in tetrahydrofuran (120ml) was treated with methyl (1R,4S)-4-(2,5-dimethyl-1H-pyrrol-1-yl)cyclopent-2-ene-1-carboxylate (14.02g, 63.9mmol) while keeping the temperature less than -33ºC. The cold reaction was stirred for 40 minutes and then a solution of ethyl iodide (13.63g, 87.4mmol) in tetrahydrofuran (5ml) was added slowly while keeping the temperature less than -33ºC. The reaction was stirred with the cold bath in place for four hours and allowed to slowly warm. The reaction was poured into NH4Cl soln (300ml), then extracted with ethyl acetate (2x200ml), washed with brine dried over $MgSO_4$, and concentrated under reduced pressure. The resulting brown oil was passed through acolumn of silica gel with10% ethyl acetate/hexanes to give methyl (1R,4S)-4-(2,5-dimethyl-1H-pyrrol-1-yl)-1-ethylcyclopent-2-ene-1-carboxylate as a brown oil (12.96g, 82%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 5.98-5.96 (1H), 5.93-5.91 (1H), 5.73 (2H), 5.30-5.24 (1H), 3.71 (3H), 2.45-2.34 (2H), 2.19 (6H), 1.79-1.73 (2H), 0.91-0.87 (3H).

Step 2: Preparation of (1R,4S)-4-(2,5-dimethyl-1H-pyrrol-1-yl)-1-ethylcyclopent-2-ene-1-carboxylic acid



A solution of methyl (1R,4S)-4-(2,5-dimethyl-1H-pyrrol-1-yl)-1-ethylcyclopent-2-ene-1-carboxylate (12.94g, 52.3mmol) in methanol (100ml) was treated with 2.5N NaOH (30ml, 75.0mmol) and stirred at room temperature. After 15 hours more 2.5N NaOH (10ml, 25.0mmol) was added and the reaction was stirred for an additional four days. The methanol was removed under reduced pressure and the residue partitioned between diethyl ether and water. The layers were separated and the aqueous was acidified with 4N HCl, extracted twice with ethyl acetate, washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure to give (1R,4S)-4-(2,5-dimethyl-1H-pyrrol-1-yl)-1-ethylcyclopent-2-ene-1-carboxylic acid as a brown oil (11.83g, 97%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 5.98-5.96 (2H), 5.73 (2H), 5.30-5.26 (1H), 2.47-2.35 (2H), 2.20 (6H), 1.82-1.77 (2H), 0.96-0.92 (3H).

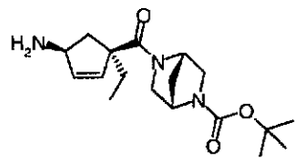
Step 3: Preparation of tert-butyl (1S,4S)-5-{[(1R,4S)-4-(2,5-dimethyl-1H-pyrrol-1-yl)-1-ethylcyclopent-2-en-1-yl]carbonyl}-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate



BOP= benzotriazol-1-yloxytris(dimethylamino) phosphoniumhexafluorophosphate

A solution of (1R,4S)-4-(2,5-dimethyl-1H-pyrrol-1-yl)-1-ethylcyclopent-2-ene-1-carboxylic acid (6.59g, 28.2mmol) in DMF (40ml) was treated with N,N-diisopropylethylamine (14.7ml, 84.4mmol) and BOP (14.51g, 32.8mmol) and stirred under nitrogen at room temperature for 20 minutes. A solution of (1S,4S)-2-BOC-2,5-diazabicyclo[2.2.1]heptane (5.66g,28.5mmol) in DMF (5ml) was added and the reaction was stirred for 24 hours. The reaction was diluted with ethyl acetate (100ml) and washed with 60% saturated $NaHCO_3$ (125ml). The aqueous layer was extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure to give a brown oil (21.25g). The oil was passed through a column of silica gel with 50% ethyl acetate/hexanes to give tert-butyl (1S,4S)-5-{[(1R,4S)-4-(2,5-dimethyl-1H-pyrrol-1-yl)-1-ethylcyclopent-2-en-1-yl]carbonyl}-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate as a white foam (8.14g, 70%). ^1H NMR (400 MHz, $CDCl_3$) δ ppm 6.24-6.17 (1H), 5.90-5.86 (1H), 5.73-5.68 (2H), 5.34-5.22 (1H), 5.02-4.41 (2H), 3.71-3.24 (4H), 2.61-2.39 (1H), 2.27-2.16 (7H), 1.89-1.59 (4H), 1.49-1.32 (9H), 0.95-0.85 (3H).

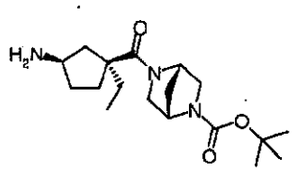
Step 4: Preparation of tert-butyl (1S,4S)-5-{[(1R,4S)-4-amino-1-ethylcyclopent-2-en-1-yl]carbonyl}-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate



A solution of tert-butyl (1S,4S)-5-{[(1R,4S)-4-(2,5-dimethyl-1H-pyrrol-1-yl)-1-ethylcyclopent-2-en-1-yl]carbonyl}-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (2.61g, 6.3mmol) in methanol (40ml) and water (10ml) was treated with hydroxylamine hydrochloride (2.73g, 39.1mmol) and 50 weight% solution of hydroxylamine (2.4ml, 39.2mmol). The reaction was stirred under nitrogen and heated to 68ºC for 38.5 hours. The reaction was cooled to room temperature,

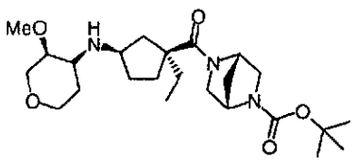
diluted with water, and made basic (pH~11) by the addition of 2.5N NaOH. The reaction mixture was extracted with ethyl acetate (3x100ml), washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure to give a crude mixture of tert-butyl (1S,4S)-5-{[(1R,4S)-4-amino-1-ethylcyclopent-2-en-1-yl]carbonyl}-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate as a yellow oil (2.68g, theoretical yield 2.12g) which was used without further purification in the next step.

Step 5: Preparation of tert-butyl (1S,4S)-5-{[(1S,3R)-3-amino-1-ethylcyclopentyl]carbonyl}-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate



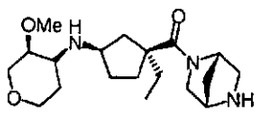
A mixture of tert-butyl (1S,4S)-5-{[(1R,4S)-4-amino-1-ethylcyclopent-2-en-1-yl]carbonyl}-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (2.12g, 6.32mmol) and 5% palladium on carbon in methanol (35ml) was stirred at room temperature under 48psi of hydrogen for 21 hours. The reaction was filtered through celite and the filter cake washed with methanol. The filtrate and washings were concentrated under reduced pressure to give tert-butyl (1S,4S)-5-{[(1S,3R)-3-amino-1-ethylcyclopentyl]carbonyl}-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate as a brown oil/foam (2.46g, theoretical yield 2.13g) which was used without further purification in the next step.

Step 6: Preparation of (1S,4S)-tert-butyl 5-((1S,3R)-1-ethyl-3-((3S,4R)-3-methoxy-tetrahydro-2H-pyran-4-ylamino)cyclopentanecarbonyl)-2,5-diaza-bicyclo[2.2.1]heptane-2-carboxylate



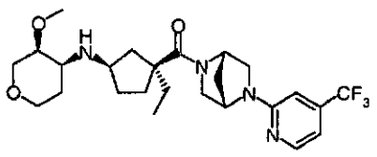
A 0ºC solution of tert-butyl (1S,4S)-5-{[(1S,3R)-3-amino-1-ethylcyclopentyl]carbonyl}-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (1.58g, 4.7mmol) in dichloromethane (25ml) was treated with sodium triacetoxyborohydride (2.36g, 11.1mmol) and 3R)-3-methoxytetrahydro-4H-pyran-4-one (0.76g, 7.6mmol). The reaction was stirred under nitrogen at 0ºC for 30 minutes then allowed to warm to room temperature and stirred for 15 hours. The reaction was treated with 2.5N NaOH (10mL) and stirred for 10 minutes. The reaction was diluted with water and the layers separated. The aqueous layer was extracted twice with ethyl acetate. The dichloromethane layer was concentrated under reduced pressure and partitioned between ethyl acetate and water. The organic layers were combined, washed with brine, dried over $MgSO_4$, concentrated under reduced pressure and purified with the Biotage (0-100% methanol/ethyl acetate, 15 column volumes) to give the desired product, 1,5-anhydro-3-{[(1R,3S)-3-{[(1S,4S)-5-(tert-butoxycarbonyl)-2,5-diazabicyclo[2.2.1]hept-2-yl]carbonyl}-3-ethylcyclopentyl]amino}-2,3-dideoxy-4-O-methyl-D-erythro-pentitol. . LC/MS (M+H) = 452.3124 exp, 452.3135 obs; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 4.94-4.41 (2H), 4.11-4.04 (1H), 3.97-3.91 (1H), 3.53-3.18 (11H), 2.83-2.75 (1H), 2.60-2.30 (1H), 2.03-1.55 (10H), 1.48-1.37 (11H), 0.85-0.78 (3H)

Step 7: Preparation of (1S,4S)-2,5-diaza-bicyclo[2.2.1]heptan-2-yl((1S,3R)-1-ethyl-3-((3S,4R)-3-methoxy-tetrahydro-2H-pyran-4-ylamino)cyclopentyl)methanone



To a solution of (1S,4S)-tert-butyl 5-((1S,3R)-1-ethyl-3-((3S,4R)-3-methoxy-tetrahydro-2H-pyran-4-ylamino)cyclopentanecarbonyl)-2,5-diaza-bicyclo[2.2.1]heptane-2-carboxylate(1.22g, 2.89mmol) in 1,4-dioxane (15ml) was added 4N HCl/1,4-dioxane (15ml). The reaction was stirred at room temperature for 18 hours. The liquid was decanted leaving a gummy solid which was dissolved in methanol and concentrated under reduced pressure. The residue was dissolved in methylene chloride and concentrated to give the product HCl salt of as a brown foam (1.23g, theoretical yield 1.03g) which was used in the next step without further purification.

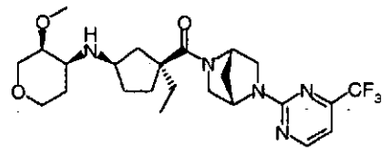
Step 8: Preparation of 1,5-anhydro-2,3-dideoxy-3-{[(1R,3S)-3-ethyl-3-({(1S,4S)-5-[4-(trifluoromethyl)pyridin-2-yl]-2,5-diazabicyclo[2.2.1]hept-2 yl}carbonyl)cyclopentyl]amino}-4-O-methyl-D-erythro-pentitol



To a solution of HCl salt of (1S,4S)-2,5-diaza-bicyclo[2.2.1]heptan-2-yl((1S,3R)-1-ethyl-3-((3S,4R)-3-methoxy-tetrahydro-2H-pyran-4-ylamino)cyclopentyl)methanone
(118mg, 0.33mmol) in DMSO (2ml) was added triethylamine (0.15ml, 1.08mmol) and the 2-chloro-4-(trifluoromethyl)pyridine (183mg, 1.01mmol). The reaction was heated to 120ºC for 15 hours. The reaction was cooled to room temperature,

and added to stirring ice water. The mixture was extracted with ethyl acetate(3x). The combined organics were washed with brine, dried over $MgSO_4$ concentrated under reduced pressure and purified with the Biotage (0-100% methanol/ethyl acetate, 15 column volumes) to give the product as a brown foam (40mg 26%). LC/MS (M+H) = 497.2739 exp, 497.2884 obs; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.25-8.24 (1H), 6.75-6.74 (1H), 6.51-6.45 (1H), 5.13-4.76 (2H), 4.10-4.03 (1H), 3.95-3.90 (1H), 3.72-3.16 (11H), 2.82-2.67 (1H), 2.58-2.36 (1H), 2.06-1.36 (12H), 0.86-0.67 (3H)

Example 2

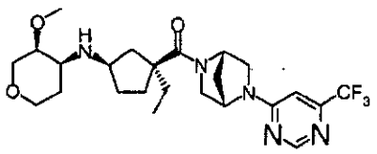


1,5-anhydro-2,3-dideoxy-3-{[(1R,3S)-3-ethyl-3-({(1S,4S)-5-[4-(trifluoromethyl)pyrimidin-2-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methyl-D-erythro-pentitol

Prepared as described in example 1 using 2-chloro-4-(trifluoromethyl)pyrimidine in place of 2-chloro-4-(trifluoromethyl)pyridine and modifying step 8 as follows. The HCl salt of amine (91mg, 0.25mmol) was placed in flask with 1,4-dioxane (3ml). Triethylamine (0.12ml, 0.86mmol) was added as well as 2-chloro-4-(trifluoromethyl)pyrimidine (148mg, 0.81mmol). DMSO (0.3ml) was added for solubility and the reaction was heated to 100ºC for 20 hours. The reaction was cooled to room temperature and concentrated under reduced pressure. The residue was partitioned between ethyl acetate and water. The aqueous layer was extracted with ethyl acetate and the combined organics were washed with brine, dried over $MgSO_4$, concentrated under reduced pressure and purified with the Biotage (0-100% methanol/ethyl acetate 15 column volumes) to give the product as a brown foam (43mg, 58%). LC/MS (M+H) = 498.2692 exp, 498.2799 obs; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.48-8.47 (1H), 6.80-6.78 (1H), 5.16-4.71 (2H),

4.09-4.00 (1H), 3.93-3.86 (1H), 3.70-3.51 (3H), 3.45-3.13 (8H), 2.85-2.66 (1H), 2.60-2.33 (1H), 2.06-1.35 (12H), 0.87-0.66 (3H)

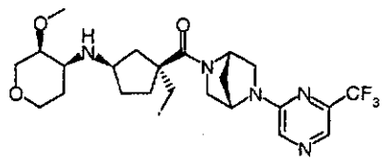
Example 3



1,5-anhydro-2,3-dideoxy-3-{[(1R,3S)-3-ethyl-3-({(1S,4S)-5-[6-(trifluoromethyl)pyrimidin-4-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methyl-D-erythro-pentitol

Prepared as described in example 1 using 4-chloro-6-(trifluoromethyl)pyrimidine in place of 2-chloro-4-(trifluoromethyl)pyridine and modifying step 8 as follows.The HCl salt of amine (227mg, 0.63mmol) was placed in a flask with 1,4-dioxane (3ml). To the stirred solution was added Xantphos (26mg, 0.045mmol), $Pd_2(dba)_3$ (39mg, 0.042mmol), Cs_2CO_3 (258mg, 0.79mmol), and 4-chloro-6-(trifluoromethyl)pyrimidine (261mg, 1.43mmol) dissolved in 1,4-dioxane (1ml). DMSO (0.3ml) was added for solubility and the reaction was heated to 100ºC for 15 hours. The reaction was allowed to cool to room temperature and filtered through celite. The filtrate was concentrated under reduced pressure and purified with the Biotage (0-100% methanol/ethyl acetate 15 column volumes) to give the product as a brown foam (93mg, 37%). LC/MS (M+H) = 498.2692 exp, 498.2853 obs; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.63 (1H), 6.76-6.42 (1H), 5.31-4.54 (2H), 4.12-4.03 (1H), 3.96-3.85 (1H), 3.72-3.15 (11H), 2.80-2.66 (1H), 2.57-2.35 (1H), 2.09-1.33 (12H), 0.88-0.64 (3H)

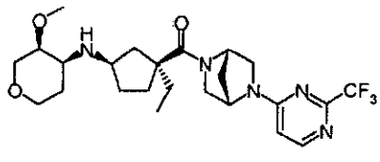
Example 4



1,5-anhydro-2,3-dideoxy-3-{[(1R,3S)-3-ethyl-3-({(1S,4S)-5-[6-(trifluoromethyl)pyrazin-2-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methyl-D-erythro-pentitol

Prepared as described in example 3 using 2-iodo-6-(trifluoromethyl)pyrazine in place of 4-chloro-6-(trifluoromethyl)pyrimidine in step 8. LC/MS (M+H) = 498.2692 exp, 498.2867 obs; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.16 (1H), 8.05-7.97 (1H), 5.18-4.78 (2H), 4.12-4.02 (1H), 3.99-3.88 (1H), 3.74-3.14 (11H), 2.82-2.66 (1H), 2.61-2.36 (1H), 2.07-1.36 (12H), 0.86-0.68 (3H)

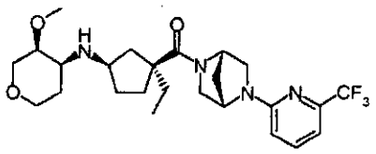
Example 5



1,5-anhydro-2,3-dideoxy-3-{[(1R,3S)-3-ethyl-3-({(1S,4S)-5-[2-(trifluoromethyl)pyrimidin-4-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methyl-D-erythro-pentitol

Prepared as described in example 3 using 4-chloro-2-(trifluoromethyl)pyrimidine in place of 4-chloro-6-(trifluoromethyl)pyrimidine in step 8. LC/MS (M+H) = 498.2692 exp, 498.2839 obs; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.24-8.22 (1H), 6.54-6.19 (1H), 5.31-4.50 (2H), 4.09-4.00 (1H), 3.90-3.85 (1H), 3.72-3.17 (11H), 2.78-2.62 (1H), 2.55-2.35 (1H), 2.04-1.32 (12H), 0.85-0.63 (3H)

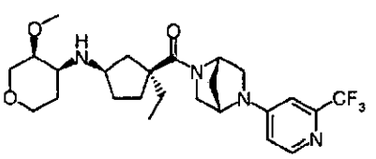
Example 6



1,5-anhydro-2,3-dideoxy-3-{[(1R,3S)-3-ethyl-3-({(1S,4S)-5-[6-(trifluoromethyl)pyridin-2-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methyl-D-erythro-pentitol

Prepared as described in example 1 using 2-chloro-6-(trifluoromethyl)pyridine in place of 4-chloro-6-(trifluoromethyl)pyrimidine in step 8. LC/MS (M+H) = 497.2739 exp, 497.2641 obs; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.56-7.52 (1H), 6.92-6.90 (1H), 6.52-6.41 (1H), 5.11-4.73 (2H), 4.08-4.03 (1H), 3.95-3.89 (1H), 3.73-3.13 (11H), 2.82-2.64 (1H), 2.58-2.35 (1H), 2.05-1.35 (12H), 0.85-0.66 (3H)

Example 7

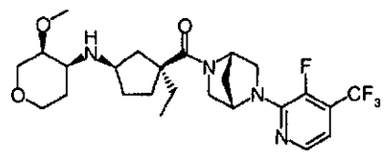


1,5-anhydro-2,3-dideoxy-3-{[(1R,3S)-3-ethyl-3-({(1S,4S)-5-[2-(trifluoromethyl)pyridin-4-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methyl-D-erythro-pentitol

Prepared as described in example 3 using using 4-iodo-2-(trifluoromethyl)pyridine in place of 4-chloro-6-(trifluoromethyl)pyrimidine in step

8. LC/MS (M+H) = 497.2739 exp, 497.2878 obs; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.30-8.28 (1H), 6.76-6.69 (1H), 6.52-6.44 (1H), 5.16-4.79 (1H), 4.54 (1H), 4.07-4.04 (1H), 3.93-3.90 (1H), 3.68-3.14 (11H), 2.81-2.64 (1H), 2.59-2.31 (1H), 2.08-1.35 (12H), 0.87-0.65 (3H)

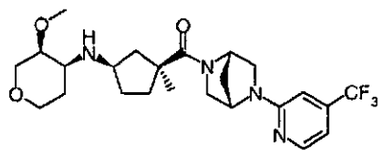
Example 8



1,5-anhydro-2,3-dideoxy-3-{[(1R,3S)-3-ethyl-3-({(1S,4S)-5-[3-fluoro-4-(trifluoromethyl)pyridin-2-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methyl-D-erythro-pentitol

Prepared as described in example 3 using 2-chloro-3-fluoro-4-(trifluoromethyl)pyridine in place of 4-chloro-6-(trifluoromethyl)pyrimidine in step 8. LC/MS (M+H) = 515.2645 exp, 515.2772 obs; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.00-7.99 (1H), 6.75-6.73 (1H), 5.09-4.69 (2H), 4.09-4.04 (1H), 3.96-3.90 (1H), 3.86-3.78 (1H), 3.69-3.53 (3H), 3.42-3.17 (7H), 2.81-2.68 (1H), 2.57-2.38 (1H), 2.04-1.36 (12H), 0.88-0.69 (3H)

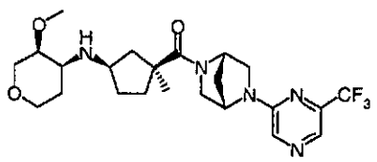
Example 9



1,5-anhydro-2,3-dideoxy-3-{[(1R,3S)-3-methyl-3-({(1S,4S)-5-[4-(trifluoromethyl)pyridin-2-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methyl-D-erythro-pentitol

Prepared as described in example 1 using methyl iodide in place of ethyl iodide in step 1. LC/MS (M+H) = 483.2583 exp, 483.2543 obs; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.25-8.24 (1H), 6.75-6.74 (1H), 6.51-6.45 (1H), 5.09-4.76 (2H), 4.09-4.03 (1H), 3.96-3.90 (1H), 3.70-3.23 (11H), 2.81-2.65 (1H), 2.53-2.27 (1H), 2.07-1.02 (13H); HRMS *m/z* 483.2543 (calcd for M+H, 483.2583).

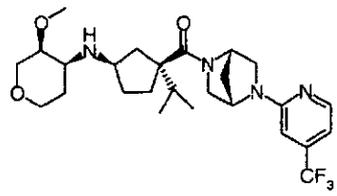
Example 10



1,5-anhydro-2,3-dideoxy-3-{[(1R,3S)-3-methyl-3-({(1S,4S)-5-[6-(trifluoromethyl)pyrazin-2-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methyl-D-erythro-pentitol

Prepared as described in example 3 using methyl iodide in place of ethyl iodide in step 1 and 2-iodo-6-(trifluoromethyl)pyrazine in place of 4-chloro-6-(trifluoromethyl)pyrimidine in step 8. LC/MS (M+H) = 483.2583 exp, 483.2543 obs; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.25-8.24 (1H), 6.75-6.74 (1H), 6.51-6.45 (1H), 5.09-4.76 (2H), 4.09-4.03 (1H), 3.96-3.90 (1H), 3.70-3.23 (11H), 2.81-2.65 (1H), 2.53-2.27 (1H), 2.07-1.02 (13H)

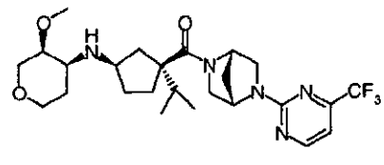
Example 11



1,5-anhydro-2,3-dideoxy-3-{[(1R,3S)-3-isopropyl-3-({(1S,4S)-5-[4-(trifluoromethyl)pyridin-2-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methyl-D-erythro-pentitol

Prepared as described in example 1 starting with (1S,4S)-4-(2,5-dimethyl-1H-pyrrol-1-yl)-1-isopropylcyclopent-2-ene-1-carboxylic acid and skipping steps 1 and 2. LC/MS (M+H) = 511.2896 exp, 511.3218 obs; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.23-8.22 (1H), 6.73-6.72 (1H), 6.49-6.44 (1H), 5.11-4.73 (2H), 4.06-4.03 (1H), 3.92-3.89 (1H), 3.67-3.52 (2H), 3.44-3.22 (8H), 3.12-3.03 (1H), 2.80-2.61 (1H), 2.51-2.40 (1H), 2.09-1.72 (6H), 1.68-1.42 (4H), 1.35-1.25 (1H), 0.92-0.75 (6H)

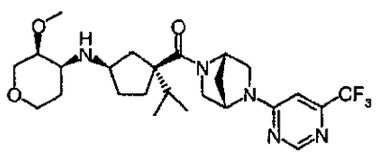
Example 12



1,5-anhydro-2,3-dideoxy-3-{[(1R,3S)-3-isopropyl-3-({(1S,4S)-5-[4-(trifluoromethyl)pyrimidin-2-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methyl-D-erythro-pentitol

Prepared as described in example 2 starting with (1S,4S)-4-(2,5-dimethyl-1H-pyrrol-1-yl)-1-isopropylcyclopent-2-ene-1-carboxylic acid and skipping steps 1 and 2. LC/MS (M+H) = 512.2849 exp, 512.2827 obs; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.45-8.44 (1H), 6.77-6.76 (1H), 5.09-4.71 (2H), 4.07-4.01 (1H), 3.92-3.87 (1H), 3.67-3.51 (3H), 3.42-3.23 (7H), 3.15-3.08 (1H), 2.83-2.76 (1H), 2.58-2.33 (2H), 2.11-1.56 (8H), 1.51-1.42 (1H), 1.38-1.30 (1H), 0.91-0.74 (6H)

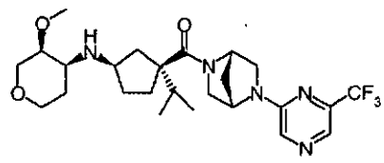
Example 13



1,5-anhydro-2,3-dideoxy-3-{[(1R,3S)-3-isopropyl-3-({(1S,4S)-5-[6-(trifluoromethyl)pyrimidin-4-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methyl-D-erythro-pentitol

Prepared as described in example 3 starting with (1S,4S)-4-(2,5-dimethyl-1H-pyrrol-1-yl)-1-isopropylcyclopent-2-ene-1-carboxylic acid and skipping steps 1 and 2. LC/MS (M+H) = 512.2849 exp, 512.3227 obs; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.61 (1H), 6.73-6.44 (1H), 5.25-4.52 (2H), 4.05-4.01 (1H), 3.91-3.86 (1H), 3.68-3.46 (2H), 3.38-3.17 (8H), 3.10-3.03 (1H), 2.76-2.63 (1H), 2.48-2.37 (1H), 2.07-1.39 (10H), 1.34-1.23 (1H), 0.90-0.74 (6H)

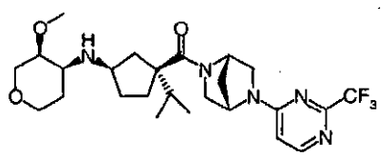
Example 14



1,5-anhydro-2,3-dideoxy-3-{[(1R,3S)-3-isopropyl-3-({(1S,4S)-5-[6-(trifluoromethyl)pyrazin-2-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methyl-D-erythro-pentitol

Prepared as described in example 3 starting with (1S,4S)-4-(2,5-dimethyl-1H-pyrrol-1-yl)-1-isopropylcyclopent-2-ene-1-carboxylic acid and skipping steps 1 and 2 and using 2-iodo-6-(trifluoromethyl)pyrazine in place of 4-chloro-6-(trifluoromethyl)pyrimidine in step 8. LC/MS (M+H) = 512.2849 exp, 512.3221 obs; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.12 (1H), 8.01-7.97 (1H), 5.14-4.75 (2H), 4.05-4.01 (1H), 3.90-3.87 (1H), 3.67-3.56 (2H), 3.44-3.20 (8H), 3.11-3.02 (1H), 2.78-2.60 (1H), 2.48-2.39 (1H), 2.10-1.86 (4H), 1.82-1.71 (2H), 1.68-1.53 (2H), 1.50-1.38 (2H), 1.33-1.24 (1H), 0.91-0.74 (6H)

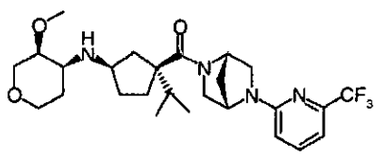
Example 15



1,5-anhydro-2,3-dideoxy-3-{[(1R,3S)-3-isopropyl-3-({(1S,4S)-5-[2-(trifluoromethyl)pyrimidin-4-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methyl-D-erythro-pentitol

Prepared as described in example 3 starting with (1S,4S)-4-(2,5-dimethyl-1H-pyrrol-1-yl)-1-isopropylcyclopent-2-ene-1-carboxylic acid and skipping steps 1 and 2 and using 4-chloro-2-(trifluoromethyl)pyrimidine in place of 4-chloro-6-(trifluoromethyl)pyrimidine in step 8. LC/MS (M+H) = 512.2849 exp, 512.2891 obs; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.25-8.24 (1H), 6.52-6.23 (1H), 5.30-4.47 (2H), 4.05-4.02 (1H), 3.91-3.88 (1H), 3.70-3.54 (2H), 3.52-3.18 (8H), 3.12-3.03 (1H), 2.78-2.61 (1H), 2.49-2.39 (1H), 2.08-1.85 (5H), 1.82-1.72 (1H), 1.68-1.41 (4H), 1.35-1.24 (1H), 0.93-0.75 (6H)

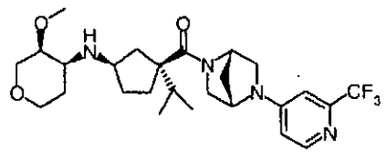
Example 16



1,5-anhydro-2,3-dideoxy-3-{[(1R,3S)-3-isopropyl-3-({(1S,4S)-5-[6-(trifluoromethyl)pyridin-2-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methyl-D-erythro-pentitol

Prepared as described in example 1 starting with (1S,4S)-4-(2,5-dimethyl-1H-pyrrol-1-yl)-1-isopropylcyclopent-2-ene-1-carboxylic acid and skipping steps 1 and 2 and using 2-chloro-6-(trifluoromethyl)pyridine in place of 2-chloro-4-(trifluoromethyl)pyridine in step 8. LC/MS (M+H) = 511.2896 exp, 511.2856 obs; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.54-7.50 (1H), 6.90-6.88 (1H), 6.50-6.41 (1H), 5.08-4.70 (2H), 4.08-3.99 (1H), 3.94-3.87 (1H), 3.73-3.46 (2H), 3.46-3.13 (8H), 3.13-2.97 (1H), 2.81-2.58 (1H), 2.52-2.38 (1H), 2.10-1.70 (5H), 1.70-1.40 (5H), 1.36-1.25 (1H), 0.94-0.73 (6H)
0.75 (6H)

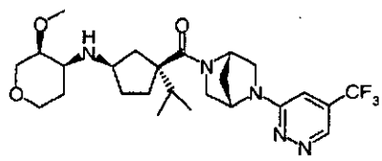
Example 17



1,5-anhydro-2,3-dideoxy-3-{[(1R,3S)-3-isopropyl-3-({(1S,4S)-5-[2-(trifluoromethyl)pyridin-4-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methyl-D-erythro-pentitol

Prepared as described in example 3 starting with (1S,4S)-4-(2,5-dimethyl-1H-pyrrol-1-yl)-1-isopropylcyclopent-2-ene-1-carboxylic acid and skipping steps 1 and 2 and using 4-iodo-2-(trifluoromethyl)pyridine in place of 2-chloro-4-(trifluoromethyl)pyridine in step 8. LC/MS (M+H) = 511.2896 exp, 511.2958 obs; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.27-8.26 (1H), 6.72-6.69 (1H), 6.49-6.44 (1H), 5.09-4.75 (1H), 4.52 (1H), 4.05-4.02 (1H), 3.91-3.88 (1H), 3.65-3.50 (3H), 3.41-3.03 (8H), 2.78-2.55 (1H), 2.49-2.35 (1H), 2.08-1.87 (4H), 1.84-1.72 (2H), 1.68-1.53 (2H), 1.51-1.38 (2H), 1.34-1.26 (1H), 0.92-0.75 (6H)

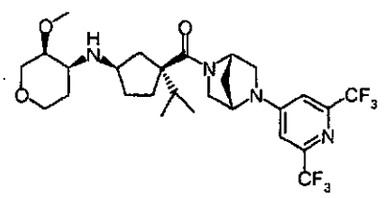
Example 18



1,5-anhydro-2,3-dideoxy-3-{[(1R,3S)-3-isopropyl-3-({(1S,4S)-5-[5-(trifluoromethyl)pyridazin-3-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methyl-D-erythro-pentitol

Prepared as described in example 2 starting with (1S,4S)-4-(2,5-dimethyl-1H-pyrrol-1-yl)-1-isopropylcyclopent-2-ene-1-carboxylic acid and skipping steps 1 and 2 and using 3-chloro-5-(trifluoromethyl)pyridazine in place of 2-chloro-4-(trifluoromethyl)pyrimidine in step 8. LC/MS (M+H) = 512.2849 exp, 512.2864 obs; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.73 (1H), 6.75-6.68 (1H), 5.32-4.79 (2H), 4.07-4.04 (1H), 3.93-3.89 (1H), 3.80-3.55 (2H), 3.52-3.16 (8H), 3.13-3.03 (1H), 2.82-2.63 (1H), 2.51-2.38 (1H), 2.09-1.42 (10H), 1.36-1.24 (1H), 0.93-0.75 (6H)

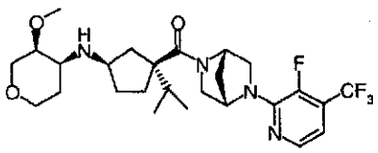
Example 19



1,5-anhydro-3-{[(1R,3S)-3-isopropyl-3-({(1S,4S)-5-[2,6-bis(trifluoromethyl)pyridin-4-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)-3-isopropylcyclopentyl]amino}-2,3-dideoxy-4-O-methyl-D-erythro-pentitol

Prepared as described in example 3 starting with (1S,4S)-4-(2,5-dimethyl-1H-pyrrol-1-yl)-1-isopropylcyclopent-2-ene-1-carboxylic acid and skipping steps 1 and 2 and using 4-chloro-2,6-bis(trifluoromethyl)pyridine in place of 4-chloro-6-(trifluoromethyl)pyrimidine in step 8. LC/MS (M+H) = 579.2770 exp, 579.2667 obs; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 6.94-6.67 (2H), 5.17-4.78 (1H), 4.60 (1H), 4.06-4.04 (1H), 3.92-3.89 (1H), 3.68-3.57 (2H), 3.42-3.16 (8H), 3.13-3.05 (1H), 2.79-2.62 (1H), 2.48-2.37 (1H), 2.08-1.86 (3H), 1.83-1.54 (6H), 1.52-1.42 (1H), 1.37-1.24 (1H), 0.92-0.76 (6H)

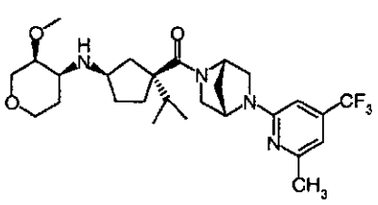
Example 20



1,5-anhydro-2,3-dideoxy-3-{[(1R,3S)-3-({(1S,4S)-5-[3-fluoro-4-(trifluoromethyl)pyridin-2-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)-3-isopropylcyclopentyl]amino}-4-O-methyl-D-erythro-pentitol

Prepared as described in example 3 starting with (1S,4S)-4-(2,5-dimethyl-1H-pyrrol-1-yl)-1-isopropylcyclopent-2-ene-1-carboxylic acid and skipping steps 1 and 2 and using 2-chloro-3-fluoro-4-(trifluoromethyl)pyridine in place of 4-chloro-6-(trifluoromethyl)pyrimidine in step 8. LC/MS (M+H) = 529.2802 exp, 529.3431 obs; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.98-7.97 (1H), 6.73-6.71 (1H), 5.07-4.67 (2H), 4.08-4.02 (1H), 3.94-3.88 (1H), 3.84-3.78 (1H), 3.64-3.47 (3H), 3.40-3.21 (6H), 3.13-3.04 (1H), 2.80-2.69 (1H), 2.49-2.39 (1H), 2.10-1.56 (9H), 1.54-1.42 (1H), 1.37-1.28 (1H), 0.92-0.75 (6H)

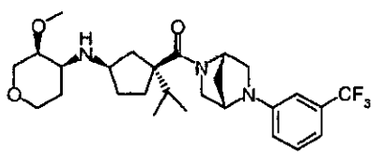
Example 21



1,5-anhydro-2,3-dideoxy-3-{[(1R,3S)-3-isopropyl-3-({(1S,4S)-5-[6-methyl-4-(trifluoromethyl)pyridin-2-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methyl-D-erythro-pentitol

Prepared as described in example 3 starting with (1S,4S)-4-(2,5-dimethyl-1H-pyrrol-1-yl)-1-isopropylcyclopent-2-ene-1-carboxylic acid and skipping steps 1 and 2 and using 2-chloro-6-methyl-4-(trifluoromethyl)pyridine in place of 4-chloro-6-(trifluoromethyl)pyrimidine in step 8. LC/MS (M+H) = 525.3052 exp, 525.3242 obs; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 6.61 (1H), 6.29-6.24 (1H), 5.14-4.71 (2H), 4.17-4.04 (2H), 3.98-3.90 (1H), 3.70-3.49 (3H), 3.48-3.13 (7H), 2.91-2.72 (1H), 2.50-2.32 (4H), 2.11-1.39 (11H), 0.94-0.71 (6H)

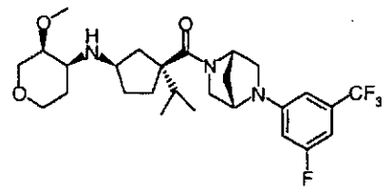
Example 22



1,5-anhydro-2,3-dideoxy-3-{[(1R,3S)-3-isopropyl-3-({(1S,4S)-5-[3-(trifluoromethyl)phenyl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methyl-D-erythro-pentitol

Prepared as described in example 3 starting with (1S,4S)-4-(2,5-dimethyl-1H-pyrrol-1-yl)-1-isopropylcyclopent-2-ene-1-carboxylic acid and skipping steps 1 and 2 and using 3-iodo-benzotrifluoride in place of 4-chloro-6-(trifluoromethyl)pyrimidine in step 8. LC/MS (M+H) = 510.2943 exp, 510.2976 obs; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.30-7.25 (1H), 6.92-6.90 (1H), 6.72-6.65 (2H), 5.06-4.68 (1H), 4.44 (1H), 4.07-3.99 (1H), 3.94-3.86 (1H), 3.71-3.51 (2H), 3.48-3.19 (7H), 3.14-3.01 (1H), 2.81-2.69 (1H), 2.61-2.35 (1H), 2.09-1.54 (9H), 1.51-1.40 (1H), 1.35-1.27 (1H), 0.94-0.72 (6H)

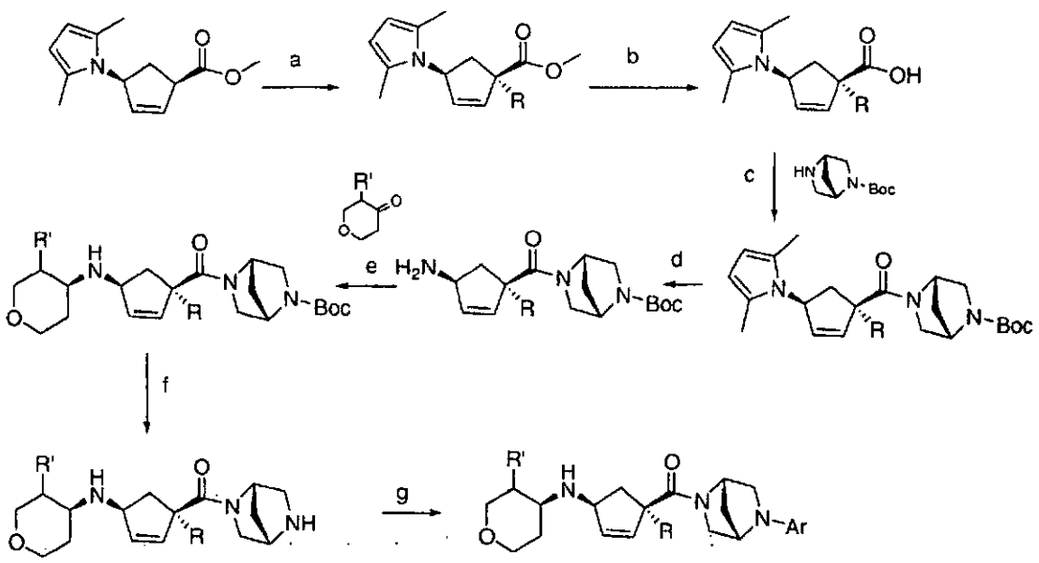
Example 23



1,5-anhydro-2,3-dideoxy-3-{[(1R,3S)-3-({(1S,4S)-5-[3-fluoro-5-(trifluoromethyl)phenyl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)-3-isopropylcyclopentyl]amino}-4-O-methyl-D-erythro-pentitol

Prepared as described in example 3 starting with (1S,4S)-4-(2,5-dimethyl-1H-pyrrol-1-yl)-1-isopropylcyclopent-2-ene-1-carboxylic acid and skipping steps 1 and 2 and using 3-bromo-5-fluorobenzotrifluoride in place of 4-chloro-6-(trifluoromethyl)pyrimidine in step 8. LC/MS (M+H) = 528.2849 exp, 528.2996 obs; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 6.61-6.58 (1H), 6.48 (1H), 6.35-6.33 (1H), 5.06-4.69 (1H), 4.39 (1H), 4.06-4.00 (1H), 3.94-3.86 (1H), 3.65-3.50 (2H), 3.46-3.15 (7H), 3.12-3.00 (1H), 2.80-2.70 (1H), 2.49-2.32 (1H), 2.06-1.73 (6H), 1.69-1.40 (4H), 1.36-1.27 (1H), 0.94-0.72 (6H)

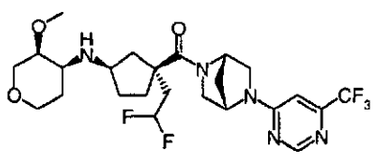
Scheme 2. Preparation of examples 24-44



a) LDA or NaHMDS, R-X, THF; b) 2.5N NaOH, MeOH; c) 2.2.1-Boc, DMF, DIPEA, Bop; d) H_2NOH^*HCl, MeOH, $NH_2OH(aq)$; e) pyranone, DCM, $Na(OAc)_3BH$; f) 4N HCl/1,4-dioxane; g) cond a or cond b or cond c

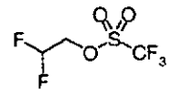
cond a = Ar-X, DMSO, Et_3N, 120 °C
cond b = Ar-X, Cs_2CO_3, XantPhos, $Pd_2(dba)_3$, dioxane, DMSO
cond c = Ar-X, 1,4-dioxane, Et_3N, 100 °C

Example 24



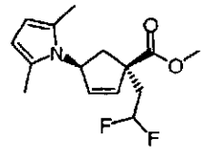
1,5-anhydro-2,3-dideoxy-3-{[(1R,3S)-3-(2,2-difluoroethyl)-3-({(1S,4S)-5-[6-(trifluoromethyl)pyrimidin-4-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methyl-D-erythro-pentitol

Step 1: Preparation of 2,2-difluoroethyl trifluoromethanesulfonate



Triflic anhydride (27.9g, 99.1mmol) was placed in a flask and cooled with an ice bath. 2,2-Difluoroethanol (8.1g, 99.1mmol) was added and the reaction was heated to 84ºC for 1hour. The reaction was cooled in an ice bath and poured into 100ml cold 5%$NaHCO_3$ solution. The mixture was extracted with diethyl ether, dried over $MgSO_4$, and concentrated under reduced pressure to remove the ether. The residue was vaccuum distilled to give 2,2-difluoroethyl trifluoromethanesulfonate as a clear liquid (13.6g, 64%, bp~55ºC). ^1H NMR (400 MHz, $CDCl_3$) δ ppm 6.17-5.88 (1H), 4.61-4.13 (2H)

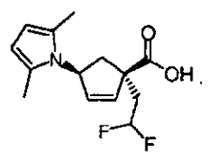
Step 2: Preparation of methyl (1S,4S)-1-(2,2-difluoroethyl)-4-(2,5-dimethyl-1H-pyrrol-1-yl)cyclopent-2-ene-1-carboxylate



A -40ºC solution of 2M (in Ethylbenzene/THF/Heptane) LDA (36ml, 72mmol) in THF (80ml) was placed in flask with THF (80ml) was treated with a solution of methyl (1R,4S)-4-(2,5-dimethyl-1H-pyrrol-1-yl)cyclopent-2-ene-1-carboxylate (7.9g, 36.3mmol) in THF (17ml) while keeping the temperature less than -32ºC. The reaction was stirred for 30min and then 2,2-difluoroethyl trifluoromethanesulfonate was added slowly, keeping the temperature <-28ºC. The reaction was stirred with cold bath in place and allow to slowly warm. After 4 hours the reaction was poured into NH_4Cl solution and extracted twice with ethyl

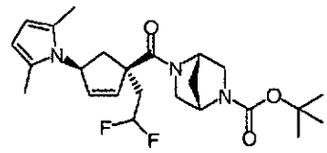
acetate. The combined organics were washed with brine, dried over $MgSO_4$ and concentrated to give a brown oil. The oil was passed through a column of silica gel with 10% ethyl acetate/hexanes to give methyl (1S,4S)-1-(2,2-difluoroethyl)-4-(2,5-dimethyl-1H-pyrrol-1-yl)cyclopent-2-ene-1-carboxylate as a brown oil. (7.5g, 73%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 6.07-6.04 (1H), 6.02-6.00 (0.25H) 5.98-5.96 (1H), 5.88-5.86 (0.5H), 5.75-5.72 (2.25H), 5.36-5.30 (1H), 3.74 (3H), 2.53-2.41 (2H), 2.39-2.22 (2H), 2.19 (6H)

Step 3: Preparation of (1S,4S)-1-(2,2-difluoroethyl)-4-(2,5-dimethyl-1H-pyrrol-1-yl)cyclopent-2-ene-1-carboxylic acid



A solution of methyl (1S,4S)-1-(2,2-difluoroethyl)-4-(2,5-dimethyl-1H-pyrrol-1-yl)cyclopent-2-ene-1-carboxylate (7.54g, 26.6mmol) in methanol (60ml) was treated with 2.5N NaOH (15ml, 37.5mmol) and stirred at room temperature for 22 hours. The methanol was removed under reduced pressure and the residue partitioned between diethyl ether and water. The layers were separated and the aqueous was acidified with 4N HCl, extracted with ethyl acetate, washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure to give (1S,4S)-1-(2,2-difluoroethyl)-4-(2,5-dimethyl-1H-pyrrol-1-yl)cyclopent-2-ene-1-carboxylic acid as a brown oil (6.59g, 92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 6.12-6.09 (1H), 6.07-6.05 (0.25H), 5.99-5.96 (1H), 5.93-5.91 (0.5H), 5.79-5.76 (0.25H), 5.74 (2H), 5.38-5.32 (1H), 2.54-2.46 (2H), 2.43-2.25 (2H), 2.20 (6H).

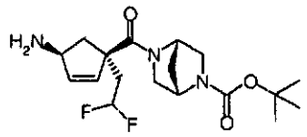
Step 4: Preparation of tert-butyl (1S,4S)-5-{[(1S,4S)-1-(2,2-difluoroethyl)-4-(2,5-dimethyl-1H-pyrrol-1-yl)cyclopent-2-en-1-yl]carbonyl}-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate



BOP= benzotriazol-1-yloxytris(dimethylamino) phosphoniumhexafluorophosphate

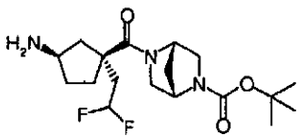
A solution of (1S,4S)-1-(2,2-difluoroethyl)-4-(2,5-dimethyl-1H-pyrrol-1-yl)cyclopent-2-ene-1-carboxylic acid (6.12g, 22.6mmol) in DMF (45ml) was treated with N,N-diisopropylethylamine (11.7ml, 67.2mmol) and BOP (11.93g, 27.0mmol) and stirred under nitrogen at room temperature for 40 minutes. The (1S,4S)-2-BOC-2,5-diazabicyclo[2.2.1]heptane (4.46g,22.5mmol) was added and the reaction was stirred for 18 hours.The reaction was diluted with ethyl acetate (100ml) and washed with 60% saturated $NaHCO_3$ (125ml). The aqueous layer was extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure to give a brown oil (16.8g). The oil was passed through a column of silica gel with 50% ethyl acetate/hexanes to give tert-butyl (1S,4S)-5-{[(1S,4S)-1-(2,2-difluoroethyl)-4-(2,5-dimethyl-1H-pyrrol-1-yl)cyclopent-2-en-1-yl]carbonyl}-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate as a brown foam (7.86g, 78%). ^1H NMR (400 MHz, $CDCl_3$) δ ppm 6.25-6.19 (1H), 6.04-5.96 (1.25H), 5.85-5.81 (0.5H), 5.74-5.68 (2.25H), 5.37-5.25 (1H), 4.98-4.43 (2H), 3.73-3.29 (4H), 2.77-2.29 (2H), 2.26-2.09 (8H), 1.93-1.67 (2H), 1.46-1.34 (9H).

Step 5: Preparation of tert-butyl (1S,4S)-5-{[(1S,4S)-4-amino-1-(2,2-difluoroethyl)cyclopent-2-en-1-yl]carbonyl}-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate



A solution of tert-butyl (1S,4S)-5-{[(1S,4S)-1-(2,2-difluoroethyl)-4-(2,5-dimethyl-1H-pyrrol-1-yl)cyclopent-2-en-1-yl]carbonyl}-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (7.86g, 17.5mmol) in methanol (100ml) and water (30ml) was treated with hydroxylamine hydrochloride (6.35g, 91.0mmol) and 50 weight% solution of hydroxylamine (5.0ml, 81.6mmol). The reaction was stirred under nitrogen and heated to 66ºC for 39 hours. The reaction was cooled to room temperature, diluted with water, and made basic (pH~11) by the addition of 2.5N NaOH. The reaction mixture was extracted with ethyl acetate (3x150ml), washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure to give a crude mixture of tert-butyl (1S,4S)-5-{[(1S,4S)-4-amino-1-(2,2-difluoroethyl)cyclopent-2-en-1-yl]carbonyl}-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate as a brown oil (9.12g, theoretical yield 6.50g) which was used without further purification in the next step.

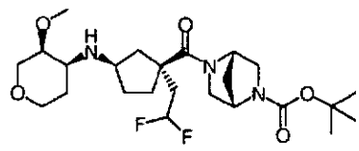
Step 6: Preparation of tert-butyl (1S,4S)-5-{[(1S,3R)-3-amino-1-(2,2-difluoroethyl)cyclopentyl]carbonyl}-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate



A mixture of tert-butyl (1S,4S)-5-{[(1S,4S)-4-amino-1-(2,2-difluoroethyl)cyclopent-2-en-1-yl]carbonyl}-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (6.50g, 17.5mmol) and 5% palladium on carbon in methanol (100ml) was stirred at room temperature under 46psi of hydrogen for 21 hours. The reaction was filtered through celite and the filter cake washed with methanol. The filtrate and

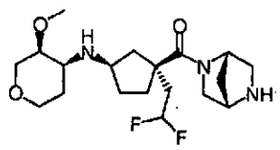
washings were concentrated under reduced pressure to give tert-butyl (1S,4S)-5-{[(1S,3R)-3-amino-1-(2,2-difluoroethyl)cyclopentyl]carbonyl}-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate as a brown oil (6.67g, theoretical yield 6.54g) which was used without further purification in the next step.

Step 7: Preparation of 1,5-anhydro-3-{[(1R,3S)-3-{[(1S,4S)-5-(tert-butoxycarbonyl)-2,5-diazabicyclo[2.2.1]hept-2-yl]carbonyl}-3-(2,2-difluoroethyl)cyclopentyl]amino}-2,3-dideoxy-4-O-methyl-D-erythro-pentitol



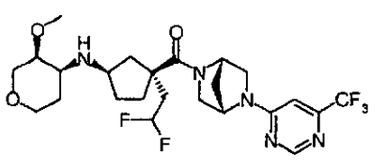
A 0ºC solution of tert-butyl (1S,4S)-5-{[(1S,3R)-3-amino-1-(2,2-difluoroethyl)cyclopentyl]carbonyl}-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (3.45g, 9.2mmol) in dichloromethane (50ml) was treated with sodium triacetoxyborohydride (5.34g, 25.2mmol) and (3R)-3-methoxytetrahydro-4H-pyran-4-one (2.31g, 17.8mmol). The reaction was stirred under nitrogen at 0ºC for 30 minutes then allowed to warm to room temperature and stirred for 47 hours. The reaction was treated with 2.5N NaOH (35mL) and stirred for 10 minutes. The reaction was diluted with water and the layers separated. The aqueous layer was extracted twice with ethyl acetate. The dichloromethane layer was concentrated under reduced pressure and partitioned between ethyl acetate and water. The organic layers were combined, washed with brine, dried over $MgSO_4$, concentrated under reduced pressure and purified with the Biotage (0-100% methanol/ethyl acetate, 15 column volumes) to give1,5-anhydro-3-{[(1R,3S)-3-{[(1S,4S)-5-(tert-butoxycarbonyl)-2,5-diazabicyclo[2.2.1]hept-2-yl]carbonyl}-3-(2,2-difluoroethyl)cyclopentyl]amino}-2,3-dideoxy-4-O-methyl-D-erythro-pentitol (2.13g, 47%) which was used without further purification in the next step.

Step 8: Preparation of 1,5-anhydro-2,3-dideoxy-3-{[(1R,3S)-3-{[(1S,4S)-2,5-diazabicyclo[2.2.1]hept-2-yl]carbonyl}-3-(2,2-difluoroethyl)cyclopentyl]amino}-4-O-methyl-D-erythro-pentitol (HCl salt)



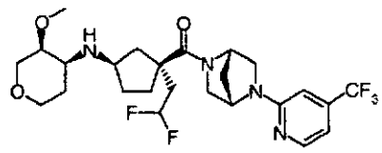
To a solution of 1,5-anhydro-3-{[(1R,3S)-3-{[(1S,4S)-5-(tert-butoxycarbonyl)-2,5-diazabicyclo[2.2.1]hept-2-yl]carbonyl}-3-(2,2-difluoroethyl)cyclopentyl]amino}-2,3-dideoxy-4-O-methyl-D-erythro-pentitol (2.13g, 4.4mmol) in 1,4-dioxane (20ml) was added 4N HCl/1,4-dioxane (20ml). The reaction was stirred at room temperature for 16 hours. The liquid was decanted leaving a gummy solid which was dissolved in methanol and concentrated under reduced pressure. The residue was dissolved in methanol/methylene chloride and concentrated to give the HCl salt of 1,5-anhydro-2,3-dideoxy-3-{[(1R,3S)-3-{[(1S,4S)-2,5-diazabicyclo[2.2.1]hept-2-yl]carbonyl}-3-(2,2-difluoroethyl)cyclopentyl]amino}-4-O-methyl-D-erythro-pentitol as a brown foam (2.23g, theoretical yield 1.85g) which was used in the next step without further purification.

Step 9: Preparation of 1,5-anhydro-2,3-dideoxy-3-{[(1R,3S)-3-(2,2-difluoroethyl)-3-({(1S,4S)-5-[6-(trifluoromethyl)pyrimidin-4-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methyl-D-erythro-pentitol



The HCl salt of 1,5-anhydro-2,3-dideoxy-3-{[(1R,3S)-3-{[(1S,4S)-2,5-diazabicyclo[2.2.1]hept-2-yl]carbonyl}-3-(2,2-difluoroethyl)cyclopentyl]amino}-4-O-methyl-D-erythro-pentitol (177mg, 0.42mmol) was placed in a flask with 1,4-dioxane (3ml). To the stirred solution was added Xantphos (36mg, 0.062mmol), $Pd_2(dba)_3$ (22mg, 0.024mmol), Cs_2CO_3 (350mg, 1.07mmol), and 4-chloro-6-(trifluoromethyl)pyrimidine (195mg, 1.07mmol) dissolved in 1,4-dioxane (1ml). DMSO (0.5ml) was added for solubility and the reaction was heated to 100ºC for 21.5 hours. The reaction was allowed to cool to room temperature and filtered through celite. The filtrate was concentrated under reduced pressure and purified with the Biotage (0-100% methanol/ethyl acetate 15 column volumes) to give 1,5-anhydro-2,3-dideoxy-3-{[(1R,3S)-3-(2,2-difluoroethyl)-3-({(1S,4S)-5-[6-(trifluoromethyl)pyrimidin-4-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methyl-D-erythro-pentitol as a white foam (43mg, 20%). LC/MS (M+H) = 534.2504 exp, 534.2597 obs; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.62 (1H), 6.74-6.46 (1H), 5.93-5.62 (1H), 5.29-4.50 (2H), 4.08-4.03 (1H), 3.93-3.88 (1H), 3.77-3.55 (2H), 3.52-3.32 (6H), 3.30-3.21 (3H), 2.76-2.65 (1H), 2.51-2.33 (1H), 2.21-1.84 (7H), 1.70-1.40 (5H)

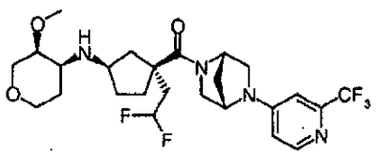
Example 25



1,5-anhydro-2,3-dideoxy-3-{[(1R,3S)-3-(2,2-difluoroethyl)-3-({(1S,4S)-5-[4-(trifluoromethyl)pyridin-2-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methyl-D-erythro-pentitol

Prepared as described in example 24 using 2-chloro-4-(trifluoromethyl)pyridine in place of 4-chloro-6-(trifluoromethyl)pyrimidine in step 9. LC/MS (M+H) = 533.2551 exp, 533.2651 obs; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.24-8.20 (1H), 6.74-6.73 (1H), 6.49-6.44 (1H), 5.95-5.57 (1H), 5.07-4.73 (2H), 4.06-4.01 (1H), 3.93-3.87 (1H), 3.70-3.49 (2H), 3.45-3.30 (6H), 3.28-3.20 (3H), 2.77-2.64 (1H), 2.53-2.36 (1H), 2.23-1.81 (7H), 1.73-1.41 (5H)

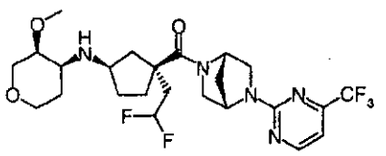
Example 26



1,5-anhydro-2,3-dideoxy-3-{[(1R,3S)-3-(2,2-difluoroethyl)-3-({(1S,4S)-5-[2-(trifluoromethyl)pyridin-4-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methyl-D-erythro-pentitol

Prepared as described in example 24 using 4-iodo-2-(trifluoromethyl)pyridine in place of 4-chloro-6-(trifluoromethyl)pyrimidine in step 9. LC/MS (M+H) = 533.2551 exp, 533.2598 obs; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.29-8.27 (1H), 6.74-6.70 (1H), 6.50-6.43 (1H), 5.93-5.59 (1H), 5.09-4.74 (1H), 4.54 (1H), 4.07-4.02 (1H), 3.93-3.88 (1H), 3.68-3.48 (2H), 3.39-3.20 (7H), 2.74-2.62 (1H), 2.51-2.37 (1H), 2.19-1.77 (7H), 1.70-1.40 (5H)

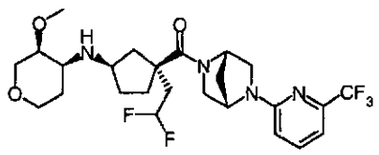
Example 27



1,5-anhydro-2,3-dideoxy-3-{[(1R,3S)-3-(2,2-difluoroethyl)-3-({(1S,4S)-5-[4-(trifluoromethyl)pyrimidin-2-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methyl-D-erythro-pentitol

Prepared as described in example 24 using 2-chloro-4-(trifluoromethyl)pyrimidine in place of 4-chloro-6-(trifluoromethyl)pyrimidine and modifying step 9 as follows. The HCl salt of 1,5-anhydro-2,3-dideoxy-3-{[(1R,3S)-3-{[(1S,4S)-2,5-diazabicyclo[2.2.1]hept-2-yl]carbonyl}-3-(2,2-difluoroethyl)cyclopentyl]amino}-4-O-methyl-D-erythro-pentitol (175mg, 0.41mmol) was placed in flask with 1,4-dioxane (3ml). Triethylamine (0.2ml, 1.43mmol) was added as well as 2-chloro-4-(trifluoromethyl)pyrimidine (237mg, 1.30mmol). DMSO (0.3ml) was added for solubility and the reaction was heated to 100ºC for 14.5 hours. The reaction was cooled to room temperature and partitioned between ethyl acetate and water. The aqueous layer was extracted with ethyl acetate and the combined organics were washed with brine, dried over $MgSO_4$, concentrated under reduced pressure and purified with the Biotage (0-100% methanol/ethyl acetate 15 column volumes) to give 1,5-anhydro-2,3-dideoxy-3-{[(1R,3S)-3-(2,2-difluoroethyl)-3-({(1S,4S)-5-[4-(trifluoromethyl)pyrimidin-2-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methyl-D-erythro-pentitol as a brown foam (126mg, 58%). LC/MS (M+H) = 534.2504 exp, 534.2452 obs; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.48-8.45 (1H), 6.79-6.78 (1H), 5.96-5.58 (1H), 5.10-4.71 (2H), 4.07-4.01 (1H), 3.93-3.87 (1H), 3.69-3.55 (4H), 3.39-3.32 (4H), 3.30-3.21 (3H), 2.77-2.66 (1H), 2.52-2.40 (1H), 2.23-1.82 (7H), 1.70-1.39 (5H)

Example 28

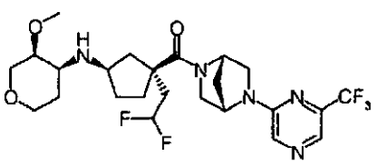


1,5-anhydro-2,3-dideoxy-3-{[(1R,3S)-3-(2,2-difluoroethyl)-3-({(1S,4S)-5-[6-(trifluoromethyl)pyridin-2-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methyl-D-erythro-pentitol

Prepared as described in example 24 using 2-chloro-6-(trifluoromethyl)pyridine in place of 4-chloro-6-(trifluoromethyl)pyrimidine and modifying step 9 as follows. To a solution of HCl salt of 1,5-anhydro-2,3-dideoxy-3-{[(1R,3S)-3-{[(1S,4S)-2,5-diazabicyclo[2.2.1]hept-2-yl]carbonyl}-3-(2,2-difluoroethyl)cyclopentyl]amino}-4-O-methyl-D-erythro-pentitol (183mg, 0.43mmol) in DMSO (2ml) was added triethylamine (0.2ml, 1.43mmol) and 2-chloro-6-(trifluoromethyl)pyridine (179mg, 1.05mmol). The reaction was heated to 120 ºC for 14.5 hours. The reaction was cooled to room temperature, and added to stirring ice water. The mixture was extracted with ethyl acetate(3x). The combined organics were washed with brine, dried over $MgSO_4$ concentrated under reduced pressure and purified with the Biotage (0-100% methanol/ethyl acetate, 15 column volumes) to give 1,5-anhydro-2,3-dideoxy-3-{[(1R,3S)-3-(2,2-difluoroethyl)-3-({(1S,4S)-5-[6-(trifluoromethyl)pyridin-2-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methyl-D-erythro-pentitol as a brown foam (58mg 28%). LC/MS (M+H) = 533.2551 exp, 533.2546 obs; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.54-7.51 (1H), 6.91-6.89 (1H), 6.51-6.38 (1H), 5.94-5.54 (1H), 5.11-4.70 (2H), 4.06-4.01 (1H), 3.93-3.87 (1H), 3.70-3.53 (2H),

3.51-3.31 (6H), 3.27-3.20 (3H), 2.78-2.61 (1H), 2.53-2.36 (1H), 2.20-1.80 (7H), 1.68-1.38 (5H)

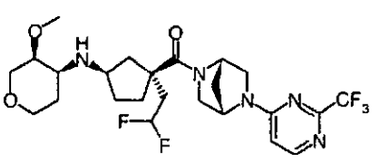
Example 29



1,5-anhydro-2,3-dideoxy-3-{[(1R,3S)-3-(2,2-difluoroethyl)-3-({(1S,4S)-5-[6-(trifluoromethyl)pyrazin-2-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methyl-D-erythro-pentitol

Prepared as described in example 24 using 2-iodo-6-(trifluoromethyl)pyrazine in place of 4-chloro-6-(trifluoromethyl)pyrimidine in step 9. LC/MS (M+H) = 534.2504 exp, 534.2548 obs; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.13 (1H), 8.01-7.93 (1H), 5.92-5.57 (1H), 5.09-4.75 (2H), 4.06-4.01 (1H), 3.92-3.87 (1H), 3.68-3.48 (4H), 3.38-3.30 (4H), 3.28-3.20 (3H), 2.74-2.63 (1H), 2.51-2.32 (1H), 2.21-1.83 (7H), 1.75-1.42 (5H)

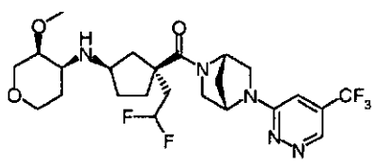
Example 30



1,5-anhydro-2,3-dideoxy-3-{[(1R,3S)-3-(2,2-difluoroethyl)-3-({(1S,4S)-5-[2-(trifluoromethyl)pyrimidin-4-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methyl-D-erythro-pentitol

Prepared as described in example 24 using 4-chloro-2-(trifluoromethyl)pyrimidine in place of 4-chloro-6-(trifluoromethyl)pyrimidine in step 9. LC/MS (M+H) = 534.2504 exp, 534.2521 obs; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.28-8.26 (1H), 6.52-6.24 (1H), 5.93-5.62 (1H), 5.33-4.38 (2H), 4.08-4.03 (1H), 3.94-3.89 (1H), 3.71-3.57 (2H), 3.49-3.33 (6H), 3.29-3.21 (3H), 2.75-2.66 (1H), 2.50-2.36 (1H), 2.22-1.86 (7H), 1.69-1.41 (5H)

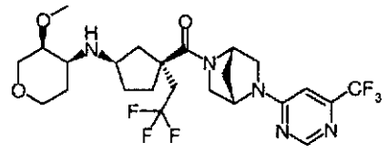
Example 31



1,5-anhydro-2,3-dideoxy-3-{[(1R,3S)-3-(2,2-difluoroethyl)-3-({(1S,4S)-5-[5-(trifluoromethyl)pyridazin-3-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methyl-D-erythro-pentitol

Prepared as described in example 27 using 3-chloro-5-(trifluoromethyl)pyridazine in place of 2-chloro-4-(trifluoromethyl)pyrimidine in step 9. LC/MS (M+H) = 534.2504 exp, 534.2531 obs; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.76 (1H), 6.74-6.68 (1H), 5.96-5.90 (1H), 5.37-4.84 (2H), 4.10-4.04 (1H), 3.96-3.90 (1H), 3.81-3.54 (3H), 3.47-3.34 (4H), 3.32-3.22 (4H), 2.77-2.67 (1H), 2.51-2.37 (1H), 2.22-1.86 (7H), 1.72-1.46 (5H)

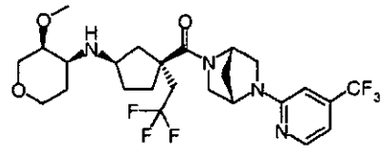
Example 32



1,5-anhydro-2,3-dideoxy-4-O-methyl-3-{[(1R,3S)-3-(2,2,2-trifluoroethyl)-3-({(1S,4S)-5-[6-(trifluoromethyl)pyrimidin-4-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-D-erythro-pentitol

Prepared as described in example 24 using 3,3,3-trifluoroethanol in place of 2,2-difluoroethanol in step 1. LC/MS (M+H) = 552.2409 exp, 552.2432 obs; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.61 (1H), 6.70-6.45 (1H), 5.26-5.21 (1H), 5.08-4.96 (1H), 4.08-4.03 (1H), 3.92-3.87 (1H), 3.68-3.61 (2H), 3.53-3.44 (1H), 3.42-3.20 (8H), 2.72-2.65 (1H), 2.56-2.27 (3H), 2.08-1.88 (5H), 1.80-1.47 (5H)

Example 33

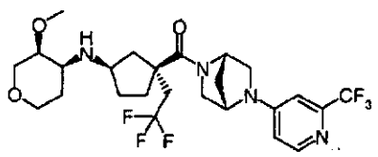


1,5-anhydro-2,3-dideoxy-4-O-methyl-3-{[(1R,3S)-3-(2,2,2-trifluoroethyl)-3-({(1S,4S)-5-[4-(trifluoromethyl)pyridin-2-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-D-erythro-pentitol

Prepared as described in example 24 using 3,3,3-trifluoroethanol in place of 2,2-difluoroethanol in step 1 and using 2-chloro-4-(trifluoromethyl)pyridine in place of

2-chloro-6-(trifluoromethyl)pyridine in step 9. LC/MS (M+H) = 551.2457 exp, 551.2703 obs; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.22-8.21 (1H), 6.74-6.73 (1H), 6.47-6.43 (1H), 5.06-4.71 (2H), 4.06-4.01 (1H), 3.92-3.87 (1H), 3.65-3.50 (3H), 3.40-3.20 (8H), 2.72-2.63 (1H), 2.53-2.27 (3H), 2.08-1.82 (5H), 1.78-1.45 (5H)

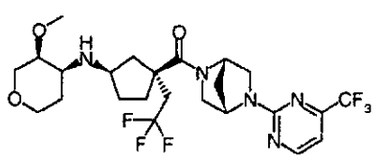
Example 34



1,5-anhydro-2,3-dideoxy-4-O-methyl-3-{[(1R,3S)-3-(2,2,2-trifluoroethyl)-3-({(1S,4S)-5-[2-(trifluoromethyl)pyridin-4-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-D-erythro-pentitol

Prepared as described in example 24 using 3,3,3-trifluoroethanol in place of 2,2-difluoroethanol in step 1 and using 4-iodo-2-(trifluoromethyl)pyridine in place of 2-chloro-4-(trifluoromethyl)pyrimidine in step 9. LC/MS (M+H) = 551.2457 exp, 551.2610 obs; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.26-8.25 (1H), 6.71-6.68 (1H), 6.46-6.42 (1H), 5.09-4.83 (1H), 4.55-4.52 (1H), 4.05-4.01 (1H), 3.90-3.85 (1H), 3.66-3.48 (3H), 3.36-3.18 (8H), 2.70-2.62 (1H), 2.51-2.27 (3H), 2.06-1.87 (5H), 1.80-1.45 (5H)

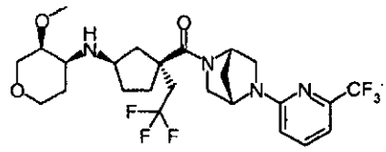
Example 35



1,5-anhydro-2,3-dideoxy-4-O-methyl-3-{[(1R,3S)-3-(2,2,2-trifluoroethyl)-3-({(1S,4S)-5-[4-(trifluoromethyl)pyrimidin-2-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-D-erythro-pentitol

Prepared as described in example 27 using 3,3,3-trifluoroethanol in place of 2,2-difluoroethanol in step 1. LC/MS (M+H) = 552.2409 exp, 551.2426 obs; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.50-8.46 (1H), 6.81-6.80 (1H), 5.11-4.74 (2H), 4.13-4.06 (1H), 3.97-3.92 (1H), 3.67-3.59 (4H), 3.41-3.25 (7H), 2.90-2.75 (1H), 2.54-2.33 (3H), 2.07-1.88 (5H), 1.79-1.58 (5H)

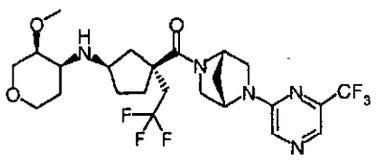
Example 36



1,5-anhydro-2,3-dideoxy-4-O-methyl-3-{[(1R,3S)-3-(2,2,2-trifluoroethyl)-3-({(1S,4S)-5-[6-(trifluoromethyl)pyridin-2-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-D-erythro-pentitol

Prepared as described in example 27 using 3,3,3-trifluoroethanol in place of 2,2-difluoroethanol in step 1 and using 2-chloro-6-(trifluoromethyl)pyridine in place of 2-chloro-4-(trifluoromethyl)pyrimidine in step 9.. LC/MS (M+H) = 551.2457 exp, 551.2581 obs; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.55-7.51 (1H), 6.92-6.90 (1H), 6.47-6.40 (1H), 5.12-4.70 (2H), 4.07-4.03 (1H), 3.93-3.88 (1H), 3.72-3.47 (3H), 3.40-3.31 (5H), 3.28-3.20 (3H), 2.73-2.64 (1H), 2.53-2.25 (3H), 2.10-1.80 (5H), 1.77-1.44 (5H)

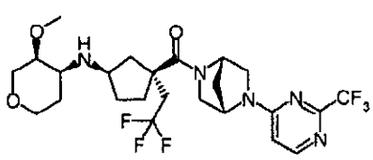
Example 37



1,5-anhydro-2,3-dideoxy-4-O-methyl-3-{[(1R,3S)-3-(2,2,2-trifluoroethyl)-3-({(1S,4S)-5-[6-(trifluoromethyl)pyrazin-2-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-D-erythro-pentitol

Prepared as described in example 24 using 3,3,3-trifluoroethanol in place of 2,2-difluoroethanol in step 1 and using 1-iodo-6-(trifluoromethyl)pyrazine in place of 4-chloro-6-(trifluoromethyl)pyrimidine in step 9. LC/MS (M+H) = 552.2409 exp, 552.2443 obs; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.16 (1H), 8.01-7.96 (1H), 5.09-4.96 (2H), 4.09-4.04 (1H), 3.94-3.89 (1H), 3.68-3.57 (3H), 3.53-3.49 (1H), 3.39-3.23 (7H), 2.74-2.67 (1H), 2.54-2.29 (3H), 2.09-1.90 (5H), 1.81-1.49 (5H)

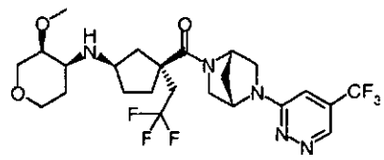
Example 38



1,5-anhydro-2,3-dideoxy-4-O-methyl-3-{[(1R,3S)-3-(2,2,2-trifluoroethyl)-3-({(1S,4S)-5-[2-(trifluoromethyl)pyrimidin-4-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-D-erythro-pentitol

Prepared as described in example 24 using 3,3,3-trifluoroethanol in place of 2,2-difluoroethanol in step 1 and using 4-chloro-2-(trifluoromethyl)pyrimidine in place of 4-chloro-6-(trifluoromethyl)pyrimidine in step 9. LC/MS (M+H) = 552.2409 exp, 552.3073 obs; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.23-8.21 (1H), 6.49-6.22 (1H), 5.25-4.93 (2H), 4.04-3.99 (1H), 3.89-3.83 (1H), 3.65-3.57 (2H), 3.46-3.17 (9H), 2.68-2.62 (1H), 2.52-2.26 (3H), 2.05-1.85 (5H), 1.76-1.43 (5H)

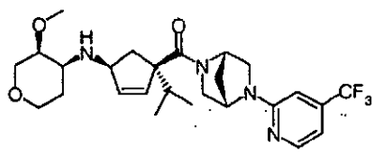
Example 39



1,5-anhydro-2,3-dideoxy-4-O-methyl-3-{[(1R,3S)-3-(2,2,2-trifluoroethyl)-3-({(1S,4S)-5-[5-(trifluoromethyl)pyridazin-3-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-D-erythro-pentitol

Prepared as described in example 27 using 3,3,3-trifluoroethanol in place of 2,2-difluoroethanol in step 1 and using 3-chloro-5-(trifluoromethyl)pyridazine in place of 2-chloro-4-(trifluoromethyl)pyrimidine in step 9. LC/MS (M+H) = 552.2409 exp, 552.2344 obs; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.72 (1H), 6.72-6.64 (1H), 5.32-4.82 (2H), 4.06-4.01 (1H), 3.91-3.86 (1H), 3.78-3.53 (3H), 3.42-3.18 (8H), 2.69-2.64 (1H), 2.52-2.24 (3H), 2.07-1.84 (5H), 1.76-1.44 (5H)

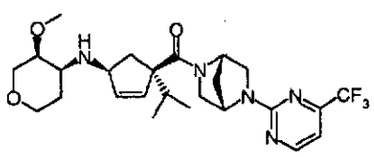
Example 40



1,5-anhydro-2,3-dideoxy-3-{[(1S,4S)-4-isopropyll-4-({(1S,4S)-5-[4-(trifluoromethyl)pyridin-2-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopent-2-en-1-yl]amino}-4-O-methyl-D-erythro-pentitol

Prepared as described in example 1 starting with (1S,4S)-4-(2,5-dimethyl-1H-pyrrol-1-yl)-1-isopropylcyclopent-2-ene-1-carboxylic acid and skipping steps 1, 2 and 5. LC/MS (M+H) = 509.2739 exp, 509.2724 obs; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.19 (1H), 6.72-6.68 (1H), 6.46-6.38 (1H), 5.90-5.75 (2H), 5.09-4.82 (2H), 4.02-3.12 (13H), 2.86-2.67 (1H), 2.46-2.16 (1H), 2.08-1.47 (7H), 0.84-0.64 (6H)

Example 41

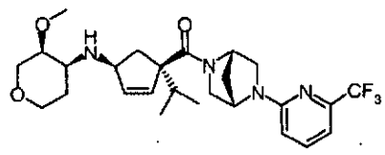


1,5-anhydro-2,3-dideoxy-3-{[(1S,4S)-4-isopropyll-4-({(1S,4S)-5-[4-(trifluoromethyl)pyrimidin-2-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopent-2-en-1-yl]amino}-4-O-methyl-D-erythro-pentitol

Prepared as described in example 2 starting with (1S,4S)-4-(2,5-dimethyl-1H-pyrrol-1-yl)-1-isopropylcyclopent-2-ene-1-carboxylic acid and skipping steps 1, 2

and 5. LC/MS (M+H) = 510.2692 exp, 510.2926 obs; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.43-8.42 (1H), 6.75-6.74 (1H), 5.90-5.77 (2H), 5.09-4.80 (2H), 4.01-3.16 (13H), 2.86-2.69 (1H), 2.45-2.17 (1H), 2.08-1.30 (7H), 0.82-0.66 (6H)

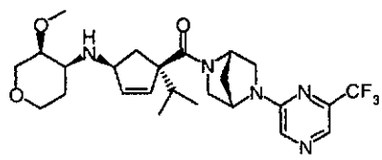
Example 42



1,5-anhydro-2,3-dideoxy-3-{[(1S,4S)-4-isopropyll-4-({(1S,4S)-5-[6-(trifluoromethyl)pyridin-2-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopent-2-en-1-yl]amino}-4-O-methyl-D-erythro-pentitol

Prepared as described in example 1 starting with (1S,4S)-4-(2,5-dimethyl-1H-pyrrol-1-yl)-1-isopropylcyclopent-2-ene-1-carboxylic acid and skipping steps 1, 2 and 5. LC/MS (M+H) = 509.2739 exp, 509.2680 obs; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.55-7.52 (1H), 6.94-6.89 (1H), 6.52-6.40 (1H), 5.96-5.78 (2H), 5.12-4.84 (2H), 4.07-3.16 (13H), 2.90-2.69 (1H), 2.49-2.21 (1H), 2.12-1.42 (7H), 0.87-0.68 (3H)

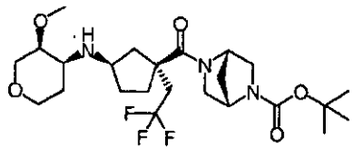
Example 43



1,5-anhydro-2,3-dideoxy-3-{[(1S,4S)-4-isopropyll-4-({(1S,4S)-5-[6-(trifluoromethyl)pyrazin-2-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopent-2-en-1-yl]amino}-4-O-methyl-D-erythro-pentitol

Prepared as described in example 3 starting with (1S,4S)-4-(2,5-dimethyl-1H-pyrrol-1-yl)-1-isopropylcyclopent-2-ene-1-carboxylic acid and skipping steps 1 and 2, skipping step 5, using (3R)-3-methoxytetrahydro-4H-pyran-4-one in step 6, and 2-chloro-6-(trifluoromethyl)pyrazine in place of 4-chloro-6-(trifluoromethyl)pyrimidine in step 8. LC/MS (M+H) = 510.2692 exp, 510.2699 obs; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.15 (1H), 8.04-7.95 (1H), 5.93-5.82 (2H), 5.17-4.91 (2H), 4.16-3.18 (13H), 2.91-2.69 (1H), 2.48-2.21 (1H), 2.10-1.52 (7H), 0.85-0.67 (6H)

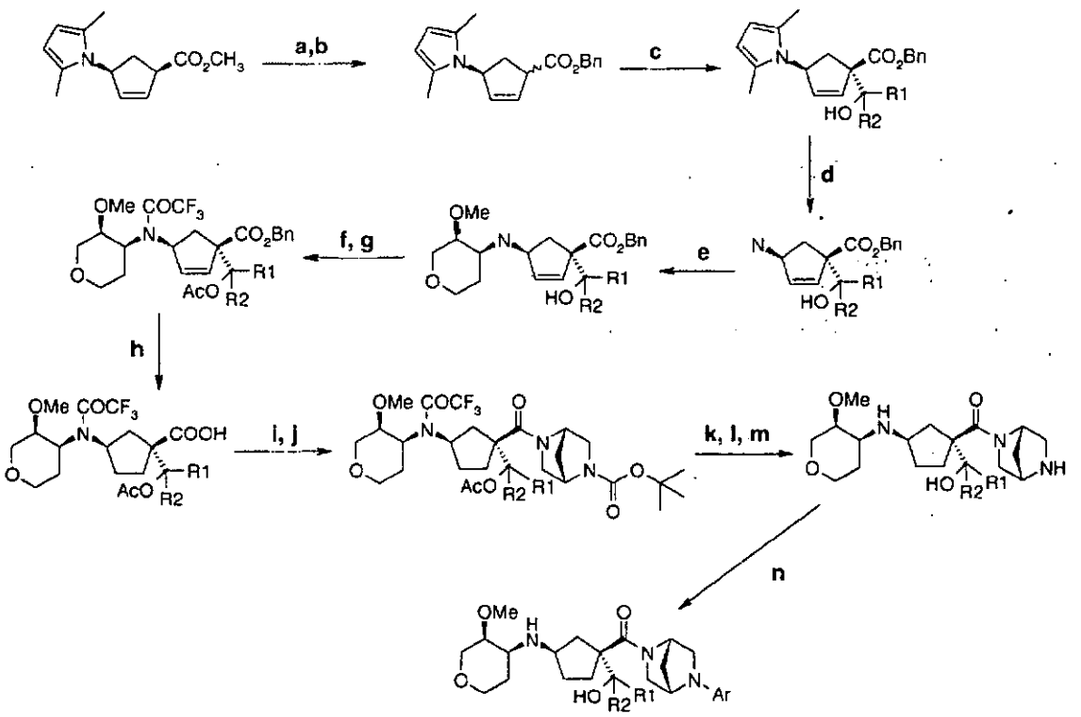
Example 44



1,5-anhydro-3-{[(1R,3S)-3-{[(1S,4S)-5-(tert-butoxycarbonyl)-2,5-diazabicyclo[2.2.1]hept-2-yl]carbonyl}-3-(2,2,2-trifluoroethyl)cyclopentyl]amino}-2,3-dideoxy-4-O-methyl-D-erythro-pentitol

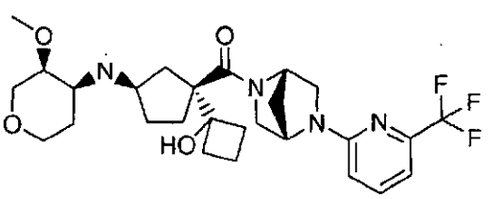
Prepared as described in example 24 using 2,2,2-trifluoroethanol in place of 2,2-difluoroethanol in step 1 and skipping steps 8 and 9. LC/MS (M+H) = 506.2842 exp, 506.3033 obs; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 4.86-4.65 (1H), 4.52-4.38 (1H), 4.09-4.03 (1H), 3.93-3.87 (1H), 3.68-3.23 (11H), 2.73-2.68 (1H), 2.55-2.24 (3H), 2.10-2.03 (1H), 1.96-1.89 (1H), 1.85-1.59 (7H), 1.54-1.47 (1H), 1.44-1.39 (9H)

Scheme 3. Preparation of Examples 45-59



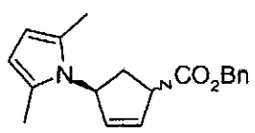
a) NaOH, MeOH, H_2O; b) BnOH, EDC, DMAP; c) LDA, R_1COR_2; d) $NH_2OH*HCl$, NH_2OH*H_2O, MeOH; e) MeO-pyranone, $Na(OAc)_3BH$; f) TFAA; g) AcCl, pyridine; h) H_2, Pt/C; i) $(COCl)_2$; j) arylpiperazine; k) K_2CO_3, MeOH; l) $NaBH_4$; m) HCl/dioxane; n) Ar-Cl, heat or Pd catalyst

Example 45



1,5-Anhydro-2,3-dideoxy-3-{[(1R,3S)-3-(1-hydroxycyclobutyl)-3-({(1S,4S)-5-[6-(trifluoromethyl)pyridin-2-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methyl-D-erythro-pentitol

Step 1. Benzyl (4S)-4-(2,5-dimethyl-1H-pyrrol-1-yl)cyclopent-2-ene-1-carboxylate

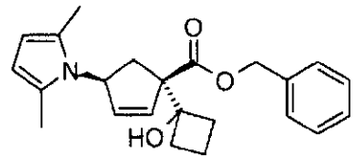


A solution of 11.04 g (50.4 mmol) of methyl (1R,4S)-4-(2,5-dimethyl-1H-pyrrol-1-yl)cyclopent-2-ene-1-carboxylate and 40 mL of 2.5 M sodium hydroxide in 100 mL of MeOH was stirred at ambient temperature for 45 minutes, then concentrated under reduced pressure to remove methanol. The residual aqueous solution was added to a stirred mixture of 20 g citric acid, 100 mL of water, and 100 mL of dichloromethane. The phases were separated and the aqueous extracted with two additional portions of dichloromethane. The organic phase was dried (Na_2SO_4) and concentrated under reduced pressure to provide the correponding acid as a brown gum (10.98 g).

To a stirred solution of this acid, 10 mL (96 mmol) of benzyl alcohol, and 1.74 g (14 mmol) of DMAP in 50 mL of dichloromethane was added 13 g (69 mmol) of EDC, in five equal portions over 30 min. After 18 h, the solution was concentrated under reduced pressure, and the residual syrup partitioned between ether and water. The organic phase was washed with water and brine, with one back-extraction of the aqueous phases with ether. The combined organic phase was dried ($MgSO_4$), and concentrated under reduced pressure. Flash chromatography of the crude material on silica using 10% ethyl acetate in heptane afforded 13.75 g (93%) of the title compound as a colorless oil. 1H NMR (400 MHz, CHLOROFORM-*d*) showed a 60:40 mixture of epimers: δ ppm 2.09 - 2.32 (m, 1 H) 2.20 (s, 6 H) 2.67 - 2.85 (m, 1 H) 3.62 - 3.70 (m, 0.6 H) 3.85 - 3.92 (m, 0.4 H) 5.16 (2s, 2 H) 5.26 - 5.34 (m, 0.6 H) 5.49 - 5.56 (m, 0.4 H) 5.74 (br. s.,

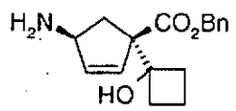
2 H) 5.93 - 6.04 (m, 2 H) 7.30 - 7.42 (m, 5 H). TLC Rf 0.32 and 0.25 (10% ethyl acetate in hexane). LC-MS ES+ 296.2.

Step 2. Benzyl (1R,4S)-4-(2,5-dimethyl-1H-pyrrol-1-yl)-1-(1-hydroxycyclobutyl)cyclopent-2-ene-1-carboxylate



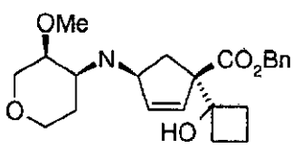
To a cold (-78 C), stirred solution of 6.17 g (20.9 mmol) of benzyl (4S)-4-(2,5-dimethyl-1H-pyrrol-1-yl)cyclopent-2-ene-1-carboxylate (Preparation SRT-0233) in 40 mL of dry THF, under Ar, was slowly added 23.3 mL of a commercial 1.8 M solution of LDA. The resulting solution was warmed to 0 C, stirreed at that temperature for 10 min, and then recooled to -78 C for the addition of 2.3 mL (31 mmol) of cyclobutanone. This solution was stirred at -78 C for 1 h, then quenched at -78 C by the slow addition of a solution of 4.0 mL of 12N HCl in 10 mL of THF. Ethyl acetate and excess 1 M citric acid were added and the mixture was allowed to warm to RT. Extractive workup was followed by flash chromatography on silica using 25% ethyl acetate in heptane to provide 5.55 g (73%) of the title compound as a thick amber oil. ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.44 - 1.56 (m, 1 H) 1.88 - 2.31 (m, 6 H) 2.12 (s, 6 H) 2.27 (dd, *J*=14.7, 7.5 Hz, 1 H) 2.76 (dd, *J*=14.5, 9.0 Hz, 1 H) 5.18 (s, 2 H) 5.26 - 5.32 (m, 1 H) 5.71 (s, 2 H) 6.06 (dd, 1 H) 6.10 (dd, 1 H) 7.30 - 7.39 (m, 5 H). TLC Rf 0.36 (30% ethyl acetate in hexane). LC-MS ES+ 366.2.

Step 3. Benzyl (1R,4S)-4-amino-1-(1-hydroxycyclobutyl)cyclopent-2-ene-1-carboxylate



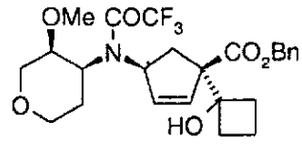
A mixture of 5.52 g (15.1 mmol) of benzyl (1R,4S)-4-(2,5-dimethyl-1H-pyrrol-1-yl)-1-(1-hydroxycyclobutyl)cyclopent-2-ene-1-carboxylate (Preparation SRT-0229), 8.20 g (120 mmol) of hydroxylamine hydrochloride, and 7.0 mL of 50% aqueous hydroxylamine (100 mmol) in 50 mL of methanol was heated at 68 C for 8 h, then cooled. Sufficient water was added to dissolve the crystals which deposited, and the solution was concentrated under reduced pressure to remove methanol. The resulting mixture was brought to pH ~10 with aq. NaOH and then extracted with several portions of dichloromethane. The organic phase was dried over Na_2SO_4 and then concentrated under reduced pressure to afford 4.15 g (96%) of the title amine as a nearly colorless oil, of sufficient purity for the subsequent reaction. ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.42 - 1.53 (m, 1 H) 1.85 (dd, 1 H) 1.88 - 2.08 (m, 4 H) 2.19 - 2.27 (m, 1 H) 2.46 (dd, *J*=14.5, 8.3 Hz, 1 H) 3.97 - 4.02 (m, 1 H) 4.70 (s, 1 H) 5.16 (s, 2 H) 5.84 (dd, *J*=5.6, 1.6 Hz, 1 H) 5.98 (dd, *J*=5.6, 2.1 Hz, 1 H) 7.31 - 7.38 (m, 5 H). LC-MS ES+ 288.2.

Step 4. 1,5-Anhydro-3-{[(1S,4R)-4-[(benzyloxy)carbonyl]-4-(1-hydroxycyclobutyl)cyclopent-2-en-1-yl]amino}-2,3-dideoxy-4-O-methyl-D-erythro-pentitol



A solution of 3.83 g (13.3 mmol) of benzyl (1R,4S)-4-amino-1-(1-hydroxycyclobutyl)cyclopent-2-ene-1-carboxylate (Preparation SRT-0235) and 1.89 g (14.5 mmol) of (3R)-3-methoxytetrahydro-4H-pyran-4-one in 26 mL of dichloromethane was stirred with activated 3A molecular sieves for 10 min, then cooled to 0 C. Sodium triacetoxyborohydride (3.35 g, 15.8 mmol) was added in several portions over 10 min, and the mixture was stirred for 1.5 h. The cloudy mixture was added to dichloromethane and aqueous $NaHCO_3$ + NaOH (pH ~14), and the aqueous phase was extracted with several additional portions of dichloromethane. The organic phase was dried (Na_2SO_4) and concentrated under reduced pressure. Flash chromatography of the residue on silica using 3-5% methanolic ammonia (7M) in dichloromethane afforded 3.94 g (74%) of the title compound as a yellow oil. ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.41 - 1.52 (m, 1 H) 1.55 - 1.64 (m, 1 H) 1.64 - 1.79 (m, 2 H) 1.86 - 2.09 (m, 5 H) 2.19 - 2.29 (m, 1 H) 2.41 (dd, *J*=14.2, 7.7 Hz, 1 H) 2.84 - 2.91 (m, 1 H) 3.17 - 3.44 (m, 4 H) 3.34 (s, 3 H) 3.88 - 3.96 (m, 2 H) 4.00 (dd, *J*=12.3, 4.4 Hz, 1 H) 5.10 - 5.20 (m, 2 H) 5.88 - 5.93 (m, 1 H) 6.00 (dd, *J*=5.6, 1.9 Hz, 1 H) 7.28 - 7.39 (m, 5 H). TLC Rf 0.41 (4% 7M methanolic ammonia in dichloromethane). LC-MS ES+ 402.1.

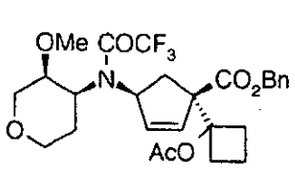
Step 5. 1,5-Anhydro-3-{[(1S,4R)-4-[(benzyloxy)carbonyl]-4-(1-hydroxycyclobutyl)cyclopent-2-en-1-yl](trifluoroacetyl)amino}-2,3-dideoxy-4-O-methyl-D-erythro-pentitol



To a cold (0 C), stirred solution of 805 mg (2.00 mmol) of 1,5-anhydro-3-{[(1S,4R)-4-[(benzyloxy)carbonyl]-4-(1-hydroxycyclobutyl)cyclopent-2-en-1-yl]amino}-2,3-dideoxy-4-O-methyl-D-erythro-pentitol and 0.87 mL (5.0 mmol) of diisopropylethylamine in 6 mL of dichloromethane was added dropwise 0.61 mL (4.4 mmol) of trifluoroacetic anhydride. The solution was stirred for 2 h, then

stirred with aqueous sodium citrate for 30 min. The organic phase was separated, dried (Na_2SO_4), and concentrated under reduced pressure to 1.36 g of brown oil. This was dissolved in 5 mL of methanol and treated with 2 mL of 7M methanolic ammonia. After 1 h, the solution was concentrated under reduced pressure, and the residue chromatographed on silica using 15-20% ethyl acetate in dichloromethane to provide 1.11 g (111%) of the title compound as an amber oil, still retaining some solvent. ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.37 - 1.49 (m, 1 H) 1.50 - 1.57 (m, 1 H) 1.78 - 2.00 (m, 3 H) 2.01 - 2.10 (m, 1 H) 2.26 - 2.38 (m, 3 H) 2.40 - 2.53 (m, 1 H) 3.10 (br. s., 0 H) 3.31 (d, *J*=13.0 Hz, 1 H) 3.39 - 3.45 (m, 1 H) 3.43 (s, 3 H) 3.50 (t, *J*=11.4 Hz, 1 H) 3.89 (d, *J*=11.6 Hz, 1 H) 4.06 - 4.14 (m, 1 H) 4.19 (d, *J*=13.0 Hz, 1 H) 5.00 (t, 1 H) 5.14 (d, *J*=12.3 Hz, 1 H) 5.30 (d, *J*=12.3 Hz, 1 H) 5.78 (dd, *J*=5.8, 2.0 Hz, 1 H) 6.12 (dd, *J*=5.8, 2.0 Hz, 1 H) 6.57 (br. s., 1 H) 7.28 - 7.42 (m, 5 H). TLC Rf 0.34 (25% ethyl acetate in dichloromethane). LC-MS ES+ 498.2.

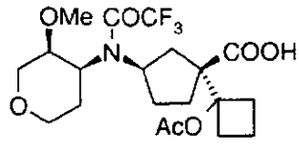
Step 6. 3-[{(1S,4R)-4-[1-(Acetyloxy)cyclobutyl]-4-[(benzyloxy)carbonyl]cyclopent-2-en-1-yl}(trifluoroacetyl)amino]-1,5-anhydro-2,3-dideoxy-4-O-methyl-D-erythro-pentitol



To a stirred solution of 3.58 g (7.2 mmol) of 1,5-anhydro-3-{[(1S,4R)-4-[(benzyloxy)carbonyl]-4-(1-hydroxycyclobutyl)cyclopent-2-en-1-yl](trifluoroacetyl)amino}-2,3-dideoxy-4-O-methyl-D-erythro-pentitol, 1.6 mL (9.2 mmol) of diisopropylethylamine, and 100 mg (0.82 mmol) of DMAP in 10 mL of dichloromethane was added dropwise 5.1 mL (72 mmol) of acetyl chloride. The solution was stirred at ambient temperature for 18 h, then cooled in ice and quenched with aqueous $NaHCO_3$. The aqueous phase was extracted with additional dichloromethane, and the combined organic phases dried (Na_2SO_4)

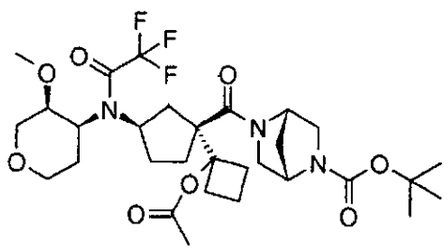
and concentrated under reduced pressure. Flash chromatography of the residue on silica using 8-10% ethyl acetate in dichloromethane provided 2.63 g (68%) of the title compound as a viscous yellow oil. ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.35 - 1.48 (m, 1 H) 1.54 - 1.61 (m, 1 H) 1.82 - 1.94 (m, 1 H) 1.88 (s, 3 H) 2.17 - 2.26 (m, 1 H) 2.34 (dd, *J*=14.7, 9.9 Hz, 1 H) 2.43 - 2.64 (m, 5 H) 3.32 (d, *J*=12.6 Hz, 1 H) 3.37 - 3.43 (m, 1 H) 3.43 (s, 3 H) 3.46 - 3.55 (m, 1 H) 3.84 - 3.94 (m, 1 H) 4.09 - 4.15 (m, 1 H) 4.19 (d, *J*=13.0 Hz, 1 H) 4.98 - 5.05 (m, 1 H) 5.08 (d, *J*=12.3 Hz, 1 H) 5.23 (d, *J*=12.3 Hz, 1 H) 5.75 (dd, *J*=5.8, 2.0 Hz, 1 H) 6.16 (dd, *J*=5.8, 2.4 Hz, 1 H) 7.28 - 7.43 (m, 5 H). TLC Rf 0.39 (10% ethyl acetate-dichloromethane). LC-MS ES+ 540.2.

Step 7. 3-[{(1R,3S)-3-[1-(Acetyloxy)cyclobutyl]-3-carboxycyclopentyl}(trifluoroacetyl)amino]-1,5-anhydro-2,3-dideoxy-4-O-methyl-D-erythro-pentitol



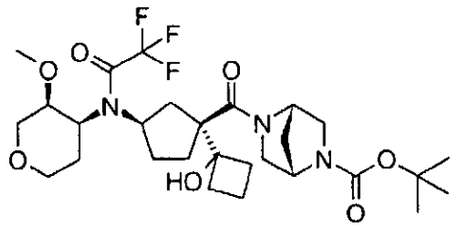
A mixture of 2.62 g (4.86 mmol) of 3-[{(1S,4R)-4-[1-(acetyloxy)cyclobutyl]-4-[(benzyloxy)carbonyl]cyclopent-2-en-1-yl}(trifluoroacetyl)amino]-1,5-anhydro-2,3-dideoxy-4-O-methyl-D-erythro-pentitol and 750 mg each of 5% Pt/C and 5% Pd/C in 10 mL of acetic acid was stirred rapidly under 50 psi hydrogen gas for 18 h, then filtered through diatomaceous earth to remove catalyst. The filtrate was concentrated under reduced pressure, with added toluene to azeotropically remove acetic acid, to provide 2.25 g (103%) of the title compound as a white foam. ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.50 - 1.71 (m, 3 H) 1.74 - 1.84 (m, 1 H) 2.02 (s, 3 H) 2.04 - 2.17 (m, 1 H) 2.34 - 2.55 (m, 5 H) 2.60 (dd, *J*=14.3, 8.5 Hz, 1 H) 2.66 - 2.81 (m, 2 H) 3.30 (d, *J*=13.0 Hz, 1 H) 3.35 - 3.39 (m, 1 H) 3.42 (s, 3 H) 3.47 - 3.56 (m, 1 H) 3.83 - 3.91 (m, 1 H) 4.13 (dd, *J*=11.6, 4.4 Hz, 1 H) 4.16 - 4.23 (m, 1 H) 4.26 - 4.38 (m, 1 H). LC-MS ES+ 452.1.

Step 8. 3-{[(1R,3S)-3-[1-(Acetyloxy)cyclobutyl]-3-{[(1S,4S)-5-(tert-butoxycarbonyl)-2,5-diazabicyclo[2.2.1]hept-2-yl]carbonyl}cyclopentyl](trifluoroacetyl)amino}-1,5-anhydro-2,3-dideoxy-4-O-methyl-D-erythro-pentitol



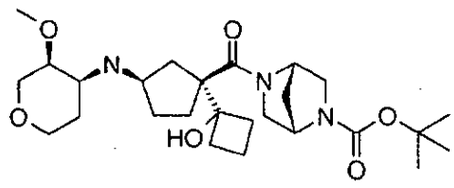
A stirred solution of 1.42 g (3.15 mmol) of 3-[{(1R,3S)-3-[1-(acetyloxy)cyclobutyl]-3-carboxycyclopentyl}(trifluoroacetyl)amino]-1,5-anhydro-2,3-dideoxy-4-O-methyl-D-erythro-pentitol in 6 mL of dichloromethane was treated under argon with 6.5 mL of a 2M dichloromethane solution of oxalyl chloride and 2 drops of dry DMF. After 2 h, the solution was taken to dryness under reduced pressure to give the acid chloride as a yellow foam.
This material was dissolved in 8 mL of dichloromethane. To 6 mL of the stirred solution was added 562 mg (2.84 mmol) of (1S,4S)-(-)-2-Boc-2,5-diazabicyclo[2.2.1]heptane and 1.2 mL (6.9 mmol) of diisopropylethylamine. The reaction mixture was stirred at ambient temperature for 18 h, then partitioned between dichloromethane and 1M aqueous citric acid. The organic phase was dried (Na_2SO_4) and concentrated under reduced pressure. Flash chromatography of the residue on silica using 40-50% ethyl acetate in dichloromethane afforded 1.44 g (97%) of the title compound as a white foam. ^1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.34 - 1.62 (m, 12 H) 1.73 - 1.88 (m, 2 H) 1.88 - 2.27 (m, 7 H) 2.29 - 2.41 (m, 1 H) 2.40 - 2.65 (m, 4 H) 2.66 - 2.80 (m, 1 H) 3.27 - 3.64 (m, 9 H) 3.81 - 3.89 (m, 1 H) 4.08 - 4.24 (m, 2 H) 4.37 - 4.60 (m, 2 H) 4.85 - 4.94 (m, 1 H). TLC Rf 0.36 (1:1 ethyl acetate in dichloromethane). LC-MS ES+ 632.3.

Step 9. 1,5-Anhydro-3-{[(1R,3S)-3-{[(1S,4S)-5-(tert-butoxycarbonyl)-2,5-diazabicyclo[2.2.1]hept-2-yl]carbonyl}-3-(1-hydroxycyclobutyl)cyclopentyl](trifluoroacetyl)amino}-2,3-dideoxy-4-O-methyl-D-erythro-pentitol



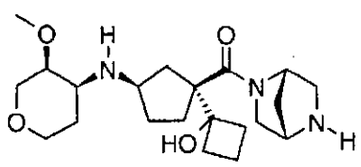
A mixture of 1.43 g (2.26 mmol) of 3-{[(1R,3S)-3-[1-(acetyloxy)cyclobutyl]-3-{[(1S,4S)-5-(tert-butoxycarbonyl)-2,5-diazabicyclo[2.2.1]hept-2-yl]carbonyl}cyclopentyl](trifluoroacetyl)amino}-1,5-anhydro-2,3-dideoxy-4-O-methyl-D-erythro-pentitol and 1.60 g (11.6 mmol) of powdered potassium carbonate in 8 mL of methanol was stirred at ambient temperature for 18 h, then partitioned between dichloromethane and brine, with sufficient water to dissolve solids. The organic phase was dried (Na_2SO_4) and concentrated under reduced pressure. Flash chromatography of the residue on silica using acetate to provide 1.33 g (100%) of the title compound as a white foam. ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.34 - 1.62 (m, 10 H) 1.66 - 2.93 (m, 15 H) 3.20 - 3.63 (m, 8 H) 3.66 - 4.03 (m, 3 H) 4.06 - 4.24 (m, 3 H) 4.25 - 4.65 (m, 2 H) 4.68 - 5.29 (m, 1 H). TLC Rf 0.33 (EtOAc). LC-MS ES+ 590.3.

Step 10. 1,5-Anhydro-3-{[(1R,3S)-3-{[(1S,4S)-5-(tert-butoxycarbonyl)-2,5-diazabicyclo[2.2.1]hept-2-yl]carbonyl}-3-(1-hydroxycyclobutyl)cyclopentyl]amino}-2,3-dideoxy-4-O-methyl-D-erythro-pentitol



A mixture of 1.31 g (2.23 mmol) of 1,5-anhydro-3-{[(1R,3S)-3-{[(1S,4S)-5-(tert-butoxycarbonyl)-2,5-diazabicyclo[2.2.1]hept-2-yl]carbonyl}-3-(1-hydroxycyclobutyl)cyclopentyl](trifluoroacetyl)amino}-2,3-dideoxy-4-O-methyl-D-erythro-pentitol and 860 mg (23 mmol) of sodium borohydride in 6.3 mL of ethanol was stirred at ambient temperature for 18 h, then partitioned between water and dichloromethane. The aqueous phase was extracted with additional dichloromethane, and the combined organic phase dried (Na_2SO_4) and concentrated under reduced pressure. Flash chromatography on silica using 6-15% methanol in dichloromethane afforded 1.08 g (98%) of the title compound as a white foam. ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.42 - 1.47 (m, 9 H) 1.56 - 2.35 (m, 14 H) 2.72 (br. s., 1 H) 3.11 - 3.68 (m, 10 H) 3.90 - 3.98 (m, 1 H) 4.08 (dd, *J*=12.6, 2.7 Hz, 1 H) 4.38 - 4.58 (m, 1 H) 4.84 - 5.16 (m, 1 H). LC-MS ES+ 494.3. HRMS calculated for $C_{26}H_{43}N_3O_6$: 494.3230; found: 494.3260.

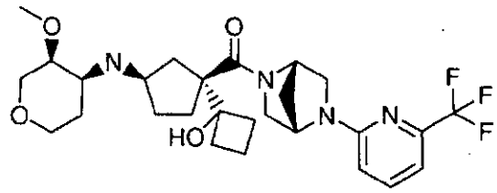
Step 11. 1,5-Anhydro-2,3-dideoxy-3-{[(1R,3S)-3-[(1S,4S)-2,5-diazabicyclo[2.2.1]hept-2-ylcarbonyl]-3-(1-hydroxycyclobutyl)cyclopentyl]amino}-4-O-methyl-D-erythro-pentitol dihydrochloride



To 902 mg (1.827 mmol) of 1,5-anhydro-3-{[(1R,3S)-3-{[(1S,4S)-5-(tert-butoxycarbonyl)-2,5-diazabicyclo[2.2.1]hept-2-yl]carbonyl}-3-(1-hydroxycyclobutyl)cyclopentyl]amino}-2,3-dideoxy-4-O-methyl-D-erythro-pentitol was added 10 mL of 4M HCl in dioxane, and a few drops of methanol sufficient to give a clear solution. The solution was stirred at ambient temperature for 45 minutes, then concentrated under reduced pressure to give 973 mg of the intermediate salt as a foam. ^{1}H NMR (400 MHz, MeOD) δ ppm 1.57 - 1.70 (m, 1 H) 1.73 - 1.93 (m, 4 H) 1.93 - 2.10 (m, 4 H) 2.14 - 2.28 (m, 2 H) 2.29 - 2.44 (m, 3

H) 2.46 - 2.59 (m, 2 H) 3.35 - 3.77 (m, 12 H) 3.98 (dd, *J*=11.6, 4.4 Hz, 1 H) 4.26 (d, *J*=13.3 Hz, 1 H) 4.45 (s, 1 H) 5.21 (br. s., 1 H). LC-MS ES+ 394.2.

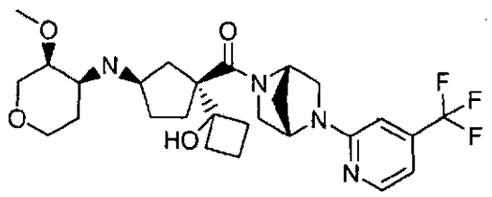
Example 45



1,5-Anhydro-2,3-dideoxy-3-{[(1R,3S)-3-(1-hydroxycyclobutyl)-3-({(1S,4S)-5-[6-(trifluoromethyl)pyridin-2-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methyl-D-erythro-pentitol

A solution of 93 mg (0.20 mmol) of 1,5-anhydro-2,3-dideoxy-3-{[(1R,3S)-3-[(1S,4S)-2,5-diazabicyclo[2.2.1]hept-2-ylcarbonyl]-3-(1-hydroxycyclobutyl)cyclopentyl]amino}-4-O-methyl-D-erythro-pentitol dihydrochloride, 91 mg (0.49 mmol) of 2-chloro-6-trifluoromethylpyridine, and 0.14 mL (0.80 mmol) of diisopropylethylamine in 0.5 mL of DMSO was heated at 80 C for 18 h, then cooled and partitioned between ethyl acetate and water. The organic phase was dried (Na_2SO_4) and concentrated under reduced pressure. The crude material was purified by preparative RP-HPLC using as the mobile phase acetonitrile-water containing 0.05% TFA. ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.46 - 2.52 (m, 16 H) 3.26 - 3.54 (m, 8 H) 3.53 - 3.92 (m, 4 H) 4.02 (dd, *J*=11.8, 4.3 Hz, 1 H) 4.22 (d, *J*=13.0 Hz, 1 H) 5.01 (d, *J*=14.3 Hz, 2 H) 6.47 (d, *J*=8.5 Hz, 1 H) 6.93 (d, *J*=7.5 Hz, 1 H) 7.56 (t, *J*=8.0 Hz, 1 H). HRMS calculated for $C_{27}H_{37}N_4O_4F_3$: 539.2845; found: 539.2894.

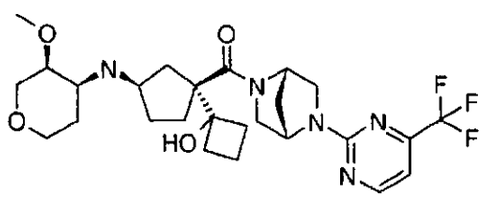
Example 46



1,5-Anhydro-2,3-dideoxy-3-{[(1R,3S)-3-(1-hydroxycyclobutyl)-3-({(1S,4S)-5-[4-(trifluoromethyl)pyridin-2-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methyl-D-erythro-pentitol

The title compound was prepared in a fashion analogous to that described in Preparation Ex. 45. ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.57 - 2.31 (m, 14 H) 2.33 - 2.47 (m, 2 H) 2.49 - 2.62 (m, 1 H) 3.28 - 3.54 (m, 7 H) 3.57 - 3.91 (m, 4 H) 4.02 (dd, *J*=11.8, 4.3 Hz, 1 H) 4.22 (d, *J*=13.3 Hz, 1 H) 5.07 (br. s., 1 H) 5.25 (s, 1 H) 6.88 - 6.96 (m, 2 H) 8.14 (d, *J*=6.5 Hz, 1 H). HRMS calculated for C27H37N4O4F3: 539.2845; found: 539.2894.

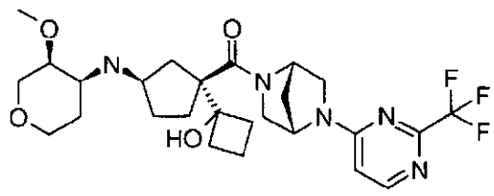
Example 47



1,5-Anhydro-2,3-dideoxy-3-{[(1R,3S)-3-(1-hydroxycyclobutyl)-3-({(1S,4S)-5-[4-(trifluoromethyl)pyrimidin-2-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methyl-D-erythro-pentitol

The title compound was prepared in a fashion analogous to that described in Preparation Example 45. ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.65 - 2.51 (m, 15 H) 2.52 - 2.64 (m, 1 H) 3.35 (s, 3 H) 3.44 (d, *J*=13.7 Hz, 1 H) 3.49 - 3.98 (m, 7 H) 4.19 (dd, *J*=11.4, 4.6 Hz, 1 H) 4.35 (d, *J*=14.0 Hz, 1 H) 5.07 - 5.48 (m, 2 H) 7.16 (d, *J*=6.5 Hz, 1 H) 8.49 (d, *J*=6.5 Hz, 1 H). HRMS calculated for C26H36N5O4F3: 540.2797; found: 540.2812.

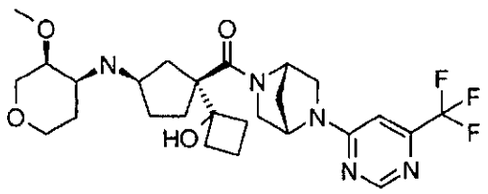
Example 48



1,5-Anhydro-2,3-dideoxy-3-{[(1R,3S)-3-(1-hydroxycyclobutyl)-3-({(1S,4S)-5-[2-(trifluoromethyl)pyrimidin-4-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methyl-D-erythro-pentitol

The title compound was prepared in a fashion analogous to that described in Preparation Example 45. ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.57 - 2.53 (m, 16 H) 3.31 (d, *J*=13.3 Hz, 1 H) 3.35 - 3.79 (m, 10 H) 4.03 (dd, *J*=11.4, 4.3 Hz, 1 H) 4.23 (d, *J*=12.6 Hz, 1 H) 5.11 (s, 1 H) 5.29 (br. s., 1 H) 6.23 - 6.75 (m, 2 H) 8.30 (d, *J*=6.1 Hz, 1 H). HRMS calculated for C26H36N5O4F3: 540.2797; found: 540.2891.

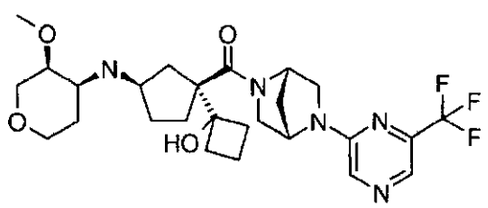
Example 49



1,5-anhydro-2,3-dideoxy-3-{[(1R,3S)-3-(1-hydroxycyclobutyl)-3-({(1S,4S)-5-[6-(trifluoromethyl)pyrimidin-4-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methyl-D-erythro-pentitol

The title compound was prepared in a fashion analogous to that described in Preparation Example 45. ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.56 - 2.35 (m, 14 H) 2.36 - 2.44 (m, 1 H) 2.45 - 2.54 (m, 1 H) 3.32 (d, *J*=13.3 Hz, 1 H) 3.36 - 3.92 (m, 10 H) 4.04 (dd, *J*=12.3, 4.1 Hz, 1 H) 4.24 (d, *J*=13.0 Hz, 1 H) 5.15 (s, 1 H) 5.23 - 5.30 (m, 1 H) 6.45 - 7.05 (m, 3 H) 8.67 (s, 1 H). HRMS calculated for C26H36N5O4F3: 540.2797; found: 540.2830.

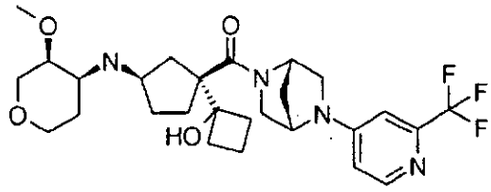
Example 50



1,5-Anhydro-2,3-dideoxy-3-{[(1R,3S)-3-(1-hydroxycyclobutyl)-3-({(1S,4S)-5-[6-(trifluoromethyl)pyrazin-2-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methyl-D-erythro-pentitol

A solution of 93 mg (0.20 mmol) of 1,5-anhydro-2,3-dideoxy-3-{[(1R,3S)-3-[(1S,4S)-2,5-diazabicyclo[2.2.1]hept-2-ylcarbonyl]-3-(1-hydroxycyclobutyl)cyclopentyl]amino}-4-O-methyl-D-erythro-pentitol dihydrochloride 121 mg (0.442 mmol) of 2-iodo-6-trifluoromethylpyrazine, 326 mg (1.0 mmol) of cesium carbonate, 24 mg (40 umol) of XantPhos, and 16 mg (28 umol) of tris(dibenzylideneacetone) palladium (0) in 0.8 mL of dioxane and 0.4 mL of DMSO was heated at 80 C under argon for 18 h, then cooled and partitioned between ethyl acetate and water. The organic phase was dried (Na_2SO_4) and concentrated under reduced pressure. Flash chromatography of the residue on silica using 0-2-4% methanolic ammonia and 3% methanol in dichloromethane afforded 89 mg (82%) of the title compound. ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.51 - 2.40 (m, 16 H) 2.65 - 2.74 (m, 1 H) 3.09 - 3.49 (m, 10 H) 3.54 (d, *J*=9.6 Hz, 1 H) 3.61 - 3.80 (m, 2 H) 3.88 - 3.96 (m, 1 H) 4.06 (dd, *J*=12.5, 2.9 Hz, 1 H) 4.96 (br. s., 1 H) 5.21 (br. s., 1 H) 8.02 (s, 1 H) 8.15 (s, 1 H). HRMS calculated for C26H36N5O4F3: 540.2797; found: 540.2896.

Example 51

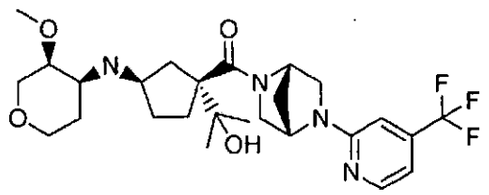


1,5-Anhydro-2,3-dideoxy-3-{[(1R,3S)-3-(1-hydroxycyclobutyl)-3-({(1S,4S)-5-[2-(trifluoromethyl)pyridin-4-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methyl-D-erythro-pentitol

The title compound was prepared in a fashion analogous to that described in Example 45. ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.51 - 2.40 (m, 18 H) 2.65 - 2.73 (m, 1 H) 3.04 - 3.47 (m, 8 H) 3.59 (d, *J*=8.5 Hz, 1 H) 3.70 (d, *J*=9.9 Hz, 1 H) 3.86 - 3.95 (m, 1 H) 4.05 (dd, *J*=12.3, 2.4 Hz, 1 H) 4.52 (s, 1 H) 5.17 (br.

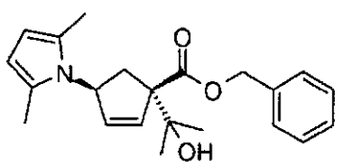
s., 1 H) 6.48 (br. s., 1 H) 6.72 (br. s., 1 H) 8.26 (d, *J*=5.8 Hz, 1 H). HRMS calculated for C27H37N4O4F3: 539.2845; found: 539.2979.

Example 52



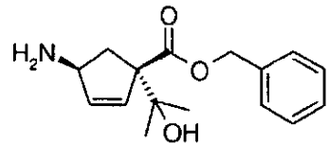
1,5-Anhydro-2,3-dideoxy-3-{[3-(1-hydroxy-1-methylethyl)-3-({5-[4-(trifluoromethyl)pyridin-2-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methylpentitol

Step 1. Benzyl 4-(2,5-dimethyl-1H-pyrrol-1-yl)-1-(1-hydroxy-1-methylethyl)cyclopent-2-ene-1-carboxylate



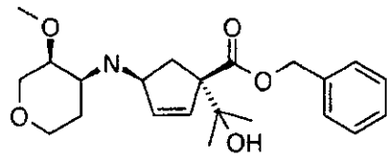
The title compound was prepared in a manner analogous to that described in Example 45, Step 2 above. ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.18 (s, 3 H) 1.22 (s, 3 H) 2.11 (s, 6 H) 2.22 (dd, *J*=14.7, 7.5 Hz, 1 H) 2.88 (dd, *J*=14.7, 8.5 Hz, 1 H) 3.43 (s, 1 H) 5.15 - 5.23 (m, 2 H) 5.24 - 5.31 (m, 1 H) 5.71 (s, 2 H) 5.99 (dd, 1 H) 6.03 (dd, 1 H) 7.30 - 7.40 (m, 5 H). TLC Rf 0.29 (30% ethyl acetate in hexane). LC-MS ES+ 354.2.

Step 2 Benzyl 4-amino-1-(1-hydroxy-1-methylethyl)cyclopent-2-ene-1-carboxylate



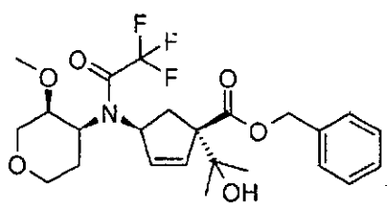
The title compound was prepared in a manner analogous to that described in Example 45, Step 3 above. ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.11 (s, 3 H) 1.14 (s, 3 H) 1.81 (dd, *J*=14.5, 4.9 Hz, 1 H) 1.85 - 1.92 (m, 1 H) 2.67 (dd, *J*=14.3, 8.2 Hz, 1 H) 3.97 - 4.03 (m, 1 H) 5.18 (s, 2 H) 5.83 (dd, 1 H) 5.89 (dd, 1 H) 7.32 - 7.42 (m, 5 H). LC-MS ES+ 276.2.

Step 3 1,5-Anhydro-3-({4-[(benzyloxy)carbonyl]-4-(1-hydroxy-1-methylethyl)cyclopent-2-en-1-yl}amino)-2,3-dideoxy-4-O-methylpentitol



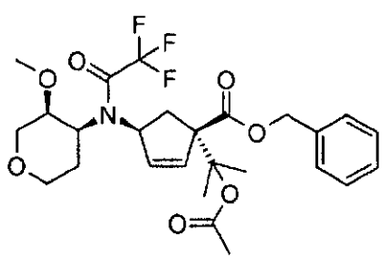
The title compound was prepared in a manner analogous to that described in Example 45,step 4 above. ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.11 (s, 3 H) 1.15 (s, 3 H) 1.41 - 1.66 (m, 2 H) 1.68 - 1.80 (m, 1 H) 1.87 - 1.94 (m, 1 H) 2.56 - 2.65 (m, 1 H) 2.82 - 2.89 (m, 1 H) 3.24 - 3.46 (m, 7 H) 3.87 - 3.97 (m, 2 H) 3.98 - 4.07 (m, 1 H) 5.11 - 5.21 (m, 2 H) 5.84 - 5.97 (m, 2 H) 7.30 - 7.41 (m, 5 H). TLC Rf 0.34 (4% methanolic ammonia in dichloromethane). LC-MS ES+ 390.2.

Step 4. 1,5-Anhydro-3-[{4-[(benzyloxy)carbonyl]-4-(1-hydroxy-1-methylethyl)cyclopent-2-en-1-yl}(trifluoroacetyl)amino]-2,3-dideoxy-4-O-methylpentitol



The title compound was prepared in a manner analogous to that described in example 45, step 5 above. ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.35 - 1.75 (m, 2 H) 1.78 - 2.08 (m, 4 H) 2.24 - 2.54 (m, 4 H) 3.31 (d, *J*=12.6 Hz, 1 H) 3.38 - 3.45 (m, 2 H) 3.43 (s, 3 H) 3.45 - 3.55 (m, 1 H) 3.84 - 3.94 (m, 1 H) 4.07 - 4.14 (m, 1 H) 4.19 (d, *J*=13.0 Hz, 1 H) 4.95 - 5.05 (m, 1 H) 5.14 (d, *J*=12.3 Hz, 1 H) 5.31 (d, 1 H) 5.78 (dd, *J*=5.6, 2.2 Hz, 1 H) 6.12 (dd, *J*=5.8, 2.4 Hz, 1 H) 7.27 - 7.44 (m, 5 H). Rf ~0.34 (25% ethyl acetate-dichloromethane). LC-MS ES+ 498.2.

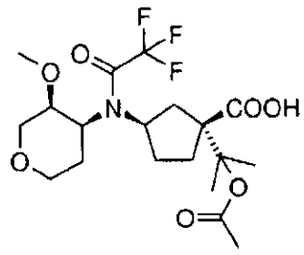
Step 5. 3-[{4-[1-(acetyloxy)-1-methylethyl]-4-[(benzyloxy)carbonyl]cyclopent-2-en-1-yl}(trifluoroacetyl)amino]-1,5-anhydro-2,3-dideoxy-4-O-methylpentitol



The title compound was prepared in a manner analogous to that described in example 45, step 6 above. ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.49 (s, 3 H) 1.53 - 1.61 (m, 4 H) 1.82 - 1.86 (m, 3 H) 2.38 - 2.57 (m, 2 H) 3.32 (d, *J*=13.0 Hz, 1 H) 3.37 - 3.44 (m, 3 H) 3.45 - 3.56 (m, 2 H) 3.84 - 3.95 (m, 1 H) 4.05 - 4.23 (m, 2 H) 4.93 - 5.04 (m, 1 H) 5.08 - 5.15 (m, 1 H) 5.26 - 5.36 (m, 3 H) 6.11 (dd,

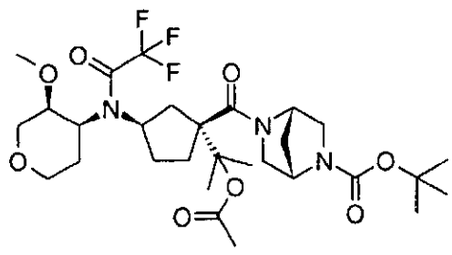
J=5.8, 2.4 Hz, 1 H) 7.28 - 7.42 (m, 5 H). TLC Rf 0.29 (40% ethyl acetate-hexane). LC-MS ES+ 550.2 for M+Na.

Step 6. 3-[{3-[1-(Acetyloxy)-1-methylethyl]-3-carboxycyclopentyl}(trifluoroacetyl)amino]-1,5-anhydro-2,3-dideoxy-4-O-methylpentitol



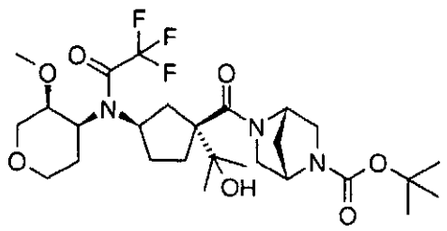
The title compound was prepared in a manner analogous to that described in example 45, step 7 above. ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 0.86 (none, 1 H) 1.51 - 1.91 (m, 10 H) 2.02 - 2.04 (m, 3 H) 2.24 - 2.54 (m, 3 H) 3.31 (d, *J*=13.0 Hz, 1 H) 3.37 (br. s., 1 H) 3.41 - 3.46 (m, 3 H) 3.46 - 3.56 (m, 1 H) 3.82 - 3.91 (m, 1 H) 4.08 - 4.16 (m, 1 H) 4.16 - 4.23 (m, 1 H) 4.25 - 4.39 (m, 1 H). LC-MS ES+ 440.2.

Step 7. 3-[(3-[1-(Acetyloxy)-1-methylethyl]-3-{[5-(tert-butoxycarbonyl)-2,5-diazabicyclo[2.2.1]hept-2-yl]carbonyl}cyclopentyl)(trifluoroacetyl)amino]-1,5-anhydro-2,3-dideoxy-4-O-methylpentitol



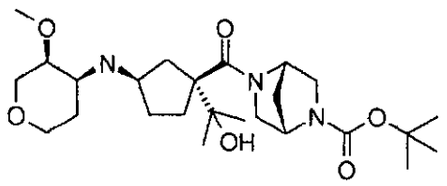
The title compound was prepared in a manner analogous to that described in example 45, step 8 above. ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.35 - 1.51 (m, 9 H) 1.54 - 1.66 (m, 6 H) 1.72 - 1.87 (m, 2 H) 1.97 - 2.33 (m, 7 H) 2.36 - 2.65 (m, 2 H) 3.25 - 3.68 (m, 9 H) 3.80 - 3.90 (m, 1 H) 4.06 - 4.25 (m, 2 H) 4.34 - 4.64 (m, 2 H) 4.88 - 4.99 (m, 1 H). TLC Rf 0.38. LC-MS ES+ 642.3 (M+Na).

Step 8. 1,5-Anhydro-3-{[3-{[5-(tert-butoxycarbonyl)-2,5-diazabicyclo[2.2.1]hept-2-yl]carbonyl}-3-(1-hydroxy-1-methylethyl)cyclopentyl](trifluoroacetyl)amino}-2,3-dideoxy-4-O-methylpentitol



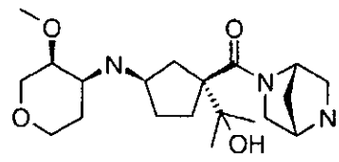
The title compound was prepared in a manner analogous to that described in example 45, Step 9 above. ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.08 - 1.28 (m, 5 H) 1.36 - 2.77 (m, 18 H) 3.25 - 3.57 (m, 8 H) 3.68 - 3.91 (m, 2 H) 4.06 - 4.24 (m, 2 H) 4.37 - 4.73 (m, 2 H) 4.82 - 5.00 (m, 1 H). TLC Rf 0.30 (2% MeOH in ethyl acetate). LC-MS ES+ 578.3.

Step 9. 1,5-anhydro-3-{[3-{[5-(tert-butoxycarbonyl)-2,5-diazabicyclo[2.2.1]hept-2-yl]carbonyl}-3-(1-hydroxy-1-methylethyl)cyclopentyl]amino}-2,3-dideoxy-4-O-methylpentitol



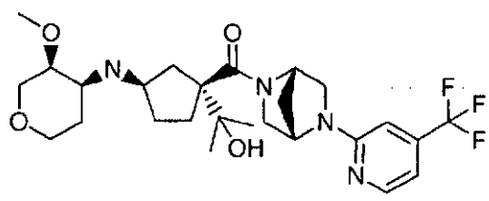
The title compound was prepared in a manner analogous to that described in example 45, step 10. ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.10 - 1.26 (m, 6 H) 1.37 - 1.90 (m, 16 H) 2.23 - 2.52 (m, 2 H) 2.63 - 2.74 (m, 1 H) 3.10 - 3.72 (m, 10 H) 3.84 - 3.97 (m, 1 H) 4.03 - 4.12 (m, 1 H) 4.34 - 4.62 (m, 1 H) 4.80 - 4.99 (m, 1 H). TLC Rf 0.19 (4% methanolic ammonia in dichloromethane). HRMS calculated for C25H43N3O6: 482.3230; found: 482.3276.

Step 10 1,5-Anhydro-2,3-dideoxy-3-{[3-(2,5-diazabicyclo[2.2.1]hept-2-ylcarbonyl)-3-(1-hydroxy-1-methylethyl)cyclopentyl]amino}-4-O-methylpentitol



The title compound was prepared in a manner analogous to that described in example 45, step 11 above. ^{1}H NMR (400 MHz, CD3OD) δ ppm 1.16 (s, 3 H) 1.23 - 1.25 (m, 3 H) 1.62 - 2.34 (m, 7 H) 2.66 (br. s., 2 H) 3.33 - 3.68 (m, 14 H) 3.98 (dd, *J*=11.8, 4.6 Hz, 1 H) 4.26 (d, *J*=13.3 Hz, 1 H) 4.44 (s, 1 H). LC-MS ES+ 382.3.

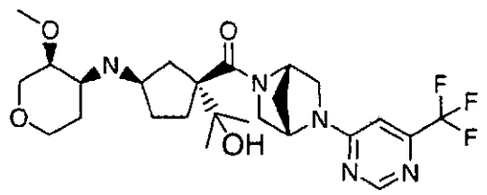
Example 52



1,5-Anhydro-2,3-dideoxy-3-{[3-(1-hydroxy-1-methylethyl)-3-({5-[4-(trifluoromethyl)pyridin-2-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methylpentitol

The title compound was prepared in a manner analogous to that described in Example 45. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.00 - 1.20 (m, 6 H) 1.48 - 1.60 (m, 1 H) 1.65 - 2.47 (m, 8 H) 3.13 - 3.22 (m, 1 H) 3.23 - 3.54 (m, 8 H) 3.55 - 3.64 (m, 1 H) 3.80 - 3.90 (m, 1 H) 4.08 - 4.16 (m, 1 H) 4.87 - 5.02 (m, 1 H) 5.15 - 5.26 (m, 1 H) 6.84 (d, *J*=5.1 Hz, 1 H) 8.28 (d, *J*=5.5 Hz, 1 H). HRMS calculated for C26H37N4O4F3: 527.2845; found: 527.2939.

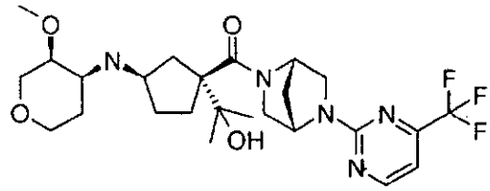
Example 53



1,5-Anhydro-2,3-dideoxy-3-{[3-(1-hydroxy-1-methylethyl)-3-({5-[6-(trifluoromethyl)pyrimidin-4-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methylpentitol

The title compound was prepared in a manner analogous to that described in Example 45. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.92 - 1.19 (m, 6 H) 1.48 - 1.62 (m, 1 H) 1.64 - 2.47 (m, 8 H) 3.09 - 3.68 (m, 10 H) 3.81 - 3.91 (m, 1 H) 4.06 - 4.18 (m, 1 H) 4.87 - 5.04 (m, 1 H) 5.09 - 5.33 (m, 1 H) 8.29 - 8.64 (m, 2 H). HRMS calculated for C25H36N5O4F3: 528.2797; found: 528.2812.

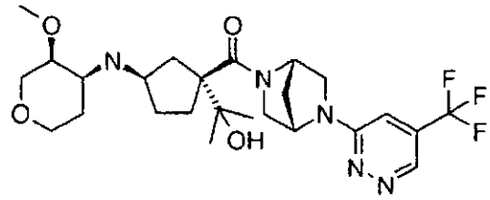
Example 54



1,5-Anhydro-2,3-dideoxy-3-{[3-(1-hydroxy-1-methylethyl)-3-({5-[4-(trifluoromethyl)pyrimidin-2-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methylpentitol

The title compound was prepared in a manner analogous to that described in Example 45. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.99 - 1.20 (m, 6 H) 1.45 - 1.64 (m, 1 H) 1.63 - 2.18 (m, 7 H) 2.25 - 2.47 (m, 2 H) 3.13 - 3.65 (m, 10 H) 3.78 - 3.91 (m, 1 H) 4.12 (dd, 1 H) 4.87 - 5.04 (m, 2 H) 5.20 (br. s., 1 H) 8.67 (d, *J*=3.8 Hz, 1 H). HRMS calculated for C25H36N5O4F3: 528.2797; found: 528.2856.

Example 55

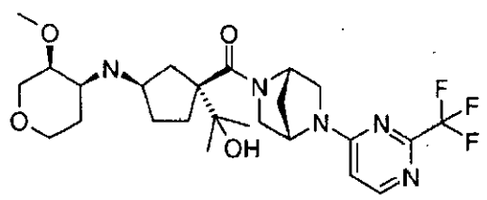


1,5-Anhydro-2,3-dideoxy-3-{[3-(1-hydroxy-1-methylethyl)-3-({5-[5-(trifluoromethyl)pyridazin-3-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methylpentitol

The title compound was prepared in a manner analogous to that described in Example 45. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.87 - 1.20 (m, 7 H) 1.49 -

2.46 (m, 10 H) 3.16 - 3.73 (m, 10 H) 3.79 - 3.89 (m, 1 H) 4.08 - 4.17 (m, 1 H) 5.20 - 5.31 (m, 1 H) 8.30 - 8.61 (m, 2 H) 8.84 (s, 1 H). HRMS calculated for C25H36N5O4F3: 528.2797; found: 528.2863.

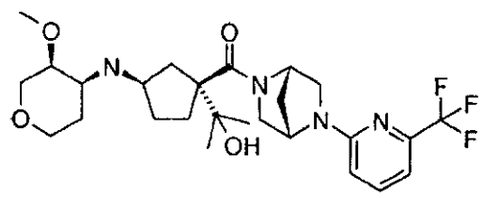
Example 56



1,5-Anhydro-2,3-dideoxy-3-{[3-(1-hydroxy-1-methylethyl)-3-({5-[2-(trifluoromethyl)pyrimidin-4-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methylpentitol

The title compound was prepared in a manner analogous to that described in Example 45. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.96 - 1.20 (m, 6 H) 1.45 - 2.48 (m, 9 H) 3.08 - 3.66 (m, 10 H) 3.80 - 3.89 (m, 1 H) 4.08 - 4.17 (m, 1 H) 4.85 - 5.11 (m, 1 H) 5.16 - 5.29 (m, 1 H) 8.27 - 8.34 (m, 1 H). HRMS calculated for C25H36N5O4F3: 528.2797; found: 528.2927.

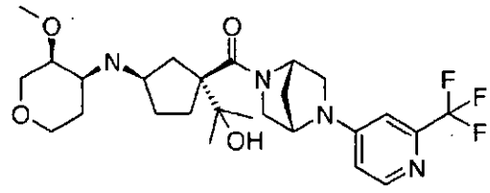
Example 57



1,5-Anhydro-2,3-dideoxy-3-{[3-(1-hydroxy-1-methylethyl)-3-({5-[6-(trifluoromethyl)pyridin-2-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methylpentitol

The title compound was prepared in a manner analogous to that described in Example 45. ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 0.82 - 1.37 (m, 6 H) 1.64 - 2.67 (m, 10 H) 3.19 - 3.78 (m, 11 H) 3.91 - 4.08 (m, 1 H) 4.15 - 4.28 (m, 1 H) 4.93 - 5.09 (m, 1 H) 6.40 - 6.54 (m, 1 H) 6.92 (d, *J*=7.2 Hz, 1 H) 7.55 (t, *J*=8.0 Hz, 1 H). HRMS calculated for C26H37N4O4F3: 527.2845; found: 527.2869.

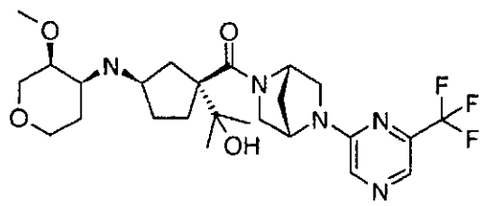
Example 58



1,5-Anhydro-2,3-dideoxy-3-{[3-(1-hydroxy-1-methylethyl)-3-({5-[2-(trifluoromethyl)pyridin-4-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methylpentitol

The title compound was prepared in a manner analogous to that described in Example 45. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.99 - 1.19 (m, 6 H) 1.47 - 1.62 (m, 1 H) 1.64 - 2.46 (m, 9 H) 3.08 - 3.68 (m, 11 H) 3.80 - 3.91 (m, 1 H) 4.07 - 4.18 (m, 1 H) 4.75 - 5.28 (m, 2 H) 8.24 (d, *J*=5.8 Hz, 1 H) 8.30 - 8.77 (m, 2 H). HRMS calculated for C26H37N4O4F3: 527.2845; found: 527.2943.

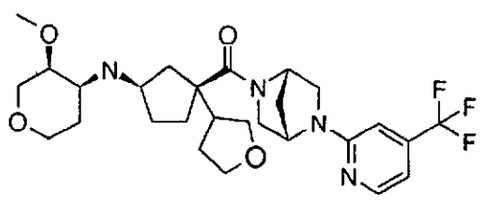
Example 59



1,5-Anhydro-2,3-dideoxy-3-{[3-(1-hydroxy-1-methylethyl)-3-({5-[6-(trifluoromethyl)pyrazin-2-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methylpentitol

The title compound was prepared in a manner analogous to that described in Example 50. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.99 - 1.19 (m, 6 H) 1.45 - 2.48 (m, 10 H) 3.15 - 3.69 (m, 10 H) 3.80 - 3.90 (m, 1 H) 4.07 - 4.17 (m, 1 H) 4.88 - 5.31 (m, 2 H) 8.20 (s, 1 H) 8.28 - 8.63 (m, 3 H). HRMS calculated for C25H36N5O4F3: 528.2797; found: 528.2905.

Example 60/61

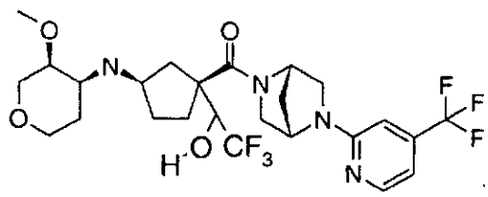


((1S,3R)-3-((3S,4S)-3-methoxy-tetrahydro-2H-pyran-4-ylamino)-1-(tetrahydrofuran-3-yl)cyclopentyl)((1S,4S)-5-(4-(trifluoromethyl)pyridin-2-yl)-2,5-diaza-bicyclo[2.2.1]heptan-2-yl)methanone

^{1}HNMR (400 MHz, CD_3OD) δ 8.20 (d, 1H), 7.18 (s, 1H), 6.97 (d, 1H), 5.11 (m, 2H), 4.24 (d, 1H), 3.38-3.99 (m, 17H), 2.87 (m, 1H), 2.65 (m, 1H), 2.48 (m, 1H), 1.90-2.39 (m, 8H), 1.81 (m, 2H), 1.65 (m, 1H).

^{1}HNMR (400 MHz, CD_3OD) δ 8.20 (d, 1H), 7.18 (s, 1H), 6.97 (d, 1H), 5.11 (m, 2H), 4.24 (d, 1H), 3.38-3.99 (m, 17H), 2.87 (m, 1H), 2.65 (m, 1H), 2.48 (m, 1H), 1.90-2.39 (m, 8H), 1.81 (m, 2H), 1.65 (m, 1H).

Example 62/63

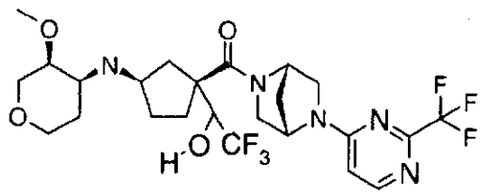


((1S,3R)-3-((3S,4S)-3-methoxy-tetrahydro-2H-pyran-4-ylamino)-1-(2,2,2-trifluoro-1-hydroxyethyl)cyclopentyl)((1S,4S)-5-(4-(trifluoromethyl)pyridin-2-yl)-2,5-diaza-bicyclo[2.2.1]heptan-2-yl)methanone

^{1}HNMR (400 MHz, CD3OD) δ 8.23 (d, J= 8Hz, 1H), 6.8 (d, J=8Hz, 1H), 6.72 (d, J=8 Hz, 1H), 5.0 (m, 1H), 4.2, (m, 1H), 3.85 (m, 2H), 3.6 (m, 1H), 3.52 (m, 1H), 3.30 (s, 3H) 3.4 (m, 4H), 2.7 (m, 2H), 2.4 (m,1H), 2.0 (m, 4H), 1.8 (m, 4H), 1.6 (m, 4H)

1HNMR (400 MHz, CD3OD) δ 8.23 (d, J= 8Hz, 1H), 6.8 (d, J=8Hz, 1H), 6.72 (d, J=8 Hz, 1H), 5.0 (m, 1H), 4.2, (m, 1H), 3.85 (m, 2H), 3.6 (m, 1H), 3.30 (s, 3H), 3.52 (m, 1H),3.4 (m, 4H), 2.7 (m, 2H), 2.4 (m,1H), 2.0 (m, 4H), 1.8 (m, 4H), 1.6 (m, 4H)

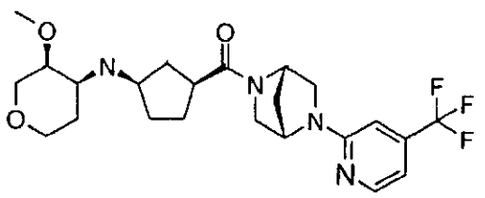
Example 64



((1S,3R)-3-((3S,4S)-3-methoxy-tetrahydro-2H-pyran-4-ylamino)-1-(2,2,2-trifluoro-1-hydroxyethyl)cyclopentyl)((1S,4S)-5-(2-(trifluoromethyl)pyrimidin-4-yl)-2,5-diaza-bicyclo[2.2.1]heptan-2-yl)methanone

^{1}HNMR (400 MHz, CD3OD) δ 8.23(m, 1H), 6.6 (m, 1H), 4.25 (m, 1H), 4.0 (m, 2H), 3.85 (m, 1H), 3.7 (m, 1H) 3.6 (m, 4H), 3.42 (m, 4H), 2.52 (m, 2H), 2.25 (m, 2H), 2.1 (m, 2H) 2.0 (m, 4H), 1.6 (m, 2H)

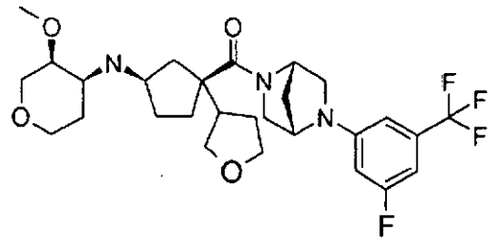
Example 65



((1S,3R)-3-((3S,4S)-3-methoxy-tetrahydro-2H-pyran-4-ylamino)cyclopentyl)((1S,4S)-5-(4-(trifluoromethyl)pyridin-2-yl)-2,5-diaza-bicyclo[2.2.1]heptan-2-yl)methanone

^{1}HNMR (400 MHz, CD3OD) δ 8.23 (d, J= 8Hz, 1H), 6.8 (d, J=8Hz, 1H), 6.72 (d, J=16 Hz, 1H), 5.0 (m, 1H), 4.2, (m, 1H), 3.9 (m, 1H), 3.85 (m, 1H), 3.8 (m, 4H), 3.4 (m, 4H), 3.30 (m, 3H), 3.2 (m, 4H), 2.0 (m, 4H), 1.8 (m, 4H)

Example 66

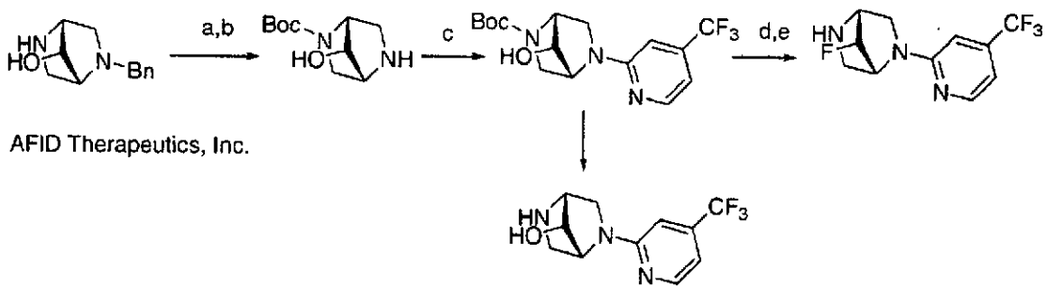


((1S,4S)-5-(3-fluoro-5-(trifluoromethyl)phenyl)-2,5-diaza-bicyclo[2.2.1]heptan-2-yl)((1S,3R)-3-((3S,4S)-3-methoxy-tetrahydro-2H-pyran-4-ylamino)-1-(tetrahydrofuran-3-yl)cyclopentyl)methanone

1HNMR (400Mhz, CD3OD), δ 6.6 (m, 3H), 5.0 (m, 1H), 4.6 (m, 1H), 4.25 (d, J=4Hz, 1H), 4.0 (m, 1H), 3.85 (m, 1H), 3.8 (m, 2H), 3.7 (m, 2H), 3.65 (m, 2H) 3.5 (m, 2H), 3.4 (3H), 3.2 (d, J=4Hz, 2H), 2.8 (m, 1H), 2.6 (m, 1H), 2.5 (m, 1H), 2.35 (m, 1H), 2.2 (m, 1H), 2.1 (m, 2H), 2.05 (m, 2H), 2.0 (m, 2H), 1.8 (m, 2H),1.6 (m, 2H)

Preparation of Examples 67-71

Scheme. Prep of F-221



a) Boc_2O, DIPEA; b) NBS, CCl_4 then 10% Pd/C, H_2; c) Cl-pyridine-CF_3, DIPEA, DMF; d) DAST, DCM, 0 °C; e) 4N HCl/dioxane, rt

Step 1. Preparation of (1R,4S)-tert-butyl 7-hydroxy-5-(4-(trifluoromethyl)pyridin-2-yl)-2,5-diaza-bicyclo[2.2.1]heptane-2-carboxylate

To a solution of alcohol (2.48 g, 11.6 mmol) in DMSO (30 mL) was added 2-chloro-5-(trifluoromethyl)pyridine (2.0 g, 11.0 mmol) and TEA (3.4 mL, 24.2 mmol). After heating the mixture at 95 °C overnight the mixture was poured into H_2O and the aqueous mixture extracted 2X with ether. The organic extracts were dried (Na_2SO_4) and the solvent removed to give an oil, which after chromatography (silica, EtOAc:Heptane) gave the product (1.0 g). LC/MS (M+Na) = 382 exp, 382 obs.

Step 2. Preparation of (1R,4S)-tert-butyl 7-fluoro-5-(4-(trifluoromethyl)pyridin-2-yl)-2,5-diaza-bicyclo[2.2.1]heptane-2-carboxylate

To a solution of alcohol in DCM at 0 °C was added DAST dropwise. After addition was complete the reaction mixture was allowed to warm to rt and stirred at rt overnight. The reaction mixture was poured into saturated $NaHCO_3$/DCM and the layers separated. The organic layer was collected, dried (Na_2SO_4) and the solvent removed to give an oil, which after chromatography (silica,

EtOAc:Heptane) gave the desired product (750 mg). LC/MS (M+H) = 362.1491 exp, 362.1491 obs. 1H NMR (400 MHz, *DMSO-d_6*) δ ppm 8.31 (1 H, d, *J*=5.5 Hz), 6.85 - 6.96 (2 H, m), 5.35 (1 H, d, *J*=55.6 Hz), 4.90 (1 H, br. s.), 4.47 (1 H, d, *J*=22.7 Hz), 3.64 (1 H, dd, *J*=10.2, 1.8 Hz), 3.47 - 3.57 (1 H, m), 3.39 - 3.46 (1 H, m), 3.26 - 3.32 (1 H, m), 1.39 (9 H, d, *J*=12.4 Hz).

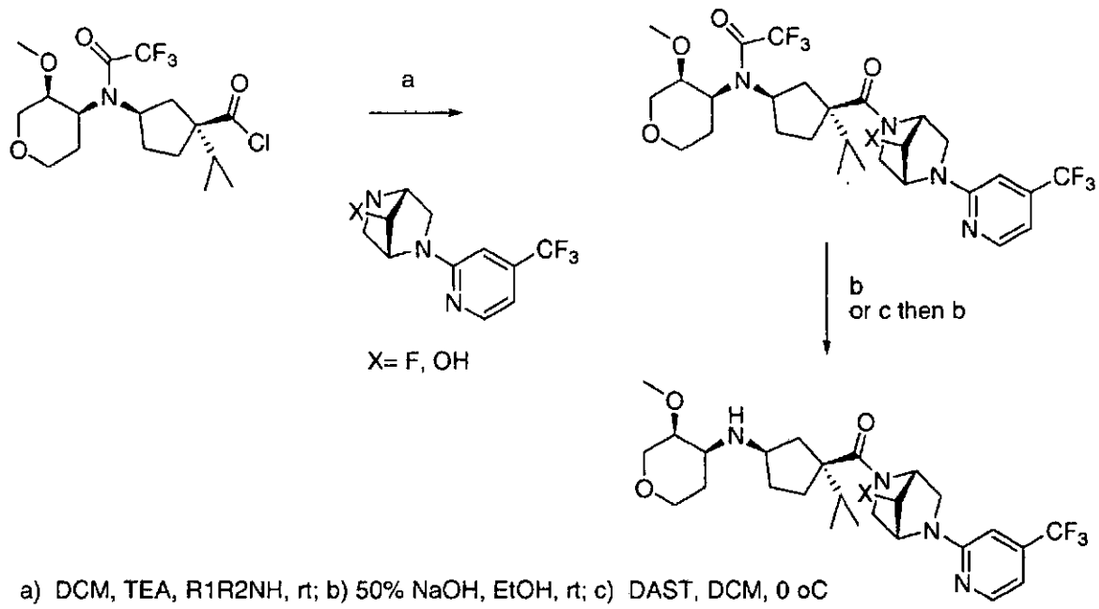
Step 3. Preparation of (1S,4R)-7-fluoro-2-(4-(trifluoromethyl)pyridin-2-yl)-2,5-diaza-bicyclo[2.2.1]heptane

To a solution of (1R,4S)-tert-butyl 7-fluoro-5-(4-(trifluoromethyl)pyridin-2-yl)-2,5-diaza-bicyclo[2.2.1]heptane-2-carboxylate (700 mg, 1.9 mmol) in dioxane (2 ml) was added 4N HCl/dioxane (5 mL). The reaction mixture was stirred at rt for 5 hr and then diluted with ether to give a precipitate that was filtered and collected to give the product as the HCl salt (506 mg). LC/MS (M+H) = 262.0967 exp, 262.1308 obs; 1H NMR (400 MHz, *METHANOL-d_4*) δ ppm 8.26 (1 H, d, *J*=6.1 Hz), 7.40 (1 H, s), 7.20 (1 H, dd, *J*=6.3, 1.0 Hz), 5.65 (1 H, dd, *J*=52.4, 1.9 Hz), 5.28 (1 H, s), 4.70 (1 H, s), 3.92 - 4.09 (2 H, m), 3.66 - 3.81 (2 H, m), 3.62 (1 H, s)

Step 4. Preparation of (1S,4R)-7-hydroxy-2-(4-(trifluoromethyl)pyridin-2-yl)-2,5-diaza-bicyclo[2.2.1]heptane

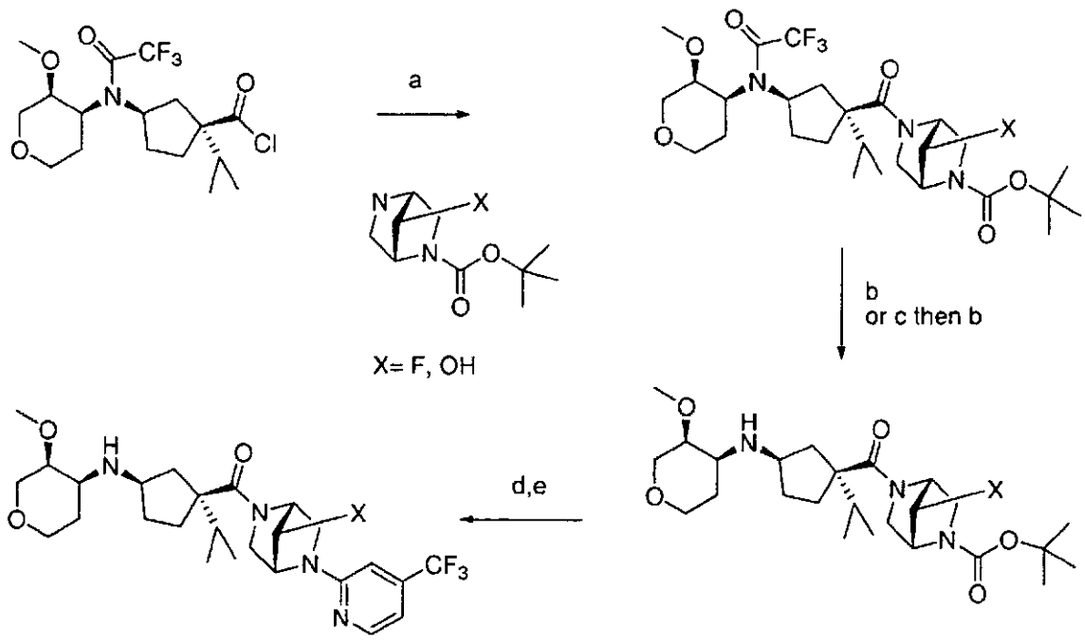
To a solution of (1R,4S)-tert-butyl 7-hydroxy-5-(4-(trifluoromethyl)pyridin-2-yl)-2,5-diaza-bicyclo[2.2.1]heptane-2-carboxylate (5 g, 14 mmol) in dioxane (5 ml) was added 4N HCl/dioxane (15 mL). The reaction mixture was stirred at rt for 6 hr and then diluted with ether to give a precipitate that was filtered and collected to give the product as the HCl salt (4.0 g). LC/MS (M+H) = 260.0 exp, 260.0 obs; 1H NMR (500 MHz, DMSO-d_6) δ ppm 3.42 - 3.50 (m, 1 H) 3.67 - 3.72 (m, 1 H) 3.75 - 3.82 (m, 1 H) 4.16 (br. s., 1 H) 4.50 (d, J=1.81 Hz, 1 H) 4.72 (br. s., 1 H) 6.95 (d, J=5.13 Hz, 2 H) 8.31 (d, J=5.43 Hz, 1 H) 9.34 (br. s., 1 H) 9.75 (br. s., 1 H)

Scheme 5



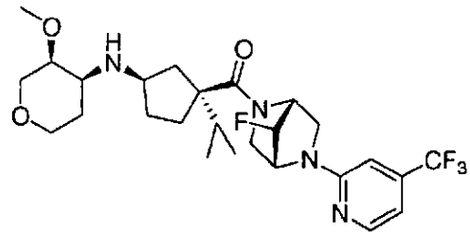
a) DCM, TEA, R1R2NH, rt; b) 50% NaOH, EtOH, rt; c) DAST, DCM, 0 oC

Scheme 6



a) DCM, TEA, R1R2NH, rt; b) 50% NaOH, EtOH, rt; c) DAST, DCM, 0 oC; d) 4N HCl/dioxane; e) Pyr-Cl Et3N, DMSO, 100 oC

Example 67

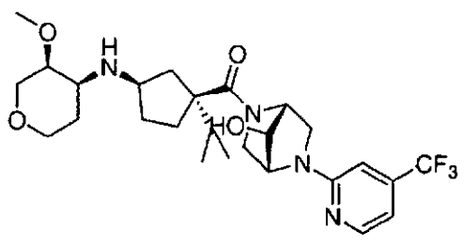


((1R,4R,7S)-7-fluoro-5-(4-(trifluoromethyl)pyridin-2-yl)-2,5-diaza-bicyclo[2.2.1]heptan-2-yl)((1S,3R)-1-isopropyl-3-((3S,4S)-3-methoxy-tetrahydro-2H-pyran-4-ylamino)cyclopentyl)methanone

Prepared in a manner analogous to example 1, except using (1R,4R,7R)-7-fluoro-2-(4-(trifluoromethyl)pyridin-2-yl)-2,5-diaza-bicyclo[2.2.1]heptane as the coupling amine. LC/MS (M+H) = 529 exp, 529 obs; 1H NMR (400 MHz, *DMSO-d_6*) δ ppm 8.31 (1 H, d, *J*=5.1 Hz), 6.92 (2 H, d, *J*=5.1 Hz), 5.39 (1 H, d, *J*=55.6

Hz), 4.81 - 4.98 (2 H, m), 3.78 - 3.88 (1 H, m), 3.66 - 3.75 (2 H, m), 3.57 - 3.65 (1 H, m), 3.37 - 3.43 (1 H, m), 3.23 - 3.31 (2 H, m), 3.15 - 3.22 (4 H, m), 3.06 - 3.10 (1 H, m), 2.95 - 3.03 (1 H, m), 2.68 - 2.77 (1 H, m), 2.22 - 2.32 (1 H, m), 1.93 - 2.09 (2 H, m), 1.61 - 1.72 (2 H, m), 1.35 - 1.53 (3 H, m), 1.21 - 1.29 (1 H, m), 1.08 - 1.20 (1 H, m), 0.82 (2 H, d, *J*=6.2 Hz), 0.64 - 0.77 (4 H, m)

Example 68

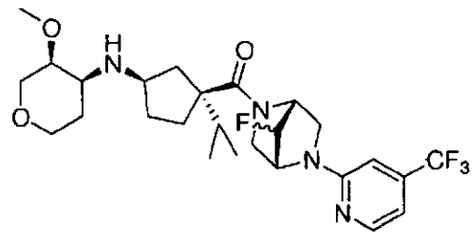


((1R,4R,7S)-7-hydroxy-5-(4-(trifluoromethyl)pyridin-2-yl)-2,5-diaza-bicyclo[2.2.1]heptan-2-yl)((1S,3R)-1-isopropyl-3-((3S,4S)-3-methoxy-tetrahydro-2H-pyran-4-ylamino)cyclopentyl)methanone

To a solution of the (1S,3R)-1-isopropyl-3-(2,2,2-trifluoro-N-((3S,4S)-3-methoxy-tetrahydro-2H-pyran-4-yl)acetamido)cyclopentanecarbonyl chloride (185mg, 0.463mmol) in CH_2Cl_2 (2mL) was added Et_3N (0.161ml, 1.16mmol) and (1R,4R,7R)-7-hydroxy-2-(4-(trifluoromethyl)pyridin-2-yl)-2,5-diaza-bicyclo[2.2.1]heptane (100mg, 0.386mmol). The mixture was stirred for 4 hrs. at RT. The solution was then washed with $NaHCO_3$ (1 X 3ml), and brine (1 X3ml). The organic layer was then dried over MgSO4, filtered and concentrated, purified by chromatopraphy with (100% EtOAc- 70% MeOH/EtOAc) to yield TFA protected product, which was then treated with 2N NaOH (0.5ml, 1mmol) in THF (2ml) at RT for 4 hrs., then purified by chromatography with (100% EtOAc- 100% MeOH) to yield 60 mg desired product (30%). LC/MS (M+H) = 527.2845 exp, 527.2996 obs; 1H NMR (400 MHz, DMSO-d_6) δ ppm 0.64 - 0.76 (m, 4 H) 0.77 - 0.88 (m, 3 H) 1.13 (d, *J*=1.83 Hz, 1 H) 1.34 (br. s., 1 H) 1.36 - 1.48 (m, 3 H) 1.66 (dt, *J*=7.69, 3.84 Hz, 1 H) 1.77 - 1.90 (m, 1 H) 1.99 (dt, *J*=13.55, 6.77 Hz, 2 H) 2.29 (dd, *J*=12.08, 8.05 Hz, 1 H) 2.73 - 2.79 (m, 1 H) 2.97 - 3.04 (m, 1 H) 3.07 -

3.14 (m, 2 H) 3.15 - 3.24 (m, 5 H) 3.59 (br. s., 1 H) 3.61 - 3.72 (m, 2 H) 3.75 - 3.88 (m, 1 H) 4.26 (d, *J*=0.73 Hz, 1 H) 4.44 - 4.55 (m, 2 H) 5.72 (d, *J*=3.29 Hz, 1 H) 6.75 - 6.85 (m, 2 H) 8.27 (d, *J*=5.49 Hz, 1 H)

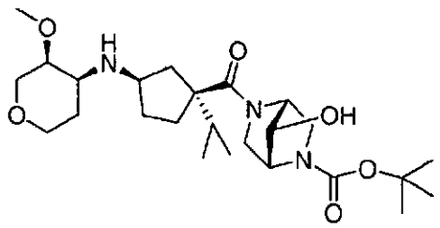
Example 69



((1R,4R)-7-fluoro-5-(4-(trifluoromethyl)pyridin-2-yl)-2,5-diaza-bicyclo[2.2.1]heptan-2-yl)((1S,3R)-1-isopropyl-3-((3S,4S)-3-methoxy-tetrahydro-2H-pyran-4-ylamino)cyclopentyl)methanone

2,2,2-trifluoro-N-((1R,3S)-3-((1R,4R,7S)-7-hydroxyl-2-(4-(trifluoromethyl)pyridin-2-yl)-2,5-diaza-bicyclo[2.2.1]heptane-5-carbonyl)-3-isopropylcyclopentyl)-N-((3S,4S)-3-methoxy-tetrahydro-2H-pyran-4-yl)acetamide (30 mg, 0.057 mmol) in CH_2Cl_2 (2ml) was cooled to 0 °C and DAST (0.025ml, 0.086mmol) was added to the solution. The reaction mixture was stirred overnight and purified by chromatography (10% EtOAc to 100% MeOH) to yield desired product (16mg, 32%). LC/MS (M+H) = 529.2802 exp, 529.3112 obs; 1H NMR (400 MHz, DMSO-d_6) δ ppm 0.67 - 0.78 (m, 5 H) 0.82 (d, *J*=6.59 Hz, 3 H) 1.23 (br. s., 1 H) 1.50 (d, *J*=3.66 Hz, 3 H) 1.75 (d, *J*=4.39 Hz, 2 H) 1.94 - 2.03 (m, 1 H) 2.24 - 2.32 (m, 1 H) 2.98 (s, 1 H) 3.12 (br. s., 1 H) 3.18 - 3.23 (m, 4 H) 3.31 - 3.34 (m, 1 H) 3.40 (d, *J*=10.98 Hz, 1 H) 3.62 (d, *J*=12.08 Hz, 1 H) 3.72 (d, *J*=10.62 Hz, 3 H) 3.80 - 3.92 (m, 1 H) 4.87 (br. s., 1 H) 4.90 - 4.96 (m, 1 H) 5.31 (d, *J*=1.83 Hz, 1 H) 5.40 - 5.46 (m, 1 H) 6.86 - 6.94 (m, 2 H) 8.31 (d, *J*=5.49 Hz, 1 H)

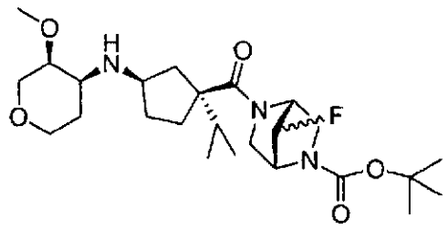
Example 70



(1R,4R,7S)-tert-butyl 7-hydroxy-5-((1S)-1-isopropyl-3-(3-methoxy-tetrahydro-2H-pyran-4-ylamino)cyclopentanecarbonyl)-2,5-diaza-bicyclo[2.2.1]heptane-2-carboxylate

To a solution of the (1S,3R)-1-isopropyl-3-(2,2,2-trifluoro-N-((3S,4S)-3-methoxy-tetrahydro-2H-pyran-4-yl)acetamido)cyclopentanecarboxylic acid (0.95g, 2.5mmol) in CH_2Cl_2 (5mL) under N2 at 0 °C is added oxalyl chloride (623mg, 4.98mmol) and DMF (3 drops). The mixture is allowed to warm to RT and stir for 2 hr, It was then concentrated. The acid chloride was redissolved in DCM (10ml), cooled to 0 °C, and treated with (1R,4R,7S)-tert-butyl 7-hydroxy-2,5-diaza-bicyclo[2.2.1]heptane-2-carboxylate (534mg, 0.249mmol), followed by Et3N (0.1ml, 0.75mmol). The resulting mixture was warmed to RT and stirred for 2hrs. The solution was then washed with $NaHCO_3$ (1 X5ml), and brine (1 X 5ml). The organic layer was then dried over MgSO4, filtered and concentrated, purified by chromatography (100% EtOAc- 60% MeOH/EtOAc) to yield crude intermediate which was dried and concentrated. Then it was dissolved in EtOH (2ml) and treated with NaOH (3ml, 7.5mmol) overnight. The reaction mixture was then purified by chromatography (100% EtOAc- 100% MeOH) to yield desired product (300mg, 25%). LC/MS (M+H) = 482.3230 exp, 482.3334 obs; 1H NMR (400 MHz, DMSO-d_6) δ ppm 0.67 (dd, *J*=6.95, 3.66 Hz, 3 H) 0.80 (dd, *J*=6.59, 2.93 Hz, 3 H) 1.22 (br. s., 1 H) 1.35 - 1.41 (m, 12 H) 1.43 - 1.48 (m, 2 H) 1.55 - 1.68 (m, 2 H) 1.85 - 1.93 (m, 1 H) 1.95 - 2.04 (m, 1 H) 2.16 - 2.28 (m, 1 H) 2.66 - 2.80 (m, 1 H) 2.97 - 3.02 (m, 1 H) 3.03 - 3.10 (m, 2 H) 3.17 - 3.29 (m, 5 H) 3.37 - 3.47 (m, 1 H) 3.47 - 3.58 (m, 1 H) 3.61 - 3.74 (m, 1 H) 3.81 - 3.89 (m, 1 H) 3.94 - 4.04 (m, 2 H) 4.24 (br. s., 1 H) 5.65 - 5.77 (m, 1 H)

Example 71



tert-butyl 7-fluoro-5-((1S,3R)-1-isopropyl-3-((3S,4S)-3-methoxy-tetrahydro-2H-pyran-4-ylamino)cyclopentanecarbonyl)-2,5-diaza-bicyclo[2.2.1]heptane-2-carboxylate

tert-butyl 7-hydroxy-5-((1S)-1-isopropyl-3-(2,2,2-trifluoro-N-(3-methoxy-tetrahydro-2H-pyran-4-yl)acetamido)cyclopentanecarbonyl)-2,5-diaza-bicyclo[2.2.1]heptane-2-carboxylate (100 mg, 0.173 mmol) in CH_2Cl_2 (2 ml) was cooled to 0 °C and DAST (0.036ml, 0.259mmol) was added to the solution. The reaction mixture was stirred overnight and purified by chromatography (10% EtOAc to 100% MeOH) to yield TFA protected product, which was then treated with 2.5N NaOH (0.014ml, 0.5mmol) in THF (2ml) at RT for 4 hrs., then purified by chromatopraphy with (100% EtOAc- 100% MeOH) to yield 12 mg desired product (14%). LC/MS (M+H) = 484.3187 exp, 484.3197 obs; 1H NMR (400 MHz, DMSO-d_6) δ ppm 0.63 - 0.72 (m, 3 H) 0.81 (dd, *J*=7.14, 1.65 Hz, 3 H) 1.22 (br. s., 1 H) 1.36 - 1.48 (m, 13 H) 1.56 - 1.68 (m, 2 H) 1.85 - 1.96 (m, 2 H) 2.16 - 2.28 (m, 1 H) 2.68 - 2.79 (m, 1 H) 2.95 - 3.05 (m, 1 H) 3.15 (br. s., 1 H) 3.17 - 3.29 (m, 7 H) 3.52 (d, *J*=10.62 Hz, 2 H) 3.66 - 3.74 (m, 1 H) 3.82 - 3.90 (m, 1 H) 4.27 - 4.37 (m, 1 H) 4.69 (br. s., 1 H) 5.08 - 5.35 (m, 1 H)

Biological Data

CCR2 in vitro assays

The capacity of the novel compounds of the invention to antagonize chemokine receptor (*e.g.*, CCR2) function can be determined using a suitable

screen (*e.g.*, high through-put assay). For example, an agent can be tested in an extracellular acidification assay, calcium flux assay, ligand binding assay or chemotaxis assay (see, for example, Hesselgesser et al., J Biol. Chem. 273(25):15687-15692 (1998); WO 00/05265 and WO 98/02151).

In a suitable assay, a CCR2 protein which can be isolated or recombinantly derived is used which has at least one property, activity or functional characteristic of a mammalian CCR2 protein. The specific property can be a binding property (to, for example, a ligand or inhibitor), a signalling activity (e.g., activation of a mammalian G protein, induction of rapid and transient increase in the concentration of cytosolic free calcium [Ca++]i, cellular response function (e.g., stimulation of chemotaxis or inflammatory mediator release by leukocytes), and the like.

In an example binding assay, a composition containing a CCR2 protein or variant thereof is maintained under conditions suitable for binding. The CCR2 receptor is contacted with a compound to be tested, and binding is detected or measured.

In an example cell-based assay, cells are used which are stably or transiently transfected with a vector or expression cassette having a nucleic acid sequence which encodes the CCR2 receptor. The cells are maintained under conditions appropriate for expression of the receptor and are contacted with an agent under conditions appropriate for binding to occur. Binding can be detected using standard techniques. For example, the extent of binding can be determined relative to a suitable control. Also, a cellular fraction, such as a membrane fraction, containing the receptor can be used in lieu of whole cells.

Detection of binding or complex formation in an assay can be detected directly or indirectly. For example, the agent can be labeled with a suitable label (*e.g.*, fluorescent label, label, isotope label, enzyme label, and the like) and binding can be determined by detection of the label. Specific and/or competitive binding can be assessed by competition or displacement studies, using unlabeled agent or a ligand as a competitor.

The CCR2 antagonist activity of compounds of the invention can be reported as the inhibitor concentration required for 50% inhibition (IC50 values) of specific binding in receptor binding assays using 125I-labeled MCP-1, as ligand, and Peripheral Blood Mononuclear Cells (PBMCs) prepared from normal human whole blood via density gradient centrifugation. Specific binding is defined as the total binding (e.g., total cpm on filters) minus the non-specific binding. Non-specific binding is defined as the amount of cpm still detected in the presence of excess unlabeled competitor (*e.g.*, MCP-1).

CCR2 binding IC_{50}

Human PBMCs were used to test compounds of the invention in a binding assay. For example, 200,000 to 500,000 cells were incubated with 0.1 to 0.2 nM 125I-labeled MCP-1, with or without unlabeled competitor (10 nM MCP-1) or various concentrations of compounds to be tested. 125I-labeled MCP-1, were prepared by suitable methods or purchased from commercial vendors (Perkin Elmer, Boston MA). The binding reactions were performed in 50 to 250 µL of a binding buffer consisting of 1M HEPES pH 7.2, and 0.1% BSA (bovine serum albumin), for 30 minutes at room temperature. The binding reactions were terminated by harvesting the membranes by rapid filtration through glass fiber filters (Perkin Elmer) which was presoaked in 0.3% polyethyleneimine or Phosphate Buffered Saline (PBS). The filters were rinsed with approximately 600 µL of binding buffer containing 0.5 M NaCl or PBS, then dried, and the amount of bound radioactivity was determined by counting on a Gamma Counter (Perkin Elmer).

More specifically, the following assay may be employed to determine IC_{50} values for the compounds of the present invention.

hCCR2 (125-I hMCP-1) Small Molecule Binding Assay

The following reagents and supplies have been used in the preceding assay:

MCP-1
Biosource # PHC1013
1 mg
reconstitute with 2 ml binding buffer (0.5 mg per ml or 60 uM)

125I MCP-1
Perkin Elmer #NEX332
25 uCi
reconstitute with 0.2 ml PBS

RPMI 1640 with L-glutamine
MediaTech/Cellgro # 10-040-CM

BSA
Sigma # A2153

HEPES
1 M solution
MediaTech/Cellgro # 25-060-CL

NaCl
Sigma # S7653

SUPPLIES

Muliscreen BV Filter Plates
Millipore # MABVN1250

Multiscreen Punch Tips
Millipore #MADP19650

Multiscreen Filtration System Vacuum Manifold

Millipore # MAVM0960R

Normal human leukophoresis pack contents, available from Biological Specialty Corporation, Colmar, PA., is diluted 1:1 with PBS, divided into 50ml conical tubes (preferably less than 40mls per tube), and underlayed with 10 mls of Ficoll-Paque PLUS (GE Healthcare 17-1440-02). The tubes are centrifuged at 2800rpm in a clinical centrifuge at room temperature for 30 minutes, with no brake. The plasma layer is suctioned, and the buffycoat layer is collected. The collected buffycoat layer is washed twice with 50 mls PBS, and centrifuged at 1400rpm with brake. The cells are counted. The cells are then diluted to $1x10^7$ cells per ml in binding buffer.

96 well plates (such as, for example, Millipore MultiScreen96 plates) are pre-wet with about 100 µl binding buffer (RPMI+0.1% BSA + 20mM HEPES), and blotted just prior to compound addition.

Plates with compound to be tested may be advantagously stored or managed with an automated system, such as, for example,.TelCel (Hamilton Storage Technologies, Inc., 103 South Street, Hopkinton, MA 01748 USA)

5 µl of 50 µM test compounds in 100% DMSO are dotted onto U-bottom polypropylene 96-well plates.

245 µl per well of Binding Buffer is added to each well for 1µM compound concentration in 2% DMSO.

50µl of 1µM compound is transferred to pre-wetted Millipore plates.
50 µl per well of 1x10E7 cells per ml of freshly prepared human PBMCs are added.

The samples are pre-incubated at room temperature for 30 minutes or 1 hour.

50 µl of 450pM 125-I-hMCP-1 (Perkin-Elmer/NEN cat#NEX332025UC) is added for a final concentration 125-I-hMCP-1 of 150pM per well.

The final test compound concentration is 0.333uM in 150µl total volume with 0.67% DMSO in all wells. Controls for this assay consist of 0% inhibition and

100% inhibition with 1 uM hMCP-1 (saturating conditions). All wells are run in duplicate. Controls may be in replicates of eight.

The samples are incubated at room temperature for 30 minutes.

The buffer is suctioned through the Millipore plates. The plates are washed three times with Wash Buffer (PRMI + 0.1% BSA + 20mM HEPES + 0.4 M NaC).

The plate underdrain is removed. The plate filters are allowed to dry. The filters are then punched out into plastic tubes.

Finally, the sample is counted on a Gamma Counter.

All IC50 plates were repeated for an n=2.

The following table summarizes the IC_{50} values identified through the described assay.

Table 1. Biological Data

Example	IC_{50} (nM) 30 min preinc	IC_{50} (nM) 1 hr preinc
1	2.47	
2	3.16	
3	17.8	
4	3.98	
5	13.3	
6	1.73	
7	17.1	
8	10.7	
9	30.7	
10	83.8	
11	6.72	2.44
12	11.1	1.7
13	25.4	3.68
14	10.4	2.3
15	40	4.6
16	9.95	1.1
17	13.7	5.8
18	37.6	8.5
19	20.4	6.35
20	8.59	
21		3.1
22		1.1
23		0.94
24	79.7	8.87
25	6.58	0.93
26	29.3	7.85
27	16.2	2.04
28		1.88
29		2.75
30	32.9	11.8
31		6.35
32	13.8	11.7
33	57.3	11.7
34	66.5	6.94
35	28.4	5.52
36	12.6	2.19
37		3.68
38	68.7	2.02
39	82.9	5.81
40	18.3	

Example	IC_{50} (nM) 30 min preinc	IC_{50} (nM) 1 hr preinc
41	63.6	
42	70.9	
43	47.3	
44		8.1
45	25.3	
46	3.19	
47	6.16	
48	25.3	
49	35.8	
50	7.14	
51	22.8	
52	5.4	
53	27.6	
54	8.46	
55	28.3	
56	32.8	
57	4.34	
58	38.5	
59	17.7	
60	2.4	
61	5.9	
62	1.3	
63		1.1
64		4.7
65		1.5%@300nM
66	1.7	
67	3.4	
68	5.4	
69	4.3	
70	8.7	
71	3.7	

Diabetic Nephropathy Rat Model

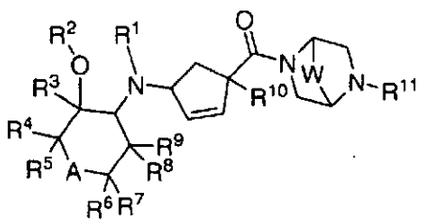
A rat model of diabetic nephropathy was used to determine the renal protective effect of pharmacological inhibition of CCR2. The streptozotocin (STZ)-induced diabetic rat model has been extensively used for studying the progression of diabetic renal disease. STZ injection causes immediate destruction of pancreatic β-cells, consequently hyperglycemia and progression of nephropathy similar to that seen in human diabetes mellitus. Diabetes was induced in male Wistar rats by single administration of STZ (45 mg/kg, iv). Three

days after the induction of diabetes, fasting blood glucose levels were assessed. Animals with fasting blood glucose levels higher than 200mg/dL were included in the study. All the treatments were then initiated. 1,5-anhydro-2,3-dideoxy-3-{[(1R,3S)-3-isopropyl-3-({(1S,4S)-5-[6-(trifluoromethyl)pyrimidin-4-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methyl-D-erythro-pentitol was administered at doses of 0.03, 0.3, 1, and 10 mg/kg (mpk) (in the chow) for 11 weeks. 24-hour urine collections were obtained at 1, 4, 8, and 11 weeks after the treatment for assessing 24-hour urinary albumin excretion (UAE). As expected, following the induction of diabetes there was a persistent elevation in UAE over the 11 week course of this study. 1,5-anhydro-2,3-dideoxy-3-{[(1R,3S)-3-isopropyl-3-({(1S,4S)-5-[6-(trifluoromethyl)pyrimidin-4-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methyl-D-erythro-pentitol treatment significantly reduced UAE at doses of 0.3 mpk (1.73±0.69 mg/24h), 1 mpk (1.09±0.20 mg/24h), and 10 mpk (0.71±0.22 mg/24h) compared to untreated STZ rats (4.32±1.34 mg/24h) at week 8, and at all doses (2.17±1.31, 1.96±0.85, 1.66±0.65, and 1.02±0.32 mg/24h, at 0.03, 0.3, 1, and 10 mpk dose, respectively, vs. 6.36±2.08 mg/24h, untreated STZ rats) at week 11. These data demonstrate that pharmacological inhibition of CCR2 provides renal protection during the development and progression of diabetic nephropathy and support CCR2 antagonism as a new therapeutic strategy to treat diabetic renal disease.

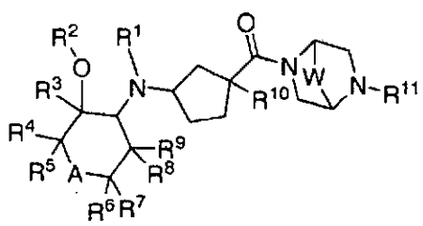
Claims

What is claimed is:

1. A compound of Formula I(a) or I(b):



I(a)



I(b)

or a pharmaceutically acceptable salt thereof, wherein:

A is O or CF_2;

W is $CR^{13}R^{14}$, C(O), $CHOR^{15}$, CHF, CF_2, O or S

R^1 is H or $(C_1$-$C_6)$alkyl optionally substituted by 1-3 substituents selected from halo, OH, CO_2H, CO_2-$(C_1$-$C_6)$ alkyl, or $(C_1$-$C_3)$ alkoxy;

R^2 and R^3 are each, independently, H, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$ haloalkyl, halo, $(C_3$-$C_6)$ cycloalkyl, CN, OH, CO_2R, $OCOR^{12}$; wherein said $(C_1$-$C_6)$alkyl is optionally substituted with one or more substituents selected from F, $(C_1$-$C_3)$ alkoxy, OH, CN or CO_2R^{12};

R^8 and R^9 are each, independently, H, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_3$-$C_6)$cycloalkyl, CN, OH, CO_2R, $OCOR^{12}$; wherein said $(C_1$-$C_6)$alkyl is optionally substituted with one or more substituents selected from F, $(C_1$-$C_3)$ alkoxy, OH, CN or CO_2R^{12};

R^2 and R^9, taken together may form a 5-8 membered ring;

R^4 and R^7, taken together may form a 5-8 membered ring;

R^4 and R^5 are each, independently, H, CN, $(C_1$-$C_6)$alkyl, halo, $(C_1$-$C_3)$alkoxy, $(C_1$-$C_3)$haloalkoxy, $(C_3$-$C_6)$cycloalkyl, OH, CO_2R^{12}, $OCOR^{12}$, wherein said $(C_1$-$C_6)$alkyl is optionally substituted with one or more substituents selected from F, $(C_1$-$C_3)$ alkoxy, OH or CO_2R^{12};

R^6 and R^7 are each, independently, H, CN, $(C_1$-$C_6)$alkyl, halo, $(C_1$-$C_3)$alkoxy, $(C_1$-$C_3)$haloalkoxy, $(C_3$-$C_6)$cycloalkyl, OH, CO_2R^{12}, $OCOR^{12}$, wherein said $(C_1$-$C_6)$alkyl is optionally substituted with one or more substituents selected from F, $(C_1$-$C_3)$ alkoxy, OH or CO_2R^{12};

or R^2 and R^3 together with the carbon atom to which they are attached form a 3-7 membered spirocyclyl group;

or R^4 and R^5 together with the carbon atom to which they are attached form a 3-7 membered spirocyclyl group;

or R^3 and R^4 together with the C atoms to which they are attached form a fused 3-7 membered cycloalkyl group or 3-7 membered heterocycloalkyl group;

R^{10} is $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_1$-$C_6)$hydroxyalkyl, $(C_1$-$C_6)$alkoxy, $(C_3$-$C_6)$cycloalkyl, hydroxy$(C_3$-$C_6)$cycloalkyl, alkoxy cycloalkyl, OH, $(C_1$-$C_5)$heterocyclyl, amino, aryl or CN,

R^{11} is aryl or heteroaryl, said R^{11} optionally, independently substituted by one or more (C_1-C_6) alkyl, halo, (C_1C_6)haloalky (C_1-C_3)alkoxy, OH, amino, $C(O)NH_2$, NH_2SO_2, SF_5,or CN;

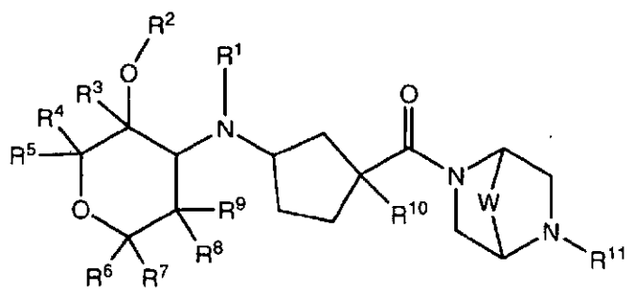
R^{12} is H, (C_1-C_4)alkyl, or (C_3-C_6)cycloalkyl;

R^{13} is H, halo, (C_1-C_4)alkyl, (C_1-C_4)alkoxy,or OH;

R^{14} is H, halo, (C_1-C_4)alkyl, (C_1-C_4)alkoxy or OH; and

R^{15} is H ,(C_1-C_6)alkyl or (C_3-C_6)cycloalkyl.

2. A compound of Formula II:



(II)

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is H, (C_1-C_6)alkyl or (C_3-C_6)cycloalkyl, said (C_1-C_6)alkyl optionally substituted by halo, CN, C(O)OH or OH;

R^2 is (C_1-C_6)alkyl (C_1-C_6)haloalkyl or (C_3-C_6)cycloalkyl;

R^3 R^4, R^5, R^6, R^7, R^8 and R^9 are independently H, C_1-C_4 alkyl, CN, halo or amino;

R^{10} is $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$haloalkyl, $(C_1\text{-}C_6)$hydroxyalkyl, $(C_1\text{-}C_6)$alkoxy, $(C_3\text{-}C_6)$cycloalkyl, hydroxy$(C_3\text{-}C_6)$cycloalkyl, alkoxy $(C_3\text{-}C_6)$cycloalkyl, OH, $(C_1\text{-}C_5)$heterocyclyl, amino, aryl or CN;

R^{11} is aryl or heteroaryl, said R^{11} optionally, independently substituted by one or more $(C_1\text{-}C_6)$ alkyl, halo, $(C_1\text{-}C_6)$haloalky $(C_1\text{-}C_6)$alkoxy, OH, amino, $C(O)NH_2$, NH_2SO_2, SF_5 or CN;

W is $CR^{13}R^{14}$, C(O), $CHOR^{15}$, CHF, CF_2, O or S;

R^{13} and R^{14} are independently H halo, $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkoxy,or OH; and

R^{15} is H, $(C_1\text{-}C_6)$alkyl or $(C_3\text{-}C_6)$cycloalkyl.

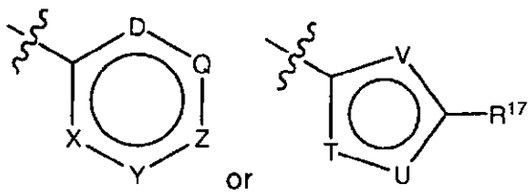
3. The compound of claim 2 or a pharmaceutically acceptable salt thereof, wherein:

R^1 is H or $(C_1\text{-}C_6)$alkyl

R^2 is $(C_1\text{-}C_6)$alkyl or $(C_1\text{-}C_6)$haloalkyl

R^3, R^4, R^5, R^6, R^7, R^8 and R^9 are each H;

R^{11} is



or

, wherein X, Y, Z, Q and D are independently N or CR^{16}, and wherein 0, 1, 2 or 3 of X, Y, Z, Q and D are N; and

wherein T, U and V are independently selected from CH, N, S, or O, provided that T and U are not both simultaneously O or S;

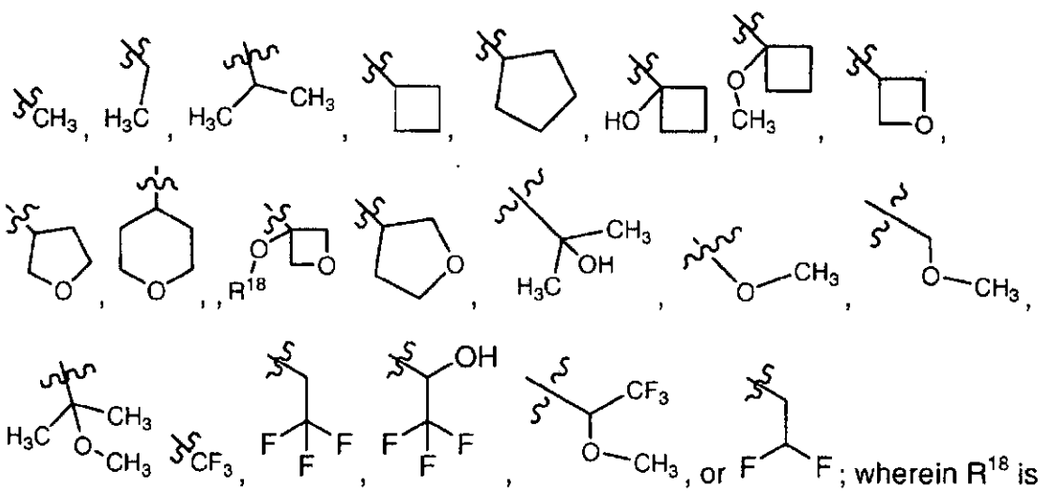
each R^{16} is independently H, halo, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$haloalkyl, $(C_1\text{-}C_6)$alkoxy or CN;

R^{17} is H, $(C_1\text{-}C_6)$alky, $(C_1\text{-}C_6)$haloalky, or $(C_1\text{-}C_6)$alkoxy; and

W is $CR^{13}R^{14}$, C(O), $CHOR^{15}$, CHF or CF_2.

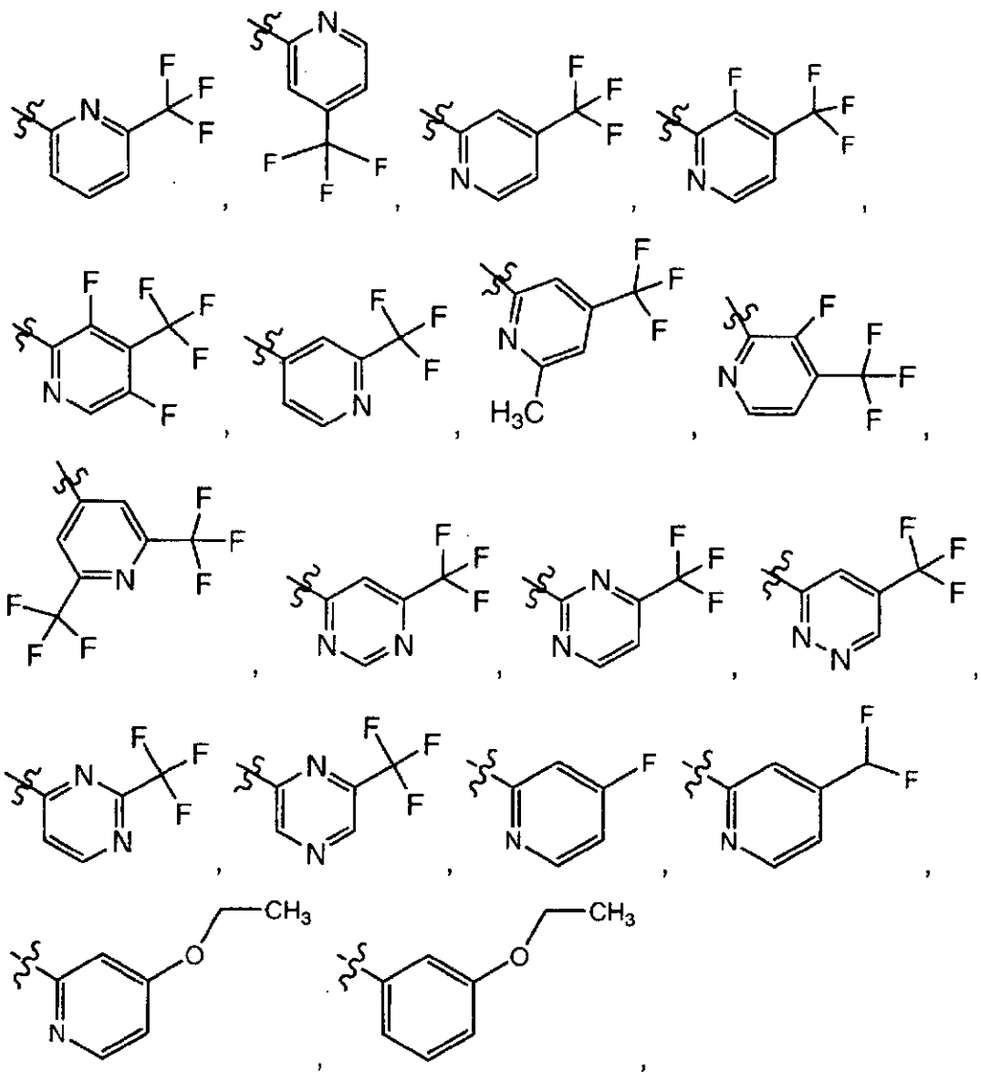
4. The compound of claim 3, or a pharmaceutically acceptable salt thereof, wherein R^2 is methyl.

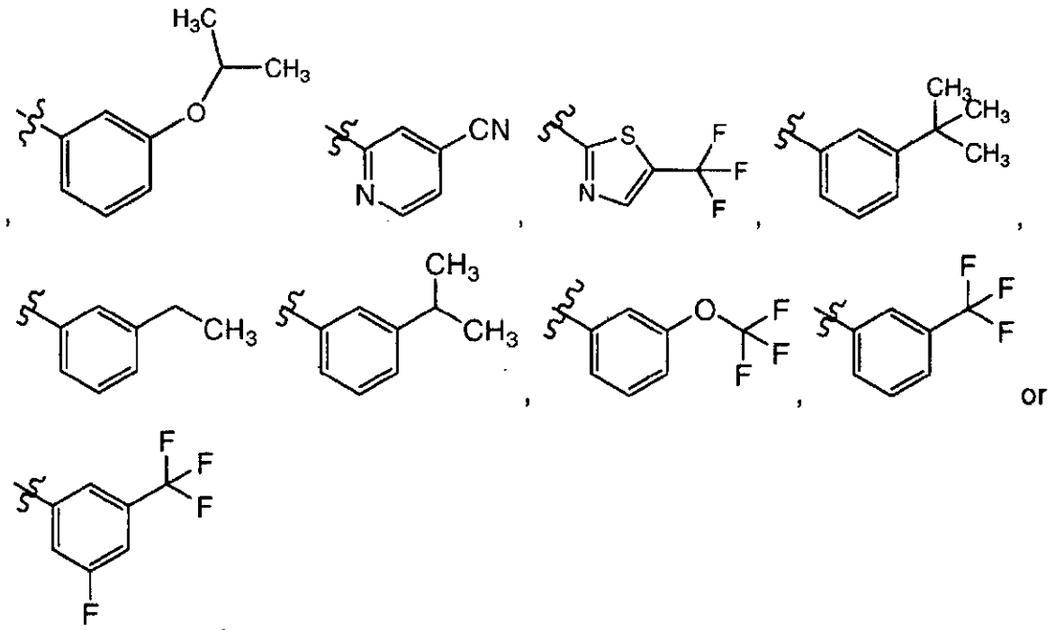
5. The compound of claim 4 wherein R^{10} is



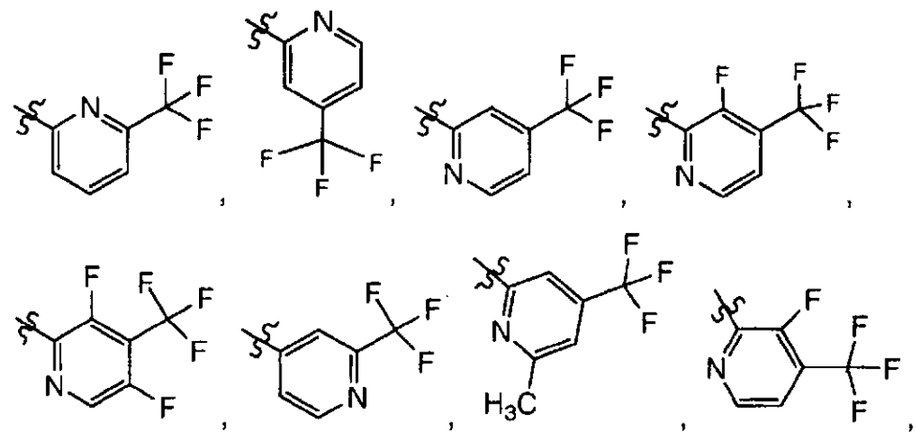
; wherein R^{18} is H or $(C_1\text{-}C_6)$ alkyl.

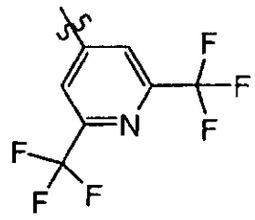
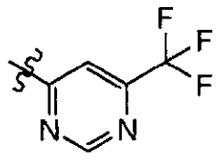
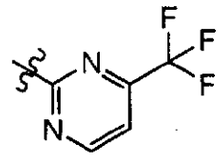
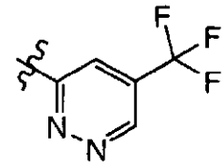
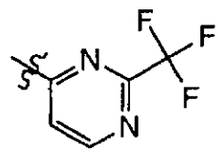
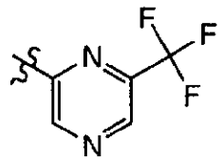
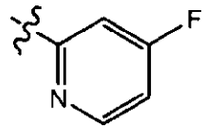
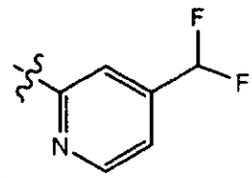
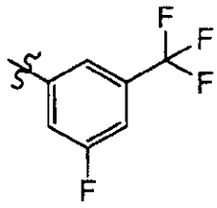
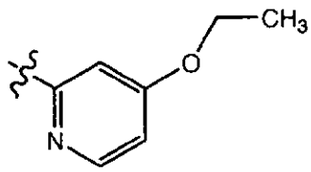
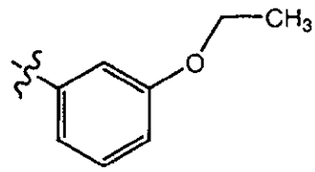
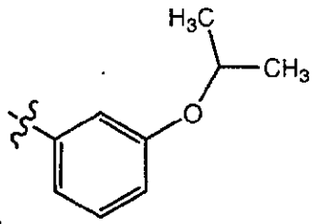
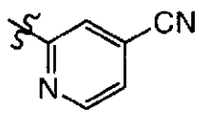
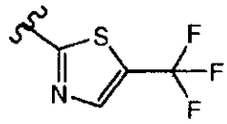
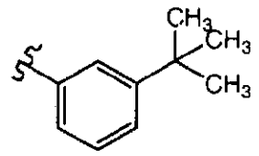
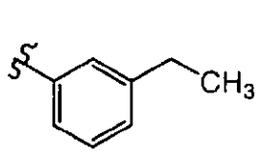
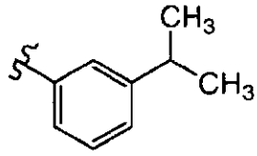
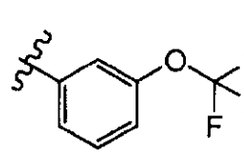
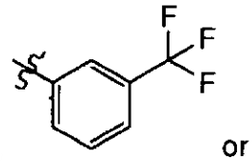
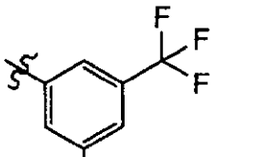
6. The compound of claim 3, or a pharmaceutically acceptable salt thereof, wherein R^{11} is

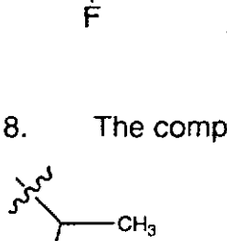




7. The compound of claim 5 or a pharmaceutically acceptable salt thereof, wherein R^{11} is

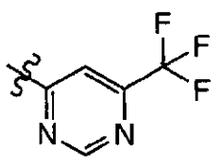
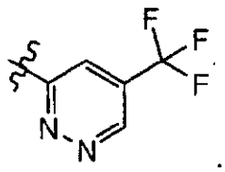




8. The compound of claim 7 wherein R^{10} is

, or and

R^{11} is  , or  .

9. A compound selected from the group consisting of:
1,5-anhydro-2,3-dideoxy-3-{[(1R,3S)-3-ethyl-3-({(1S,4S)-5-[4-(trifluoromethyl)pyridin-2-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methyl-D-erythro-pentitol;

1,5-anhydro-2,3-dideoxy-3-{[(1R,3S)-3-ethyl-3-({(1S,4S)-5-[4-(trifluoromethyl)pyrimidin-2-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methyl-D-erythro-pentitol;

1,5-anhydro-2,3-dideoxy-3-{[(1R,3S)-3-ethyl-3-({(1S,4S)-5-[6-(trifluoromethyl)pyrimidin-4-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methyl-D-erythro-pentitol;

1,5-anhydro-2,3-dideoxy-3-{[(1R,3S)-3-ethyl-3-({(1S,4S)-5-[6-(trifluoromethyl)pyrazin-2-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methyl-D-erythro-pentitol;

1,5-anhydro-2,3-dideoxy-3-{[(1R,3S)-3-ethyl-3-({(1S,4S)-5-[2-(trifluoromethyl)pyrimidin-4-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methyl-D-erythro-pentitol;

1,5-anhydro-2,3-dideoxy-3-{[(1R,3S)-3-ethyl-3-({(1S,4S)-5-[6-(trifluoromethyl)pyridin-2-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methyl-D-erythro-pentitol;

1,5-anhydro-2,3-dideoxy-3-{[(1R,3S)-3-ethyl-3-({(1S,4S)-5-[2-(trifluoromethyl)pyridin-4-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methyl-D-erythro-pentitol;

1,5-anhydro-2,3-dideoxy-3-{[(1R,3S)-3-ethyl-3-({(1S,4S)-5-[3-fluoro-4-(trifluoromethyl)pyridin-2-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methyl-D-erythro-pentitol;

1,5-anhydro-2,3-dideoxy-3-{[(1R,3S)-3-methyl-3-({(1S,4S)-5-[4-(trifluoromethyl)pyridin-2-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methyl-D-erythro-pentitol;

1,5-anhydro-2,3-dideoxy-3-{[(1R,3S)-3-methyl-3-({(1S,4S)-5-[6-(trifluoromethyl)pyrazin-2-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methyl-D-erythro-pentitol;

1,5-anhydro-2,3-dideoxy-3-{[(1R,3S)-3-isopropyl-3-({(1S,4S)-5-[4-(trifluoromethyl)pyridin-2-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methyl-D-erythro-pentitol;

1,5-anhydro-2,3-dideoxy-3-{[(1R,3S)-3-isopropyl-3-({(1S,4S)-5-[4-(trifluoromethyl)pyrimidin-2-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methyl-D-erythro-pentitol;

1,5-anhydro-2,3-dideoxy-3-{[(1R,3S)-3-isopropyl-3-({(1S,4S)-5-[6-(trifluoromethyl)pyrimidin-4-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methyl-D-erythro-pentitol;

1,5-anhydro-2,3-dideoxy-3-{[(1R,3S)-3-isopropyl-3-({(1S,4S)-5-[6-(trifluoromethyl)pyrazin-2-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methyl-D-erythro-pentitol;

1,5-anhydro-2,3-dideoxy-3-{[(1R,3S)-3-isopropyl-3-({(1S,4S)-5-[2-(trifluoromethyl)pyrimidin-4-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methyl-D-erythro-pentitol;

1,5-anhydro-2,3-dideoxy-3-{[(1R,3S)-3-isopropyl-3-({(1S,4S)-5-[6-(trifluoromethyl)pyridin-2-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methyl-D-erythro-pentitol;

1,5-anhydro-2,3-dideoxy-3-{[(1R,3S)-3-isopropyl-3-({(1S,4S)-5-[2-(trifluoromethyl)pyridin-4-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methyl-D-erythro-pentitol;

1,5-anhydro-2,3-dideoxy-3-{[(1R,3S)-3-isopropyl-3-({(1S,4S)-5-[5-(trifluoromethyl)pyridazin-3-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methyl-D-erythro-pentitol;

1,5-anhydro-3-{[(1R,3S)-3-isopropyl-3-({(1S,4S)-5-[2,6-bis(trifluoromethyl)pyridin-4-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)-3-isopropylcyclopentyl]amino}-2,3-dideoxy-4-O-methyl-D-erythro-pentitol;

1,5-anhydro-2,3-dideoxy-3-{[(1R,3S)-3-({(1S,4S)-5-[3-fluoro-4-(trifluoromethyl)pyridin-2-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)-3-isopropylcyclopentyl]amino}-4-O-methyl-D-erythro-pentitol;

1,5-anhydro-2,3-dideoxy-3-{[(1R,3S)-3-isopropyl-3-({(1S,4S)-5-[6-methyl-4-(trifluoromethyl)pyridin-2-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methyl-D-erythro-pentitol;

1,5-anhydro-2,3-dideoxy-3-{[(1R,3S)-3-isopropyl-3-({(1S,4S)-5-[3-(trifluoromethyl)phenyl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methyl-D-erythro-pentitol;

1,5-anhydro-2,3-dideoxy-3-{[(1R,3S)-3-({(1S,4S)-5-[3-fluoro-5-(trifluoromethyl)phenyl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)-3-isopropylcyclopentyl]amino}-4-O-methyl-D-erythro-pentitol;

1,5-anhydro-2,3-dideoxy-3-{[(1R,3S)-3-(2,2-difluoroethyl)-3-({(1S,4S)-5-[6-(trifluoromethyl)pyrimidin-4-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methyl-D-erythro-pentitol;

1,5-anhydro-2,3-dideoxy-3-{[(1R,3S)-3-(2,2-difluoroethyl)-3-({(1S,4S)-5-[4-(trifluoromethyl)pyridin-2-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methyl-D-erythro-pentitol;

1,5-anhydro-2,3-dideoxy-3-{[(1R,3S)-3-(2,2-difluoroethyl)-3-({(1S,4S)-5-[2-(trifluoromethyl)pyridin-4-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methyl-D-erythro-pentitol;

1,5-anhydro-2,3-dideoxy-3-{[(1R,3S)-3-(2,2-difluoroethyl)-3-({(1S,4S)-5-[4-(trifluoromethyl)pyrimidin-2-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methyl-D-erythro-pentitol;

1,5-anhydro-2,3-dideoxy-3-{[(1R,3S)-3-(2,2-difluoroethyl)-3-({(1S,4S)-5-[6-(trifluoromethyl)pyridin-2-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methyl-D-erythro-pentitol;

1,5-anhydro-2,3-dideoxy-3-{[(1R,3S)-3-(2,2-difluoroethyl)-3-({(1S,4S)-5-[6-(trifluoromethyl)pyrazin-2-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methyl-D-erythro-pentitol;

1,5-anhydro-2,3-dideoxy-3-{[(1R,3S)-3-(2,2-difluoroethyl)-3-{{(1S,4S)-5-[2-(trifluoromethyl)pyrimidin-4-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methyl-D-erythro-pentitol;

1,5-anhydro-2,3-dideoxy-3-{[(1R,3S)-3-(2,2-difluoroethyl)-3-{{(1S,4S)-5-[5-(trifluoromethyl)pyridazin-3-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methyl-D-erythro-pentitol;

1,5-anhydro-2,3-dideoxy-4-O-methyl-3-{[(1R,3S)-3-(2,2,2-trifluoroethyl)-3-{{(1S,4S)-5-[6-(trifluoromethyl)pyrimidin-4-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-D-erythro-pentitol;

1,5-anhydro-2,3-dideoxy-4-O-methyl-3-{[(1R,3S)-3-(2,2,2-trifluoroethyl)-3-{{(1S,4S)-5-[4-(trifluoromethyl)pyridin-2-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-D-erythro-pentitol;

1,5-anhydro-2,3-dideoxy-4-O-methyl-3-{[(1R,3S)-3-(2,2,2-trifluoroethyl)-3-{{(1S,4S)-5-[2-(trifluoromethyl)pyridin-4-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-D-erythro-pentitol;

1,5-anhydro-2,3-dideoxy-4-O-methyl-3-{[(1R,3S)-3-(2,2,2-trifluoroethyl)-3-{{(1S,4S)-5-[4-(trifluoromethyl)pyrimidin-2-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-D-erythro-pentitol;

1,5-anhydro-2,3-dideoxy-4-O-methyl-3-{[(1R,3S)-3-(2,2,2-trifluoroethyl)-3-{{(1S,4S)-5-[6-(trifluoromethyl)pyridin-2-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-D-erythro-pentitol;

1,5-anhydro-2,3-dideoxy-4-O-methyl-3-{[(1R,3S)-3-(2,2,2-trifluoroethyl)-3-({(1S,4S)-5-[6-(trifluoromethyl)pyrazin-2-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-D-erythro-pentitol;

1,5-anhydro-2,3-dideoxy-4-O-methyl-3-{[(1R,3S)-3-(2,2,2-trifluoroethyl)-3-({(1S,4S)-5-[2-(trifluoromethyl)pyrimidin-4-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-D-erythro-pentitol;

1,5-anhydro-2,3-dideoxy-4-O-methyl-3-{[(1R,3S)-3-(2,2,2-trifluoroethyl)-3-({(1S,4S)-5-[5-(trifluoromethyl)pyridazin-3-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-D-erythro-pentitol;

1,5-anhydro-2,3-dideoxy-3-{[(1S,4S)-4-isopropyll-4-({(1S,4S)-5-[4-(trifluoromethyl)pyridin-2-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopent-2-en-1-yl]amino}-4-O-methyl-D-erythro-pentitol;

1,5-anhydro-2,3-dideoxy-3-{[(1S,4S)-4-isopropyll-4-({(1S,4S)-5-[4-(trifluoromethyl)pyrimidin-2-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopent-2-en-1-yl]amino}-4-O-methyl-D-erythro-pentitol;

1,5-anhydro-2,3-dideoxy-3-{[(1S,4S)-4-isopropyll-4-({(1S,4S)-5-[6-(trifluoromethyl)pyridin-2-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopent-2-en-1-yl]amino}-4-O-methyl-D-erythro-pentitol;

1,5-anhydro-2,3-dideoxy-3-{[(1S,4S)-4-isopropyll-4-({(1S,4S)-5-[6-(trifluoromethyl)pyrazin-2-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopent-2-en-1-yl]amino}-4-O-methyl-D-erythro-pentitol;

1,5-anhydro-3-{[(1R,3S)-3-{[(1S,4S)-5-(tert-butoxycarbonyl)-2,5-diazabicyclo[2.2.1]hept-2-yl]carbonyl}-3-ethylcyclopentyl]amino}-2,3-dideoxy-4-O-methyl-D-erythro-pentitol;

1,5-anhydro-3-{[(1R,3S)-3-{[(1S,4S)-5-(tert-butoxycarbonyl)-2,5-diazabicyclo[2.2.1]hept-2-yl]carbonyl}-3-(2,2,2-trifluoroethyl)cyclopentyl]amino}-2,3-dideoxy-4-O-methyl-D-erythro-pentitol;

1,5-Anhydro-2,3-dideoxy-3-{[(1R,3S)-3-(1-hydroxycyclobutyl)-3-({(1S,4S)-5-[6-(trifluoromethyl)pyridin-2-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methyl-D-erythro-pentitol;

1,5-Anhydro-2,3-dideoxy-3-{[(1R,3S)-3-(1-hydroxycyclobutyl)-3-({(1S,4S)-5-[4-(trifluoromethyl)pyridin-2-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methyl-D-erythro-pentitol;

1,5-Anhydro-2,3-dideoxy-3-{[(1R,3S)-3-(1-hydroxycyclobutyl)-3-({(1S,4S)-5-[4-(trifluoromethyl)pyrimidin-2-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methyl-D-erythro-pentitol;

1,5-Anhydro-2,3-dideoxy-3-{[(1R,3S)-3-(1-hydroxycyclobutyl)-3-({(1S,4S)-5-[2-(trifluoromethyl)pyrimidin-4-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methyl-D-erythro-pentitol

1,5-anhydro-2,3-dideoxy-3-{[(1R,3S)-3-(1-hydroxycyclobutyl)-3-({(1S,4S)-5-[6-(trifluoromethyl)pyrimidin-4-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methyl-D-erythro-pentitol;

1,5-Anhydro-2,3-dideoxy-3-{[(1R,3S)-3-(1-hydroxycyclobutyl)-3-({(1S,4S)-5-[6-(trifluoromethyl)pyrazin-2-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methyl-D-erythro-pentitol;

1,5-Anhydro-2,3-dideoxy-3-{[(1R,3S)-3-(1-hydroxycyclobutyl)-3-({(1S,4S)-5-[2-(trifluoromethyl)pyridin-4-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methyl-D-erythro-pentitol;

1,5-Anhydro-2,3-dideoxy-3-{[3-(1-hydroxy-1-methylethyl)-3-({5-[4-(trifluoromethyl)pyridin-2-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methylpentitol;

1,5-Anhydro-2,3-dideoxy-3-{[3-(1-hydroxy-1-methylethyl)-3-({5-[6-(trifluoromethyl)pyrimidin-4-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methylpentitol;

1,5-Anhydro-2,3-dideoxy-3-{[3-(1-hydroxy-1-methylethyl)-3-({5-[4-(trifluoromethyl)pyrimidin-2-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methylpentitol;

1,5-Anhydro-2,3-dideoxy-3-{[3-(1-hydroxy-1-methylethyl)-3-({5-[5-(trifluoromethyl)pyridazin-3-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methylpentitol;

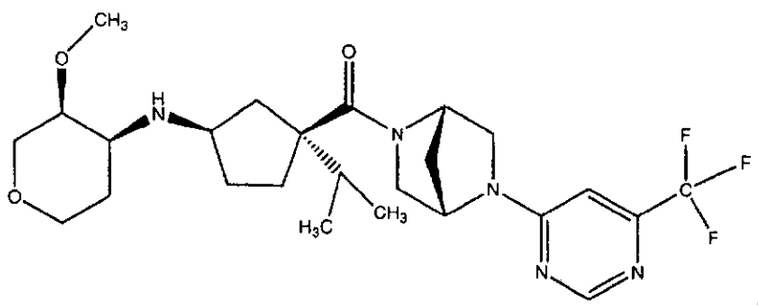
1,5-Anhydro-2,3-dideoxy-3-{[3-(1-hydroxy-1-methylethyl)-3-({5-[2-(trifluoromethyl)pyrimidin-4-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methylpentitol;

1,5-Anhydro-2,3-dideoxy-3-{[3-(1-hydroxy-1-methylethyl)-3-({5-[6-(trifluoromethyl)pyridin-2-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methylpentitol;

1,5-Anhydro-2,3-dideoxy-3-{[3-(1-hydroxy-1-methylethyl)-3-({5-[2-(trifluoromethyl)pyridin-4-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methylpentitol; and

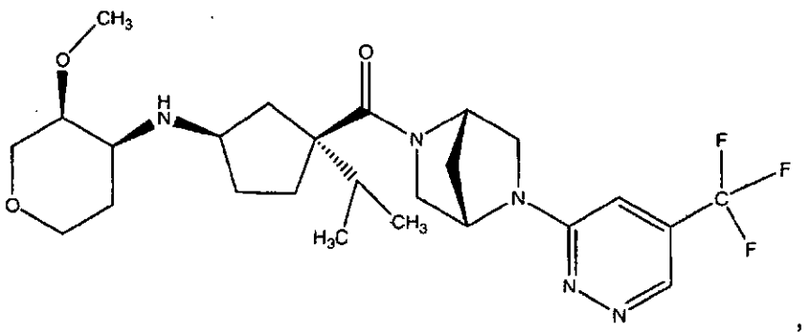
1,5-Anhydro-2,3-dideoxy-3-{[3-(1-hydroxy-1-methylethyl)-3-({5-[6-(trifluoromethyl)pyrazin-2-yl]-2,5-diazabicyclo[2.2.1]hept-2-yl}carbonyl)cyclopentyl]amino}-4-O-methylpentitol.

10. A compound of formula:



, or a pharmaceutically acceptable salt thereof.

11. A compound of formula



, or a pharmaceutically acceptable salt thereof.

12. A composition comprising a compound of claim 2, or a pharmaceutically acceptable salt therof, and a carrier.

13. A method of treating a disease associated with expression or activity of a chemokine receptor in a patient comprising administering to said patient a compound of claim 2, or a pharmaceutically acceptable salt thereof.

14. The method of claim 13 wherein said chemokine receptor is CCR2 or CCR5.

15. The method of claim 13 wherein said disease is rheumatoid arthritis, atherosclerosis, lupus, multiple sclerosis, pain, transplant rejection, diabetes, liver fibrosis, viral disease, cancer, asthma, seasonal and perennial allergic rhinitis, sinusitis, conjunctivitis, age-related macular degeneration, food allergy, scombroid poisoning, psoriasis, undifferentiated spondyloarthropy, gout, urticaria, pruritus, eczema, inflammatory bowel disease, thrombotic disease, otitis media, fibrosis, liver cirrhosis, cardiac disease, Alzheimer's disease, sepsis, restenosis, Crohn's disease, ulcerative colitis, irritable bowel syndrome, hypersensitivity lung diseases, drug-induced pulmonary fibrosis, chronic obstructive pulmonary disease, arthritis, nephritis, atopic dermatitis, stroke, acute nerve injury, sarcoidosis, hepatitis, endometriosis, neuropathic pain, hypersensitivity pneumonitis, eosinophilic pneumonias, delayed-type hypersensitivity, interstitial lung disease, eye disorders or obesity.

16. Use of a compound of any of claims 1-11, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of rheumatoid arthritis, atherosclerosis, lupus, multiple sclerosis, pain, transplant rejection, diabetes, liver fibrosis, viral disease, cancer, asthma, seasonal and perennial allergic rhinitis, sinusitis, conjunctivitis, age-related macular degeneration, food allergy, scombroid poisoning, psoriasis, undifferentiated spondyloarthropy, gout, urticaria, pruritus, eczema, inflammatory bowel disease, thrombotic disease, otitis media, fibrosis, liver cirrhosis, cardiac disease, Alzheimer's disease, sepsis, restenosis, Crohn's disease, ulcerative colitis, irritable bowel syndrome, hypersensitivity lung diseases, drug-induced pulmonary fibrosis, chronic obstructive pulmonary disease, arthritis, nephritis, atopic dermatitis, stroke, acute

nerve injury, sarcoidosis, hepatitis, endometriosis, neuropathic pain, hypersensitivity pneumonitis, eosinophilic pneumonias, delayed-type hypersensitivity, interstitial lung disease, eye disorders or obesity.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2009/055232

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D487/08 A61K31/407 A61P29/02 A61P35/00

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 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2006/020133 A1 (XUE CHU-BIAO [US] ET AL) 26 January 2006 (2006-01-26) claim 1; examples 1-4,15-34	1-16
A	US 2005/234034 A1 (PENNELL ANDREW M [US] ET AL PENNELL ANDREW M K [US] ET AL) 20 October 2005 (2005-10-20) claim 1 3rd compound of page 45	1-16

☐ 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

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 February 2010	09/03/2010

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Fax: (+31–70) 340–3016	Matés Valdivielso, J

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2009/055232

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2006020133 A1	26-01-2006	US 2009208485 A1	20-08-2009
US 2005234034 A1	20-10-2005	US 2006074121 A1	06-04-2006

PC33776

3-AMINOCICLOPENTANCARBOXAMIDAS

La presente solicitud reivindica el beneficio de la solicitud provisional estadounidense No. 61/118,053 presentada el 26 de noviembre de 2008.

CAMPO DE LA INVENCIÓN

La presente invención se refiere a compuestos que modulan la actividad de receptores de quimiocina, tales como CCR2 y CCR5. Los compuestos se pueden usar, por ejemplo, para tratar enfermedades asociadas con la expresión o actividad del receptor de quimiocina.

ANTECEDENTES DE LA INVENCIÓN

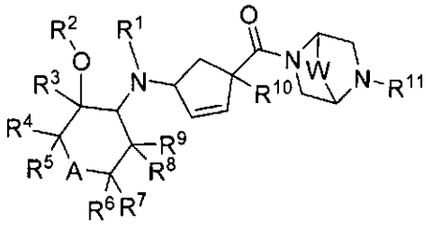
La migración y el transporte de leucocitos desde los vasos sanguíneos hasta los tejidos enfermos participan en el inicio de respuestas inflamatorias normales que combaten las enfermedades. El proceso, también conocido como reclutamiento de leucocitos, también se refiere al inicio y al avance de enfermedades inflamatorias y autoinmunes. La patología resultante de estas enfermedades deriva del ataque de las defensas del sistema inmunológico del cuerpo a los tejidos normales. En consecuencia, la prevención y el bloqueo del reclutamiento de leucocitos en los tejidos blanco en enfermedades inflamatorias y autoinmunes y en cáncer sería un enfoque eficaz a la intervención terapéutica.

La infiltración de monocitos/macrófagos en lugares de inflamación se relaciona con proteínas, tal como la proteína quimioatrayente de monocito 1 (MCP-1, CCL2). Los macrófagos producen quimiocinas, tal como la proteína inflamatoria de macrófago 1-beta (MIP-1β, CCL4). Esas proteínas interactúan con receptores de quimiocina, por ejemplo, CCR2 y CCR5. La modulación, tal como antagonismo o inhibición, de CCR2 o CCR5 sería útil para tratar un amplio rango de enfermedades.

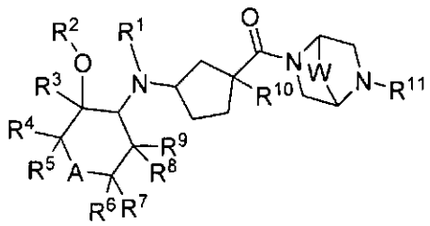
La identificación de compuestos que modulan la actividad de receptores de quimiocina representa un diseño de fármaco deseable para desarrollar agentes farmacológicos para el tratamiento de enfermedades asociadas con la actividad del receptor de quimiocina. Los compuestos de la presente invención ayudan a satisfacer estas y otras necesidades.

SÍNTESIS DE LA INVENCIÓN

En una forma de realización de la presente invención, se provee un compuesto de la Fórmula I(a) o I(b):



I(a)



I(b)

o su sal farmacéuticamente aceptable, en donde

A es O o CF_2;

W es $CR^{13}R^{14}$, C(O), $CHOR^{15}$, CHF, CF_2, O o S

R^1 es H o C_{1-6} alquilo opcionalmente sustituido con 1-3 sustituyentes seleccionados de halo, OH, CO_2H, CO_2-(C_{1-6} alquil) o C_{1-3} alcoxi;

R^2 y R^3 son cada uno, independientemente, H, (C_1-C_6)alquilo, (C_1-C_6)haloalquilo, halo, (C_3-C_6)cicloalquilo, CN, OH, CO_2R, $OCOR^{12}$; en donde dicho (C_1-C_6)alquilo se sustituye opcionalmente con uno o más sustituyentes seleccionados de F, (C_1-C_3) alcoxi, OH, CN o CO_2R^{12};

R^8 y R^9 son cada uno, independientemente, H, (C_1-C_6)alquilo, (C_1-C_6)haloalquilo, (C_3-C_6)cicloalquilo, (C_3-C_6)cicloalquiloxi, CN, OH, CO_2R, $OCOR^{12}$; en donde dicho (C_1-C_6)alquilo se sustituye opcionalmente con uno o más sustituyentes seleccionados de F, (C_1-C_3)alcoxi, OH, CN o CO_2R^{12};

R^2 y R^9, cuando se toman en forma conjunta, pueden formar un anillo de 5-8 miembros;

R^4 y R^7, cuando se toman en forma conjunta, pueden formar un anillo de 5-8 miembros.

R^4 y R^5 son cada uno, independientemente, H, CN, (C_1-C_6)alquilo, halo, (C_1-C_3) alcoxi, (C_1-C_3)haloalcoxi, (C_3-C_6)cicloalquilo, OH, CO_2R^{12}, $OCOR^{12}$, en donde dicho (C_1-C_6)alquilo se sustituye opcionalmente con uno o más sustituyentes seleccionados de F, (C_1-C_3) alcoxi, OH o CO_2R^{12};

R^6 y R^7 son cada uno, independientemente, H, CN, (C_1-C_6)alquilo, halo, (C_1-C_3)alcoxi, (C_1-C_3)haloalcoxi, (C_3-C_6)cicloalquilo, OH, CO_2R^{12}, $OCOR^{12}$, en donde dicho (C_1-C_6)alquilo se sustituye opcionalmente con uno o más sustituyentes seleccionados de F, (C_1-C_3) alcoxi, OH o CO_2R^{12};

o R^2 y R^3, junto con el átomo de carbono al que están unidos, forman un grupo espirociclilo de 3-7 miembros;

o R^4 y R^5, junto con el átomo de carbono al que están unidos, forman un grupo

espirociclilo de 4-7 miembros;

o R^3 y R^4, junto con los átomos C a los que están unidos, forman un grupo cicloalquilo de 3-7 miembros o un grupo heterocicloalquilo de 3-7 miembros fusionados;

R^{10} es $(C_1\text{-}C_6)$alquilo, $(C_1\text{-}C_6)$haloalquilo, $(C_1\text{-}C_6)$hidroxialquilo, $(C_1\text{-}C_6)$alcoxi, $(C_3\text{-}C_6)$cicloalquilo, hidroxi$(C_3\text{-}C_6)$cicloalquilo, $(C_1\text{-}C_6)$alcoxi cicloalquilo, OH, $(C_1\text{-}C_5)$heterociclilo, amino, arilo o CN,

R^{11} es arilo o heteroarilo, en donde dicho R^{11} se sustituye, opcional e independientemente, con uno o más $(C_1\text{-}C_6)$alquilo, halo, $(C_1\text{-}C_6)$haloalquilo $(C_1\text{-}C_6)$alcoxi, OH, amino, $C(O)NH_2$, NH_2SO_2, SF_5 o CN;

R^{12} es H, $(C_1\text{-}C_4)$alquilo o $(C_3\text{-}C_6)$cicloalquilo;

R^{13} es H, halo, $(C_1\text{-}C_4)$alquilo, $(C_1\text{-}C_4)$alcoxi u OH;

R^{14} es H, halo, $(C_1\text{-}C_4)$alquilo, $(C_1\text{-}C_4)$alcoxi u OH; y

R^{15} es H, $(C_1\text{-}C_6)$alquilo o $(C_3\text{-}C_6)$cicloalquilo.

DESCRIPCIÓN DETALLADA DE LA INVENCIÓN

Estas invenciones no se limitan a las formas de realización descritas en la presente memoria descriptiva y se pueden modificar.

A. Definiciones

Para los siguientes términos se aplicarán estas definiciones, a menos que se provea una definición diferente en las reivindicaciones o en otra parte de esta memoria descriptiva.

El término "grupos arilo" pretende incluir grupos carbocíclicos aromáticos, tales como fenilo, bifenililo, indenilo, naftilo así como carbociclos aromáticos fusionados con un heterociclo, tales como benzotienilo, benzofuranilo, indolilo, quinolinilo, benzotiazol, benzooxazol, benzimidazol, isoquinolinilo, isoindolilo, benzotriazol, indazol y acridinilo.

El término "heteroarilo" incluye anillos aromáticos mono- y policíclicos que contienen de 3 a 20, o de 4 a 10 átomos del anillo, y al menos uno de ellos es un heteroátomo, tal como oxígeno, azufre, fósforo o nitrógeno. Los ejemplos de esos grupos incluyen furilo, tienilo, pirrolilo, imidazolilo, triazolilo, tiazolilo, tetrazolilo, oxazolilo, isoxazolilo, pirazolilo, piridilo, pirimidinilo, pirazinilo, piridazinilo, triazinilo, quinolinilo, iosquinolinilo, quinoxalinilo, benztiazolilo, benzoxazolilo, benzotienilo o benzofurilo.

El término "cicloalquilo" se refiere a hidrocarburos ciclizados (mono y policíclicos), tales como grupos alquilo, alquenilo o alquinilo ciclizados. En algunas formas de realización, el grupo cicloalquilo es $C_{3\text{-}14}$, $C_{3\text{-}10}$, $C_{3\text{-}8}$, $C_{3\text{-}7}$, $C_{3\text{-}6}$ o $C_{3\text{-}5}$. En

algunas formas de realización, cada una de las porciones de cicloalquilo tiene de 3 a 14, de 3 a 10 o de 3 a 6 átomos de carbono que forman el anillo. En algunas formas de realización, el grupo cicloalquilo tiene 0, 1 o 2 enlaces dobles o triples. Los ejemplos de grupos cicloalquilo incluyen ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, cicloheptilo, ciclopentenilo, etc. En la presente solicitud, cicloalquilo también pretende incluir hidrocarburos cíclicos con puente, tales como grupos adamantilo y similares.

Los heterociclos son anillos carbocíclicos (mono o policíclicos) que incluyen uno o más heteroátomos, tales como nitrógeno, oxígeno o azufre en el anillo. En algunas formas de realización, el heterociclo contiene de 3 a 8 miembros del anillo. En algunas formas de realización, el heterociclo contiene de 3 a 6 miembros del anillo. En algunas formas de realización, el heterociclo contiene de 1, 2 o 3 heteroátomos. Los heterociclos pueden ser saturados o insaturados. En algunas formas de realización, los heterociclos contienen 0, 1 o 2 enlaces dobles o enlaces triples. Los heteroátomos o átomos de carbono que forman anillos también pueden tener sustituyentes de oxo o sulfuro (tales como CO, CS, SO, SO_2, NO y similares). Los ejemplos de heterociclos incluyen tetrahirofuranilo, tetrahidrotiofenilo, morfolino, tiomorfolino, azetidinilo, pirrolidinilo, piperazinilo, piperidinilo, pirano, dioxano y tiazolidinilo.

El arilo monosustituido se refiere a un grupo arilo que tiene un sustituyente. El arilo polisustituido se refiere a arilo que tiene 2 o más subsustituyentes (tales como 2-4 sustituyentes). El heteroarilo monosustituido se refiere a un grupo heteroarilo que tiene un sustituyente. El heteroarilo polisustituido se refiere a heteroarilo que tiene 2 o más subsustituyentes (tales como 2-4 sustituyentes). El cicloalquilo (o carbociclo) monosustituido se refiere a un grupo cicloalquilo que tiene un sustituyente. El cicloalquilo (o carbociclo) polisustituido se refiere a cicloalquilo que tiene 2 o más subsustituyentes (tales como 2-4 sustituyentes). El heterociclo monosustituido se refiere a heterociclo que tiene un sustituyente. El heterociclo polisustituido se refiere a heterociclo que tiene 2 o más subsustituyentes (tales como 2-4 sustituyentes).

El término "halo", por sí mismo o como parte de otro sustituyente, significa, a menos que se indique de otro modo, flúor, cloro, bromo o yodo. De modo similar, los términos tales como "haloalquilo" pretenden incluir monohaloalquilo y polihaloalquilo. Por ejemplo, el término haloalquilo, tal como halo(C_1-C_4)alquilo, pretende incluir trifluorometilo, 2,2,2-trifluoroetilo, 4-clorobutilo, 3-bromopropilo y similares.

El término "alquilo", cuando se usa solo o como sufijo, incluye estructuras de cadena lineal o ramificada, tales como grupos alquilo primarios, grupos alquilo

secundarios y grupos alquilo terciarios. Estos grupos pueden contener hasta 15, hasta 8 o hasta 4 átomos de carbono. En algunas formas de realización, el grupo alquilo es C_{1-10}, C_{1-8}, C_{1-6}, C_{1-5}, C_{1-4} o C_{1-3}. Los ejemplos de radicales de alquilo incluyen grupos, tales como metilo, etilo, n-propilo, isopropilo, n-butilo, t-butilo, isobutilo y sec-butilo. De modo similar, los términos "alquenilo" y "alquinilo" se refieren a estructuras insaturadas de cadena lineal o ramificada que contienen, por ejemplo, de 2 a 12 o de 2 a 6 átomos de carbono. En algunas formas de realización, el grupo alquenilo o alquinilo es C_{2-10}, C_{2-8}, C_{2-6}, C_{2-5}, C_{2-4} o C_{2-3}. Los ejemplos de grupos alquenilo y alquinilo incluyen vinilo, 2-propenilo, crotilo, 2-isopentenilo, 2-(butadienilo), 2,4-pentadienilo, 3-(1,4-pentadienilo), etinilo, 1- y 3-propinilo, 3-butinilo, y los homólogos e isómeros superiores.

El término "portador" describe un ingrediente que no es un compuesto. Los portadores pueden ser materiales o vehículos farmacéuticamente aceptables. Los ejemplos incluyen agentes de relleno, diluyentes, excipientes, solventes o materiales de encapsulamiento líquidos o sólidos.

La frase "contacto con un receptor de quimiocina" significa que el contacto *in vivo*, *ex vivo* o *in vitro* se realiza con un receptor de quimiocina e incluye la administración de un compuesto o una sal de la presente invención a un sujeto que tiene un receptores de quimiocina, así como, por ejemplo, la introducción de un compuesto o una sal de la invención en una muestra que contiene una preparación celular, no purificada o purificada que contiene un receptor de quimiocina. Por ejemplo, el contacto incluye interacciones entre el compuesto y el receptor, tal como unión.

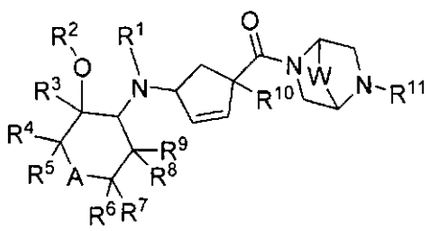
El término "sujeto" se refiere a cualquier animal, que incluye mamíferos, tales como ratones, ratas, otros roedores, conejos, perros, gatos, cerdos, ganado vacuno, ovejas, caballos, primates o seres humanos.

El término "que trata" (y los términos correspondientes "tratar" y "tratamiento") incluye el tratamiento paliativo, curativo o preventivo ("profiláctico") de un sujeto. El término "tratamiento paliativo" se refiere al tratamiento que facilita o reduce el efecto o la intensidad de una afección en un sujeto sin curarla. El término "tratamiento preventivo" (y el término correspondiente "tratamiento profiláctico") se refiere al tratamiento que evita la aparición de una afección en un sujeto. El término "tratamiento curativo" ("restaurativo") se refiere al tratamiento que detiene el avance, reduce las manifestaciones patológicas o elimina por completo una afección en un sujeto. El tratamiento se puede realizar con una cantidad terapéuticamente eficaz de un compuesto, sal o composición que provoca la respuesta biológica o medicinal de un

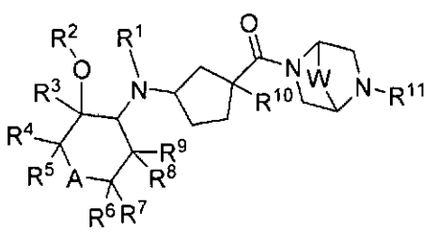
tejido, sistema o sujeto que busca un individuo, tal como un investigador, doctor, veterinario o médico clínico.

B. Compuestos

En una forma de realización de la presente invención, se provee un compuesto de I(a) o I(b):



I(a)



I(b)

o su sal farmacéuticamente aceptable, en donde

A es O o CF_2;

W es $CR^{13}R^{14}$, C(O), $CHOR^{15}$, CHF, CF_2, O o S

R^1 es H o C_{1-6} alquilo opcionalmente sustituido con 1-3 sustituyentes seleccionados de halo, OH, CO_2H, CO_2-(C_{1-6} alquil) o C_{1-3} alcoxi;

R^2 y R^3 son cada uno, independientemente, H, (C_1-C_6)alquilo, (C_1-C_6)haloalquilo, halo, (C_3-C_6)cicloalquilo, CN, OH, CO_2R, $OCOR^{12}$; en donde dicho (C_1-C_6)alquilo se sustituye opcionalmente con uno o más sustituyentes seleccionados de F, (C_1-C_3)alcoxi, OH, CN o CO_2R^{12};

R^8 y R^9 son cada uno, independientemente, H, (C_1-C_6)alquilo, (C_1-C_6)haloalquilo, (C_3-C_6)cicloalquilo, CN, OH, CO_2R, $OCOR^{12}$; en donde dicho (C_1-C_6)alquilo se sustituye opcionalmente con uno o más sustituyentes seleccionados de F, (C_1-C_3)alcoxi, OH, CN o CO_2R^{12};

R^2 y R^9, cuando se toman en forma conjunta, pueden formar un anillo de 5-8 miembros;

R^4 y R^7, cuando se toman en forma conjunta, pueden formar un anillo de 5-8 miembros.

R^4 y R^5 son cada uno, independientemente, H, CN, (C_1-C_6)alquilo, halo, (C_1-C_3)alcoxi, (C_1-C_3)haloalcoxi, (C_3-C_6)cicloalquilo, OH, CO_2R^{12}, $OCOR^{12}$, en donde dicho (C_1-C_6)alquilo se sustituye opcionalmente con uno o más sustituyentes seleccionados de F, (C_1-C_3) alcoxi, OH o CO_2R^{12};

R^6 y R^7 son cada uno, independientemente, H, CN, (C_1-C_6)alquilo, halo, (C_1-C_3)alcoxi, (C_1-C_3)haloalcoxi, (C_3-C_6)cicloalquilo, OH, CO_2R^{12}, $OCOR^{12}$, en donde dicho

$(C_1\text{-}C_6)$alquilo se sustituye opcionalmente con uno o más sustituyentes seleccionados de F, $(C_1\text{-}C_3)$ alcoxi, OH o CO_2R^{12};

o R^2 y R^3, junto con el átomo de carbono al que están unidos, forman un grupo espirociclilo de 3-7 miembros;

o R^4 y R^5, junto con el átomo de carbono al que están unidos, forman un grupo espirociclilo de 3-7 miembros;

o R^3 y R^4, junto con los átomos C a los que están unidos, forman un grupo cicloalquilo de 3-7 miembros o un grupo heterocicloalquilo de 3-7 miembros fusionados;

R^{10} es $(C_1\text{-}C_6)$alquilo, $(C_1\text{-}C_6)$haloalquilo, $(C_1\text{-}C_6)$hidroxialquilo, $(C_1\text{-}C_6)$alcoxi, $(C_3\text{-}C_6)$cicloalquilo, hidroxi$(C_3\text{-}C_6)$cicloalquilo, alcoxi cicloalquilo, OH, $(C_1\text{-}C_5)$heterociclilo, amino, arilo o CN,

R^{11} es arilo o heteroarilo, en donde dicho R^{11} se sustituye, opcional e independientemente, con uno o más $(C_1\text{-}C_6)$alquilo, halo, $(C_1\text{-}C_6)$haloalquilo $(C_1\text{-}C_6)$alcoxi, OH, amino, $C(O)NH_2$, NH_2SO_2, SF_5 o CN;

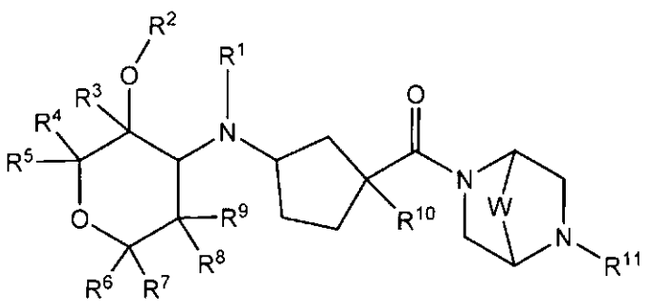
R^{12} es H, $(C_1\text{-}C_4)$alquilo o $(C_3\text{-}C_6)$cicloalquilo;

R^{13} es H, halo, $(C_1\text{-}C_4)$alquilo, $(C_1\text{-}C_4)$alcoxi u OH;

R^{14} es H, halo, $(C_1\text{-}C_4)$alquilo, $(C_1\text{-}C_4)$alcoxi u OH; y

R^{15} es H, $(C_1\text{-}C_6)$alquilo o $(C_3\text{-}C_6)$cicloalquilo.

En otra forma de realización de la presente invención, se provee un compuesto de la Fórmula II:



(II)

o su sal farmacéuticamente aceptable, en donde

R^1 es H, $(C_1\text{-}C_6)$alquilo o ciclopropilo, en donde dicho $(C_1\text{-}C_6)$alquilo se sustituye opcionalmente con halo, CN, C(O)OH u OH;

R^2 es $(C_1\text{-}C_6)$alquilo $(C_1\text{-}C_6)$haloalquilo o $(C_3\text{-}C_6)$cicloalquilo;

R^3, R^4, R^5, R^6, R^7, R^8 y R^9 son, independientemente, H, $(C_1\text{-}C_4)$ alquilo, CN, halo o amino;

R^{10} es $(C_1\text{-}C_6)$alquilo, $(C_1\text{-}C_6)$haloalquilo, $(C_1\text{-}C_6)$hidroxialquilo, $(C_1\text{-}C_6)$alcoxi, $(C_3\text{-}$

C_6)cicloalquilo, hidroxi(C_3-C_6)cicloalquilo, alcoxi (C_3-C_6)cicloalquilo, OH, (C_1-C_5)heterociclilo, amino, arilo o CN;

R^{11} es arilo o heteroarilo, en donde dicho R^{11} se sustituye, opcional e independientemente, con uno o más (C_1-C_6)alquilo, halo, (C_1-C_6)haloalquilo (C_1-C_6)alcoxi, OH, amino, $C(O)NH_2$, NH_2SO_2, SF_5 o CN;

W es $CR^{13}R^{14}$, C(O), $CHOR^{15}$, CHF, CF_2, O o S;

R^{13} y R^{14} son, independientemente, H, halo, (C_1-C_4)alquilo, (C_1-C_4)alcoxi u OH; y

R^{15} es H, (C_1-C_6)alquilo o (C_3-C_6)cicloalquilo.

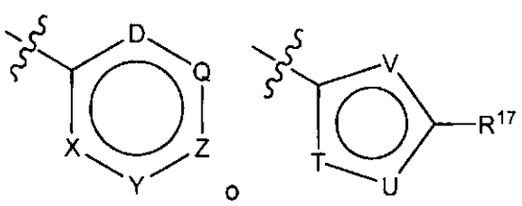
En otra forma de realización, se provee un compuesto de la Fórmula II o una sal de éste farmacéuticamente aceptable, en donde:

R^1 es H o (C_1-C_6)alquilo,

R^2 es (C_1-C_6)alquilo o (C_1-C_6)haloalquilo

R^3, R^4, R^5, R^6, R^7, R^8 y R^9 son cada uno H;

R^{11} es



o

en donde X, Y, Z, Q y D son, independientemente, N o CR^{16}, y en donde 0, 1, 2 o 3 de X, Y, Z, Q y D son N; y

en donde T, U y V se seleccionan, independientemente, de CH, N, S u O, siempre que T y U no sean ambos, simultáneamente, O o S;

cada R^{16} es, independientemente, H, halo, (C_1-C_6)alquilo, (C_1-C_6)haloalquilo, (C_1-C_6)alcoxi o CN;

R^{17} es H, (C_1-C_6)alquilo, (C_1-C_6)haloalquilo o (C_1-C_6)alcoxi; y

W es $CR^{13}R^{14}$, C(O), $CHOR^{15}$, CHF o CF_2.

En algunas formas de realización del compuesto de la Fórmula II o una sal de éste farmacéuticamente aceptable, R^2 es metilo.

En algunas formas de realización del compuesto de la Fórmula II o una sal de éste farmacéuticamente aceptable

R^1 es H, (C_1-C_6)alquilo o ciclopropilo, en donde dicho (C_1-C_6)alquilo se sustituye opcionalmente con halo, CN, C(O)OH u OH;

R^2 es metilo;

R^3, R^4, R^5, R^6, R^7, R^8 y R^9 son, independientemente, H, (C_1-C_4) alquilo, CN, halo o amino;

R^{10} es $(C_1\text{-}C_6)$alquilo, $(C_1\text{-}C_6)$haloalquilo, $(C_1\text{-}C_6)$hidroxialquilo, $(C_1\text{-}C_6)$alcoxi, $(C_3\text{-}C_6)$cicloalquilo, hidroxi$(C_3\text{-}C_6)$cicloalquilo, alcoxi $(C_3\text{-}C_6)$cicloalquilo, OH, $(C_1\text{-}C_5)$heterociclilo, amino, arilo o CN;

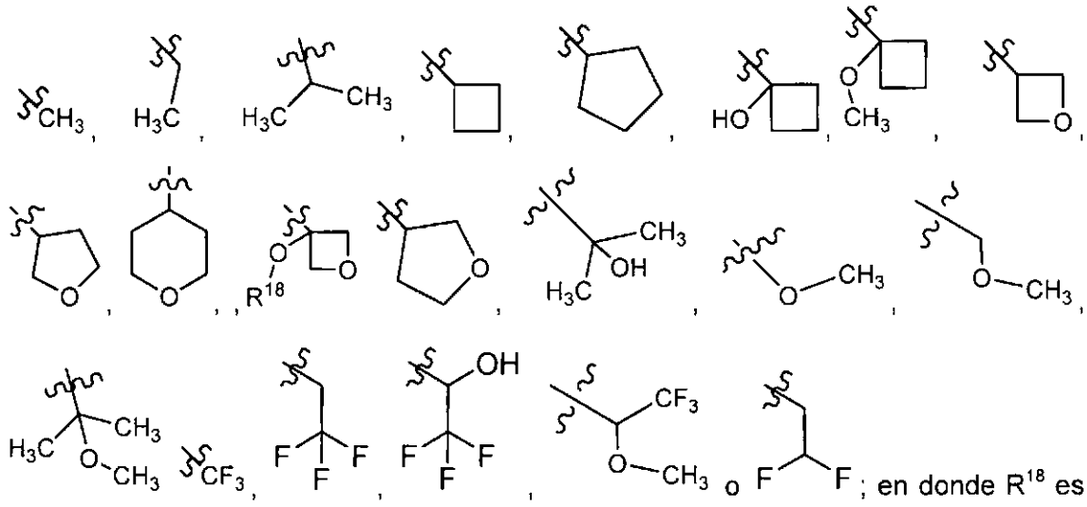
R^{11} es arilo o heteroarilo, en donde dicho R^{11} se sustituye, opcional e independientemente, con uno o más $(C_1\text{-}C_6)$alquilo, halo, $(C_1\text{-}C_6)$haloalquilo $(C_1\text{-}C_6)$alcoxi, OH, amino, $C(O)NH_2$, NH_2SO_2, SF_5 o CN;

W es $CR^{13}R^{14}$, C(O), $CHOR^{15}$, CHF, CF_2, O o S;

R^{13} y R^{14} son, independientemente, H, halo, $(C_1\text{-}C_4)$alquilo, $(C_1\text{-}C_4)$alcoxi u OH; y

R^{15} es H, $(C_1\text{-}C_6)$alquilo o $(C_3\text{-}C_6)$cicloalquilo.

En algunas formas de realización del compuesto de la Fórmula II o una sal de éste farmacéuticamente aceptable, R^{10} es



; en donde R^{18} es H o $(C_1\text{-}C_6)$alquilo

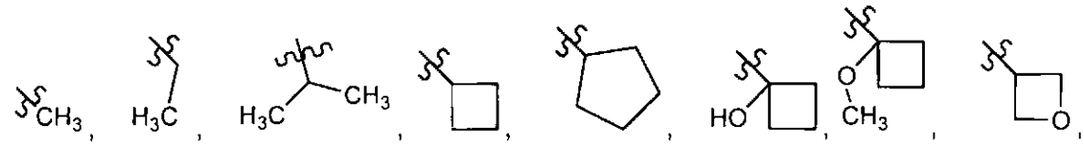
En algunas formas de realización del compuesto de la Fórmula II o una sal de éste farmacéuticamente aceptable

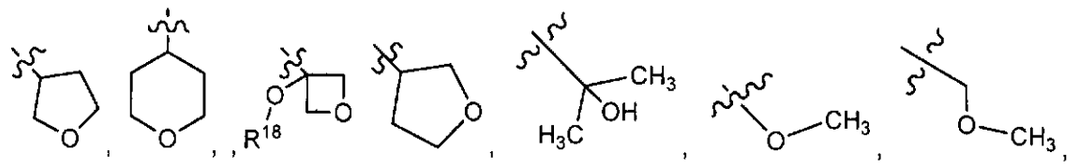
R^1 es H, $(C_1\text{-}C_6)$alquilo o ciclopropilo, en donde dicho $(C_1\text{-}C_6)$alquilo se sustituye opcionalmente con halo, CN, C(O)OH u OH;

R^2 es metilo;

R^3, R^4, R^5, R^6, R^7, R^8 y R^9 son, independientemente, H, $C_1\text{-}C_4$ alquilo, CN, halo o amino;

R^{10} es





R^{11} es arilo o heteroarilo, en donde dicho R^{11} se sustituye, opcional e independientemente, con uno o más (C_1-C_6)alquilo, halo, (C_1-C_6)haloalquilo (C_1-C_6)alcoxi, OH, amino, $C(O)NH_2$, NH_2SO_2, SF_5 o CN;

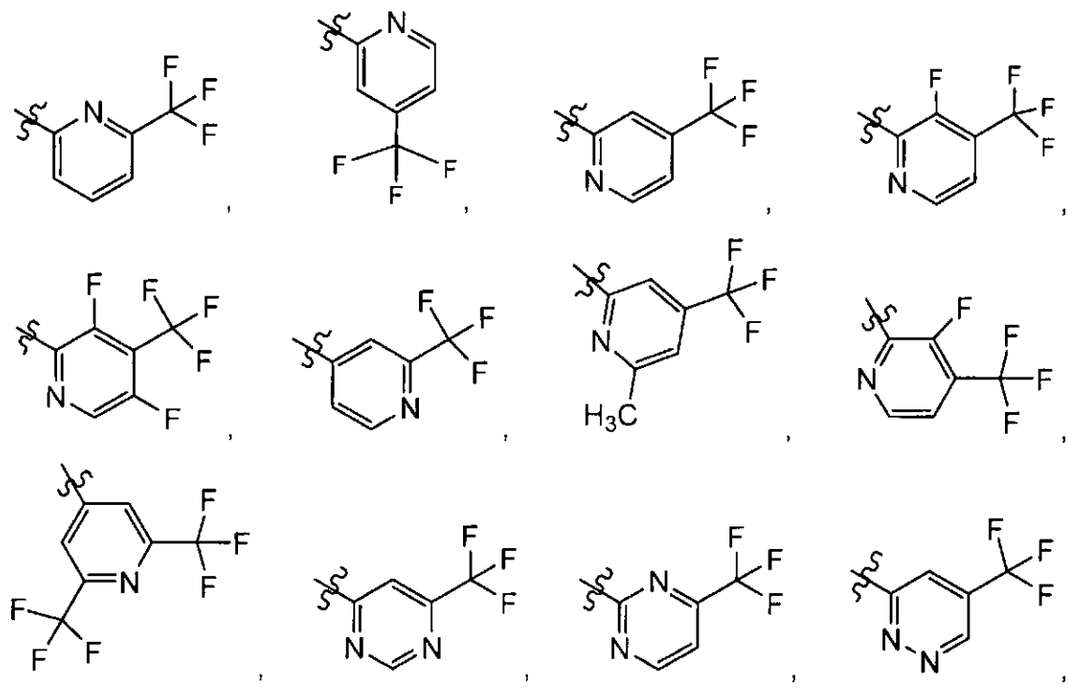
W es $CR^{13}R^{14}$, C(O), $CHOR^{15}$, CHF, CF_2, O o S;

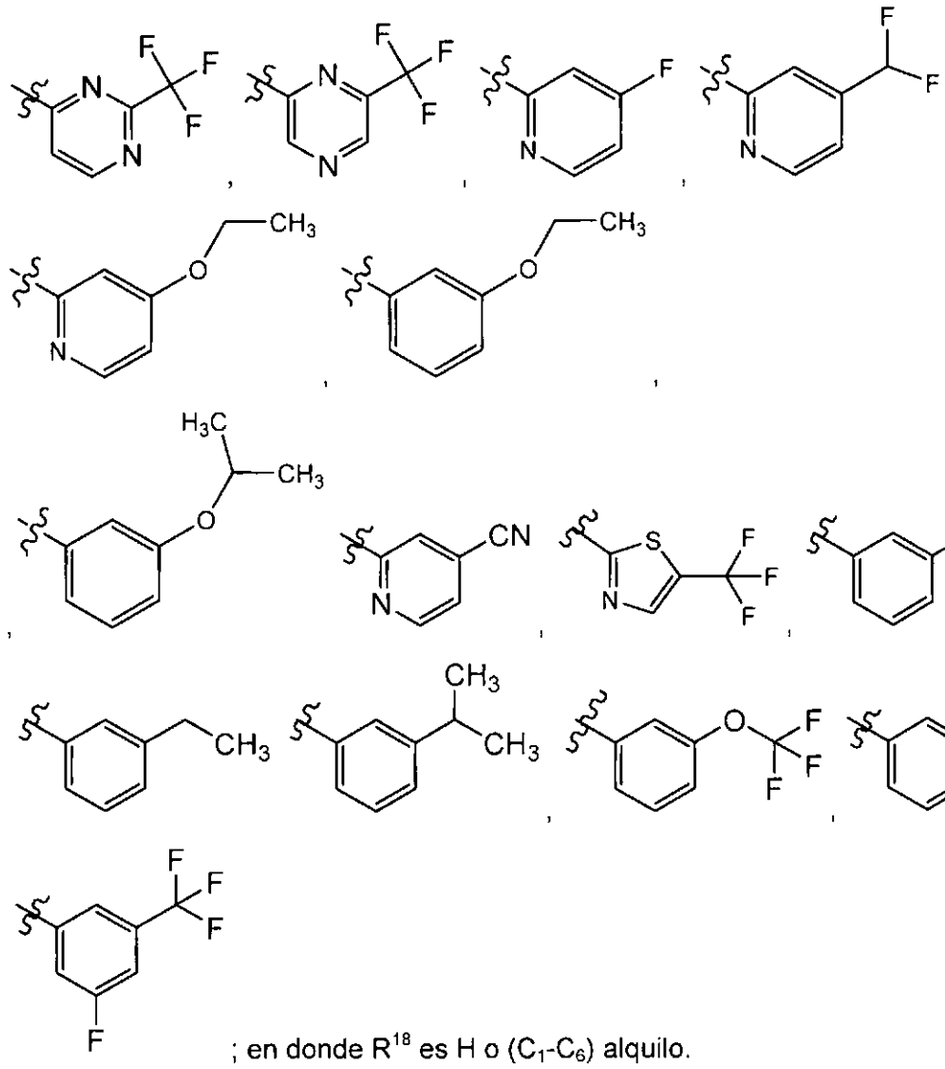
R^{13} y R^{14} son, independientemente, H, halo, (C_1-C_4)alquilo, (C_1-C_4)alcoxi u OH;

R^{15} es H, (C_1-C_6)alquilo o (C_3-C_6)cicloalquilo; y

R^{18} es H o (C_1-C_6)alquilo.

En algunas formas de realización de la presente invención, se provee un compuesto de la Fórmula II o una sal de éste farmacéuticamente aceptable, en donde R^{11} es





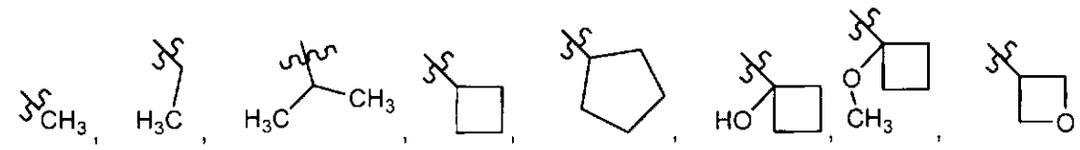
; en donde R^{18} es H o (C_1-C_6) alquilo.

En algunas formas de realización de la presente invención, se provee un compuesto de la Fórmula II o una sal de éste farmacéuticamente aceptable, en donde R^1 es H, (C_1-C_6)alquilo o ciclopropilo, en donde dicho (C_1-C_6)alquilo se sustituye opcionalmente con halo, CN, C(O)OH u OH;

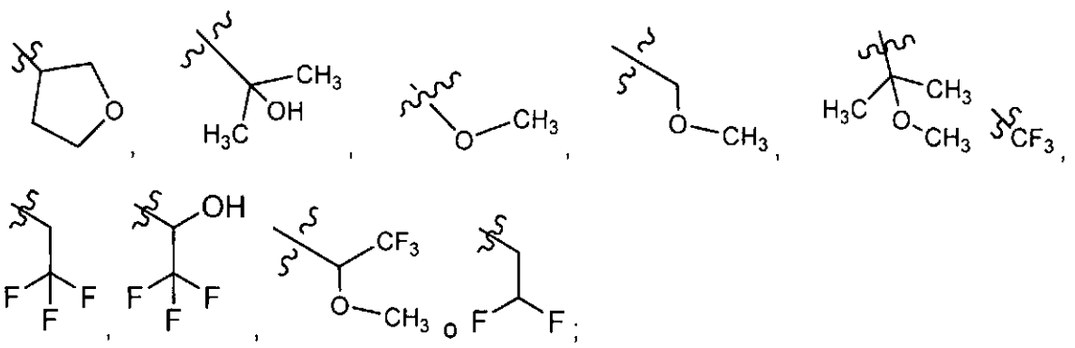
R^2 es metilo;

R^3, R^4, R^5, R^6, R^7, R^8 y R^9 son, independientemente, H, C_1-C_4 alquilo, CN, halo o amino;

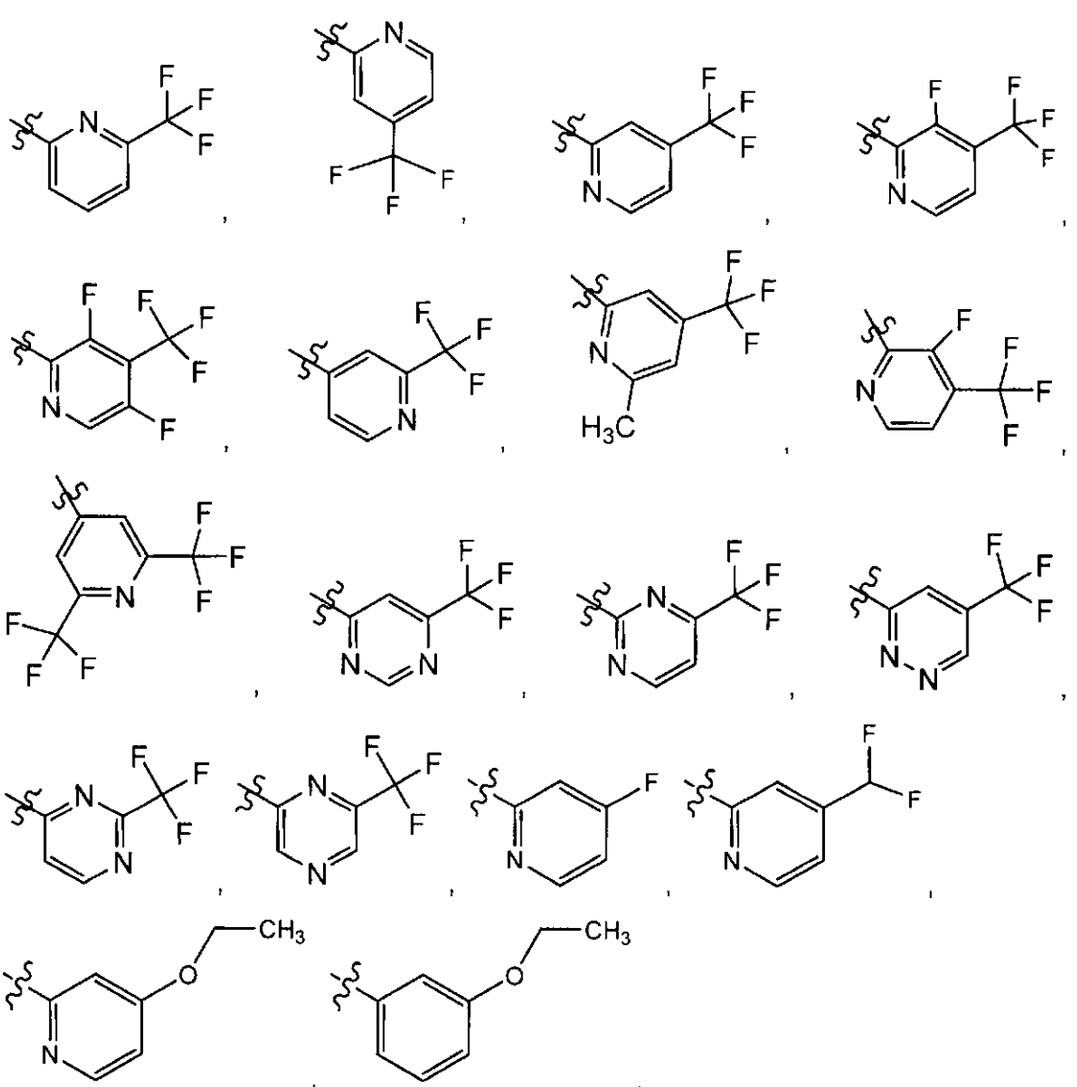
R^{10} es

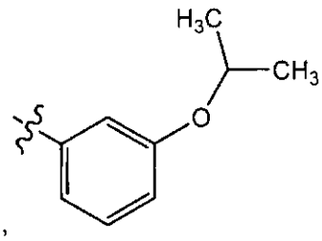
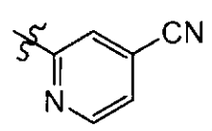
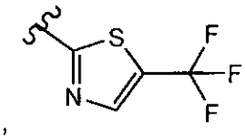
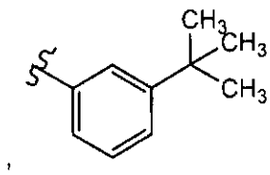
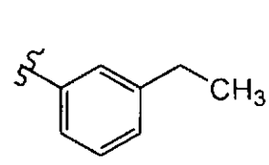
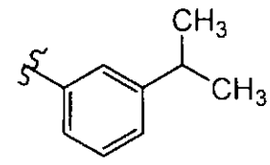
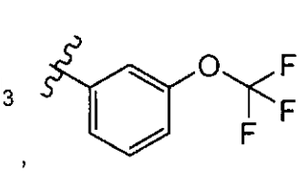
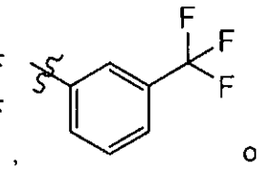
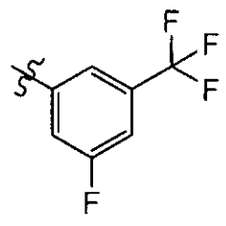


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R^{11} es



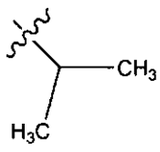
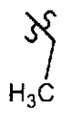
; en donde R^{18} es H o (C_1-C_6) alquilo;

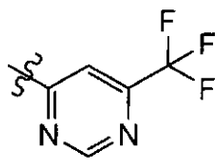
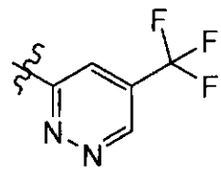
W es $CR^{13}R^{14}$, C(O), $CHOR^{15}$, CHF, CF_2, O o S;

R^{13} y R^{14} son, independientemente, H, halo, (C_1-C_4)alquilo, (C_1-C_4)alcoxi u OH; y

R^{15} es H, (C_1-C_6)alquilo o (C_3-C_6)cicloalquilo.

En algunas formas de realización, se provee un compuesto de la Fórmula II o una sal de éste farmacéuticamente aceptable, en donde R^{10} es


, o  y

R^{11} es  o  .

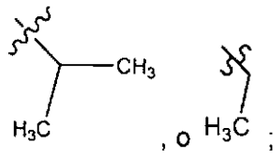
En algunas formas de realización, se provee un compuesto de la Fórmula II o una sal de éste farmacéuticamente aceptable, en donde

R^1 es H;

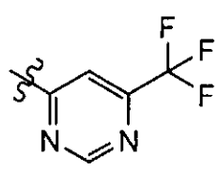
R^2 es metilo;

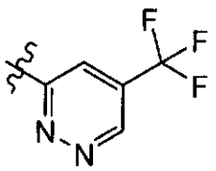
R^3, R^4, R^5, R^6, R^7, R^8 y R^9 son cada uno H;

R^{10} es



, o ;



R^{11} es  ; y

W es CH_2.

En otra forma de realización, se provee un compuesto o una sal de éste farmacéuticamente aceptable, seleccionado del grupo que consiste en:

1,5-anhidro-2,3-dideoxi-3-{[(1R,3S)-3-etil-3-({(1S,4S)-5-[4-(trifluorometil)piridin-2-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metil-D-eritro-pentitol;

1,5-anhidro-2,3-dideoxi-3-{[(1R,3S)-3-etil-3-({(1S,4S)-5-[4-(trifluorometil)pirimidin-2-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metil-D-eritro-pentitol;

1,5-anhidro-2,3-dideoxi-3-{[(1R,3S)-3-etil-3-({(1S,4S)-5-[6-(trifluorometil)pirimidin-4-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metil-D-eritro-pentitol;

1,5-anhidro-2,3-dideoxi-3-{[(1R,3S)-3-etil-3-({(1S,4S)-5-[6-(trifluorometil)pirazin-2-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metil-D-eritro-pentitol;

1,5-anhidro-2,3-dideoxi-3-{[(1R,3S)-3-etil-3-({(1S,4S)-5-[2-(trifluorometil)pirimidin-4-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metil-D-eritro-pentitol;

1,5-anhidro-2,3-dideoxi-3-{[(1R,3S)-3-etil-3-({(1S,4S)-5-[6-(trifluorometil)piridin-2-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metil-D-eritro-pentitol;

1,5-anhidro-2,3-dideoxi-3-{[(1R,3S)-3-etil-3-({(1S,4S)-5-[2-(trifluorometil)piridin-4-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metil-D-eritro-pentitol;

1,5-anhidro-2,3-dideoxi-3-{[(1R,3S)-3-etil-3-({(1S,4S)-5-[3--fluoro-4-(trifluorometil)piridin-2-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metil-D-eritro-pentitol;

1,5-anhidro-2,3-dideoxi-3-{[(1R,3S)-3-metil-3-({(1S,4S)-5-[4-(trifluorometil)piridin-2-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metil-D-eritro-pentitol;

1,5-anhidro-2,3-dideoxi-3-{[(1R,3S)-3-metil-3-({(1S,4S)-5-[6-(trifluorometil)pirazin-2-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metil-D-eritro-pentitol;

1,5-anhidro-2,3-dideoxi-3-{[(1R,3S)-3-isopropil-3-({(1S,4S)-5-[4-(trifluorometil)piridin-2-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metil-D-eritro-pentitol;

1,5-anhidro-2,3-dideoxi-3-{[(1R,3S)-3-isopropil-3-({(1S,4S)-5-[4-(trifluorometil)pirimidin-

2-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metil-D-eritro-pentitol;
1,5-anhidro-2,3-dideoxi-3-{[(1R,3S)-3-isopropil-3-({(1S,4S)-5-[6-(trifluorometil)pirimidin-4-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metil-D-eritro-pentitol;
1,5-anhidro-2,3-dideoxi-3-{[(1R,3S)-3-isopropil-3-({(1S,4S)-5-[6-(trifluorometil)pirazin-2-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metil-D-eritro-pentitol;
1,5-anhidro-2,3-dideoxi-3-{[(1R,3S)-3-isopropil-3-({(1S,4S)-5-[2-(trifluorometil)pirimidin-4-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metil-D-eritro-pentitol;
1,5-anhidro-2,3-dideoxi-3-{[(1R,3S)-3-isopropil-3-({(1S,4S)-5-[6-(trifluorometil)piridin-2-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metil-D-eritro-pentitol;
1,5-anhidro-2,3-dideoxi-3-{[(1R,3S)-3-isopropil-3-({(1S,4S)-5-[2-(trifluorometil)piridin-4-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metil-D-eritro-pentitol;
1,5-anhidro-2,3-dideoxi-3-{[(1R,3S)-3-isopropil-3-({(1S,4S)-5-[5-(trifluorometil)piridazin-3-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metil-D-eritro-pentitol;
1,5-anhidro-3-{[(1R,3S)-3-isopropil-3-({(1S,4S)-5-[2,6-bis(trifluorometil)piridin-4-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)-3-isopropilciclopentil]amino}-2,3-dideoxi-4-O-metil-D-eritro-pentitol;
1,5-anhidro-2,3-dideoxi-3-{[(1R,3S)-3-({(1S,4S)-5-[3-fluoro-4-(trifluorometil)piridin-2-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)-3-isopropilciclopentil]amino}-4-O-metil-D-eritro-pentitol;
1,5-anhidro-2,3-dideoxi-3-{[(1R,3S)-3-isopropil-3-({(1S,4S)-5-[6-metil-4-(trifluorometil)piridin-2-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metil-D-eritro-pentitol;
1,5-anhidro-2,3-dideoxi-3-{[(1R,3S)-3-isopropil-3-({(1S,4S)-5-[3-(trifluorometil)fenil]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metil-D-eritro-pentitol;
1,5-anhidro-2,3-dideoxi-3-{[(1R,3S)-3-({(1S,4S)-5-[3-fluoro-5-(trifluorometil)fenil]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)-3-isopropilciclopentil]amino}-4-O-metil-D-eritro-pentitol;
1,5-anhidro-2,3-dideoxi-3-{[(1R,3S)-3-(2,2-difluoroetil)-3-({(1S,4S)-5-[6-(trifluorometil)pirimidin-4-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metil-D-eritro-pentitol;
1,5-anhidro-2,3-dideoxi-3-{[(1R,3S)-3-(2,2-difluoroetil)-3-({(1S,4S)-5-[4-

(trifluorometil)piridin-2-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metil-D-eritro-pentitol;

1,5-anhidro-2,3-dideoxi-3-{[(1R,3S)-3-(2,2-difluoroetil)-3-({(1S,4S)-5-[2-(trifluorometil)piridin-4-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metil-D-eritro-pentitol;

1,5-anhidro-2,3-dideoxi-3-{[(1R,3S)-3-(2,2-difluoroetil)-3-({(1S,4S)-5-[4-(trifluorometil)pirimidin-2-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metil-D-eritro-pentitol;

1,5-anhidro-2,3-dideoxi-3-{[(1R,3S)-3-(2,2-difluoroetil)-3-({(1S,4S)-5-[6-(trifluorometil)piridin-2-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metil-D-eritro-pentitol;

1,5-anhidro-2,3-dideoxi-3-{[(1R,3S)-3-(2,2-difluoroetil)-3-({(1S,4S)-5-[6-(trifluorometil)pirazin-2-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metil-D-eritro-pentitol;

1,5-anhidro-2,3-dideoxi-3-{[(1R,3S)-3-(2,2-difluoroetil)-3-({(1S,4S)-5-[2-(trifluorometil)pirimidin-4-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metil-D-eritro-pentitol;

1,5-anhidro-2,3-dideoxi-3-{[(1R,3S)-3-(2,2-difluoroetil)-3-({(1S,4S)-5-[5-(trifluorometil)piridazin-3-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metil-D-eritro-pentitol;

1,5-anhidro-2,3-dideoxi-4-O-metil-3-{[(1R,3S)-3-(2,2,2-trifluoroetil)-3-({(1S,4S)-5-[6-(trifluorometil)pirimidin-4-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-D-eritro-pentitol;

1,5-anhidro-2,3-dideoxi-4-O-metil-3-{[(1R,3S)-3-(2,2,2-trifluoroetil)-3-({(1S,4S)-5-[4-(trifluorometil)piridin-2-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-D-eritro-pentitol;

1,5-anhidro-2,3-dideoxi-4-O-metil-3-{[(1R,3S)-3-(2,2,2-trifluoroetil)-3-({(1S,4S)-5-[2-(trifluorometil)piridin-4-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-D-eritro-pentitol;

1,5-anhidro-2,3-dideoxi-4-O-metil-3-{[(1R,3S)-3-(2,2,2-trifluoroetil)-3-({(1S,4S)-5-[4-(trifluorometil)pirimidin-2-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-D-eritro-pentitol;

1,5-anhidro-2,3-dideoxi-4-O-metil-3-{[(1R,3S)-3-(2,2,2-trifluoroetil)-3-({(1S,4S)-5-[6-(trifluorometil)piridin-2-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-D-eritro-pentitol;

100

1,5-anhidro-2,3-dideoxi-4-O-metil-3-{[(1R,3S)-3-(2,2,2-trifluoroetil)-3-({(1S,4S)-5-[6-(trifluorometil)pirazin-2-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-D-eritro-pentitol;

1,5-anhidro-2,3-dideoxi-4-O-metil-3-{[(1R,3S)-3-(2,2,2-trifluoroetil)-3-({(1S,4S)-5-[2-(trifluorometil)pirimidin-4-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-D-eritro-pentitol;

1,5-anhidro-2,3-dideoxi-4-O-metil-3-{[(1R,3S)-3-(2,2,2-trifluoroetil)-3-({(1S,4S)-5-[5-(trifluorometil)piridazin-3-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-D-eritro-pentitol;

1,5-anhidro-2,3-dideoxi-3-{[(1S,4S)-4-isopropill-4-({(1S,4S)-5-[4-(trifluorometil)piridin-2-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopent-2-en-1-il]amino}-4-O-metil-D-eritro-pentitol;

1,5-anhidro-2,3-dideoxi-3-{[(1S,4S)-4-isopropill-4-({(1S,4S)-5-[4-(trifluorometil)pirimidin-2-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopent-2-en-1-il]amino}-4-O-metil-D-eritro-pentitol;

1,5-anhidro-2,3-dideoxi-3-{[(1S,4S)-4-isopropill-4-({(1S,4S)-5-[6-(trifluorometil)piridin-2-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopent-2-en-1-il]amino}-4-O-metil-D-eritro-pentitol;

1,5-anhidro-2,3-dideoxi-3-{[(1S,4S)-4-isopropill-4-({(1S,4S)-5-[6-(trifluorometil)pirazin-2-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopent-2-en-1-il]amino}-4-O-metil-D-eritro-pentitol;

1,5-anhidro-3-{[(1R,3S)-3-{[(1S,4S)-5-(ter-butoxicarbonil)-2,5-diazabiciclo[2.2.1]hept-2-il]carbonil}-3-etilciclopentil]amino}-2,3-dideoxi-4-O-metil-D-eritro-pentitol;

1,5-anhidro-3-{[(1R,3S)-3-{[(1S,4S)-5-(ter-butoxicarbonil)-2,5-diazabiciclo[2.2.1]hept-2-il]carbonil}-3-(2,2,2-trifluoroetil)ciclopentil]amino}-2,3-dideoxi-4-O-metil-D-eritro-pentitol;

1,5-anhidro-2,3-dideoxi-3-{[(1R,3S)-3-(1-hidroxiciclobutil)-3-({(1S,4S)-5-[6-(trifluorometil)piridin-2-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metil-D-eritro-pentitol;

1,5-anhidro-2,3-dideoxi-3-{[(1R,3S)-3-(1-hidroxiciclobutil)-3-({(1S,4S)-5-[4-(trifluorometil)piridin-2-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metil-D-eritro-pentitol;

1,5-anhidro-2,3-dideoxi-3-{[(1R,3S)-3-(1-hidroxiciclobutil)-3-({(1S,4S)-5-[4-(trifluorometil)pirimidin-2-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metil-D-eritro-pentitol;

1,5-anhidro-2,3-dideoxi-3-{[(1R,3S)-3-(1-hidroxiciclobutil)-3-({(1S,4S)-5-[2-

(trifluorometil)pirimidin-4-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metil-D-eritro-pentitol;

1,5-anhidro-2,3-dideoxi-3-{[(1R,3S)-3-(1-hidroxiciclobutil)-3-({(1S,4S)-5-[6-(trifluorometil)pirimidin-4-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metil-D-eritro-pentitol;

1,5-anhidro-2,3-dideoxi-3-{[(1R,3S)-3-(1-hidroxiciclobutil)-3-({(1S,4S)-5-[6-(trifluorometil)pirazin-2-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metil-D-eritro-pentitol;

1,5-anhidro-2,3-dideoxi-3-{[(1R,3S)-3-(1-hidroxiciclobutil)-3-({(1S,4S)-5-[2-(trifluorometil)piridin-4-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metil-D-eritro-pentitol;

1,5-anhidro-2,3-dideoxi-3-{[3-(1-hidroxi-1-metiletil)-3-({5-[4-(trifluorometil)piridin-2-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metilpentitol;

1,5-anhidro-2,3-dideoxi-3-{[3-(1-hidroxi-1-metiletil)-3-({5-[6-(trifluorometil)pirimidin-4-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metilpentitol;

1,5-anhidro-2,3-dideoxi-3-{[3-(1-hidroxi-1-metiletil)-3-({5-[4-(trifluorometil)pirimidin-2-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metilpentitol;

1,5-anhidro-2,3-dideoxi-3-{[3-(1-hidroxi-1-metiletil)-3-({5-[5-(trifluorometil)piridazin-3-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metilpentitol;

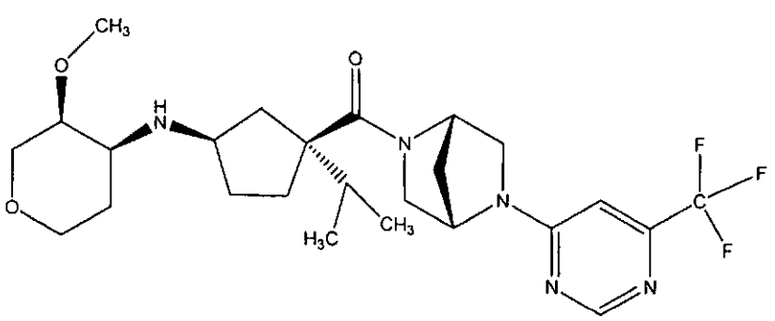
1,5-anhidro-2,3-dideoxi-3-{[3-(1-hidroxi-1-metiletil)-3-({5-[2-(trifluorometil)pirimidin-4-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metilpentitol;

1,5-anhidro-2,3-dideoxi-3-{[3-(1-hidroxi-1-metiletil)-3-({5-[6-(trifluorometil)piridin-2-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metilpentitol;

1,5-anhidro-2,3-dideoxi-3-{[3-(1-hidroxi-1-metiletil)-3-({5-[2-(trifluorometil)piridin-4-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metilpentitol; y

1,5-anhidro-2,3-dideoxi-3-{[3-(1-hidroxi-1-metiletil)-3-({5-[6-(trifluorometil)pirazin-2-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metilpentitol.

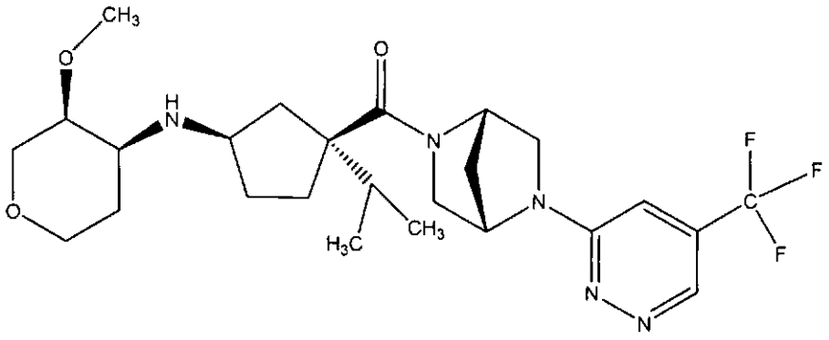
En otra forma de realización, se provee un compuesto de la Fórmula



o su sal

farmacéuticamente aceptable.

En otra forma de realización, se provee un compuesto de la Fórmula



o su sal farmacéuticamente aceptable.

En otra forma de realización de la presente invención, se provee una composición que comprende un compuesto de la Fórmula I o II o una sal de éste farmacéuticamente aceptable y un portador.

En otra forma de realización, se provee un método para tratar una enfermedad asociada con la expresión o actividad de un receptor de quimiocina en un paciente, que comprende administrarle al paciente un compuesto de la Fórmula I o II, o una sal de éste farmacéuticamente aceptable.

En una forma de realización del método, el receptor de quimiocina es CCR2 o CCR5.

En otra forma de realización del método, la enfermedad es artritis reumatoide, ateroesclerosis, lupus, esclerosis múltiple, dolor, rechazo al trasplante, diabetes, nefropatía diabética, afecciones diabéticas, fibrosis hepática, enfermedad viral, cáncer, asma, rinitis alérgica estacional y perenne, sinusitis, conjuntivitis, degeneración macular relacionada con la edad, alergia a los alimentos, intoxicación escombroide, soriasis, espondiloartropatía indiferenciada, gota, urticaria, prurito, eczema, enfermedad del intestino inflamable, enfermedad trombótica, otitis media, fibrosis, cirrosis hepática, enfermedad cardíaca, enfermedad de Alzheimer, sepsis, restenosis, enfermedad de Crohn, colitis ulcerativa, síndrome del intestino irritable, enfermedades pulmonares por hipersensibilidad, fibrosis pulmonar inducida por drogas, enfermedad pulmonar obstructiva crónica, artritis, nefritis, dermatitis atópica, apoplejía, lesión aguda del nervio, sarcoidosis, hepatitis, endometriosis, dolor neuropático, neumonitis por hipersensibilidad, neumonía eosinofílica, hipersensibilidad demorada, enfermedad pulmonar intersticial, trastornos oculares u obesidad .

En otra forma de realización de la presente invención, se provee el uso de un compuesto de la Fórmula I o II, o una sal de éste aceptable farmacéuticamente, para

la fabricación de un medicamento para el tratamiento de artritis reumatoide, ateroesclerosis, lupus, esclerosis múltiple, dolor, rechazo al trasplante, diabetes, nefropatía diabética, afecciones diabéticas, fibrosis hepática, enfermedad viral, cáncer, asma, rinitis alérgica estacional y perenne, sinusitis, conjuntivitis, degeneración macular relacionada con la edad, alergia a los alimentos, intoxicación escombroide, soriasis, espondiloartropatía indiferenciada, gota, urticaria, prurito, eczema, enfermedad del intestino inflamable, enfermedad trombótica, otitis media, fibrosis, cirrosis hepática, enfermedad cardíaca, enfermedad de Alzheimer, sepsis, restenosis, enfermedad de Crohn, colitis ulcerativa, síndrome del intestino irritable, enfermedades pulmonares por hipersensibilidad, fibrosis pulmonar inducida por drogas, enfermedad pulmonar obstructiva crónica, artritis, nefritis, dermatitis atópica, apoplejía, lesión aguda del nervio, sarcoidosis, hepatitis, endometriosis, dolor neuropático, neumonitis por hipersensibilidad, neumonía eosinofílica, hipersensibilidad demorada, enfermedad pulmonar intersticial, trastornos oculares u obesidad .

En otra forma de realización, la presente invención se refiere a una combinación para tratar una enfermedad, trastorno o afección mediados por CCR2 o CCR2/CCR5, en donde dicha combinación comprende un compuesto de la Fórmula I o II como se definió anteriormente, o una sal de éste farmacéuticamente aceptable, y uno o más agentes terapéuticos adicionales.

En otra forma de realización, la presente invención se refiere a un compuesto de la Fórmula I o II, como se definió anteriormente, o una sal de éste farmacéuticamente aceptable, como se definió anteriormente, para usar como medicamento.

En otra forma de realización, la presente invención se refiere a un método para tratar una enfermedad, trastorno o afección mediados por CCR2 o CCR2/CCR5 en un sujeto que necesita dicho tratamiento, mediante la administración al sujeto de una cantidad terapéuticamente eficaz de un compuesto de la Fórmula I o II, como se definió anteriormente, o una sal o solvato de éste farmacéuticamente aceptable.

En otra forma de realización, la presente invención se refiere a un compuesto de la Fórmula I o II, como se definió anteriormente, o una sal de éste farmacéuticamente aceptable para usar en el tratamiento de una enfermedad, trastorno o afección mediados por CCR2 o CCR2/CCR5.

En otra forma de realización, la presente invención se refiere al uso de un compuesto de la Fórmula I o II, como se definió anteriormente, o una sal o solvato de éste farmacéuticamente aceptable para la fabricación de un medicamento a fin de

tratar una enfermedad, trastorno o afección mediados por CCR2 o CCR2/CCR5.

Las sales de los compuestos de la invención pueden incluir sus sales de adición ácida o sales de adición básica (incluso disales). Las sales pueden ser farmacéuticamente aceptables.

Las sales de adición ácida adecuadas se forman de ácidos que forman sales no tóxicas. Los ejemplos incluyen sales de acetato, aspartato, benzoato, besilato, bicarbonato/carbonato, bisulfato/sulfato, borato, camsilato, citrato, edisilato, esilato, formiato, fumarato, gluceptato, gluconato, glucuronato, hexafluorofosfato, hibenzato, clorhidrato/cloruro, bromhidrato/bromuro, yodhidrato/yoduro, isetionato, lactato, malato, maleato, malonato, mesilato, metilsulfato, naftilato, 2-napsilato, nicotinato, nitrato, orotato, oxalato, palmitato, pamoato, fosfato/fosfato ácido/fosfato diácido, sacarato, estearato, succinato, tartrato, tosilato y trifluoroacetato.

Las sales básicas adecuadas se forman de bases que forman sales no tóxicas. Los ejemplos incluyen sales de aluminio, arginina, benzatina, calcio, colina, dietilamina, diolamina, glicina, lisina, magnesio, meglumina, olamina, potasio, sodio, trometamina y zinc.

También se pueden formar hemisales de ácidos y bases, por ejemplo, sales de hemisulfato y hemicalcio.

Para una reseña de sales adecuadas, véase Handbook of Pharmaceutical Salts: Properties, Selection, and Use de Stahl and Wermuth (Wiley-VCH, Weinheim, Alemania, 2002).

Una sal se puede preparar con facilidad al mezclar soluciones de compuestos de la presente invención con el ácido o la base deseados, según se requiera. La sal puede precipitar de la solución y recolectarse por filtración o puede recuperarse por evaporación del solvente. El grado de ionización en la sal puede variar de completamente ionizada a casi no ionizada.

Los compuestos de la presente invención se pueden administrar como profármacos. Por lo tanto, ciertos derivados que tienen poca o ninguna actividad farmacológica se pueden convertir, cuando se los administra en el cuerpo, en compuestos de la presente invención que tienen la actividad deseada, por ejemplo, mediante clivaje hidrolítico. Esos derivados se denominan "profármacos". Más información sobre el uso de profármacos se puede hallar en 'Pro-drugs as Novel Delivery Systems, Vol. 14, ACS Symposium Series (T Higuchi and W Stella) y 'Bioreversible Carriers in Drug Design', Pergamon Press, 1987 (ed. E B Roche, American Pharmaceutical Association).

Los profármacos se pueden producir, por ejemplo, mediante el reemplazo de las funcionalidades adecuadas presentes en los compuestos de esta invención con ciertas porciones conocidas por los expertos en el arte como 'pro-porciones' como se describe, por ejemplo, en "Design of Prodrugs" de H Bundgaard (Elsevier, 1985)

Algunos ejemplos de esos profármacos incluyen:

(i) en donde el compuesto contiene una funcionalidad de alcohol (-OH), un éter de éste, por ejemplo, el reemplazo del hidrógeno con (C_1-C_6)alcanoiloximetilo; y

(ii) en donde el compuesto contiene una funcionalidad de amino secundaria, una amida de éste, por ejemplo, el reemplazo del hidrógeno con (C_1-C_{10})alcanoilo.

Todos los isómeros, tales como estereoisómeros, isómeros geométricos (*cis/trans* o Z/E) y formas tautoméricas de los compuestos y sales se incluyen en el alcance de la presente invención, que incluyen compuestos o sales que tienen más de un tipo de isomerismo y mezclas de uno o más de estos.

También se incluyen las sales de adición ácida o básicas, en donde el contraión es ópticamente activo, por ejemplo, D-lactato o L-lisina, o racémico, por ejemplo, DL-tartrato o DL-arginina.

Los isómeros se pueden separar por técnicas convencionales conocidas por los expertos en el arte.

La presente invención incluye compuestos de la invención etiquetados de manera isotópica, en donde uno o más átomos se reemplazan con átomos que tienen el mismo número atómico, pero una masa atómica o número de masa diferente de la masa atómica o número de masa atómica que se encuentra habitualmente en la naturaleza.

En general, los compuestos de la invención etiquetados de manera isotópica se pueden preparar mediante técnicas convencionales conocidas por los expertos en el arte o mediante procesos análogos a los descritos en los Ejemplos y Preparaciones adjuntas mediante el uso de reactivos adecuados etiquetados de manera isotópica en lugar de los reactivos no etiquetados que se usaron previamente.

Para el tratamiento de las afecciones a las que se hace referencia más adelante, se pueden administrar los compuestos de la presente invención. También se pueden usar las sales de los compuestos de la presente invención.

C. Composiciones

Los compuestos o las sales de la presente invención pueden ser parte de una composición. Las composiciones también pueden incluir uno o más compuestos o

sales de la presente invención. La composición también puede incluir un exceso enantiomérico de uno o más compuestos de la presente invención. Otras sustancias y portadores farmacéuticamente activos se pueden incluir en la composición.

Una forma de realización es una composición que comprende un compuesto de la Fórmula I o II, o una sal de éste. Otra forma de realización es una composición que comprende un compuesto de la Fórmula I o II, o una sal de éste y un portador.

Por ejemplo, el portador puede ser un excipiente. La elección de excipiente dependerá, en gran medida, de factores, tales como el modo de administración particular, el efecto del excipiente en la solubilidad y estabilidad, y la naturaleza de la forma de dosificación.

La composición puede ser un sólido, un líquido o ambos, y se puede formular con el compuesto como una composición de dosis unitaria, por ejemplo, un comprimido, que puede contener de 0,05% a 95% en peso de los compuestos activos. Los compuestos o las sales de la presente invención se pueden acoplar con polímeros adecuados como portadores de fármacos dirigibles.

D. Métodos

En algunas formas de realización, los compuestos de la invención se pueden usar en métodos que modulan la actividad de uno o más receptores de quimiocina.

En consecuencia, la invención incluye métodos que comprenden poner en contacto un receptor de quimiocina con un compuesto de la Fórmula I o II, o una sal de éste. En algunas formas de realización, el receptor de quimiocina es CCR2. En otras formas de realización, el receptor de quimiocina es CCR5. En otras formas de realización, la invención incluye métodos para modular un receptor de quimiocina mediante el contacto del receptor con uno o más de los compuestos o composiciones descritos en la presente. En algunas formas de realización, los compuestos de la presente invención pueden actuar como inhibidores o antagonistas de receptores de quimiocina. En otras formas de realización, los compuestos de la invención se pueden usar para modular la actividad de un receptor de quimiocina en un individuo que necesita modulación del receptor, mediante la administración de una cantidad moduladora de un compuesto de la Fórmula I o II, o una sal de éste.

Los receptores de quimiocina a los que se unen los compuestos de la presente y/o modulan incluyen cualquier receptor de quimiocina. En algunas formas de realización, el receptor de quimiocina pertenece a la familia CC de receptores de quimiocina que incluyen, por ejemplo, CCR1, CCR2, CCR3, CCR4, CCR5, CCR6, CCR7, CCR8 y CCR10. En algunas formas de realización, el receptor de quimiocina

es CCR2 o CCR5. En otras formas de realización, el receptor de quimiocina es CCR2. En algunas formas de realización, el receptor de quimiocina es CCR5. En algunas formas de realización, el receptor de quimiocina se une y/o modula tanto CCR2 como CCR5.

Los compuestos de la invención pueden ser selectivos, es decir, un compuesto se une o inhibe un receptor de quimiocina con mayor afinidad o potencia, respectivamente, en comparación con al menos otro receptor de quimiocina.

Los compuestos de la invención pueden ser aglutinantes o inhibidores duales de CCR2 y CCR5, es decir que los compuestos de la invención pueden unir o inhibir tanto CCR2 como CCR5 con mayor afinidad o potencia, respectivamente, que otros receptores de quimiocina, tales como CCR1, CCR3, CCR4, CCR6, CCR7, CCR8 y CCR10. En algunas formas de realización, los compuestos de la invención tienen selectividad de unión o inhibición para CCR2 y CCR5 con respecto a cualquier otro receptor de quimiocina. La afinidad de unión y la potencia del inhibidor se pueden medir de acuerdo con métodos de rutina conocidos en el arte, tales como de acuerdo con los ensayos provistos en la presente.

La presente invención también provee métodos para tratar una enfermedad o un trastorno asociados al receptor de quimiocina en un individuo (por ejemplo, un paciente) mediante la administración al individuo que necesita dicho tratamiento de una dosis o cantidad terapéuticamente eficaz de un compuesto de la presente invención o una composición farmacéutica de éste. En otras formas de realización, la invención incluye un método para tratar una afección mediada por un receptor de quimiocina en un sujeto, que comprende administrarle al sujeto un compuesto de la Fórmula I o II, o una sal de éste farmacéuticamente aceptable.

Una enfermedad o afección asociadas al receptor de quimiocina pueden incluir cualquier enfermedad, trastorno o afección que se liga directa o indirectamente a la expresión o actividad del receptor de quimiocina. Una enfermedad o afección asociadas al receptor de quimiocina pueden incluir cualquier enfermedad, trastorno o afección que se puede evitar, mejorar o curar mediante la modulación de la actividad del receptor de quimiocina. Una enfermedad asociada al receptor de quimiocina también puede incluir cualquier enfermedad, trastorno o afección que se caracteriza por unir un agente infeccioso, tal como un virus o proteína viral con un receptor de quimiocina. En algunas formas de realización, la enfermedad asociada al receptor de quimiocina es una enfermedad asociada a CCR5, tal como infección por VIH.

Los ejemplos de una afección mediada por receptor de quimiocina incluyen

inflamación, enfermedades inflamatorias, trastornos autoinmunes, dolores, cáncer o infecciones virales.

Los ejemplos de una afección mediada por receptor de quimiocina incluyen inflamación, enfermedades inflamatorias, trastornos autoinmunes, dolores, cáncer o infecciones virales.

Los ejemplos de enfermedades inflamatorias incluyen enfermedades que se cree tienen un componente inflamatorio, tal como asma, rinitis alérgica estacional y perenne, sinusitis, conjuntivitis, degeneración macular relacionada con la edad, alergia a los alimentos, intoxicación escombroide, soriasis, espondiloartropatía indiferenciada, espondiloartritis juvenil, gota, urticaria, prurito, eczema, enfermedad del intestino inflamable, enfermedad trombótica, otitis media, fibrosis, fibrosis hepática, cirrosis hepática, enfermedad cardíaca, enfermedad de Alzheimer, sepsis, restenosis, aterosclerosis, esclerosis múltiple, enfermedad de Crohn, colitis ulcerativa, síndrome del intestino irritable, enfermedad del intestino inflamable, enfermedades pulmonares por hipersensibilidad, fibrosis pulmonar inducida por drogas, enfermedad pulmonar obstructiva crónica (COPD), artritis, nefritis, colitis ulcerativa, dermatitis atópica, apoplejía, lesión aguda del nervio, sarcoidosis, hepatitis, endometriosis, dolor neuropático, neumonitis por hipersensibilidad, neumonía eosinofílica, hipersensibilidad demorada, enfermedad pulmonar intersticial (ILD) (por ejemplo, fibrosis pulmonar idiopática o ILD asociada con artritis reumatoide, lupus eritematoso sistémico, espondilitis anquilosante, esteatosis sistémica, síndrome de Sjogren, polimiositis o dermatomiositis, trastornos oculares (por ejemplo, neurodegeneración de la retina, neovascularización coroidal, etc.) y similares.

Los ejemplos de trastornos inmunológicos incluyen artritis reumatoide, artritis soriásica, lupus eritematoso sistémico, miastenia grave, diabetes juvenil; glomerulonefritis, tiroiditis autoinmune, rechazo al trasplante de órganos, que incluye rechazo al aloinjerto y enfermedad del injerto versus el huésped.

Los ejemplos de dolor incluyen dolor nociceptivo y neuropático. El dolor puede ser agudo o crónico. El dolor incluye dolor cutáneo, dolor somático, dolor visceral y dolor del miembro fantasma. El dolor también incluye fibromialgia, dolor por artritis reumatoide, dolor por osteoartritis y dolor asociado con otras enfermedades y afecciones detalladas en la presente.

Los ejemplos de cáncer incluyen cáncer de mama, cáncer de ovarios, mieloma múltiple y similares que se caracterizan por la infiltración de macrófagos (por ejemplo, macrófagos asociados al tumor, TAM) en tumores o tejidos enfermos.

Los ejemplos de infecciones virales incluyen influenza, influenza aviar, infección por herpes, infección por VIH o SIDA.

Otras enfermedades inflamatorias o inmunes que se pueden tratar con la administración de un compuesto de la presente invención incluyen, por ejemplo, nefritis autoinmune, nefritis lúpica, nefritis por síndrome de Goodpasture y nefritis granulomatosa de Wegeners, lupus eritematoso, síndrome de Goodpasture y granulomatosis de Wegeners.

Los ejemplos de afecciones diabéticas incluyen diabetes, resistencia a la insulina, neuropatía diabética, nefropatía diabética, retinopatía diabética, cataratas, hiperglucemia, hipercolesterolemia, hipertensión, hiperinsulinemia, hiperlipidemia, aterosclerosis, isquemia tisular, cardiomiopatía diabética, microangiopatía diabética, macroangiopatía diabética y úlceras de pie. En el tratamiento de la diabetes se incluye la prevención o atenuación de afecciones a largo plazo, tales como neuropatía, nefropatía, retinopatía o cataratas.

En algunas formas de realización, la afección que se desea tratar es artritis reumatoide, aterosclerosis, lupus, esclerosis múltiple, dolor neuropático, rechazo al trasplante, diabetes, nefropatía diabética, afecciones diabéticas u obesidad.

En algunas formas de realización, la afección es artritis reumatoide.

En algunas formas de realización, la afección es diabetes.

En algunas formas de realización, la afección es nefropatía diabética.

En algunas formas de realización, la afección es fibrosis hepática.

En algunas formas de realización, la afección es dolor por osteoartritis.

En algunas formas de realización, la afección es cáncer de mama, cáncer de ovarios o mieloma múltiple.

En algunas formas de realización, la afección es infección por VIH.

E. Dosificación y administración

Formulaciones farmacéuticas y formas de dosificación

Cuando se usan agentes farmacéuticos, los compuestos de la Fórmula I o II se pueden administrar en forma de composiciones farmacéuticas. Estas composiciones se pueden preparar de una manera conocida en el arte farmacéutico, y se pueden administrar mediante varias vías, según si se desea que el tratamiento local o sistémico y según el área que se tratará. La administración puede ser tópica (incluso oftálmica y en las membranas mucosas, incluso por suministro intranasal, vaginal y rectal), pulmonar (por ejemplo, mediante inhalación o insuflación de polvos o aerosoles, incluso mediante nebulizador; intratraqueal, intranasal, epidérmica y

transdérmica), oral o parenteral. La administración parenteral incluye administración intravenosa, intraarterial, subcutánea, intraperitoneal, intramuscular o inyección o infusión; o intracraneal, por ejemplo, intratecal o intraventricular. La administración parenteral puede ser en forma de una única dosis de bolo o puede ser, por ejemplo, mediante una bomba de perfusión continua. Las composiciones y formulaciones farmacéuticas para la administración tópica pueden incluir parches transdérmicos, pomadas, lociones, cremas, geles, gotas, supositorios, sprays, líquidos y polvos. Los portadores, las bases acuosas, en polvo u oleosas y los espesantes farmacéuticos convencionales pueden ser necesarios o deseables. También pueden ser útiles los preservativos recubiertos, los guantes y similares.

La presente invención también incluye composiciones farmacéuticas que contienen, como ingrediente activo, uno o más de los compuestos de la Fórmula I o II anteriores combinados con uno o más portadores farmacéuticamente aceptables. Al preparar las composiciones de la invención, el ingrediente activo generalmente se mezcla con un excipiente, se diluye con un excipiente o se recubre con dicho portador en forma, por ejemplo, de cápsula, sachet, papel u otro recipiente. Cuando el excipiente sirve como diluyente, éste puede ser un material sólido, semisólido o líquido, que actúa como vehículo, portador o medio para el ingrediente activo. De este modo, las composiciones pueden ser en forma de comprimidos, píldoras, polvos, grageas, sachets, sellos, elíxires, suspensiones, emulsiones, soluciones, jarabes, aerosoles (como un sólido o en un medio líquido), pomadas que contienen, por ejemplo, hasta 10% en peso del compuesto activo, cápsulas de gelatina blanda y dura, supositorios, soluciones inyectables estériles y polvos envasados estériles.

Al preparar una formulación, el compuesto activo se puede moler para obtener el tamaño de partícula adecuado antes de combinarlo con los otros ingredientes. Si el compuesto activo es sustancialmente insoluble, se lo puede moler hasta obtener un tamaño de partícula menor de 200 mesh. Si el compuesto activo es sustancialmente hidrosoluble, el tamaño de partícula se puede ajustar mediante molido para obtener una distribución sustancialmente uniforme en la formulación, por ejemplo, alrededor de 40 mesh.

Algunos ejemplos de excipientes adecuados incluyen lactosa, dextrosa, sacarosa, sorbitol, mannitol, almidones, goma acacia, fosfato de calcio, alginatos, tragacanto, gelatina, silicato de calcio, celulosa microcristalina, polivinilpirrolidona, celulosa, agua, jarabe y metilcelulosa. Las formulaciones también pueden incluir agentes lubricantes, tales como talco, estearato de magnesio y aceite mineral; agentes

humectantes; agentes emulgentes y de suspensión; agentes conservantes, tales como benzoato de metilo y propilhidroxi; agentes endulzantes y agentes saborizantes. Las composiciones de la invención se pueden formular para proporcionar una liberación rápida, sostenida o demorada del ingrediente activo luego de la administración al paciente mediante procedimientos conocidos en el arte.

Las composiciones se pueden formular en una forma de dosificación unitaria, en donde cada dosis contiene de alrededor de 5 a alrededor de 1000 mg (1 g), más habitualmente, de alrededor de 100 a alrededor de 500 mg del ingrediente activo. El término "formas de dosificación unitarias" se refiere a unidades físicamente diferenciadas adecuadas como formas de dosificación unitarias para sujetos humanos y otros mamíferos; donde cada unidad contiene una cantidad predeterminada de material activo calculado para producir el efecto terapéutico deseado en asociación con un excipiente farmacéutico adecuado.

En algunas formas de realización, los compuestos o las composiciones de la invención contienen de alrededor de 5 a alrededor de 50 mg del ingrediente activo. Un experto en el arte tendrá en cuenta que esto incluye compuestos o composiciones que contienen de alrededor de 5 a alrededor de 10, de alrededor de 10 a alrededor de 15, de alrededor de 15 a alrededor de 20, de alrededor de 20 a alrededor de 25, de alrededor de 25 a alrededor de 30, de alrededor de 30 a alrededor de 35, de alrededor de 35 a alrededor de 40, de alrededor de 40 a alrededor de 45, o de alrededor de 45 a alrededor de 50 mg del ingrediente activo. En otra forma de realización, la dosis puede ser de 35-45 mg.

En algunas formas de realización, los compuestos o las composiciones de la invención contienen de alrededor de 50 a alrededor de 500 mg del ingrediente activo. Un experto en el arte tendrá en cuenta que esto incluye compuestos o composiciones que contienen de alrededor de 50 a alrededor de 75, de alrededor de 75 a alrededor de 100, de alrededor de 100 a alrededor de 125, de alrededor de 125 a alrededor de 150, de alrededor de 150 a alrededor de 175, de alrededor de 175 a alrededor de 200, de alrededor de 200 a alrededor de 225, de alrededor de 225 a alrededor de 250, de alrededor de 250 a alrededor de 275, de alrededor de 275 a alrededor de 300, de alrededor de 300 a alrededor de 325, de alrededor de 325 a alrededor de 350, de alrededor de 350 a alrededor de 375, de alrededor de 375 a alrededor de 400, de alrededor de 400 a alrededor de 425, de alrededor de 425 a alrededor de 450, de alrededor de 450 a alrededor de 475, o de alrededor de 475 a alrededor de 500 mg del ingrediente activo.

En algunas formas de realización, los compuestos o las composiciones de la invención contienen de alrededor de 500 a alrededor de 1000 mg del ingrediente activo. Un experto en el arte tendrá en cuenta que esto incluye compuestos o composiciones que contienen de alrededor de 500 a alrededor de 550, de alrededor de 550 a alrededor de 600, de alrededor de 600 a alrededor de 650, de alrededor de 650 a alrededor de 700, de alrededor de 700 a alrededor de 750, de alrededor de 750 a alrededor de 800, de alrededor de 800 a alrededor de 850, de alrededor de 850 a alrededor de 900, de alrededor de 900 a alrededor de 950, o de alrededor de 950 a alrededor de 1000 mg del ingrediente activo.

El compuesto activo puede ser eficaz en un amplio rango de dosificación y, en general, se administra en una cantidad farmacéuticamente eficaz. Sin embargo, debe tenerse en cuenta que la cantidad real de compuesto que se administra la determinará un médico, en función de las circunstancias pertinentes, que incluyen la afección que se desea tratar, la vía de administración seleccionada, el compuesto que se administrará, la edad, el peso y la respuesta del paciente individual, así como la gravedad de los síntomas del paciente y similares.

Para preparar composiciones sólidas, tales como comprimidos, el ingrediente activo principal se mezcla con un excipiente farmacéutico para formar una composición de preformulación sólida que contiene una mezcla homogénea de un compuesto de la presente invención. Cuando estas composiciones de preformulación se indican como homogéneas, el ingrediente activo generalmente se dispersa de manera uniforme en la composición, de manera que ésta se pueda subdividir con facilidad en formas de dosificación unitarias igualmente eficaces, tales como comprimidos, píldoras y cápsulas. Esta preformulación sólida luego se subdivide en formas de dosificación unitarias del tipo descrito con anterioridad que contienen, por ejemplo, de 0,1 a alrededor de 1000 mg del ingrediente activo de la presente invención.

Los comprimidos o las píldoras de la presente invención se pueden recubrir o de otro modo combinar para proveer una forma de dosificación que genere la ventaja de acción prolongada. Por ejemplo, el comprimido o la píldora pueden comprender un componente interno de dosificación y un componente externo de dosificación; este último envuelve al primero. Los dos componentes se pueden separar mediante una capa entérica que sirve para resistir la desintegración en el estómago y para permitir que el componente interno pase intacto al duodeno o se demore su liberación. Se pueden usar varios materiales para los recubrimientos o capas entéricas, que incluyen

varios ácidos poliméricos y mezclas de ácidos poliméricos con esos materiales, tales como laca, alcohol de cetilo y acetato de celulosa.

Las formas líquidas en las que se pueden incorporar los compuestos y las composiciones de la presente invención para la administración oral o por inyección incluyen soluciones acuosas, jarabes saborizados, suspensiones acuosas u oleosas y emulsiones saborizadas con aceites comestibles, tales como aceite de semilla de algodón, aceite de sésamo, aceite de coco o aceite de maní, así como elixires y vehículos farmacéuticos similares.

Las composiciones para inhalación o insuflación incluyen soluciones y suspensiones en solventes acuosos u orgánicos farmacéuticamente aceptables o mezclas de estos, y polvos. Las composiciones líquidas o sólidas pueden contener excipientes farmacéuticamente aceptables, como se describió anteriormente. En algunas formas de realización, las composiciones se administran mediante la vía respiratoria oral o nasal para lograr efecto local o sistémico. Las composiciones se pueden nebulizar con gases inertes. Las soluciones nebulizadas se pueden aspirar directamente del nebulizador, o el nebulizador se puede unir a mascarilla facial o respirador de presión positiva intermitente. Las composiciones en solución, suspensión o polvo se pueden administrar de manera oral o nasal de dispositivos que suministran la formulación de manera adecuada.

La cantidad de compuesto o composición administrada a un paciente variará según lo que se administra, la finalidad de la administración, tal como profilaxis o terapia, el estado del paciente, la forma de administración y similares. En las aplicaciones terapéuticas, las composiciones se pueden administrar a un paciente que ya sufre una enfermedad en una cantidad suficiente para curar o detener, al menos parcialmente, los síntomas de la enfermedad y sus complicaciones. Las dosis eficaces dependerán de la enfermedad o afección que se trate así como del criterio del médico tratante según factores tales como la gravedad de la enfermedad, la edad, el peso, el estado general del paciente y similares.

Las composiciones que se le administran a un paciente pueden estar en la forma de composiciones farmacéuticas antes descritas. Estas composiciones se pueden esterilizar mediante técnicas de esterilización convencionales o se pueden esterilizar por filtro. Las soluciones acuosas se pueden envasar para usar tal como se encuentran o se pueden liofilizar; la preparación liofilizada se combina con un portador acuoso estéril antes de la administración. En general, el pH de las preparaciones del compuesto se encuentra entre 3 y 11, entre 5 y 9, o entre 7 y 8. Se debe tener en

cuenta que el uso de ciertos de los excipientes, portadores o estabilizadores anteriores dará como resultado la formación de sales farmacéuticas.

La dosis terapéutica de los compuestos de la presente invención puede variar, por ejemplo, de acuerdo con el uso particular para el cual se realiza el tratamiento, el modo de administración del compuesto, la salud y afección del paciente y el criterio del médico tratante. La concentración o proporción de un compuesto de la invención en una composición farmacéutica puede variar según varios factores, que incluyen dosificación, características químicas (por ejemplo, hidrofobicidad) y vía de administración. Por ejemplo, los compuestos de la invención se pueden proveer en una solución de tampón fisiológica acuosa que contiene de alrededor de 0,1 a alrededor de 10% p/v del compuesto para la administración parenteral. Algunos rangos de dosis típicos son de alrededor de 1 µg/kg a alrededor de 1 g/kg de peso corporal por día. En algunas formas de realización, el rango de dosis es de alrededor de 0,01 mg/kg a alrededor de 100 mg/kg de peso corporal por día. Es probable que la dosis dependa de variables tales como el tipo y el grado de avance de la enfermedad o trastorno, el estado general de salud del paciente particular, la eficacia biológica relativa del compuesto seleccionado, la formulación del excipiente y la vía de administración. Las dosis eficaces se pueden extrapolar de las curvas de respuesta a la dosis, derivadas de sistemas de prueba en animales modelos o *in vitro*.

El compuesto de la invención también se puede formular en combinación con uno o más ingredientes activos adicionales que pueden incluir cualquier agente farmacéutico, tal como anticuerpos, inmunosupresores, agentes antiinflamatorios, agentes quimioterapéuticos, agentes reductores de lípidos, agentes que aumentan HDL, sensibilizadores o secretagogos de insulina, fármacos usados para el tratamiento de artritis reumatoidea y similares.

Régimen de tratamiento para la artritis reumatoide (RA)

Los pacientes con artritis reumatoide (RA), tratados de manera agresiva con agentes modificadores de la enfermedad (metotrexato, antimalariales, oro, penicilamina, sulfasalazina, dapsona, leflunamida o biológicos), pueden lograr diversos grados de control de la enfermedad, incluso remisiones completas. Estas respuestas clínicas se asocian con la mejora en puntajes estandarizados de actividad de la enfermedad, específicamente, el criterio ACR que incluye dolor, función, cantidad de articulaciones delicadas, cantidad de articulaciones hinchadas, evaluación global del paciente, evaluación física global, medición de inflamación en laboratorio (CRP y ESR)

y evaluación radiológica del daño estructural de las articulaciones. Los actuales fármacos modificadores de enfermedades (DMARD) requieren la administración continua para mantener un beneficio óptimo. La dosificación crónica de estos agentes se asocia con una toxicidad significativa y compromete las defensas del huésped. Además, los pacientes usualmente se vuelven refractarios a una terapia particular y requieren un régimen alternativo. Por ello, una nueva terapia eficaz que permita retirar los DMARD estándar sería un progreso clínico importante.

Los pacientes con una respuesta considerable a las terapias contra TNF (infliximab, etanercept, adalimumab), terapia contra IL-1 (kinaret) u otros fármacos antireumáticos modificadores de la enfermedad (DMARD), que incluyen, pero no se limitan a, methotrexate, cyclosporine, sales de oro, antimalariales, penicilamina o leflunamida, que lograron la remisión clínica de la enfermedad se pueden tratar con una sustancia que inhibe la expresión y/o actividad de CCR2, que incluye, por ejemplo, ácidos nucleicos (por ejemplo, moléculas antisentido o siARN), proteínas (por ejemplo, anticuerpos contra CCR2), inhibidores de molécula pequeña (por ejemplo, los compuestos descritos en la presente y otros inhibidores del receptor de quimiocina conocidos en el arte).

En algunas formas de realización, la sustancia que inhibe la expresión y/o actividad de CCR2 es un inhibidor (o antagonista) de CCR2 de molécula pequeña. El antagonista de CCR2 se puede administrar en dosis orales una vez al día (q.d.) o dos veces al día (b.i.d.) en una dosis que no exceda alrededor de 500 mg por día. A los pacientes se les puede retirar o disminuir la dosis de su terapia actual y permanecerán en tratamiento con el antagonista de CCR2. El tratamiento de los pacientes con una combinación de antagonista de CCR2 y su actual terapia se puede realizar, por ejemplo, de alrededor de un día a alrededor de dos días, antes de discontinuar o disminuir la dosis de DMARD y continuar con el antagonista de CCR2.

Las ventajas de sustituir DMARDS tradicionales con antagonistas de CCR2 son numerosas. Los DMARD tradicionales tienen graves efectos secundarios acumulativos que limitan las dosis; los más habituales son el daño hepático y las acciones inmunosupresoras. Se espera que el antagonismo de CCR2 tenga un mejor perfil de seguridad a largo plazo sin las características inmunosupresoras asociadas con los DMARD tradicionales. Además, la vida media de los productos biológicos es usualmente de días o semanas, lo cual es un problema cuando se trata con reacciones adversas. Se espera que la vida media de un antagonista de CCR2 biodisponible por vía oral sea de alrededor de horas, por lo que el riesgo de una

exposición continua al fármaco luego de un evento adverso sea mínimo en comparación con los agentes biológicos. Además, los agentes biológicos actuales (infliximab, etanercept, adalimumab, kinaret) generalmente se suministran de manera i.v. o s.c., lo que requiere la administración por parte del médico o la autoinyección por parte del paciente. Esto genera la posibilidad de reacción a la infusión o reacciones en el sitio de la inyección. Estos se pueden evitar mediante la administración oral de un antagonista de CCR2.

Régimen de tratamiento para la diabetes y resistencia a la insulina.

La diabetes de tipo 2 es una de las causas principales de morbilidad y mortalidad en las sociedades occidentales. En la gran mayoría de los pacientes, la enfermedad se caracteriza por presentar disfunción de células beta pancreáticas acompañado por resistencia a la insulina en el hígado y en tejidos periféricos. Sobre la base de los mecanismos primarios que se asocian con la enfermedad, existen dos clases generales de terapias orales disponibles para tratar la diabetes de tipo 2: los secretagogos de insulina (sulfonilureas, tales como glyburide) y sensibilizadores de insulina (metformin y thiazolidinediones, tales como, rosiglitazone). Se demostró que una terapia de combinación que abarca ambos mecanismos controla los defectos metabólicos de esta enfermedad y, en muchos casos, se puede demostrar que disminuye la necesidad de administración exógena de insulina. Sin embargo, con el tiempo, la resistencia a la insulina usualmente progresa, lo cual genera la necesidad de administrar más insulina. Asimismo, se ha demostrado que un estado prediabético, denominado síndrome metabólico, se caracteriza por una disminución de la tolerancia a la glucosa, en particular, asociada con la obesidad. La mayoría de los pacientes que desarrollan diabetes de tipo 2 comienzan por desarrollar resistencia a la insulina, y la hiperglucemia ocurre cuando estos pacientes ya no pueden sostener el grado de hiperinsulinemia necesario para evitar la pérdida de homeostasis de la glucosa. El inicio de los componentes de resistencia a la insulina predice en gran medida el inicio de la enfermedad, y se asocia con un aumento del riesgo de desarrollar diabetes de tipo 2, hipertensión y enfermedad cardíaca coronaria.

Una de las consecuencias más importantes de la disminución de la tolerancia a la glucosa y del progreso desde un estado de resistencia a la insulina hasta la diabetes de tipo 2 es la presencia de obesidad central. La mayoría de los pacientes con diabetes de tipo 2 son obesos, y la obesidad misma se asocia con la resistencia a la insulina. Es claro que la adiposidad central es un factor de riesgo principal para el

desarrollo de la resistencia a la insulina que conduce a la diabetes de tipo 2; esto sugiere que las señales de grasa visceral contribuyen al desarrollo de la resistencia a la insulina y al avance de la enfermedad. Además de los factores de proteína secretados, la obesidad induce una respuesta inflamatoria celular en donde los micrófagos derivados de la médula ósea se acumulan en depósitos adiposos y se transforman en micrófagos del tejido adiposo. Los macrófagos del tejido adiposo se acumulan en el tejido adiposo proporcionalmente a las medidas de adiposidad. Los macrófagos que se filtran en el tejido son una fuente de muchas de las citocinas inflamatorias que se demostró inducen la resistencia a la insulina en adipocitos.

El tejido adiposo produce MCP-1 en proporción a la adiposidad, lo que sugiere que su actividad mediante señalización a través de CCR2 también puede tener una función importante en la acumulación de macrófagos en el tejido adiposo. Se desconoce si la interacción de MCP-1/CCR2 es directamente responsable del reclutamiento de monocitos en el tejido adiposo, si el reclutamiento disminuido de micrófagos en el tejido adiposo en seres humanos conducirá directamente a una menor producción de moléculas proinflamatorias, y si la producción de moléculas proinflamatorias se liga directamente con la resistencia a la insulina.

Los pacientes que mostraron resistencia a la insulina, ya sea prediabética (normoglucémica) o diabética (hiperglucémica), pueden tratarse con una sustancia que inhibe la expresión y/o actividad de CCR2, incluso, por ejemplo, ácidos nucleicos (por ejemplo, moléculas antisentido o siARN), proteínas (por ejemplo, anticuerpos contra CCR2), inhibidores de molécula pequeña (por ejemplo, los compuestos descritos en la presente y otros inhibidores del receptor de quimiocina conocidos en el arte). En algunas formas de realización, la sustancia que inhibe la expresión y/o actividad de CCR2 es un inhibidor (o antagonista) de CCR2 de molécula pequeña. El antagonista de CCR2 se puede administrar en dosis orales q.d. o b.i.d. A los pacientes se les puede retirar o disminuir la dosis de su terapia actual y permanecerán en tratamiento con el antagonista de CCR2. De modo alternativo, el tratamiento con antagonista de CCR2 se puede usar para complementar la terapia actual a fin de aumentar su eficacia o evitar el avance a una mayor insulinodependencia.

Las ventajas de sustituir o complementar agentes tradicionales con antagonistas de CCR2 son numerosas. Dichos agentes pueden ser útiles, por ejemplo, para evitar el progreso de un estado prediabético de resistencia a la insulina a un estado diabético. Los agentes pueden reducir o reemplazar la necesidad de usar sensibilizadores de insulina, con sus respectivas toxicidades. Los agentes también

pueden reducir la necesidad de complementación exógena de insulina o prolongar el período hasta se requiera complementación exógena de insulina.

Régimen de tratamiento para la ateroesclerosis

La ateroesclerosis es una afección que se caracteriza por el depósito de sustancias grasas en las paredes de las arterias. Las placas abarcan los depósitos de sustancias grasas, colesterol, productos de desecho celular, calcio y otras sustancias que se acumulan en la pared interior de una arteria. Las placas se pueden agrandar lo suficiente como para reducir considerablemente el flujo sanguíneo a través de la arteria. Sin embargo, se produce un daño importante cuando la placa se vuelve inestable y se rompe. Las placas que se rompen causan coágulos de sangre que pueden bloquear el flujo sanguíneo o desprenderse y desplazarse hacia otras partes del cuerpo. Si el coágulo bloquea un vaso sanguíneo que alimenta el corazón, éste causa un ataque cardíaco. Si bloquea un vaso sanguíneo que alimenta el cerebro, éste causa una apoplejía. La ateroesclerosis es una enfermedad lenta y compleja que generalmente comienza en la niñez y a menudo progresa a medida que las personas envejecen.

Un alto nivel de colesterol en sangre es un factor de riesgo importante para una enfermedad cardíaca coronaria. Debido a que el colesterol es un componente principal de las placas, el avance de la formación de placas se controla mediante la reducción del colesterol circulante o mediante un aumento de las lipoproteínas de alta densidad que transportan colesterol (HDL). El colesterol circulante se puede reducir, por ejemplo, al inhibir su síntesis en el hígado o al reducir la ingesta de alimentos. Los medicamentos que actúan mediante este mecanismo pueden incluir medicinas que se usan para disminuir los altos niveles de colesterol: absorbedores del ácido biliar, inhibidores de la síntesis de lipoproteínas, inhibidores de la síntesis del colesterol y derivados del ácido fíbrico. Las HDL circulantes también se pueden aumentar mediante la administración, por ejemplo, de probuchol o altas dosis de niacina. Se demostró que la terapia que abarca varios mecanismos disminuye el avance de la enfermedad y de la ruptura de las placas.

La ateroesclerosis generalmente trae aparejada una respuesta inflamatoria celular en la que los micrófagos derivados de la médula ósea se acumulan en betas de grasa a lo largo de la pared de los vasos y se transforman en células espumosas. Las células espumosas son una fuente de muchas de las citocinas inflamatorias que demostraron inducen el avance de las placas y de las enzimas que pueden promover

la desestabilización de las placas. El tejido ateroesclerótico también produce MCP-1, lo que sugiere que su actividad mediante señalización a través de CCR2 también puede tener una función importante en la acumulación de macrófagos como células espumosas en las placas. Se demostró que los ratones CCR2-/ tienen una cantidad de micrófagos significativamente reducida en betas de grasa generadas como resultado de una dieta alta en grasas o de la alteración genética en el metabolismo de los lípidos.

Los pacientes que muestran un alto nivel de colesterol circulante, baja HDL o alto CRP circulante, o que presentan placas en las paredes de los vasos al observarlas mediante formación de imágenes, o cualquier otro indicio de la presencia de ateroesclerosis se pueden tratar con una sustancia que inhibe la expresión y/o actividad de CCR2, incluso, por ejemplo, ácidos nucleicos (por ejemplo, moléculas antisentido o siARN), proteínas (por ejemplo, anticuerpos contra CCR2), inhibidores de molécula pequeña (por ejemplo, los compuestos descritos en la presente y otros inhibidores del receptor de quimiocina conocidos en el arte). En algunas formas de realización, la sustancia que inhibe la expresión y/o actividad de CCR2 es un inhibidor (o antagonista) de CCR2 de molécula pequeña, tal como un compuesto de la invención. El antagonista de CCR2 se puede administrar en dosis orales q.d. o b.i.d. en una dosis que no exceda alrededor de 500 mg por día. A los pacientes se les puede retirar o disminuir la dosis de su terapia actual y permanecerán en tratamiento con el antagonista de CCR2. De modo alternativo, el tratamiento con antagonista de CCR2 se puede usar para complementar su terapia actual a fin de mejorar su eficacia, por ejemplo, para evitar el avance de las placas, estabilizar las placas que ya se formaron o inducir el retroceso de las placas.

Las ventajas de sustituir o complementar agentes tradicionales con antagonistas de CCR2 son numerosas. Dichos agentes pueden ser útiles, por ejemplo, para evitar el avance de las placas hasta un estado de inestabilidad con su correspondiente riesgo de ruptura de placas. Los agentes pueden reducir o reemplazar la necesidad de usar fármacos que modifican el colesterol o fármacos que elevan la HDL, y sus respectivas toxicidades, que incluyen, pero no se limitan a, enrojecimiento *(flushing)*, daño hepático y daño muscular, tal como miopatía. Los agentes también pueden reducir la necesidad de cirugía o prolongar el período hasta que se requiera cirugía para abrir la pared del vaso, o hasta que se requieran anticoagulantes para limitar el daño debido a la posible ruptura de las placas.

Compuestos etiquetados y métodos de ensayo

Otro aspecto de la presente invención se refiere a una tintura fluorescente, sonda de radicales (*spin label*), compuestos radioetiquetados o metal pesado de la Fórmula I que podrían ser útiles no sólo en la formación de imágenes sino también en ensayos, *in vitro* e *in vivo*, para localizar y cuantificar el receptor de quimiocina en muestras de tejido, incluso de tejido humano, y para identificar ligandos del receptor de quimiocina mediante la inhibición de la unión de un compuesto etiquetado. En consecuencia, la presente invención incluye ensayos del receptor de quimiocina que contienen dichos compuestos etiquetados.

La presente invención además incluye compuestos etiquetados de manera isotópica de la Fórmula I. Un compuesto etiquetado "de manera isotópica" o "radioetiquetado" es un compuesto de la invención en el cual uno o más átomos se reemplazan o sustituyen con un átomo que tiene una masa atómica o un número de masa diferente de la masa atómica o del número de masa que usualmente tiene en la naturaleza (es decir, de origen natural). Los radioucleidos adecuados que se pueden incorporar en compuestos de la presente invención incluyen, pero no se limitan a, ^{2}H, ^{3}H (también escrito como T para tritio), ^{11}C, ^{13}C, ^{14}C, ^{13}N, ^{15}N, ^{15}O, ^{17}O, ^{18}O, ^{18}F, ^{35}S, ^{36}Cl, ^{82}Br, ^{75}Br, ^{76}Br, ^{77}Br, ^{123}I, ^{124}I, ^{125}I e ^{131}I. El radionucleido que se incorpora en los compuestos radioetiquetados de la presente dependerá de la aplicación específica del compuesto radioetiquetado. Por ejemplo, para los ensayos de competición y el etiquetado de receptores de quimiocina *in vitro*, los compuestos que incorporan ^{3}H, ^{14}C, ^{82}Br, ^{125}I , ^{131}I o ^{35}S son generalmente los más útiles. Para las aplicaciones de imágenes por radiación ^{11}C, ^{18}F, ^{125}I, ^{123}I, ^{124}I, ^{131}I, ^{75}Br, ^{76}Br o ^{77}Br son generalmente los más útiles.

Se entiende que un compuesto "radioetiquetado" o "etiquetado" es un compuesto que tiene incorporado al menos un radionucleido. En algunas formas de realización, el radionucleido se selecciona del grupo que consiste en ^{3}H, ^{14}C, ^{125}I, ^{35}S y ^{82}Br.

Los métodos de síntesis para incorporar radioisótopos en compuestos orgánicos se pueden aplicar a los compuestos de la invención y son conocidos en el arte. Un compuesto radioequitado de la invención se puede usar en un ensayo de control para identificar/evaluar compuestos. En términos generales, un compuesto recién sintetizado o identificado (es decir, un compuesto de prueba) se puede evaluar para determinar su capacidad de reducir la unión del compuesto radioetiquetado de la invención con el receptor de quimiocina. En consecuencia, la capacidad de un

compuesto de prueba de competir con el compuesto radioetiquetado para unirse directamente al receptor de quimiocina se correlaciona de manera directa con su afinidad de unión.

Kits

La presente invención también incluye kits farmacéuticos útiles, por ejemplo, para el tratamiento o la prevención de enfermedades asociadas con quimiocina, que incluyen uno o más recipientes que contienen una composición farmacéutica que comprende una cantidad terapéuticamente eficaz de un compuesto de la Fórmula I. Dichos kits también pueden incluir, si se desea, uno o varios componentes de kits farmacéuticos convencionales, tales como, por ejemplo, recipientes con uno o más portadores farmacéuticamente aceptables, recipientes adicionales, etc., como será evidente para los expertos en el arte. También se pueden incluir en el kit instrucciones, ya sea como etiquetas o prospectos, que indiquen las cantidades de los componentes que se administrarán, indicaciones para la administración y/o indicaciones para mezclar los componentes.

Combinación

Los compuestos o las sales de la invención, o las mezclas de estos, se pueden administrar en combinación con uno o más agentes terapéuticos, tales como un fármaco. El compuesto de la presente invención o la sal de éste se pueden administrar en el mismo momento o en un momento diferente como uno o más agentes terapéuticos distintos.

Por ejemplo, "en combinación" incluye la administración simultánea de una combinación de compuesto o sal de la invención y un agente terapéutico a un sujeto, cuando dichos componentes se formulan juntos en una forma de dosificación única que libera dichos componentes sustancialmente al mismo tiempo al sujeto; la administración sustancialmente simultánea de una combinación de compuesto o sal de la invención y un agente terapéutico a un sujeto que necesita el tratamiento, cuando dichos componentes se formulan por separado en diferentes formas de dosificación que se toman sustancialmente al mismo tiempo por el sujeto, por lo cual dichos componentes se liberan sustancialmente al mismo tiempo en el sujeto; la administración secuencial de una combinación de compuesto o sal de la invención y un agente terapéutico a un sujeto, cuando dichos componentes se formulan por separado en diferentes formas de dosificación que se toman de manera consecutiva por el sujeto con un intervalo de tiempo considerable entre cada administración, por lo cual dichos componentes se liberan en momentos sustancialmente diferentes al

sujeto; y la administración secuencial de dicha combinación de compuesto o sal de la invención y un agente terapéutico a un sujeto, cuando dichos componentes se formulan de manera conjunta en una forma de dosificación unitaria que libera dichos componentes de manera controlada, por lo cual se administran de manera concurrente, consecutiva y/o superpuesta al mismo tiempo y/o en diferentes momentos al sujeto, en donde cada parte se puede administrar por la misma vía o por vías diferentes.

Uno o más agentes farmacéuticos adicionales, tales como, por ejemplo, anticuerpos, agentes antiinflamatorios, inmunosupresores, agentes quimioterapéuticos, se pueden usar en combinación con los compuestos de la presente invención para el tratamiento de enfermedades, trastornos o afecciones asociados con el receptor de quimiocina.

Uno o más agentes farmacéuticos adicionales, tales como, por ejemplo, agentes antivirales, anticuerpos, agente antiinflamatorios, sensibilizadores y secretagogos de insulina, agentes moduladores del portador de lípidos y serolípidos y/o inmunosupresores, se pueden usar en combinación con los compuestos de la presente invención para el tratamiento de enfermedades, trastornos o afecciones asociados con el receptor de quimiocina. Los agentes se pueden combinar con los presentes compuestos en una forma de dosificación unitaria o continua o los agentes se pueden administrar de manera simultánea o secuencial como formas de dosificación separadas.

Los agentes antivirales adecuados contemplados para usar en combinación con los compuestos de la presente invención pueden comprender inhibidores de transcriptasa inversa de nucleósido y nucleótido (NRTI), inhibidores de transcriptasa inversa de no nucleósido (NNRTI), inhibidores de proteasa y otros fármacos antivirales.

Los agentes antivirales adecuados contemplados para usar en combinación con los compuestos de la presente invención pueden comprender inhibidores de transcriptasa inversa de nucleósido y nucleótido (NRTI), inhibidores de transcriptasa inversa de no nucleósido (NNRTI), inhibidores de proteasa, inhibidores de entrada, inhibidores de fusión, inhibidores de maduración y otros fármacos antivirales.

Los NRTI adecuados de ejemplo incluyen zidovudine (AZT); didanosine (ddI); zalcitabine (ddC); stavudine (d4T); lamivudine (3TC); abacavir (1592U89); adefovir dipivoxil [bis(POM)-PMEA]; lobucavir (BMS-180194); BCH-10652; emitricitabine [(-)-FTC]; beta-L-FD4 (también denominado beta-L-D4C y beta-L-2', 3'-dicleoxi-5-fluoro-

citidena); DAPD, ((-)-beta-D-2,6,-diamino-purindioxolano); y lodenosine (FddA).

Los NNRTI adecuados típicos incluyen nevirapine (BI-RG-587); delaviradine (BHAP, U-90152); efavirenz (DMP-266); PNU-142721; AG-1549; MKC-442 (1-(etoxi-metil)-5-(1-metiletil)-6-(fenilmetil)-(2,4(1H,3H)-pirimidindiona); y (+)-calanolide A (NSC-675451) y B.

Los inhibidores de proteasa adecuados típicos incluyen saquinavir (Ro 31-8959); ritonavir (ABT-538); indinavir (MK-639); nelfnavir (AG-1343); amprenavir (141W94); lasinavir (BMS-234475); DMP-450; BMS-2322623; ABT-378; y AG-1 549.

Otros agentes antivirales incluyen hidroxiurea, ribavirin, IL-2, IL-12, pentafuside, enfuvirtide, C-34, ciclotriazadisulfonamida CADA, PA-457 e Yissum Proyecto No.11607.

En algunas formas de realización, los agentes antiinflamatorios o analgésicos para usar en combinación con los compuestos de la presente invención pueden comprender, por ejemplo, un agonista de opiato, un inhibidor de lipoxigenasa, tal como un inhibidor de 5-lipoxigenasa, un inhibidor de ciclooxigenasa, tal como un inhibidor de ciclooxigenasa-2, un inhibidor de interleucina, tal como un inhibidor de interleucina-1, un inhibidor de TNF, tal como infliximab, etanercept o adalimumab, un antagonista de NNMA, un inhibidor de óxido nítrico o un inhibidor de la síntesis de óxido nítrico, un agente antiinflamatorio no esteroideo, o un agente antiinflamatorio supresor de citocina, por ejemplo, acetaminophen, aspirin, codeine, fentanyl, ibuprofen, indomethacin, ketodolac, morphine, naproxen, phenacetin, piroxicam, un analgésico esteroideo, sufentanyl, sunlindac, tenidap y similares. De modo similar, los compuestos de la presente se pueden administrar con un analgésico; un potenciador, tal como cafeína, un antagonista de H2, simethicone, hidróxido de magnesio o aluminio; un descongestivo, tal como fenilefrina, fenilpropanolamina, pseudofedrina, oximetazolina, efinefrina, nafazolina, xilometazolina, propilhexedfina o levo-desoxiefedrina; un antitusivo, tal como codeína, hidrocodona, caramifeno, carbetapentano o dextrometorfano; un diurético; y un antihistamínico sedativo o no sedativo.

En algunas formas de realización, los agentes farmacéuticos contemplados para usar en combinación con los compuestos de la presente invención pueden comprender, pero no se limitan a, (a) antagonistas de VLA-4, tales como los descritos en US 5.510.332, W095/15973, W096/01644, W096/06108, W096/20216, W096/229661, W096/31206, W096/4078, W097/030941, W097/022897 WO 98/426567 W098/53814, W098/53817, W098/538185, W098/54207 y W098/58902; (b)

esteroides, tales como beclornethasone, methylpi-ednisolone, betarnethasone, prednisone, dexamethasone e hydrocortisone; (c) inmunosupresores, tales como cyclosporin, tacrolimus, raparnycin y otros inmunosupresores tipo FK506; (d) antihistamínicos (antagonistas de HI-histamina), tales como bromopheniramine, chlorpheniramine, dexchlorpheniramine, triprolidine, clemastine, diphenhydramine, diphenylpyraline, tripelennamine, hydroxyzine, methdilazine, promethazine, trimeprazine, azatadine, cyproheptadine, antazoline, pheniramine pyrilarnine, asternizole, terfenadine, loratadine, cetirizine, fexofenadine, desearboethoxyloratadine y similares; (e) antihistamínicos no esteroideos, tales como terbutaline, metaproterenol, fenoterol, isoethaiine, albuterol, bitolterol, pirbuterol, theophylline, cromolyn sodium, atropine, ipratropium bromide, antagonistas de leucotrieno (por ejemplo, zafirlukast, montelukast, pranlukast, iralukast, pobilukast, SKB-106,203), inhibidores de la biosíntesis de leucotrieno (por ejemplo, zileuton, BAY-1005); (f) agentes antiinflamatorios no esteroideos (NSAID), tales como derivados del ácido propiónico (por ejemplo, alminoprofen, benoxaprofen, ácido buclóxico, carprofen, fenbufen, fenoprofen, fluprofen, flurbiprofen, ibuprofen, indoprofen, ketoprofen, miroprofen, naproxen, oxaprozin, pirprofen, pranoprofen, suprofen, ácido tiaprofénico y tioxaprofen), derivados del ácido acético (por ejemplo, indomethacin, acernetacin, alclofenac, clidanac, diclofenac, fenclofenac, ácido fenclózico, fentiazac, furofenac, ibufenac, isoxepac, oxpinac, sulindac, tiopinac, tolmetin, zidometacin y zomepirac), derivados del ácido fenárnico (ácido flufenárnico, ácido meclofenámico, ácido rnefenámico, ácido niflúmico y ácido tolfenárnico), derivados del ácido bifenilcarboxílico (diflunisal y flufenisal), oxicarns (isoxicarn, piroxicam, sudoxicam y tenoxican), salicilatos (ácido acetil salicílico) y pirazolonas (apazone, bezpiperylon, feprazone, mofebutazone, oxyphenbutazone, phenylbutazone); (g) inhibidores de ciclooxigenasa-2 (COX-2); (h) inhibidores de fosfodiesterasa tipo IV (PDE-IV); (i) otros antagonistas de los receptores de quimiocina, en especial, CXCR-4, CCR1, CCR2, CCR3 y CCR5 ; (j) agentes que disminuyen el colesterol, tales como inhibidores de HMG-CoA reductasa (lovastatin, sirrivastatin y pravastatin, fluvastatin, atorvastatin y otras estatinas), secuestrantes (cholestyramine y colestipol), ácido nicotínico, derivados del ácido fenofíbrico (gemfibrozil, clofibrat, fenofibrate y benzafibrate) y probucol; (k) agentes biológicos antiinflamatorios, tales como terapias contra TNF, receptor anti-IL-1, CTLA-4Ig, anticuerpos contra CD20 y contra VLA4; (l) agentes antidiabéticos, tales como insulina, sulfonilureas, biguanidas (metformin), inhibidores de U.-glucosidasa (acarbose) y orlitazonas (troglitazone y pioglitazone); (m)

preparaciones de interferón beta (interferón beta- Io., interferón beta-1 P); (n) otros compuestos, tales como ácido aminosalicílicos, antimetabolitos, tales como azathioprine y 6-mercaptopurina, y agentes quimioterapéuticos citotóxicos para el cáncer. La relación en peso entre el compuesto de la presente invención y el segundo ingrediente activo se puede variar y dependerá de la dosis eficaz de cada ingrediente.

Por ejemplo, un antagonista de CCR2 y/o CCR5 se puede usar en combinación con un agente farmacéutico antiinflamatorio para el tratamiento de inflamación, enfermedades metabólicas, enfermedades autoinmunes, dolor, cáncer o infección viral para mejorar la respuesta al tratamiento, en comparación con la respuesta al agente terapéutico solo, sin exacerbación de sus efectos tóxicos. Los efectos aditivos o sinérgicos son resultados deseables de la combinación de un antagonista de CCR2 y/o CCR5 de la presente invención con un agente adicional. Además, la resistencia de las células cancerosas a agentes, tales como dexametasona, puede ser reversible luego del tratamiento con un antagonista de CCR2 y/o CCR5 de la presente invención.

F. Uso en la preparación de una composición o un medicamento

En una forma de realización, la presente invención comprende métodos para la preparación de una composición o un medicamento que comprende los compuestos o las sales de la presente invención para usar en el tratamiento de una afección mediada por receptores de quimiocina.

En otra forma de realización, la invención comprende el uso de uno o más compuestos o sales de la presente invención para la preparación de una composición o un medicamento para inflamación, enfermedades inflamatorias, trastornos autoinmunes, dolor, cáncer o infección viral.

La presente invención también incluye el uso de uno o más compuestos o sales de la presente invención para la preparación de una composición o un medicamento para tratar una o más afecciones detalladas en la sección Métodos.

G. Esquemas

Los compuestos de la presente invención se pueden preparar con los métodos ilustrados en los esquemas de síntesis general y procedimientos experimentales que se detallan a continuación. Las reacciones de los métodos de síntesis de la presente se realizan en solventes adecuados que puede seleccionar fácilmente el experto en el arte de la síntesis orgánica; dichos solventes adecuados generalmente son cualquier solvente que es prácticamente no reactivo con los materiales de inicio (reactivos), los intermediarios o productos a las temperaturas a las que se realizan las reacciones. Una reacción determinada se puede realizar en un solvente o una mezcla de más de

un solvente. Según la etapa de reacción particular, se pueden seleccionar solventes adecuados para una etapa de reacción particular.

La preparación de compuestos de la invención puede incluir la protección y desprotección de varios grupos químicos. La necesidad de protección y desprotección y la selección de grupos protectores adecuados las pueden determinar con facilidad un experto en el arte. La química de los grupos protectores se puede hallar, por ejemplo, en T.W. Greene and P.G.M. Wuts, *Protective Groups in Organic Synthesis*, 3ra. Ed., Wiley & Sons, Inc., New York (1999), que se incorporan a la presente en su totalidad por referencia.

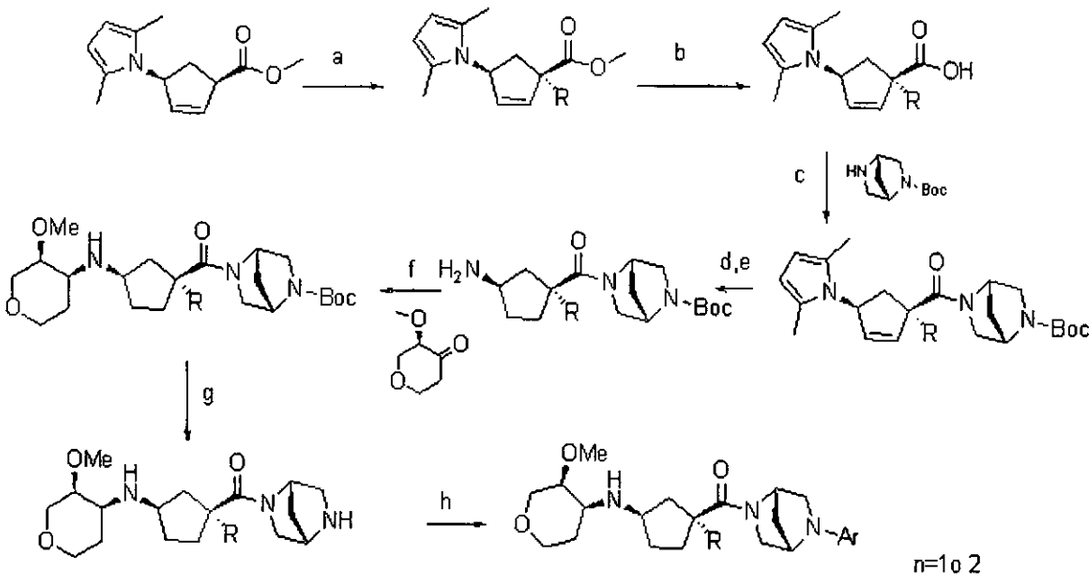
Las reacciones se pueden controlar de acuerdo con cualquier método adecuado conocido en el arte. Por ejemplo, la formación de productos se puede controlar mediante medios espectroscópicos, tales como espectroscopía de resonancia magnética nuclear (por ejemplo, ^{1}H o ^{13}C), espectrometría infrarroja, espectrofotometría (por ejemplo, UV visible) o espectrometría de masa, o mediante cromatografía, tal como cromatografía líquida de alto rendimiento (HPLC) o cromatografía de capa delgada.

Los materiales de inicio que se usan en la presente se encuentran disponibles en el comercio o se pueden preparar mediante métodos de síntesis de rutina.

Los esquemas de síntesis general se presentan con fines ilustrativos y no pretenden ser limitativos.

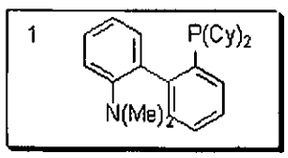
Esquema 1 Preparación de los Ejemplos 1- 23

Esquema 1

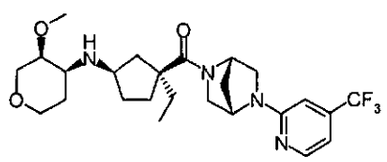


a) LDA o NaHMDS, R-X, THF; b) 2.5N NaOH, MeOH; c) 2.2.1-Boc, DMF, DIPEA, Bop; d) H_2NOH^*HCl, MeOH, $NH_2OH(aq)$; e) 5% Pd/C, MeOH, 50 psi H_2; f) piranona, DCM, $Na(OAc)_3BH$; g) 4N HCl/1,4- dioxano h) cond a o cond b o cond c o cond d

cond a = Ar-X, DMSO, Et_3N, 120 °C
cond b = Ar-X, Cs_2CO_3, XantPhos, $Pd_2(dba)_3$ dioxano, DMSO
cond c = Ar-X, 1,4- dioxano, Et_3N, 100 °C
cond d = Ar-X, NaOtBu, catalizador 1, $Pd_2(dba)_3$, dioxano, DMSO

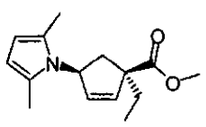


Ejemplo 1



1,5-anhidro-2,3-dideoxi-3-{[(1R,3S)-3-etil-3-({(1S,4S)-5-[4-(trifluorometil)piridin-2-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metil-D-eritro-pentitol

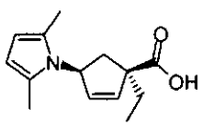
Etapa 1: Preparación de (1R,4S)-4-(2,5-dimetil-1H-pirrol-1-il)-1-etilciclopent-2-en-1-carboxilato de metilo



Una solución a -40°C de LDA 2M (en THF/etilbenceno/heptano) (68ml, 138 mmol) en tetrahidrofurano (120ml) se trató con (1R,4S)-4-(2,5-dimetil-1H-pirrol-1-il)ciclopent-2-en-1-carboxilato de metilo (14,02g, 63,9 mmol), mientras se mantuvo la

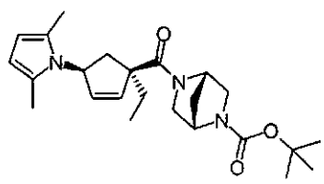
temperatura a menos de -33°C. La reacción fría se agitó durante 40 minutos, y luego se agregó lentamente una solución de yoduro de etilo (13,63g, 87,4mmol) en tetrahidrofurano (5ml), mientras se mantuvo la temperatura a menos de -33°C. La reacción se agitó con el baño frío en el lugar durante 4 horas y se dejó calentar lentamente. La reacción se vertió en solución NH4Cl (300ml), luego se extrajo con acetato de etilo (2x200ml), se lavó con salmuera, se secó en $MgSO_4$ y se concentró a presión reducida. El aceite marrón resultante se pasó a través de una columna de gel de sílice con acetato de etilo/hexanos al 10% para obtener (1R,4S)-4-(2,5-dimetil-1H-pirrol-1-il)-1-etilciclopent-2-en-1-carboxilato de metilo como un aceite marrón (12,96g, 82%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 5.98-5.96 (1H), 5.93-5.91 (1H), 5.73 (2H), 5.30-5.24 (1H), 3.71 (3H), 2.45-2.34 (2H), 2.19 (6H), 1.79-1.73 (2H), 0.91-0.87 (3H).

Etapa 2: Preparación del ácido (1R,4S)-4-(2,5-dimetil-1H-pirrol-1-il)-1-etilciclopent-2-en-1-carboxílico



Una solución de (1R,4S)-4-(2,5-dimetil-1H-pirrol-1-il)-1-etilciclopent-2-en-1-carboxilato de metilo (12,94g, 52,3mmol) en metanol (100ml) se trató con NaOH 2,5N (30ml, 75,0mmol) y se agitó a temperatura ambiente. Luego de 15 horas, se agregó NaOH 2,5N (10ml, 25,0mmol), y la reacción se agitó durante 4 horas más. El metanol se retiró a presión reducida, y el residuo se dividió entre agua y dietiléter. Las capas se separaron, y la capa acuosa se acidificó con HCl 4N, se extrajo con acetato de etilo, se lavó con salmuera, se secó en $MgSO_4$ y se concentró a presión reducida para producir ácido (1R,4S)-4-(2,5-dimetil-1H-pirrol-1-il)-1-etilciclopent-2-en-1-carboxílico como un aceite marrón (11,83g, 97%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 5.98-5.96 (2H), 5.73 (2H), 5.30-5.26 (1H), 2.47-2.35 (2H), 2.20 (6H), 1.82-1.77 (2H), 0.96-0.92 (3H).

Etapa 3: Preparación de (1S,4S)-5-{[(1R,4S)-4-(2,5-dimetil-1H-pirrol-1-il)-1-etilciclopent-2-en-1-il]carbonil}-2,5-diazabiciclo[2.2.1]heptan-2-carboxilato de ter-butilo

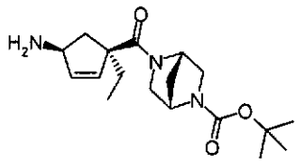


BOP= benzotriazol-1-iloxitris(dimetilamino) fosfoniohexafluorofosfato

Una solución de ácido (1R,4S)-4-(2,5-dimetil-1H-pirrol-1-il)-1-etilciclopent-2-en-1-carboxílico (6,59g, 28,2mmol) en DMF (40ml) se trató con N,N-diisopropiletilamina

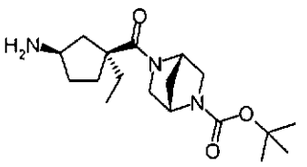
(14,7ml, 84,4mmol) y BOP (14,51g, 32,8mmol) y se agitó en nitrógeno a temperatura ambiente durante 20 minutos. Se agregó una solución de (1S,4S)-2-BOC-2,5-diazabiciclo[2.2.1]heptano (5,66g,28,5mmol) en DMF (5ml), y la reacción se agitó durante 24 horas. La reacción se diluyó en acetato de etilo (100 ml) y se lavó con $NaHCO_3$ saturado al 60% (125 ml). La capa acuosa se extrajo con acetato de etilo. Las capas orgánicas se combinaron, se lavaron con salmuera, se secaron con $MgSO_4$ y se concentraron a presión reducida para producir un aceite marrón (21,25g). El aceite se pasó a través de una columna de gel de sílice con acetato de etilo/hexanos al 50% para producir (1S,4S)-5-{[(1R,4S)-4-(2,5-dimetil-1H-pirrol-1-il)-1-etilciclopent-2-en-1-il]carbonil}-2,5-diazabiciclo[2.2.1]heptan-2-carboxilato de ter-butilo como una espuma blanca (8,14g, 70%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 6.24-6.17 (1H), 5.90-5.86 (1H), 5.73-5.68 (2H), 5.34-5.22 (1H), 5.02-4.41 (2H), 3.71-3.24 (4H), 2.61-2.39 (1H), 2.27-2.16 (7H), 1.89-1.59 (4H), 1.49-1.32 (9H), 0.95-0.85 (3H).

Etapa 4: Preparación de (1S,4S)-5-{[(1R,4S)-4-amino-1-etilciclopent-2-en-1-il]carbonil}-2,5-diazabiciclo[2.2.1]heptan-2-carboxilato de ter-butilo



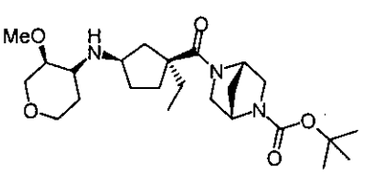
Una solución de (1S,4S)-5-{[(1R,4S)-4-(2,5-dimetil-1H-pirrol-1-il)-1-etilciclopent-2-en-1-il]carbonil}-2,5-diazabiciclo[2.2.1]heptan-2-carboxilato de ter-butilo (2,61g, 6,3mmol) en metanol (40ml) y agua (10ml) se trató con clorhidrato de hidroxilamina (2,73g, 39,1mmol) y 50 % en peso de solución de hidroxilamiina (2,4ml, 39,2mmol). La reacción se agitó en nitrógeno y se calentó a 68°C durante 38,5 horas. La reacción se enfrió a temperatura ambiente, se diluyó con agua y se tornó básica (pH~11) mediante la adición de NaOH 2,5N. La mezcla de reacción se extrajo con acetato de etilo (3x100ml), se lavó con salmuera, se secó en $MgSO_4$ y se concentró a presión reducida para producir una mezcla cruda de (1S,4S)-5-{[(1R,4S)-4-amino-1-etilciclopent-2-en-1-il]carbonil}-2,5-diazabiciclo[2.2.1]heptan-2-carboxilato de ter-butilo como un aceite amarillo (2,68g, rendimiento teórico 2,12g) que se usó sin purificación adicional en la siguiente etapa.

Etapa 5: Preparación de (1S,4S)-5-{[(1S,3R)-3-amino-1-etilciclopentil]carbonil}-2,5-diazabiciclo[2.2.1]heptan-2-carboxilato de ter-butilo



Una mezcla de (1S,4S)-5-{[(1R,4S)-4-amino-1-etilciclopent-2-en-1-il]carbonil}-2,5-diazabiciclo[2.2.1]heptan-2-carboxilato de ter-butilo (2,12g, 6,32mmol) y paladio carbón en metanol al 5% (35ml) se agitó a temperatura ambiente a 48 psi de hidrógeno durante 21 horas. La reacción se filtró a través de Celite, y la torta de filtro se lavó con metanol. El filtrado y los lavados se concentraron a presión reducida para producir (1S,4S)-5-{[(1S,3R)-3-amino-1-etilciclopentil]carbonil}-2,5-diazabiciclo[2.2.1]heptan-2-carboxilato de ter-butilo como un aceite/espuma marrón (2,46g, rendimiento teórico 2,13g) que se usó sin purificación adicional en la siguiente etapa.

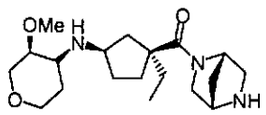
Etapa 6: Preparación de 5-((1S,3R)-1-etil-3-((3S,4R)-3-metoxi-tetrahidro-2H-piran-4-ilamino)ciclopentancarbonil)-2,5-diaza-biciclo[2.2.1]heptan-2-carboxilato de (1S,4S)-ter-butilo



Una solución a 0°C de (1S,4S)-5-{[(1S,3R)-3-amino-1-etilciclopentil]carbonil}-2,5-diazabiciclo[2.2.1]heptan-2-carboxilato de ter-butilo (1,58g, 4,7mmol) en diclorometano (25ml) se trató con triacetoxiborohidruro de sodio (2,36g, 11,1mmol) y (3R)-3-metoxitetrahidro-4H-piran-4-ona (0,76g, 7,6mmol). La reacción se agitó en nitrógeno a 0°C durante 30 minutos, luego se dejó calentar a temperatura ambiente y se agitó durante 15 horas. La reacción se trató con NaOH 2,5N (10mL) y se agitó durante 10 minutos. La reacción se diluyó con agua, y las capas se separaron. La capa acuosa se extrajo dos veces con acetato de etilo. La capa de diclorometano se concentró a presión reducida y se dividió entre acetato de etilo y agua. Las capas orgánicas se combinaron, se lavaron con salmuera, se secaron en $MgSO_4$, se concentraron a presión reducida y se purificaron con Biotage (0-100% de metanol/acetato de etilo, 15 volúmenes de columna) para obtener el producto deseado, 1,5-anhidro-3-{[(1R,3S)-3-{[(1S,4S)-5-(ter-butoxicarbonil)-2,5-diazabiciclo[2.2.1]hept-2-il]carbonil}-3-etilciclopentil]amino}-2,3-dideoxi-4-O-metil-D-

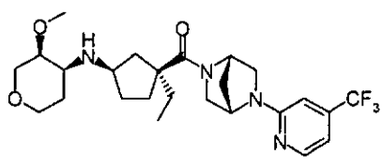
eritro-pentitol. . LC/MS (M+H) = 452.3124 exp, 452.3135 obs; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 4.94-4.41 (2H), 4.11-4.04 (1H), 3.97-3.91 (1H), 3.53-3.18 (11H), 2.83-2.75 (1H), 2.60-2.30 (1H), 2.03-1.55 (10H), 1.48-1.37 (11H), 0.85-0.78 (3H)

Etapa 7: Preparación de (1S,4S)-2,5-diaza-biciclo[2.2.1]heptan-2-il((1S,3R)-1-etil-3-((3S,4R)-3-metoxi-tetrahidro-2H-piran-4-ilamino)ciclopentil)metanona



A una solución de 5-((1S,3R)-1-etil-3-((3S,4R)-3-metoxi-tetrahidro-2H-piran-4-ilamino)ciclopentancarbonil)-2,5-diaza-biciclo[2.2.1]heptan-2-carboxilato de (1S,4S)-ter-butilo (1,22g, 2,89mmol) en 1,4-dioxano (15ml) se agregó HCl/1,4-dioxano 4N (15ml). La mezcla se agitó a temperatura ambiente durante 18 horas. El líquido se decantó y dejó un sólido gomoso que se disolvió en metanol y se concentró a presión reducida. El residuo se disolvió en cloruro de metileno y se concentró para producir la sal HCl del producto como una espuma marrón (1,23g, rendimiento teórico 1,03g) que se usó en la siguiente etapa sin purificación adicional.

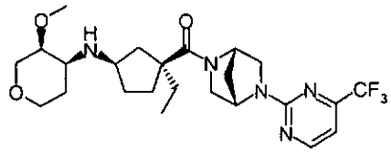
Etapa 8: Preparación de 1,5-anhidro-2,3-dideoxi-3-{[(1R,3S)-3-etil-3-({(1S,4S)-5-[4-(trifluorometil)piridin-2-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metil-D-eritro-pentitol



A una solución de la sal de HCl de (1S,4S)-2,5-diaza-biciclo[2.2.1]heptan-2-il((1S,3R)-1-etil-3-((3S,4R)-3-metoxi-tetrahidro-2H-piran-4-ilamino)ciclopentil)metanona (118mg, 0,33mmol) en DMSO (2ml) se agregó trietilamina (0,15ml, 1,08mmol) y 2-cloro-4-(trifluorometil)piridina (183mg, 1,01mmol). La reacción se calentó a 120□ durante 15 horas. La reacción se enfrió a temperatura ambiente y se agregó a agua helada con agitación. La mezcla se extrajo con acetato de etilo (3 x). Los orgánicos combinados se lavaron con salmuera, se secaron en $MgSO_4$, se concentraron a presión reducida y se purificaron con Biotage (0-100% de metanol/acetato de etilo, 15 volúmenes de columna) para generar el producto como una espuma marrón (40mg, 26%). LC/MS (M+H) = 497.2739 exp, 497.2884 obs; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.25-8.24 (1H), 6.75-6.74 (1H), 6.51-6.45 (1H), 5.13-4.76 (2H), 4.10-4.03 (1H), 3.95-3.90 (1H), 3.72-3.16 (11H), 2.82-2.67 (1H), 2.58-2.36 (1H), 2.06-1.36 (12H), 0.86-0.67

(3H).

Ejemplo 2

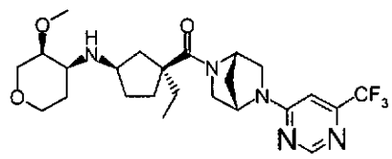


1,5-anhidro-2,3-dideoxi-3-{[(1R,3S)-3-etil-3-({(1S,4S)-5-[4-(trifluorometil)pirimidin-2-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metil-D-eritro-pentitol

Se prepara del modo descrito en el Ejemplo 1 con 2-cloro-4-(trifluorometil)pirimidina en lugar de 2-cloro-4-(trifluorometil)piridina y se modifica la etapa 8 de la siguiente manera:

La sal de HCl de amina (91 mg, 0,25 mmol) se colocó en un matraz con 1,4-dioxano (3 ml). Se agregó trietilamina (0,12 ml, 0,86 mmol) y 2-cloro-4-(trifluorometil)pirimidina (148 mg, 0,81 mmol). Se agregó DMSO (0,3 ml) para lograr una mayor solubilidad, y la reacción se calentó a 100°C durante 20 horas. La reacción se enfrió a temperatura ambiente y se concentró a presión reducida. El residuo se dividió en acetato de etilo y agua. La capa orgánica se extrajo con acetato de etilo, y las capas orgánicas combinadas se lavaron con salmuera, se secaron en $MgSO_4$, se concentraron a presión reducida y se purificaron con Biotage (0-100% de metanol/acetato de etilo, 15 volúmenes de columna) para generar el producto como una espuma marrón (43mg, 58%). LC/MS (M+H) = 498.2692 exp, 498.2799 obs; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 8.48-8.47 (1H), 6.80-6.78 (1H), 5.16-4.71 (2H), 4.09-4.00 (1H), 3.93-3.86 (1H), 3.70-3.51 (3H), 3.45-3.13 (8H), 2.85-2.66 (1H), 2.60-2.33 (1H), 2.06-1.35 (12H), 0.87-0.66 (3H)

Ejemplo 3

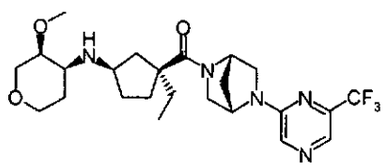


1,5-anhidro-2,3-dideoxi-3-{[(1R,3S)-3-etil-3-({(1S,4S)-5-[6-(trifluorometil)pirimidin-4-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metil-D-eritro-pentitol

Se prepara del modo descrito en el ejemplo 1 con 4-cloro-6(trifluorometil)pirimidina en lugar de 2-cloro-4-(trifluorometil)piridina y se modifica la etapa 8 de la siguiente manera. La sal de HCl de amina (227 mg, 0,63 mmol) se colocó en un matraz con 1,4-dioxano (3ml). A la solución agitada se agregó Xantphos

(26mg, 0,045 mmol), $Pd_2(dba)_3$ (39 mg, 0,042 mmol), Cs_2CO_3 (258 mg, 0,79 mmol) y 4-cloro-6-(trifluorometil)pirimidina (261 mg, 1,43 mmol) disuelta en 1,4-dioxano (1 ml). Se agregó DMSO (0,3 ml) para lograr una mayor solubilidad, y la reacción se calentó a 100°C durante 15 horas. La reacción se dejó enfriar a temperatura ambiente y se filtró a través de Celite. El filtrado se concentró a presión reducida y se purificó con Biotage (0-100% de metanol/acetato de etilo, 15 volúmenes de columna) para generar el producto como una espuma marrón (93mg, 37%). LC/MS (M+H) = 498.2692 exp, 498.2853 obs; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.63 (1H), 6.76-6.42 (1H), 5.31-4.54 (2H), 4.12-4.03 (1H), 3.96-3.85 (1H), 3.72-3.15 (11H), 2.80-2.66 (1H), 2.57-2.35 (1H), 2.09-1.33 (12H), 0.88-0.64 (3H)

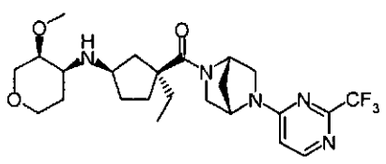
Ejemplo 4



1,5-anhidro-2,3-dideoxi-3-{[(1R,3S)-3-etil-3-({(1S,4S)-5-[6-(trifluorometil)pirazin-2-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metil-D-eritro-pentitol

Se prepara del modo descrito en el ejemplo 3 con 2-iodo-6-(trifluorometil)pirazina en lugar de 4-cloro-6-(trifluorometil)pirimidina en la etapa 8. LC/MS (M+H) = 498.2692 exp, 498.2867 obs; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.16 (1H), 8.05-7.97 (1H), 5.18-4.78 (2H), 4.12-4.02 (1H), 3.99-3.88 (1H), 3.74-3.14 (11H), 2.82-2.66 (1H), 2.61-2.36 (1H), 2.07-1.36 (12H), 0.86-0.68 (3H)

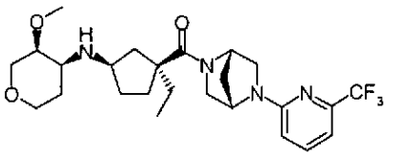
Ejemplo 5



1,5-anhidro-2,3-dideoxi-3-{[(1R,3S)-3-etil-3-({(1S,4S)-5-[2-(trifluorometil)pirimidin-4-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metil-D-eritro-pentitol

Se prepara del modo descrito en el ejemplo 3 con 4-cloro-2-(trifluorometil)pirimidina en lugar de 4-cloro-6-(trifluorometil)pirimidina en la etapa 8. LC/MS (M+H) = 498.2692 exp, 498.2839 obs; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.24-8.22 (1H), 6.54-6.19 (1H), 5.31-4.50 (2H), 4.09-4.00 (1H), 3.90-3.85 (1H), 3.72-3.17 (11H), 2.78-2.62 (1H), 2.55-2.35 (1H), 2.04-1.32 (12H), 0.85-0.63 (3H)

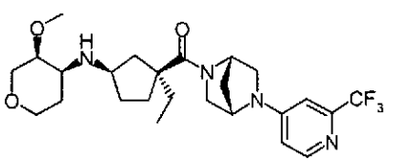
Ejemplo 6



1,5-anhidro-2,3-dideoxi-3-{[(1R,3S)-3-etil-3-({(1S,4S)-5-[6-(trifluorometil)piridin-2-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metil-D-eritro-pentitol

Se prepara del modo descrito en el ejemplo 1 con 2-cloro-6-(trifluorometil)piridina en lugar de 4-cloro-6-(trifluorometil)pirimidina en la etapa 8. LC/MS (M+H) = 497.2739 exp, 497.2641 obs; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.56-7.52 (1H), 6.92-6.90 (1H), 6.52-6.41 (1H), 5.11-4.73 (2H), 4.08-4.03 (1H), 3.95-3.89 (1H), 3.73-3.13 (11H), 2.82-2.64 (1H), 2.58-2.35 (1H), 2.05-1.35 (12H), 0.85-0.66 (3H)

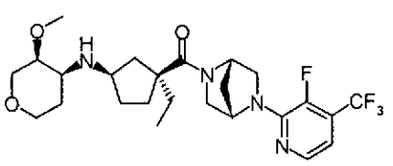
Ejemplo 7



1,5-anhidro-2,3-dideoxi-3-{[(1R,3S)-3-etil-3-({(1S,4S)-5-[2-(trifluorometil)piridin-4-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metil-D-eritro-pentitol

Se prepara del modo descrito en el ejemplo 3 con 4-iodo-2-(trifluorometil)piridina en lugar de 4-cloro-6-(trifluorometil)pirimidina en la etapa 8. LC/MS (M+H) = 497.2739 exp, 497.2878 obs; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.30-8.28 (1H), 6.76-6.69 (1H), 6.52-6.44 (1H), 5.16-4.79 (1H), 4.54 (1H), 4.07-4.04 (1H), 3.93-3.90 (1H), 3.68-3.14 (11H), 2.81-2.64 (1H), 2.59-2.31 (1H), 2.08-1.35 (12H), 0.87-0.65 (3H)

Ejemplo 8

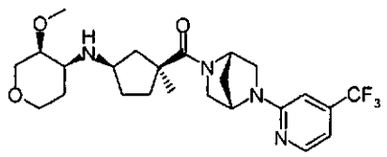


1,5-anhidro-2,3-dideoxi-3-{[(1R,3S)-3-etil-3-({(1S,4S)-5-[3-fluoro-4-(trifluorometil)piridin-2-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metil-D-eritro-pentitol

Se prepara del modo descrito en el ejemplo 3 con 2-cloro-3-fluoro-4-(trifluorometil)piridina en lugar de 4-cloro-6-(trifluorometil)pirimidina en la etapa 8. LC/MS (M+H) = 515.2645 exp, 515.2772 obs; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.00-

7.99 (1H), 6.75-6.73 (1H), 5.09-4.69 (2H), 4.09-4.04 (1H), 3.96-3.90 (1H), 3.86-3.78 (1H), 3.69-3.53 (3H), 3.42-3.17 (7H), 2.81-2.68 (1H), 2.57-2.38 (1H), 2.04-1.36 (12H), 0.88-0.69 (3H)

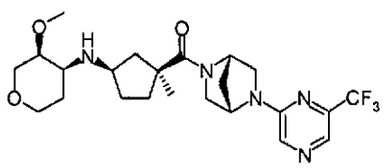
Ejemplo 9



1,5-anhidro-2,3-dideoxi-3-{[(1R,3S)-3-metil-3-({(1S,4S)-5-[4-(trifluorometil)piridin-2-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metil-D-eritro-pentitol

Se prepara del modo descrito en el ejemplo 1 con yoduro de metilo en lugar de yoduro de etilo en la etapa 1. LC/MS (M+H) = 483.2583 exp, 483.2543 obs; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.25-8.24 (1H), 6.75-6.74 (1H), 6.51-6.45 (1H), 5.09-4.76 (2H), 4.09-4.03 (1H), 3.96-3.90 (1H), 3.70-3.23 (11H), 2.81-2.65 (1H), 2.53-2.27 (1H), 2.07-1.02 (13H); HRMS *m/z* 483.2543 (calc. para M+H, 483.2583).

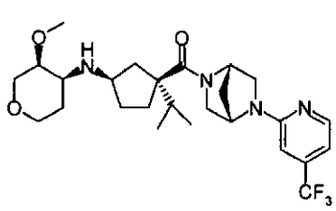
Ejemplo 10



1,5-anhidro-2,3-dideoxi-3-{[(1R,3S)-3-metil-3-({(1S,4S)-5-[6-(trifluorometil)pirazin-2-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metil-D-eritro-pentitol

Se prepara del modo descrito en el ejemplo 3 con yoduro de metilo en lugar de yoduro de etilo en la etapa 1 y 2-iodo-6-(trifluorometil)pirazina en lugar de 4-cloro-6-(trifluorometil)pirimidina en la etapa 8. LC/MS (M+H) = 483.2583 exp, 483.2543 obs; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.25-8.24 (1H), 6.75-6.74 (1H), 6.51-6.45 (1H), 5.09-4.76 (2H), 4.09-4.03 (1H), 3.96-3.90 (1H), 3.70-3.23 (11H), 2.81-2.65 (1H), 2.53-2.27 (1H), 2.07-1.02 (13H)

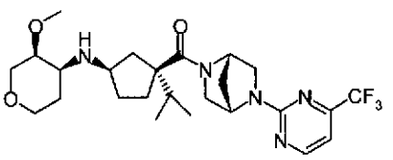
Ejemplo 11



1,5-anhidro-2,3-dideoxi-3-{[(1R,3S)-3-isopropil-3-({(1S,4S)-5-[4-(trifluorometil)piridin-2-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metil-D-eritro-pentitol

Se prepara del modo descrito en el ejemplo 1 comenzando con ácido (1S,4S)-4-(2,5-dimetil-1H-pirrol-1-il)-1-isopropilciclopent-2-en-1-carboxílico y se saltean las etapas 1 y 2. LC/MS (M+H) = 511.2896 exp, 511.3218 obs; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.23-8.22 (1H), 6.73-6.72 (1H), 6.49-6.44 (1H), 5.11-4.73 (2H), 4.06-4.03 (1H), 3.92-3.89 (1H), 3.67-3.52 (2H), 3.44-3.22 (8H), 3.12-3.03 (1H), 2.80-2.61 (1H), 2.51-2.40 (1H), 2.09-1.72 (6H), 1.68-1.42 (4H), 1.35-1.25 (1H), 0.92-0.75 (6H)

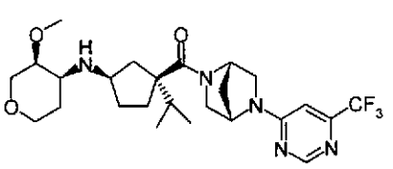
Ejemplo 12



1,5-anhidro-2,3-dideoxi-3-{[(1R,3S)-3-isopropil-3-({(1S,4S)-5-[4-(trifluorometil)pirimidin-2-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metil-D-eritro-pentitol

Se prepara del modo descrito en el ejemplo 2 comenzando con ácido (1S,4S)-4-(2,5-dimetil-1H-pirrol-1-il)-1-isopropilciclopent-2-en-1-carboxílico y se saltean las etapas 1 y 2. LC/MS (M+H) = 512.2849 exp, 512.2827 obs; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.45-8.44 (1H), 6.77-6.76 (1H), 5.09-4.71 (2H), 4.07-4.01 (1H), 3.92-3.87 (1H), 3.67-3.51 (3H), 3.42-3.23 (7H), 3.15-3.08 (1H), 2.83-2.76 (1H), 2.58-2.33 (2H), 2.11-1.56 (8H), 1.51-1.42 (1H), 1.38-1.30 (1H), 0.91-0.74 (6H)

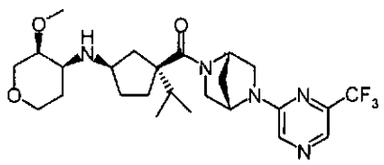
Ejemplo 13



1,5-anhidro-2,3-dideoxi-3-{[(1R,3S)-3-isopropil-3-({(1S,4S)-5-[6-(trifluorometil)pirimidin-4-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metil-D-eritro-pentitol

Se prepara del modo descrito en el ejemplo 3 comenzando con ácido (1S,4S)-4-(2,5-dimetil-1H-pirrol-1-il)-1-isopropilciclopent-2-en-1-carboxílico y se saltean las etapas 1 y 2. LC/MS (M+H) = 512.2849 exp, 512.3227 obs; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.61 (1H), 6.73-6.44 (1H), 5.25-4.52 (2H), 4.05-4.01 (1H), 3.91-3.86 (1H), 3.68-3.46 (2H), 3.38-3.17 (8H), 3.10-3.03 (1H), 2.76-2.63 (1H), 2.48-2.37 (1H), 2.07-1.39 (10H), 1.34-1.23 (1H), 0.90-0.74 (6H)

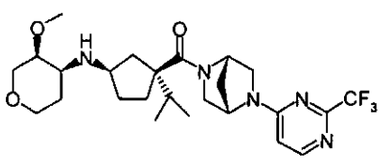
Ejemplo 14



1,5-anhidro-2,3-dideoxi-3-{[(1R,3S)-3-isopropil-3-({(1S,4S)-5-[6-(trifluorometil)pirazin-2-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metil-D-eritro-pentitol

Se prepara del modo descrito en el ejemplo 3 comenzando con ácido (1S,4S)-4-(2,5-dimetil-1H-pirrol-1-il)-1-isopropilciclopent-2-en-1-carboxílico y se saltean las etapas 1 y 2, y se usa 2-iodo-6-(trifluorometil)pirazina en lugar de 4-cloro-6-(trifluorometil)pirimidina en la etapa 8. LC/MS (M+H) = 512.2849 exp, 512.3221 obs; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.12 (1H), 8.01-7.97 (1H), 5.14-4.75 (2H), 4.05-4.01 (1H), 3.90-3.87 (1H), 3.67-3.56 (2H), 3.44-3.20 (8H), 3.11-3.02 (1H), 2.78-2.60 (1H), 2.48-2.39 (1H), 2.10-1.86 (4H), 1.82-1.71 (2H), 1.68-1.53 (2H), 1.50-1.38 (2H), 1.33-1.24 (1H), 0.91-0.74 (6H)

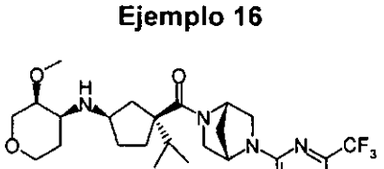
Ejemplo 15



1,5-anhidro-2,3-dideoxi-3-{[(1R,3S)-3-isopropil-3-({(1S,4S)-5-[2-(trifluorometil)pirimidin-4-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metil-D-eritro-pentitol

Se prepara del modo descrito en el ejemplo 3 comenzando con ácido (1S,4S)-4-(2,5-dimetil-1H-pirrol-1-il)-1-isopropilciclopent-2-en-1-carboxílico y se saltean las etapas 1 y 2, y se usa 4-cloro-2-(trifluorometil)pirimidina en lugar de 4-cloro-6-(trifluorometil)pirimidina en la etapa 8. LC/MS (M+H) = 512.2849 exp, 512.2891 obs; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.25-8.24 (1H), 6.52-6.23 (1H), 5.30-4.47 (2H), 4.05-4.02 (1H), 3.91-3.88 (1H), 3.70-3.54 (2H), 3.52-3.18 (8H), 3.12-3.03 (1H), 2.78-2.61 (1H), 2.49-2.39 (1H), 2.08-1.85 (5H), 1.82-1.72 (1H), 1.68-1.41 (4H), 1.35-1.24 (1H), 0.93-0.75 (6H)

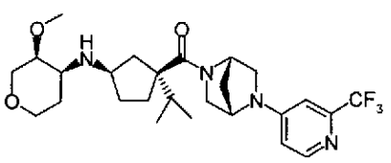
Ejemplo 16



1,5-anhidro-2,3-dideoxi-3-{[(1R,3S)-3-isopropil-3-({(1S,4S)-5-[6-(trifluorometil)piridin-2-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metil-D-eritro-pentitol

Se prepara del modo descrito en el ejemplo 1 comenzando con ácido (1S,4S)-4-(2,5-dimetil-1H-pirrol-1-il)-1-isopropilciclopent-2-en-1-carboxílico y se saltean las etapas 1 y 2, y se usa 2-cloro-6-(trifluorometil)piridina en lugar de 2-cloro-4-(trifluorometil)piridina en la etapa 8. LC/MS (M+H) = 511.2896 exp, 511.2856 obs; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.54-7.50 (1H), 6.90-6.88 (1H), 6.50-6.41 (1H), 5.08-4.70 (2H), 4.08-3.99 (1H), 3.94-3.87 (1H), 3.73-3.46 (2H), 3.46-3.13 (8H), 3.13-2.97 (1H), 2.81-2.58 (1H), 2.52-2.38 (1H), 2.10-1.70 (5H), 1.70-1.40 (5H), 1.36-1.25 (1H), 0.94-0.73 (6H)
0.75 (6H)

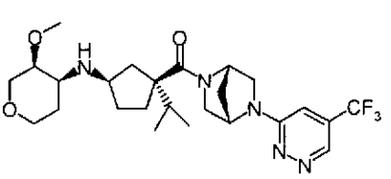
Ejemplo 17



1,5-anhidro-2,3-dideoxi-3-{[(1R,3S)-3-isopropil-3-({(1S,4S)-5-[2-(trifluorometil)piridin-4-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metil-D-eritro-pentitol

Se prepara del modo descrito en el ejemplo 3 comenzando con ácido (1S,4S)-4-(2,5-dimetil-1H-pirrol-1-il)-1-isopropilciclopent-2-en-1-carboxílico y se saltean las etapas 1 y 2, y se usa 4-iodo-2-(trifluorometil)piridina en lugar de 2-cloro-4-(trifluorometil)piridina en la etapa 8. LC/MS (M+H) = 511.2896 exp, 511.2958 obs; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.27-8.26 (1H), 6.72-6.69 (1H), 6.49-6.44 (1H), 5.09-4.75 (1H), 4.52 (1H), 4.05-4.02 (1H), 3.91-3.88 (1H), 3.65-3.50 (3H), 3.41-3.03 (8H), 2.78-2.55 (1H), 2.49-2.35 (1H), 2.08-1.87 (4H), 1.84-1.72 (2H), 1.68-1.53 (2H), 1.51-1.38 (2H), 1.34-1.26 (1H), 0.92-0.75 (6H)

Ejemplo 18

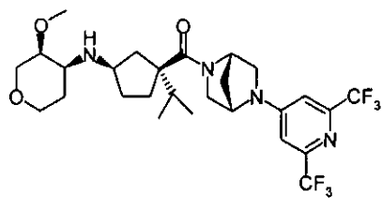


1,5-anhidro-2,3-dideoxi-3-{[(1R,3S)-3-isopropil-3-({(1S,4S)-5-[5-(trifluorometil)piridazin-3-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metil-D-eritro-pentitol

Se prepara del modo descrito en el ejemplo 2 comenzando con ácido (1S,4S)-

4-(2,5-dimetil-1H-pirrol-1-il)-1-isopropilciclopent-2-en-1-carboxílico y se saltean las etapas 1 y 2, y se usa 3-cloro-5-(trifluorometil)piridazina en lugar de 2-cloro-4-(trifluorometil)pirimidina en la etapa 8. LC/MS (M+H) = 512.2849 exp, 512.2864 obs; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.73 (1H), 6.75-6.68 (1H), 5.32-4.79 (2H), 4.07-4.04 (1H), 3.93-3.89 (1H), 3.80-3.55 (2H), 3.52-3.16 (8H), 3.13-3.03 (1H), 2.82-2.63 (1H), 2.51-2.38 (1H), 2.09-1.42 (10H), 1.36-1.24 (1H), 0.93-0.75 (6H)

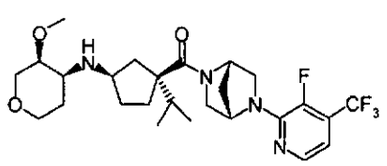
Ejemplo 19



1,5-anhidro-3-{[(1R,3S)-3-isopropil-3-({(1S,4S)-5-[2,6-bis(trifluorometil)piridin-4-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)-3-isopropilciclopentil]amino}-2,3-dideoxi-4-O-metil-D-eritro-pentitol

Se prepara del modo descrito en el ejemplo 3 comenzando con ácido (1S,4S)-4-(2,5-dimetil-1H-pirrol-1-il)-1-isopropilciclopent-2-en-1-carboxílico y se saltean las etapas 1 y 2, y se usa 4-cloro-2,6-bis-(trifluorometil)piridina en lugar de 4-cloro-6-(trifluorometil)pirimidina en la etapa 8. LC/MS (M+H) = 579.2770 exp, 579.2667 obs; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 6.94-6.67 (2H), 5.17-4.78 (1H), 4.60 (1H), 4.06-4.04 (1H), 3.92-3.89 (1H), 3.68-3.57 (2H), 3.42-3.16 (8H), 3.13-3.05 (1H), 2.79-2.62 (1H), 2.48-2.37 (1H), 2.08-1.86 (3H), 1.83-1.54 (6H), 1.52-1.42 (1H), 1.37-1.24 (1H), 0.92-0.76 (6H)

Ejemplo 20



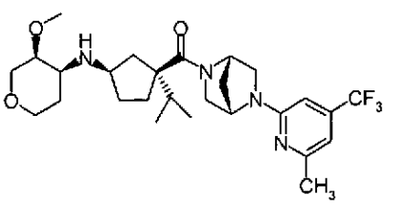
1,5-anhidro-2,3-dideoxi-3-{[(1R,3S)-3-({(1S,4S)-5-[3-fluoro-4-(trifluorometil)piridin-2-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)-3-isopropilciclopentil]amino}-4-O-metil-D-eritro-pentitol

Se prepara del modo descrito en el ejemplo 3 comenzando con ácido (1S,4S)-4-(2,5-dimetil-1H-pirrol-1-il)-1-isopropilciclopent-2-en-1-carboxílico y se saltean las etapas 1 y 2, y se usa 2-cloro-3-fluoro-4-(trifluorometil)piridina en lugar de 4-cloro-6-(trifluorometil)pirimidina en la etapa 8. LC/MS (M+H) = 529.2802 exp, 529.3431 obs; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.98-7.97 (1H), 6.73-6.71 (1H), 5.07-4.67 (2H), 4.08-

120

4.02 (1H), 3.94-3.88 (1H), 3.84-3.78 (1H), 3.64-3.47 (3H), 3.40-3.21 (6H), 3.13-3.04 (1H), 2.80-2.69 (1H), 2.49-2.39 (1H), 2.10-1.56 (9H), 1.54-1.42 (1H), 1.37-1.28 (1H), 0.92-0.75 (6H)

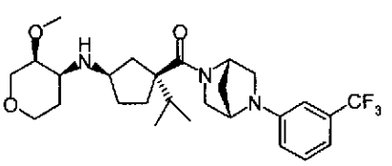
Ejemplo 21



1,5-anhidro-2,3-dideoxi-3-{[(1R,3S)-3-isopropil-3-({(1S,4S)-5-[6-metil-4-(trifluorometil) piridin-2-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metil-D-eritro-pentitol

Se prepara del modo descrito en el ejemplo 3 comenzando con ácido (1S,4S)-4-(2,5-dimetil-1H-pirrol-1-il)-1-isopropilciclopent-2-en-1-carboxílico y se saltean las etapas 1 y 2, y se usa 2-cloro-6-metil-4-(trifluorometil)piridina en lugar de 4-cloro-6-(trifluorometil)pirimidina en la etapa 8. LC/MS (M+H) = 525.3052 exp, 525.3242 obs; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 6.61 (1H), 6.29-6.24 (1H), 5.14-4.71 (2H), 4.17-4.04 (2H), 3.98-3.90 (1H), 3.70-3.49 (3H), 3.48-3.13 (7H), 2.91-2.72 (1H), 2.50-2.32 (4H), 2.11-1.39 (11H), 0.94-0.71 (6H)

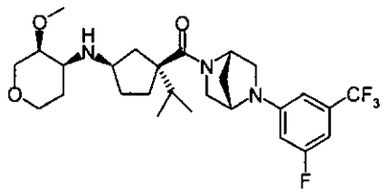
Ejemplo 22



1,5-anhidro-2,3-dideoxi-3-{[(1R,3S)-3-isopropil-3-({(1S,4S)-5-[3-(trifluorometil)fenil]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metil-D-eritro-pentitol

Se prepara del modo descrito en el ejemplo 3 comenzando con ácido (1S,4S)-4-(2,5-dimetil-1H-pirrol-1-il)-1-isopropilciclopent-2-en-1-carboxílico y se saltean las etapas 1 y 2, y se usa 3-iodo-benzotrifluoruro en lugar de 4-cloro-6-(trifluorometil)pirimidina en la etapa 8. LC/MS (M+H) = 510.2943 exp, 510.2976 obs; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.30-7.25 (1H), 6.92-6.90 (1H), 6.72-6.65 (2H), 5.06-4.68 (1H), 4.44 (1H), 4.07-3.99 (1H), 3.94-3.86 (1H), 3.71-3.51 (2H), 3.48-3.19 (7H), 3.14-3.01 (1H), 2.81-2.69 (1H), 2.61-2.35 (1H), 2.09-1.54 (9H), 1.51-1.40 (1H), 1.35-1.27 (1H), 0.94-0.72 (6H)

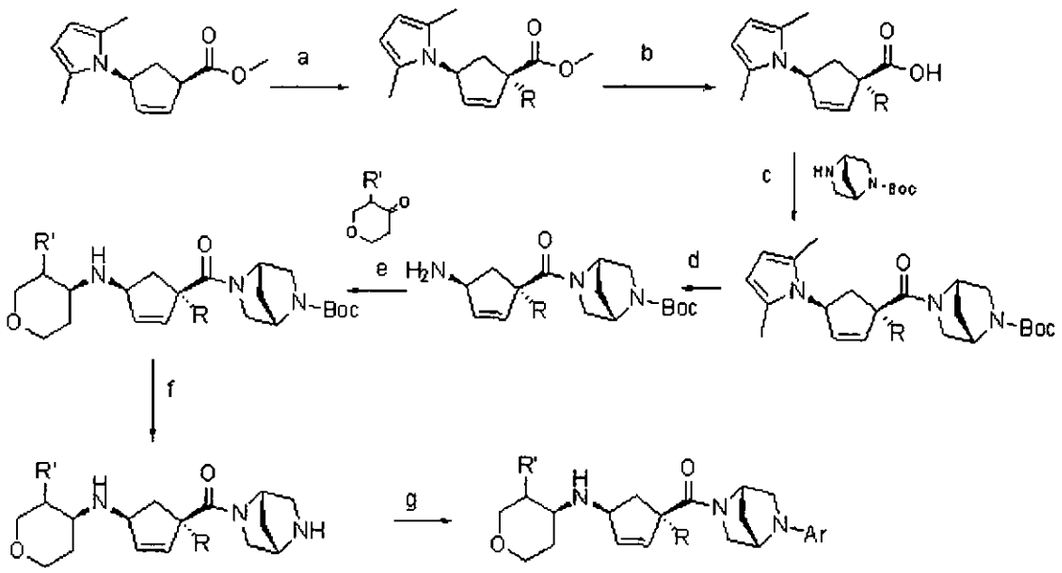
Ejemplo 23



1,5-anhidro-2,3-dideoxi-3-{[(1R,3S)-3-({(1S,4S)-5-[3-fluoro-5-(trifluorometil)fenil]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)-3-isopropilciclopentil]amino}-4-O-metil-D-eritro-pentitol

Se prepara del modo descrito en el ejemplo 3 comenzando con ácido (1S,4S)-4-(2,5-dimetil-1H-pirrol-1-il)-1-isopropilciclopent-2-en-1-carboxílico y se saltean las etapas 1 y 2, y se usa 3-bromo-5-fluorobenzotrifluoruro en lugar de 4-cloro-6-(trifluorometil)pirimidina en la etapa 8. LC/MS (M+H) = 528.2849 exp, 528.2996 obs; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 6.61-6.58 (1H), 6.48 (1H), 6.35-6.33 (1H), 5.06-4.69 (1H), 4.39 (1H), 4.06-4.00 (1H), 3.94-3.86 (1H), 3.65-3.50 (2H), 3.46-3.15 (7H), 3.12-3.00 (1H), 2.80-2.70 (1H), 2.49-2.32 (1H), 2.06-1.73 (6H), 1.69-1.40 (4H), 1.36-1.27 (1H), 0.94-0.72 (6H)

Esquema 2. Preparación de los ejemplos 24-44

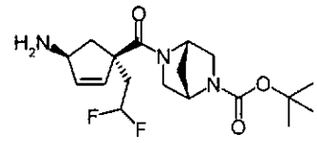


a) LDA o NaHMDS, R-X, THF; b) 2.5N NaOH, MeOH; c) 2.2.1-Boc, DMF, DIPEA, Bop; d) H_2NOH*HCl, MeOH, NH_2OH(aq); e) piranona, DCM, $Na(OAc)_3BH$; f) 4N HCl/1,4-dioxano; g) cond a o cond b o cond c

cond a = Ar-X, DMSO, Et_3N, 120 °C
cond b = Ar-X, Cs_2CO_3, XantPhos, $Pd_2(dba)_3$, dioxano, DMSO
cond c = Ar-X, 1,4-dioxano, Et_3N, 100 °C

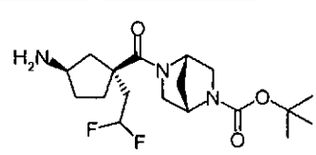
saturado al 60% (125 ml). La capa acuosa se extrajo con acetato de etilo. Las capas orgánicas se combinaron, se lavaron con salmuera, se secaron en $MgSO_4$ y se concentró a presión reducida para producir un aceite marrón (16,8 g). El aceite se pasó a través de una columna de gel de sílice con 50% de acetato de etilo/hexanos para producir (1S,4S)-5-{[(1S,4S)-1-(2,2-difluoroetil)-4-(2,5-dimetil-1H-pirrol-1-il)ciclopent-2-en-1-il]carbonil}-2,5-diazabiciclo[2.2.1]heptan-2-carboxilato de ter-butilo como una espuma marrón (7,86 g, 78%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 6.25-6.19 (1H), 6.04-5.96 (1.25H), 5.85-5.81 (0.5H), 5.74-5.68 (2.25H), 5.37-5.25 (1H), 4.98-4.43 (2H), 3.73-3.29 (4H), 2.77-2.29 (2H), 2.26-2.09 (8H), 1.93-1.67 (2H), 1.46-1.34 (9H).

Etapa 5: Preparación de (1S,4S)-5-{[(1S,4S)-4-amino-1-(2,2-difluoroetil)ciclopent-2-en-1-il]carbonil}-2,5-diazabiciclo[2.2.1]heptan-2-carboxilato de ter-butilo



Una solución de (1S,4S)-5-{[(1S,4S)-1-(2,2-difluoroetil)-4-(2,5-dimetil-1H-pirrol-1-il)ciclopent-2-en-1-il]carbonil}-2,5-diazabiciclo[2.2.1]heptano-2-carboxilato de ter-butilo (7,86 g, 17,5 mmol) en metanol (100ml) y agua (30 ml) se trató con clorhidrato de hidroxilamina (6,35 g, 91,0 mmol) y 50 %peso de una solución de hidroxilamina (5,0 ml, 81,6 mmol). La reacción se agitó en nitrógeno y se calentó a 66°C durante 39 horas. La reacción se enfrió a temperatura ambiente, se diluyó con agua y se tornó básica (pH~11) mediante la adición de NaOH 2,5N. La mezcla de reacción se extrajo con acetato de etilo (3x150ml), se lavó con salmuera, se secó en $MgSO_4$ y se concentró a presión reducida para producir una mezcla cruda de (1S,4S)-5-{[(1S,4S)-4-amino-1-(2,2-difluoroetil)ciclopent-2-en-1-il]carbonil}-2,5-diazabiciclo[2.2.1]heptan-2-carboxilato de ter-butilo como un aceite marrón (9,12 g, rendimiento teórico 6,50 g) que se usó sin purificación adicional en la siguiente etapa.

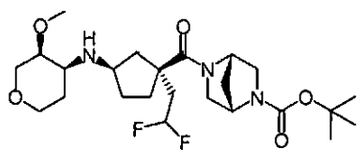
Etapa 6: Preparación de (1S,4S)-5-{[(1S,3R)-3-amino-1-(2,2-difluoroetil)ciclopentil}carbonil}-2,5-diazabiciclo[2.2.1]heptan-2-carboxilato de ter-butilo



Una mezcla de (1S,4S)-5-{[(1S,4S)-4-amino-1-(2,2-difluoroetil)ciclopent-2-en-1-il]carbonil}-2,5-diazabiciclo[2.2.1]heptan-2-carboxilato de ter-butilo (6,50g, 17,5mmol) y paladio en carbón al 5% en metanol (100 ml) se agitó a temperatura ambiente a 46 psi

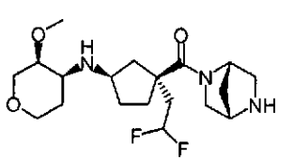
de hidrógeno durante 21 horas. La reacción se filtró a través de Celite, y la torta de filtro se lavó con metanol. El filtrado y los lavados se concentraron a presión reducida para producir (1S,4S)-5-{[(1S,3R)-3-amino-1-(2,2-difluoroetil)ciclopentil]carbonil}-2,5-diazabiciclo[2.2.1]heptan-2-carboxilato de ter-butilo como un aceite marrón (6,67 g, rendimiento teórico 6,54 g) que se usó sin purificación adicional en la siguiente etapa.

Etapa 7: Preparación de 1,5-anhidro-3-{[(1R,3S)-3-{[(1S,4S)-5-(ter-butoxicarbonil)-2,5-diazabiciclo[2.2.1]hept-2-il]carbonil}-3-(2,2-difluoroetil)ciclopentil]amino}-2,3-dideoxi-4-O-metil-D-eritro-pentitol



Una solución a 0°C de (1S,4S)-5-{[(1S,3R)-3-amino-1-(2,2-difluoroetil)ciclopentil]carbonil}-2,5-diazabiciclo[2.2.1]heptan-2-carboxilato de ter-butilo (3,45g, 9,2mmol) en diclorometano (50ml) se trató con triacetoxiborohidruro de sodio (5,34g, 25,2mmol) y (3R)-3-metoxitetrahidro-4H-piran-4-ona (2,31g, 17,8mmol). La reacción se agitó en nitrógeno a 0°C durante 30 minutos, luego se dejó calentar a temperatura ambiente y se agitó durante 47 horas. La reacción se trató con NaOH 2,5N (35 mL) y se agitó durante 10 minutos. La reacción se diluyó con agua, y las capas se separaron. La capa acuosa se extrajo dos veces con acetato de etilo. La capa de diclorometano se concentró a presión reducida y se dividió en acetato de etilo y agua. Las capas orgánicas se combinaron, se lavaron con salmuera, se secaron en $MgSO_4$, se concentraron a presión reducida y se purificaron en Biotage (0-100% de metanol/acetato de etilo, 15 volúmenes de columna) para producir 1,5-anhidro-3-{[(1R,3S)-3-{[(1S,4S)-5-(ter-butoxicarbonil)-2,5-diazabiciclo[2.2.1]hept-2-il]carbonil}-3-(2,2-difluoroetil)ciclopentil]amino}-2,3-dideoxi-4-O-metil-D-eritro-pentitol (2,13g, 47%) que se usó sin purificación adicional en la siguiente etapa.

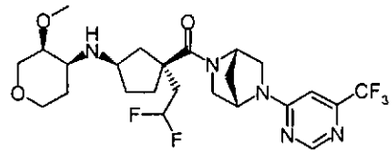
Etapa 8: Preparación de 1,5-anhidro-2,3-dideoxi-3-{[(1R,3S)-3-{[(1S,4S)-2,5-diazabiciclo[2.2.1]hept-2-il]carbonil}-3-(2,2-difluoroetil)ciclopentil]amino}-4-O-metil-D-eritro-pentitol (sal de HCl)



A una solución de 1,5-anhidro-3-{[(1R,3S)-3-{[(1S,4S)-5-(ter-butoxicarbonil)-2,5-diazabiciclo[2.2.1]hept-2-il]carbonil}-3-(2,2-difluoroetil)ciclopentil]amino}-2,3-

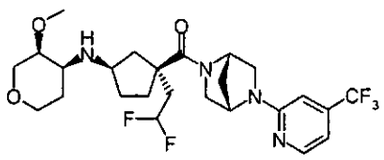
dideoxi-4-O-metil-D-eritro-pentitol (2,13g, 4,4mmol) en 1,4-dioxano (20ml) se agregó HCl/1,4-dioxano 4N (20ml). La reacción se agitó a temperatura ambiente durante 16 horas. El líquido se decantó y dejó un sólido gomoso que se disolvió en metanol y se concentró a presión reducida. El residuo se disolvió en metanol/cloruro de metileno y se concentró para producir la sal de HCl de 1,5-anhidro-2,3-dideoxi-3-{[(1R,3S)-3-{[(1S,4S)-2,5-diazabiciclo[2.2.1]hept-2-il]carbonil}-3-(2,2-difluoroetil)ciclopentil]amino}-4-O-metil-D-eritro-pentitol como una espuma marrón (2,23 g, rendimiento teórico 1,85 g) que se usó en la siguiente etapa sin purificación adicional.

Etapa 9: Preparación de 1,5-anhidro-2,3-dideoxi-3-{[(1R,3S)-3-(2,2-difluoroetil)-3-({(1S,4S)-5-[6-(trifluorometil)pirimidin-4-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metil-D-eritro-pentitol



La sal de HCl de 1,5-anhidro-2,3-dideoxi-3-{[(1R,3S)-3-{[(1S,4S)-2,5-diazabiciclo[2.2.1]hept-2-il]carbonil}-3-(2,2-difluoroetil)ciclopentil]amino}-4-O-metil-D-eritro-pentitol (177 mg, 0,42 mmol) se colocó en un matraz con 1,4-dioxano (3ml). A la solución agitada se agregó Xantphos (36mg, 0,062mmol), $Pd_2(dba)_3$ (22mg, 0,024mmol), Cs_2CO_3 (350mg, 1,07mmol) y 4-cloro-6-(trifluorometil)pirimidina (195mg, 1,07mmol) disuelta en 1,4-dioxano (1ml). Se agregó DMSO (0,5ml) para lograr una mayor solubilidad, y la reacción se calentó a 100°C durante 21,5 horas. La reacción se dejó enfriar a temperatura ambiente y se filtró a través de Celite. El filtrado se concentró a presión reducida y se purificó con Biotage (0-100% de metanol/acetato de etilo, 15 volúmenes de columna) para producir 1,5-anhidro-2,3-dideoxi-3-{[(1R,3S)-3-(2,2-difluoroetil)-3-({(1S,4S)-5-[6-(trifluorometil)pirimidin-4-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metil-D-eritro-pentitol como una espuma blanca (43 mg, 20%) LC/MS (M+H) = 534.2504 exp, 534.2597 obs; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.62 (1H), 6.74-6.46 (1H), 5.93-5.62 (1H), 5.29-4.50 (2H), 4.08-4.03 (1H), 3.93-3.88 (1H), 3.77-3.55 (2H), 3.52-3.32 (6H), 3.30-3.21 (3H), 2.76-2.65 (1H), 2.51-2.33 (1H), 2.21-1.84 (7H), 1.70-1.40 (5H)

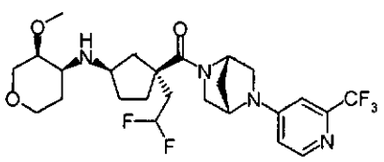
Ejemplo 25



1,5-anhidro-2,3-dideoxi-3-{[(1R,3S)-3-(2,2-difluoroetil)-3-({(1S,4S)-5-[4-(trifluorometil)piridin-2-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metil-D-eritro-pentitol

Se prepara del modo descrito en el ejemplo 24 con 2-cloro-4-(trifluorometil)piridina en lugar de 4-cloro-6-(trifluorometil)pirimidina en la etapa 9. LC/MS (M+H) = 533.2551 exp, 533.2651 obs; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.24-8.20 (1H), 6.74-6.73 (1H), 6.49-6.44 (1H), 5.95-5.57 (1H), 5.07-4.73 (2H), 4.06-4.01 (1H), 3.93-3.87 (1H), 3.70-3.49 (2H), 3.45-3.30 (6H), 3.28-3.20 (3H), 2.77-2.64 (1H), 2.53-2.36 (1H), 2.23-1.81 (7H), 1.73-1.41 (5H)

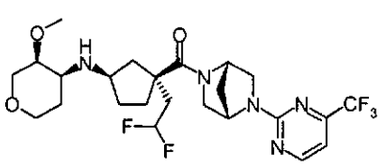
Ejemplo 26



1,5-anhidro-2,3-dideoxi-3-{[(1R,3S)-3-(2,2-difluoroetil)-3-({(1S,4S)-5-[2-(trifluorometil)piridin-4-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metil-D-eritro-pentitol

Se prepara del modo descrito en el ejemplo 24 con 4-iodo-2-(trifluorometil)piridina en lugar de 4-cloro-6-(trifluorometil)pirimidina en la etapa 9. LC/MS (M+H) = 533.2551 exp, 533.2598 obs; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.29-8.27 (1H), 6.74-6.70 (1H), 6.50-6.43 (1H), 5.93-5.59 (1H), 5.09-4.74 (1H), 4.54 (1H), 4.07-4.02 (1H), 3.93-3.88 (1H), 3.68-3.48 (2H), 3.39-3.20 (7H), 2.74-2.62 (1H), 2.51-2.37 (1H), 2.19-1.77 (7H), 1.70-1.40 (5H)

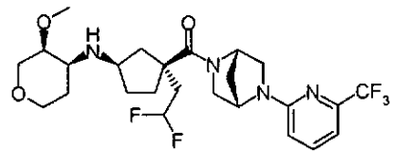
Ejemplo 27



1,5-anhidro-2,3-dideoxi-3-{[(1R,3S)-3-(2,2-difluoroetil)-3-({(1S,4S)-5-[4-(trifluorometil)pirimidin-2-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metil-D-eritro-pentitol

Se prepara del modo descrito en el ejemplo 24 con 2-cloro-4-(trifluorometil)pirimidina en lugar de 4-cloro-6-(trifluorometil)pirimidina y se modifica la etapa 9 de la siguiente manera. La sal de HCl de 1,5-anhidro-2,3-dideoxi-3-{[(1R,3S)-3-{[(1S,4S)-2,5-diazabiciclo[2.2.1]hept-2-il]carbonil}-3-(2,2-difluoroetil)ciclopentil]amino}-4-O-metil-D-eritro-pentitol (175 mg, 0,41 mmol) se colocó en un matraz con 1,4-dioxano (3 ml). Se agregó trietilamina (0,2ml, 1,43mmol) y 2-cloro-4-(trifluorometil)pirimidina (237mg, 1,30mmol). Se agregó DMSO (0,3ml) para lograr una mayor solubilidad, y la reacción se calentó a 100°C durante 14,5 horas. La reacción se enfrió a temperatura ambiente y se dividió en acetato de etilo y agua. La capa acuosa se extrajo con acetato de etilo, y las capas orgánicas combinadas se lavaron con salmuera, se secaron en $MgSO_4$, se concentraron a presión reducida y se purificaron con Biotage (0-100% de metanol/acetato de etilo, 15 volúmenes de columna) para producir 1,5-anhidro-2,3-dideoxi-3-{[(1R,3S)-3-(2,2-difluoroetil)-3-({(1S,4S)-5-[4-(trifluorometil)pirimidin-2-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metil-D-eritro-pentitol como una espuma marrón (126 mg, 58%) LC/MS (M+H) = 534.2504 exp, 534.2452 obs; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.48-8.45 (1H), 6.79-6.78 (1H), 5.96-5.58 (1H), 5.10-4.71 (2H), 4.07-4.01 (1H), 3.93-3.87 (1H), 3.69-3.55 (4H), 3.39-3.32 (4H), 3.30-3.21 (3H), 2.77-2.66 (1H), 2.52-2.40 (1H), 2.23-1.82 (7H), 1.70-1.39 (5H)

Ejemplo 28



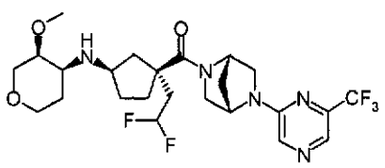
1,5-anhidro-2,3-dideoxi-3-{[(1R,3S)-3-(2,2-difluoroetil)-3-({(1S,4S)-5-[6-(trifluorometil)piridin-2-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metil-D-eritro-pentitol

Se prepara del modo descrito en el ejemplo 24 con 2-cloro-6-(trifluorometil)piridina en lugar de 4-cloro-6-(trifluorometil)pirimidina y se modifica la etapa 9 de la siguiente manera. A una solución de sal de HCl de 1,5-anhidro-2,3-dideoxi-3-{[(1R,3S)-3-{[(1S,4S)-2,5-diazabiciclo[2.2.1]hept-2-il]carbonil}-3-(2,2-difluoroetil)ciclopentil]amino}-4-O-metil-D-eritro-pentitol (183 mg, 0,43 mmol) en DMSO (2 ml) se agregó trietilamina (0,2 ml, 1,43 mmol) y 2-cloro-6-(trifluorometil)piridina (179 mg, 1,05 mmol). La reacción se calentó a 120°C durante 14,5 horas. La reacción se enfrió a temperatura ambiente y se agregó a agua helada con agitación. La mezcla se

extrajo con acetato de etilo (3 x). Las capas orgánicas combinadas se lavaron con salmuera, se secaron en $MgSO_4$, se concentraron a presión reducida y se purificaron con Biotage (0-100% de metanol/acetato de etilo, 15 volúmenes de columna) para producir 1,5-anhidro-2,3-dideoxi-3-{[(1R,3S)-3-(2,2-difluoroetil)-3-({(1S,4S)-5-[6-(trifluorometil)piridin-2-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metil-D-eritro-pentitol

como una espuma marrón (58 mg, 28%). LC/MS (M+H) = 533.2551 exp, 533.2546 obs; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.54-7.51 (1H), 6.91-6.89 (1H), 6.51-6.38 (1H), 5.94-5.54 (1H), 5.11-4.70 (2H), 4.06-4.01 (1H), 3.93-3.87 (1H), 3.70-3.53 (2H), 3.51-3.31 (6H), 3.27-3.20 (3H), 2.78-2.61 (1H), 2.53-2.36 (1H), 2.20-1.80 (7H), 1.68-1.38 (5H)

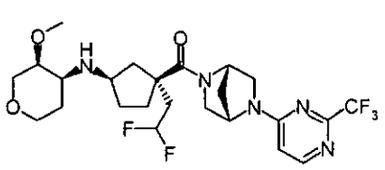
Ejemplo 29



1,5-anhidro-2,3-dideoxi-3-{[(1R,3S)-3-(2,2-difluoroetil)-3-({(1S,4S)-5-[6-(trifluorometil)pirazin-2-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metil-D-eritro-pentitol

Se prepara del modo descrito en el ejemplo 24 con 2-iodo-6-(trifluorometil)pirazina en lugar de 4-cloro-6-(trifluorometil)pirimidina en la etapa 9. LC/MS (M+H) = 534.2504 exp, 534.2548 obs; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.13 (1H), 8.01-7.93 (1H), 5.92-5.57 (1H), 5.09-4.75 (2H), 4.06-4.01 (1H), 3.92-3.87 (1H), 3.68-3.48 (4H), 3.38-3.30 (4H), 3.28-3.20 (3H), 2.74-2.63 (1H), 2.51-2.32 (1H), 2.21-1.83 (7H), 1.75-1.42 (5H)

Ejemplo 30

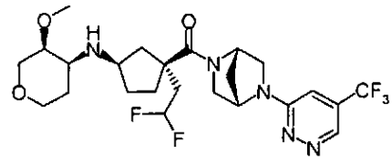


1,5-anhidro-2,3-dideoxi-3-{[(1R,3S)-3-(2,2-difluoroetil)-3-({(1S,4S)-5-[2-(trifluorometil)pirimidin-4-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metil-D-eritro-pentitol

Se prepara del modo descrito en el ejemplo 24 con 4-cloro-2-(trifluorometil)pirimidina en lugar de 4-cloro-6-(trifluorometil)pirimidina en la etapa 9.

LC/MS (M+H) = 534.2504 exp, 534.2521 obs; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.28-8.26 (1H), 6.52-6.24 (1H), 5.93-5.62 (1H), 5.33-4.38 (2H), 4.08-4.03 (1H), 3.94-3.89 (1H), 3.71-3.57 (2H), 3.49-3.33 (6H), 3.29-3.21 (3H), 2.75-2.66 (1H), 2.50-2.36 (1H), 2.22-1.86 (7H), 1.69-1.41 (5H)

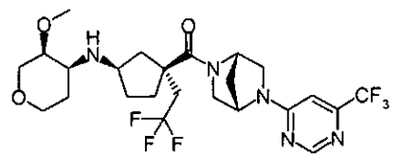
Ejemplo 31



1,5-anhidro-2,3-dideoxi-3-{[(1R,3S)-3-(2,2-difluoroetil)-3-({(1S,4S)-5-[5-(trifluorometil)piridazin-3-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metil-D-eritro-pentitol

Se prepara del modo descrito en el ejemplo 27 con 3-cloro-5-(trifluorometil)piridazina en lugar de 2-cloro-4-(trifluorometil)pirimidina en la etapa 9. LC/MS (M+H) = 534.2504 exp, 534.2531 obs; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.76 (1H), 6.74-6.68 (1H), 5.96-5.90 (1H), 5.37-4.84 (2H), 4.10-4.04 (1H), 3.96-3.90 (1H), 3.81-3.54 (3H), 3.47-3.34 (4H), 3.32-3.22 (4H), 2.77-2.67 (1H), 2.51-2.37 (1H), 2.22-1.86 (7H), 1.72-1.46 (5H)

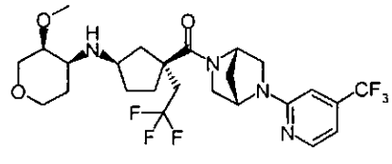
Ejemplo 32



1,5-anhidro-2,3-dideoxi-4-O-metil-3-{[(1R,3S)-3-(2,2,2-trifluoroetil)-3-({(1S,4S)-5-[6-(trifluorometil)pirimidin-4-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-D-eritro-pentitol

Se prepara del modo descrito en el ejemplo 24 con 3,3,3-trifluoroetanol en lugar de 2,2-difluoroetanol en la etapa 1. LC/MS (M+H) = 552.2409 exp, 552.2432 obs; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.61 (1H), 6.70-6.45 (1H), 5.26-5.21 (1H), 5.08-4.96 (1H), 4.08-4.03 (1H), 3.92-3.87 (1H), 3.68-3.61 (2H), 3.53-3.44 (1H), 3.42-3.20 (8H), 2.72-2.65 (1H), 2.56-2.27 (3H), 2.08-1.88 (5H), 1.80-1.47 (5H)

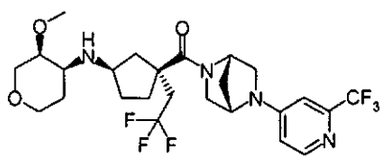
Ejemplo 33



1,5-anhidro-2,3-dideoxi-4-O-metil-3-{[(1R,3S)-3-(2,2,2-trifluoroetil)-3-({(1S,4S)-5-[4-(trifluorometil)piridin-2-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-D-eritro-pentitol

Se prepara del modo descrito en el ejemplo 24 con 3,3,3-trifluoroetanol en lugar de 2,2-difluoroetanol en la etapa 1 y con 2-cloro-4-(trifluorometil)piridina en lugar de 2-cloro-6-(trifluorometil)piridina en la etapa 9. LC/MS (M+H) = 551.2457 exp, 551.2703 obs; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.22-8.21 (1H), 6.74-6.73 (1H), 6.47-6.43 (1H), 5.06-4.71 (2H), 4.06-4.01 (1H), 3.92-3.87 (1H), 3.65-3.50 (3H), 3.40-3.20 (8H), 2.72-2.63 (1H), 2.53-2.27 (3H), 2.08-1.82 (5H), 1.78-1.45 (5H)

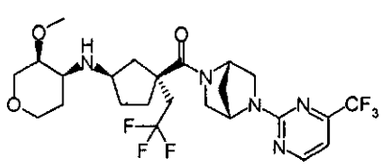
Ejemplo 34



1,5-anhidro-2,3-dideoxi-4-O-metil-3-{[(1R,3S)-3-(2,2,2-trifluoroetil)-3-({(1S,4S)-5-[2-(trifluorometil)piridin-4-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-D-eritro-pentitol

Se prepara del modo descrito en el ejemplo 24 con 3,3,3-trifluoroetanol en lugar de 2,2-difluoroetanol en la etapa 1 y con 4-iodo-2-(trifluorometil)piridina en lugar de 2-cloro-4-(trifluorometil)pirimidina en la etapa 9. LC/MS (M+H) = 551.2457 exp, 551.2610 obs; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.26-8.25 (1H), 6.71-6.68 (1H), 6.46-6.42 (1H), 5.09-4.83 (1H), 4.55-4.52 (1H), 4.05-4.01 (1H), 3.90-3.85 (1H), 3.66-3.48 (3H), 3.36-3.18 (8H), 2.70-2.62 (1H), 2.51-2.27 (3H), 2.06-1.87 (5H), 1.80-1.45 (5H)

Ejemplo 35

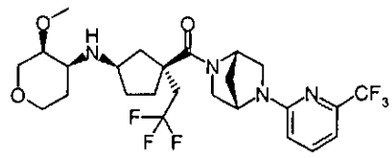


1,5-anhidro-2,3-dideoxi-4-O-metil-3-{[(1R,3S)-3-(2,2,2-trifluoroetil)-3-({(1S,4S)-5-[4-(trifluorometil)pirimidin-2-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-D-eritro-pentitol

Se prepara del modo descrito en el ejemplo 27 con 3,3,3-trifluoroetanol en lugar de 2,2-difluoroetanol en la etapa 1. LC/MS (M+H) = 552.2409 exp, 551.2426 obs; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.50-8.46 (1H), 6.81-6.80 (1H), 5.11-4.74 (2H), 4.13-4.06 (1H), 3.97-3.92 (1H), 3.67-3.59 (4H), 3.41-3.25 (7H), 2.90-2.75 (1H), 2.54-2.33

(3H), 2.07-1.88 (5H), 1.79-1.58 (5H)

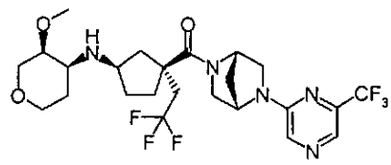
Ejemplo 36



1,5-anhidro-2,3-dideoxi-4-O-metil-3-{[(1R,3S)-3-(2,2,2-trifluoroetil)-3-({(1S,4S)-5-[6-(trifluorometil)piridin-2-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-D-eritro-pentitol

Se prepara del modo descrito en el ejemplo 27 con 3,3,3-trifluoroetanol en lugar de 2,2-difluoroetanol en la etapa 1 y con 2-cloro-6-(trifluorometil)piridina en lugar de 2-cloro-4-(trifluorometil)pirimidina en la etapa 9. LC/MS (M+H) = 551.2457 exp, 551.2581 obs; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.55-7.51 (1H), 6.92-6.90 (1H), 6.47-6.40 (1H), 5.12-4.70 (2H), 4.07-4.03 (1H), 3.93-3.88 (1H), 3.72-3.47 (3H), 3.40-3.31 (5H), 3.28-3.20 (3H), 2.73-2.64 (1H), 2.53-2.25 (3H), 2.10-1.80 (5H), 1.77-1.44 (5H)

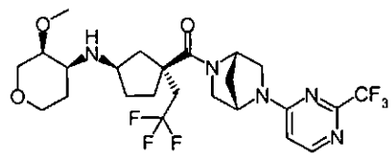
Ejemplo 37



1,5-anhidro-2,3-dideoxi-4-O-metil-3-{[(1R,3S)-3-(2,2,2-trifluoroetil)-3-({(1S,4S)-5-[6-(trifluorometil)pirazin-2-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-D-eritro-pentitol

Se prepara del modo descrito en el ejemplo 24 con 3,3,3-trifluoroetanol en lugar de 2,2-difluoroetanol en la etapa 1 y con 1-iodo-6-(trifluorometil)pirazina en lugar de 4-cloro-6-(trifluorometil)pirimidina en la etapa 9. LC/MS (M+H) = 552.2409 exp, 552.2443 obs; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.16 (1H), 8.01-7.96 (1H), 5.09-4.96 (2H), 4.09-4.04 (1H), 3.94-3.89 (1H), 3.68-3.57 (3H), 3.53-3.49 (1H), 3.39-3.23 (7H), 2.74-2.67 (1H), 2.54-2.29 (3H), 2.09-1.90 (5H), 1.81-1.49 (5H)

Ejemplo 38

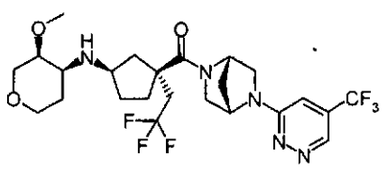


1,5-anhidro-2,3-dideoxi-4-O-metil-3-{[(1R,3S)-3-(2,2,2-trifluoroetil)-3-({(1S,4S)-5-[2-(trifluorometil)pirimidin-4-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-

D-eritro-pentitol

Se prepara del modo descrito en el ejemplo 24 con 3,3,3-trifluoroetanol en lugar de 2,2-difluoroetanol en la etapa 1 y con 4-cloro-2-(trifluorometil)pirimidina en lugar de 4-cloro-6-(trifluorometil)pirimidina en la etapa 9. LC/MS (M+H) = 552.2409 exp, 552.3073 obs; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.23-8.21 (1H), 6.49-6.22 (1H), 5.25-4.93 (2H), 4.04-3.99 (1H), 3.89-3.83 (1H), 3.65-3.57 (2H), 3.46-3.17 (9H), 2.68-2.62 (1H), 2.52-2.26 (3H), 2.05-1.85 (5H), 1.76-1.43 (5H)

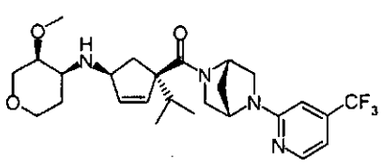
Ejemplo 39



1,5-anhidro-2,3-dideoxi-4-O-metil-3-{[(1R,3S)-3-(2,2,2-trifluoroetil)-3-({(1S,4S)-5-[5-(trifluorometil)piridazin-3-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-D-eritro-pentitol

Se prepara del modo descrito en el ejemplo 27 con 3,3,3-trifluoroetanol en lugar de 2,2-difluoroetanol en la etapa 1 y con 3-cloro-5-(trifluorometil)piridazina en lugar de 2-cloro-4-(trifluorometil)pirimidina en la etapa 9. LC/MS (M+H) = 552.2409 exp, 552.2344 obs; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.72 (1H), 6.72-6.64 (1H), 5.32-4.82 (2H), 4.06-4.01 (1H), 3.91-3.86 (1H), 3.78-3.53 (3H), 3.42-3.18 (8H), 2.69-2.64 (1H), 2.52-2.24 (3H), 2.07-1.84 (5H), 1.76-1.44 (5H)

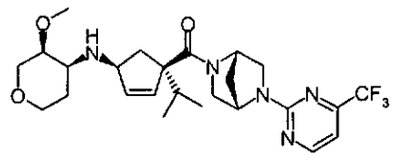
Ejemplo 40



1,5-anhidro-2,3-dideoxi-3-{[(1S,4S)-4-isopropil-4-({(1S,4S)-5-[4-(trifluorometil)piridin-2-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopent-2-en-1-il]amino}-4-O-metil-D-eritro-pentitol

Se prepara del modo descrito en el ejemplo 1 comenzando con ácido (1S,4S)-4-(2,5-dimetil-1H-pirrol-1-il)-1-isopropilciclopent-2-en-1-carboxílico y se saltean las etapas 1, 2 y 5. LC/MS (M+H) = 509.2739 exp, 509.2724 obs; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.19 (1H), 6.72-6.68 (1H), 6.46-6.38 (1H), 5.90-5.75 (2H), 5.09-4.82 (2H), 4.02-3.12 (13H), 2.86-2.67 (1H), 2.46-2.16 (1H), 2.08-1.47 (7H), 0.84-0.64 (6H)

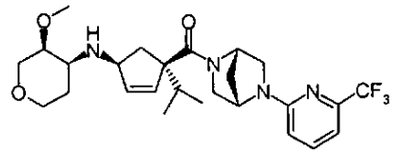
Ejemplo 41



1,5-anhidro-2,3-dideoxi-3-{[(1S,4S)-4-isopropill-4-({(1S,4S)-5-[4-(trifluorometil)pirimidin-2-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopent-2-en-1-il]amino}-4-O-metil-D-eritro-pentitol

Se prepara del modo descrito en el ejemplo 2 comenzando con ácido (1S,4S)-4-(2,5-dimetil-1H-pirrol-1-il)-1-isopropilciclopent-2-en-1-carboxílico y se saltean las etapas 1, 2 y 5. LC/MS (M+H) = 510.2692 exp, 510.2926 obs; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.43-8.42 (1H), 6.75-6.74 (1H), 5.90-5.77 (2H), 5.09-4.80 (2H), 4.01-3.16 (13H), 2.86-2.69 (1H), 2.45-2.17 (1H), 2.08-1.30 (7H), 0.82-0.66 (6H)

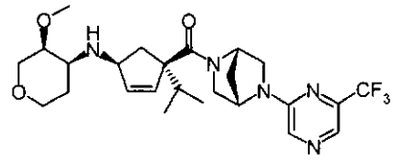
Ejemplo 42



1,5-anhidro-2,3-dideoxi-3-{[(1S,4S)-4-isopropill-4-({(1S,4S)-5-[6-(trifluorometil)piridin-2-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopent-2-en-1-il]amino}-4-O-metil-D-eritro-pentitol

Se prepara del modo descrito en el ejemplo 1 comenzando con ácido (1S,4S)-4-(2,5-dimetil-1H-pirrol-1-il)-1-isopropilciclopent-2-en-1-carboxílico y se saltean las etapas 1, 2 y 5. LC/MS (M+H) = 509.2739 exp, 509.2680 obs; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.55-7.52 (1H), 6.94-6.89 (1H), 6.52-6.40 (1H), 5.96-5.78 (2H), 5.12-4.84 (2H), 4.07-3.16 (13H), 2.90-2.69 (1H), 2.49-2.21 (1H), 2.12-1.42 (7H), 0.87-0.68 (3H)

Ejemplo 43

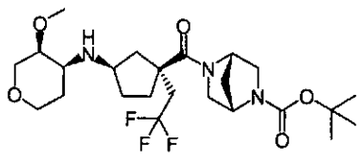


1,5-anhidro-2,3-dideoxi-3-{[(1S,4S)-4-isopropill-4-({(1S,4S)-5-[6-(trifluorometil)pirazin-2-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopent-2-en-1-il]amino}-4-O-metil-D-eritro-pentitol

Se prepara del modo descrito en el ejemplo 3 comenzando con ácido (1S,4S)-4-(2,5-dimetil-1H-pirrol-1-il)-1-isopropilciclopent-2-en-1-carboxílico y se saltean las

etapas 1 y 2, se saltea la etapa 5 y se usa (3R)-3-metoxitetrahidro-4H-piran-4-ona en la etapa 6 y 2-cloro-6-(trifluorometil)pirazina en lugar de 4-cloro-6-(trifluorometil)pirimidina en la etapa 8. LC/MS (M+H) = 510.2692 exp, 510.2699 obs; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.15 (1H), 8.04-7.95 (1H), 5.93-5.82 (2H), 5.17-4.91 (2H), 4.16-3.18 (13H), 2.91-2.69 (1H), 2.48-2.21 (1H), 2.10-1.52 (7H), 0.85-0.67 (6H)

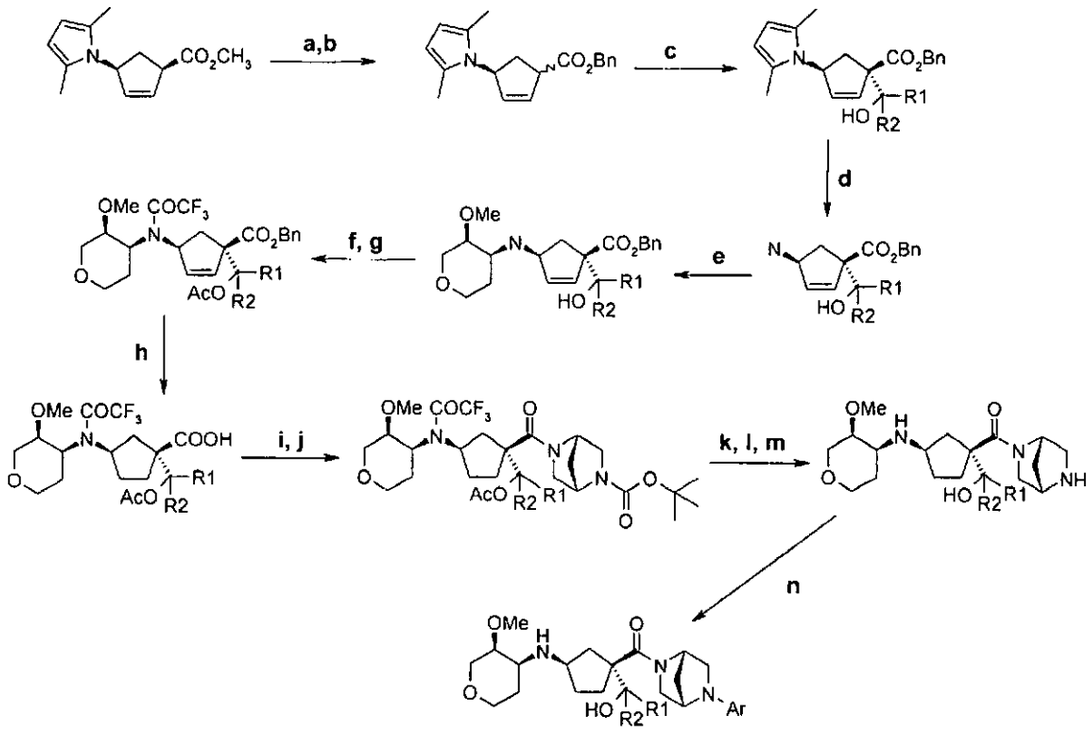
Ejemplo 44



1,5-anhidro-3-{[(1R,3S)-3-{[(1S,4S)-5-(ter-butoxicarbonil)-2,5-diazabiciclo[2.2.1]hept-2-il]carbonil}-3-(2,2,2-trifluoroetil)ciclopentil]amino}-2,3-dideoxi-4-O-metil-D-eritro-pentitol

Se prepara del modo descrito en el ejemplo 24 con 2,2,2-trifluoroetanol en lugar de 2,2-difluoroetanol en la etapa 1 y se saltean las etapas 8 y 9. LC/MS (M+H) = 506.2842 exp, 506.3033 obs; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 4.86-4.65 (1H), 4.52-4.38 (1H), 4.09-4.03 (1H), 3.93-3.87 (1H), 3.68-3.23 (11H), 2.73-2.68 (1H), 2.55-2.24 (3H), 2.10-2.03 (1H), 1.96-1.89 (1H), 1.85-1.59 (7H), 1.54-1.47 (1H), 1.44-1.39 (9H)

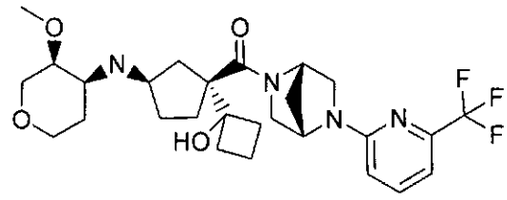
Esquema 3. Preparación de los ejemplos 45-59



a) NaOH, MeOH, H_2O; b) BnOH, EDC, DMAP; c) LDA, R_1COR_2; d) NH_2OH*HCl,

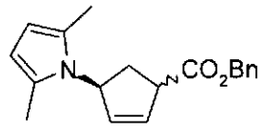
NH_2OH*H_2O, MeOH; e) MeO-piranona, $Na(OAc)_3BH$; f) TFAA; g) AcCl, piridina; h) H_2, Pt/C; i) $(COCl)_2$; j) arilpiperazina; k) K_2CO_3, MeOH; l) $NaBH_4$; m) HCl/dioxano; n) Ar-Cl, calor o catalizador de Pd.

Ejemplo 45



1,5-anhidro-2,3-dideoxi-3-{[(1R,3S)-3-(1-hidroxiciclobutil)-3-({(1S,4S)-5-[6-(trifluorometil)piridin-2-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metil-D-eritro-pentitol

Etapa 1: (4S)-4-(2,5-dimetil-1H-pirrol-1-il)ciclopent-2-en-1-carboxilato de bencilo

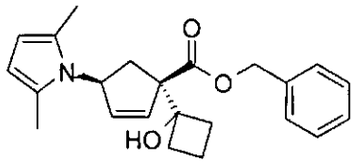


Una solución de 11,04 g (50,4 mmol) de (1R,4S)-4-(2,5-dimetil-1H-pirrol-1-il)ciclopent-2-en-1-carboxilato de metilo y 40 mL de de hidróxido de sodio 2,5 M en 100 mL de MeOH se agitó a temperatura ambiente durante 45 minutos y luego se concentró a presión reducida para retirar metanol. La solución acuosa residual se agregó a una mezcla agitada de 20 g de ácido cítrico, 100 mL de agua y 100 mL de diclorometano. Las fases se separaron, y la fase acuosa se extrajo con dos porciones adicionales de diclorometano. La fase orgánica se secó (Na_2SO_4) y se concentró a presión reducida para generar el ácido correspondiente como una goma marrón (10,98 g).

A una solución agitada de este ácido, 10 mL (96 mmol) de alcohol de bencilo y 1,74 g (14 mmol) de DMAP en 50 mL de diclorometano se agregaron 13 g (69 mmol) de EDC, en 5 porciones iguales durante 30 minutos. Luego de 18 horas, la solución se concentró a presión reducida, y el jarabe residual se dividió en éter y agua. La fase orgánica se lavó con agua y salmuera con una retroextracción de las fases acuosas con éter. La fase orgánica combinada se secó ($MgSO_4$) y se concentró a presión reducida. La cromatografía flash del material crudo en sílice con acetato de etilo al 10% en heptano generó 13,75 g (93%) del compuesto de título como un aceite incoloro. 1H NMR (400 MHz, CLOROFORMO-*d*) mostró una mezcla de epímeros 60:40: δ ppm 2.09 - 2.32 (m, 1 H) 2.20 (s, 6 H) 2.67 - 2.85 (m, 1 H) 3.62 - 3.70 (m, 0.6

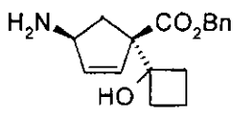
H) 3.85 - 3.92 (m, 0.4 H) 5.16 (2s, 2 H) 5.26 - 5.34 (m, 0.6 H) 5.49 - 5.56 (m, 0.4 H) 5.74 (br. s., 2 H) 5.93 - 6.04 (m, 2 H) 7.30 - 7.42 (m, 5 H). TLC Rf 0,32 y 0,25 (acetato de etilo al 10% en hexano). LC-MS ES+ 296.2.

Etapa 2: (1R,4S)-4-(2,5-dimetil-1H-pirrol-1-il)-1-(1-hidroxiciclobutil)ciclopent-2-en-1-carboxilato de bencilo



A una solución agitada y fría (-78 C) de 6,17 g (20,9 mmol) de (4S)-4-(2,5-dimetil-1H-pirrol-1-il)ciclopent-2-en-1-carboxilato de bencilo (preparación SRT-0233) en 40 mL de THF seco, en Ar, se agregaron lentamente 23,3 mL de una solución de LDA comercial 1,8 M. La solución resultante se calentó a 0 C, se agitó a esa temperatura durante 10 minutos y luego se volvió a enfriar a -78 C para la adición de 2,3 mL (31 mmol) de ciclobutanona. Esta solución se agitó a -78 C durante 1 hora, luego se inactivó a -78 C mediante la adición lenta de una solución de 4,0 mL de HCl 12N en 10 mL de THF. Se agregaron acetato de etilo y exceso de ácido cítrico 1 M, y se dejó que la mezcla se calentara a temperatura ambiente. Luego de la preparación extractiva se realizó cromatografía flash en sílice con acetato de etilo al 25% en heptano para generar 5,55 g (73%) del compuesto del título como un aceite ámbar espeso. ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.44 - 1.56 (m, 1 H) 1.88 - 2.31 (m, 6 H) 2.12 (s, 6 H) 2.27 (dd, *J*=14.7, 7.5 Hz, 1 H) 2.76 (dd, *J*=14.5, 9.0 Hz, 1 H) 5.18 (s, 2 H) 5.26 - 5.32 (m, 1 H) 5.71 (s, 2 H) 6.06 (dd, 1 H) 6.10 (dd, 1 H) 7.30 - 7.39 (m, 5 H). TLC Rf 0,36 (acetato de etilo al 30% en hexano). LC-MS ES+ 366.2.

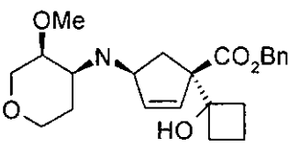
Etapa 3: (1R,4S)-4-amino-1-(1-hidroxiciclobutil)ciclopent-2-en-1-carboxilato de bencilo



Una mezcla de 5,52 g (15,1 mmol) de (1R,4S)-4-(2,5-dimetil-1H-pirrol-1-il)-1-(1-hidroxiciclobutil)ciclopent-2-en-1-carboxilato de bencilo (preparación SRT-0229), 8,20 g (120 mmol) de clorhidrato de hidroxilamina y 7,0 mL de hidroxilamina acuosa al 50% (100 mmol) en 50 mL de metanol se calentó a 68 C durante 8 horas y luego se enfrió. Se agregó suficiente agua para disolver los cristales que se depositaron, y la solución se concentró a presión reducida para retirar metanol. La mezcla resultante se llevó a pH ~10 con NaOH acuoso y luego se extrajo con varias porciones de diclorometano.

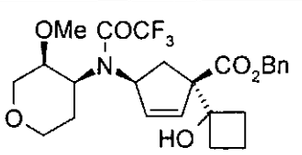
La fase orgánica se secó en Na_2SO_4 y luego se concentró a presión reducida para producir 4,15 g (96%) de la amina del título como un aceite prácticamente incoloro con una pureza suficiente para la reacción posterior. ^{1}H NMR (400 MHz, CLOROFORMO-*d*) δ ppm 1.42 - 1.53 (m, 1 H) 1.85 (dd, 1 H) 1.88 - 2.08 (m, 4 H) 2.19 - 2.27 (m, 1 H) 2.46 (dd, *J*=14.5, 8.3 Hz, 1 H) 3.97 - 4.02 (m, 1 H) 4.70 (s, 1 H) 5.16 (s, 2 H) 5.84 (dd, *J*=5.6, 1.6 Hz, 1 H) 5.98 (dd, *J*=5.6, 2.1 Hz, 1 H) 7.31 - 7.38 (m, 5 H). LC-MS ES+ 288.2.

Etapa 4: 1,5-anhidro-3-{[(1S,4R)-4-[(benciloxi)carbonil]-4-(1-hidroxiciclobutil)ciclopent-2-en-1-il]amino}-2,3-dideoxi-4-O-metil-D-eritro-pentitol



Una solución de 3,83 g (13,3 mmol) de (1R,4S)-4-amino-1-(1-hidroxiciclobutil)ciclopent-2-en-1-carboxilato de bencilo (preparación SRT-0235) y 1,89 g (14,5 mmol) de (3R)-3-metoxitetrahidro-4H-piran-4-ona en 26 mL de diclorometano se agitó con un tamiz molecular 3A activado durante 10 minutos y luego se enfrió a 0° C. Se agregó triacetoxiborohidruro de sodio (3,35 g, 15,8 mmol) en varias porciones durante 10 minutos, y la mezcla se agitó durante 1,5 horas. Se agregó la mezcla turbia a diclorometano y $NaHCO_3$ + NaOH (pH ~14) acuoso, y la fase acuosa se extrajo con varias porciones adicionales de diclorometano. La fase orgánica se secó (Na_2SO_4) y se concentró a presión reducida. La cromatografía flash del residuo en sílice con 3-5% de amoníaco metanólico (7M) en diclorometano generó 3,94 g (74%) del compuesto del título como un aceite amarillo. ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.41 - 1.52 (m, 1 H) 1.55 - 1.64 (m, 1 H) 1.64 - 1.79 (m, 2 H) 1.86 - 2.09 (m, 5 H) 2.19 - 2.29 (m, 1 H) 2.41 (dd, *J*=14.2, 7.7 Hz, 1 H) 2.84 - 2.91 (m, 1 H) 3.17 - 3.44 (m, 4 H) 3.34 (s, 3 H) 3.88 - 3.96 (m, 2 H) 4.00 (dd, *J*=12.3, 4.4 Hz, 1 H) 5.10 - 5.20 (m, 2 H) 5.88 - 5.93 (m, 1 H) 6.00 (dd, *J*=5.6, 1.9 Hz, 1 H) 7.28 - 7.39 (m, 5 H). TLC Rf 0,41 (amoníaco metanólico 7M al 4% en diclorometano). LC-MS ES+ 402.1.

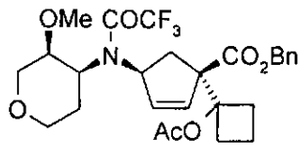
Etapa 5: 1,5-anhidro-3-{[(1S,4R)-4-[(benciloxi)carbonil]-4-(1-hidroxiciclobutil)ciclopent-2-en-1-il](trifluoroacetil)amino}-2,3-dideoxi-4-O-metil-D-eritro-pentitol



A una solución agitada y fría (0 C) de 805 mg (2,00 mmol) de 1,5-anhidro-3-

{[(1S,4R)-4-[(benciloxi)carbonil]-4-(1-hidroxiciclobutil)ciclopent-2-en-1-il]amino}-2,3-dideoxi-4-O-metil-D-eritro-pentitol y 0,87 mL (5,0 mmol) de diisopropiletilamina en 6 mL de diclorometano se agregó por goteo 0,61 mL (4,4 mmol) de anhídrido trifluoroacético. La solución se agitó durante 2 horas y luego se agitó con citrato de sodio acuoso durante 30 minutos. La fase orgánica se separó, se secó (Na_2SO_4) y se concentró a presión reducida para obtener 1,36 g de aceite marrón. Éste se disolvió en 5 mL de metanol y se trató con 2 mL de amoníaco metanólico 7M. Luego de 1 hora, la solución se concentró a presión reducida, y el residuo se sometió a cromatografía en sílice con acetato de etilo al 15-20% en diclorometano para generar 1,11 g (111%) del compuesto del título como un aceite ámbar, manteniendo aún un poco de solvente. ^{1}H NMR (400 MHz, CLOROFORMO-*d*) δ ppm 1.37 - 1.49 (m, 1 H) 1.50 - 1.57 (m, 1 H) 1.78 - 2.00 (m, 3 H) 2.01 - 2.10 (m, 1 H) 2.26 - 2.38 (m, 3 H) 2.40 - 2.53 (m, 1 H) 3.10 (br. s., 0 H) 3.31 (d, *J*=13.0 Hz, 1 H) 3.39 - 3.45 (m, 1 H) 3.43 (s, 3 H) 3.50 (t, *J*=11.4 Hz, 1 H) 3.89 (d, *J*=11.6 Hz, 1 H) 4.06 - 4.14 (m, 1 H) 4.19 (d, *J*=13.0 Hz, 1 H) 5.00 (t, 1 H) 5.14 (d, *J*=12.3 Hz, 1 H) 5.30 (d, *J*=12.3 Hz, 1 H) 5.78 (dd, *J*=5.8, 2.0 Hz, 1 H) 6.12 (dd, *J*=5.8, 2.0 Hz, 1 H) 6.57 (br. s., 1 H) 7.28 - 7.42 (m, 5 H). TLC Rf 0,34 (acetato de etilo al 25% en diclorometano). LC-MS ES+ 498.2.

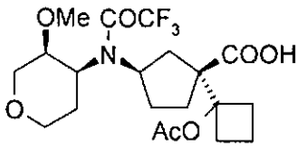
Etapa 6: 3-[{(1S,4R)-4-[1-(acetiloxi)ciclobutil]-4-[(benciloxi)carbonil]ciclopent-2-en-1-il}(trifluoroacetil)amino]-1,5-anhidro-2,3-dideoxi-4-O-metil-D-eritro-pentitol



A una solución agitada de 3,58 g (7,2 mmol) de 1,5-anhidro-3-{[(1S,4R)-4-[(benciloxi)carbonil]-4-(1-hidroxiciclobutil)ciclopent-2-en-1-il](trifluroacetil)amino}-2,3-dideoxi-4-O-metil-D-eritro-pentitol, 1,6 mL (9,2 mmol) de diisopropiletilamina y 100 mg (0,82 mmol) de DMAP en 10 mL de diclorometano se agregó por goteo 5,1 mL (72 mmol) de cloruro de acetilo. La solución se agitó a temperatura ambiente durante 18 horas, luego se enfrió en hielo y se inactivó con $NaHCO_3$ acuoso. La fase acuosa se extrajo con diclorometano adicional, y las fases orgánicas combinadas se secaron (Na_2SO_4) y se concentraron a presión reducida. La cromatografía flash del residuo en sílice con acetato de etilo al 8-10% en diclorometano generó 2,63 g (68%) del compuesto del título como un aceite amarillo viscoso. ^{1}H NMR (400 MHz, CLOROFORMO-*d*) δ ppm 1.35 - 1.48 (m, 1 H) 1.54 - 1.61 (m, 1 H) 1.82 - 1.94 (m, 1 H) 1.88 (s, 3 H) 2.17 - 2.26 (m, 1 H) 2.34 (dd, *J*=14.7, 9.9 Hz, 1 H) 2.43 - 2.64 (m, 5 H)

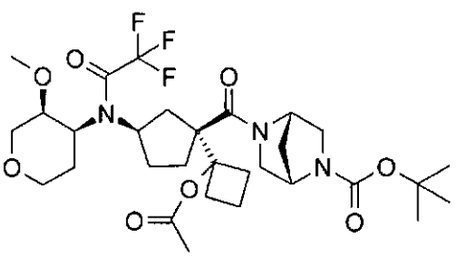
3.32 (d, *J*=12.6 Hz, 1 H) 3.37 - 3.43 (m, 1 H) 3.43 (s, 3 H) 3.46 - 3.55 (m, 1 H) 3.84 - 3.94 (m, 1 H) 4.09 - 4.15 (m, 1 H) 4.19 (d, *J*=13.0 Hz, 1 H) 4.98 - 5.05 (m, 1 H) 5.08 (d, *J*=12.3 Hz, 1 H) 5.23 (d, *J*=12.3 Hz, 1 H) 5.75 (dd, *J*=5.8, 2.0 Hz, 1 H) 6.16 (dd, *J*=5.8, 2.4 Hz, 1 H) 7.28 - 7.43 (m, 5 H). TLC Rf 0,39 (acetato de etilo al 10% en diclorometano). LC-MS ES+ 540.2.

Etapa 7: 3-[{(1R,3S)-3-[1-(acetiloxi)ciclobutil]-3-carboxiciclopentil}(trifluoroacetil)amino]-1,5-anhidro-2,3-dideoxi-4-O-metil-D-eritro-pentitol



Una mezcla de 2,62 g (4,86 mmol) de 3-[{(1S,4R)-4-[1-(acetiloxi)ciclobutil]-4-[(benciloxi)carbonil]ciclopent-2-en-1-il}(trifluoroacetil)amino]-1,5-anhidro-2,3-dideoxi-4-O-metil-D-eritro-pentitol y 750 mg de cada uno de Pt/C al 5% y Pd/C al 5% en 10 mL de ácido acético se agitó rápidamente a 50 psi de gas hidrógeno durante 18 horas y luego se filtró a través de tierra diatomácea para retirar el catalizador. El filtrado se concentró a presión reducida y se agregó tolueno para retirar de manera azeotrópica el ácido acético y así generar 2,25 g (103%) del compuesto del título como una espuma blanca. ^{1}H NMR (400 MHz, CLOROFORMO-*d*) δ ppm 1.50 - 1.71 (m, 3 H) 1.74 - 1.84 (m, 1 H) 2.02 (s, 3 H) 2.04 - 2.17 (m, 1 H) 2.34 - 2.55 (m, 5 H) 2.60 (dd, *J*=14.3, 8.5 Hz, 1 H) 2.66 - 2.81 (m, 2 H) 3.30 (d, *J*=13.0 Hz, 1 H) 3.35 - 3.39 (m, 1 H) 3.42 (s, 3 H) 3.47 - 3.56 (m, 1 H) 3.83 - 3.91 (m, 1 H) 4.13 (dd, *J*=11.6, 4.4 Hz, 1 H) 4.16 - 4.23 (m, 1 H) 4.26 - 4.38 (m, 1 H). LC-MS ES+ 452.1.

Etapa 8: 3-{[(1R,3S)-3-[1-(acetiloxi)ciclobutil]-3-{[(1S,4S)-5-(ter-butoxicarbonil)-2,5-diazabiciclo[2.2.1]hept-2-il]carbonil}ciclopentil](trifluoroacetil)amino}-1,5-anhidro-2,3-dideoxi-4-O-metil-D-eritro-pentitol

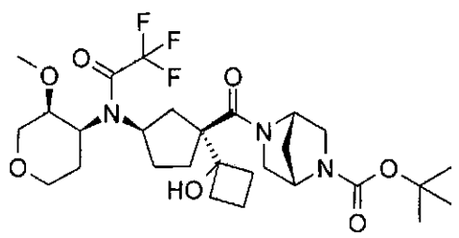


Una solución agitada de 1,42 g (3,15 mmol) de 3-[{(1R,3S)-3-[1-(acetiloxi)ciclobutil]-3-carboxiciclopentil}(trifluoroacetil)amino]-1,5-anhidro-2,3-dideoxi-4-O-metil-D-eritro-pentitol en 6 mL de diclorometano se trató en argón con 6,5 mL de una solución de diclorometano 2M de cloruro de oxalilo y 2 gotas de DMF seco. Luego

de 2 horas, la solución se secó a presión reducida para producir el cloruro de ácido como una espuma amarilla.

Este material se disolvió en 8 mL de diclorometano. A 6 mL de la solución agitada se agregaron 562 mg (2,84 mmol) de (1S,4S)-(-)-2-Boc-2,5-diazabiciclo[2.2.1]heptano y 1,2 mL (6,9 mmol) de diisopropiletilamina. La mezcla de reacción se agitó a temperatura ambiente durante 18 horas y luego se dividió en diclorometano y ácido cítrico acuoso 1M. La fase orgánica se secó (Na_2SO_4) y se concentró a presión reducida. La cromatografía flash del residuo en sílice con acetato de etilo al 40-50% en diclorometano generó 1,44 g (97%) del compuesto del título como una espuma blanca. ^{1}H NMR (400 MHz, CLOROFORMO-*d*) δ ppm 1.34 - 1.62 (m, 12 H) 1.73 - 1.88 (m, 2 H) 1.88 - 2.27 (m, 7 H) 2.29 - 2.41 (m, 1 H) 2.40 - 2.65 (m, 4 H) 2.66 - 2.80 (m, 1 H) 3.27 - 3.64 (m, 9 H) 3.81 - 3.89 (m, 1 H) 4.08 - 4.24 (m, 2 H) 4.37 - 4.60 (m, 2 H) 4.85 - 4.94 (m, 1 H). TLC Rf 0.36 (1:1 de acetato de etilo en diclorometano). LC-MS ES+ 632.3.

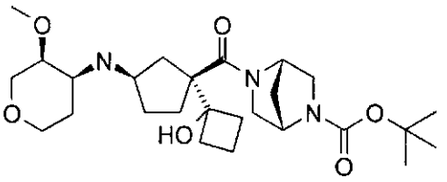
Etapa 9: 1,5-anhidro-3-{[(1R,3S)-3-{[(1S,4S)-5-(ter-butoxicarbonil)-2,5-diazabiciclo[2.2.1]hept-2-il]carbonil}-3-(1-hidroxiciclobutil)ciclopentil](trifluoroacetil)amino}-2,3-dideoxi-4-O-metil-D-eritro-pentitol



Una mezcla de 1,43 g (2,26 mmol) de 3-{[(1R,3S)-3-[1-(acetiloxi)ciclobutil]-3-{[(1S,4S)-5-(ter-butoxicarbonil)-2,5-diazabiciclo[2.2.1]hept-2-il]carbonil}ciclopentil](trifluoroacetil)amino}-1,5-anhidro-2,3-dideoxi-4-O-metil-D-eritro-pentitol y 1,60 g (11,6 mmol) de carbonato de potasio en polvo en 8 mL de metanol se agitó a temperatura ambiente durante 18 horas y luego se dividió en diclorometano y salmuera con suficiente agua para disolver sólidos. La fase orgánica se secó (Na_2SO_4) y se concentró a presión reducida. La cromatografía flash del residuo en sílice con acetato generó 1,33 g (100%) del compuesto del título como una espuma blanca. ^{1}H NMR (400 MHz, CLOROFORMO-*d*) δ ppm 1.34 - 1.62 (m, 10 H) 1.66 - 2.93 (m, 15 H) 3.20 - 3.63 (m, 8 H) 3.66 - 4.03 (m, 3 H) 4.06 - 4.24 (m, 3 H) 4.25 - 4.65 (m, 2 H) 4.68 - 5.29 (m, 1 H). TLC Rf 0.33 (EtOAc). LC-MS ES+ 590.3.

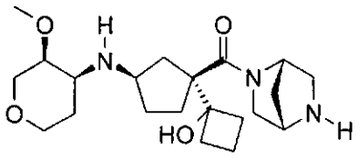
Etapa 10: 1,5-anhidro-3-{[(1R,3S)-3-{[(1S,4S)-5-(ter-butoxicarbonil)-2,5-diazabiciclo[2.2.1]hept-2-il]carbonil}-3-(1-hidroxiciclobutil)ciclopentil]amino}-2,3-dideoxi-

4-O-metil-D-eritro-pentitol



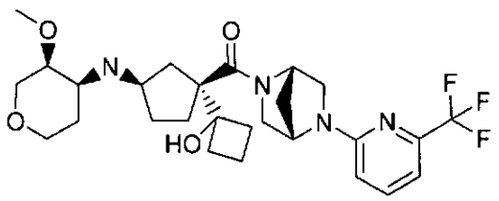
Una mezcla de 1,31 g (2,23 mmol) de 1,5-anhidro-3-{[(1R,3S)-3-{[(1S,4S)-5-(ter-butoxicarbonil)-2,5-diazabiciclo[2.2.1]hept-2-il]carbonil}-3-(1-hidroxiciclobutil)ciclopentil](trifluoroacetil)amino}-2,3-dideoxi-4-O-metil-D-eritro-pentitol y 860 mg (23 mmol) de borohidruro de sodio en 6,3 mL de etanol se agitó a temperatura ambiente durante 18 horas y luego se dividió en agua y diclorometano. La fase acuosa se extrajo con diclorometano adicional, y la fase orgánica combinada se secó (Na_2SO_4) y se concentró a presión reducida. La cromatografía flash en sílice con 6-15% de metanol en diclorometano generó 1,08 g (98%) del compuesto del título como una espuma blanca. ^{1}H NMR (400 MHz, CLOROFORMO-*d*) δ ppm 1.42 - 1.47 (m, 9 H) 1.56 - 2.35 (m, 14 H) 2.72 (br. s., 1 H) 3.11 - 3.68 (m, 10 H) 3.90 - 3.98 (m, 1 H) 4.08 (dd, *J*=12.6, 2.7 Hz, 1 H) 4.38 - 4.58 (m, 1 H) 4.84 - 5.16 (m, 1 H). LC-MS ES+ 494.3. HRMS calculado para $C_{26}H_{43}N_3O_6$: 494.3230; encontrado: 494,3260.

Etapa 11: Diclorhidrato de 1,5-anhidro-2,3-dideoxi-3-{[(1R,3S)-3-[(1S,4S)-2,5-diazabiciclo[2.2.1]hept-2-ilcarbonil]-3-(1-hidroxiciclobutil)ciclopentil]amino}-4-O-metil-D-eritro-pentitol



A 902 mg (1,827 mmol) de 1,5-anhidro-3-{[(1R,3S)-3-{[(1S,4S)-5-(ter-butoxicarbonil)-2,5-diazabiciclo[2.2.1]hept-2-il]carbonil}-3-(1-hidroxiciclobutil)ciclopentil]amino}-2,3-dideoxi-4-O-metil-D-eritro-pentitol se agregaron 10 mL de HCl 4M en dioxano y unas gotas de metanol suficiente para generar una solución transparente. La solución se agitó a temperatura ambiente durante 45 minutos y luego se concentró a presión reducida para producir 973 mg de la sal intermediaria como una espuma. ^{1}H NMR (400 MHz, MeOD) δ ppm 1.57 - 1.70 (m, 1 H) 1.73 - 1.93 (m, 4 H) 1.93 - 2.10 (m, 4 H) 2.14 - 2.28 (m, 2 H) 2.29 - 2.44 (m, 3 H) 2.46 - 2.59 (m, 2 H) 3.35 - 3.77 (m, 12 H) 3.98 (dd, *J*=11.6, 4.4 Hz, 1 H) 4.26 (d, *J*=13.3 Hz, 1 H) 4.45 (s, 1 H) 5.21 (br. s., 1 H). LC-MS ES+ 394.2.

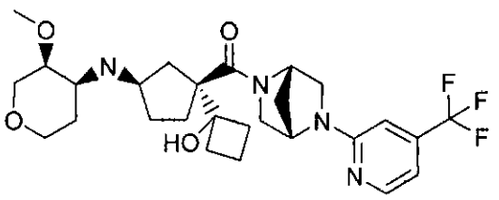
Ejemplo 45



1,5-anhidro-2,3-dideoxi-3-{[(1R,3S)-3-(1-hidroxiciclobutil)-3-({(1S,4S)-5-[6-(trifluorometil)piridin-2-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metil-D-eritro-pentitol

Una solución de 93 mg (0,20 mmol) de diclorhidrato de 1,5-anhidro-2,3-dideoxi-3-{[(1R,3S)-3-[(1S,4S)-2,5-diazabiciclo[2.2.1]hept-2-ilcarbonil]-3-(1-hidroxiciclobutil)ciclopentil]amino}-4-O-metil-D-eritro-pentitol, 91 mg (0,49 mmol) de 2-cloro-6-trifluorometilpiridina y 0,14 mL (0,80 mmol) de diisopropiletilamina en 0,5 mL de DMSO se calentó a 80 C durante 18 horas y luego se enfrió y dividió en acetato de etilo y agua. La fase orgánica se secó (Na_2SO_4) y se concentró a presión reducida. El material crudo se purificó mediante RP-HPLC preparativa con acetonitrilo-agua como fase móvil que contenía TFA al 0,05%. ^{1}H NMR (400 MHz, CLOROFORMO-*d*) δ ppm 1.46 - 2.52 (m, 16 H) 3.26 - 3.54 (m, 8 H) 3.53 - 3.92 (m, 4 H) 4.02 (dd, *J*=11.8, 4.3 Hz, 1 H) 4.22 (d, *J*=13.0 Hz, 1 H) 5.01 (d, *J*=14.3 Hz, 2 H) 6.47 (d, *J*=8.5 Hz, 1 H) 6.93 (d, *J*=7.5 Hz, 1 H) 7.56 (t, *J*=8.0 Hz, 1 H). HRMS calculado para $C_{27}H_{37}N_4O_4F_3$: 539.2845; encontrado: 539,2894.

Ejemplo 46

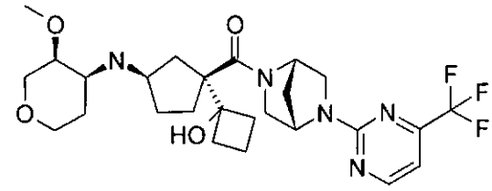


1,5-anhidro-2,3-dideoxi-3-{[(1R,3S)-3-(1-hidroxiciclobutil)-3-({(1S,4S)-5-[4-(trifluorometil)piridin-2-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metil-D-eritro-pentitol

El compuesto del título se preparó de modo análogo al que se describe en el Ejemplo de preparación 45. ^{1}H NMR (400 MHz, CLOROFORMO-*d*) δ ppm 1.57 - 2.31 (m, 14 H) 2.33 - 2.47 (m, 2 H) 2.49 - 2.62 (m, 1 H) 3.28 - 3.54 (m, 7 H) 3.57 - 3.91 (m, 4 H) 4.02 (dd, *J*=11.8, 4.3 Hz, 1 H) 4.22 (d, *J*=13.3 Hz, 1 H) 5.07 (br. s., 1 H) 5.25 (s, 1 H) 6.88 - 6.96 (m, 2 H) 8.14 (d, *J*=6.5 Hz, 1 H). HRMS calculado para C27H37N4O4F3: 539.2845; encontrado: 539,2894.

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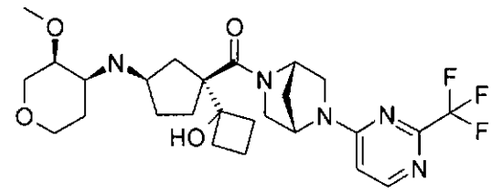
Ejemplo 47



1,5-anhidro-2,3-dideoxi-3-{[(1R,3S)-3-(1-hidroxiciclobutil)-3-({(1S,4S)-5-[4-(trifluorometil)pirimidin-2-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metil-D-eritro-pentitol

El compuesto del título se preparó de modo análogo al que se describe en el Ejemplo de preparación 45. ^{1}H NMR (400 MHz, CLOROFORMO-*d*) δ ppm 1.65 - 2.51 (m, 15 H) 2.52 - 2.64 (m, 1 H) 3.35 (s, 3 H) 3.44 (d, *J*=13.7 Hz, 1 H) 3.49 - 3.98 (m, 7 H) 4.19 (dd, *J*=11.4, 4.6 Hz, 1 H) 4.35 (d, *J*=14.0 Hz, 1 H) 5.07 - 5.48 (m, 2 H) 7.16 (d, *J*=6.5 Hz, 1 H) 8.49 (d, *J*=6.5 Hz, 1 H). HRMS calculado para C26H36N5O4F3: 540.2797; encontrado: 540,2812.

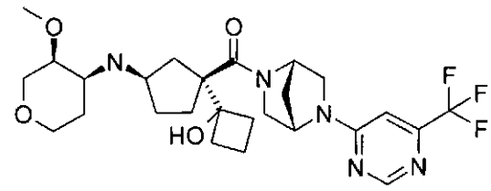
Ejemplo 48



1,5-anhidro-2,3-dideoxi-3-{[(1R,3S)-3-(1-hidroxiciclobutil)-3-({(1S,4S)-5-[2-(trifluorometil)pirimidin-4-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metil-D-eritro-pentitol

El compuesto del título se preparó de modo análogo al que se describe en el Ejemplo de preparación 45. ^{1}H NMR (400 MHz, CLOROFORMO-*d*) δ ppm 1.57 - 2.53 (m, 16 H) 3.31 (d, *J*=13.3 Hz, 1 H) 3.35 - 3.79 (m, 10 H) 4.03 (dd, *J*=11.4, 4.3 Hz, 1 H) 4.23 (d, *J*=12.6 Hz, 1 H) 5.11 (s, 1 H) 5.29 (br. s., 1 H) 6.23 - 6.75 (m, 2 H) 8.30 (d, *J*=6.1 Hz, 1 H). HRMS calculado para C26H36N5O4F3: 540.2797; encontrado: 540,2891.

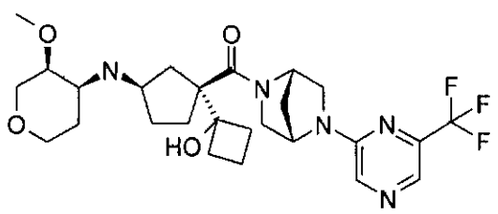
Ejemplo 49



1,5-anhidro-2,3-dideoxi-3-{[(1R,3S)-3-(1-hidroxiciclobutil)-3-({(1S,4S)-5-[6-(trifluorometil)pirimidin-4-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metil-D-eritro-pentitol

El compuesto del título se preparó de modo análogo al que se describe en el Ejemplo de preparación 45. ^{1}H NMR (400 MHz, CLOROFORMO-*d*) δ ppm 1.56 - 2.35 (m, 14 H) 2.36 - 2.44 (m, 1 H) 2.45 - 2.54 (m, 1 H) 3.32 (d, *J*=13.3 Hz, 1 H) 3.36 - 3.92 (m, 10 H) 4.04 (dd, *J*=12.3, 4.1 Hz, 1 H) 4.24 (d, *J*=13.0 Hz, 1 H) 5.15 (s, 1 H) 5.23 - 5.30 (m, 1 H) 6.45 - 7.05 (m, 3 H) 8.67 (s, 1 H). HRMS calculado para C26H36N5O4F3: 540.2797; encontrado: 540,2830.

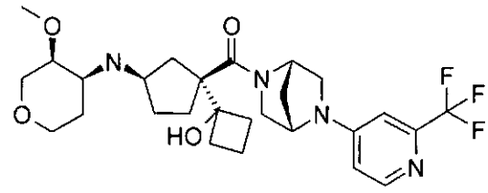
Ejemplo 50



1,5-anhidro-2,3-dideoxi-3-{[(1R,3S)-3-(1-hidroxiciclobutil)-3-({(1S,4S)-5-[6-(trifluorometil)pirazin-2-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metil-D-eritro-pentitol

Una solución de 93 mg (0,20 mmol) de diclorhidrato de 1,5-anhidro-2,3-dideoxi-3-{[(1R,3S)-3-[(1S,4S)-2,5-diazabiciclo[2.2.1]hept-2-ilcarbonil]-3-(1-hidroxiciclobutil)ciclopentil]amino}-4-O-metil-D-eritro-pentitol, 121 mg (0,442 mmol) de 2-iodo-6-trifluorometilpirazina, 326 mg (1,0 mmol) de carbonato de cesio, 24 mg (40 umol) de XantPhos y 16 mg (28 umol) de tris(dibencilidenacetona) paladio (0) en 0,8 mL de dioxano y 0,4 mL de DMSO se calentó a 80 C en argón durante 18 horas, luego se enfrió y se dividió en acetato de etilo y agua. La fase orgánica se secó (Na_2SO_4) y se concentró a presión reducida. La cromatografía flash del residuo en sílice con 0-2-4% de amoníaco metanólico y 3% de metanol en diclorometano generó 89 mg (82%) del compuesto del título. ^{1}H NMR (400 MHz, CLOROFORMO-*d*) δ ppm 1.51 - 2.40 (m, 16 H) 2.65 - 2.74 (m, 1 H) 3.09 - 3.49 (m, 10 H) 3.54 (d, *J*=9.6 Hz, 1 H) 3.61 - 3.80 (m, 2 H) 3.88 - 3.96 (m, 1 H) 4.06 (dd, *J*=12.5, 2.9 Hz, 1 H) 4.96 (br. s., 1 H) 5.21 (br. s., 1 H) 8.02 (s, 1 H) 8.15 (s, 1 H). HRMS calculado para C26H36N5O4F3: 540.2797; encontrado: 540,2896.

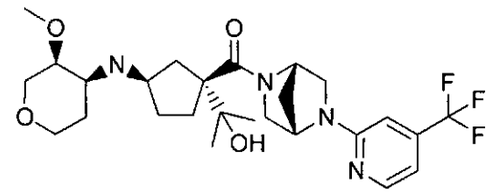
Ejemplo 51



1,5-anhidro-2,3-dideoxi-3-{[(1R,3S)-3-(1-hidroxiciclobutil)-3-({(1S,4S)-5-[2-(trifluorometil)piridin-4-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metil-D-eritro-pentitol

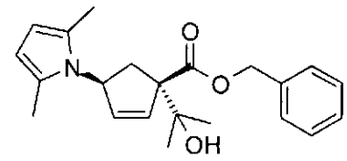
El compuesto del título se preparó de modo análogo al que se describe en el Ejemplo 45. ^{1}H NMR (400 MHz, CLOROFORMO-*d*) δ ppm 1.51 - 2.40 (m, 18 H) 2.65 - 2.73 (m, 1 H) 3.04 - 3.47 (m, 8 H) 3.59 (d, *J*=8.5 Hz, 1 H) 3.70 (d, *J*=9.9 Hz, 1 H) 3.86 - 3.95 (m, 1 H) 4.05 (dd, *J*=12.3, 2.4 Hz, 1 H) 4.52 (s, 1 H) 5.17 (br. s., 1 H) 6.48 (br. s., 1 H) 6.72 (br. s., 1 H) 8.26 (d, *J*=5.8 Hz, 1 H). HRMS calculado para C27H37N4O4F3: 539.2845; encontrado: 539,2979.

Ejemplo 52



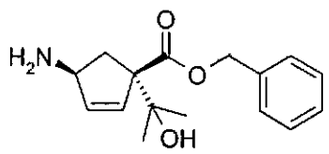
1,5-anhidro-2,3-dideoxi-3-{[3-(1-hidroxi-1-metiletil)-3-({5-[4-(trifluorometil)piridin-2-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metilpentitol

Etapa 1: 4-(2,5-dimetil-1H-pirrol-1-il)-1-(1-hidroxi-1-metiletil)ciclopent-2-en-1-carboxilato de bencilo



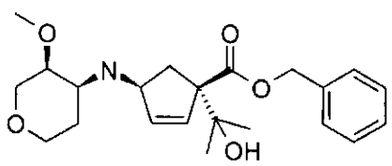
El compuesto del título se preparó de modo análogo al que se describe en el Ejemplo 45, Etapa 2 anterior. ^{1}H NMR (400 MHz, CLOROFORMO-*d*) δ ppm 1.18 (s, 3 H) 1.22 (s, 3 H) 2.11 (s, 6 H) 2.22 (dd, *J*=14.7, 7.5 Hz, 1 H) 2.88 (dd, *J*=14.7, 8.5 Hz, 1 H) 3.43 (s, 1 H) 5.15 - 5.23 (m, 2 H) 5.24 - 5.31 (m, 1 H) 5.71 (s, 2 H) 5.99 (dd, 1 H) 6.03 (dd, 1 H) 7.30 - 7.40 (m, 5 H). TLC Rf 0,29 (acetato de etilo al 30% en hexano). LC-MS ES+ 354.2.

Etapa 2 4-amino-1-(1-hidroxi-1-metiletil)ciclopent-2-en-1-carboxilato de bencilo



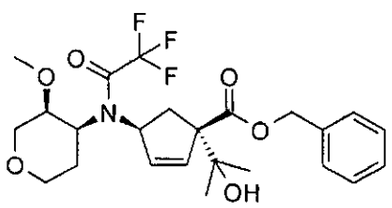
El compuesto del título se preparó de modo análogo al que se describe en el Ejemplo 45, Etapa 3 anterior. ^{1}H NMR (400 MHz, CLOROFORMO-*d*) δ ppm 1.11 (s, 3 H) 1.14 (s, 3 H) 1.81 (dd, *J*=14.5, 4.9 Hz, 1 H) 1.85 - 1.92 (m, 1 H) 2.67 (dd, *J*=14.3, 8.2 Hz, 1 H) 3.97 - 4.03 (m, 1 H) 5.18 (s, 2 H) 5.83 (dd, 1 H) 5.89 (dd, 1 H) 7.32 - 7.42 (m, 5 H). LC-MS ES+ 276.2.

Etapa 3 1,5-anhidro-3-({4-[(benciloxi)carbonil]-4-(1-hidroxi-1-metiletil)ciclopent-2-en-1-il}amino)-2,3-dideoxi-4-O-metilpentitol



El compuesto del título se preparó de modo análogo al que se describe en el Ejemplo 45, Etapa 4 anterior. ^{1}H NMR (400 MHz, CLOROFORMO-*d*) δ ppm 1.11 (s, 3 H) 1.15 (s, 3 H) 1.41 - 1.66 (m, 2 H) 1.68 - 1.80 (m, 1 H) 1.87 - 1.94 (m, 1 H) 2.56 - 2.65 (m, 1 H) 2.82 - 2.89 (m, 1 H) 3.24 - 3.46 (m, 7 H) 3.87 - 3.97 (m, 2 H) 3.98 - 4.07 (m, 1 H) 5.11 - 5.21 (m, 2 H) 5.84 - 5.97 (m, 2 H) 7.30 - 7.41 (m, 5 H). TLC Rf 0,34 (amoníaco metanólico al 4% en diclorometano). LC-MS ES+ 390.2.

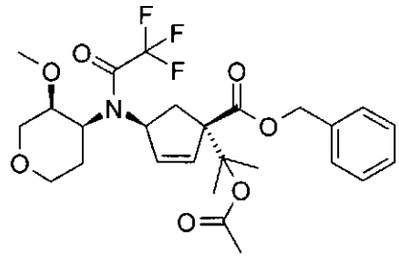
Etapa 4: 1,5-anhidro-3-[{4-[(benciloxi)carbonil]-4-(1-hidroxi-1-metiletil)ciclopent-2-en-1-il}(trifluoroacetil)amino]-2,3-dideoxi-4-O-metilpentitol



El compuesto del título se preparó de modo análogo al que se describe en el Ejemplo 45, Etapa 5 anterior. ^{1}H NMR (400 MHz, CLOROFORMO-*d*) δ ppm 1.35 - 1.75 (m, 2 H) 1.78 - 2.08 (m, 4 H) 2.24 - 2.54 (m, 4 H) 3.31 (d, *J*=12.6 Hz, 1 H) 3.38 - 3.45 (m, 2 H) 3.43 (s, 3 H) 3.45 - 3.55 (m, 1 H) 3.84 - 3.94 (m, 1 H) 4.07 - 4.14 (m, 1 H) 4.19 (d, *J*=13.0 Hz, 1 H) 4.95 - 5.05 (m, 1 H) 5.14 (d, *J*=12.3 Hz, 1 H) 5.31 (d, 1 H) 5.78 (dd, *J*=5.6, 2.2 Hz, 1 H) 6.12 (dd, *J*=5.8, 2.4 Hz, 1 H) 7.27 - 7.44 (m, 5 H). Rf ~0,34 (acetato de etilo al 25% en diclorometano). LC-MS ES+ 498.2.

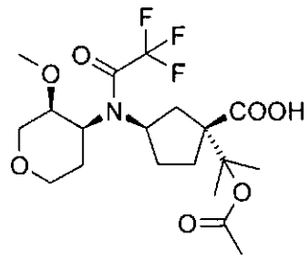
Etapa 5: 3-[{4-[1-(acetiloxi)-1-metiletil]-4-[(benciloxi)carbonil]ciclopent-2-en-1-

il}(trifluoroacetil)amino]-1,5-anhidro-2,3-dideoxi-4-O-metilpentitol



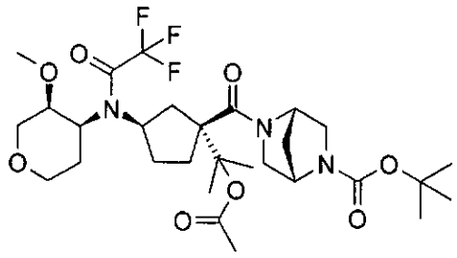
El compuesto del título se preparó de modo análogo al que se describe en el Ejemplo 45, Etapa 6 anterior. ^{1}H NMR (400 MHz, CLOROFORMO-*d*) δ ppm 1.49 (s, 3 H) 1.53 - 1.61 (m, 4 H) 1.82 - 1.86 (m, 3 H) 2.38 - 2.57 (m, 2 H) 3.32 (d, *J*=13.0 Hz, 1 H) 3.37 - 3.44 (m, 3 H) 3.45 - 3.56 (m, 2 H) 3.84 - 3.95 (m, 1 H) 4.05 - 4.23 (m, 2 H) 4.93 - 5.04 (m, 1 H) 5.08 - 5.15 (m, 1 H) 5.26 - 5.36 (m, 3 H) 6.11 (dd, *J*=5.8, 2.4 Hz, 1 H) 7.28 - 7.42 (m, 5 H). TLC Rf 0,29 (acetato de etilo al 40% en hexano). LC-MS ES+ 550.2 para M+Na.

Etapa 6: 3-[{3-[1-(acetiloxi)-1-metiletil]-3-carboxiciclopentil}(trifluoroacetil)amino]-1,5-anhidro-2,3-dideoxi-4-O-metilpentitol



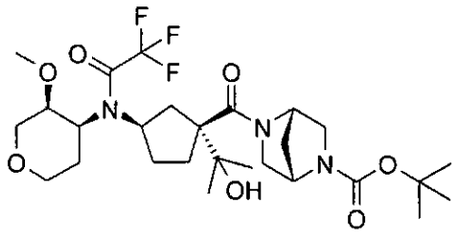
El compuesto del título se preparó de modo análogo al que se describe en el Ejemplo 45, Etapa 7 anterior. ^{1}H NMR (400 MHz, CLOROFORMO-*d*) δ ppm 0.86 (ninguno, 1 H) 1.51 - 1.91 (m, 10 H) 2.02 - 2.04 (m, 3 H) 2.24 - 2.54 (m, 3 H) 3.31 (d, *J*=13.0 Hz, 1 H) 3.37 (br. s., 1 H) 3.41 - 3.46 (m, 3 H) 3.46 - 3.56 (m, 1 H) 3.82 - 3.91 (m, 1 H) 4.08 - 4.16 (m, 1 H) 4.16 - 4.23 (m, 1 H) 4.25 - 4.39 (m, 1 H). LC-MS ES+ 440.2.

Etapa 7: 3-[(3-[1-(acetiloxi)-1-metiletil]-3-{[5-(ter-butoxicarbonil)-2,5-diazabiciclo[2.2.1]hept-2-il]carbonil}ciclopentil)(trifluoroacetil)amino]-1,5-anhidro-2,3-dideoxi-4-O-metilpentitol



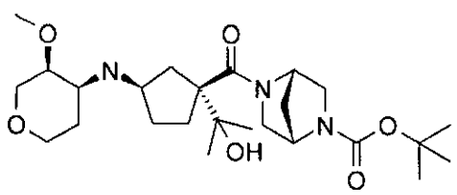
El compuesto del título se preparó de modo análogo al que se describe en el Ejemplo 45, Etapa 8 anterior. ^{1}H NMR (400 MHz, CLOROFORMO-*d*) δ ppm 1.35 - 1.51 (m, 9 H) 1.54 - 1.66 (m, 6 H) 1.72 - 1.87 (m, 2 H) 1.97 - 2.33 (m, 7 H) 2.36 - 2.65 (m, 2 H) 3.25 - 3.68 (m, 9 H) 3.80 - 3.90 (m, 1 H) 4.06 - 4.25 (m, 2 H) 4.34 - 4.64 (m, 2 H) 4.88 - 4.99 (m, 1 H). TLC Rf 0.38. LC-MS ES+ 642.3 (M+Na).

Etapa 8: 1,5-anhidro-3-{[3-{[5-(ter-butoxicarbonil)-2,5-diazabiciclo[2.2.1]hept-2-il]carbonil}-3-(1-hidroxi-1-metiletil)ciclopentil](trifluoroacetil)amino}-2,3-dideoxi-4-O-metilpentitol



El compuesto del título se preparó de modo análogo al que se describe en el Ejemplo 45, Etapa 9 anterior. ^{1}H NMR (400 MHz, CLOROFORMO-*d*) δ ppm 1.08 - 1.28 (m, 5 H) 1.36 - 2.77 (m, 18 H) 3.25 - 3.57 (m, 8 H) 3.68 - 3.91 (m, 2 H) 4.06 - 4.24 (m, 2 H) 4.37 - 4.73 (m, 2 H) 4.82 - 5.00 (m, 1 H). TLC Rf 0,30 (MeOH al 2% en acetato de etilo). LC-MS ES+ 578.3.

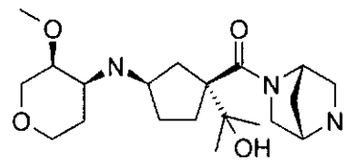
Etapa 9: 1,5-anhidro-3-{[3-{[5-(ter-butoxicarbonil)-2,5-diazabiciclo[2.2.1]hept-2-il]carbonil}-3-(1-hidroxi-1-metiletil)ciclopentil]amino}-2,3-dideoxi-4-O-metilpentitol



El compuesto del título se preparó de modo análogo al que se describe en el Ejemplo 45, Etapa 10. ^{1}H NMR (400 MHz, CLOROFORMO-*d*) δ ppm 1.10 - 1.26 (m, 6 H) 1.37 - 1.90 (m, 16 H) 2.23 - 2.52 (m, 2 H) 2.63 - 2.74 (m, 1 H) 3.10 - 3.72 (m, 10 H) 3.84 - 3.97 (m, 1 H) 4.03 - 4.12 (m, 1 H) 4.34 - 4.62 (m, 1 H) 4.80 - 4.99 (m, 1 H). TLC

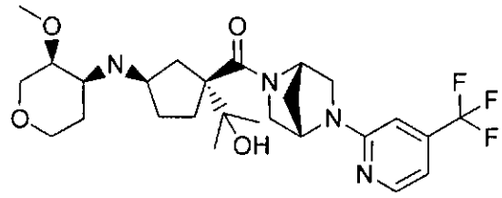
Rf 0,19 (amoníaco metanólico al 4% en diclorometano). HRMS calculado para C25H43N3O6: 482.3230; encontrado: 482,3276.

Etapa 10 1,5-anhidro-2,3-dideoxi-3-{[3-(2,5-diazabiciclo[2.2.1]hept-2-ilcarbonil)-3-(1-hidroxi-1-metiletil)ciclopentil]amino}-4-O-metilpentitol



El compuesto del título se preparó de modo análogo al que se describe en el Ejemplo 45, Etapa 11 anterior. ^{1}H NMR (400 MHz, CD3OD) δ ppm 1.16 (s, 3 H) 1.23 - 1.25 (m, 3 H) 1.62 - 2.34 (m, 7 H) 2.66 (br. s., 2 H) 3.33 - 3.68 (m, 14 H) 3.98 (dd, *J*=11.8, 4.6 Hz, 1 H) 4.26 (d, *J*=13.3 Hz, 1 H) 4.44 (s, 1 H). LC-MS ES+ 382.3.

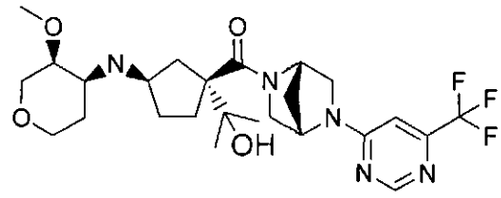
Ejemplo 52



1,5-anhidro-2,3-dideoxi-3-{[3-(1-hidroxi-1-metiletil)-3-({5-[4-(trifluorometil)piridin-2-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metilpentitol

El compuesto del título se preparó de modo análogo al que se describe en el Ejemplo 45. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.00 - 1.20 (m, 6 H) 1.48 - 1.60 (m, 1 H) 1.65 - 2.47 (m, 8 H) 3.13 - 3.22 (m, 1 H) 3.23 - 3.54 (m, 8 H) 3.55 - 3.64 (m, 1 H) 3.80 - 3.90 (m, 1 H) 4.08 - 4.16 (m, 1 H) 4.87 - 5.02 (m, 1 H) 5.15 - 5.26 (m, 1 H) 6.84 (d, *J*=5.1 Hz, 1 H) 8.28 (d, *J*=5.5 Hz, 1 H). HRMS calculado para C26H37N4O4F3: 527.2845; encontrado: 527,2939.

Ejemplo 53

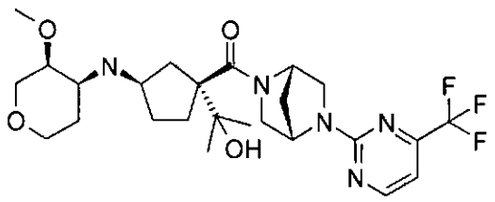


1,5-anhidro-2,3-dideoxi-3-{[3-(1-hidroxi-1-metiletil)-3-({5-[6-(trifluorometil)pirimidin-4-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metilpentitol

El compuesto del título se preparó de modo análogo al que se describe en el Ejemplo 45. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.92 - 1.19 (m, 6 H) 1.48 - 1.62 (m, 1

H) 1.64 - 2.47 (m, 8 H) 3.09 - 3.68 (m, 10 H) 3.81 - 3.91 (m, 1 H) 4.06 - 4.18 (m, 1 H) 4.87 - 5.04 (m, 1 H) 5.09 - 5.33 (m, 1 H) 8.29 - 8.64 (m, 2 H). HRMS calculado para C25H36N5O4F3: 528.2797; encontrado: 528,2812.

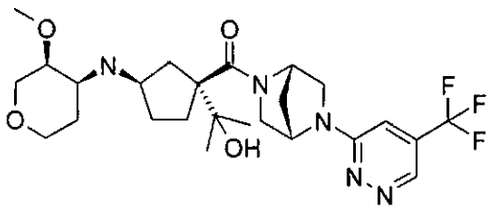
Ejemplo 54



1,5-anhidro-2,3-dideoxi-3-{[3-(1-hidroxi-1-metiletil)-3-({5-[4-(trifluorometil)pirimidin-2-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metilpentitol

El compuesto del título se preparó de modo análogo al que se describe en el Ejemplo 45. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.99 - 1.20 (m, 6 H) 1.45 - 1.64 (m, 1 H) 1.63 - 2.18 (m, 7 H) 2.25 - 2.47 (m, 2 H) 3.13 - 3.65 (m, 10 H) 3.78 - 3.91 (m, 1 H) 4.12 (dd, 1 H) 4.87 - 5.04 (m, 2 H) 5.20 (br. s., 1 H) 8.67 (d, *J*=3.8 Hz, 1 H). HRMS calculado para C25H36N5O4F3: 528.2797; encontrado: 528,2856.

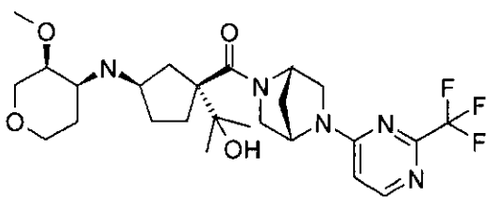
Ejemplo 55



1,5-anhidro-2,3-dideoxi-3-{[3-(1-hidroxi-1-metiletil)-3-({5-[5-(trifluorometil)piridazin-3-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metilpentitol

El compuesto del título se preparó de modo análogo al que se describe en el Ejemplo 45. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.87 - 1.20 (m, 7 H) 1.49 - 2.46 (m, 10 H) 3.16 - 3.73 (m, 10 H) 3.79 - 3.89 (m, 1 H) 4.08 - 4.17 (m, 1 H) 5.20 - 5.31 (m, 1 H) 8.30 - 8.61 (m, 2 H) 8.84 (s, 1 H). HRMS calculado para C25H36N5O4F3: 528.2797; encontrado: 528,2863.

Ejemplo 56



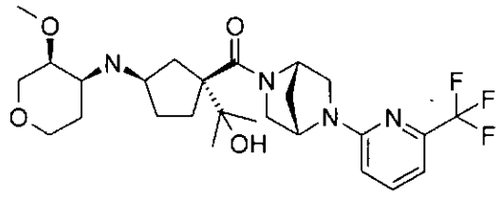
1,5-anhidro-2,3-dideoxi-3-{[3-(1-hidroxi-1-metiletil)-3-({5-[2-(trifluorometil)pirimidin-4-il]-

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2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metilpentitol

El compuesto del título se preparó de modo análogo al que se describe en el Ejemplo 45. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.96 - 1.20 (m, 6 H) 1.45 - 2.48 (m, 9 H) 3.08 - 3.66 (m, 10 H) 3.80 - 3.89 (m, 1 H) 4.08 - 4.17 (m, 1 H) 4.85 - 5.11 (m, 1 H) 5.16 - 5.29 (m, 1 H) 8.27 - 8.34 (s, 1 H). HRMS calculado para C25H36N5O4F3: 528.2797; encontrado: 528,2927.

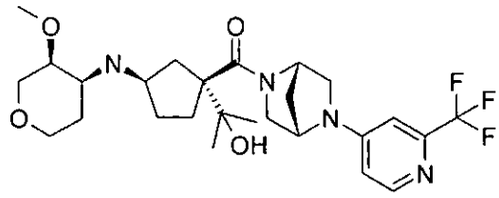
Ejemplo 57



1,5-anhidro-2,3-dideoxi-3-{[3-(1-hidroxi-1-metiletil)-3-({5-[6-(trifluorometil)piridin-2-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metilpentitol

El compuesto del título se preparó de modo análogo al que se describe en el Ejemplo 45. ^{1}H NMR (400 MHz, CLOROFORMO-d) δ ppm 0.82 - 1.37 (m, 6 H) 1.64 - 2.67 (m, 10 H) 3.19 - 3.78 (m, 11 H) 3.91 - 4.08 (m, 1 H) 4.15 - 4.28 (m, 1 H) 4.93 - 5.09 (m, 1 H) 6.40 - 6.54 (m, 1 H) 6.92 (d, J=7.2 Hz, 1 H) 7.55 (t, J=8.0 Hz, 1 H). HRMS calculado para C26H37N4O4F3: 527.2845; encontrado: 527,2869.

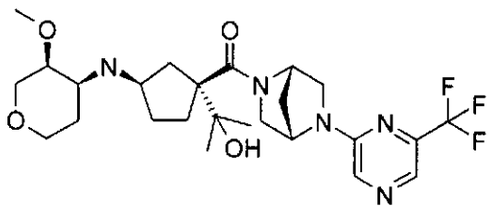
Ejemplo 58



1,5-anhidro-2,3-dideoxi-3-{[3-(1-hidroxi-1-metiletil)-3-({5-[2-(trifluorometil)piridin-4-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metilpentitol

El compuesto del título se preparó de modo análogo al que se describe en el Ejemplo 45. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.99 - 1.19 (m, 6 H) 1.47 - 1.62 (m, 1 H) 1.64 - 2.46 (m, 9 H) 3.08 - 3.68 (m, 11 H) 3.80 - 3.91 (m, 1 H) 4.07 - 4.18 (m, 1 H) 4.75 - 5.28 (m, 2 H) 8.24 (d, J=5.8 Hz, 1 H) 8.30 - 8.77 (m, 2 H). HRMS calculado para C26H37N4O4F3: 527.2845; encontrado: 527,2943.

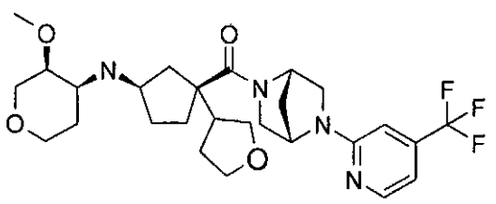
Ejemplo 59



1,5-anhidro-2,3-dideoxi-3-{[3-(1-hidroxi-1-metiletil)-3-({5-[6-(trifluorometil)pirazin-2-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metilpentitol

El compuesto del título se preparó de modo análogo al que se describe en el Ejemplo 50. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.99 - 1.19 (m, 6 H) 1.45 - 2.48 (m, 10 H) 3.15 - 3.69 (m, 10 H) 3.80 - 3.90 (m, 1 H) 4.07 - 4.17 (m, 1 H) 4.88 - 5.31 (m, 2 H) 8.20 (s, 1 H) 8.28 - 8.63 (m, 3 H). HRMS calculado para C25H36N5O4F3: 528.2797; encontrado: 528,2905.

Ejemplo 60/61

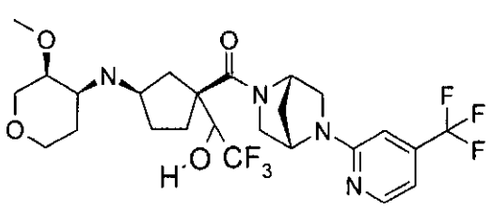


((1S,3R)-3-((3S,4S)-3-metoxi-tetrahidro-2H-piran-4-ilamino)-1-(tetrahidrofuran-3-il)ciclopentil)((1S,4S)-5-(4-(trifluorometil)piridin-2-il)-2,5-diaza-biciclo[2.2.1]heptan-2-il)metanona

^{1}HNMR (400 MHz, CD_3OD) δ 8.20 (d, 1H), 7.18 (s, 1H), 6.97 (d, 1H), 5.11 (m, 2H), 4.24 (d, 1H), 3.38-3.99 (m, 17H), 2.87 (m, 1H), 2.65 (m, 1H), 2.48 (m, 1H), 1.90-2.39 (m, 8H), 1.81 (m, 2H), 1.65 (m, 1H).

^{1}HNMR (400 MHz, CD_3OD) δ 8.20 (d, 1H), 7.18 (s, 1H), 6.97 (d, 1H), 5.11 (m, 2H), 4.24 (d, 1H), 3.38-3.99 (m, 17H), 2.87 (m, 1H), 2.65 (m, 1H), 2.48 (m, 1H), 1.90-2.39 (m, 8H), 1.81 (m, 2H), 1.65 (m, 1H).

Ejemplo 62/63



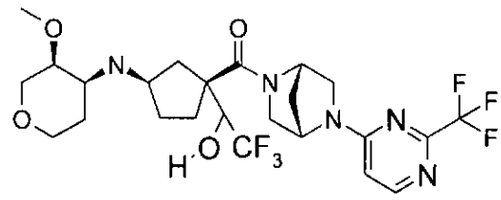
((1S,3R)-3-((3S,4S)-3-metoxi-tetrahidro-2H-piran-4-ilamino)-1-(2,2,2--trifluoro-1-

hidroxietil)ciclopentil)((1S,4S)-5-(4-(trifluorometil)piridin-2-il)-2,5-diaza-biciclo[2.2.1]heptan-2-il)metanona

^{1}HNMR (400 MHz, CD3OD) δ 8.23 (d, J= 8Hz, 1H), 6.8 (d, J=8Hz, 1H), 6.72 (d, J=8 Hz, 1H), 5.0 (m, 1H), 4.2, (m, 1H), 3.85 (m, 2H), 3.6 (m, 1H), 3.52 (m, 1H), 3.30 (s, 3H) 3.4 (m, 4H), 2.7 (m, 2H), 2.4 (m,1H), 2.0 (m, 4H), 1.8 (m, 4H), 1.6 (m, 4H)

1HNMR (400 MHz, CD3OD) δ 8.23 (d, J= 8Hz, 1H), 6.8 (d, J=8Hz, 1H), 6.72 (d, J=8 Hz, 1H), 5.0 (m, 1H), 4.2, (m, 1H), 3.85 (m, 2H), 3.6 (m, 1H), 3.30 (s, 3H), 3.52 (m, 1H),3.4 (m, 4H), 2.7 (m, 2H), 2.4 (m,1H), 2.0 (m, 4H), 1.8 (m, 4H), 1.6 (m, 4H)

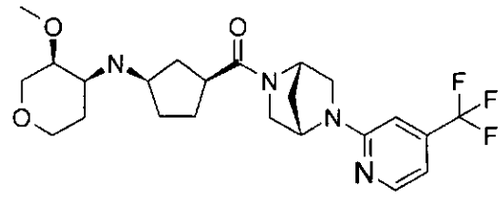
Ejemplo 64



((1S,3R)-3-((3S,4S)-3-metoxi-tetrahidro-2H-piran-4-ilamino)-1-(2,2,2-trifluoro-1-hidroxietil)ciclopentil)((1S,4S)-5-(2-(trifluorometil)pirimidin-4-il)-2,5-diaza-biciclo[2.2.1]heptan-2-il)metanona

^{1}HNMR (400 MHz, CD3OD) δ 8.23(m, 1H), 6.6 (m, 1H), 4.25 (m, 1H), 4.0 (m, 2H), 3.85 (m, 1H), 3.7 (m, 1H) 3.6 (m, 4H), 3.42 (m, 4H), 2.52 (m, 2H), 2.25 (m, 2H), 2.1 (m, 2H) 2.0 (m, 4H), 1.6 (m, 2H)

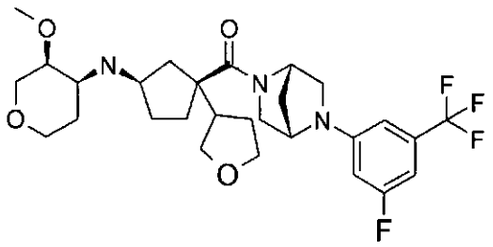
Ejemplo 65



((1S,3R)-3-((3S,4S)-3-metoxi-tetrahidro-2H-piran-4-ilamino)ciclopentil)((1S,4S)-5-(4-(trifluorometil)piridin-2-il)-2,5-diaza-biciclo[2.2.1]heptan-2-il)metanona

^{1}HNMR (400 MHz, CD3OD) δ 8.23 (d, J= 8Hz, 1H), 6.8 (d, J=8Hz, 1H), 6.72 (d, J=16 Hz, 1H), 5.0 (m, 1H), 4.2, (m, 1H), 3.9 (m, 1H), 3.85 (m, 1H), 3.8 (m, 4H), 3.4 (m, 4H), 3.30 (m, 3H), 3.2 (m, 4H), 2.0 (m, 4H), 1.8 (m, 4H)

Ejemplo 66

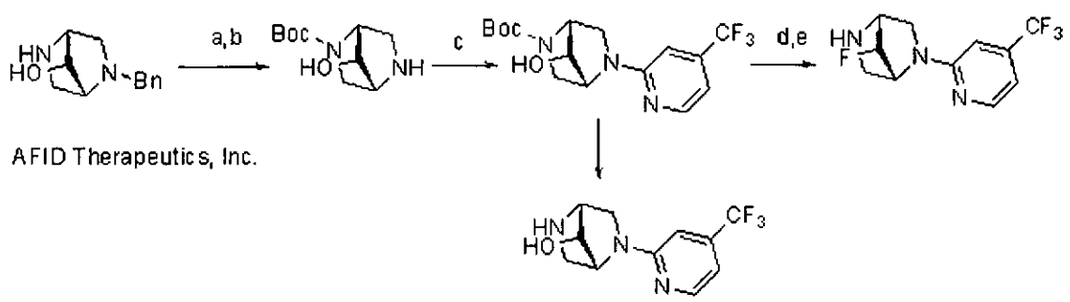


((1S,4S)-5-(3-fluoro-5-(trifluorometil)fenil)-2,5-diaza-biciclo[2.2.1]heptan-2-il)((1S,3R)-3-((3S,4S)-3-metoxi-tetrahidro-2H-piran-4-ilamino)-1-(tetrahidrofuran-3-il)ciclopentil)metanona

1HNMR (400Mhz, CD3OD), δ 6.6 (m, 3H), 5.0 (m, 1H), 4.6 (m, 1H), 4.25 (d, J=4Hz, 1H), 4.0 (m, 1H), 3.85 (m, 1H), 3.8 (m, 2H), 3.7 (m, 2H), 3.65 (m, 2H) 3.5 (m, 2H), 3.4 (3H), 3.2 (d, J=4Hz, 2H), 2.8 (m, 1H), 2.6 (m, 1H), 2.5 (m, 1H), 2.35 (m, 1H), 2.2 (m, 1H), 2.1 (m, 2H), 2.05 (m, 2H), 2.0 (m, 2H), 1.8 (m, 2H),1.6 (m, 2H)

Preparación de los ejemplos 67-71

Esquema. Preparación de F-221



a) Boc_2O, DIPEA; b) NBS, CCl_4 luego 10% Pd/C, H_2; c) Cl-piridin -CF_3, DIPEA, DMF; d) DAST, DCM, 0 °C; e) 4N HCl/dioxano, temperatura ambiente

Etapa 1: Preparación de 7-hidroxi-5-(4-(trifluorometil)piridin-2-il)-2,5-diaza-biciclo[2.2.1]heptan-2-carboxilato de (1R,4S)-ter-butilo

A una solución de alcohol (2,48 g, 11,6 mmol) en DMSO (30 mL) se agregó 2-cloro-5-(trifluorometil)piridina (2,0 g, 11,0 mmol) y TEA (3,4 mL, 24,2 mmol). Luego de calentar la mezcla a 95 °C durante la noche, se vertió en H_2O y la mezcla acuosa se extrajo 2X con éter. Los extractos orgánicos se secaron (Na_2SO_4), y el solvente se retiró para producir un aceite que, luego de la cromatografía (sílice, EtOAc:Heptano), generó el producto (1,0 g). LC/MS (M+Na) = 382 exp, 382 obs.

Etapa 2: Preparación de 7-fluoro-5-(4-(trifluorometil)piridin-2-il)-2,5-diaza-biciclo[2.2.1]heptan-2-carboxilato de (1R,4S)-ter-butilo

A una solución de alcohol en DCM a 0 °C se agregó DAST por goteo. Cuando se completó la adición, se dejó que la mezcla de reacción se calentara a temperatura ambiente y se agitó a temperatura ambiente durante la noche. La mezcla de reacción se vertió en $NaHCO_3$/DCM saturado, y las capas se separaron. La capa orgánica se recolectó, se secó (Na_2SO_4), y el solvente se retiró para producir un aceite que, luego de la cromatografía (sílice, EtOAc:Heptano), generó el producto deseado (750 mg). LC/MS (M+H) = 362.1491 exp, 362.1491 obs. 1H NMR (400 MHz, *DMSO-d_6*) δ ppm 8.31 (1 H, d, *J*=5.5 Hz), 6.85 - 6.96 (2 H, m), 5.35 (1 H, d, *J*=55.6 Hz), 4.90 (1 H, br. s.), 4.47 (1 H, d, *J*=22.7 Hz), 3.64 (1 H, dd, *J*=10.2, 1.8 Hz), 3.47 - 3.57 (1 H, m), 3.39 - 3.46 (1 H, m), 3.26 - 3.32 (1 H, m), 1.39 (9 H, d, *J*=12.4 Hz).

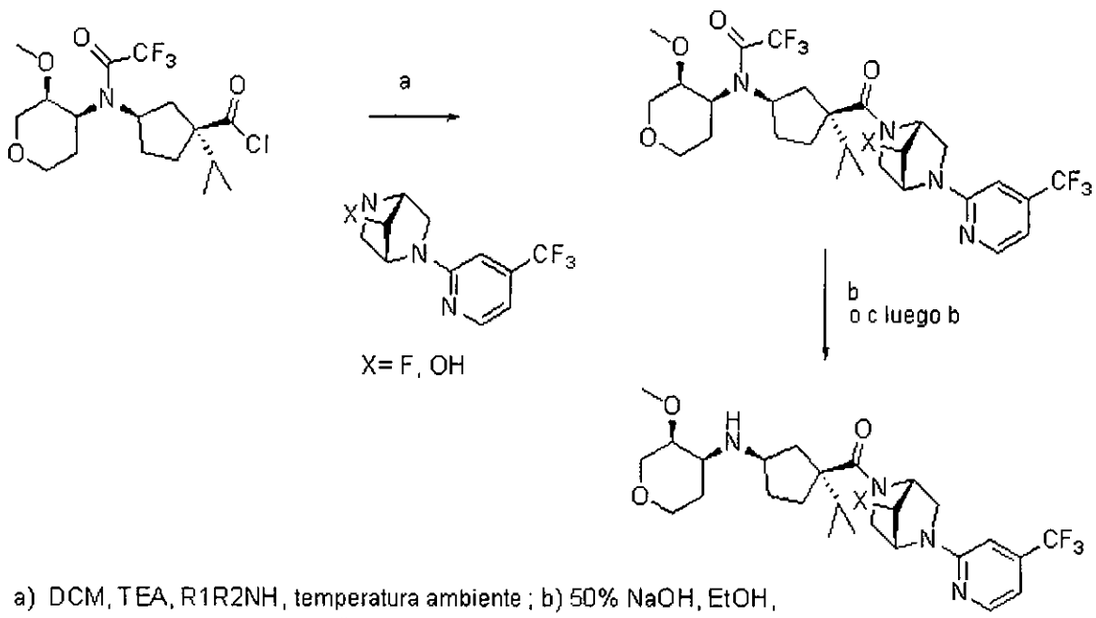
Etapa 3: Preparación de (1S,4R)-7-fluoro-2-(4-(trifluorometil)piridin-2-il)-2,5-diaza-biciclo[2.2.1]heptano

A una solución de 7-fluoro-5-(4-(trifluorometil)piridin-2-il)-2,5-diaza-biciclo[2.2.1]heptan-2-carboxilato de (1R,4S)-ter-butilo (700 mg, 1,9 mmol) en dioxano (2 ml) se agregó HCl/dioxano 4N (5 mL). La mezcla de reacción se agitó a temperatura ambiente durante 5 horas y luego se diluyó con éter para obtener un precipitado que se filtró y recolectó para generar el producto como la sal de HCl (506 mg). LC/MS (M+H) = 262.0967 exp, 262.1308 obs; 1H NMR (400 MHz, *METANOL-d_4*) δ ppm 8.26 (1 H, d, *J*=6.1 Hz), 7.40 (1 H, s), 7.20 (1 H, dd, *J*=6.3, 1.0 Hz), 5.65 (1 H, dd, *J*=52.4, 1.9 Hz), 5.28 (1 H, s), 4.70 (1 H, s), 3.92 - 4.09 (2 H, m), 3.66 - 3.81 (2 H, m), 3.62 (1 H, s)

Etapa 4: Preparación de (1S,4R)-7-hidroxi-2-(4-(trifluorometil)piridin-2-il)-2,5-diaza-biciclo[2.2.1]heptano

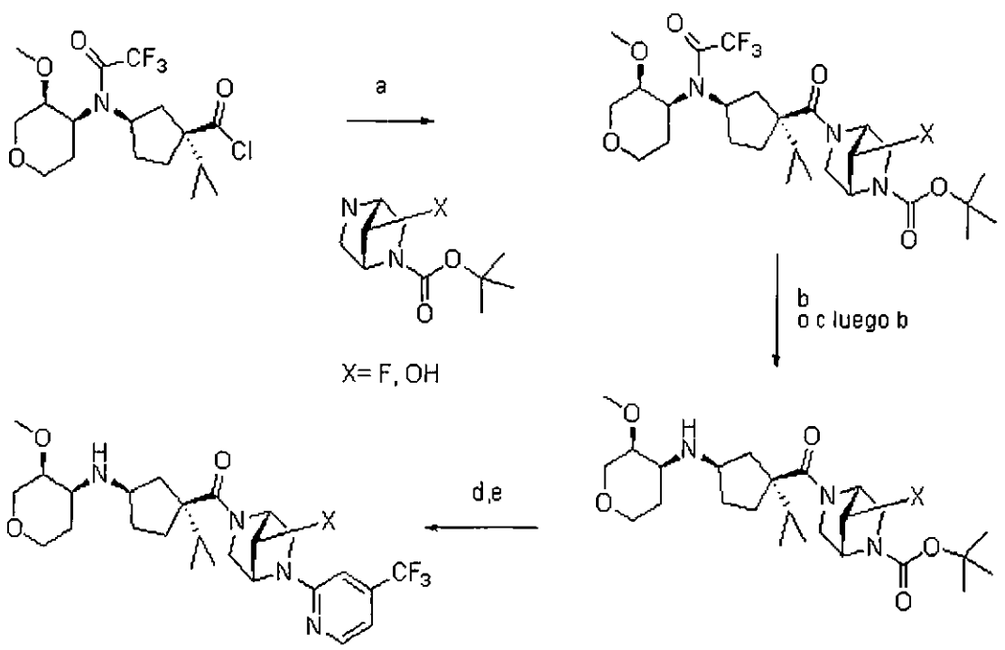
A una solución de 7-hidroxi-5-(4-(trifluorometil)piridin-2-il)-2,5-diaza-biciclo[2.2.1]heptan-2-carboxilato de (1R,4S)-ter-butilo (5 g, 14 mmol) en dioxano (5 ml) se agregó HCl/dioxano 4N (15 mL). La mezcla de reacción se agitó a temperatura ambiente durante 6 horas y luego se diluyó con éter para obtener un precipitado que se filtró y recolectó para generar el producto como la sal de HCl (4,0 g). LC/MS (M+H) = 260.0 exp, 260.0 obs; 1H NMR (500 MHz, DMSO-d_6) δ ppm 3.42 - 3.50 (m, 1 H) 3.67 - 3.72 (m, 1 H) 3.75 - 3.82 (m, 1 H) 4.16 (br. s., 1 H) 4.50 (d, J=1.81 Hz, 1 H) 4.72 (br. s., 1 H) 6.95 (d, J=5.13 Hz, 2 H) 8.31 (d, J=5.43 Hz, 1 H) 9.34 (br. s., 1 H) 9.75 (br. s., 1 H)

Esquema 5



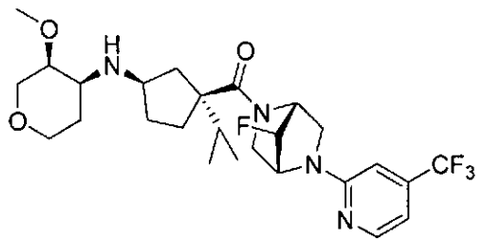
a) DCM, TEA, R1R2NH, temperatura ambiente ; b) 50% NaOH, EtOH, temperatura ambiente ; c) DAST, DCM, 0 oC

Esquema 6



a) DCM. TEA. R1R2NH. temperatura ambiente; b) 50% NaOH, EtOH, temperatura ambiente ; c) DAST, DCM, 0 oC; d) 4N HCl/ dioxano; e) Pyr-Cl Et3N, DMSO, 100 oC

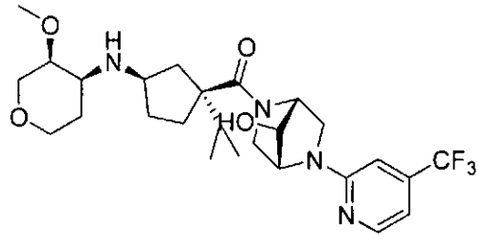
Ejemplo 67



((1R,4R,7S)-7-fluoro-5-(4-(trifluorometil)piridin-2-il)-2,5-diaza-biciclo[2.2.1]heptan-2-il)((1S,3R)-1-isopropil-3-((3S,4S)-3-metoxi-tetrahidro-2H-piran-4-ilamino)ciclopentil)metanona

Se preparó de modo análogo al ejemplo 1, excepto que se usó (1R,4R,7R)-7-fluoro-2-(4-(trifluorometil)piridin-2-il)-2,5-diaza-biciclo[2.2.1]heptano como la amina de acoplamiento. LC/MS (M+H) = 529 exp, 529 obs; 1H NMR (400 MHz, *DMSO-d_6*) δ ppm 8.31 (1 H, d, *J*=5.1 Hz), 6.92 (2 H, d, *J*=5.1 Hz), 5.39 (1 H, d, *J*=55.6 Hz), 4.81 - 4.98 (2 H, m), 3.78 - 3.88 (1 H, m), 3.66 - 3.75 (2 H, m), 3.57 - 3.65 (1 H, m), 3.37 - 3.43 (1 H, m), 3.23 - 3.31 (2 H, m), 3.15 - 3.22 (4 H, m), 3.06 - 3.10 (1 H, m), 2.95 - 3.03 (1 H, m), 2.68 - 2.77 (1 H, m), 2.22 - 2.32 (1 H, m), 1.93 - 2.09 (2 H, m), 1.61 - 1.72 (2 H, m), 1.35 - 1.53 (3 H, m), 1.21 - 1.29 (1 H, m), 1.08 - 1.20 (1 H, m), 0.82 (2 H, d, *J*=6.2 Hz), 0.64 - 0.77 (4 H, m)

Ejemplo 68

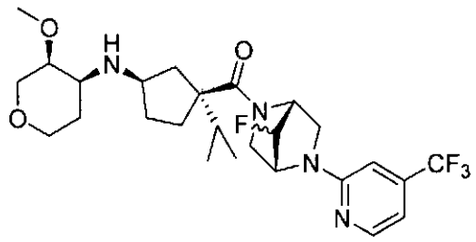


((1R,4R,7S)-7-hidroxi-5-(4-(trifluorometil)piridin-2-il)-2,5-diaza-biciclo[2.2.1]heptan-2-il)((1S,3R)-1-isopropil-3-((3S,4S)-3-metoxi-tetrahidro-2H-piran-4-ilamino)ciclopentil)metanona

A una solución de cloruro de (1S,3R)-1-isopropil-3-(2,2,2-trifluoro-N-((3S,4S)-3-metoxi-tetrahidro-2H-piran-4-il)acetamido)ciclopentancarbonilo (185 mg, 0,463 mmol) en CH_2Cl_2 (2 mL) se agregó Et_3N (0,161 ml, 1,16 mmol) y (1R,4R,7R)-7-hidroxi-2-(4-(trifluorometil)piridin-2-il)-2,5-diaza-biciclo[2.2.1]heptano (100 mg, 0,386 mmol). La mezcla se agitó durante 4 horas a temperatura ambiente. La solución luego se lavó con $NaHCO_3$ (1 X 3 ml) y salmuera (1 X3 ml). Luego, la capa orgánica se secó en $MgSO_4$, se filtró y se concentró, se purificó mediante cromatografía con (100% de EtOAc- 70% de MeOH/EtOAc) para generar el producto protegido TFA, que luego se

trató con NaOH 2N (0,5 ml, 1 mmol) en THF (2 ml) a temperatura ambiente durante 4 horas, luego se purificó mediante cromatografía con (100% de EtOAc - 100% de MeOH) para generar 60 mg del producto deseado (30 %). LC/MS (M+H) = 527.2845 exp, 527.2996 obs; 1H NMR (400 MHz, DMSO-d_6) δ ppm 0.64 - 0.76 (m, 4 H) 0.77 - 0.88 (m, 3 H) 1.13 (d, *J*=1.83 Hz, 1 H) 1.34 (br. s., 1 H) 1.36 - 1.48 (m, 3 H) 1.66 (dt, *J*=7.69, 3.84 Hz, 1 H) 1.77 - 1.90 (m, 1 H) 1.99 (dt, *J*=13.55, 6.77 Hz, 2 H) 2.29 (dd, *J*=12.08, 8.05 Hz, 1 H) 2.73 - 2.79 (m, 1 H) 2.97 - 3.04 (m, 1 H) 3.07 - 3.14 (m, 2 H) 3.15 - 3.24 (m, 5 H) 3.59 (br. s., 1 H) 3.61 - 3.72 (m, 2 H) 3.75 - 3.88 (m, 1 H) 4.26 (d, *J*=0.73 Hz, 1 H) 4.44 - 4.55 (m, 2 H) 5.72 (d, *J*=3.29 Hz, 1 H) 6.75 - 6.85 (m, 2 H) 8.27 (d, *J*=5.49 Hz, 1 H)

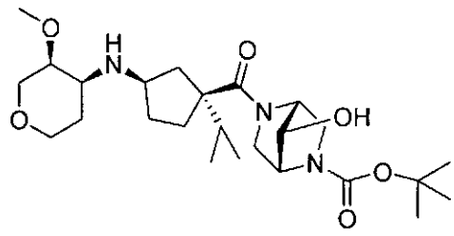
Ejemplo 69



((1R,4R)-7-fluoro-5-(4-(trifluorometil)piridin-2-il)-2,5-diaza-biciclo[2.2.1]heptan-2-il)((1S,3R)-1-isopropil-3-((3S,4S)-3-metoxi-tetrahidro-2H-piran-4-ilamino)ciclopentil)metanona

2,2,2-trifluoro-N-((1R,3S)-3-((1R,4R,7S)-7-hidroxil-2-(4-(trifluorometil)piridin-2-il)-2,5-diaza-biciclo[2.2.1]heptan-5-carbonil)-3-isopropilciclopentil)-N-((3S,4S)-3-metoxi-tetrahidro-2H-piran-4-il)acetamida (30 mg, 0,057 mmol) en CH_2Cl_2 (2ml) se enfrió a 0 °C y se agregó DAST (0,025 ml, 0,086 mmol) a la solución. La mezcla de reacción se agitó durante la noche y se purificó mediante cromatografía (10% de EtOAc a 100% de MeOH) para generar el producto deseado (16mg, 32%). LC/MS (M+H) = 529.2802 exp, 529.3112 obs; 1H NMR (400 MHz, DMSO-d_6) δ ppm 0.67 - 0.78 (m, 5 H) 0.82 (d, *J*=6.59 Hz, 3 H) 1.23 (br. s., 1 H) 1.50 (d, *J*=3.66 Hz, 3 H) 1.75 (d, *J*=4.39 Hz, 2 H) 1.94 - 2.03 (m, 1 H) 2.24 - 2.32 (m, 1 H) 2.98 (s, 1 H) 3.12 (br. s., 1 H) 3.18 - 3.23 (m, 4 H) 3.31 - 3.34 (m, 1 H) 3.40 (d, *J*=10.98 Hz, 1 H) 3.62 (d, *J*=12.08 Hz, 1 H) 3.72 (d, *J*=10.62 Hz, 3 H) 3.80 - 3.92 (m, 1 H) 4.87 (br. s., 1 H) 4.90 - 4.96 (m, 1 H) 5.31 (d, *J*=1.83 Hz, 1 H) 5.40 - 5.46 (m, 1 H) 6.86 - 6.94 (m, 2 H) 8.31 (d, *J*=5.49 Hz, 1 H)

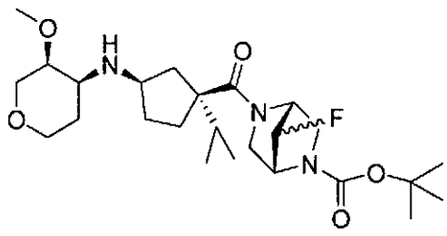
Ejemplo 70



7-hidroxi-5-((1S)-1-isopropil-3-(3-metoxi-tetrahidro-2H-piran-4-ilamino)ciclopentancarbonil)-2,5-diaza-biciclo[2.2.1]heptan-2-carboxilato de (1R,4R,7S)-ter-butilo

A una solución del ácido (1S,3R)-1-isopropil-3-(2,2,2-trifluoro-N-((3S,4S)-3-metoxi-tetrahidro-2H-piran-4-il)acetamido)ciclopentancarboxílico (0,95 g, 2,5 mmol) en CH_2Cl_2 (5 mL) en N2 a 0 °C se agregó cloruro de oxalilo (623 mg, 4,98 mmol) y DMF (3 gotas). Se dejó calentar la mezcla a temperatura ambiente y se agitó durante 2 horas. Luego se concentró. El cloruro de ácido se disolvió nuevamente en DCM (10ml), se enfrió a 0 °C y se trató con 7-hidroxi-2,5-diaza-biciclo[2.2.1]heptan-2-carboxilato de (1R,4R,7S)-ter-butilo (534 mg, 0,249 mmol) seguido de Et_3N (0,1 ml, 0,75 mmol). La mezcla resultante se calentó a temperatura ambiente y se agitó durante 2 horas. La solución luego se lavó con $NaHCO_3$ (1 X 5 ml) y salmuera (1 X5 ml). Luego, la capa orgánica se secó en MgSO4, se filtró y se concentró, se purificó mediante cromatografía (100% de EtOAc- 60% de MeOH/EtOAc) para producir un intermediario crudo que se secó y se concentró. Luego se disolvió en EtOH (2 ml) y se trató con NaOH (3 ml, 7,5 mmol) durante la noche. A continuación, la mezcla de reacción se purificó mediante cromatografía (100% de EtOAc - 100% de MeOH) para generar el producto deseado (300 mg, 25%). LC/MS (M+H) = 482.3230 exp, 482.3334 obs; 1H NMR (400 MHz, DMSO-d_6) δ ppm 0.67 (dd, *J*=6.95, 3.66 Hz, 3 H) 0.80 (dd, *J*=6.59, 2.93 Hz, 3 H) 1.22 (br. s., 1 H) 1.35 - 1.41 (m, 12 H) 1.43 - 1.48 (m, 2 H) 1.55 - 1.68 (m, 2 H) 1.85 - 1.93 (m, 1 H) 1.95 - 2.04 (m, 1 H) 2.16 - 2.28 (m, 1 H) 2.66 - 2.80 (m, 1 H) 2.97 - 3.02 (m, 1 H) 3.03 - 3.10 (m, 2 H) 3.17 - 3.29 (m, 5 H) 3.37 - 3.47 (m, 1 H) 3.47 - 3.58 (m, 1 H) 3.61 - 3.74 (m, 1 H) 3.81 - 3.89 (m, 1 H) 3.94 - 4.04 (m, 2 H) 4.24 (br. s., 1 H) 5.65 - 5.77 (m, 1 H)

Ejemplo 71



7-fluoro-5-((1S,3R)-1-isopropil-3-((3S,4S)-3-metoxi-tetrahidro-2H-piran-4-ilamino)ciclopentancarbonil)-2,5-diaza-biciclo[2.2.1]heptan-2-carboxilato de ter-butilo

7-hidroxi-5-((1S)-1-isopropil-3-(2,2,2-trifluoro-N-(3-metoxi-tetrahidro-2H-piran-4-il)acetamido)ciclopentancarbonil)-2,5-diaza-biciclo[2.2.1]heptan-2-carboxilato de ter-butilo (100 mg, 0,173 mmol) en CH_2Cl_2 (2 ml) se enfrió a 0 °C y se agregó DAST (0,036ml, 0,259mmol) a la solución. La mezcla de reacción se agitó durante la noche y se purificó mediante cromatografía (10% de EtOAc a 100% de MeOH) para generar un producto protegido TFA, que luego se trató con NaOH 2,5N (0,014 ml, 0,5 mmol) en THF (2 ml) a temperatura ambiente durante 4 horas, luego se purificó mediante cromatografía con (100% de EtOAc- 100% de MeOH) para generar 12 mg del producto deseado (14%). LC/MS (M+H) = 484.3187 exp, 484.3197 obs; 1H NMR (400 MHz, DMSO-d_6) δ ppm 0.63 - 0.72 (m, 3 H) 0.81 (dd, *J*=7.14, 1.65 Hz, 3 H) 1.22 (br. s., 1 H) 1.36 - 1.48 (m, 13 H) 1.56 - 1.68 (m, 2 H) 1.85 - 1.96 (m, 2 H) 2.16 - 2.28 (m, 1 H) 2.68 - 2.79 (m, 1 H) 2.95 - 3.05 (m, 1 H) 3.15 (br. s., 1 H) 3.17 - 3.29 (m, 7 H) 3.52 (d, *J*=10.62 Hz, 2 H) 3.66 - 3.74 (m, 1 H) 3.82 - 3.90 (m, 1 H) 4.27 - 4.37 (m, 1 H) 4.69 (br. s., 1 H) 5.08 - 5.35 (m, 1 H)

Datos biológicos

Ensayos de CCR2 *in vitro*

La capacidad de los compuestos nuevos de la invención para antagonizar la función del receptor de quimiocina (por ejemplo, CCR2) se puede determinar con un barrido adecuado (por ejemplo, ensayo de alto rendimiento). Por ejemplo, se puede evaluar un agente en un ensayo de acidificación extracelular, ensayo de flujo de calcio, ensayo de unión a ligando o ensayo de quimiotaxis (véase, por ejemplo, Hesselgesser et al., J Biol. Chem. 273(25):15687-15692 (1998); WO 00/05265 y WO 98/02151).

En un ensayo adecuado, se usa una proteína CCR2 que se puede aislar o derivar de manera recombinante, que tiene al menos una propiedad, actividad o característica funcional de una proteína CCR2 de mamífero. La propiedad específica puede ser una propiedad de unión (por ejemplo, a un ligando o inhibidor), una actividad de señalización (por ejemplo, activación de una proteína G de mamífero,

inducción de aumento rápido y transitorio en la concentración de calcio libre cistólico [Ca++]i, función de respuesta celular (por ejemplo, estimulación de quimiotaxis o liberación del mediador inflamatorio mediante leucocitos) y similares.

En un ejemplo de ensayo de unión, se mantiene una composición que contiene una proteína CCR2 o una variante de ésta en condiciones adecuadas para la unión. El receptor CCR2 se pone en contacto con un compuesto que se desea evaluar, y se detecta o mide la unión.

En un ejemplo de ensayo basado en células, se usan células que son transfectadas de manera estable o transitoria con un vector o casete de expresión que tiene una secuencia de ácidos nucleicos que codifica el receptor CCR2. Las células se mantienen en condiciones adecuadas para la expresión del receptor y se ponen en contacto con un agente en condiciones adecuadas para que ocurra la unión. Se puede detectar la unión mediante técnicas estándar. Por ejemplo, el alcance de la unión se puede determinar con respecto a un control adecuado. Además, una fracción celular, tal como una fracción de membrana, que contiene el receptor se puede usar en lugar de las células enteras.

La detección de la formación del complejo o unión en un ensayo se puede detectar de manera directa o indirecta. Por ejemplo, el agente se puede etiquetar con una etiqueta adecuada (por ejemplo, una etiqueta fluorescente, etiqueta, etiqueta de isótopo, etiqueta de enzima y similares), y la unión se puede determinar mediante la detección de la etiqueta. La unión específica y/o competitiva se puede evaluar mediante estudios de competición o desplazamiento mediante el uso de un agente no etiquetado o de un ligando como competidor.

La actividad del antagonista CCR2 de los compuesto de la invención se puede informar como la concentración de inhibidor requerida para un 50% de inhibición (valores IC50) de unión específica en ensayos de unión a receptor con MCP-1 etiquetado con 125I, como ligando, y células mononucleares de sangre periférica (PBMC) preparadas de sangre entera humana normal mediante centrifugación en gradiente de densidad. La unión específica se define como la unión total (por ejemplo, cpm total en los filtros) menos la unión no específica. La unión no específica se define como la cantidad de cpm que aún se detecta en presencia de exceso de competidor no etiquetado (por ejemplo, MCP-1)

IC_{50} de unión a CCR2

Se usaron PBMC humanas para evaluar compuestos de la invención en un ensayo de unión. Por ejemplo, se incubaron de 200.000 a 500.000 células con 0,1 a

0,2 nM de MCP-1 etiquetado con 125I, con o sin competidor no etiquetado (10 nM de MCP-1) o varias concentraciones de compuestos que se desean evaluar. MCP-1 etiquetado con 125I se prepararon mediante métodos adecuados o se adquirieron de vendedores comerciales (Perkin Elmer, Boston MA). Las reacciones de unión se realizaron en 50 a 250 µL de tampón de unión que consistía en HEPES 1M, pH 7,2 y 0,1% de BSA (seroalbúmina bovina) durante 30 minutos a temperatura ambiente. Las reacciones de unión se terminaron mediante la cosecha de las membranas por medio de una rápida filtración a través de filtros de fibra de vidrio (Perkin Elmer) que se empaparon previamente en polietilenimina al 0,3% o solución salina tamponada con fosfato (PBS). Los filtros se enjuagaron con aproximadamente 600 µL de tampón de unión que contenía NaCl 0,5M o PBS, luego se secaron, y la cantidad de radioactividad unida se determinó mediante el conteo en un contador gama (Perkin Elmer).

Más específicamente, el siguiente ensayo se puede usar para determinar valores IC_{50} para los compuestos de la presente invención.

Ensayo de unión a molécula pequeña hCCR2 (125-I hMCP-1)

Los siguientes reactivos y suministros se usaron en el ensayo precedente:

MCP-1
Biosource # PHC1013
1 mg
reconstituido con 2 ml de tampón de unión (0,5 mg por ml o 60 uM)

125I MCP-1
Perkin Elmer #NEX332
25 uCi
reconstituído con 0,2 ml de PBS

RPMI 1640 con L-glutamina
MediaTech/Cellgro # 10-040-CM

BSA
Sigma # A2153

HEPES
Solución 1M

MediaTech/Cellgro # 25-060-CL

NaCl
Sigma # S7653

SUMINISTROS
Placas de filtro Multiscreen BV
Millipore # MABVN1250

Puntas de perforación Multiscreen
Millipore #MADP19650

Sistema de filtración al vacío Multiscreen
Millipore # MAVM0960R

El contenido del paquete de leucoforesis humana normal, disponible de Biological Specialty Corporation, Colmar, PA., se diluye 1:1 con PBS, dividido en tubos cónicos de 50 ml (preferentemente, menos de 40 mls por tubo) y se superpone con 10 mls de Ficoll-Paque PLUS (GE Healthcare 17-1440-02). Los tubos se centrifugan a 2800 rpm en una centrífuga clínica a temperatura ambiente durante 30 minutos, sin interrupción. La capa de plasma se succiona, y se recolecta la capa leucocitaria *(buffycoat)*. La capa leucocitaria recolectada se lava dos veces con 50 mls de PBS y se centrifuga a 1400 rpm con interrupción. Se cuentan las células. Luego se diluyen las células a $1x10^7$ células por ml en tampón de unión.

Se humedecen previamente placas de 96 cavidades (tales como, por ejemplo, placas Millipore MultiScreen96) con alrededor de 100 µl de tampón de unión (RPMI+0,1% de BSA + 20 mM de HEPES) y se manchan justo antes de la adición del compuesto.

Las placas con compuesto que se van a evaluar se pueden manejar o almacenar ventajosamente con un sistema automatizado, tal como, por ejemplo, TelCel (Hamilton Storage Technologies, Inc., 103 South Street, Hopkinton, MA 01748 EEUU).

Se manchan 5 µl de 50 µM de compuestos de prueba en 100% de DMSO en placas de 96 cavidades de polipropileno con fondo en forma de U.

Se agregan 245 µl por cavidad de tampón de unión a cada cavidad para 1µM

de concentración de compuesto en 2% de DMSO.

Se transfieren 50µl de 1µM de compuesto a placas Millipore previamente humedecidas.

Se agregan 50 µl por cavidad de 1x10E7 células por ml de PBMC humanas recién preparadas.

Las muestras se incuban previamente a temperatura ambiente durante 30 minutos o 1 hora.

Se agregan 50 µl de 450pM de 125-I-hMCP-1 (Perkin-Elmer/NEN cat#NEX332025UC) para una concentración final de 125-I-hMCP-1 de 150 pM por cavidad.

La concentración final del compuesto de prueba es de 0,333 uM en 150 µl de volumen total con 0,67% de DMSO en todas las cavidades. Los controles para este ensayo consisten en 0% de inhibición y 100% de inhibición con 1 uM de hMCP-1 (en condiciones de saturación). Todas las cavidades se corren por duplicado. Los controles pueden estar en réplicas de 8.

Las muestras se incuban a temperatura ambiente durante 30 minutos.

El tampón se succiona a través de placas de Millipore. Las placas se lavan tres veces con tampón de lavado (PRMI + 0,1% de BSA + 20mM de HEPES + NaC 0,4 M).

Se retira la placa de drenaje. Los filtros de la placa se dejan secar. Los filtros luego se perforan en tubos plásticos.

Finalmente, la muestra se cuenta en un contador gama.

Todas las placas IC50 se repitieron para n=2.

La siguiente tabla sintetiza los valores IC_{50} identificados mediante el ensayo descrito.

Tabla 1. Datos biológicos

Ejemplo	IC_{50} (nM) 30 min inc. previa	IC_{50} (nM) 1 h inc. previa
1	2,47	
2	3,16	
3	17,8	
4	3,98	
5	13,3	
6	1,73	
7	17,1	
8	10,7	
9	30,7	
10	83,8	
11	6,72	2,44
12	11,1	1,7
13	25,4	3,68

Ejemplo	IC_{50} (nM) 30 min inc. previa	IC_{50} (nM) 1 h inc. previa
14	10,4	2,3
15	40	4,6
16	9,95	1,1
17	13,7	5,8
18	37,6	8,5
19	20,4	6,35
20	8,59	
21		3,1
22		1,1
23		0,94
24	79,7	8,87
25	6,58	0,93
26	29,3	7,85
27	16,2	2,04
28		1,88
29		2,75
30	32,9	11,8
31		6,35
32	13,8	11,7
33	57,3	11,7
34	66,5	6,94
35	28,4	5,52
36	12,6	2,19
37		3,68
38	68,7	2,02
39	82,9	5,81
40	18,3	
41	63,6	
42	70,9	
43	47,3	
44		8,1
45	25,3	
46	3,19	
47	6,16	
48	25,3	
49	35,8	
50	7,14	
51	22,8	
52	5,4	
53	27,6	
54	8,46	
55	28,3	
56	32,8	
57	4,34	
58	38,5	
59	17,7	
60	2,4	
61	5,9	
62	1,3	

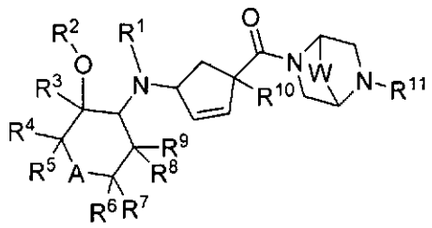
Ejemplo	IC_{50} (nM) 30 min inc. previa	IC_{50} (nM) 1 h inc. previa
63		1,1
64		4,7
65		1,5%@300nM
66	1,7	
67	3,4	
68	5,4	
69	4,3	
70	8,7	
71	3,7	

Modelo de rata con nefropatía diabética

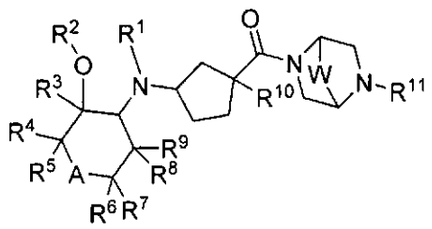
Se usó un modelo de rata con nefropatía diabética para determinar el efecto protector renal de la inhibición farmacológica de CCR2. El modelo de rata con diabetes inducida por estreptozotocina (STZ) se usó extensamente para estudiar el avance de una enfermedad renal diabética. La inyección de STZ causa la destrucción inmediata de células β pancreáticas y, en consecuencia, de la hiperglucemia y el avance de la nefropatía similar a la que se observa en diabetes melitus humana. La diabetes se indujo en ratas macho Wistar mediante una única administración de STZ (45 mg/kg, iv). Tres días después de la inducción de la diabetes, se evaluaron los niveles de glucosa en sangre en ayunas. Se incluyeron en este estudio animales con un nivel de glucosa en sangre en ayunas superior a 200 mg/dL. Luego se iniciaron todos los tratamientos. Se administró 1,5-anhidro-2,3-dideoxi-3-{[(1R,3S)-3-isopropil-3-({(1S,4S)-5-[6-(trifluorometil)pirimidin-4-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metil-D-eritro-pentitol en dosis de 0,03, 0,3, 1 y 10 mg/kg (mpk) (en el alimento) durante 11 semanas. Se recolectó orina de 24 horas en las semanas 1, 4, 8 y 11 luego del tratamiento para evaluar la excreción urinaria de albúmina (UAE) a las 24 horas. Como se esperaba, luego de la inducción de la diabetes, se observó un incremento persistente de UAE durante las 11 semanas que duró el estudio. El tratamiento con 1,5-anhidro-2,3-dideoxi-3-{[(1R,3S)-3-isopropil-3-({(1S,4S)-5-[6-(trifluorometil)pirimidin-4-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metil-D-eritro-pentitol redujo de modo considerable la UAE en dosis de 0,3 mpk (1,73±0,69 mg/24 h), 1 mpk (1,09±0,20 mg/24 h) y 10 mpk (0,71±0,22 mg/24 h) en comparación con las ratas STZ no tratadas (4,32±1,34 mg/24 h) en la semana 8, y en todas las dosis (2,17±1,31, 1,96±0,85, 1,66±0,65 y 1,02±0,32 mg/24 h, en dosis de 0,03, 0,3, 1 y 10 mpk, respectivamente, con respecto a 6,36±2,08 mg/24 h, en ratas STZ no tratada) en la semana 11. Esto datos demuestran que la inhibición farmacológica de CCR2 provee protección renal durante el desarrollo y el

REIVINDICACIONES

1. Un compuesto de la Fórmula I(a) o I(b):



I(a)



I(b)

o su sal farmacéuticamente aceptable, en donde

A es O o CF_2;

W es $CR^{13}R^{14}$, C(O), $CHOR^{15}$, CHF, CF_2, O o S

R^1 es H o (C_1-C_6)alquilo opcionalmente sustituido con 1-3 sustituyentes seleccionados de halo, OH, CO_2H, CO_2-(C_1-C_6) alquilo o (C_1-C_3) alcoxi;

R^2 y R^3 son cada uno, independientemente, H, (C_1-C_6)alquilo, (C_1-C_6)haloalquilo, halo, (C_3-C_6)cicloalquilo, CN, OH, CO_2R, $OCOR^{12}$; en donde dicho (C_1-C_6)alquilo se sustituye opcionalmente con uno o más sustituyentes seleccionados de F, (C_1-C_3) alcoxi, OH, CN o CO_2R^{12};

R^8 y R^9 son cada uno, independientemente, H, (C_1-C_6)alquilo, (C_1-C_6)haloalquilo, (C_3-C_6)cicloalquilo, CN, OH, CO_2R, $OCOR^{12}$; en donde dicho (C_1-C_6)alquilo se sustituye opcionalmente con uno o más sustituyentes seleccionados de F, (C_1-C_3) alcoxi, OH, CN o CO_2R^{12};

R^2 y R^9, cuando se toman en forma conjunta, pueden formar un anillo de 5-8 miembros;

R^4 y R^7, cuando se toman en forma conjunta, pueden formar un anillo de 5-8 miembros;

R^4 y R^5 son cada uno, independientemente, H, CN, (C_1-C_6)alquilo, halo, (C_1-C_3)alcoxi, (C_1-C_3)haloalcoxi, (C_3-C_6)cicloalquilo, OH, CO_2R^{12}, $OCOR^{12}$, en donde dicho (C_1-C_6)alquilo se sustituye opcionalmente con uno o más sustituyentes seleccionados de F, (C_1-C_3) alcoxi, OH o CO_2R^{12};

R^6 y R^7 son cada uno, independientemente, H, CN, (C_1-C_6)alquilo, halo, (C_1-C_3)alcoxi, (C_1-C_3)haloalcoxi, (C_3-C_6)cicloalquilo, OH, CO_2R^{12}, $OCOR^{12}$, en donde dicho (C_1-C_6)alquilo se sustituye opcionalmente con uno o más sustituyentes seleccionados de F, (C_1-C_3) alcoxi, OH o CO_2R^{12};

o R^2 y R^3, junto con el átomo de carbono al que están unidos, forman un grupo

espirociclilo de 3-7 miembros;

o R^4 y R^5, junto con el átomo de carbono al que están unidos, forman un grupo espirociclilo de 3-7 miembros;

o R^3 y R^4, junto con los átomos C a los que están unidos, forman un grupo cicloalquilo de 3-7 miembros o un grupo heterocicloalquilo de 3-7 miembros fusionados;

R^{10} es $(C_1\text{-}C_6)$alquilo, $(C_1\text{-}C_6)$haloalquilo, $(C_1\text{-}C_6)$hidroxialquilo, $(C_1\text{-}C_6)$alcoxi, $(C_3\text{-}C_6)$cicloalquilo, hidroxi$(C_3\text{-}C_6)$cicloalquilo, alcoxi cicloalquilo, OH, $(C_1\text{-}C_5)$heterociclilo, amino, arilo o CN,

R^{11} es arilo o heteroarilo, en donde dicho R^{11} se sustituye, opcional e independientemente, con uno o más $(C_1\text{-}C_6)$alquilo, halo, $(C_1\text{-}C_6)$haloalquilo $(C_1\text{-}C_3)$alcoxi, OH, amino, C(O)NH_2, NH_2SO_2, SF_5 o CN;

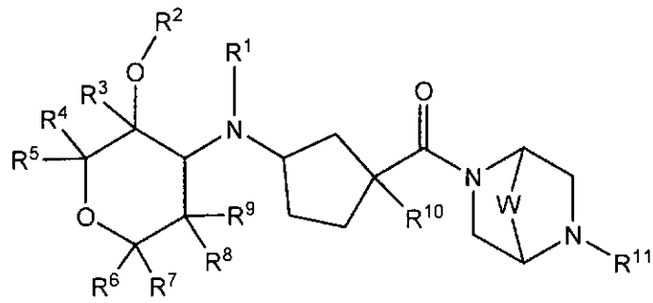
R^{12} es H, $(C_1\text{-}C_4)$alquilo o $(C_3\text{-}C_6)$cicloalquilo;

R^{13} es H, halo, $(C_1\text{-}C_4)$alquilo, $(C_1\text{-}C_4)$alcoxi u OH;

R^{14} es H, halo, $(C_1\text{-}C_4)$alquilo, $(C_1\text{-}C_4)$alcoxi u OH; y

R^{15} es H, $(C_1\text{-}C_6)$alquilo o $(C_3\text{-}C_6)$cicloalquilo.

2. Un compuesto de la Fórmula II:



(II)

o su sal farmacéuticamente aceptable, en donde

R^1 es H, $(C_1\text{-}C_6)$alquilo o $(C_3\text{-}C_6)$cicloalquilo, en donde dicho $(C_1\text{-}C_6)$alquilo se sustituye opcionalmente con halo, CN, C(O)OH u OH;

R^2 es $(C_1\text{-}C_6)$alquilo $(C_1.C_6)$haloalquilo o $(C_3\text{-}C_6)$cicloalquilo;

R^3, R^4, R^5, R^6, R^7, R^8 y R^9 son, independientemente, H, $C_1\text{-}C_4$ alquilo, CN, halo o amino;

R^{10} es $(C_1\text{-}C_6)$alquilo, $(C_1\text{-}C_6)$haloalquilo, $(C_1\text{-}C_6)$hidroxialquilo, $(C_1\text{-}C_6)$alcoxi, $(C_3\text{-}C_6)$cicloalquilo, hidroxi$(C_3\text{-}C_6)$cicloalquilo, alcoxi $(C_3\text{-}C_6)$cicloalquilo, OH, $(C_1\text{-}C_5)$heterociclilo, amino, arilo o CN;

R^{11} es arilo o heteroarilo, en donde dicho R^{11} se sustituye, opcional e independientemente, con uno o más $(C_1\text{-}C_6)$alquilo, halo, $(C_1\text{-}C_6)$haloalquilo

(C_1-C_6)alcoxi, OH, amino, $C(O)NH_2$, NH_2SO_2, SF_5 o CN;

W es $CR^{13}R^{14}$, C(O), $CHOR^{15}$, CHF, CF_2, O o S

R^{13} y R^{14} son, independientemente, H, halo, (C_1-C_4)alquilo, (C_1-C_4)alcoxi u OH; y

R^{15} es H, (C_1-C_6)alquilo o (C_3-C_6)cicloalquilo.

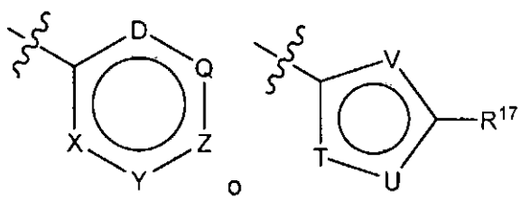
3. El compuesto de acuerdo con la reivindicación 2 o una sal de éste farmacéuticamente aceptable, en donde:

R^1 es H o (C_1-C_6)alquilo

R^2 es (C_1-C_6)alquilo o (C_1-C_6)haloalquilo

R^3, R^4, R^5, R^6, R^7, R^8 y R^9 son cada uno H;

R^{11} es



en donde X, Y, Z, Q y D son, independientemente, N o CR^{16}, y en donde 0, 1, 2 o 3 de X, Y, Z, Q y D son N; y

en donde T, U y V se seleccionan, independientemente, de CH, N, S u O, siempre que T y U no sean ambos, simultáneamente, O o S;

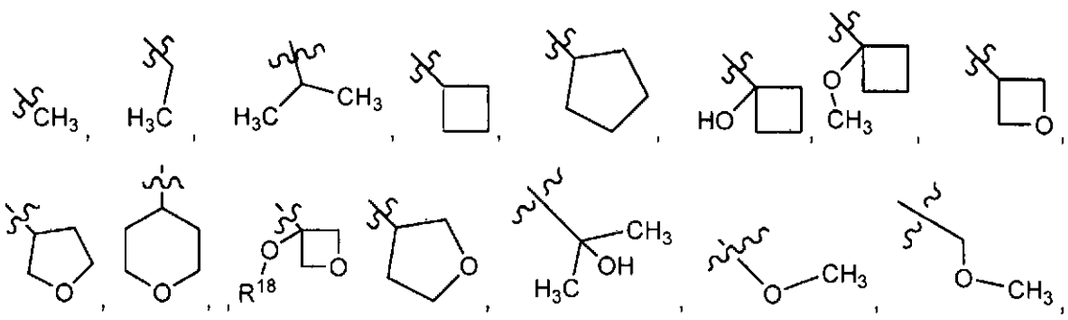
cada R^{16} es, independientemente, H, halo, (C_1-C_6)alquilo, (C_1-C_6)haloalquilo, (C_1-C_6)alcoxi o CN;

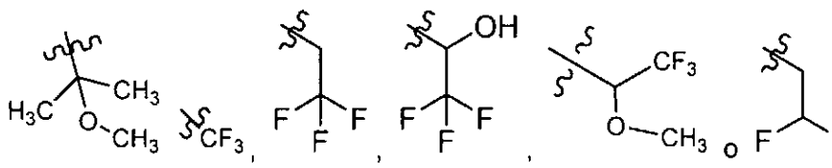
R^{17} es H, (C_1-C_6)alquilo, (C_1-C_6)haloalquilo o (C_1-C_6)alcoxi; y

W es $CR^{13}R^{14}$, C(O), $CHOR^{15}$, CHF o CF_2.

4. El compuesto de acuerdo con la reivindicación 3 o una sal de éste farmacéuticamente aceptable, en donde R^2 es metilo.

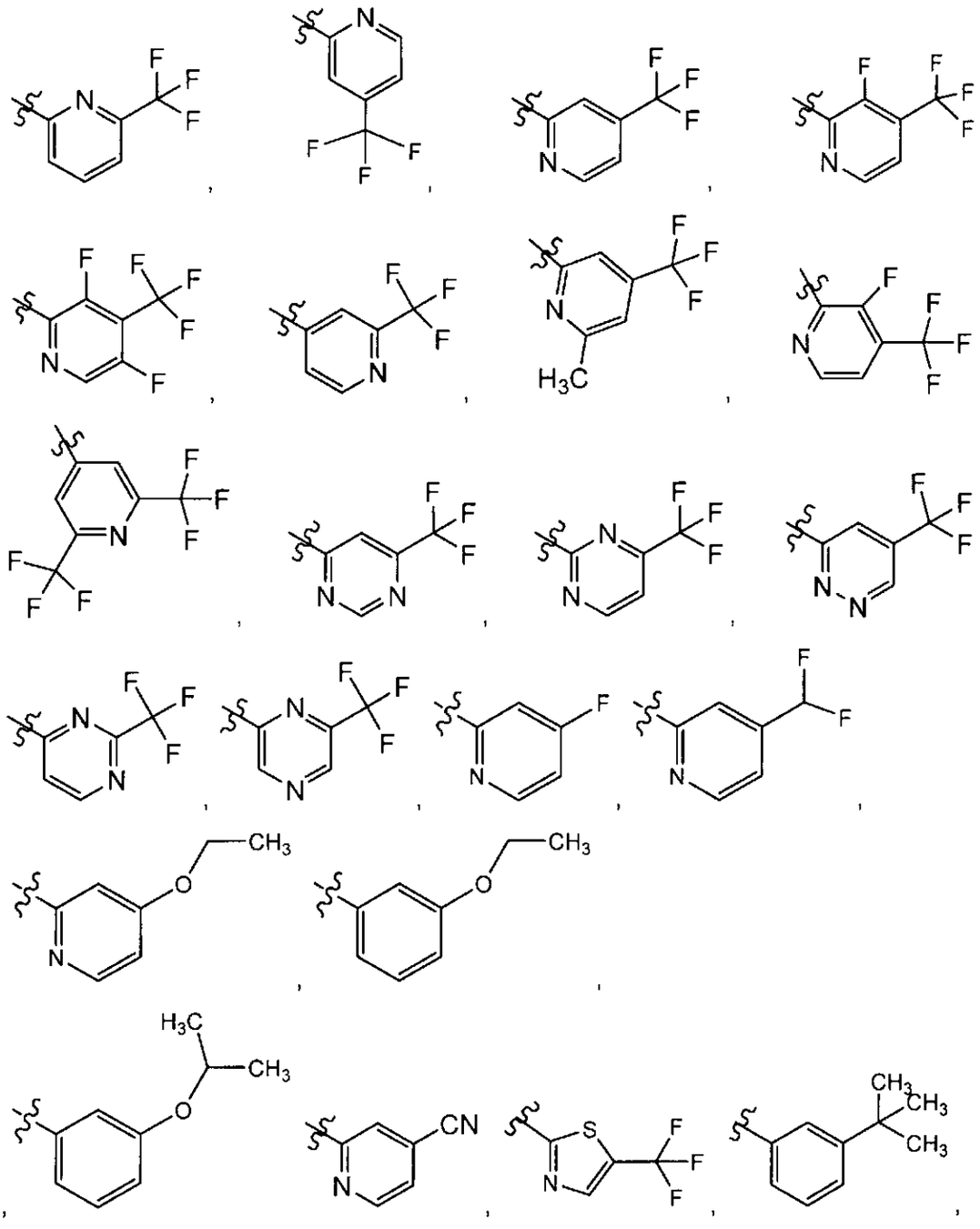
5. El compuesto de acuerdo con la reivindicación 4, en donde R^{10} es

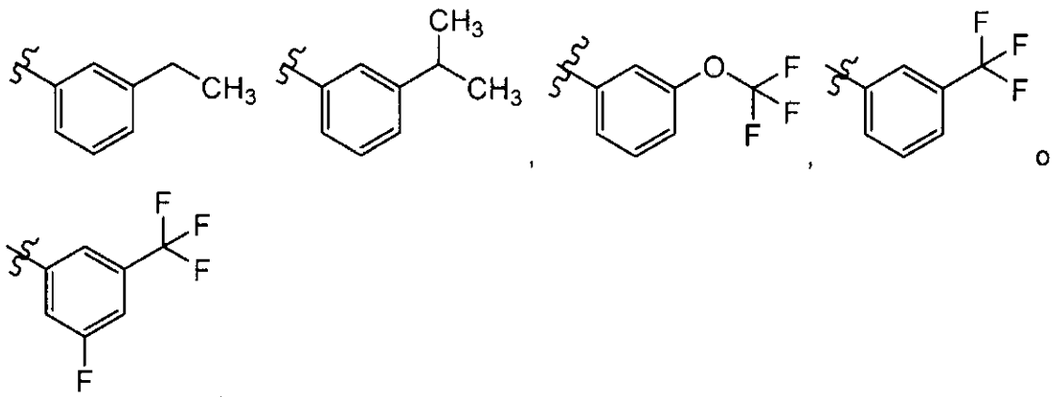




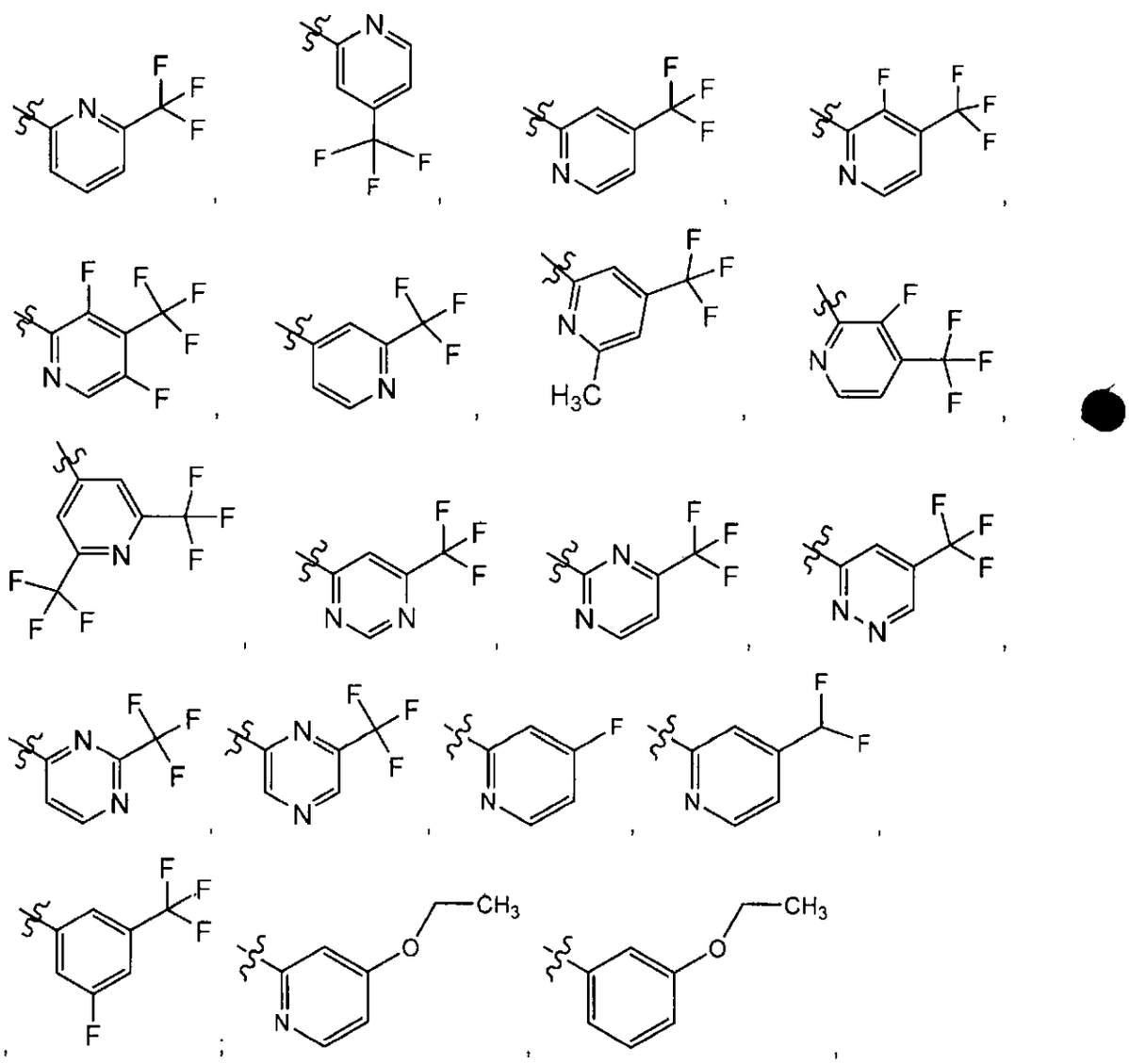
H o (C_1-C_6) alquilo.

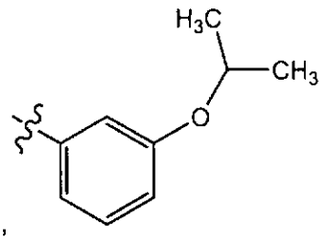
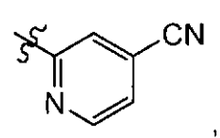
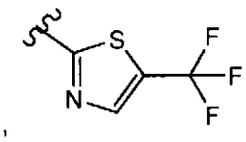
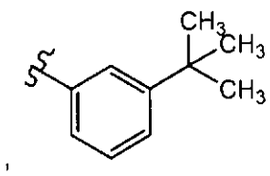
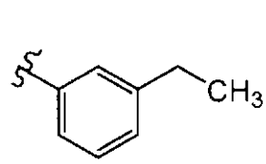
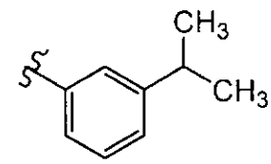
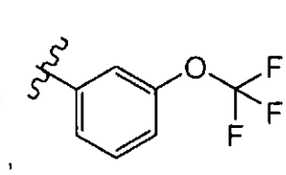
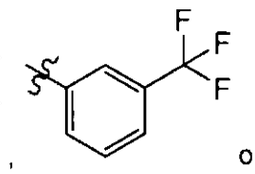
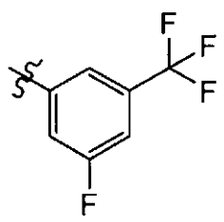
6. El compuesto de acuerdo con la reivindicación 3 o una sal de éste farmacéuticamente aceptable, en donde R^{11} es



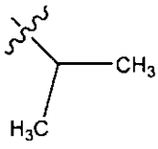
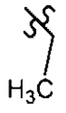


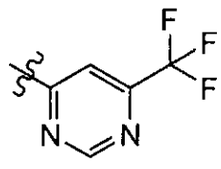
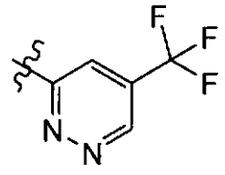
7. El compuesto de acuerdo con la reivindicación 5 o una sal de éste farmacéuticamente aceptable, en donde R^{11} es



8. El compuesto de acuerdo con la reivindicación 7, en donde R^{10} es

R^{11} es  o  .

9. Un compuesto seleccionado del grupo que consiste en:

1,5-anhidro-2,3-dideoxi-3-{[(1R,3S)-3-etil-3-({(1S,4S)-5-[4-(trifluorometil)piridin-2-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metil-D-eritro-pentitol;

1,5-anhidro-2,3-dideoxi-3-{[(1R,3S)-3-etil-3-({(1S,4S)-5-[4-(trifluorometil)pirimidin-2-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metil-D-eritro-pentitol;

1,5-anhidro-2,3-dideoxi-3-{[(1R,3S)-3-etil-3-({(1S,4S)-5-[6-(trifluorometil)pirimidin-4-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metil-D-eritro-pentitol;

1,5-anhidro-2,3-dideoxi-3-{[(1R,3S)-3-etil-3-({(1S,4S)-5-[6-(trifluorometil)pirazin-2-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metil-D-eritro-pentitol;

1,5-anhidro-2,3-dideoxi-3-{[(1R,3S)-3-etil-3-({(1S,4S)-5-[2-(trifluorometil)pirimidin-4-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metil-D-eritro-pentitol;

1,5-anhidro-2,3-dideoxi-3-{[(1R,3S)-3-etil-3-({(1S,4S)-5-[6-(trifluorometil)piridin-2-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metil-D-eritro-pentitol;

1,5-anhidro-2,3-dideoxi-3-{[(1R,3S)-3-etil-3-({(1S,4S)-5-[2-(trifluorometil)piridin-4-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metil-D-eritro-pentitol;
1,5-anhidro-2,3-dideoxi-3-{[(1R,3S)-3-etil-3-({(1S,4S)-5-[3-fluoro-4-(trifluorometil)piridin-2-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metil-D-eritro-pentitol;
1,5-anhidro-2,3-dideoxi-3-{[(1R,3S)-3-metil-3-({(1S,4S)-5-[4-(trifluorometil)piridin-2-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metil-D-eritro-pentitol;
1,5-anhidro-2,3-dideoxi-3-{[(1R,3S)-3-metil-3-({(1S,4S)-5-[6-(trifluorometil)pirazin-2-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metil-D-eritro-pentitol;
1,5-anhidro-2,3-dideoxi-3-{[(1R,3S)-3-isopropil-3-({(1S,4S)-5-[4-(trifluorometil)piridin-2-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metil-D-eritro-pentitol;
1,5-anhidro-2,3-dideoxi-3-{[(1R,3S)-3-isopropil-3-({(1S,4S)-5-[4-(trifluorometil)pirimidin-2-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metil-D-eritro-pentitol;
1,5-anhidro-2,3-dideoxi-3-{[(1R,3S)-3-isopropil-3-({(1S,4S)-5-[6-(trifluorometil)pirimidin-4-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metil-D-eritro-pentitol;
1,5-anhidro-2,3-dideoxi-3-{[(1R,3S)-3-isopropil-3-({(1S,4S)-5-[6-(trifluorometil)pirazin-2-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metil-D-eritro-pentitol;
1,5-anhidro-2,3-dideoxi-3-{[(1R,3S)-3-isopropil-3-({(1S,4S)-5-[2-(trifluorometil)pirimidin-4-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metil-D-eritro-pentitol;
1,5-anhidro-2,3-dideoxi-3-{[(1R,3S)-3-isopropil-3-({(1S,4S)-5-[6-(trifluorometil)piridin-2-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metil-D-eritro-pentitol;
1,5-anhidro-2,3-dideoxi-3-{[(1R,3S)-3-isopropil-3-({(1S,4S)-5-[2-(trifluorometil)piridin-4-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metil-D-eritro-pentitol;
1,5-anhidro-2,3-dideoxi-3-{[(1R,3S)-3-isopropil-3-({(1S,4S)-5-[5-(trifluorometil)piridazin-3-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metil-D-eritro-pentitol;
1,5-anhidro-3-{[(1R,3S)-3-isopropil-3-({(1S,4S)-5-[2,6-bis(trifluorometil)piridin-4-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)-3-isopropilciclopentil]amino}-2,3-dideoxi-4-O-metil-D-eritro-pentitol;
1,5-anhidro-2,3-dideoxi-3-{[(1R,3S)-3-({(1S,4S)-5-[3-fluoro-4-(trifluorometil)piridin-2-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)-3-isopropilciclopentil]amino}-4-O-metil-D-eritro-pentitol;

1,5-anhidro-2,3-dideoxi-3-{[(1R,3S)-3-isopropil-3-({(1S,4S)-5-[6-metil-4-(trifluorometil)piridin-2-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metil-D-eritro-pentitol;

1,5-anhidro-2,3-dideoxi-3-{[(1R,3S)-3-isopropil-3-({(1S,4S)-5-[3-(trifluorometil)fenil]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metil-D-eritro-pentitol;

1,5-anhidro-2,3-dideoxi-3-{[(1R,3S)-3-({(1S,4S)-5-[3-fluoro-5-(trifluorometil)fenil]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)-3-isopropilciclopentil]amino}-4-O-metil-D-eritro-pentitol;

1,5-anhidro-2,3-dideoxi-3-{[(1R,3S)-3-(2,2-difluoroetil)-3-({(1S,4S)-5-[6-(trifluorometil)pirimidin-4-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metil-D-eritro-pentitol;

1,5-anhidro-2,3-dideoxi-3-{[(1R,3S)-3-(2,2-difluoroetil)-3-({(1S,4S)-5-[4-(trifluorometil)piridin-2-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metil-D-eritro-pentitol;

1,5-anhidro-2,3-dideoxi-3-{[(1R,3S)-3-(2,2-difluoroetil)-3-({(1S,4S)-5-[2-(trifluorometil)piridin-4-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metil-D-eritro-pentitol;

1,5-anhidro-2,3-dideoxi-3-{[(1R,3S)-3-(2,2-difluoroetil)-3-({(1S,4S)-5-[4-(trifluorometil)pirimidin-2-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metil-D-eritro-pentitol;

1,5-anhidro-2,3-dideoxi-3-{[(1R,3S)-3-(2,2-difluoroetil)-3-({(1S,4S)-5-[6-(trifluorometil)piridin-2-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metil-D-eritro-pentitol;

1,5-anhidro-2,3-dideoxi-3-{[(1R,3S)-3-(2,2-difluoroetil)-3-({(1S,4S)-5-[6-(trifluorometil)pirazin-2-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metil-D-eritro-pentitol;

1,5-anhidro-2,3-dideoxi-3-{[(1R,3S)-3-(2,2-difluoroetil)-3-({(1S,4S)-5-[2-(trifluorometil)pirimidin-4-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metil-D-eritro-pentitol;

1,5-anhidro-2,3-dideoxi-3-{[(1R,3S)-3-(2,2-difluoroetil)-3-({(1S,4S)-5-[5-(trifluorometil)piridazin-3-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metil-D-eritro-pentitol;

1,5-anhidro-2,3-dideoxi-4-O-metil-3-{[(1R,3S)-3-(2,2,2-trifluoroetil)-3-({(1S,4S)-5-[6-(trifluorometil)pirimidin-4-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-D-eritro-pentitol;

1,5-anhidro-2,3-dideoxi-4-O-metil-3-{[(1R,3S)-3-(2,2,2-trifluoroetil)-3-({(1S,4S)-5-[4-(trifluorometil)piridin-2-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-D-eritro-pentitol;

1,5-anhidro-2,3-dideoxi-4-O-metil-3-{[(1R,3S)-3-(2,2,2-trifluoroetil)-3-({(1S,4S)-5-[2-(trifluorometil)piridin-4-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-D-eritro-pentitol;

1,5-anhidro-2,3-dideoxi-4-O-metil-3-{[(1R,3S)-3-(2,2,2-trifluoroetil)-3-({(1S,4S)-5-[4-(trifluorometil)pirimidin-2-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-D-eritro-pentitol;

1,5-anhidro-2,3-dideoxi-4-O-metil-3-{[(1R,3S)-3-(2,2,2-trifluoroetil)-3-({(1S,4S)-5-[6-(trifluorometil)piridin-2-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-D-eritro-pentitol;

1,5-anhidro-2,3-dideoxi-4-O-metil-3-{[(1R,3S)-3-(2,2,2-trifluoroetil)-3-({(1S,4S)-5-[6-(trifluorometil)pirazin-2-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-D-eritro-pentitol;

1,5-anhidro-2,3-dideoxi-4-O-metil-3-{[(1R,3S)-3-(2,2,2-trifluoroetil)-3-({(1S,4S)-5-[2-(trifluorometil)pirimidin-4-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-D-eritro-pentitol;

1,5-anhidro-2,3-dideoxi-4-O-metil-3-{[(1R,3S)-3-(2,2,2-trifluoroetil)-3-({(1S,4S)-5-[5-(trifluorometil)piridazin-3-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-D-eritro-pentitol;

1,5-anhidro-2,3-dideoxi-3-{[(1S,4S)-4-isopropill-4-({(1S,4S)-5-[4-(trifluorometil)piridin-2-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopent-2-en-1-il]amino}-4-O-metil-D-eritro-pentitol;

1,5-anhidro-2,3-dideoxi-3-{[(1S,4S)-4-isopropill-4-({(1S,4S)-5-[4-(trifluorometil)pirimidin-2-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopent-2-en-1-il]amino}-4-O-metil-D-eritro-pentitol;

1,5-anhidro-2,3-dideoxi-3-{[(1S,4S)-4-isopropill-4-({(1S,4S)-5-[6-(trifluorometil)piridin-2-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopent-2-en-1-il]amino}-4-O-metil-D-eritro-pentitol;

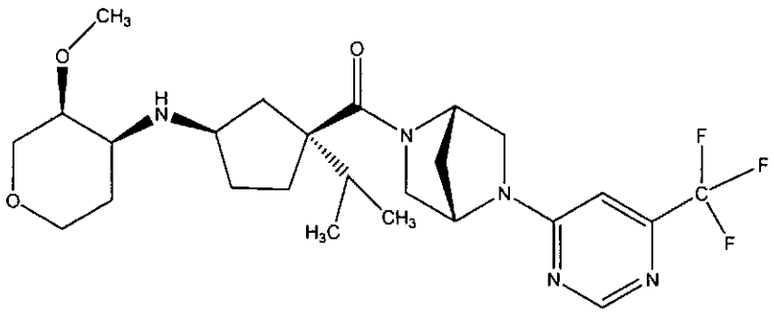
1,5-anhidro-2,3-dideoxi-3-{[(1S,4S)-4-isopropill-4-({(1S,4S)-5-[6-(trifluorometil)pirazin-2-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopent-2-en-1-il]amino}-4-O-metil-D-eritro-pentitol;

1,5-anhidro-3-{[(1R,3S)-3-{[(1S,4S)-5-(ter-butoxicarbonil)-2,5-diazabiciclo[2.2.1]hept-2-il]carbonil}-3-etilciclopentil]amino}-2,3-dideoxi-4-O-metil-D-eritro-pentitol;

1,5-anhidro-3-{[(1R,3S)-3-{[(1S,4S)-5-(ter-butoxicarbonil)-2,5-diazabiciclo[2.2.1]hept-2-il]carbonil}-3-(2,2,2-trifluoroetil)ciclopentil]amino}-2,3-dideoxi-4-O-metil-D-eritro-pentitol;
1,5-anhidro-2,3-dideoxi-3-{[(1R,3S)-3-(1-hidroxiciclobutil)-3-({(1S,4S)-5-[6-(trifluorometil)piridin-2-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metil-D-eritro-pentitol;
1,5-anhidro-2,3-dideoxi-3-{[(1R,3S)-3-(1-hidroxiciclobutil)-3-({(1S,4S)-5-[4-(trifluorometil)piridin-2-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metil-D-eritro-pentitol;
1,5-anhidro-2,3-dideoxi-3-{[(1R,3S)-3-(1-hidroxiciclobutil)-3-({(1S,4S)-5-[4-(trifluorometil)pirimidin-2-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metil-D-eritro-pentitol;
1,5-anhidro-2,3-dideoxi-3-{[(1R,3S)-3-(1-hidroxiciclobutil)-3-({(1S,4S)-5-[2-(trifluorometil)pirimidin-4-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metil-D-eritro-pentitol;
1,5-anhidro-2,3-dideoxi-3-{[(1R,3S)-3-(1-hidroxiciclobutil)-3-({(1S,4S)-5-[6-(trifluorometil)pirimidin-4-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metil-D-eritro-pentitol;
1,5-anhidro-2,3-dideoxi-3-{[(1R,3S)-3-(1-hidroxiciclobutil)-3-({(1S,4S)-5-[6-(trifluorometil)pirazin-2-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metil-D-eritro-pentitol;
1,5-anhidro-2,3-dideoxi-3-{[(1R,3S)-3-(1-hidroxiciclobutil)-3-({(1S,4S)-5-[2-(trifluorometil)piridin-4-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metil-D-eritro-pentitol;
1,5-anhidro-2,3-dideoxi-3-{[3-(1-hidroxi-1-metiletil)-3-({5-[4-(trifluorometil)piridin-2-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metilpentitol;
1,5-anhidro-2,3-dideoxi-3-{[3-(1-hidroxi-1-metiletil)-3-({5-[6-(trifluorometil)pirimidin-4-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metilpentitol;
1,5-anhidro-2,3-dideoxi-3-{[3-(1-hidroxi-1-metiletil)-3-({5-[4-(trifluorometil)pirimidin-2-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metilpentitol;
1,5-anhidro-2,3-dideoxi-3-{[3-(1-hidroxi-1-metiletil)-3-({5-[5-(trifluorometil)piridazin-3-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metilpentitol;
1,5-anhidro-2,3-dideoxi-3-{[3-(1-hidroxi-1-metiletil)-3-({5-[2-(trifluorometil)pirimidin-4-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metilpentitol;
1,5-anhidro-2,3-dideoxi-3-{[3-(1-hidroxi-1-metiletil)-3-({5-[6-(trifluorometil)piridin-2-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metilpentitol;

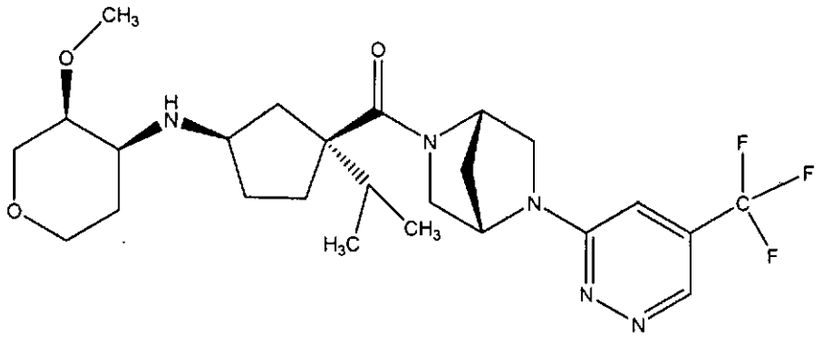
1,5-anhidro-2,3-dideoxi-3-{[3-(1-hidroxi-1-metiletil)-3-({5-[2-(trifluorometil)piridin-4-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metilpentitol; y
1,5-anhidro-2,3-dideoxi-3-{[3-(1-hidroxi-1-metiletil)-3-({5-[6-(trifluorometil)pirazin-2-il]-2,5-diazabiciclo[2.2.1]hept-2-il}carbonil)ciclopentil]amino}-4-O-metilpentitol.

10. Un compuesto de la Fórmula:



o una sal de éste farmacéuticamente aceptable.

11. Un compuesto de la Fórmula



o una sal de éste farmacéuticamente aceptable.

12. Una composición que comprende un compuesto de acuerdo con la reivindicación 2 o una sal de éste farmacéuticamente aceptable y un portador.

13. Un método para tratar una enfermedad asociada con la expresión o actividad de un receptor de quimiocina en un paciente, que comprende administrarle al paciente un compuesto de acuerdo con la reivindicación 2 o una sal de éste farmacéuticamente aceptable.

14. El método de acuerdo con la reivindicación 13, en donde dicho receptor de quimiocina es CCR2 o CCR5.

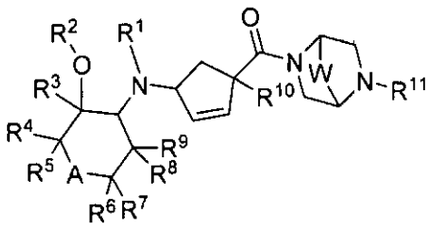
15. El método de acuerdo con la reivindicación 13, en donde dicha enfermedad es artritis reumatoide, ateroesclerosis, lupus, esclerosis múltiple, dolor, rechazo al trasplante, diabetes, fibrosis hepática, enfermedad viral, cáncer, asma, rinitis alérgica estacional y perenne, sinusitis, conjuntivitis, degeneración macular relacionada con la edad, alergia a los alimentos, intoxicación escombroide, soriasis, espondiloartropatía

indiferenciada, gota, urticaria, prurito, eczema, enfermedad del intestino inflamable, enfermedad trombótica, otitis media, fibrosis, cirrosis hepática, enfermedad cardíaca, enfermedad de Alzheimer, sepsis, restenosis, enfermedad de Crohn, colitis ulcerativa, síndrome del intestino irritable, enfermedades pulmonares por hipersensibilidad, fibrosis pulmonar inducida por drogas, enfermedad pulmonar obstructiva crónica, artritis, nefritis, dermatitis atópica, apoplejía, lesión aguda del nervio, sarcoidosis, hepatitis, endometriosis, dolor neuropático, neumonitis por hipersensibilidad, neumonía eosinofílica, hipersensibilidad demorada, enfermedad pulmonar intersticial, trastornos oculares u obesidad .

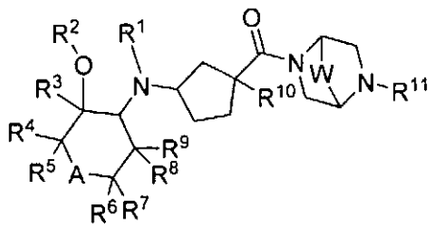
16. El uso de un compuesto de acuerdo con cualquiera de las reivindicaciones 1-11 o una sal de éste aceptable farmacéuticamente para la fabricación de un medicamento para el tratamiento de artritis reumatoide, ateroesclerosis, lupus, esclerosis múltiple, dolor, rechazo al trasplante, diabetes, fibrosis hepática, enfermedad viral, cáncer, asma, rinitis alérgica estacional y perenne, sinusitis, conjuntivitis, degeneración macular relacionada con la edad, alergia a los alimentos, intoxicación escombroide, soriasis, espondiloartropatía indiferenciada, gota, urticaria, prurito, eczema, enfermedad del intestino inflamable, enfermedad trombótica, otitis media, fibrosis, cirrosis hepática, enfermedad cardíaca, enfermedad de Alzheimer, sepsis, restenosis, enfermedad de Crohn, colitis ulcerativa, síndrome del intestino irritable, enfermedades pulmonares por hipersensibilidad, fibrosis pulmonar inducida por drogas, enfermedad pulmonar obstructiva crónica, artritis, nefritis, dermatitis atópica, apoplejía, lesión aguda del nervio, sarcoidosis, hepatitis, endometriosis, dolor neuropático, neumonitis por hipersensibilidad, neumonía eosinofílica, hipersensibilidad demorada, enfermedad pulmonar intersticial, trastornos oculares u obesidad .

RESUMEN

Se provee un compuesto de la Fórmula I(a) o I(b):



I(a)



I(b)

o una sal de éste farmacéuticamente aceptable, en donde varios sustituyentes se definen en la presente.

PC33776A

IN THE INTERNATIONAL BUREAU

IN RE THE APPLICATION OF: **PFIZER INC.**
INTERNATIONAL APPLICATION NUMBER: **PCT/IB2009/5232**
INTERNATIONAL FILING DATE: **20 NOVEMBER 2009 (20.11.2009)**
PRIORITY DATE(S) CLAIMED: **26 NOVEMBER 2008**
FOR: **3-AMINOCYCLOPENTANECARBOXAMIDES AS CHEMOKINE RECEPTOR MODULATORS**
OUR REF: **PC33776A**

PCT International Bureau
Receiving Office
World Intellectual Property Organization
34, chemin des Colombettes
1211 Geneva 20
Switzerland (CH)

REQUEST FOR ADDRESS CHANGE

SENT VIA FACSIMILE ONLY

Sirs:

Applicant(s) hereby request change of addresses under Rule 92bis. The following address changes are as follows:

Rajesh Devraj
301 Palomino Hill Court
Chesterfield, MO 63005

Wei Huang
919 Crown Pointe Estates Drive
Wildwood, MO 63021

Robert Hughes
Pfizer Global Research & Development
200 Cambridge Park Drive
Cambridge, MA 02140

Donald Joseph Rogier Jr.
Pfizer Global Research & Development
Eastern Point Road
Groton, CT 06340

John Trujillo
Pfizer Global Research & Development
Eastern Point Road
Groton, CT 06340

Steve Turner
125 Skyview Lane
Labadie, MO 63055

Date: APR 29 2011

Very truly yours,

Groton, Connecticut, USA

Gregg C. Benson, Vice President and
Assistant General Counsel,

Pfizer Inc.
Eastern Point Road, Mailstop 8260-1615
Groton, Connecticut 06340
United States of America
212-573-2521

152

PATENT COOPERATION TREATY PCT/IB2009/055232

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92*bis*.1 and Administrative Instructions, Section 422)

To:

BENSON, Gregg C.
Pfizer Inc. Eastern Point Road, MS 9114
Groton, Connecticut 06340
ETATS-UNIS D'AMERIQUE

Date of mailing *(day/month/year)*
20 May 2011 (20.05.2011)

Applicant's or agent's file reference
PC 33776A

IMPORTANT NOTIFICATION

International application No.
PCT/IB2009/055232

International filing date *(day/month/year)*
20 November 2009 (20.11.2009)

1. The following indications appeared on record concerning:

☒ the applicant ☒ the inventor ☐ the agent ☐ the common representative

Name and Address

DEVRAJ, Rajesh Venkateswaran
Pfizer Global Research & Development
700 Chesterfield Parkway West
Chesterfield, Missouri 63017
United States of America

State of Nationality: IN
State of Residence: US
Telephone No.:
Facsimile No.:
E-mail address:

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person ☐ the name ☒ the address ☐ the nationality ☐ the residence

Name and Address

DEVRAJ, Rajesh Venkateswaran
301 Palomino Hill Court
Chesterfield, MO 63005
United States of America

State of Nationality: IN
State of Residence: US
Telephone No.:
Facsimile No.:
E-mail address:
☐ Notifications by e-mail authorized

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

☐ the receiving Office
☐ the International Searching Authority
☐ the Authority(ies) specified for supplementary search
☐ the International Preliminary Examining Authority
☒ the designated Offices concerned
☐ the elected Offices concerned
☐ other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. +41 22 910 06 10

Authorized officer
Ouchoukhi Mohamed
e-mail ro.ib@wipo.int
Telephone No. +4122 338 8566

153

PATENT COOPERATION TREATY PCT/IB2009/055232

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(PCT Rule 92*bis*.1 and Administrative Instructions, Section 422)

To:

BENSON, Gregg C.
Pfizer Inc. Eastern Point Road, MS 9114
Groton, Connecticut 06340
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PC 33776A

IMPORTANT NOTIFICATION

International application No.
PCT/IB2009/055232

International filing date *(day/month/year)*
20 November 2009 (20.11.2009)

1. The following indications appeared on record concerning:

☒ the applicant ☒ the inventor ☐ the agent ☐ the common representative

Name and Address
HUANG, Wei
Pfizer Global Research & Development
700 Chesterfield Parkway West
Chesterfield, Missouri 63017
United States of America

State of Nationality: US
State of Residence: US
Telephone No.:
Facsimile No.:
E-mail address:

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person ☐ the name ☒ the address ☐ the nationality ☐ the residence

Name and Address
HUANG, Wei
919 Crown Pointe Estates Drive
Wildwood, MO 63021
United States of America

State of Nationality: US
State of Residence: US
Telephone No.:
Facsimile No.:
E-mail address:
☐ Notifications by e-mail authorized

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

☐ the receiving Office
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☐ other:

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34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. +41 22 910 06 10

Authorized officer
Ouchoukhi Mohamed
e-mail ro.ib@wipo.int
Telephone No. +4122 338 8566

154

PATENT COOPERATION TREATY PCT/IB2009/055232

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IMPORTANT NOTIFICATION

International application No.
PCT/IB2009/055232

International filing date *(day/month/year)*
20 November 2009 (20.11.2009)

1. The following indications appeared on record concerning:

☒ the applicant ☒ the inventor ☐ the agent ☐ the common representative

Name and Address
HUGHES, Robert Owen
Pfizer Global Research & Development
700 Chesterfield Parkway West
Chesterfield, Missouri 63017
United States of America

State of Nationality: GB
State of Residence: US
Telephone No.:
Facsimile No.:
E-mail address:

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person ☐ the name ☒ the address ☐ the nationality ☐ the residence

Name and Address
HUGHES, Robert Owen
Pfizer Global Research & Development
200 Cambridge Park Drive
Cambridge, MA 02140
United States of America

State of Nationality: GB
State of Residence: US
Telephone No.:
Facsimile No.:
E-mail address:
☐ Notifications by e-mail authorized

3. Further observations, if necessary:

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☐ the International Preliminary Examining Authority
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☐ the elected Offices concerned
☐ other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. +41 22 910 06 10

Authorized officer
Ouchoukhi Mohamed
e-mail ro.ib@wipo.int
Telephone No. +4122 338 8566

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PATENT COOPERATION TREATY PCT/IB2009/055232

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20 May 2011 (20.05.2011)

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PC 33776A

IMPORTANT NOTIFICATION

International application No.
PCT/IB2009/055232

International filing date *(day/month/year)*
20 November 2009 (20.11.2009)

1. The following indications appeared on record concerning:

☒ the applicant ☒ the inventor ☐ the agent ☐ the common representative

Name and Address
ROGIER JR., Donald Joseph
Pfizer Global Research & Development
700 Chesterfield Parkway West
Chesterfield, Missouri 63017
United States of America

State of Nationality: US
State of Residence: US
Telephone No.:
Facsimile No.:
E-mail address:

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person ☐ the name ☒ the address ☐ the nationality ☐ the residence

Name and Address
ROGIER JR., Donald Joseph
Pfizer Global Research & Development
Eastern Point Road
Groton, CT 06340
United States of America

State of Nationality: US
State of Residence: US
Telephone No.:
Facsimile No.:
E-mail address:
☐ Notifications by e-mail authorized

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☒ the designated Offices concerned
☐ the elected Offices concerned
☐ other:

The International Bureau of WIPO
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Authorized officer
Ouchoukhi Mohamed
e-mail ro.ib@wipo.int
Telephone No. +4122 338 8566

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Date of mailing *(day/month/year)*
20 May 2011 (20.05.2011)

Applicant's or agent's file reference
PC 33776A

IMPORTANT NOTIFICATION

International application No.
PCT/IB2009/055232

International filing date *(day/month/year)*
20 November 2009 (20.11.2009)

1. The following indications appeared on record concerning:

☒ the applicant ☒ the inventor ☐ the agent ☐ the common representative

Name and Address
TRUJILLO, John Isidro
Pfizer Global Research & Development
700 Chesterfield Parkway West
Chesterfield, Missouri 63017
United States of America

State of Nationality: US
State of Residence: US
Telephone No.:
Facsimile No.:
E-mail address:

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person ☐ the name ☒ the address ☐ the nationality ☐ the residence

Name and Address
TRUJILLO, John Isidro
Pfizer Global Research & Development
Eastern Point Road
Groton, CT 06340
United States of America

State of Nationality: US
State of Residence: US
Telephone No.:
Facsimile No.:
E-mail address:
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1211 Geneva 20, Switzerland

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Authorized officer
Ouchoukhi Mohamed
e-mail ro.ib@wipo.int
Telephone No. +4122 338 8566

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To:

BENSON, Gregg C.
Pfizer Inc. Eastern Point Road, MS 9114
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ETATS-UNIS D'AMERIQUE

Date of mailing *(day/month/year)*
20 May 2011 (20.05.2011)

Applicant's or agent's file reference
PC 33776A

IMPORTANT NOTIFICATION

International application No.
PCT/IB2009/055232

International filing date *(day/month/year)*
20 November 2009 (20.11.2009)

1. The following indications appeared on record concerning:

☒ the applicant ☒ the inventor ☐ the agent ☐ the common representative

Name and Address
TURNER, Steve Ronald
Pfizer Global Research & Development
700 Chesterfield Parkway West
Chesterfield, Missouri 63017
United States of America

State of Nationality: US
State of Residence: US
Telephone No.:
Facsimile No.:
E-mail address:

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person ☐ the name ☒ the address ☐ the nationality ☐ the residence

Name and Address
TURNER, Steve Ronald
125 Skyview Lane
Labadie, MO 63055
United States of America

State of Nationality: US
State of Residence: US
Telephone No.:
Facsimile No.:
E-mail address:
☐ Notifications by e-mail authorized

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

☐ the receiving Office
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☐ the elected Offices concerned
☐ other:

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1211 Geneva 20, Switzerland

Facsimile No. +41 22 910 06 10

Authorized officer
Ouchoukhi Mohamed
e-mail ro.ib@wipo.int
Telephone No. +4122 338 8566

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
PC 33776A		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/IB2009/055232	20/11/2009	26/11/2008
Applicant		
PFIZER INC.		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 3 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**
   a. With regard to the **language,** the international search was carried out on the basis of:
      [X] the international application in the language in which it was filed
      [ ] a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))
   b. [ ] This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).
   c. [ ] With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. [ ] **Certain claims were found unsearchable** (See Box No. II)

3. [ ] **Unity of invention is lacking** (see Box No III)

4. With regard to the **title,**
   [ ] the text is approved as submitted by the applicant
   [X] the text has been established by this Authority to read as follows:
   3-AMINOCYCLOPENTANECARBOXAMIDES AS CHEMOKINE RECEPTOR MODULATORS

5. With regard to the **abstract,**
   [X] the text is approved as submitted by the applicant
   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

6. With regard to the **drawings,**
   a. the figure of the **drawings** to be published with the abstract is Figure No. _____
      [ ] as suggested by the applicant
      [ ] as selected by this Authority, because the applicant failed to suggest a figure
      [ ] as selected by this Authority, because this figure better characterizes the invention
   b. [ ] none of the figures is to be published with the abstract

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2009/055232

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D487/08 A61K31/407 A61P29/02 A61P35/00

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 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2006/020133 A1 (XUE CHU-BIAO [US] ET AL) 26 January 2006 (2006-01-26) claim 1; examples 1-4,15-34	1-16
A	US 2005/234034 A1 (PENNELL ANDREW M [US] ET AL PENNELL ANDREW M K [US] ET AL) 20 October 2005 (2005-10-20) claim 1 3rd compound of page 45	1-16

☐ 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

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 February 2010	09/03/2010

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Fax: (+31–70) 340–3016	Matés Valdivielso, J

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2009/055232

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2006020133 A1	26-01-2006	US 2009208485 A1	20-08-2009
US 2005234034 A1	20-10-2005	US 2006074121 A1	06-04-2006

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 11-064157- -00000-0000

Fecha: 2011-05-24 16:41:17 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 159

PATENTE DE INVENCIÓN ☐ **MODELO DE**

- ☐ Indicación que se solicita una patente.
- ☐ Datos de identificación del solicitante o de la persona que presenta la solicitud
- ☐ Descripción de la invención
- ☐ Dibujos de ser estos pertinentes
- ☐ Comprobante de pago de las tasas establecidas (De ser el caso formato de descuento)

Completa ☐ Incompleta ☐

PATENTE DE INVENCIÓN PCT ☑ **MODELO DE UTILIDAD PCT** ☐ **Art.33 Decisión 486/00, Circular Única**

- ☑ Indicación que se solicita una PCT
- ☑ Copia de la solicitud en español, tal como fue presentada inicialmente (capítulo descriptivo, reivindicatorio, resumen)
- ☐ Dibujos de ser estos pertinentes
- ☑ Comprobante de pago de las tasas establecidas (de ser el caso formato de descuento)

Completa ☐ Incompleta ☐

DISEÑO INDUSTRIAL ☐ **(Art. 119 Decisión 486/00)**

- ☐ Indicación que se solicita Diseño industrial
- ☐ Datos de identificación del solicitante o de la persona que presenta la solicitud
- ☐ Representación gráfica y fotográfica del Diseño industrial o muestra del material que incorpora el diseño
- ☐ Comprobante de pago de las tasas establecidas

Completa ☐ Incompleta ☐

ESQUEMA DE TRAZADO ☐ **(Art. 92 Decisión 486/00)**

- ☐ Indicación que se solicita un esquema de trazado
- ☐ Datos de identificación del solicitante o de la persona que presenta la solicitud
- ☐ Representación gráfica de un esquema de trazado
- ☐ Comprobante de pago de las tasas establecidas

Completa ☐ Incompleta ☐

Industria y Comercio
SUPERINTENDENCIA

Bogotá,
2020

Doctor(a)
OLARTE GARCIA CARLOS REINALDO
Apoderado(a) y/o Representante de
PFIZER INC.

REFERENCIA	Radicación No.	11 64157
	Solicitud internacional	PCT/IB2009/055232
	Fecha inicio fase nacional	26/06/2011
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	010955

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. Con respecto al resumen y de conformidad con lo dispuesto en el artículo 31 D. 486 en el cual se establece que el resumen consiste en una síntesis de la divulgación técnica contenida en la solicitud de patente, debe adecuar el resumen a los dispuesto en dicha norma, teniendo en cuenta que el extracto permitirá precisar el objeto de la invención, sus elementos característicos y el campo de aplicación.

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Unica No.10 de 2001.

CARLOS DANIEL LEMUS GIRALDO
Profesional Universitario 2044-09 (P) con asignación de funciones
de la Dirección de Nuevas Creaciones.

El anterior requerimiento fue notificado por fijación en lista de fecha 15 JUL. 2011
adpa11

Industria y Comercio
SUPERINTENDENCIA

Bogotá,
2020

Doctor(a)
OLARTE GARCIA CARLOS REINALDO
Apoderado(a) y/o Representante de
PFIZER INC.

REFERENCIA	Radicación No.	11 64157
	Solicitud internacional	PCT/IB2009/055232
	Fecha inicio fase nacional	26/06/2011
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	010956

Teniendo en cuenta que el capítulo reivindicatorio presentado excede de diez reivindicaciones, es necesario que cancele la tasa establecida por cada reivindicación adicional presentada, de conformidad con lo dispuesto en la resolución de tasas vigente para la fecha de presentación de la solicitud, so pena de que no sean tenidas en cuenta dentro del presente trámite administrativo.

En consecuencia, con fundamento en lo previsto por el artículo 12 del Código Contencioso Administrativo, se le requiere para que dentro del término de dos (2) meses siguientes a la fecha de notificación del presente oficio atienda el requerimiento aquí señalado. Lo anterior, con el alcance que para tal efecto establece el artículo 13 de la misma codificación, respecto de las reivindicaciones adicionales.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del titulo primero de la Circular Única N° 10 de 2001.

CARLOS DANIEL LEMUS GIRALDO
Profesional Universitario 2044-09 (P) con asignación de funciones
de la Dirección de Nuevas Creaciones.

El anterior requerimiento fue notificado por fijación en lista de fecha 15 JUL. 2011
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