SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 11-038996- -00000-0000
Fecha: 2011-03-30 14:34:24 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 872
Industria y Com
SUPERINTENDE
INDUSTRIAL
República de Colombia
Ministerio de Comercio, Industria y Turismo

Q.P

Delegatura de Propiedad Industrial
División de Nuevas Creaciones

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
INVENTARIO

SOLICITUD DE PCT

PATENTE DE INVENCION
PCT ENTRADA EN FASE NACIONAL

(I PARTE)

21. EXPEDIENTE No. 11-38996

54. TITULO: **COMPUESTOS ANTIVIRALES**

52. CLASIFICACION INTERNACIONAL: **C07D 403/14**

71. SOLICITANTE: **ABBOTT LABORATORIES**

DOMICILIO: **100 Abbott Park Road, Abbott Park, Illinois 60064, ESTADOS UNIDOS DE AMERICA**

74. APODERADO: **Dra. MARGARITA CASTELLANOS A.**

22. BOGOTA, D.C., _____

Cw. Rivas
11-01-2012

Industria y Comercio
SUPERINTENDENCIA

ADMIS

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 11-038996- -00000-0000

Fecha: 2011-03-30 14:34:24 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 872

PATENTE DE INVENCION [ ] MODELO DE UTILIDAD [ ] **Art. 33 Decisión 486/00**

- [ ] Indicación que se solicita una patente
- [ ] Datos de identificación del solicitante o de la persona que presenta la solicitud
- [ ] Descripción de la invención
- [ ] Dibujos de ser estos pertinentes
- [ ] Comprobante de pago de las tasas establecidas (de ser el caso formato de descuento)

Completa [ ] Incompleta [ ]

PATENTE DE INVENCION PCT [X] MODELO DE UTILIDAD PCT [ ] **Art. 33 Decisión 486/00 Circular Única**

- [X] Indicación que se solicita una PCT
- [X] Datos de identificación del solicitante o de la persona que presenta la solicitud
- [X] Copia de la solicitud en español, tal como fue presentada inicialmente (capitulo descriptivo, reivindicatorio, resumen)
- [ ] Dibujos de ser estos pertinentes
- [X] Comprobante de pago de las tasas establecidas (de ser el caso formato de descuento)

Completa [X] 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 [ ]

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PETITORIO

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

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No. 11-038996- -00000-0000

Fecha: 2011-03-30 14:34:24 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 872

FORMULARIO UNICO DE SOLICITUD DE PATENTES
PCT
ENTRADA EN FASE NACIONAL

SOLICITUD DE:

(1)

[X] Patente de Invención. [ ] Patente de Modelo de Utilidad.

[X] Capítulo I [ ] Capítulo II

(2) SOLICITANTE (71)

Nombre: ABBOTT LABORATORIES

Dirección: 100 Abbott Park Road
Abbott Park, Illinois 60064
ESTADOS UNIDOS DE AMERICA

Domicilio: Abbott Park, Illinois - ESTADOS UNIDOS DE AMERICA

Lugar de Constitución: ESTADOS UNIDOS DE AMERICA

Teléfono: Fax:
E-mail:

IDENTIFICACIÓN

C.C. [ ] NIT [ ]

C.E. [ ] Otro [ ]

Cual

Número

(3) REPRESENTANTE O APODERADO

Nombre: MARGARITA CASTELLANOS A.

Dirección: CALLE 94A No. 7A-09

Teléfono: 7560770 Fax: 7550158

E-mail: info@castellanosyco.com

IDENTIFICACIÓN

C.C. [X] NIT [ ]

C.E. [ ] Otro [ ]
Cual

Número 39'779.654 TPA 70.819

(4) INVENTOR (ES) (72)

VER ANEXO # 1

(5) PCT (86)

Solicitud Internacional No. PCT/US2010/038077 Fecha 10/06/2010

Publicación Internacional No. WO 2010/144646 A2 Fecha 16/12/2010

(6) Título (54) COMPUESTOS ANTIVIRALES

(7) Clasificación Internacional (51) C07D 403/14

(8) Prioridad

SI [X] NO [ ]

(33) Pais de Origen	(32) Fecha	(31) Número de Solicitud
US	11/06/2009	61/186,291
US	16/09/2009	61/242,836
US	18/09/2009	61/243,596

(9) Comprobantes de pago Nos. 11-0028565 y 11-0028568 Fecha Marzo 29 de 2011

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

(10) Anexos

- [X] Comprobante de pago de la tasa de presentación de la solicitud.
- [X] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- [X] Poderes, si fuere el caso, junto con la sustitución del mismo a mi favor
- [ ] Documento de cesión del inventor al solicitante o a su causante.
- [ ] Declaraciones.
- [X] Copia de la solicitud internacional (Resumen, descripción, reivindicaciones, dibujos).
- [X] Traducción de la solicitud internacional al castellano (Resumen, descripción, reivindicaciones, dibujos).
- [ ] Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen Preliminar (IPEA).
- [ ] Traducción del examen preliminar internacional efectuado por la IPEA.
- [ ] De ser el caso, copia del contrato de acceso.
- [ ] De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- [ ] De ser el caso, certificado de depósito del material biológico.
- [ ] Arte final 12x12
- [ ] De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- [ ] De ser el caso, modificaciones efectuadas a la solicitud internacional.
- [X] Otros: **Tarjeta Propietario, Extracto para la publicación, Formatos IB/306 (Notificación de Cambio)**

(11) FIGURA CARACTERISTICA:

(12) Solicito la concesión de la patente,

NOMBRE: MARGARITA CASTELLANOS ABONDANO

FIRMA:

C.C. No. 39.779.654 Usaquén - TPA 70.819 C.S.J.

Instrucciones para el diligenciamiento del presente formulario, ver reverso de esta página. - MCA/gcb - P2187

CASTELLANOS & CO LTDA
ABOGADOS
Calle 94 A No. 7 A-09
Bogotá, D.C. – COLOMBIA

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Evanston, Illinois 60201
ESTADOS UNIDOS DE AMERICA

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

Industria y Comercio
SUPERINTENDENCIA

RECIBO DE CAJA

No. 11 - 0028565

Bogotá D.C., Marzo 29 de 2011 - 15:05:27

RECIBIDO DE : CASTELLANOS Y Y CO NI 800.174.641

*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	167747904	29/03/2011	5.421.000.00

*** 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. 11-038996- -00000-0000
Fecha: 2011-03-30 14:34:24 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTE(YII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 872

000007

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

Industria y Comercio
SUPERINTENDENCIA

RECIBO DE CAJA

No. 11 - 0028568

Bogotá D.C., Marzo 29 de 2011 - 15:05:27

RECIBIDO DE : CASTELLANOS Y Y CO NI 800.174.641

*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR.PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	167747904	29/03/2011	5.421.000.00

*** Conceptos Pagados ***

CANT	RENTISTICO	CONCEPTO	Vr.UNDITARIO	Vr.CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD INDUSTRIAL	99 OTROS SERVCIOS ADMINISTRATIVOS	270.000.00	270.000.00
				$270.000.00

SON: **DOSCIENTOS SETENTA MIL PESOS MONEDA CORRIENTE***

Responsable: _____

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 11-038996- -00000-0000

Fecha: 2011-03-30 14:34:24 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 872

El (los)

ABBOTT LABORATORIES

Domiciliados en

100 Abbott Park Road
Abbott Park
Illinois 60064
E.U.A.

Nombran por el presente a XIMENA CASTELLANOS A. y/o MARGARITA CASTELLANOS A. abogadas con oficinas en la Calle 94A No. 7A-09, Bogotá-Colombia para

y para obtener la protección de mi (nuestra) propiedad Industrial y con este fin autorizamos a dichos apoderados para que nos representen ante cualesquiera autoridades o personas de los órdenes administrativo, contencioso --administrativo y judicial en todo lo relacionado con los siguientes actos y gestiones:

a) Obtención de patentes de invención, modelos y dibujos industriales; registro de marcas de fabrica, de servicio, colectivas o defensivas y de denominaciones de origen, depósito de nombres y enseñas comerciales; su renovación, prórroga, inscripción de traspaso y cambio de nombre o domicilio, cancelación voluntaria y el registro de licencias de uso de esos derechos;
b) Para la obtención de registros sanitarios;
c) Acciones de oposición, observación, cancelación, nulidad, medidas cautelares y en general los juicios civiles, penales, administrativos o contencioso - administrativos que promovamos o se nos promuevan.

Pudiendo en todos los actos y gestiones arriba mencionados sustituir éste mandato, transigir, desistir, recibir, cancelar, renunciar, aceptar notificaciones y nombrar apoderados judiciales y extrajudiciales.

Finalmente, este poder ratifica la validez de todos los actos y solicitudes que, a nombre de la poderdante hubieren realizado los apoderados en relación con las facultades anteriormente enumeradas, antes de la suscripción del presente poder

Dado y firmado hoy 19 de Noviembre de 2008

en Abbott Park, Illinois,
ESTADOS UNIDOS DE AMERICA

por ABBOTT LABORATORIES
(firma ilegible) Paul D. Yasger

(El notario debe suscribir el documento en la pagina siguiente)

(Se requiere legalización consular o mediante apostilla)

I (we) the undersigned

ABBOTT LABORATORIES

Of

100 Abbott Park Road
Abbott Park
Illinois 60064
USA

hereby grant(s) Power of Attorney to XIMENA CASTELLANOS A. and /or MARGARITA CASTELLANOS a. attorneys residing at Calle 94A No. 7A-09, Bogotá- Colombia, to

and to obtain the protection of my (our Industrial Property, for which purpose we authorize the said attorneys to represent us before any authorities, or persons, specially those, administrative, contentious and judicial, in all matters concerning the following:

a) Obtainment of patents, models and designs, registration of trademarks, service, collective and defensive marks, and of designations of origin; the deposit of trade names and ensigns; its renewal, extension, recordal of assignments, change of name or domicile, voluntary cancellation, and the registration of licenses of use of the above rights;
b) For the obtainment of Sanitary registrations;
c) Actions of opposition, cancellation, nullity, infringement, granting of licenses; and in general the civil, criminal and administrative suits related to those rights; actions and suits instituted by us or against us;

In all the above matters ~~they~~ may substitute this power of attorney, compromise, desist, cancel, receive, renounce, accept notifications and appoint attorneys in fact, in or out of court.

Finally, this power of attorney ratifies the validity of all acts and applications made by the representatives in the name of the signatory of this power of attorney, with regard to the faculties above given, before the execution of the present power of attorney.

Given and signed this 19 day of November, 2008

in Abbott Park, Illinois, USA 60064

by Paul D. Yasger, Assistant Secretary, DVP, Associate General Counsel
(Notary shall execute on the other side)

(Consular legalization or apostille is required)

Esta copia coincide con el original que tuve a la vista
Bogotá D.C.
24 MAR. 2011
ALIRIO VIRVIESCAS CALVETE
NOTARIO CUARENTA Y UNO (E.P.)

CASTELLANOS & CO
ABOGADOS COLOMBIA
Calle 94A No. 7A-09- P.O.Box 6349 - Bogotá, Colombia
(571) 610 74 20 / - Fax (571) 610 07 06 - e-mail info@castellanosyco.com

*Abbott at its sole discretion

Hoy 19de Nov. del año 2008
compareció (eron) personalmente
Paul D. Yasger

a quienes conozco como la(s) personas que firma(n) en representación de la Sociedad (Compañia) denominada ABBOTT LABORATORIES

Certifico :

a) Que ABBOTT LABORATORIES

es una sociedad/Compañía legalmente consliluida y existente de acuerdo con las leyes de Estados Unidos de América

b) Que el domicilio de dicha Sociedad/Compañía es

100 Abbott Park Road
Abbott Park
Illinois 60064
EUA

c) Que el objeto u objetos para los cuales se otorga el presente poder están comprendidos dentro del objeto social de la mencionada Sociedad /Compañia.

d) Que el Sr. Paul D. Yasger

esta autorizado para otorgar el presente poder. Lo anterior esta probado por medio de los siguientes documentos, que certifico he visto*

(Ciudad) Abbott Park

(Estado) Illinois

Hoy 19del Noviembre de 2008

(Notario Público)

*Los documentos debe identificarse con fecha y origen.

Esta copia coincide con el original que tuve a la vista
Bogotá D.C.
24 MAR. 2011
ALIRIO VIRVIESCAS CALVETE
NOTARIO CUARENTA Y UNO (E.P.)

On this 19 day of November of 2008
personally appeared Paul D. Yasger,
whom I know to be the person(s) who signed this document as representative(s) of the Corporation /Company named
ABBOTT LABORATORIES

I certify:

a) That ABBOTT LABORATORIES

is a corporation (Company legally constituted and in existence in accordance with the laws of United States of America

b) That the domicile of said Corporation/Company is

100 Abbott Park Road
Abbott Park
Illinois 60064
USA

c) That the purpose or purposes for which the present Power of Attorney is granted are comprised within the object set forth in the charter of the mentioned Corporation/Company.

d) That Mr. Paul D. Yasger

is (are) authorized to grant the present Power of Attorney. The aforementioned was duly proven through the following documents and I duly certify having seen them*:Appointment of Corporate Officer dated March 6, 2008 and signed by Mile D. White, Chairman of the Board and Chief Executive Office of Abbott Laboratories

(City) Abbott Park

(State) Illinois

this 19th day of November of the year 2008

(Notary Public)

*Documents must be identified with date and origin

OFFICIAL SEAL
LINDA S LUTZ
NOTARY PUBLIC - STATE OF ILLINOIS
MY COMMISSION EXPIRES:07/23/11

CASTELLANOS & CO
ABOGADOS COLOMBIA
Calle 94A No. 7A-09- P.O.Box 6349 - Bogotá, Colombia
Tels.: (571) 610 74 20 / - Fax (571) 610 07 06 - e-mail info@castellanosyco.com

STATE OF ILLINOIS

SECRETARY OF STATE

SPRINGFIELD, ILLINOIS

APOSTILLE

(Convention de La Haye du 5 Octobre 1961)

1. Country: United States of America

   This public document

2. has been signed by LINDA S LUTZ

3. acting in the capacity of NOTARY PUBLIC, MCHENRY COUNTY

4. bears the seal/stamp of STATE OF ILLINOIS

Certified

5. Springfield, Illinois

6. NOVEMBER 26, 2008

7. by the Secretary of State, State of Illinois

8. No. S08DL14032

9. Seal/Stamp:

10. Signature:

Esta copia coincide con el original que tuve a la vista
24 MAR. 2011
ALIRIO VIRVIESCAS CALVETE
NOTARIO CUARENTA Y UNO (EN PROP.)

Jesse White

JESSE WHITE
SECRETARY OF STATE
STATE OF ILLINOIS

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----------TRADUCCION OFICIAL No. 081205----------

de un documento escrito en INGLES, el cual para su identificación lleva el sello de la Traductora e Intérprete Oficial, Res. 2755/68 y 01144/97 de Minjusticia, al igual que la presente.----------

(Adjunto a un documento de PODER de Abbott Laboratories)

(fdo) ilegible

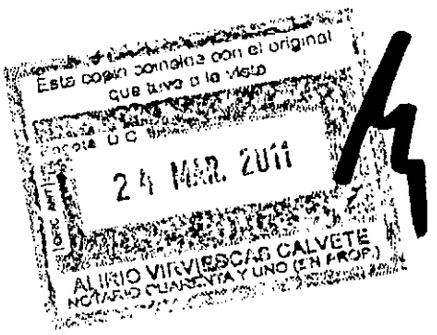
Notario Público

SELLO OFICIAL

Notario Público – Estado de Illinois

LINDA S. LUTZ

Mi comisión vence 07/23/11



ESTADO DE ILLINOIS

Secretario de Estado

Springfield, Illinois

APOSTILLA

(Convención de La Haya de 5 de Octubre de 1961)

1. País: Estados Unidos de América

Este documento público

2. ha sido firmado por LINDA S. LUTZ
3. actuando en su calidad de Notario Público, Condado de McHenry
4. lleva el sello del Estado de Illinois

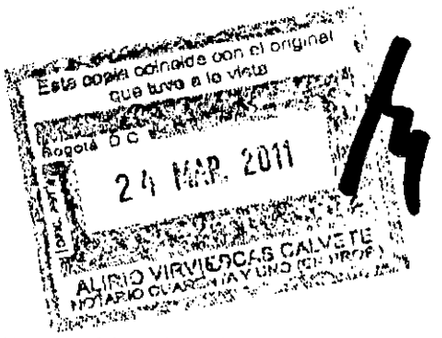
CERTIFICADO

5. en Springfield, Illinois
6. El día 26 de Noviembre de 2008
7. Por el Secretario de Estado, Estado de Illinois
8. No. S08DL14032
9. Sello
10. Firma: (fdo) Jesse White

JESSE WHITE

Secretario de Estado

Estado de Illinois



(Sello en oblea dorada)

ES TRADUCCION FIEL Y COMPLETA, a la cual me remito,

Bogotá, D. C., Diciembre 17, 2008

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
16 December 2010 (16.12.2010)

PCT

(10) International Publication Number
WO 2010/144646 A2

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C07D 403/14 (2006.01)

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61/186,291	11 June 2009 (11.06.2009)	US
61/242,836	16 September 2009 (16.09.2009)	US
61/243,596	18 September 2009 (18.09.2009)	US

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(54) Title: ANTI-VIRAL COMPOUNDS

(57) Abstract: Compounds effective in inhibiting replication of Hepatitis C virus ("HCV") are described. This invention also relates to processes of making such compounds, compositions comprising such compounds, and methods of using such compounds to treat HCV infection.

WO 2010/144646 A2

ANTI-VIRAL COMPOUNDS

The present application claims the benefit from and incorporates by reference the entire content of U.S Provisional Application Serial No. 61/186,291, filed June 11, 2009, U.S. Provisional Application Serial No. 61/242,836, filed September 16,2009, and U.S. Provisional Application Serial No. 61/243,596, filed September 18, 2009.

FIELD

The present invention relates to compounds effective in inhibiting replication of Hepatitis C virus ("HCV"). The present invention also relates to compositions comprising these compounds and methods of using these compounds to treat HCV infection.

BACKGROUND

HCV is an RNA virus belonging to the Hepacivirus genus in the Flaviviridae family. The enveloped HCV virion contains a positive stranded RNA genome encoding all known virus-specific proteins in a single, uninterrupted, open reading frame. The open reading frame comprises approximately 9500 nucleotides and encodes a single large polyprotein of about 3000 amino acids. The polyprotein comprises a core protein, envelope proteins E1 and E2, a membrane bound protein p7, and the non-structural proteins NS2, NS3, NS4A, NS4B, NS5A and NS5B.

HCV infection is associated with progressive liver pathology, including cirrhosis and hepatocellular carcinoma. Chronic hepatitis C may be treated with peginterferon-alpha in combination with ribavirin. Substantial limitations to efficacy and tolerability remain as many users suffer from side effects, and viral elimination from the body is often inadequate. Therefore, there is a need for new drugs to treat HCV infection.

SUMMARY

The present invention features compounds of Formulae I, I_A, I_B, I_C and I_D, and pharmaceutically acceptable salts thereof. These compounds and salts can inhibit the replication of HCV and therefore are useful for treating HCV infection.

The present invention also features compositions comprising the compounds or salts of the present invention. The compositions can also include additional therapeutic agents, such as HCV helicase inhibitors, HCV polymerase inhibitors, HCV protease inhibitors, HCV NS5A inhibitors, CD81 inhibitors, cyclophilin inhibitors, or internal ribosome entry site (IRES) inhibitors.

The present invention further features methods of using the compounds or salts of the present invention to inhibit HCV replication. The methods comprise contacting cells infected with HCV virus

with a compound or salt of the present invention, thereby inhibiting the replication of HCV virus in the cells.

In addition, the present invention features methods of using the compounds or salts of the present invention, or compositions comprising the same, to treat HCV infection. The methods comprise administering a compound or salt of the present invention, or a pharmaceutical composition comprising the same, to a patient in need thereof, thereby reducing the blood or tissue level of HCV virus in the patient.

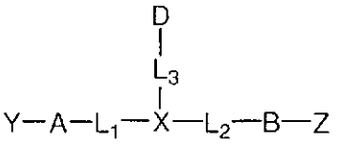
The present invention also features use of the compounds or salts of the present invention for the manufacture of medicaments for the treatment of HCV infection.

Furthermore, the present invention features processes of making the compounds or salts of the invention.

Other features, objects, and advantages of the present invention are apparent in the detailed description that follows. It should be understood, however, that the detailed description, while indicating preferred embodiments of the invention, are given by way of illustration only, not limitation. Various changes and modifications within the scope of the invention will become apparent to those skilled in the art from the detailed description.

DETAILED DESCRIPTION

The present invention features compounds having Formula I, and pharmaceutically acceptable salts thereof,



I

wherein:

X is C_3-C_{12}carbocycle or 3- to 12-membered heterocycle, and is optionally substituted with one or more R_A;

L_1 and L_2 are each independently selected from bond; or C_1-C_6alkylene, C_2-C_6alkenylene or C_2-C_6alkynylene, each of which is independently optionally substituted at each occurrence with one or more R_L;

L_3 is bond or $-L_S-K-L_S'-$, wherein K is selected from bond, –O–, –S–, $-N(R_B)-$, –C(O)–, $-S(O)_2-$, –S(O)–, –OS(O)–, $-OS(O)_2-$, $-S(O)_2O-$, –S(O)O–, –C(O)O–, –OC(O)–, –OC(O)O–, $-C(O)N(R_B)-$, $-N(R_B)C(O)-$, $-N(R_B)C(O)O-$, $-OC(O)N(R_B)-$, $-N(R_B)S(O)-$, $-N(R_B)S(O)_2-$, $-S(O)N(R_B)-$, $-S(O)_2N(R_B)-$, $-C(O)N(R_B)C(O)-$, $-N(R_B)C(O)N(R_B')-$, $-N(R_B)SO_2N(R_B')-$, or $-N(R_B)S(O)N(R_B')-$;

A and B are each independently C_3-C_{12}carbocycle or 3- to 12-membered heterocycle, and are each independently optionally substituted with one or more R_A;

D is C_3-C_{12}carbocycle or 3- to 12-membered heterocycle, and is optionally substituted with one or more R_A; or D is hydrogen or R_A;

Y is selected from $-T'-C(R_1R_2)N(R_5)-T-R_D$, $-T'-C(R_3R_4)C(R_6R_7)-T-R_D$, $-L_K-T-R_D$, or $-L_K-E$;

R_1 and R_2 are each independently R_C, and R_5 is R_B; or R_1 is R_C, and R_2 and R_5, taken together with the atoms to which they are attached, form a 3- to 12-membered heterocycle which is optionally substituted with one or more R_A;

R_3, R_4, R_6, and R_7 are each independently R_C; or R_3 and R_6 are each independently R_C, and R_4 and R_7, taken together with the atoms to which they are attached, form a 3- to 12-membered carbocycle or heterocycle which is optionally substituted with one or more R_A;

Z is selected from $-T'-C(R_8R_9)N(R_{12})-T-R_D$, $-T'-C(R_{10}R_{11})C(R_{13}R_{14})-T-R_D$, $-L_K-T-R_D$, or $-L_K-E$;

R_8 and R_9 are each independently R_C, and R_{12} is R_B; or R_8 is R_C, and R_9 and R_{12}, taken together with the atoms to which they are attached, form a 3- to 12-membered heterocycle which is optionally substituted with one or more R_A;

R_{10}, R_{11}, R_{13}, and R_{14} are each independently R_C; or R_{10} and R_{13} are each independently R_C, and R_{11} and R_{14}, taken together with the atoms to which they are attached, form a 3- to 12-membered carbocycle or heterocycle which is optionally substituted with one or more R_A;

T and T' are each independently selected at each occurrence from bond, $-L_S-$, $-L_S-M-L_S'-$, or $-L_S-M-L_S'-M'-L_S''-$, wherein M and M' are each independently selected at each occurrence from bond, $-O-$, $-S-$, $-N(R_B)-$, $-C(O)-$, $-S(O)_2-$, $-S(O)-$, $-OS(O)-$, $-OS(O)_2-$, $-S(O)_2O-$, $-S(O)O-$, $-C(O)O-$, $-OC(O)-$, $-OC(O)O-$, $-C(O)N(R_B)-$, $-N(R_B)C(O)-$, $-N(R_B)C(O)O-$, $-OC(O)N(R_B)-$, $-N(R_B)S(O)-$, $-N(R_B)S(O)_2-$, $-S(O)N(R_B)-$, $-S(O)_2N(R_B)-$, $-C(O)N(R_B)C(O)-$, $-N(R_B)C(O)N(R_B')-$, $-N(R_B)SO_2N(R_B')-$, $-N(R_B)S(O)N(R_B')-$, C_3-C_{12}carbocycle or 3- to 12-membered heterocycle, and wherein said C_3-C_{12}carbocycle and 3- to 12-membered heterocycle are each independently optionally substituted at each occurrence with one or more R_A;

L_K is independently selected at each occurrence from bond, $-L_S-N(R_B)C(O)-L_S'-$ or $-L_S-C(O)N(R_B)-L_S'-$; or C_1-C_6alkylene, C_2-C_6alkenylene or C_2-C_6alkynylene, each of which is independently optionally substituted at each occurrence with one or more R_L; or C_3-C_{12}carbocycle or 3- to 12-membered heterocycle, each of which is independently optionally substituted at each occurrence with one or more R_A;

E is independently selected at each occurrence from C_3-C_{12}carbocycle or 3- to 12-membered heterocycle, and is independently optionally substituted at each occurrence with one or more R_A;

R_D is each independently selected at each occurrence from hydrogen or R_A;

R_A is independently selected at each occurrence from halogen, nitro, oxo, phosphonoxy, phosphono, thioxo, cyano, or $-L_S-R_E$, wherein two adjacent R_A, taken together with the atoms to which they are attached and any atoms between the atoms to which they are attached, can optionally form carbocycle or heterocycle;

R_B and R_B' are each independently selected at each occurrence from hydrogen; or C_1-C_6alkyl, C_2-C_6alkenyl or C_2-C_6alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano or 3- to 6-membered carbocycle or heterocycle; or 3- to 6-membered carbocycle or heterocycle; wherein each 3- to 6-membered carbocycle or heterocycle in R_B or R_B' is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6haloalkyl, C_2-C_6haloalkenyl or C_2-C_6haloalkynyl;

R_C is independently selected at each occurrence from hydrogen, halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl or cyano; or C_1-C_6alkyl, C_2-C_6alkenyl or C_2-C_6alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano or 3- to 6-membered carbocycle or heterocycle; or 3- to 6-membered carbocycle or heterocycle; wherein each 3- to 6-membered carbocycle or heterocycle in R_C is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6haloalkyl, C_2-C_6haloalkenyl or C_2-C_6haloalkynyl;

R_E is independently selected at each occurrence from $-O-R_S$, $-S-R_S$, $-C(O)R_S$, $-OC(O)R_S$, $-C(O)OR_S$, $-N(R_SR_S')$, $-S(O)R_S$, $-SO_2R_S$, $-C(O)N(R_SR_S')$, $-N(R_S)C(O)R_S'$, $-N(R_S)C(O)N(R_S'R_S'')$, $-N(R_S)SO_2R_S'$, $-SO_2N(R_SR_S')$, $-N(R_S)SO_2N(R_S'R_S'')$, $-N(R_S)S(O)N(R_S'R_S'')$, $-OS(O)-R_S$, $-OS(O)_2-R_S$, $-S(O)_2OR_S$, $-S(O)OR_S$, $-OC(O)OR_S$, $-N(R_S)C(O)OR_S'$, $-OC(O)N(R_SR_S')$, $-N(R_S)S(O)-R_S'$, $-S(O)N(R_SR_S')$ or $-C(O)N(R_S)C(O)-R_S'$; or C_1-C_6alkyl, C_2-C_6alkenyl or C_2-C_6alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents

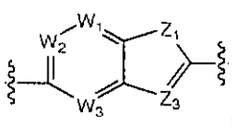
selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl or cyano; or C_3-C_6carbocycle or 3- to 6-membered heterocycle, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6haloalkyl, C_2-C_6haloalkenyl or C_2-C_6haloalkynyl;

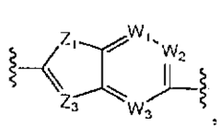
R_L is independently selected at each occurrence from halogen, nitro, oxo, phosphonoxy, phosphono, thioxo, cyano, $-O-R_S$, $-S-R_S$, $-C(O)R_S$, $-OC(O)R_S$, $-C(O)OR_S$, $-N(R_SR_S')$, $-S(O)R_S$, $-SO_2R_S$, $-C(O)N(R_SR_S')$ or $-N(R_S)C(O)R_S'$; or C_3-C_6carbocycle 3- to 6-membered heterocycle, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6haloalkyl, C_2-C_6haloalkenyl or C_2-C_6haloalkynyl; wherein two adjacent R_L, taken together with the atoms to which they are attached and any atoms between the atoms to which they are attached, can optionally form carbocycle or heterocycle;

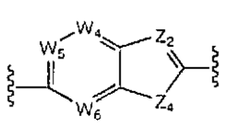
L_S, L_S' and L_S'' are each independently selected at each occurrence from bond; or C_1-C_6alkylene, C_2-C_6alkenylene or C_2-C_6alkynylene, each of which is independently optionally substituted at each occurrence with one or more R_L; and

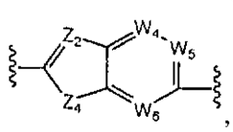
R_S, R_S' and R_S'' are each independently selected at each occurrence from hydrogen; C_1-C_6alkyl, C_2-C_6alkenyl or C_2-C_6alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano or 3- to 6-membered carbocycle or heterocycle; or 3- to 6-membered carbocycle or heterocycle; wherein each 3- to 6-membered carbocycle or heterocycle in R_S , R_S' or R_S' is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6haloalkyl, C_2-C_6haloalkenyl or C_2-C_6haloalkynyl.

A and B preferably are independently selected from C_5-C_6carbocycle (e.g., phenyl), 5- to 6-membered heterocycle (e.g., pyridinyl or thiazolyl), or 8- to 12-membered bicycles such as



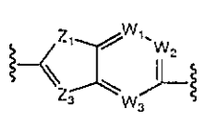
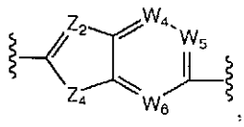
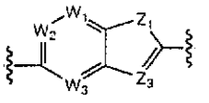
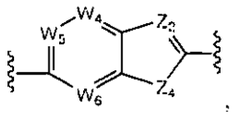
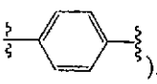
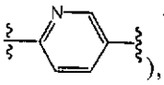
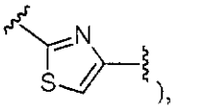
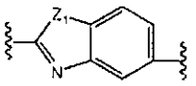
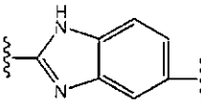
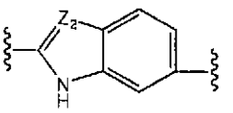
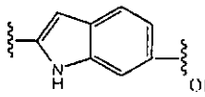
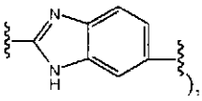
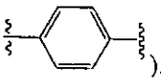
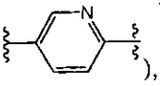
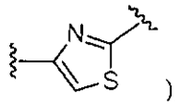
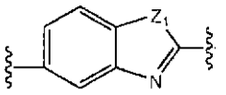
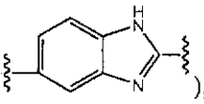
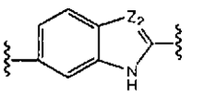
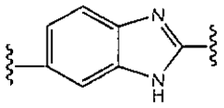
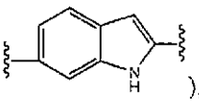
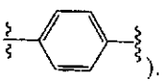
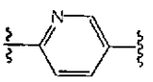
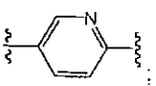
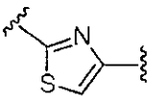
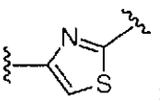
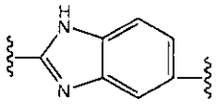
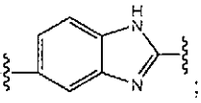
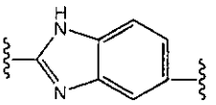
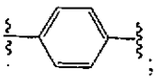
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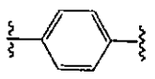
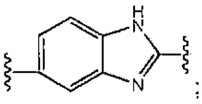
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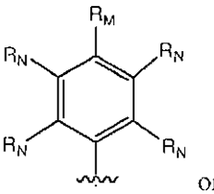
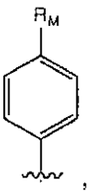
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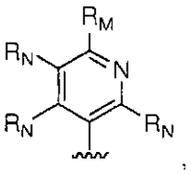
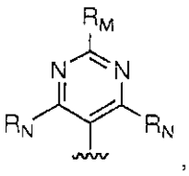
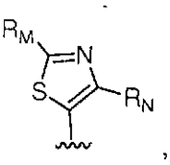
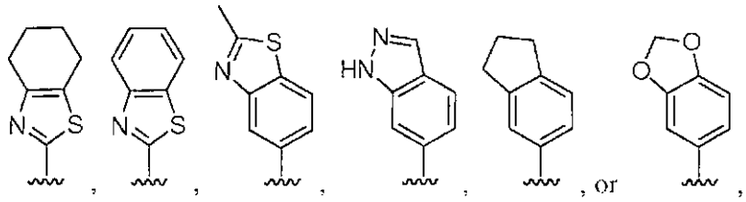
, where Z_1 is independently selected at each occurrence from O, S, NH or CH_2, Z_2 is independently selected at each occurrence from N or CH, Z_3 is independently selected at each occurrence from N or CH, Z_4 is

independently selected at each occurrence from O, S, NH or CH_2, and W_1, W_2, W_3, W_4, W_5 and W_6 are each independently selected at each occurrence from CH or N. A and B are each independently optionally substituted with one or more R_A.

More preferably, A is selected from C_5-C_6carbocycle, 5- to 6-membered heterocycle,  or  , and is optionally substituted with one or more R_A; B is selected from C_5-C_6carbocycle, 5- to 6-membered heterocycle,  or  , and is optionally substituted with one or more R_A; where Z_1, Z_2, Z_3, Z_4, W_1, W_2, W_3, W_4, W_5, W_6 are as defined above. Preferably, Z_3 is N and Z_4 is NH. For instance, A can be selected from phenyl (e.g., ), pyridinyl (e.g., ), thiazolyl (e.g., ),  (e.g., ), or  (e.g.,  or ), and is optionally substituted with one or more R_A; and B can be selected from phenyl (e.g., ), pyridinyl (e.g., ), thiazolyl (e.g., ),  (e.g., ), or  (e.g.,  or ), and is optionally substituted with one or more R_A. Highly preferably, both A and B are phenyl (e.g., both A and B are ). Also highly preferably, A is  and B is  ; or A is  and B is  ; or A is  and B is  ; or A is  and B is  ; or A

is  and B is  ; wherein each A and B is independently optionally substituted with one or more R_A.

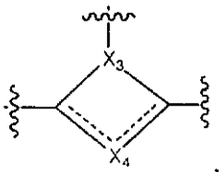
D preferably is selected from C_5-C_6carbocycle, 5- to 6-membered heterocycle, or 6- to 12-membered bicycles, and is optionally substituted with one or more R_A. D can also be preferably selected from C_1-C_6alkyl, C_2-C_6alkenyl or C_2-C_6alkynyl, and is optionally substituted with one or more substituents selected from R_L. More preferably, D is C_5-C_6carbocycle (e.g., phenyl), 5- to 6-membered heterocycle (e.g., pyridinyl, pyrimidinyl, thiazolyl), or 6- to 12-membered bicycles (e.g., indanyl, 4,5,6,7-tetrahydrobenzo[d]thiazolyl, benzo[d]thiazolyl, indazolyl, benzo[d][1,3]dioxol-5-yl), and is substituted with one or more R_M, where R_M is halogen, nitro, oxo, phosphonoxy, phosphono, thioxo, cyano, or $-L_S-R_E$. Also preferably, D is phenyl, and is optionally substituted with one or more R_A. More preferably, D is phenyl, and is substituted with one or more R_M, wherein R_M is as defined above. Highly preferably, D is  or  , wherein R_M is as defined above, and each R_N is independently selected from R_D and preferably is hydrogen. One or more R_N can also preferably be halo such as F.

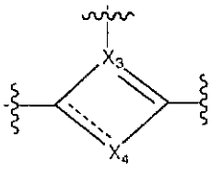
D is also preferably pyridinyl, pyrimidinyl, or thiazolyl, optionally substituted with one or more R_A. More preferably D is pyridinyl, pyrimidinyl, or thiazolyl, and is substituted with one or more R_M. Highly preferably, D is  ,  , or  , wherein R_M is as defined above, and each R_N is independently selected from R_D and preferably is hydrogen. One or more R_N can also preferably be halo such as F. D is also preferably indanyl, 4,5,6,7-tetrahydrobenzo[d]thiazolyl, benzo[d]thiazolyl, or indazolyl, and is optionally substituted with one or more R_A. More preferably D is indanyl, 4,5,6,7-tetrahydrobenzo[d]thiazolyl, benzo[d]thiazolyl, indazolyl, or benzo[d][1,3]dioxol-5-yl, and is substituted with one or more R_M. Highly preferably, D is  , and is optionally substituted with one or more R_M.

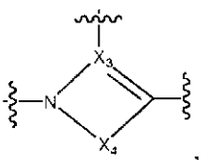
Preferably, R_M is halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, cyano; or C_1-C_6alkyl, C_2-C_6alkenyl or C_2-C_6alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl or cyano; or C_3-C_6carbocycle or 3- to 6-membered heterocycle, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6haloalkyl, C_2-C_6haloalkenyl or C_2-C_6haloalkynyl. More preferably, R_M is halogen, hydroxy, mercapto, amino, carboxy; or C_1-C_6alkyl, C_2-C_6alkenyl or C_2-C_6alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino or carboxy. Highly preferably, R_M is C_1-C_6alkyl which is optionally substituted with one or more substituents selected from halogen, hydroxy, mercapto, amino or carboxy.

Also preferably, R_M is halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, or cyano; or R_M is $-L_S-R_E$, wherein L_S is a bond or C_1-C_6alkylene, and R_E is $-N(R_SR_S')$, $-O-R_S$, $-C(O)R_S$, $-C(O)OR_S$, $-C(O)N(R_SR_S')$, $-N(R_S)C(O)R_S'$, $-N(R_S)C(O)OR_S'$, $-N(R_S)SO_2R_S'$, $-SO_2R_S$, $-SR_S$, or $-P(O)(OR_S)_2$, wherein R_S and R_S' can be, for example, each independently selected at each occurrence from (1) hydrogen or (2) C_1-C_6alkyl optionally substituted at each occurrence with one or more halogen, hydroxy, $-O-C_1$-C_6alkyl or 3- to 6-membered heterocycle; or R_M is C_1-C_6alkyl, C_2-C_6alkenyl or C_2-C_6alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl or cyano; or R_M is C_3-C_6carbocycle or 3- to 6-membered heterocycle, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6haloalkyl, C_2-C_6haloalkenyl, C_2-C_6haloalkynyl, $-C(O)OR_S$, or $-N(R_SR_S')$. More preferably, R_M is halogen (e.g., fluoro, chloro, bromo, iodo), hydroxy, mercapto, amino, carboxy, or C_1-C_6alkyl (e.g., methyl, isopropyl, tert-butyl), C_2-C_6alkenyl or C_2-C_6alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, cyano, or carboxy. For example R_M is CF_3, $-C(CF_3)_2-OH$, $-C(CH_3)_2-CN$, $-C(CH_3)_2-CH_2OH$, or $-C(CH_3)_2-CH_2NH_2$. Also preferably R_M is $-L_S-R_E$ where L_S is a bond and R_E is $-N(R_SR_S')$, $-O-R_S$, $-N(R_S)C(O)OR_S'$, $-N(R_S)SO_2R_S'$, $-SO_2R_S$, or $-SR_S$. For example where L_S is a bond, R_E is $-N(C_1$-C_6alkyl$)_2$ (e.g., $-NMe_2$); $-N(C_1$-C_6alkylene$-O-C_1$-C_6alkyl$)_2$ (e.g. $-N(CH_2CH_2OMe)_2$); $-N(C_1$-C_6alkyl$)(C_1$-C_6alkylene$-O-C_1$-C_6alkyl) (e.g. $-N(CH_3)(CH_2CH_2OMe)$);—$O-C_1$-C_6alkyl (e.g., –O–Me, –O–Et, –O–isopropyl, –O–tert-butyl, –O–n-hexyl); $-O-C_1$-C_6haloalkyl (e.g., – OCF_3, $-OCH_2CF_3$); $-O-C_1$-C_6alkylene–piperidine (e.g., –O–

CH_2CH_2–1-piperidyl); –N(C_1-C_6alkyl)C(O)OC_1-C_6alkyl (e.g., –N(CH_3)C(O)O–$CH_2CH(CH_3)_2$), –N(C_1-C_6alkyl)SO_2C_1-C_6alkyl (e.g., –N(CH_3)SO_2CH_3); –SO_2C_1-C_6alkyl (e.g., –SO_2Me); –SO_2C_1-C_6haloalkyl (e.g., –SO_2CF_3); or –S–C_1-C_6haloalkyl (e.g., SCF_3). Also preferably R_M is –L_S–R_E where L_S is C_1-C_6alkylene (e.g., –CH_2–, –$C(CH_3)_2$–, –$C(CH_3)_2$–CH_2–) and R_E is –O–R_S, –C(O)OR_S, –N(R_S)C(O)OR_S', or –P(O)(OR_S)$_2$. For example R_M is –C_1-C_6alkylene–O–R_S (e.g., –$C(CH_3)_2$–CH_2–OMe); –C_1-C_6alkylene–C(O)OR_S (e.g., –$C(CH_3)_2$–C(O)OMe); –C_1-C_6alkylene–N(R_S)C(O)OR_S' (e.g., –$C(CH_3)_2$–CH_2–NHC(O)OCH_3); or –C_1-C_6alkylene–P(O)(OR_S)$_2$ (e.g., –CH_2–P(O)$(OEt)_2$). Also more preferably R_M is C_3-C_6carbocycle or 3- to 6-membered heterocycle, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6haloalkyl, C_2-C_6haloalkenyl, C_2-C_6haloalkynyl, –C(O)OR_S, or –N($R_S R_S$'). For example R_M is cycloalkyl (e.g., cyclopropyl, 2,2-dichloro-1-methylcycloprop-1-yl, cyclohexyl), phenyl, heterocyclyl (e.g., morpholin-4-yl, 1,1-dioxidothiomorpholin-4-yl, 4-methylpiperazin-1-yl, 4-methoxycarbonylpiperazin-1-yl, pyrrolidin-1-yl, piperidin-1-yl, 4-methylpiperidin-1-yl, 3,5-dimethylpiperidin-1-yl, 4,4-difluoropiperidin-1-yl, tetrahydropyran-4-yl, pyridinyl, pyridin-3-yl, 6-(dimethylamino)pyridin-3-yl). Highly preferably, R_M is C_1-C_6alkyl which is optionally substituted with one or more substituents selected from halogen, hydroxy, mercapto, amino or carboxy (e.g., tert-butyl, CF_3).

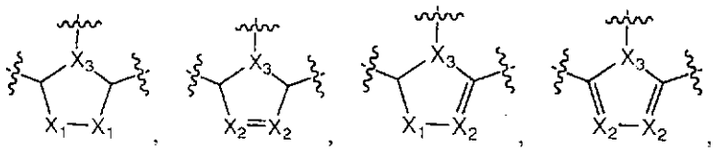
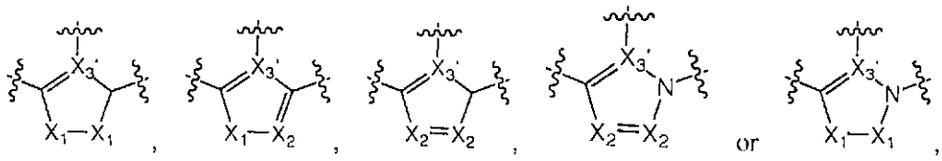
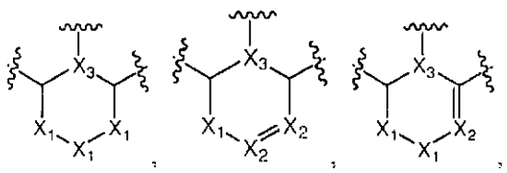
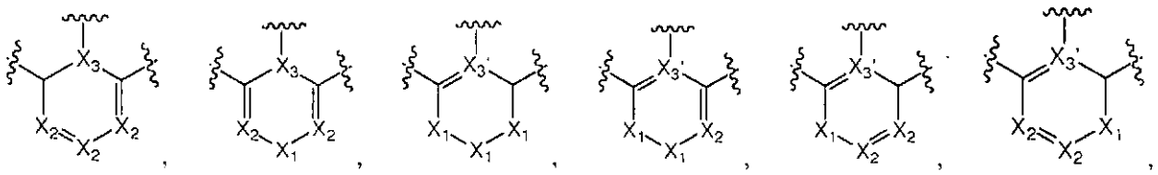
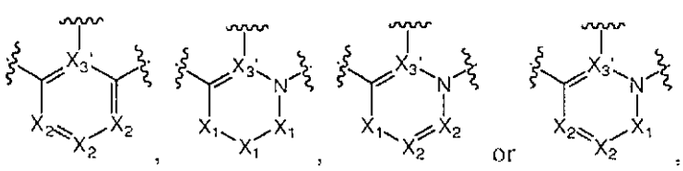
X preferably is C_5-C_6carbocycle, 5- to 6-membered heterocycle, or 6- to 12-membered bicycles, and is optionally substituted with one or more R_A. X can also be C_5-C_6carbocycle or 5- to 6-membered heterocycle which is optionally substituted with one or more R_A, wherein two adjacent R_A on X, taken together with the ring atoms to which they are attached, optionally form a 5- to 6-membered carbocycle or heterocycle. Also preferably, X is 

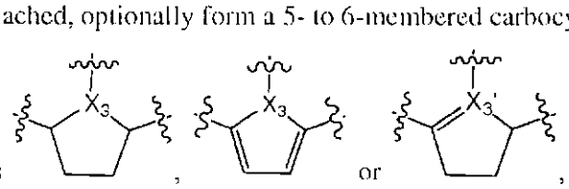
, wherein X_3 is C(H) or preferably N and is directly appended to –L_3–D; X_4 is C_2-C_4alkylene, C_2-C_4alkenylene or C_2-C_4alkynylene, each of which optionally contains one or two heteroatoms selected from O, S or N; and X is optionally substituted with one or more R_A, and two adjacent R_A on X, taken together with the ring atoms to which they are attached, can optionally form a 5- to 6-membered carbocycle or heterocycle. In addition, X can be 

or 

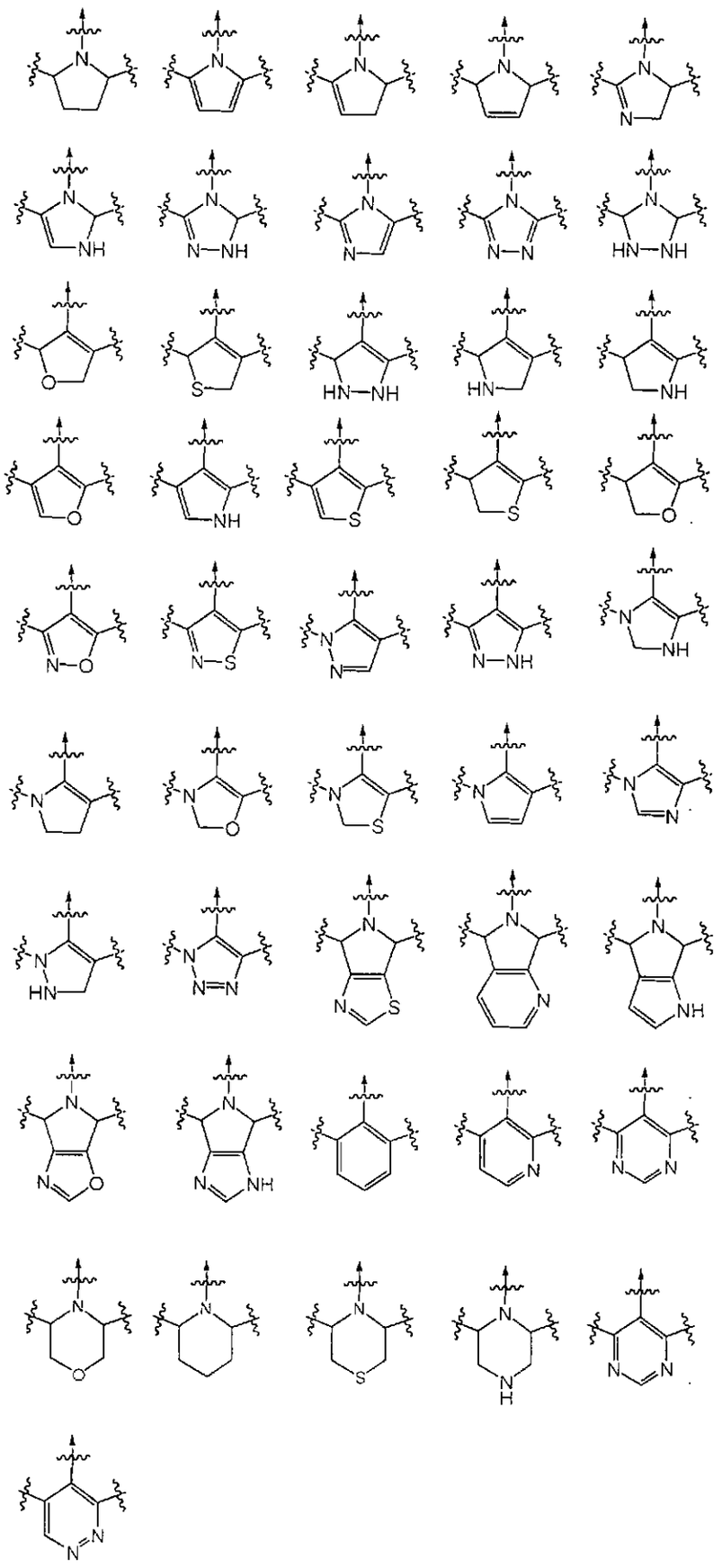
, wherein X_3 is C and is directly linked to –L_3–D, X_4 is C_2-C_4alkylene, C_2-C_4alkenylene or C_2-C_4alkynylene each of which optionally contains one or two heteroatoms selected from O, S or N, and X is optionally substituted

with one or more R_A, and two adjacent R_A on X, taken together with the ring atoms to which they are attached, optionally form a 5- to 6-membered carbocycle or heterocycle.

For instance, X can be  ,  , or , wherein X_1 is independently selected at each occurrence from CH_2, O, S or NH, X_2 is independently selected at each occurrence from CH or N, X_3 is N and is directly linked to $-L_3-D$, and X_3' is C and is directly linked to $-L_3-D$; and X is optionally substituted with one or more R_A, and two adjacent R_A on X, taken together with the ring atoms to which they are attached, optionally form a 5- to 6-membered carbocycle or heterocycle. For another example, X is  ,  , or  , wherein X_1 is independently selected at each occurrence from CH_2, O, S or NH, X_2 is independently selected at each occurrence from CH or N, X_3 is N and is directly linked to $-L_3-D$, and X_3' is C and is directly linked to $-L_3-D$; and wherein X is optionally substituted with one or more R_A, and two adjacent R_A on X, taken together with the ring atoms to which they are attached, optionally form a 5- to 6-membered carbocycle or heterocycle.

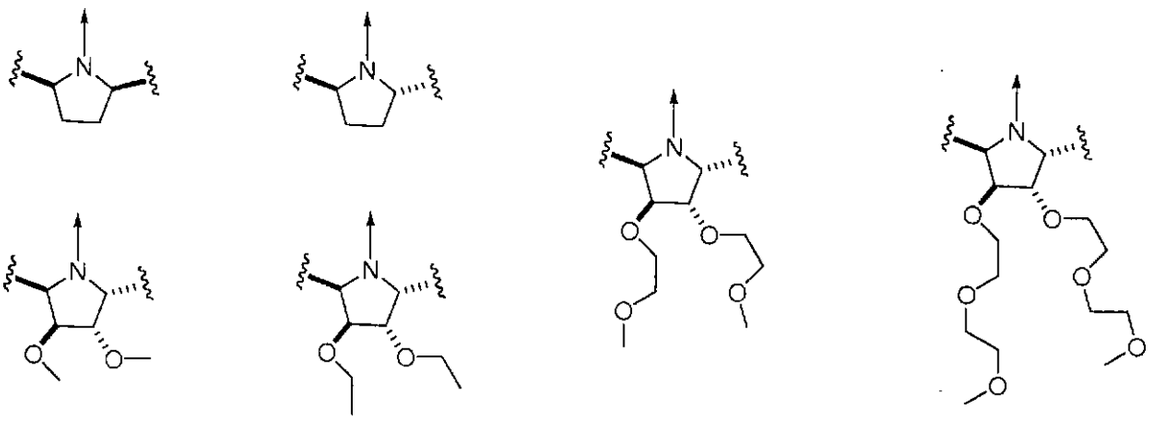
Highly preferably, X is  , or , wherein X_3 is C(H) or N and is directly linked to $-L_3-D$, X_3' is C and is directly linked to $-L_3-D$, and wherein X is optionally substituted with one or more R_A, and two adjacent R_A on X, taken together with the ring atoms to which they are attached, optionally form a 5- to 6-membered carbocycle or heterocycle. More preferably, X_3 is N.

Non-limiting examples of X include:



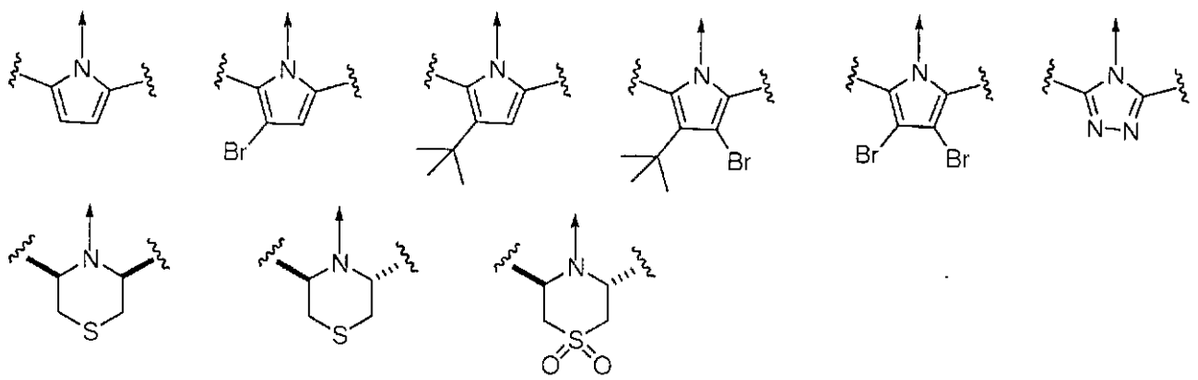
wherein "→" indicates the covalent attachment to $-L_3-D$. Each X can be optionally substituted with one or more R_A, and two adjacent R_A on X, taken together with the ring atoms to which they are attached, optionally form a 5- to 6-membered carbocycle or heterocycle.

Non-limiting examples of preferred X include the following pyrrolidine rings, each of which is optionally substituted with one or more R_A:



As shown, the relative stereochemistry at the 2- and 5-positions of the above pyrrolidine ring may be either cis or trans. The stereochemistries of optional substituents R_A at the 3- or 4-positions of the pyrrolidine may vary relative to any substituent at any other position on the pyrrolidine ring. Depending on the particular substituents attached to the pyrrolidine, the stereochemistry at any carbon may be either (R) or (S).

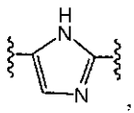
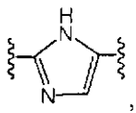
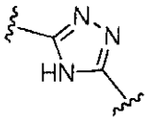
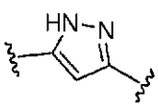
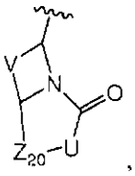
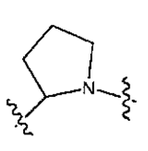
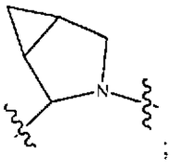
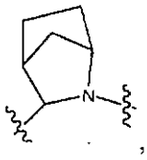
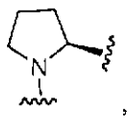
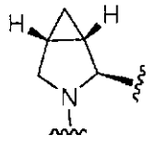
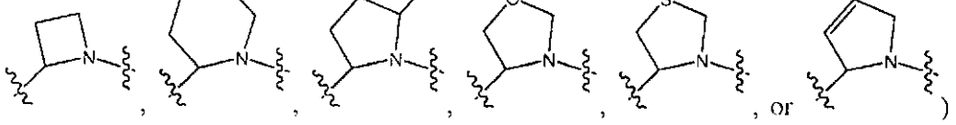
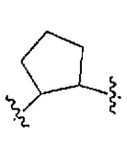
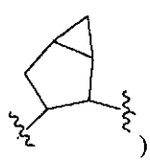
Non-limiting examples of preferred X also include the following pyrrole, triazole or thiomorpholine rings, each of which is optionally substituted with one or more R_A:



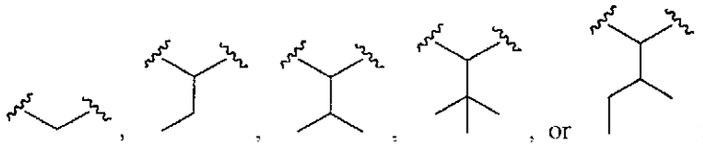
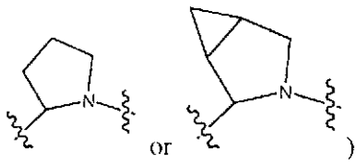
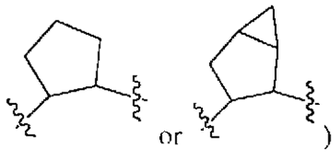
As shown, the relative stereochemistry at the 3- and 5-positions of the thiomorpholine ring may be either cis or trans. Depending on the particular substituents attached to the thiomorpholine, the stereochemistry at any carbon may be either (R) or (S).

L_1 and L_2 are preferably independently bond or C_1-C_6alkylene, L_3 is preferably selected from bond, C_1-C_6alkylene or –C(O)–, and L_1, L_2, and L_3 are each independently optionally substituted with one or more R_L. More preferably, L_1, L_2 and L_3 are each independently bond or C_1-C_6alkylene (e.g., –

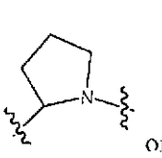
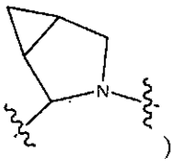
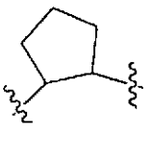
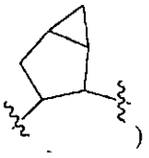
CH_2– or –CH_2CH_2–), and are each independently optionally substituted with one or more R_L. Highly preferably, L_1, L_2 and L_3 are bond.

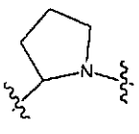
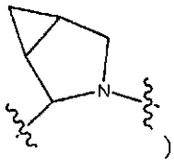
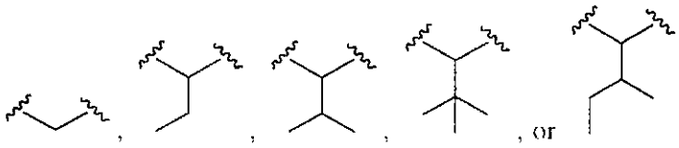
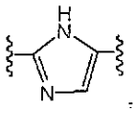
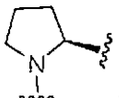
Y is preferably selected from –L_S–$C(R_1R_2)N(R_5)$–T–R_D, –L_S–$C(R_3R_4)C(R_6R_7)$–T–R_D, –G–$C(R_1R_2)N(R_5)$–T–R_D, –G–$C(R_3R_4)C(R_6R_7)$–T–R_D, –$N(R_B)C(O)C(R_1R_2)N(R_5)$–T–$R_D$, –$N(R_B)C(O)C(R_3R_4)C(R_6R_7)$–T–$R_D$, –$C(O)N(R_B)C(R_1R_2)N(R_5)$–T–$R_D$, –$C(O)N(R_B)C(R_3R_4)C(R_6R_7)$–T–$R_D$, –$N(R_B)C(O)$–$L_S$–E, or –$C(O)N(R_B)$–$L_S$–E. G is C_5-C_6carbocycle or 5- to 6-membered heterocycle, such as  ,  ,  or  , and is optionally substituted with one or more R_A (e.g., one or more chloro or bromo). E preferably is a 7- to 12-membered bicycle (such as  , wherein U is independently selected at each occurrence from -(CH_2)- or -(NH)-; V and Z_{20} are each independently selected from C_1-C_4alkylene, C_2-C_4alkenylene or C_2-C_4alkynylene, in which at least one carbon atom can be independently optionally replaced with O, S or N), and is optionally substituted with one or more R_A. More preferably, R_1 is R_C, and R_2 and R_5, taken together with the atoms to which they are attached, form a 5- to 6-membered heterocycle or 6- to 12-membered bicycle (e.g.,  or  ; or  ,  ,  ; or ) which is optionally substituted with one or more R_A (such as, but not limited to hydroxy, halo (e.g., fluoro), C_1-C_6alkyl (e.g., methyl), or C_2-C_6alkenyl (e.g., allyl)); and R_3 and R_6 are each independently R_C, and R_4 and R_7, taken together with the atoms to which they are attached, form a 5- to 6-membered carbocycle/heterocycle or 6- to 12-membered bicycle (e.g.,  or ) which is optionally substituted with one or more R_A (such as, but not limited to hydroxy, halo (e.g., fluoro), C_1-C_6alkyl (e.g., methyl), or C_2-C_6alkenyl (e.g., allyl)).

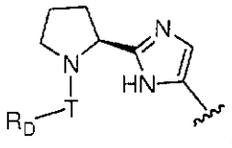
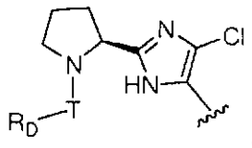
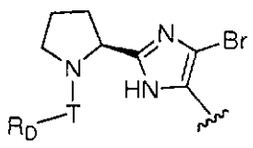
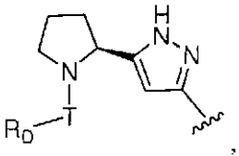
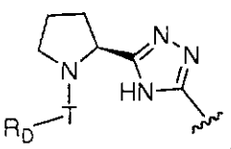
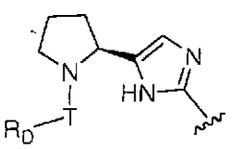
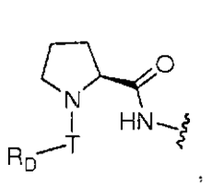
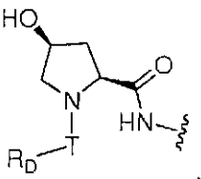
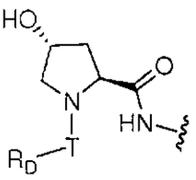
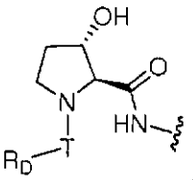
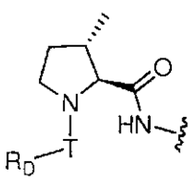
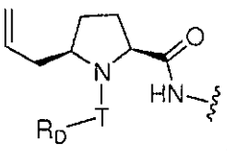
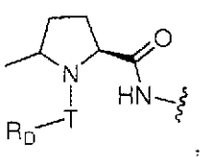
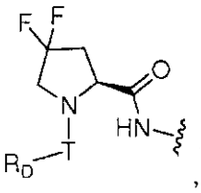
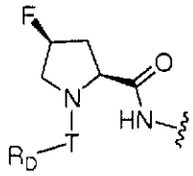
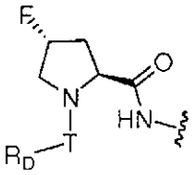
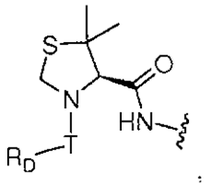
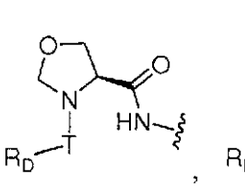
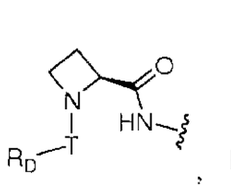
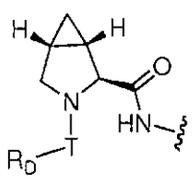
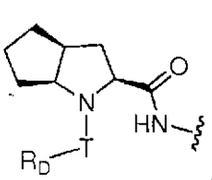
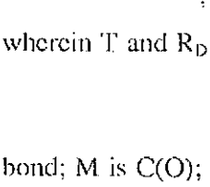
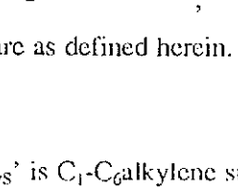
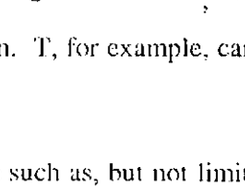
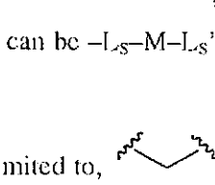
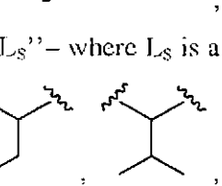
Y can also be selected from –M–$C(R_1R_2)N(R_5)$–C(O)–L_Y'–M'–R_D, –M–$C(R_1R_2)N(R_5)$–L_Y'–M'–R_D, –L_S–$C(R_1R_2)N(R_5)$–C(O)–L_Y'–M'–R_D, –L_S–$C(R_1R_2)N(R_5)$–L_Y'–M'–R_D, –M–

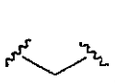
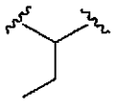
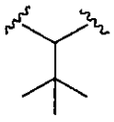
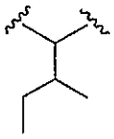
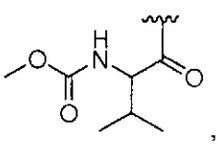
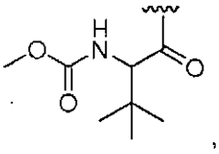
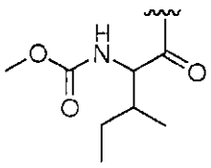
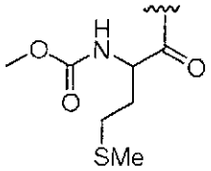
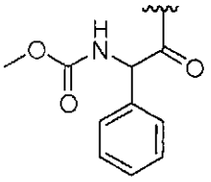
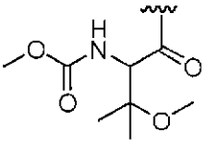
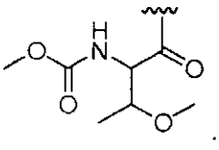
$C(R_3R_4)C(R_6R_7)–C(O)–L_Y'–M'–R_D$, $–M–C(R_3R_4)C(R_6R_7)–L_Y'–M'–R_D$, $–L_S–C(R_3R_4)C(R_6R_7)–C(O)–L_Y'–M'–R_D$, or $–L_S–C(R_3R_4)C(R_6R_7)–L_Y'–M'–R_D$, wherein M preferably is bond, $–C(O)N(R_B)–$ or $–N(R_B)C(O)–$, M' preferably is bond, $–C(O)N(R_B)–$, $–N(R_B)C(O)–$, $–N(R_B)C(O)O–$, $N(R_B)C(O)N(R_B')–$, $–N(R_B)S(O)–$ or $–N(R_B)S(O)_2–$, and L_Y' preferably is C_1-C_6alkylene which is optionally substituted with one or more R_L. L_Y', for example, is a C_1-C_6alkylene such as, but not limited to,  ; and the optional R_L is a substituent such as, but not limited to phenyl, –SMe, or methoxy. Any stereochemistry at a carbon within the group L_Y' can be either (R) or (S). More preferably, R_1 is R_C, and R_2 and R_5, taken together with the atoms to which they are attached, form a 5- to 6-membered heterocycle or 6- to 12-membered bicycle (e.g., ) which is optionally substituted with one or more R_A (e.g., one or more hydroxy); and R_3 and R_6 are each independently R_C, and R_4 and R_7, taken together with the atoms to which they are attached, form a 5- to 6-membered carbocycle/heterocycle or 6- to 12-membered bicycle (e.g., ) which is optionally substituted with one or more R_A.

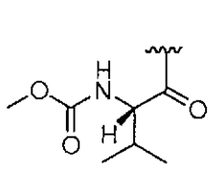
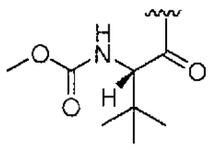
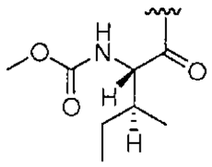
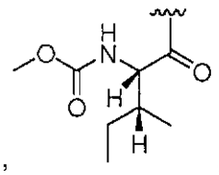
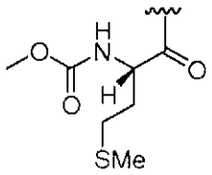
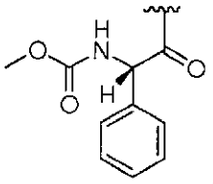
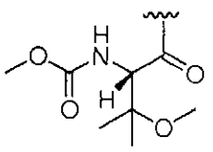
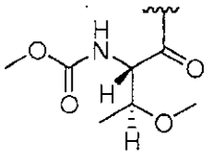
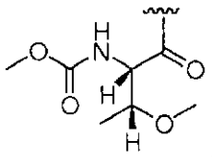
Also preferably, Y is selected from $–N(R_B)CO–C(R_1R_2)N(R_5)–C(O)–L_Y'–N(R_B)C(O)O–R_D$, $–N(R_B)CO–C(R_1R_2)N(R_5)–C(O)–L_Y'–N(R_B)C(O)–R_D$, $–N(R_B)CO–C(R_1R_2)N(R_5)–C(O)–L_Y'–N(R_B)S(O)_2–R_D$, $–N(R_B)CO–C(R_1R_2)N(R_5)–C(O)–L_Y'–N(R_BR_B')–R_D$, $–N(R_B)CO–C(R_1R_2)N(R_5)–C(O)–L_Y'–O–R_D$, $–N(R_B)CO–C(R_1R_2)N(R_5)–C(O)–L_Y'–R_D$, $–N(R_B)CO–C(R_1R_2)N(R_5)–R_D$, $–L_S–C(R_1R_2)N(R_5)–C(O)–L_Y'–N(R_B)C(O)O–R_D$, $–L_S–C(R_1R_2)N(R_5)–C(O)–L_Y'–N(R_B)C(O)–R_D$, $–L_S–C(R_1R_2)N(R_5)–C(O)–L_Y'–N(R_B)S(O)_2–R_D$, $–L_S–C(R_1R_2)N(R_5)–C(O)–L_Y'–N(R_BR_B')–R_D$, $–L_S–C(R_1R_2)N(R_5)–C(O)–L_Y'–O–R_D$, $–L_S–C(R_1R_2)N(R_5)–C(O)–L_Y'–R_D$, $–L_S–C(R_1R_2)N(R_5)–R_D$, $–N(R_B)CO–C(R_3R_4)C(R_6R_7)–C(O)–L_Y'–N(R_B)C(O)O–R_D$, $–N(R_B)CO–C(R_3R_4)C(R_6R_7)–C(O)–L_Y'–N(R_B)C(O)–R_D$, $–N(R_B)CO–C(R_3R_4)C(R_6R_7)–C(O)–L_Y'–N(R_B)S(O)_2–R_D$, $–N(R_B)CO–C(R_3R_4)C(R_6R_7)–C(O)–L_Y'–N(R_BR_B')–R_D$, $–N(R_B)CO–C(R_3R_4)C(R_6R_7)–C(O)–L_Y'–O–R_D$, $–N(R_B)CO–C(R_3R_4)C(R_6R_7)–C(O)–L_Y'–R_D$, $–N(R_B)CO–C(R_3R_4)C(R_6R_7)–R_D$, $–L_S–C(R_3R_4)C(R_6R_7)–C(O)–L_Y'–N(R_B)C(O)O–R_D$, $–L_S–C(R_3R_4)C(R_6R_7)–C(O)–L_Y'–N(R_B)C(O)–R_D$, $–L_S–C(R_3R_4)C(R_6R_7)–C(O)–L_Y'–N(R_B)S(O)_2–R_D$, $–L_S–C(R_3R_4)C(R_6R_7)–C(O)–L_Y'–N(R_BR_B')–R_D$, $–L_S–C(R_3R_4)C(R_6R_7)–C(O)–L_Y'–O–R_D$, $–L_S–C(R_3R_4)C(R_6R_7)–C(O)–L_Y'–R_D$, or $–L_S–C(R_3R_4)C(R_6R_7)–R_D$, wherein L_Y' preferably is C_1-C_6alkylene which is optionally substituted with one or more R_L. R_1

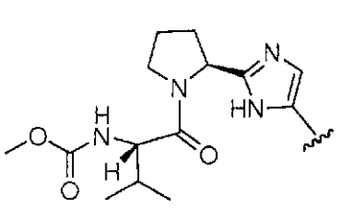
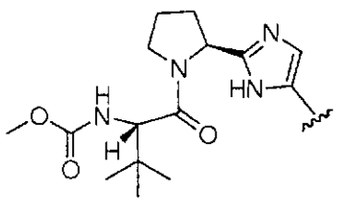
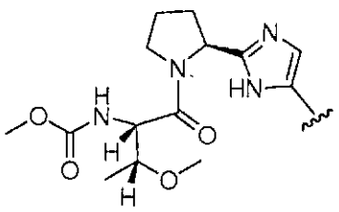
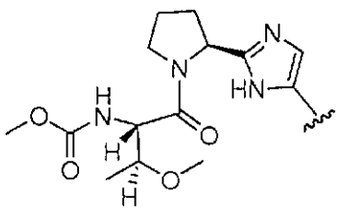
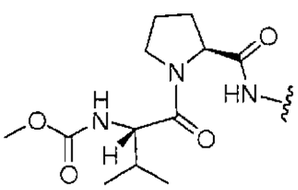
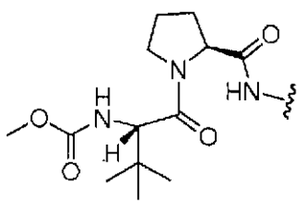
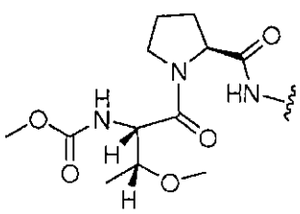
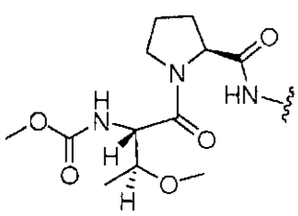
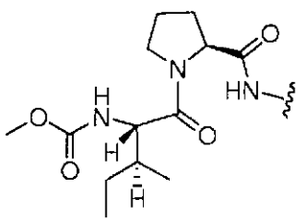
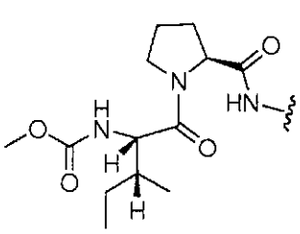
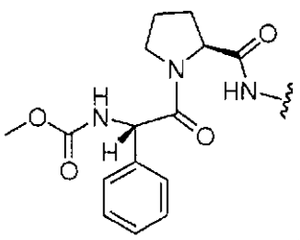
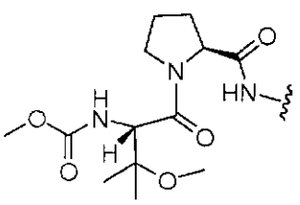
may be R_C, and R_2 and R_5, taken together with the atoms to which they are attached, may form a 5- to 6-membered heterocycle or 6- to 12-membered bicycle (e.g.,  or ) which is optionally substituted with one or more R_A; and R_3 and R_6 may be each independently R_C, and R_4 and R_7, taken together with the atoms to which they are attached, may form a 5- to 6-membered carbocycle/heterocycle or 6- to 12-membered bicycle (e.g.,  or ) which is optionally substituted with one or more R_A.

Highly preferably, Y is selected from $-N(R_B'')CO-C(R_1R_2)N(R_5)-C(O)-L_Y-N(R_B'')C(O)-L_S-R_E$ or $-C(R_1R_2)N(R_5)-C(O)-L_Y-N(R_B'')C(O)-L_S-R_E$, or Y is $-G-C(R_1R_2)N(R_5)-C(O)-L_Y-N(R_B'')C(O)-L_S-R_E$, wherein L_Y is C_1-C_6alkylene optionally substituted with one or more R_L, and R_B'' is each independently R_B. R_B'' and R_1 are each preferably hydrogen or C_1-C_6alkyl, and R_2 and R_5, taken together with the atoms to which they are attached, preferably form a 5- to 6-membered heterocycle or 6- to 12-membered bicycle (e.g.,  or ) which is optionally substituted with one or more R_A (such as, but not limited to hydroxy, halo (e.g., fluoro), C_1-C_6alkyl (e.g., methyl), or C_2-C_6alkenyl (e.g., allyl)). Preferably, L_Y is C_1-C_6alkylene substituted with one or more R_L such as a C_3-C_6carbocycle 3- to 6-membered heterocycle which is optionally substituted with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6haloalkyl, C_2-C_6haloalkenyl or C_2-C_6haloalkynyl. Highly preferably, L_Y is a C_1-C_6alkylene such as, but not limited to,  (stereochemistry at a carbon within the group L_Y can be either (R) or (S)), L_Y is optionally substituted with one or more R_L (e.g., one or more phenyl or methoxy), G preferably is  , R_B'' is hydrogen; $-C(R_1R_2)N(R_5)-$ is  ; L_S is a bond; and R_E is methoxy.

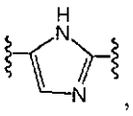
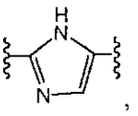
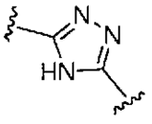
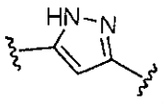
Non-limiting examples of preferred Y include:  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , or  ,  ,  ,  ,  ,

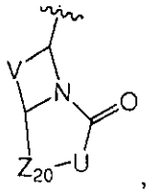
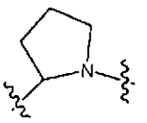
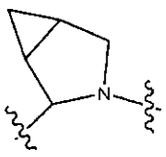
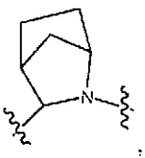
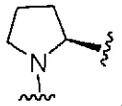
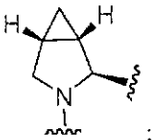
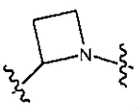
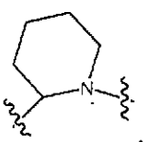
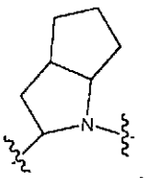
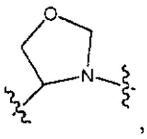
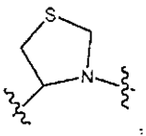
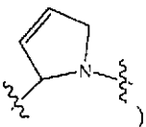
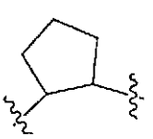
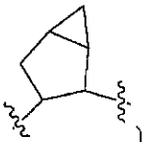
wherein T and R_D are as defined herein. T, for example, can be $-L_S-M-L_S'-M'-L_S''-$ where L_S is a bond; M is C(O); L_S' is C_1-C_6alkylene such as, but not limited to,  ,  , ,  , or  , where L_S' is optionally substituted with one or more R_L; R_L is a substituent such as, but not limited to phenyl or methoxy; M' is –NHC(O)– or –NMeC(O)–; and L_S'' is a bond. Any stereochemistry at a carbon within the group L_S' can be either (R) or (S). R_D, for example is methoxy. T-R_D includes, but is not limited to:  ,  ,  ,  ,  ,  , or  .

T-R_D may also include certain stereochemical configurations; thus T-R_D includes, but is not limited to:  ,  ,  ,  ,  ,  ,  ,  , and  .

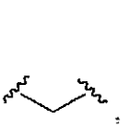
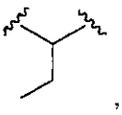
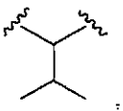
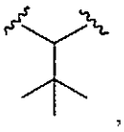
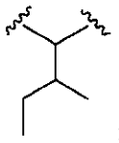
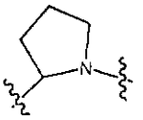
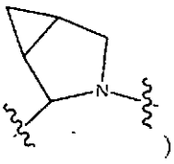
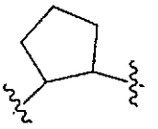
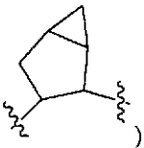
Non-limiting examples of preferred Y also include:  ,  ,  , or  ,  ,  ,  ,  ,  ,  ,  , or  .

Z is preferably selected from $-L_S-C(R_8R_9)N(R_{12})-T-R_D$, $-L_S-C(R_{10}R_{11})C(R_{13}R_{14})-T-R_D$, $-G-C(R_8R_9)N(R_{12})-T-R_D$, $-G-C(R_{10}R_{11})C(R_{13}R_{14})-T-R_D$, $-N(R_B)C(O)C(R_8R_9)N(R_{12})-T-R_D$, $-N(R_B)C(O)C(R_{10}R_{11})C(R_{13}R_{14})-T-R_D$, $-C(O)N(R_B)C(R_8R_9)N(R_{12})-T-R_D$, $-C(O)N(R_B)C(R_{10}R_{11})C(R_{13}R_{14})-T-R_D$, $-N(R_B)C(O)-L_S-E$, or $-C(O)N(R_B)-L_S-E$. G is C_5-

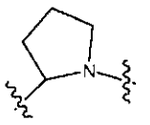
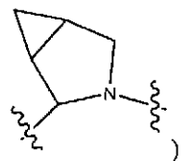
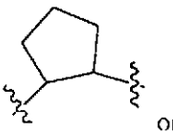
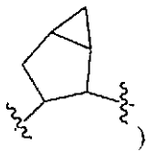
C_6carbocycle or 5- to 6-membered heterocycle, such as    or  , and is optionally substituted with one or more R_A (e.g., one or more chloro or bromo).

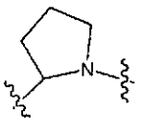
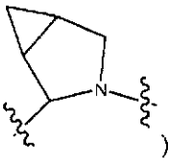
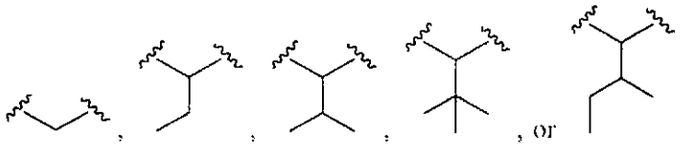
E preferably is a 8- to 12-membered bicycle (such as  , wherein U is independently selected at each occurrence from -(CH_2)- or -(NH)-; and V and Z_{20} are each independently selected from C_1-C_4alkylene, C_2-C_4alkenylene or C_2-C_4alkynylene, in which at least one carbon atom is independently optionally replaced with O, S or N), and is optionally substituted with one or more R_A. More preferably, R_8 is R_C, and R_9 and R_{12}, taken together with the atoms to which they are attached, form a 5- to 6-membered heterocycle or 6- to 12-membered bicycle (e.g.,  or  ; or    ; or    ,   or )) which is optionally substituted with one or more R_A (such as, but not limited to hydroxy, halo (e.g., fluoro), C_1-C_6alkyl (e.g., methyl), or C_2-C_6alkenyl (e.g., allyl)); and R_{10} and R_{13} are each independently R_C, and R_{11} and R_{14}, taken together with the atoms to which they are attached, form a 5- to 6-membered carbocycle/heterocycle or 6- to 12-membered bicycle (e.g.,  or ) which is optionally substituted with one or more R_A (such as, but not limited to hydroxy, halo (e.g., fluoro), C_1-C_6alkyl (e.g., methyl), or C_2-C_6alkenyl (e.g., allyl)).

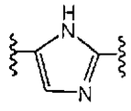
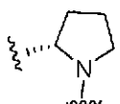
Z can also be selected from –M–$C(R_8R_9)N(R_{12})$–C(O)–L_Y'–M'–R_D, –M–$C(R_8R_9)N(R_{12})$–L_Y'–M'–R_D, –L_S–$C(R_8R_9)N(R_{12})$–C(O)–L_Y'–M'–R_D, –L_S–$C(R_8R_9)N(R_{12})$–L_Y'–M'–R_D, –M–$C(R_{10}R_{11})C(R_{13}R_{14})$–C(O)–$L_Y$'–M'–$R_D$, –M–$C(R_{10}R_{11})C(R_{13}R_{14})$–$L_Y$'–M'–$R_D$, –$L_S$–$C(R_{10}R_{11})C(R_{13}R_{14})$–C(O)–$L_Y$'–M'–$R_D$, or –$L_S$–$C(R_{10}R_{11})C(R_{13}R_{14})$–$L_Y$'–M'–$R_D$, wherein M

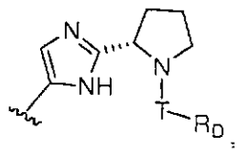
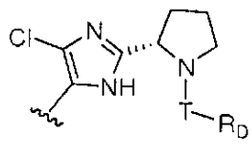
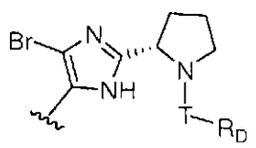
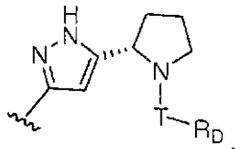
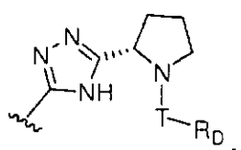
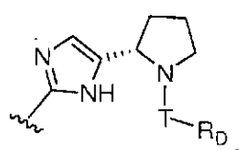
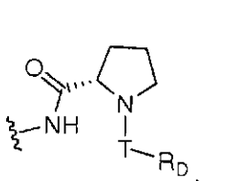
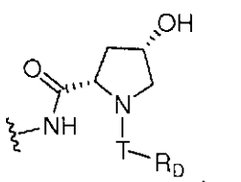
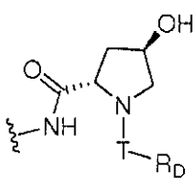
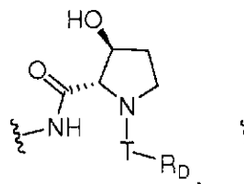
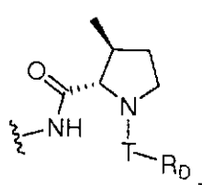
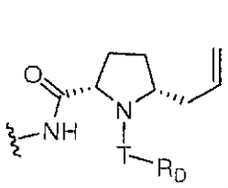
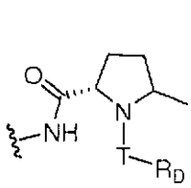
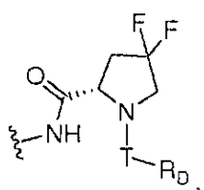
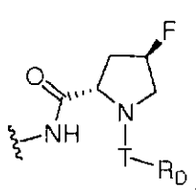
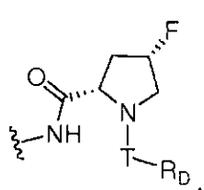
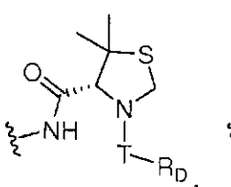
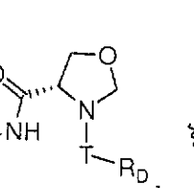
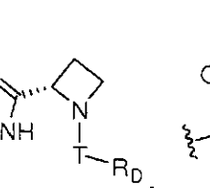
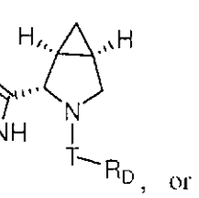
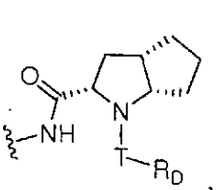
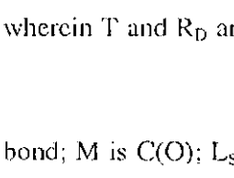
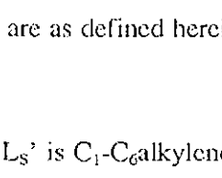
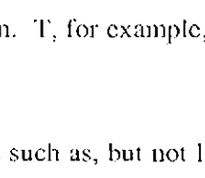
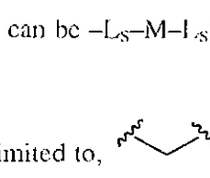
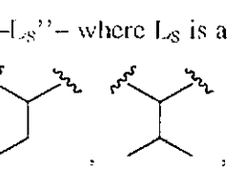
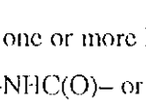
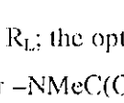
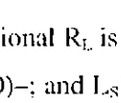
preferably is bond, $-C(O)N(R_B)-$ or $-N(R_B)C(O)-$, M' preferably is bond, $-C(O)N(R_B)-$, $-N(R_B)C(O)-$, $-N(R_B)C(O)O-$, $N(R_B)C(O)N(R_B')-$, $-N(R_B)S(O)-$ or $-N(R_B)S(O)_2-$, and L_Y' preferably is C_1-C_6alkylene which is optionally substituted with one or more R_L. L_Y', for example, is a C_1-C_6alkylene such as, but not limited to,  ,  ,  ,  , or  ; and the optional R_L is a substituent such as, but not limited to phenyl, –SMe, or methoxy. Any stereochemistry at a carbon within the group L_Y' can be either (R) or (S). More preferably, R_8 is R_C, and R_9 and R_{12}, taken together with the atoms to which they are attached, form a 5- to 6-membered heterocycle or 6- to 12-membered bicycle (e.g.,  or ) which is optionally substituted with one or more R_A (e.g., one or more hydroxy); and R_{10} and R_{13} are each independently R_C, and R_{11} and R_{14}, taken together with the atoms to which they are attached, form a 5- to 6-membered carbocycle/heterocycle or 6- to 12-membered bicycle (e.g.,  or ) which is optionally substituted with one or more R_A.

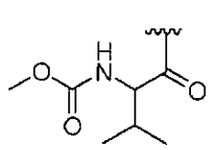
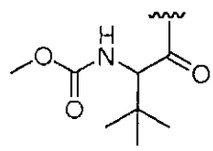
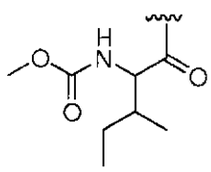
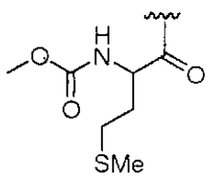
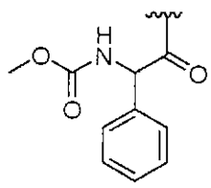
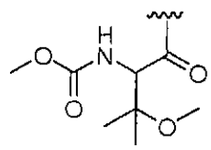
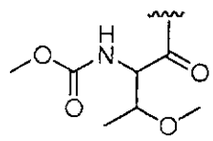
Also preferably, Z is selected from $-N(R_B)CO-C(R_8R_9)N(R_{12})-C(O)-L_Y'-N(R_B)C(O)O-R_D$, $-N(R_B)CO-C(R_8R_9)N(R_{12})-C(O)-L_Y'-N(R_B)C(O)-R_D$, $-N(R_B)CO-C(R_8R_9)N(R_{12})-C(O)-L_Y'-N(R_B)S(O)_2-R_D$, $-N(R_B)CO-C(R_8R_9)N(R_{12})-C(O)-L_Y'-N(R_BR_B')-R_D$, $-N(R_B)CO-C(R_8R_9)N(R_{12})-C(O)-L_Y'-O-R_D$, $-N(R_B)CO-C(R_8R_9)N(R_{12})-C(O)-L_Y'-R_D$, $-N(R_B)CO-C(R_8R_9)N(R_{12})-R_D$, $-L_S-C(R_8R_9)N(R_{12})-C(O)-L_Y'-N(R_B)C(O)O-R_D$, $-L_S-C(R_8R_9)N(R_{12})-C(O)-L_Y'-N(R_B)C(O)-R_D$, $-L_S-C(R_8R_9)N(R_{12})-C(O)-L_Y'-N(R_B)S(O)_2-R_D$, $-L_S-C(R_8R_9)N(R_{12})-C(O)-L_Y'-N(R_BR_B')-R_D$, $-L_S-C(R_8R_9)N(R_{12})-C(O)-L_Y'-O-R_D$, $-L_S-C(R_8R_9)N(R_{12})-C(O)-L_Y'-R_D$, $-L_S-C(R_8R_9)N(R_{12})-R_D$, $-N(R_B)CO-C(R_{10}R_{11})C(R_{13}R_{14})-C(O)-L_Y'-N(R_B)C(O)O-R_D$, $-N(R_B)CO-C(R_{10}R_{11})C(R_{13}R_{14})-C(O)-L_Y'-N(R_B)C(O)-R_D$, $-N(R_B)CO-C(R_{10}R_{11})C(R_{13}R_{14})-C(O)-L_Y'-N(R_B)S(O)_2-R_D$, $-N(R_B)CO-C(R_{10}R_{11})C(R_{13}R_{14})-C(O)-L_Y'-N(R_BR_B')-R_D$, $-N(R_B)CO-C(R_{10}R_{11})C(R_{13}R_{14})-C(O)-L_Y'-O-R_D$, $-N(R_B)CO-C(R_{10}R_{11})C(R_{13}R_{14})-C(O)-L_Y'-R_D$, $-N(R_B)CO-C(R_{10}R_{11})C(R_{13}R_{14})-R_D$, $-L_S-C(R_{10}R_{11})C(R_{13}R_{14})-C(O)-L_Y'-N(R_B)C(O)O-R_D$, $-L_S-C(R_{10}R_{11})C(R_{13}R_{14})-C(O)-L_Y'-N(R_B)C(O)-R_D$, $-L_S-C(R_{10}R_{11})C(R_{13}R_{14})-C(O)-L_Y'-N(R_B)S(O)_2-R_D$, $-L_S-C(R_{10}R_{11})C(R_{13}R_{14})-C(O)-L_Y'-$

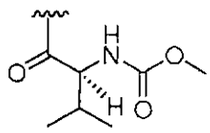
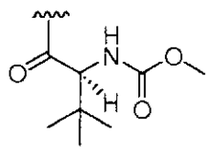
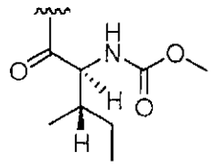
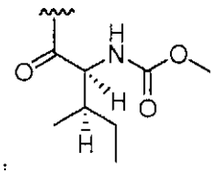
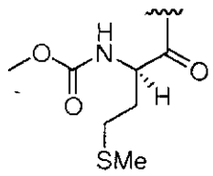
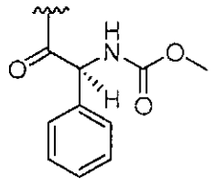
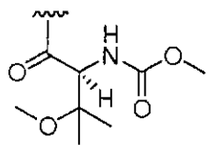
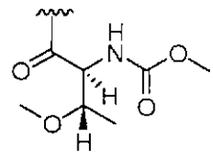
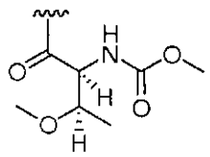
$N(R_BR_B')$–R_D, –L_S–$C(R_{10}R_{11})C(R_{13}R_{14})$–$C(O)$–$L_Y'$–$O$–$R_D$, –$L_S$–$C(R_{10}R_{11})C(R_{13}R_{14})$–$C(O)$–$L_Y'$–$R_D$, or –$L_S$–$C(R_{10}R_{11})C(R_{13}R_{14})$–$R_D$, wherein L_Y' preferably is C_1-C_6alkylene which is optionally substituted with one or more R_L. R_8 may be R_C, and R_9 and R_{12}, taken together with the atoms to which they are attached, may form a 5- to 6-membered heterocycle or 6- to 12-membered bicycle (e.g.,  or ) which is optionally substituted with one or more R_A; and R_{10} and R_{13} may be each independently R_C, and R_{11} and R_{14}, taken together with the atoms to which they are attached, may form a 5- to 6-membered carbocycle/heterocycle or 6- to 12-membered bicycle (e.g.,  or ) which is optionally substituted with one or more R_A.

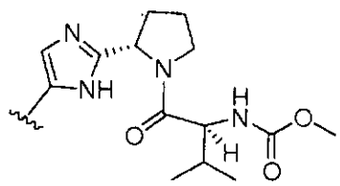
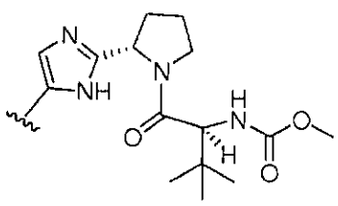
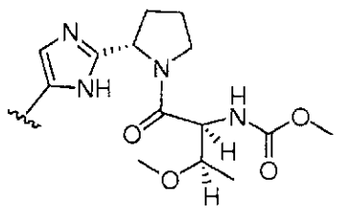
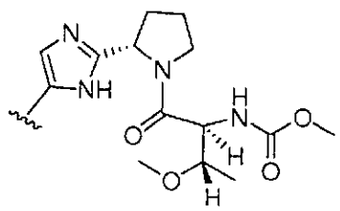
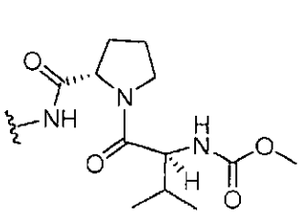
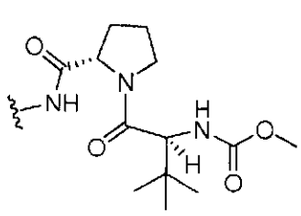
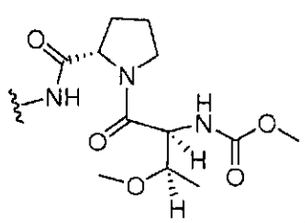
Highly preferably, Z is selected from –$N(R_B'')CO$–$C(R_8R_9)N(R_{12})$–$C(O)$–L_Y–$N(R_B'')C(O)$–L_S–R_E or –$C(R_8R_9)N(R_{12})$–$C(O)$–L_Y–$N(R_B'')C(O)$–L_S–R_E, or Z is –G–$C(R_8R_9)N(R_{12})$–$C(O)$–L_Y–$N(R_B'')C(O)$–L_S–R_E, wherein L_Y is C_1-C_6alkylene optionally substituted with one or more R_L, and R_B'' is each independently R_B. R_B'' and R_8 are each preferably hydrogen or C_1-C_6alkyl, and R_9 and R_{12}, taken together with the atoms to which they are attached, preferably form a 5- to 6-membered heterocycle or 6- to 12-membered bicycle (e.g.,  or ) which is optionally substituted with one or more R_A (such as, but not limited to hydroxy, halo (e.g., fluoro), C_1-C_6alkyl (e.g., methyl), or C_2-C_6alkenyl (e.g., allyl)). Preferably, L_Y is C_1-C_6alkylene substituted with one or more R_L such as a C_3-C_6carbocycle 3- to 6-membered heterocycle which is optionally substituted with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6haloalkyl, C_2-C_6haloalkenyl or C_2-C_6haloalkynyl. Highly preferably, L_Y is a C_1-C_6alkylene such as, but not limited to,  (stereochemistry at a carbon within the group L_Y can be either (R) or (S)); L_Y is optionally substituted with one or more R_L

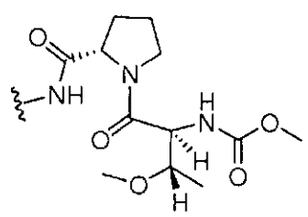
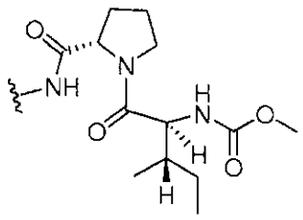
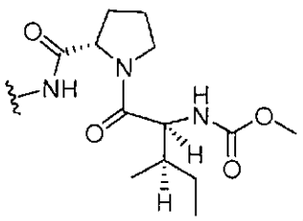
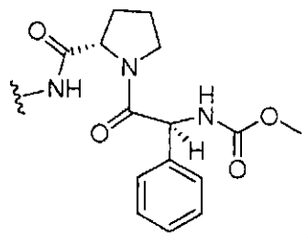
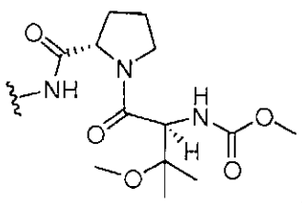
(e.g., one or more phenyl or methoxy); G preferably is  ; R_B'' is hydrogen; –$C(R_8R_9)N(R_{12})$– is  ; L_S is a bond; and R_E is methoxy.

Non-limiting examples of preferred Z include:  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , or , wherein T and R_D are as defined herein. T, for example, can be –L_S–M–L_S'–M'–L_S''– where L_S is a bond; M is C(O); L_S' is C_1-C_6alkylene such as, but not limited to,  ,  ,  , , or , where L_S' is optionally substituted with one or more R_L; the optional R_L is a substituent such as, but not limited to phenyl or methoxy; M' is –NHC(O)– or –NMeC(O)–; and L_S'' is a bond. Any stereochemistry at a carbon within the group L_S' can be either (R) or (S). R_D, for

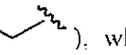
example is methoxy. T-R_D includes, but is not limited to:  ,  ,  ,  ,  ,  , or  .

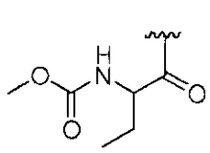
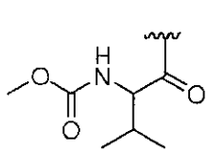
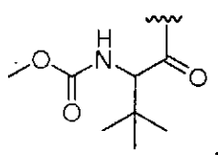
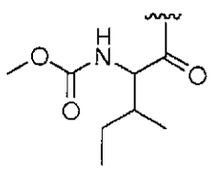
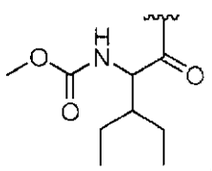
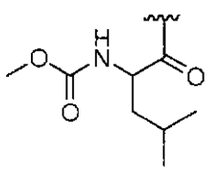
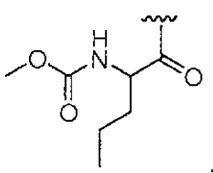
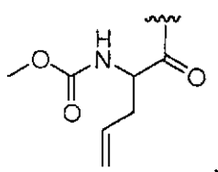
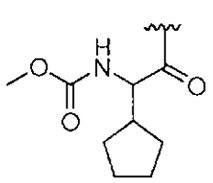
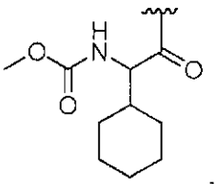
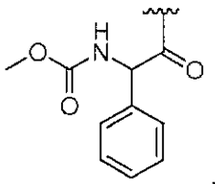
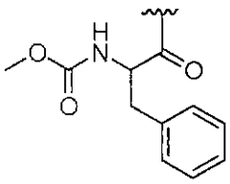
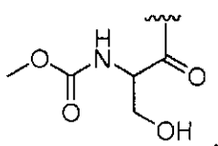
T-R_D may also include certain stereochemical configurations; thus T-R_D includes, but is not limited to:  ,  ,  ,  ,  ,  ,  ,  , and  .

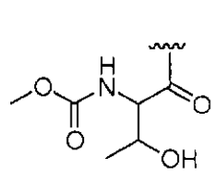
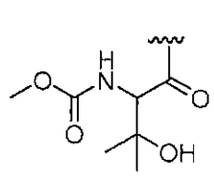
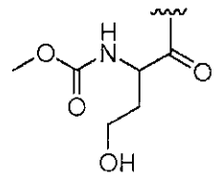
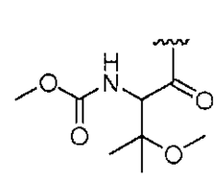
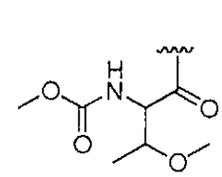
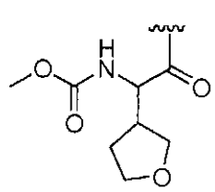
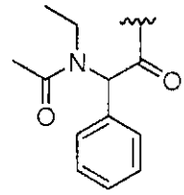
Non-limiting examples of preferred Z also include:  ,  ,  ,  ,  ,  ,  .






, or .

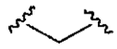
T can be, without limitation, independently selected at each occurrence from –C(O)–L_S'–, –C(O)O–L_S'–, –C(O)–L_S'–N(R_B)C(O)–L_S''–, –C(O)–L_S'–N(R_B)C(O)O–L_S''–, –N(R_B)C(O)–L_S'–N(R_B)C(O)–L_S''–, –N(R_B)C(O)–L_S'—N(R_B)C(O)O–L_S''–, or –N(R_B)C(O)–L_S'—N(R_B)–L_S''–. Preferably, T is independently selected at each occurrence from –C(O)–L_S'–M'–L_S''– or –N(R_B)C(O)–L_S'–M'–L_S''–. More preferably, T is independently selected at each occurrence from –C(O)–L_S'–N(R_B)C(O)–L_S''– or –C(O)–L_S'–N(R_B)C(O)O–L_S''–.

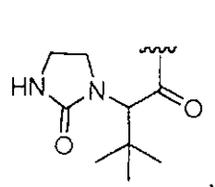
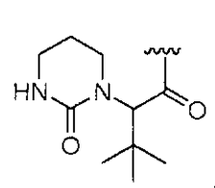
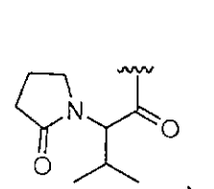
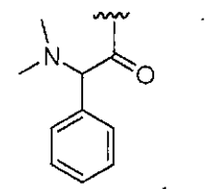
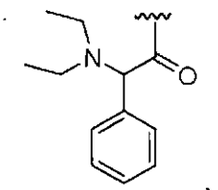
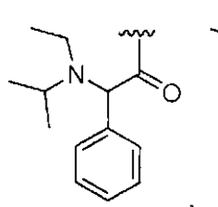
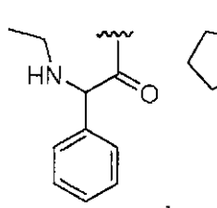
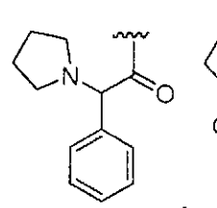
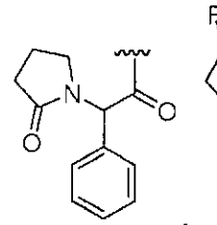
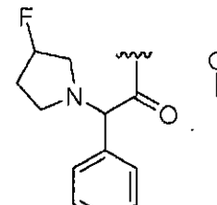
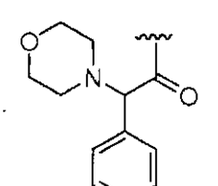
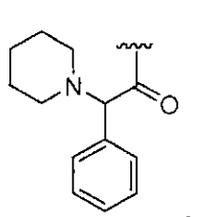
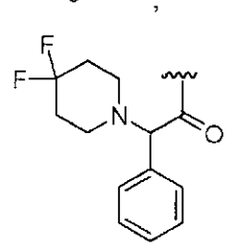
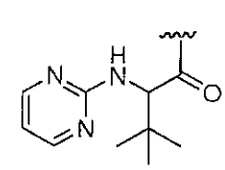
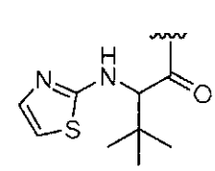
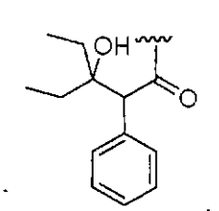
T can also be, for example, –L_S–M–L_S'–M'–L_S''– where L_S is a bond; M is C(O); L_S' is C_1-C_6alkylene (e.g., ), where L_S' is optionally substituted with R_T; the optional R_T is a substituent selected from –C_1-C_6alkyl, –C_2-C_6alkenyl, –C_1-C_6alkyl–OH, –C_1-C_6alkyl–O–C_1-C_6alkyl, 3- to 6-membered heterocycle (e.g., tetrahydrofuranyl), or C_3-C_6carbocyclyl (e.g., phenyl, cyclohexyl); M' is –NHC(O)–, –N(Et)C(O)– or –N(Me)C(O)–; and L_S'' is a bond. R_D preferably is hydrogen, –C_1-C_6alkyl (e.g., methyl), –O–C_1-C_6alkyl (e.g., methoxy, tert-butoxy), methoxymethyl, or –N(C_1-C_6alkyl)$_2$ (e.g., –NMe_2).

T-R_D can be, without limitation,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  .

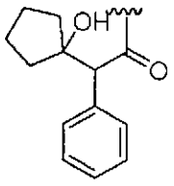
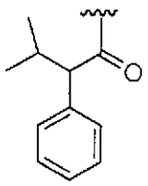
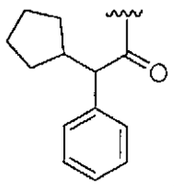
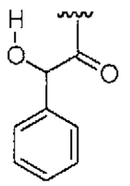
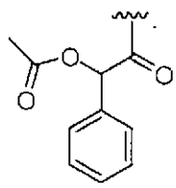








, or , wherein the stereochemistry at a carbon within the group T-R_D can be either (R) or (S).

T can also be, without limitation, $-L_S-M-L_S'-$ where L_S is a bond; M is C(O); L_S' is C_1-C_6alkylene (e.g., ) where L_S' is optionally substituted with R_T; the optional R_T is a substituent selected from $-C_1$-C_6alkyl, $-C_1$-C_6alkyl–OH, $-C_1$-C_6alkyl–O–C_1-C_6alkyl, or a C_3-C_6carbocyclyl (e.g., phenyl, cyclohexyl). R_D, for example is –OH; –OC(O)Me; $-NH(C_1$-C_6alkyl) (e.g., –NHMe, –NHEt); $-N(C_1$-C_6alkyl$)_2$ (e.g., $-NMe_2$, $-NEt_2$); a 3- to 10-membered heterocyclyl (e.g., pyrrolidinyl, imidazolidinyl, hexahydropyrimidinyl, morpholinyl, piperidinyl) optionally substituted with one or more halogen, oxo; C_3-C_{10}carbocycle (e.g., cyclopentyl) optionally substituted with –OH; $-C_1$-C_6alkyl (e.g., isopropyl, 3-pentyl) optionally substituted with –OH; or NHR_T where R_T is a 3- to 6-membered heterocyclyl (e.g., thiazolyl, pyrimidinyl). T-R_D includes, but is not limited to:

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, , , , or , wherein the stereochemistry at a carbon within the group T-R_D can be either (R) or (S).

For each compound of Formula I, L_K can also be independently selected at each occurrence from a bond; $-L_S'-N(R_B)C(O)-L_S-$; $-L_S'-C(O)N(R_B)-L_S-$; or C_1-C_6alkylene, C_2-C_6alkenylene, C_2-C_6alkynylene, C_3-C_{10}carbocycle or 3- to 10-membered heterocycle, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, R_T, $-O-R_S$, $-S-R_S$, $-N(R_SR_S')$, $-OC(O)R_S$, $-C(O)OR_S$, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl or cyano, wherein L_S and L_S' are as defined above.

For Formula I as well as Formulae I_A, I_B, I_C and I_D described below, including each and every embodiment described thereunder, R_A preferably is halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, cyano; or C_1-C_6alkyl, C_2-C_6alkenyl or C_2-C_6alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl or cyano; or C_3-C_6carbocycle or 3- to 6-membered heterocycle, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6haloalkyl, C_2-C_6haloalkenyl or C_2-C_6haloalkynyl; or $-L_A-O-R_S$, $-L_A-S-R_S$, $-L_A-C(O)R_S$, $-L_A-OC(O)R_S$, $-L_A-C(O)OR_S$, $-L_A-N(R_SR_S')$, $-L_A-S(O)R_S$, $-L_A-SO_2R_S$, $-L_A-C(O)N(R_SR_S')$, $-L_A-N(R_S)C(O)R_S'$, $-L_A-N(R_S)C(O)N(R_S'R_S'')$, $-L_A-N(R_S)SO_2R_S'$, $-L_A-SO_2N(R_SR_S')$, $-L_A-N(R_S)SO_2N(R_S'R_S'')$, $-L_A-N(R_S)S(O)N(R_S'R_S'')$, $-L_A-OS(O)-R_S$, $-L_A-OS(O)_2-R_S$, $-L_A-S(O)_2OR_S$, $-L_A-S(O)OR_S$, $-L_A-OC(O)OR_S$, $-L_A-N(R_S)C(O)OR_S'$, $-L_A-OC(O)N(R_SR_S')$, $-L_A-N(R_S)S(O)-R_S'$, $-L_A-S(O)N(R_SR_S')$ or $-L_A-C(O)N(R_S)C(O)-R_S'$, wherein L_A is bond, C_1-C_6alkylene, C_2-C_6alkenylene or C_2-C_6alkynylene.

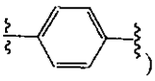
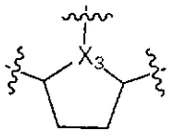
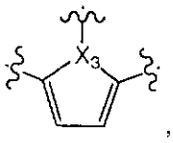
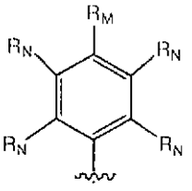
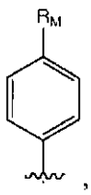
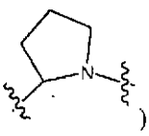
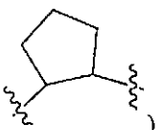
More preferably, R_A is halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, cyano; or C_1-C_6alkyl, C_2-C_6alkenyl or C_2-C_6alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl or cyano; or C_3-C_6carbocycle or 3- to 6-membered heterocycle, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6haloalkyl, C_2-C_6haloalkenyl or C_2-C_6haloalkynyl.

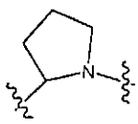
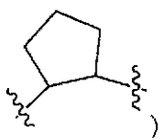
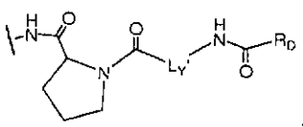
Highly preferably, R_A is halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, cyano; or C_1-C_6alkyl, C_2-C_6alkenyl or C_2-C_6alkynyl, each of which

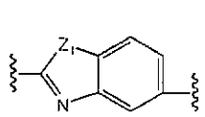
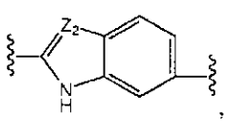
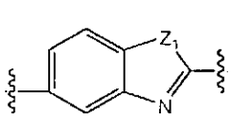
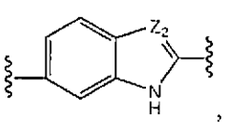
is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl or cyano.

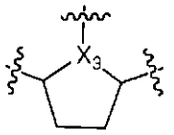
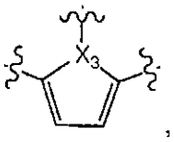
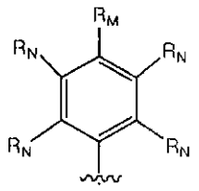
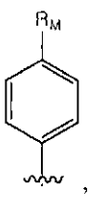
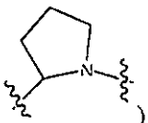
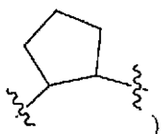
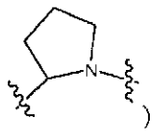
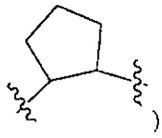
L_S, L_S' and L_S'' preferably are each independently selected at each occurrence from bond; or C_1-C_6alkylene, C_2-C_6alkenylene or C_2-C_6alkynylene.

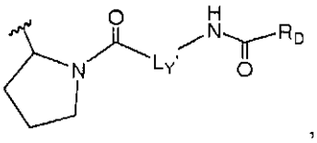
A and B can be the same or different. Likewise, L_1 and L_2, or Y and Z, or Y–A– and Z–B–, or –A–L_1– and –B–L_2–, can be the same or different. In some instances, Y–A–L_1– is identical to Z–B–L_2–. In some other instances, Y–A–L_1– is different from Z–B–L_2–.

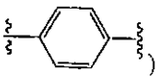
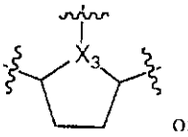
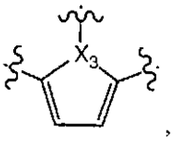
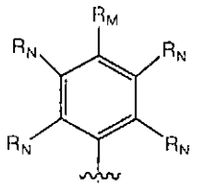
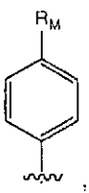
In one embodiment, A and B are each independently 5- or 6-membered carbocycle or heterocycle (e.g., phenyl such as ), and are each independently optionally substituted with one or more R_A. X is 5- or 6-membered carbocycle or heterocycle or 6- to 12-membered bicycle (e.g.,  or  , wherein X_3 is N and is directly linked to –L_3–D) and is optionally substituted with one or more R_A. Specific examples of X are described hereinabove. D is C_5-C_6carbocycle or 5- to 6-membered heterocycle (e.g., phenyl), and is optionally substituted with one or more R_A. Preferably, D is  or  , wherein R_M and R_N are as defined above. L_1 and L_2 are each independently bond or C_1-C_6alkylene, and L_3 is bond, C_1-C_6alkylene or -C(O)-, and L_1, L_2, and L_3 are each independently optionally substituted with one or more R_L. Preferably, L_1, L_2, and L_3 are bond. Y is $-N(R_B)C(O)C(R_1R_2)N(R_5)$–T–$R_D$, or $-N(R_B)C(O)C(R_3R_4)C(R_6R_7)$–T–$R_D$, and Z is $-N(R_B)C(O)C(R_8R_9)N(R_{12})$–T–$R_D$, or $-N(R_B)C(O)C(R_{10}R_{11})C(R_{13}R_{14})$–T–$R_D$. R_1 is R_C, and R_2 and R_5, taken together with the atoms to which they are attached, form a 5- to 6-membered heterocyclic ring (e.g., ) which is optionally substituted with one or more R_A; R_3 and R_6 are each independently R_C, and R_4 and R_7, taken together with the atoms to which they are attached, form a 5- to 6-membered carbocyclic or heterocyclic ring (e.g., ) which is optionally substituted with one or more R_A. R_8 is R_C, and R_9 and R_{12}, taken together with the atoms to which they are attached, form a 5- to 6-membered

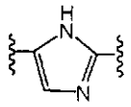
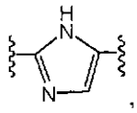
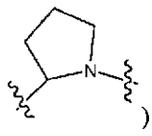
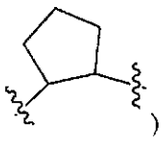
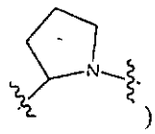
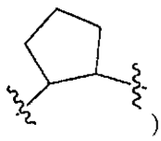
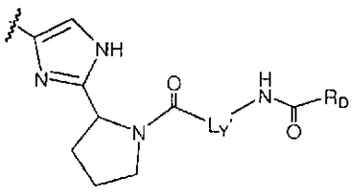
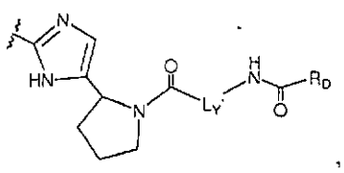
heterocyclic ring (e.g., ) which is optionally substituted with one or more R_A; and R_{10} and R_{13} are each independently R_C, and R_{11} and R_{14}, taken together with the atoms to which they are attached, form a 5- to 6-membered carbocyclic or heterocyclic ring (e.g., ) which is optionally substituted with one or more R_A. T is preferably independently selected at each occurrence from $-C(O)-L_Y'-N(R_B)C(O)-L_S''-$ or $-C(O)-L_Y'-N(R_B)C(O)O-L_S''-$. L_Y' is each independently L_S' and, preferably, is each independently C_1-C_6alkylene (e.g., $-CH_2-$) and optionally substituted with one or more substituents selected from R_L. T can also be, without limitation, selected from $-C(O)-L_Y'-L_S''-$, $-C(O)-L_Y'-O-L_S''-$, $-C(O)-L_Y'-N(R_B)-L_S''-$, or $-C(O)-L_Y'-N(R_B)S(O)_2-L_S''-$. In some cases, at least one of Y and Z is, or both Y and Z are independently,  , wherein non-limiting examples of R_D include (1) $-O-C_1$-C_6alkyl, $-O-C_2$-C_6alkenyl, $-O-C_2$-C_6alkynyl, C_1-C_6alkyl, C_2-C_6alkenyl or C_2-C_6alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, C_3-C_6carbocycle or 3- to 6-membered heterocycle; or (2) C_3-C_6carbocycle or 3- to 6-membered heterocycle each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6haloalkyl, C_2-C_6haloalkenyl or C_2-C_6haloalkynyl; and non-limiting examples of L_Y' include C_1-C_6alkylene optionally substituted with halogen, hydroxy, mercapto, amino, carboxy, phosphonoxy, $-O-C_1$-C_6alkyl, $-O-C_2$-C_6alkenyl, $-O-C_2$-C_6alkynyl, or 3- to 6-membered carbocycle or heterocycle, said 3- to 6-membered carbocycle or heterocycle being optionally substituted with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6haloalkyl, C_2-C_6haloalkenyl or C_2-C_6haloalkynyl.

In another embodiment, A is  or  , and is optionally substituted with one or more R_A; B is  or  , and is optionally substituted with one or more R_A. Z_1 is independently selected at each occurrence from O, S, NH or

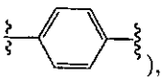
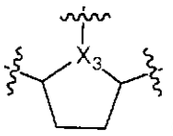
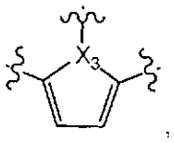
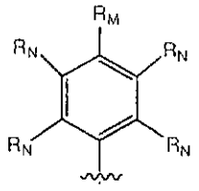
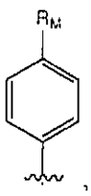
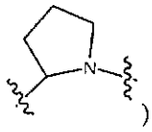
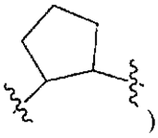
CH_2; and Z_2 is independently selected at each occurrence from N or CH. X is 5- or 6-membered carbocycle or heterocycle or 6- to 12-membered bicycle (e.g.,  or  , wherein X_3 is N and is directly linked to $-L_3-D$) and is optionally substituted with one or more R_A. Specific examples of X are described hereinabove. D is C_5-C_6carbocycle or 5- to 6-membered heterocycle (e.g., phenyl), and is optionally substituted with one or more R_A. Preferably, D is  or  , wherein R_M and R_N are as defined above. L_1 and L_2 are each independently bond or C_1-C_6alkylene, and L_3 is bond, C_1-C_6alkylene or -C(O)-, and L_1, L_2, and L_3 are each independently optionally substituted with one or more R_L. Preferably, L_1, L_2, and L_3 are bond. Y is $-L_S-C(R_1R_2)N(R_5)-T-R_D$ or $-L_S-C(R_3R_4)C(R_6R_7)-T-R_D$, and Z is $-L_S-C(R_8R_9)N(R_{12})-T-R_D$ or $-L_S-C(R_{10}R_{11})C(R_{13}R_{14})-T-R_D$. R_1 is R_C, and R_2 and R_5, taken together with the atoms to which they are attached, form a 5- to 6-membered heterocyclic ring (e.g., ) which is optionally substituted with one or more R_A; R_3 and R_6 are each independently R_C, and R_4 and R_7, taken together with the atoms to which they are attached, form a 5- to 6-membered carbocyclic or heterocyclic ring (e.g., ) which is optionally substituted with one or more R_A. R_8 is R_C, and R_9 and R_{12}, taken together with the atoms to which they are attached, form a 5- to 6-membered heterocyclic ring (e.g., ) which is optionally substituted with one or more R_A; and R_{10} and R_{13} are each independently R_C, and R_{11} and R_{14}, taken together with the atoms to which they are attached, form a 5- to 6-membered carbocyclic or heterocyclic ring (e.g., ) which is optionally substituted with one or more R_A. T is preferably independently selected at each occurrence from $-C(O)-L_Y'-N(R_B)C(O)-L_S''-$ or $-C(O)-L_Y'-N(R_B)C(O)O-L_S''-$. L_Y' is each independently L_S' and, preferably, is independently C_1-C_6alkylene (e.g., $-CH_2-$) and optionally substituted with one or more substituents selected from R_L. T can also be, without limitation, selected from $-C(O)-L_Y'-L_S''-$, $-C(O)-L_Y'-O-L_S''-$, $-C(O)-L_Y'-N(R_B)-L_S''-$, or $-C(O)-L_Y'-N(R_B)S(O)_2-L_S''-$. In some cases, at least one of Y

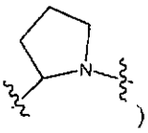
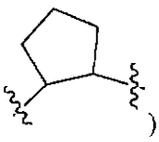
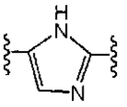
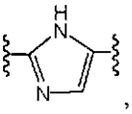
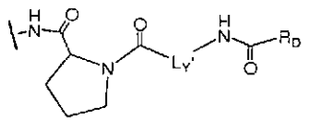
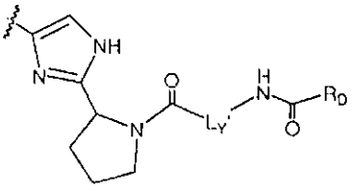
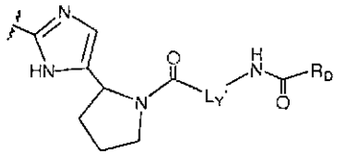
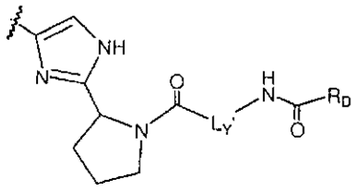
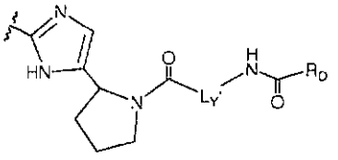
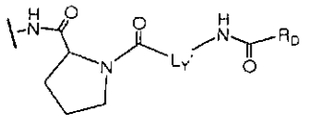
and Z is, or both Y and Z are independently,  , wherein non-limiting examples of R_D include (1) –O–C_1-C_6alkyl, –O–C_2-C_6alkenyl, –O–C_2-C_6alkynyl, C_1-C_6alkyl, C_2-C_6alkenyl or C_2-C_6alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, C_3-C_6carbocycle or 3- to 6-membered heterocycle; or (2) C_3-C_6carbocycle or 3- to 6-membered heterocycle each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6haloalkyl, C_2-C_6haloalkenyl or C_2-C_6haloalkynyl; and non-limiting examples of L_Y' include C_1-C_6alkylene optionally substituted with halogen, hydroxy, mercapto, amino, carboxy, phosphonoxy, –O–C_1-C_6alkyl, –O–C_2-C_6alkenyl, –O–C_2-C_6alkynyl, or 3- to 6-membered carbocycle or heterocycle, said 3- to 6-membered carbocycle or heterocycle being optionally substituted with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6haloalkyl, C_2-C_6haloalkenyl or C_2-C_6haloalkynyl.

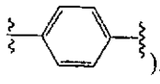
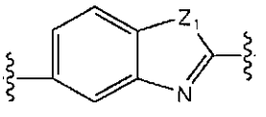
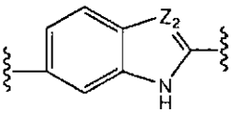
In still yet another embodiment, A and B are each independently 5- or 6-membered carbocycle or heterocycle (e.g., A and B are each independently phenyl, such as ), and are each independently optionally substituted with one or more R_A. X is 5- or 6-membered carbocycle or heterocycle or 6- to 12-membered bicycle (e.g.,  or  , wherein X_3 is N and is directly linked to –L_3–D) and is optionally substituted with one or more R_A. Specific examples of X are described hereinabove. D can be, for example, C_5-C_6carbocycle or 5- to 6-membered heterocycle (e.g., phenyl), and is optionally substituted with one or more R_A. Preferably, D is  or  , wherein R_M and R_N are as defined above. L_1 and L_2 are each independently bond or C_1-C_6alkylene, and L_3 is bond, C_1-C_6alkylene or -C(O)-, and L_1, L_2, and L_3 are each independently optionally substituted with one or more R_L. Preferably, L_1, L_2, and L_3 are bond. Y is –G–C(R_1R_2)N(R_5)–T–R_D or –G–C(R_3R_4)C(R_6R_7)–T–R_D, and Z is –G–C(R_8R_9)N(R_{12})–T–R_D or –G–C($R_{10}R_{11}$)C($R_{13}R_{14}$)–T–R_D. G is independently C_5-C_6carbocycle or 5- to 6-membered heterocycle,

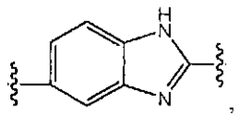
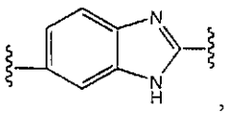
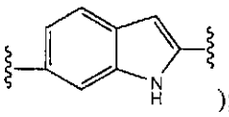
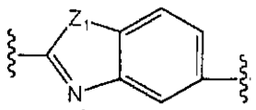
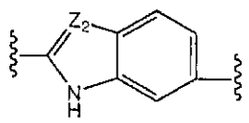
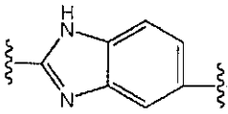
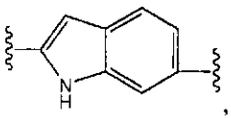
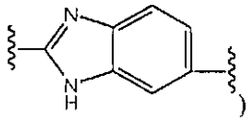
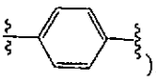
such as  or  , and is independently optionally substituted with one or more R_A. R_1 is R_C, and R_2 and R_5, taken together with the atoms to which they are attached, form a 5- to 6-membered heterocyclic ring (e.g., ) which is optionally substituted with one or more R_A; R_3 and R_6 are each independently R_C, and R_4 and R_7, taken together with the atoms to which they are attached, form a 5- to 6-membered carbocyclic or heterocyclic ring (e.g., ) which is optionally substituted with one or more R_A. R_8 is R_C, and R_9 and R_{12}, taken together with the atoms to which they are attached, form a 5- to 6-membered heterocyclic ring (e.g., ) which is optionally substituted with one or more R_A; and R_{10} and R_{13} are each independently R_C, and R_{11} and R_{14}, taken together with the atoms to which they are attached, form a 5- to 6-membered carbocyclic or heterocyclic ring (e.g., ) which is optionally substituted with one or more R_A. T is preferably independently selected at each occurrence from $-C(O)-L_Y'-N(R_B)C(O)-L_S''-$ or $-C(O)-L_Y'-N(R_B)C(O)O-L_S''-$. L_Y' is each independently L_S' and, preferably, is each independently C_1-C_6alkylene (e.g., $-CH_2-$) and optionally substituted with one or more substituents selected from R_L. T can also be, without limitation, selected from $-C(O)-L_Y'-L_S''-$, $-C(O)-L_Y'-O-L_S''-$, $-C(O)-L_Y'-N(R_B)-L_S''-$, or $-C(O)-L_Y'-N(R_B)S(O)_2-L_S''-$. In some cases, at least one of Y and Z is, or both Y and Z are independently,  or  , wherein non-limiting examples of R_D include (1) $-O-C_1$-C_6alkyl, $-O-C_2$-C_6alkenyl, $-O-C_2$-C_6alkynyl, C_1-C_6alkyl, C_2-C_6alkenyl or C_2-C_6alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, C_3-C_6carbocycle or 3- to 6-membered heterocycle; or (2) C_3-C_6carbocycle or 3- to 6-membered heterocycle each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, C_1-

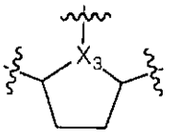
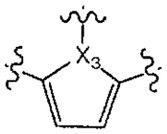
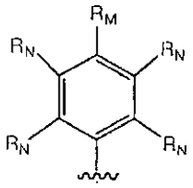
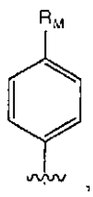
C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6haloalkyl, C_2-C_6haloalkenyl or C_2-C_6haloalkynyl; and non-limiting examples of L_Y' include C_1-C_6alkylene optionally substituted with halogen, hydroxy, mercapto, amino, carboxy, phosphonoxy, –O–C_1-C_6alkyl, –O–C_2-C_6alkenyl, –O–C_2-C_6alkynyl, or 3- to 6-membered carbocycle or heterocycle, said 3- to 6-membered carbocycle or heterocycle being optionally substituted with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6haloalkyl, C_2-C_6haloalkenyl or C_2-C_6haloalkynyl.

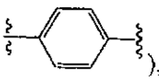
In yet another embodiment, A and B are each independently 5- or 6-membered carbocycle or heterocycle (e.g., A and B are each independently phenyl, such as ), and are each independently optionally substituted with one or more R_A. X is 5- or 6-membered carbocycle or heterocycle or 6- to 12-membered bicycle (e.g.,  or  , wherein X_3 is N and is directly linked to $–L_3–D$) and is optionally substituted with one or more R_A. Specific examples of X are described hereinabove. D can be, for example, C_5-C_6carbocycle or 5- to 6-membered heterocycle (e.g., phenyl), and is optionally substituted with one or more R_A. Preferably, D is  or  , wherein R_M and R_N are as defined above. L_1 and L_2 are each independently bond or C_1-C_6alkylene, and L_3 is bond, C_1-C_6alkylene or -C(O)-, and L_1, L_2, and L_3 are each independently optionally substituted with one or more R_L. Preferably, L_1, L_2, and L_3 are bond. Y is $–N(R_B)C(O)C(R_1R_2)N(R_5)–T–R_D$ or $–N(R_B)C(O)C(R_3R_4)C(R_6R_7)–T–R_D$, and Z is $–G–C(R_8R_9)N(R_{12})–T–R_D$ or $–G–C(R_{10}R_{11})C(R_{13}R_{14})–T–R_D$; or Y is $–G–C(R_1R_2)N(R_5)–T–R_D$ or $–G–C(R_3R_4)C(R_6R_7)–T–R_D$, and Z is $–N(R_B)C(O)C(R_8R_9)N(R_{12})–T–R_D$ or $–N(R_B)C(O)C(R_{10}R_{11})C(R_{13}R_{14})–T–R_D$. R_1 is R_C, and R_2 and R_5, taken together with the atoms to which they are attached, form a 5- to 6-membered heterocyclic ring (e.g., ) which is optionally substituted with one or more R_A; R_3 and R_6 are each independently R_C, and R_4 and R_7, taken together with the atoms to which they are attached, form a 5- to 6-membered carbocyclic or heterocyclic ring (e.g., ) which is optionally substituted with one or more R_A. R_8 is R_C, and R_9 and R_{12}, taken together with the atoms to which they are attached, form a 5- to 6-membered

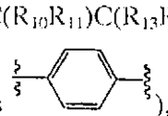
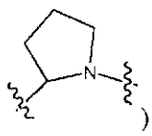
heterocyclic ring (e.g., ) which is optionally substituted with one or more R_A; and R_{10} and R_{13} are each independently R_C, and R_{11} and R_{14}, taken together with the atoms to which they are attached, form a 5- to 6-membered carbocyclic or heterocyclic ring (e.g., ) which is optionally substituted with one or more R_A. G is independently C_5-C_6carbocycle or 5- to 6-membered heterocycle, such as  or  , and is independently optionally substituted with one or more R_A. T is preferably independently selected at each occurrence from $-C(O)-L_Y'-N(R_B)C(O)-L_S''-$ or $-C(O)-L_Y'-N(R_B)C(O)O-L_S''-$. L_Y' is each independently L_S' and, preferably, is each independently C_1-C_6alkylene (e.g., $-CH_2-$) and optionally substituted with one or more substituents selected from R_L. T can also be, without limitation, selected from $-C(O)-L_Y'-L_S''-$, $-C(O)-L_Y'-O-L_S''-$, $-C(O)-L_Y'-N(R_B)-L_S''-$, or $-C(O)-L_Y'-N(R_B)S(O)_2-L_S''-$. In some cases, Y is  as described above, and Z is  or  as described above. In some other cases, Y is  or  as described above , and Z is  as described above.

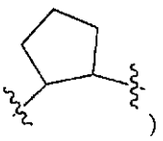
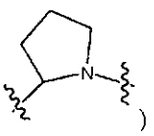
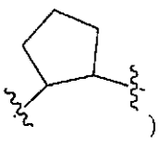
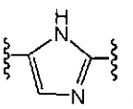
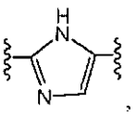
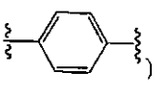
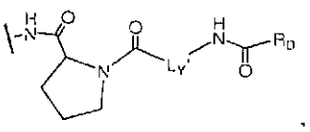
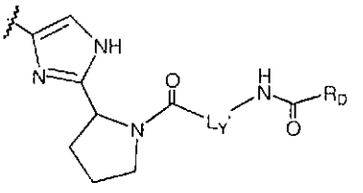
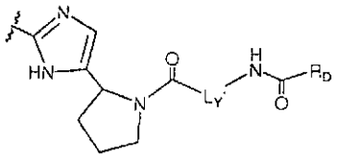
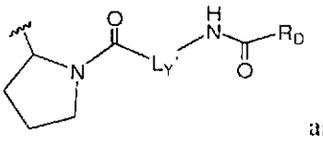
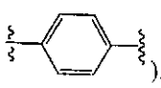
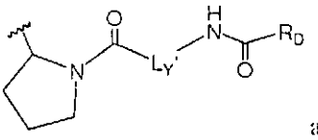
In still another embodiment, A is 5- or 6-membered carbocycle or heterocycle (e.g., phenyl such as ), and B is  or  (e.g.,

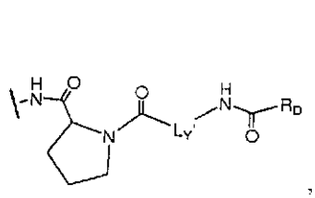
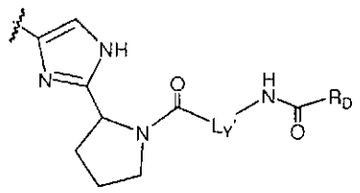
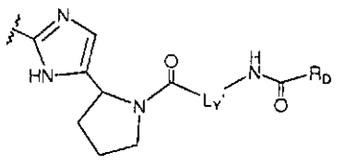
 ,  , or ); or A is  or  (e.g.,  ,  , or ), and B is 5- or 6-membered carbocycle or heterocycle (e.g., phenyl such as ). A and B are each independently optionally substituted with one or more R_A. Z_1 is independently selected at each occurrence from O, S, NH or CH_2; and Z_2 is independently selected at each occurrence from N or CH.

X is 5- or 6-membered carbocycle or heterocycle or 6- to 12-membered bicycle (e.g.,  or  , wherein X_3 is N and is directly linked to $-L_3-D$) and is optionally substituted with one or more R_A. Specific examples of X are described hereinabove. D is C_5-C_6carbocycle or 5- to 6-membered heterocycle (e.g., phenyl), and is optionally substituted with one or more R_A. Preferably, D is  or  , wherein R_M and R_N are as defined above. L_1 and L_2 are each independently bond or C_1-C_6alkylene, and L_3 is bond, C_1-C_6alkylene or -C(O)-, and L_1, L_2, and L_3 are each independently optionally substituted with one or more R_L. Preferably, L_1, L_2, and L_3 are bond.

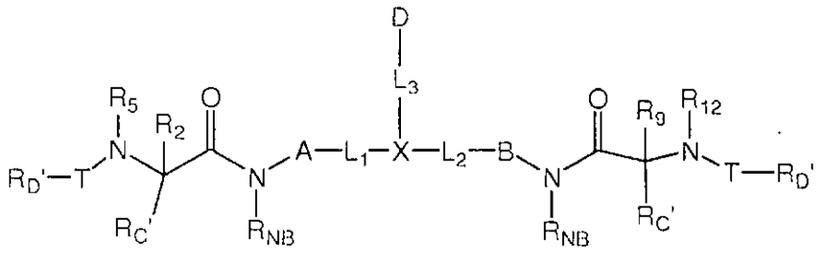
When A is 5- or 6-membered carbocycle or heterocycle (e.g., phenyl such as ), Y is $-N(R_B)C(O)C(R_1R_2)N(R_5)-T-R_D$, $-N(R_B)C(O)C(R_3R_4)C(R_6R_7)-T-R_D$, $-G-C(R_1R_2)N(R_5)-T-R_D$ or $-G-C(R_3R_4)C(R_6R_7)-T-R_D$, and Z is $-L_S-C(R_8R_9)N(R_{12})-T-R_D$ or $-L_S-C(R_{10}R_{11})C(R_{13}R_{14})-T-R_D$.

When B is 5- or 6-membered carbocycle or heterocycle (e.g., phenyl such as ), Y is $-L_S-C(R_1R_2)N(R_5)-T-R_D$ or $-L_S-C(R_3R_4)C(R_6R_7)-T-R_D$, and Z is $-N(R_B)C(O)C(R_8R_9)N(R_{12})-T-R_D$, $-N(R_B)C(O)C(R_{10}R_{11})C(R_{13}R_{14})-T-R_D$, $-G-C(R_8R_9)N(R_{12})-T-R_D$ or $-G-C(R_{10}R_{11})C(R_{13}R_{14})-T-R_D$. R_1 is R_C, and R_2 and R_5, taken together with the atoms to which they are attached, form a 5- to 6-membered heterocyclic ring (e.g., ) which is optionally substituted with one or more R_A; R_3 and R_6 are each independently R_C, and R_4 and R_7, taken together with the atoms to which they are

attached, form a 5- to 6-membered carbocyclic or heterocyclic ring (e.g., ) which is optionally substituted with one or more R_A. R_8 is R_C, and R_9 and R_{12}, taken together with the atoms to which they are attached, form a 5- to 6-membered heterocyclic ring (e.g., ) which is optionally substituted with one or more R_A; and R_{10} and R_{13} are each independently R_C, and R_{11} and R_{14}, taken together with the atoms to which they are attached, form a 5- to 6-membered carbocyclic or heterocyclic ring (e.g., ) which is optionally substituted with one or more R_A. G is independently C_5-C_6carbocycle or 5- to 6-membered heterocycle, such as  or  , and is independently optionally substituted with one or more R_A. T is preferably independently selected at each occurrence from $-C(O)-L_Y'-N(R_B)C(O)-L_S''-$ or $-C(O)-L_Y'-N(R_B)C(O)O-L_S''-$. L_Y' is each independently L_S' and, preferably, is each independently C_1-C_6alkylene (e.g., $-CH_2-$) and optionally substituted with one or more substituents selected from R_L. T can also be, without limitation, selected from $-C(O)-L_Y'-L_S''-$, $-C(O)-L_Y'-O-L_S''-$, $-C(O)-L_Y'-N(R_B)-L_S''-$, or $-C(O)-L_Y'-N(R_B)S(O)_2-L_S''-$. In some cases when A is 5- or 6-membered carbocycle or heterocycle (e.g., phenyl such as ), Y is  ,  ,  or  as described above, and Z is as described above. In some other cases when B is 5- or 6-membered carbocyclic or heterocyclic (e.g., phenyl such as ), Y is  as described above, and Z is



or

as described above.

In another aspect, the present invention features compounds of Formula I_A and pharmaceutically acceptable salts thereof.



I_A

wherein:

R_{NB} is each independently selected from R_B;

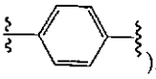
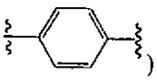
R_C' is each independently selected from R_C;

R_D' is each independently selected from R_D;

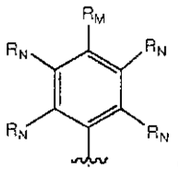
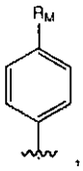
R_2 and R_5, taken together with the atoms to which they are attached, form a 3- to 12-membered heterocycle which is optionally substituted with one or more R_A;

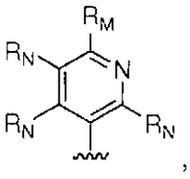
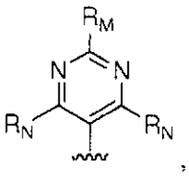
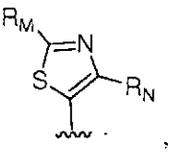
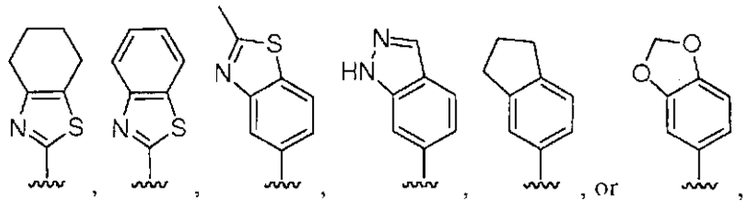
R_9 and R_{12}, taken together with the atoms to which they are attached, form a 3- to 12-membered heterocycle which is optionally substituted with one or more R_A;

A, B, D, X, L_1, L_2, L_3, T, R_A, R_B, R_C, and R_D are as described above in Formula I.

In this aspect, A and B preferably are independently selected from C_5-C_6carbocycle or 5- to 6-membered heterocycle, and are each independently optionally substituted with one or more R_A. More preferably, at least one of A and B is phenyl (e.g., ), and is optionally substituted with one or more R_A. Highly preferably, both A and B are each independently phenyl (e.g., ), and are each independently optionally substituted with one or more R_A.

D preferably is selected from C_5-C_6carbocycle, 5- to 6-membered heterocycle, or 8- to 12-membered bicycles, and is optionally substituted with one or more R_A. D can also be preferably selected from C_1-C_6alkyl, C_2-C_6alkenyl or C_2-C_6alkynyl, and is optionally substituted with one or more R_L. More preferably, D is C_5-C_6carbocycle, 5- to 6-membered heterocycle, or 6- to 12-membered bicycles, and is substituted with one or more R_M, where R_M is halogen, nitro, oxo, phosphonooxy, phosphono, thioxo, cyano, or $-L_S-R_E$. Also preferably, D is phenyl, and is optionally

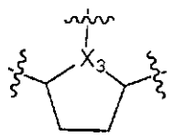
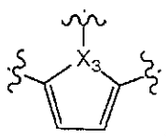
substituted with one or more R_A. More preferably, D is phenyl, and is substituted with one or more R_M, wherein R_M is as defined above. Highly preferably, D is  or  , wherein R_M is as defined above, and each R_N is independently selected from R_D and preferably is hydrogen. One or more R_N can also preferably be halo such as F.

D is also preferably pyridinyl, pyrimidinyl, or thiazolyl, optionally substituted with one or more R_A. More preferably D is pyridinyl, pyrimidinyl, or thiazolyl, and is substituted with one or more R_M. Highly preferably, D is  ,  , or  , wherein R_M is as defined above, and each R_N is independently selected from R_D and preferably is hydrogen. One or more R_N can also preferably be halo such as F. D is also preferably indanyl, 4,5,6,7-tetrahydrobenzo[d]thiazolyl, benzo[d]thiazolyl, or indazolyl, and is optionally substituted with one or more R_A. More preferably D is indanyl, 4,5,6,7-tetrahydrobenzo[d]thiazolyl, benzo[d]thiazolyl, indazolyl, or benzo[d][1,3]dioxol-5-yl, and is substituted with one or more R_M. Highly preferably, D is  , and is optionally substituted with one or more R_M.

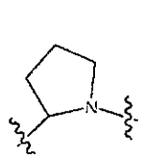
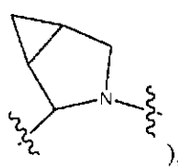
Preferably, R_M is halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, cyano; or C_1-C_6alkyl, C_2-C_6alkenyl or C_2-C_6alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl or cyano; or C_3-C_6carbocycle or 3- to 6-membered heterocycle, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6haloalkyl, C_2-C_6haloalkenyl or C_2-C_6haloalkynyl. More preferably, R_M is halogen, hydroxy, mercapto, amino, carboxy; or C_1-C_6alkyl, C_2-C_6alkenyl or C_2-C_6alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino or carboxy. Highly preferably, R_M is C_1-C_6alkyl which is optionally substituted with one or more substituents selected from halogen, hydroxy, mercapto, amino or carboxy.

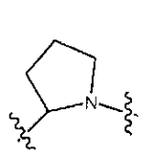
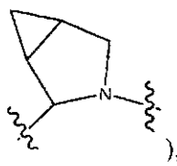
Also preferably, R_M is halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, or cyano; or R_M is $-L_S-R_E$, wherein L_S is a bond or C_1-C_6alkylene, and R_E is $-N(R_S)R_S'$, $-O-R_S$, $-C(O)R_S$, $-C(O)OR_S$, $-C(O)N(R_S)R_S'$, $-N(R_S)C(O)R_S'$, $-N(R_S)C(O)OR_S'$, $-N(R_S)SO_2R_S'$, $-SO_2R_S$, $-SR_S$, or $-P(O)(OR_S)_2$, wherein R_S and R_S' can be, for example, each independently selected at each occurrence from (1) hydrogen or (2) C_1-C_6alkyl optionally substituted at each occurrence with one or more halogen, hydroxy, $-O-C_1$-C_6alkyl or 3- to 6-membered heterocycle; or R_M is C_1-C_6alkyl, C_2-C_6alkenyl or C_2-C_6alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl or cyano; or R_M is C_3-C_6carbocycle or 3- to 6-membered heterocycle, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6haloalkyl, C_2-C_6haloalkenyl, C_2-C_6haloalkynyl, $-C(O)OR_S$, or $-N(R_S)R_S'$). More preferably, R_M is halogen (e.g., fluoro, chloro, bromo, iodo), hydroxy, mercapto, amino, carboxy, or C_1-C_6alkyl (e.g., methyl, isopropyl, tert-butyl), C_2-C_6alkenyl or C_2-C_6alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, cyano, or carboxy. For example R_M is CF_3, $-C(CF_3)_2-OH$, $-C(CH_3)_2-CN$, $-C(CH_3)_2-CH_2OH$, or $-C(CH_3)_2-CH_2NH_2$. Also preferably R_M is $-L_S-R_E$ where L_S is a bond and R_E is $-N(R_S)R_S'$), $-O-R_S$, $-N(R_S)C(O)OR_S'$, $-N(R_S)SO_2R_S'$, $-SO_2R_S$, or $-SR_S$. For example where L_S is a bond, R_E is $-N(C_1$-C_6alkyl$)_2$ (e.g., $-NMe_2$); $-N(C_1$-C_6alkylene$-O-C_1$-C_6alkyl$)_2$ (e.g. $-N(CH_2CH_2OMe)_2$); $-N(C_1$-C_6alkyl$)(C_1$-C_6alkylene$-O-C_1$-C_6alkyl) (e.g. $-N(CH_3)(CH_2CH_2OMe)$);—$O-C_1$-C_6alkyl (e.g., –O–Me, –O–Et, –O–isopropyl, –O–tert-butyl, –O–n-hexyl); $-O-C_1$-C_6haloalkyl (e.g., – OCF_3, $-OCH_2CF_3$); $-O-C_1$-C_6alkylene–piperidine (e.g., $-O-CH_2CH_2$–1-piperidyl); $-N(C_1$-C_6alkyl$)C(O)OC_1$-C_6alkyl (e.g., $-N(CH_3)C(O)O-CH_2CH(CH_3)_2$), $-N(C_1$-C_6alkyl$)SO_2C_1$-C_6alkyl (e.g., $-N(CH_3)SO_2CH_3$); $-SO_2C_1$-C_6alkyl (e.g., $-SO_2Me$); $-SO_2C_1$-C_6haloalkyl (e.g., $-SO_2CF_3$); or $-S-C_1$-C_6haloalkyl (e.g., SCF_3). Also preferably R_M is $-L_S-R_E$ where L_S is C_1-C_6alkylene (e.g., $-CH_2-$, $-C(CH_3)_2-$, $-C(CH_3)_2-CH_2-$) and R_E is $-O-R_S$, $-C(O)OR_S$, $-N(R_S)C(O)OR_S'$, or $-P(O)(OR_S)_2$. For example R_M is $-C_1$-C_6alkylene$-O-R_S$ (e.g., $-C(CH_3)_2-CH_2-OMe$); $-C_1$-C_6alkylene$-C(O)OR_S$ (e.g., $-C(CH_3)_2-C(O)OMe$); $-C_1$-C_6alkylene$-N(R_S)C(O)OR_S'$ (e.g., $-C(CH_3)_2-CH_2-NHC(O)OCH_3$); or $-C_1$-C_6alkylene$-P(O)(OR_S)_2$ (e.g., $-CH_2-P(O)(OEt)_2$). Also more preferably R_M is C_3-C_6carbocycle or 3- to 6-membered heterocycle, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6haloalkyl, C_2-C_6haloalkenyl, C_2-C_6haloalkynyl, $-C(O)OR_S$, or $-N(R_S)R_S'$). For example R_M is cycloalkyl (e.g., cyclopropyl, 2,2-dichloro-1-methylcycloprop-1-yl, cyclohexyl), phenyl, heterocyclyl (e.g., morpholin-4-yl, 1,1-

dioxidothiomorpholin-4-yl, 4-methylpiperazin-1-yl, 4-methoxycarbonylpiperazin-1-yl, pyrrolidin-1-yl, piperidin-1-yl, 4-methylpiperidin-1-yl, 3,5-dimethylpiperidin-1-yl, 4,4-difluoropiperidin-1-yl, tetrahydropyran-4-yl, pyridinyl, pyridin-3-yl, 6-(dimethylamino)pyridin-3-yl). Highly preferably, R_M is C_1-C_6alkyl which is optionally substituted with one or more substituents selected from halogen, hydroxy, mercapto, amino or carboxy (e.g., tert-butyl, CF_3).

X preferably is C_5-C_6carbocycle, 5- to 6-membered heterocycle, or 6- to 12-membered bicycles (e.g.,  or  , wherein X_3 is N and is directly linked to $-L_3-D$), and is optionally substituted with one or more R_A. Non-limiting examples of X are described hereinabove.

L_1 and L_2 are preferably independently bond or C_1-C_6alkylene, L_3 is preferably selected from bond, C_1-C_6alkylene or –C(O)–, and L_1, L_2, and L_3 are each independently optionally substituted with one or more R_L. More preferably, L_1, L_2 and L_3 are each independently bond or C_1-C_6alkylene (e.g., $-CH_2-$ or $-CH_2CH_2-$), and are each independently optionally substituted with one or more R_L. Highly preferably, L_1, L_2 and L_3 are bond.

R_2 and R_5, taken together with the atoms to which they are attached, preferably form a 5- to 6-membered heterocycle or 6- to 12-membered bicycle (e.g.,  or ), which is optionally substituted with one or more R_A.

R_9 and R_{12}, taken together with the atoms to which they are attached, preferably form a 5- to 6-membered heterocycle or 6- to 12-membered bicycle (e.g.,  or ), which is optionally substituted with one or more R_A.

-T-R_D' can be, without limitation, independently selected at each occurrence from –C(O)–L_Y'–, –C(O)O–L_Y'–R_D', –C(O)–L_Y'–N(R_B)C(O)–L_S''–R_D', –C(O)–L_Y'–N(R_B)C(O)O–L_S''–R_D', –N(R_B)C(O)–L_Y'–N(R_B)C(O)–L_S''–R_D', –N(R_B)C(O)–L_Y'—N(R_B)C(O)O–L_S''–R_D', or –N(R_B)C(O)–L_Y'—N(R_B)–L_S''–R_D', wherein L_Y' is each independently L_S' and, preferably, is each independently C_1-C_6alkylene (e.g., -CH_2-) and optionally substituted with one or more substituents selected from R_L. Preferably, -T-R_D' is independently selected at each occurrence from –C(O)–L_Y'–M'–L_S''–R_D' or –N(R_B)C(O)–L_Y'–M'–L_S''–R_D'. More preferably, -T-R_D' is independently selected at each occurrence from –C(O)–L_Y'–N(R_B)C(O)–L_S''–R_D' or –C(O)–L_Y'–N(R_B)C(O)O–L_S''–R_D'. Highly preferably, -T-R_D' is independently selected at each occurrence from –C(O)–L_Y'–N(R_B)C(O)–R_D' or –C(O)–L_Y'–

$N(R_B)C(O)O–R_D'$, wherein L_Y' preferably is each independently C_1-C_6alkylene (e.g., $-CH_2-$) and optionally substituted with one or more substituents selected from R_L.

R_{NB} and R_C' are preferably hydrogen, and R_D' preferably is independently selected at each occurrence from R_E. More preferably, R_D' is independently selected at each occurrence from C_1-C_6alkyl, C_2-C_6alkenyl or C_2-C_6alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, C_3-C_6carbocycle or 3- to 6-membered heterocycle; or C_3-C_6carbocycle or 3- to 6-membered heterocycle, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6haloalkyl, C_2-C_6haloalkenyl or C_2-C_6haloalkynyl.

R_A preferably is halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, cyano; or C_1-C_6alkyl, C_2-C_6alkenyl or C_2-C_6alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl or cyano; or C_3-C_6carbocycle or 3- to 6-membered heterocycle, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6haloalkyl, C_2-C_6haloalkenyl or C_2-C_6haloalkynyl; or $–L_A–O–R_S$, $–L_A–S–R_S$, $–L_A–C(O)R_S$, $–L_A–OC(O)R_S$, $–L_A–C(O)OR_S$, $–L_A–N(R_SR_S')$, $–L_A–S(O)R_S$, $–L_A–SO_2R_S$, $–L_A–C(O)N(R_SR_S')$, $–L_A–N(R_S)C(O)R_S'$, $–L_A–N(R_S)C(O)N(R_S'R_S'')$, $–L_A–N(R_S)SO_2R_S'$, $–L_A–SO_2N(R_SR_S')$, $–L_A–N(R_S)SO_2N(R_S'R_S'')$, $–L_A–N(R_S)S(O)N(R_S'R_S'')$, $–L_A–OS(O)–R_S$, $–L_A–OS(O)_2–R_S$, $–L_A–S(O)_2OR_S$, $–L_A–S(O)OR_S$, $–L_A–OC(O)OR_S$, $–L_A–N(R_S)C(O)OR_S'$, $–L_A–OC(O)N(R_SR_S')$, $–L_A–N(R_S)S(O)–R_S'$, $–L_A–S(O)N(R_SR_S')$ or $–L_A–C(O)N(R_S)C(O)–R_S'$, wherein L_A is bond, C_1-C_6alkylene, C_2-C_6alkenylene or C_2-C_6alkynylene.

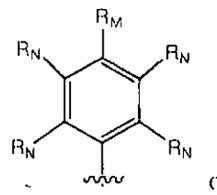
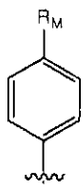
More preferably, R_A is halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, cyano; or C_1-C_6alkyl, C_2-C_6alkenyl or C_2-C_6alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl or cyano; or C_3-C_6carbocycle or 3- to 6-membered heterocycle, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6haloalkyl, C_2-C_6haloalkenyl or C_2-C_6haloalkynyl.

Highly preferably, R_A is halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, cyano; or C_1-C_6alkyl, C_2-C_6alkenyl or C_2-C_6alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from

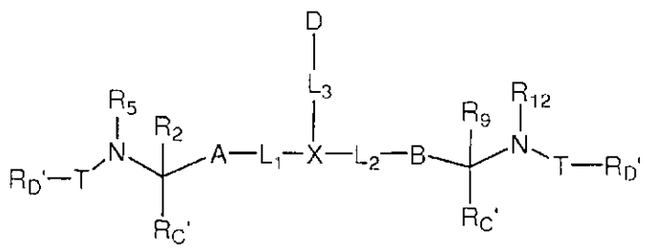
halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl or cyano.

L_S, L_S' and L_S'' preferably are each independently selected at each occurrence from bond; or C_1-C_6alkylene, C_2-C_6alkenylene or C_2-C_6alkynylene.

A and B can be the same or different. Likewise, L_1 and L_2 can be the same or different.

In one embodiment of this aspect, A, B, and D are each independently phenyl, and are each independently optionally substituted with one or more R_A. Preferably, D is  or  , wherein R_M and R_N are as defined above. L_1 and L_2 are each independently bond or C_1-C_6alkylene, and L_3 is bond, C_1-C_6alkylene or -C(O)-, and L_1, L_2, and L_3 are each independently optionally substituted with one or more R_L. Preferably, L_1, L_2, and L_3 are bond. -T-R_D' is independently selected at each occurrence from –C(O)–L_Y'–N(R_B)C(O)–L_S''–R_D' or –C(O)–L_Y'–N(R_B)C(O)O–L_S''–R_D', wherein L_Y' is C_1-C_6alkylene (e.g., -CH_2-) and optionally substituted with one or more substituents selected from R_L, and L_S'' preferably is bond. –T-R_D' can also be, without limitation, selected from –C(O)–L_Y'–L_S''–R_D', –C(O)–L_Y'–O–L_S''–R_D', –C(O)–L_Y'–N(R_B)–L_S''–R_D', or –C(O)–L_Y'–N(R_B)S(O)$_2$–L_S''–R_D'.

In still another aspect, the present invention features compounds of Formula I_B and pharmaceutically acceptable salts thereof:



I_B

wherein:

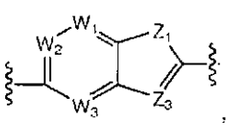
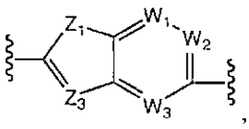
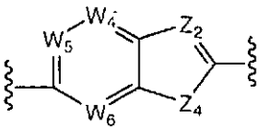
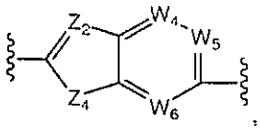
R_C' is each independently selected from R_C;

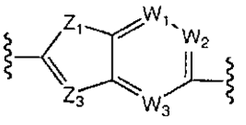
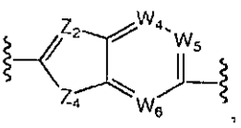
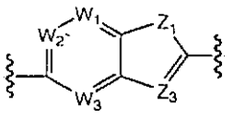
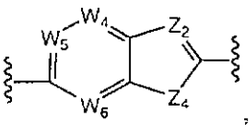
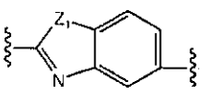
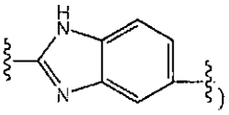
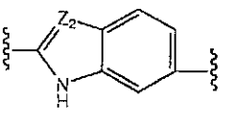
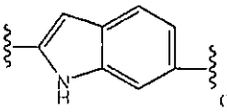
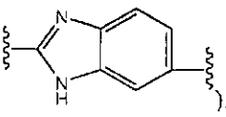
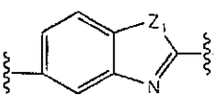
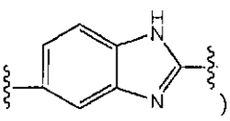
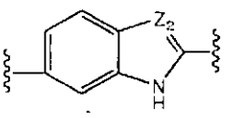
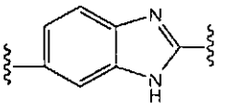
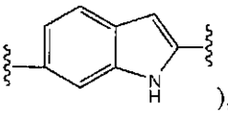
R_D' is each independently selected from R_D;

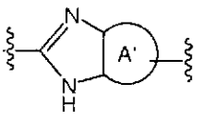
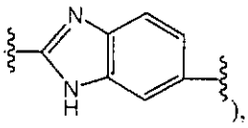
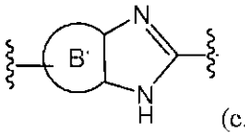
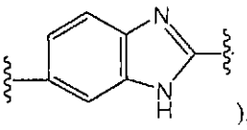
R_2 and R_5, taken together with the atoms to which they are attached, form a 3- to 12-membered heterocycle which is optionally substituted with one or more R_A;

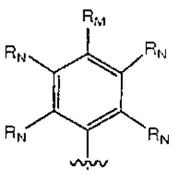
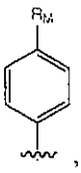
R_9 and R_{12}, taken together with the atoms to which they are attached, form a 3- to 12-membered heterocycle which is optionally substituted with one or more R_A;

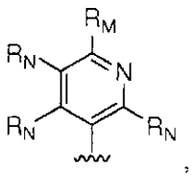
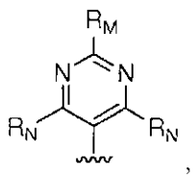
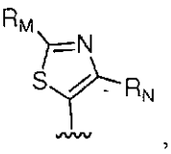
A, B, D, X, L_1, L_2, L_3, T, R_A, R_C, and R_D are as described above in Formula I.

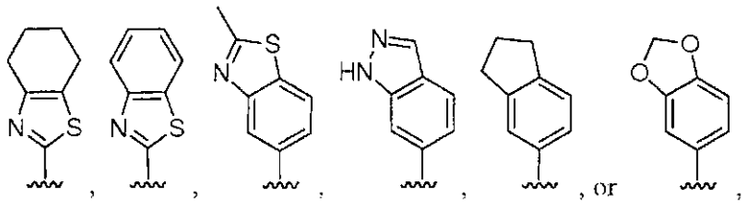
In this aspect, A and B preferably are independently selected from 8- to 12-membered bicycles such as  ,  ,  or  , where Z_1 is independently selected at each occurrence from O, S, NH or CH_2, Z_2 is independently selected at each occurrence from N or CH, Z_3 is independently selected at each occurrence from N or CH, Z_4 is independently selected at each occurrence from O, S, NH or CH_2, and W_1, W_2, W_3, W_4, W_5 and W_6 are each independently selected at each occurrence from CH or N. A and B are each independently optionally substituted with one or more R_A.

More preferably, A is selected from  or  , and is optionally substituted with one or more R_A; B is selected from  or  , and is optionally substituted with one or more R_A, where Z_1, Z_2, Z_3, Z_4, W_1, W_2, W_3, W_4, W_5, W_6 are as defined above. Preferably, Z_3 is N and Z_4 is NH. For instance, A can be selected from  (e.g., ) or  (e.g.,  or ), and is optionally substituted with one or more R_A; and B can be selected from  (e.g., ) or  (e.g.,  or ), and is optionally substituted with one or more R_A.

Also preferably, A is  (e.g., ), and B is  (e.g., ), wherein A' and B' are independently selected from C_5-C_6carbocycle or 5- to 6-membered heterocycle, and A and B are independently optionally substituted with one or more R_A.

D preferably is selected from C_5-C_6carbocycle, 5- to 6-membered heterocycle, or 6- to 12-membered bicycles, and is optionally substituted with one or more R_A. D can also be preferably selected from C_1-C_6alkyl, C_2-C_6alkenyl or C_2-C_6alkynyl, and is optionally substituted with one or more substituents selected from R_L. More preferably, D is C_5-C_6carbocycle, 5- to 6-membered heterocycle, or 6- to 12-membered bicycles, and is substituted with one or more R_M, where R_M is halogen, nitro, oxo, phosphonoxy, phosphono, thioxo, cyano, or $-L_S-R_E$. Also preferably, D is phenyl, and is optionally substituted with one or more R_A. More preferably, D is phenyl, and is substituted with one or more R_M, wherein R_M is as defined above. Highly preferably, D is  or  , wherein R_M is as defined above, and each R_N is independently selected from R_D and preferably is hydrogen. One or more R_N can also preferably be halo such as F.

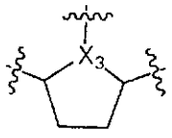
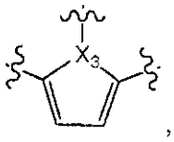
D is also preferably pyridinyl, pyrimidinyl, or thiazolyl, optionally substituted with one or more R_A. More preferably D is pyridinyl, pyrimidinyl, or thiazolyl, and is substituted with one or more R_M. Highly preferably, D is  ,  , or  , wherein R_M is as defined above, and each R_N is independently selected from R_D and preferably is hydrogen. One or more R_N can also preferably be halo such as F. D is also preferably indanyl, 4,5,6,7-tetrahydrobenzo[d]thiazolyl, benzo[d]thiazolyl, or indazolyl, and is optionally substituted with one or more R_A. More preferably D is indanyl, 4,5,6,7-tetrahydrobenzo[d]thiazolyl, benzo[d]thiazolyl, indazolyl, or benzo[d][1,3]dioxol-5-yl, and is substituted with one or more R_M. Highly preferably, D

is  , and is optionally substituted with one or more R_M.

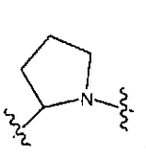
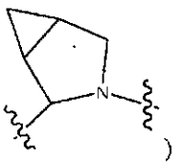
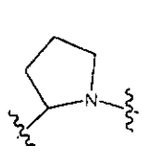
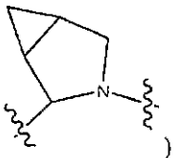
Preferably, R_M is halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, cyano; or C_1-C_6alkyl, C_2-C_6alkenyl or C_2-C_6alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl or cyano; or C_3-C_6carbocycle or 3- to 6-membered heterocycle, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6haloalkyl, C_2-C_6haloalkenyl or C_2-C_6haloalkynyl. More preferably, R_M is halogen, hydroxy, mercapto, amino, carboxy; or C_1-C_6alkyl, C_2-C_6alkenyl or C_2-C_6alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino or carboxy. Highly preferably, R_M is C_1-C_6alkyl which is optionally substituted with one or more substituents selected from halogen, hydroxy, mercapto, amino or carboxy.

Also preferably, R_M is halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, or cyano; or R_M is $-L_S-R_E$, wherein L_S is a bond or C_1-C_6alkylene, and R_E is $-N(R_S)R_S'$, $-O-R_S$, $-C(O)R_S$, $-C(O)OR_S$, $-C(O)N(R_S)R_S'$, $-N(R_S)C(O)R_S'$, $-N(R_S)C(O)OR_S'$, $-N(R_S)SO_2R_S'$, $-SO_2R_S$, $-SR_S$, or $-P(O)(OR_S)_2$, wherein R_S and R_S' can be, for example, each independently selected at each occurrence from (1) hydrogen or (2) C_1-C_6alkyl optionally substituted at each occurrence with one or more halogen, hydroxy, $-O-C_1$-C_6alkyl or 3- to 6-membered heterocycle; or R_M is C_1-C_6alkyl, C_2-C_6alkenyl or C_2-C_6alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl or cyano; or R_M is C_3-C_6carbocycle or 3- to 6-membered heterocycle, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6haloalkyl, C_2-C_6haloalkenyl, C_2-C_6haloalkynyl, $-C(O)OR_S$, or $-N(R_S)R_S'$. More preferably, R_M is halogen (e.g., fluoro, chloro, bromo, iodo), hydroxy, mercapto, amino, carboxy, or C_1-C_6alkyl (e.g., methyl, isopropyl, tert-butyl), C_2-C_6alkenyl or C_2-C_6alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, cyano, or carboxy. For example R_M is CF_3, $-C(CF_3)_2-OH$, $-C(CH_3)_2-CN$, $-C(CH_3)_2-CH_2OH$, or $-C(CH_3)_2-CH_2NH_2$. Also preferably R_M is $-L_S-$

R_E where L_S is a bond and R_E is $-N(R_S)R_S'$, $-O-R_S$, $-N(R_S)C(O)OR_S'$, $-N(R_S)SO_2R_S'$, $-SO_2R_S$, or $-SR_S$. For example where L_S is a bond, R_E is $-N(C_1\text{-}C_6alkyl)_2$ (e.g., $-NMe_2$); $-N(C_1\text{-}C_6alkylene-O-C_1\text{-}C_6alkyl)_2$ (e.g. $-N(CH_2CH_2OMe)_2$); $-N(C_1\text{-}C_6alkyl)(C_1\text{-}C_6alkylene-O-C_1\text{-}C_6alkyl)$ (e.g. $-N(CH_3)(CH_2CH_2OMe)$);—$O-C_1\text{-}C_6alkyl$ (e.g., –O–Me, –O–Et, –O–isopropyl, –O–tert-butyl, –O–n-hexyl); $-O-C_1\text{-}C_6haloalkyl$ (e.g., – OCF_3, $-OCH_2CF_3$); $-O-C_1\text{-}C_6alkylene$–piperidine (e.g., –O–$CH_2CH_2$–1-piperidyl); $-N(C_1\text{-}C_6alkyl)C(O)OC_1\text{-}C_6alkyl$ (e.g., $-N(CH_3)C(O)O-CH_2CH(CH_3)_2$), $-N(C_1\text{-}C_6alkyl)SO_2C_1\text{-}C_6alkyl$ (e.g., $-N(CH_3)SO_2CH_3$); $-SO_2C_1\text{-}C_6alkyl$ (e.g., $-SO_2Me$); $-SO_2C_1\text{-}C_6haloalkyl$ (e.g., $-SO_2CF_3$); or $-S-C_1\text{-}C_6haloalkyl$ (e.g., SCF_3). Also preferably R_M is $-L_S-R_E$ where L_S is $C_1\text{-}C_6alkylene$ (e.g., $-CH_2-$, $-C(CH_3)_2-$, $-C(CH_3)_2-CH_2-$) and R_E is $-O-R_S$, $-C(O)OR_S$, $-N(R_S)C(O)OR_S'$, or $-P(O)(OR_S)_2$. For example R_M is $-C_1\text{-}C_6alkylene-O-R_S$ (e.g., $-C(CH_3)_2-CH_2-OMe$); $-C_1\text{-}C_6alkylene-C(O)OR_S$ (e.g., $-C(CH_3)_2-C(O)OMe$); $-C_1\text{-}C_6alkylene-N(R_S)C(O)OR_S'$ (e.g., $-C(CH_3)_2-CH_2-NHC(O)OCH_3$); or $-C_1\text{-}C_6alkylene-P(O)(OR_S)_2$ (e.g., $-CH_2-P(O)(OEt)_2$). Also more preferably R_M is $C_3\text{-}C_6carbocycle$ or 3- to 6-membered heterocycle, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, $C_1\text{-}C_6alkyl$, $C_2\text{-}C_6alkenyl$, $C_2\text{-}C_6alkynyl$, $C_1\text{-}C_6haloalkyl$, $C_2\text{-}C_6haloalkenyl$, $C_2\text{-}C_6haloalkynyl$, $-C(O)OR_S$, or $-N(R_S)R_S'$). For example R_M is cycloalkyl (e.g., cyclopropyl, 2,2-dichloro-1-methylcycloprop-1-yl, cyclohexyl), phenyl, heterocyclyl (e.g., morpholin-4-yl, 1,1-dioxidothiomorpholin-4-yl, 4-methylpiperazin-1-yl, 4-methoxycarbonylpiperazin-1-yl, pyrrolidin-1-yl, piperidin-1-yl, 4-methylpiperidin-1-yl, 3,5-dimethylpiperidin-1-yl, 4,4-difluoropiperidin-1-yl, tetrahydropyran-4-yl, pyridinyl, pyridin-3-yl, 6-(dimethylamino)pyridin-3-yl). Highly preferably, R_M is $C_1\text{-}C_6alkyl$ which is optionally substituted with one or more substituents selected from halogen, hydroxy, mercapto, amino or carboxy (e.g., tert-butyl, CF_3).

X preferably is $C_5\text{-}C_6carbocycle$, 5- to 6-membered heterocycle, or 6- to 12-membered bicycles (e.g.,  or  , wherein X_3 is N and is directly linked to $-L_3-D$), and is optionally substituted with one or more R_A. Non-limiting examples of X are described hereinabove.

L_1 and L_2 are preferably independently bond or $C_1\text{-}C_6alkylene$, L_3 is preferably selected from bond, $C_1\text{-}C_6alkylene$ or –C(O)–, and L_1, L_2, and L_3 are each independently optionally substituted with one or more R_L. More preferably, L_1, L_2 and L_3 are each independently bond or $C_1\text{-}C_6alkylene$ (e.g., $-CH_2-$ or $-CH_2CH_2-$), and are each independently optionally substituted with one or more R_L. Highly preferably, L_1, L_2 and L_3 are bond.

R_2 and R_5, taken together with the atoms to which they are attached, preferably form a 5- to 6-membered heterocycle or 6- to 12-membered bicycle (e.g.,  or ) which is optionally substituted with one or more R_A. R_9 and R_{12}, taken together with the atoms to which they are attached, preferably form a 5- to 6-membered heterocycle or 6- to 12-membered bicycle (e.g.,  or ) which is optionally substituted with one or more R_A.

-T-R_D' can be, without limitation, independently selected at each occurrence from –C(O)–L_Y'–R_D', –C(O)O–L_Y'–R_D', –C(O)–L_Y'–N(R_B)C(O)–L_S''–R_D', –C(O)–L_Y'–N(R_B)C(O)O–L_S''–R_D', –N(R_B)C(O)–L_Y'–N(R_B)C(O)–L_S''–R_D', –N(R_B)C(O)–L_Y'—N(R_B)C(O)O–L_S''–R_D', or –N(R_B)C(O)–L_Y'—N(R_B)–L_S''–R_D', wherein L_Y' is each independently L_S' and, preferably, is each independently C_1-C_6alkylene (e.g., -CH_2-) and optionally substituted with one or more substituents selected from R_L. Preferably, -T-R_D' is independently selected at each occurrence from –C(O)–L_Y'–M'–L_S''–R_D' or –N(R_B)C(O)–L_Y'–M'–L_S''–R_D'. More preferably, -T-R_D' is independently selected at each occurrence from –C(O)–L_Y'–N(R_B)C(O)–L_S''–R_D' or –C(O)–L_Y'–N(R_B)C(O)O–L_S''–R_D'. Highly preferably, -T-R_D' is independently selected at each occurrence from –C(O)–L_Y'–N(R_B)C(O)–R_D' or –C(O)–L_Y'–N(R_B)C(O)O–R_D', wherein L_Y' preferably is each independently C_1-C_6alkylene (e.g., -CH_2-) and optionally substituted with one or more substituents selected from R_L.

R_C' is preferably hydrogen, and R_D' preferably is independently selected at each occurrence from R_E. More preferably, R_D' is independently selected at each occurrence from C_1-C_6alkyl, C_2-C_6alkenyl or C_2-C_6alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, C_3-C_6carbocycle or 3- to 6-membered heterocycle; or C_3-C_6carbocycle or 3- to 6-membered heterocycle, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6haloalkyl, C_2-C_6haloalkenyl or C_2-C_6haloalkynyl.

R_A preferably is halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, cyano; or C_1-C_6alkyl, C_2-C_6alkenyl or C_2-C_6alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl or cyano; or C_3-C_6carbocycle or 3- to 6-membered heterocycle, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen,

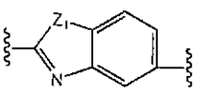
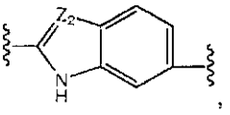
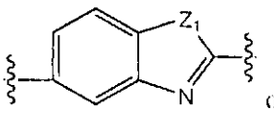
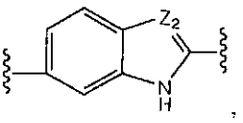
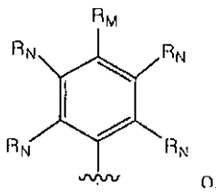
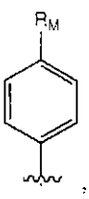
hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6haloalkyl, C_2-C_6haloalkenyl or C_2-C_6haloalkynyl; or $-L_A-O-R_S$, $-L_A-S-R_S$, $-L_A-C(O)R_S$, $-L_A-OC(O)R_S$, $-L_A-C(O)OR_S$, $-L_A-N(R_SR_S')$, $-L_A-S(O)R_S$, $-L_A-SO_2R_S$, $-L_A-C(O)N(R_SR_S')$, $-L_A-N(R_S)C(O)R_S'$, $-L_A-N(R_S)C(O)N(R_S'R_S'')$, $-L_A-N(R_S)SO_2R_S'$, $-L_A-SO_2N(R_SR_S')$, $-L_A-N(R_S)SO_2N(R_S'R_S'')$, $-L_A-N(R_S)S(O)N(R_S'R_S'')$, $-L_A-OS(O)-R_S$, $-L_A-OS(O)_2-R_S$, $-L_A-S(O)_2OR_S$, $-L_A-S(O)OR_S$, $-L_A-OC(O)OR_S$, $-L_A-N(R_S)C(O)OR_S'$, $-L_A-OC(O)N(R_SR_S')$, $-L_A-N(R_S)S(O)-R_S'$, $-L_A-S(O)N(R_SR_S')$ or $-L_A-C(O)N(R_S)C(O)-R_S'$, wherein L_A is bond, C_1-C_6alkylene, C_2-C_6alkenylene or C_2-C_6alkynylene.

More preferably, R_A is halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, cyano; or C_1-C_6alkyl, C_2-C_6alkenyl or C_2-C_6alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl or cyano; or C_3-C_6carbocycle or 3- to 6-membered heterocycle, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6haloalkyl, C_2-C_6haloalkenyl or C_2-C_6haloalkynyl.

Highly preferably, R_A is halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, cyano; or C_1-C_6alkyl, C_2-C_6alkenyl or C_2-C_6alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl or cyano.

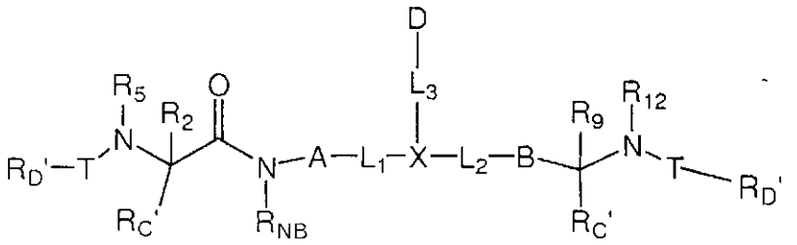
L_S, L_S' and L_S'' preferably are each independently selected at each occurrence from bond; or C_1-C_6alkylene, C_2-C_6alkenylene or C_2-C_6alkynylene.

A and B can be the same or different. Likewise, L_1 and L_2 can be the same or different.

In one embodiment of this aspect, A is  or  , and is optionally substituted with one or more R_A; B is  or  , and is optionally substituted with one or more R_A; and D is C_5-C_6carbocycle or 5- to 6-membered heterocycle (e.g., phenyl), and is optionally substituted with one or more R_A. Preferably, D is  or  , wherein R_M and R_N are as defined above. Z_1 is independently selected at each occurrence from O, S, NH or CH_2; and Z_2 is independently selected at each occurrence from N

or CH. L_1 and L_2 are each independently bond or C_1-C_6alkylene, and L_3 is bond, C_1-C_6alkylene or -C(O)-, and L_1, L_2, and L_3 are each independently optionally substituted with one or more R_L. Preferably, L_1, L_2, and L_3 are bond. $-T-R_D'$ is independently selected at each occurrence from $-C(O)-L_Y'-N(R_B)C(O)-L_S''-R_D'$ or $-C(O)-L_Y'-N(R_B)C(O)O-L_S''-R_D'$, wherein L_Y' is C_1-C_6alkylene (e.g., $-CH_2-$) and optionally substituted with one or more substituents selected from R_L, and L_S'' preferably is bond. $-T-R_D'$ can also be, without limitation, selected from $-C(O)-L_Y'-L_S''-R_D'$, $-C(O)-L_Y'-O-L_S''-R_D'$, $-C(O)-L_Y'-N(R_B)-L_S''-R_D'$, or $-C(O)-L_Y'-N(R_B)S(O)_2-L_S''-R_D'$.

In yet another aspect, the present invention further features compounds of Formula I_C and pharmaceutically acceptable salts thereof.



I_C

wherein:

R_{NB} is R_B;

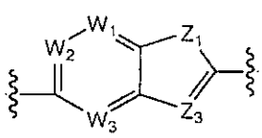
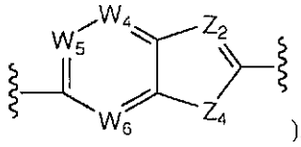
R_C' is each independently selected from R_C;

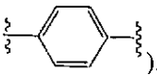
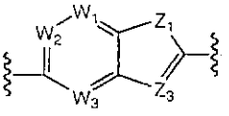
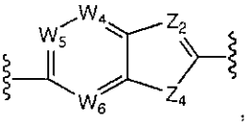
R_D' is each independently selected from R_D;

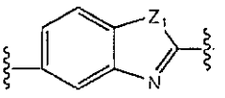
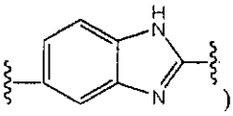
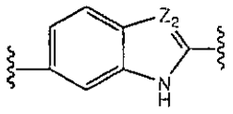
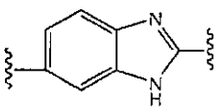
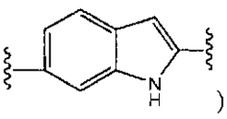
R_2 and R_5, taken together with the atoms to which they are attached, form a 3- to 12-membered heterocycle which is optionally substituted with one or more R_A;

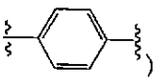
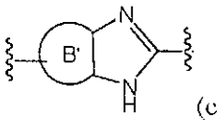
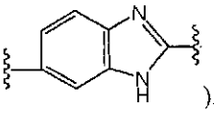
R_9 and R_{12}, taken together with the atoms to which they are attached, form a 3- to 12-membered heterocycle which is optionally substituted with one or more R_A;

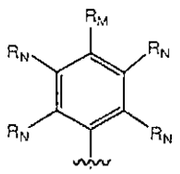
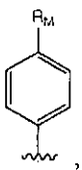
A, B, D, X, L_1, L_2, L_3, T, R_A, R_B, R_C, and R_D are as described above in Formula I.

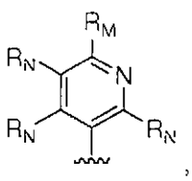
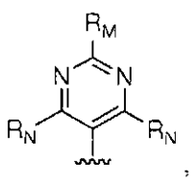
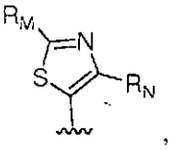
In this aspect, A preferably is C_5-C_6carbocycle or 5- to 6-membered heterocycle, and is optionally substituted with one or more R_A; and B preferably is 8- to 12-membered bicycle (such as  or ), and is optionally substituted with one or more R_A. Z_1 is O, S, NH or CH_2; Z_2 is N or CH; Z_3 is N or CH; Z_4 is O, S, NH or CH_2; and W_1, W_2, W_3, W_4, W_5 and W_6 are each independently selected from CH or N.

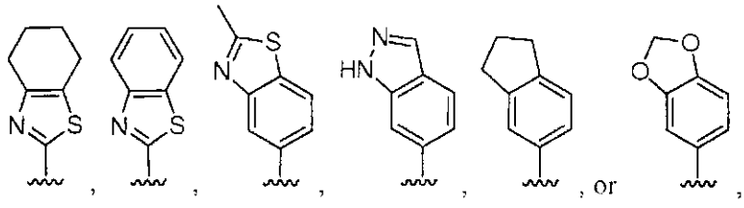
More preferably, A is phenyl (e.g., ), and is optionally substituted with one or more R_A; and B is  or  , and is optionally substituted with one

or more R_A, where Z_1, Z_2, Z_3, Z_4, W_1, W_2, W_3, W_4, W_5, W_6 are as defined above. Preferably, Z_3 is N and Z_4 is NH. For instance, B can be  (e.g., ) or  (e.g.,  or ), and is optionally substituted with one or more R_A.

Also preferably, A is C_5-C_6carbocycle (e.g., phenyl such as ) or 5- to 6-membered heterocycle; and B is  (e.g., ), wherein B' is selected from C_5-C_6carbocycle or 5- to 6-membered heterocycle. A and B are independently optionally substituted with one or more R_A.

D preferably is selected from C_5-C_6carbocycle, 5- to 6-membered heterocycle, or 6- to 12-membered bicycles, and is optionally substituted with one or more R_A. D can also be preferably selected from C_1-C_6alkyl, C_2-C_6alkenyl or C_2-C_6alkynyl, and is optionally substituted with one or more substituents selected from R_L. More preferably, D is C_5-C_6carbocycle, 5- to 6-membered heterocycle, or 6- to 12-membered bicycles, and is substituted with one or more R_M, where R_M is halogen, nitro, oxo, phosphonoxy, phosphono, thioxo, cyano, or $-L_S-R_E$. Also preferably, D is phenyl, and is optionally substituted with one or more R_A. More preferably, D is phenyl, and is substituted with one or more R_M, wherein R_M is as defined above. Highly preferably, D is  or  , wherein R_M is as defined above, and each R_N is independently selected from R_D and preferably is hydrogen. One or more R_N can also preferably be halo such as F.

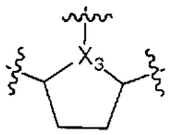
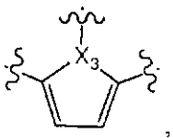
D is also preferably pyridinyl, pyrimidinyl, or thiazolyl, optionally substituted with one or more R_A. More preferably D is pyridinyl, pyrimidinyl, or thiazolyl, and is substituted with one or more R_M. Highly preferably, D is  ,  , or  , wherein R_M is as defined above, and each R_N is independently selected from R_D and preferably is hydrogen. One or more R_N can also preferably be halo such as F. D is also preferably indanyl, 4,5,6,7-tetrahydrobenzo[d]thiazolyl, benzo[d]thiazolyl, or indazolyl, and is optionally substituted with one or

more R_A. More preferably D is indanyl, 4,5,6,7-tetrahydrobenzo[d]thiazolyl, benzo[d]thiazolyl, indazolyl, or benzo[d][1,3]dioxol-5-yl, and is substituted with one or more R_M. Highly preferably, D is  , and is optionally substituted with one or more R_M.

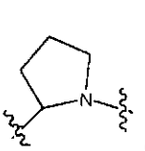
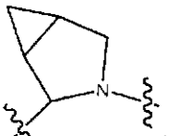
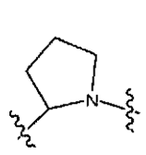
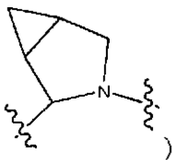
Preferably, R_M is halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, cyano; or C_1-C_6alkyl, C_2-C_6alkenyl or C_2-C_6alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl or cyano; or C_3-C_6carbocycle or 3- to 6-membered heterocycle, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6haloalkyl, C_2-C_6haloalkenyl or C_2-C_6haloalkynyl. More preferably, R_M is halogen, hydroxy, mercapto, amino, carboxy; or C_1-C_6alkyl, C_2-C_6alkenyl or C_2-C_6alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino or carboxy. Highly preferably, R_M is C_1-C_6alkyl which is optionally substituted with one or more substituents selected from halogen, hydroxy, mercapto, amino or carboxy.

Also preferably, R_M is halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, or cyano; or R_M is $-L_S-R_E$, wherein L_S is a bond or C_1-C_6alkylene, and R_E is $-N(R_SR_S')$, $-O-R_S$, $-C(O)R_S$, $-C(O)OR_S$, $-C(O)N(R_SR_S')$, $-N(R_S)C(O)R_S'$, $-N(R_S)C(O)OR_S'$, $-N(R_S)SO_2R_S'$, $-SO_2R_S$, $-SR_S$, or $-P(O)(OR_S)_2$, wherein R_S and R_S' can be, for example, each independently selected at each occurrence from (1) hydrogen or (2) C_1-C_6alkyl optionally substituted at each occurrence with one or more halogen, hydroxy, $-O-C_1$-C_6alkyl or 3- to 6-membered heterocycle; or R_M is C_1-C_6alkyl, C_2-C_6alkenyl or C_2-C_6alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl or cyano; or R_M is C_3-C_6carbocycle or 3- to 6-membered heterocycle, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6haloalkyl, C_2-C_6haloalkenyl, C_2-C_6haloalkynyl, $-C(O)OR_S$, or $-N(R_SR_S')$. More preferably, R_M is halogen (e.g., fluoro, chloro, bromo, iodo), hydroxy, mercapto, amino, carboxy, or C_1-C_6alkyl (e.g., methyl, isopropyl, tert-butyl), C_2-C_6alkenyl or C_2-C_6alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents

selected from halogen, hydroxy, mercapto, amino, cyano, or carboxy. For example R_M is CF_3, $-C(CF_3)_2-OH$, $-C(CH_3)_2-CN$, $-C(CH_3)_2-CH_2OH$, or $-C(CH_3)_2-CH_2NH_2$. Also preferably R_M is $-L_S-R_E$ where L_S is a bond and R_E is $-N(R_SR_S')$, $-O-R_S$, $-N(R_S)C(O)OR_S'$, $-N(R_S)SO_2R_S'$, $-SO_2R_S$, or $-SR_S$. For example where L_S is a bond, R_E is $-N(C_1\text{-}C_6alkyl)_2$ (e.g., $-NMe_2$); $-N(C_1\text{-}C_6alkylene-O-C_1\text{-}C_6alkyl)_2$ (e.g. $-N(CH_2CH_2OMe)_2$); $-N(C_1\text{-}C_6alkyl)(C_1\text{-}C_6alkylene-O-C_1\text{-}C_6alkyl)$ (e.g. $-N(CH_3)(CH_2CH_2OMe)$);—$O-C_1\text{-}C_6alkyl$ (e.g., –O–Me, –O–Et, –O–isopropyl, –O–tert-butyl, –O–n-hexyl); $-O-C_1\text{-}C_6haloalkyl$ (e.g., $-OCF_3$, $-OCH_2CF_3$); $-O-C_1\text{-}C_6alkylene$–piperidine (e.g., –O–$CH_2CH_2$–1-piperidyl); $-N(C_1\text{-}C_6alkyl)C(O)OC_1\text{-}C_6alkyl$ (e.g., $-N(CH_3)C(O)O-CH_2CH(CH_3)_2$), $-N(C_1\text{-}C_6alkyl)SO_2C_1\text{-}C_6alkyl$ (e.g., $-N(CH_3)SO_2CH_3$); $-SO_2C_1\text{-}C_6alkyl$ (e.g., $-SO_2Me$); $-SO_2C_1\text{-}C_6haloalkyl$ (e.g., $-SO_2CF_3$); or $-S-C_1\text{-}C_6haloalkyl$ (e.g., SCF_3). Also preferably R_M is $-L_S-R_E$ where L_S is $C_1\text{-}C_6alkylene$ (e.g., $-CH_2-$, $-C(CH_3)_2-$, $-C(CH_3)_2-CH_2-$) and R_E is $-O-R_S$, $-C(O)OR_S$, $-N(R_S)C(O)OR_S'$, or $-P(O)(OR_S)_2$. For example R_M is $-C_1\text{-}C_6alkylene-O-R_S$ (e.g., $-C(CH_3)_2-CH_2-$OMe); $-C_1\text{-}C_6alkylene-C(O)OR_S$ (e.g., $-C(CH_3)_2-C(O)OMe$); $-C_1\text{-}C_6alkylene-N(R_S)C(O)OR_S'$ (e.g., $-C(CH_3)_2-CH_2-NHC(O)OCH_3$); or $-C_1\text{-}C_6alkylene-P(O)(OR_S)_2$ (e.g., $-CH_2-P(O)(OEt)_2$). Also more preferably R_M is $C_3\text{-}C_6$carbocycle or 3- to 6-membered heterocycle, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, $C_1\text{-}C_6alkyl$, $C_2\text{-}C_6alkenyl$, $C_2\text{-}C_6alkynyl$, $C_1\text{-}C_6haloalkyl$, $C_2\text{-}C_6haloalkenyl$, $C_2\text{-}C_6haloalkynyl$, $-C(O)OR_S$, or $-N(R_SR_S')$. For example R_M is cycloalkyl (e.g., cyclopropyl, 2,2-dichloro-1-methylcycloprop-1-yl, cyclohexyl), phenyl, heterocyclyl (e.g., morpholin-4-yl, 1,1-dioxidothiomorpholin-4-yl, 4-methylpiperazin-1-yl, 4-methoxycarbonylpiperazin-1-yl, pyrrolidin-1-yl, piperidin-1-yl, 4-methylpiperidin-1-yl, 3,5-dimethylpiperidin-1-yl, 4,4-difluoropiperidin-1-yl, tetrahydropyran-4-yl, pyridinyl, pyridin-3-yl, 6-(dimethylamino)pyridin-3-yl). Highly preferably, R_M is $C_1\text{-}C_6alkyl$ which is optionally substituted with one or more substituents selected from halogen, hydroxy, mercapto, amino or carboxy (e.g., tert-butyl, CF_3).

X preferably is $C_5\text{-}C_6$carbocycle, 5- to 6-membered heterocycle, or 6- to 12-membered bicycles (e.g.,  or  , wherein X_3 is N and is directly linked to $-L_3-D$), and is optionally substituted with one or more R_A. Non-limiting examples of X are described hereinabove.

L_1 and L_2 are preferably independently bond or $C_1\text{-}C_6alkylene$, L_3 is preferably selected from bond, $C_1\text{-}C_6alkylene$ or $-C(O)-$, and L_1, L_2, and L_3 are each independently optionally substituted with one or more R_L. More preferably, L_1, L_2 and L_3 are each independently bond or $C_1\text{-}C_6alkylene$ (e.g., $-CH_2-$ or $-CH_2CH_2-$), and are each independently optionally substituted with one or more R_L. Highly preferably, L_1, L_2 and L_3 are bond. L_1 and L_2 can be the same or different.

R_2 and R_5, taken together with the atoms to which they are attached, preferably form a 5- to 6-membered heterocycle or 6- to 12-membered bicycle (e.g.,  or ) which is optionally substituted with one or more R_A. R_9 and R_{12}, taken together with the atoms to which they are attached, preferably form a 5- to 6-membered heterocycle or 6- to 12-membered bicycle (e.g.,  or ) which is optionally substituted with one or more R_A.

-T-R_D' can be, without limitation, independently selected at each occurrence from –C(O)–L_Y'–R_D', –C(O)O–L_Y'–R_D', –C(O)–L_Y'–N(R_B)C(O)–L_S''–R_D', –C(O)–L_Y'–N(R_B)C(O)O–L_S''–R_D', –N(R_B)C(O)–L_Y'–N(R_B)C(O)–L_S''–R_D', –N(R_B)C(O)–L_Y'—N(R_B)C(O)O–L_S''–R_D'; or –N(R_B)C(O)–L_Y'—N(R_B)–L_S''–R_D', wherein L_Y' is each independently L_S' and, preferably, is each independently C_1-C_6alkylene (e.g., -CH_2-) and optionally substituted with one or more substituents selected from R_L. Preferably, -T-R_D' is independently selected at each occurrence from –C(O)–L_Y'–M'–L_S''–R_D' or –N(R_B)C(O)–L_Y'–M'–L_S''–R_D'. More preferably, -T-R_D' is independently selected at each occurrence from –C(O)–L_Y'–N(R_B)C(O)–L_S''–R_D' or –C(O)–L_Y'–N(R_B)C(O)O–L_S''–R_D'. Highly preferably, -T-R_D' is independently selected at each occurrence from –C(O)–L_Y'–N(R_B)C(O)–R_D' or –C(O)–L_Y'–N(R_B)C(O)O–R_D', wherein L_Y' preferably is each independently C_1-C_6alkylene (e.g., -CH_2-) and optionally substituted with one or more substituents selected from R_L.

R_{NB} and R_C' are preferably hydrogen, and R_D' preferably is independently selected at each occurrence from R_E. More preferably, R_D' is independently selected at each occurrence from C_1-C_6alkyl, C_2-C_6alkenyl or C_2-C_6alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, C_3-C_6carbocycle or 3- to 6-membered heterocycle; or C_3-C_6carbocycle or 3- to 6-membered heterocycle, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6haloalkyl, C_2-C_6haloalkenyl or C_2-C_6haloalkynyl.

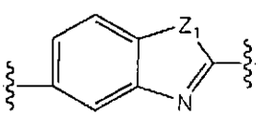
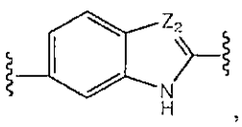
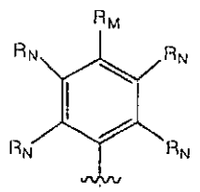
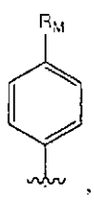
R_A preferably is halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, cyano; or C_1-C_6alkyl, C_2-C_6alkenyl or C_2-C_6alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl or cyano; or C_3-C_6carbocycle or 3- to 6-membered heterocycle, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen,

hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6haloalkyl, C_2-C_6haloalkenyl or C_2-C_6haloalkynyl; or $-L_A-O-R_S$, $-L_A-S-R_S$, $-L_A-C(O)R_S$, $-L_A-OC(O)R_S$, $-L_A-C(O)OR_S$, $-L_A-N(R_SR_S')$, $-L_A-S(O)R_S$, $-L_A-SO_2R_S$, $-L_A-C(O)N(R_SR_S')$, $-L_A-N(R_S)C(O)R_S'$, $-L_A-N(R_S)C(O)N(R_S'R_S'')$, $-L_A-N(R_S)SO_2R_S'$, $-L_A-SO_2N(R_SR_S')$, $-L_A-N(R_S)SO_2N(R_S'R_S'')$, $-L_A-N(R_S)S(O)N(R_S'R_S'')$, $-L_A-OS(O)-R_S$, $-L_A-OS(O)_2-R_S$, $-L_A-S(O)_2OR_S$, $-L_A-S(O)OR_S$, $-L_A-OC(O)OR_S$, $-L_A-N(R_S)C(O)OR_S'$, $-L_A-OC(O)N(R_SR_S')$, $-L_A-N(R_S)S(O)-R_S'$, $-L_A-S(O)N(R_SR_S')$ or $-L_A-C(O)N(R_S)C(O)-R_S'$, wherein L_A is bond, C_1-C_6alkylene, C_2-C_6alkenylene or C_2-C_6alkynylene.

More preferably, R_A is halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, cyano; or C_1-C_6alkyl, C_2-C_6alkenyl or C_2-C_6alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl or cyano; or C_3-C_6carbocycle or 3- to 6-membered heterocycle, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6haloalkyl, C_2-C_6haloalkenyl or C_2-C_6haloalkynyl.

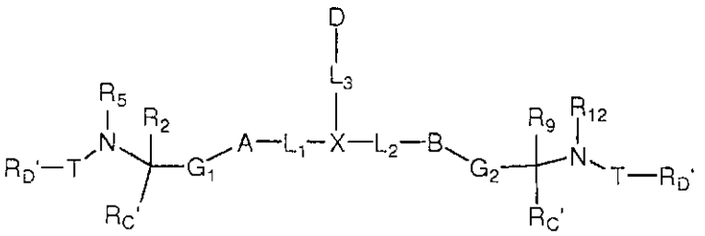
Highly preferably, R_A is halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, cyano; or C_1-C_6alkyl, C_2-C_6alkenyl or C_2-C_6alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl or cyano.

L_S, L_S' and L_S'' preferably are each independently selected at each occurrence from bond; or C_1-C_6alkylene, C_2-C_6alkenylene or C_2-C_6alkynylene.

In one embodiment of this aspect, A is phenyl, and is optionally substituted with one or more R_A; and B is  or  , and is optionally substituted with one or more R_A, wherein Z_1 is O, S, NH or CH_2; and Z_2 is N or CH. D is C_5-C_6carbocycle or 5- to 6-membered heterocycle (e.g., phenyl), and is optionally substituted with one or more R_A. Preferably, D is  or  , wherein R_M and R_N are as defined above. L_1 and L_2 are each independently bond or C_1-C_6alkylene, and L_3 is bond, C_1-C_6alkylene or -C(O)-, and L_1, L_2, and L_3 are each independently optionally substituted with one or more R_L. Preferably, L_1, L_2, and L_3 are bond. $-T-R_D'$ is independently selected at each occurrence from $-C(O)-L_Y'-N(R_B)C(O)-L_S''-R_D'$ or $-C(O)-$

L_Y'–$N(R_B)C(O)O$–L_S''–R_D', wherein L_Y' is C_1-C_6alkylene (e.g., -CH_2-) and optionally substituted with one or more substituents selected from R_L, and L_S'' preferably is bond. –T-R_D' can also be, without limitation, selected from –C(O)–L_Y'–L_S''–R_D', –C(O)–L_Y'–O–L_S''–R_D', –C(O)–L_Y'–$N(R_B)$–L_S''–R_D', or –C(O)–L_Y'–$N(R_B)S(O)_2$–L_S''–R_D'.

In yet another aspect, the present invention features compounds of Formula I_D and pharmaceutically acceptable salts thereof.



I_D

wherein:

G_1 and G_2 are each independently selected from C_5-C_6carbocycle or 5- to 6-membered heterocycle, and are each independently optionally substituted with one or more R_A;

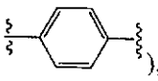
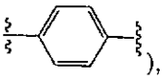
R_C' is each independently selected from R_C;

R_D' is each independently selected from R_D;

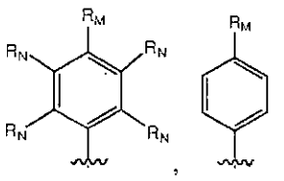
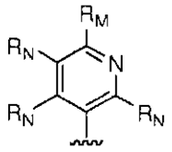
R_2 and R_5, taken together with the atoms to which they are attached, form a 3- to 12-membered heterocycle which is optionally substituted with one or more R_A;

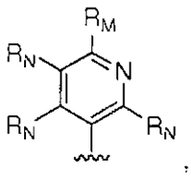
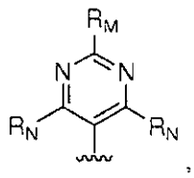
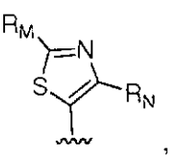
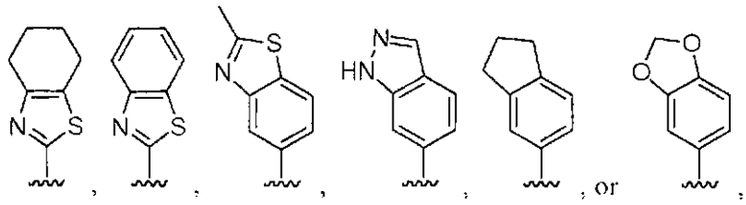
R_9 and R_{12}, taken together with the atoms to which they are attached, form a 3- to 12-membered heterocycle which is optionally substituted with one or more R_A;

A, B, D, X, L_1, L_2, L_3, T, R_A, R_C, and R_D are as described above in Formula I.

In this aspect, A and B preferably are independently selected from C_5-C_6carbocycle or 5- to 6-membered heterocycle, and are each independently optionally substituted with one or more R_A. More preferably, at least one of A and B is phenyl (e.g., ), and is optionally substituted with one or more R_A. Highly preferably, both A and B are each independently phenyl (e.g., ), and are each independently optionally substituted with one or more R_A.

D preferably is selected from C_5-C_6carbocycle, 5- to 6-membered heterocycle, or 8- to 12-membered bicycles, and is optionally substituted with one or more R_A. D can also be preferably selected from C_1-C_6alkyl, C_2-C_6alkenyl or C_2-C_6alkynyl, and is optionally substituted with one or more R_L. More preferably, D is C_5-C_6carbocycle, 5- to 6-membered heterocycle, or 6- to 12-membered bicycles, and is substituted with one or more R_M, where R_M is halogen, nitro, oxo, phosphonoxy, phosphono, thioxo, cyano, or –L_S–R_E. Also preferably, D is phenyl, and is optionally

substituted with one or more R_A. More preferably, D is phenyl, and is substituted with one or more R_M, wherein R_M is as defined above. Highly preferably, D is  or  , wherein R_M is as defined above, and each R_N is independently selected from R_D and preferably is hydrogen. One or more R_N can also preferably be halo such as F.

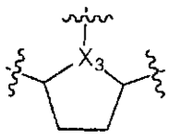
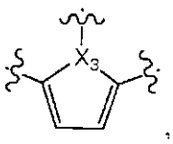
D is also preferably pyridinyl, pyrimidinyl, or thiazolyl, optionally substituted with one or more R_A. More preferably D is pyridinyl, pyrimidinyl, or thiazolyl, and is substituted with one or more R_M. Highly preferably, D is  ,  , or  , wherein R_M is as defined above, and each R_N is independently selected from R_D and preferably is hydrogen. One or more R_N can also preferably be halo such as F. D is also preferably indanyl, 4,5,6,7-tetrahydrobenzo[d]thiazolyl, benzo[d]thiazolyl, or indazolyl, and is optionally substituted with one or more R_A. More preferably D is indanyl, 4,5,6,7-tetrahydrobenzo[d]thiazolyl, benzo[d]thiazolyl, indazolyl, or benzo[d][1,3]dioxol-5-yl, and is substituted with one or more R_M. Highly preferably, D is  , and is optionally substituted with one or more R_M.

Preferably, R_M is halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, cyano; or C_1-C_6alkyl, C_2-C_6alkenyl or C_2-C_6alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl or cyano; or C_3-C_6carbocycle or 3- to 6-membered heterocycle, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6haloalkyl, C_2-C_6haloalkenyl or C_2-C_6haloalkynyl. More preferably, R_M is halogen, hydroxy, mercapto, amino, carboxy; or C_1-C_6alkyl, C_2-C_6alkenyl or C_2-C_6alkynyl, each of which is independently optionally substituted at each occurrence with one or more

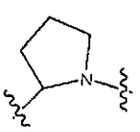
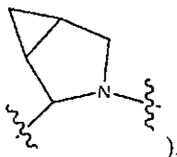
substituents selected from halogen, hydroxy, mercapto, amino or carboxy. Highly preferably, R_M is C_1-C_6alkyl which is optionally substituted with one or more substituents selected from halogen, hydroxy, mercapto, amino or carboxy.

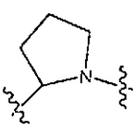
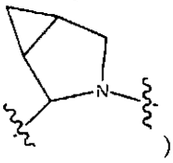
Also preferably, R_M is halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, or cyano; or R_M is $-L_S-R_E$, wherein L_S is a bond or C_1-C_6alkylene, and R_E is $-N(R_SR_S')$, $-O-R_S$, $-C(O)R_S$, $-C(O)OR_S$, $-C(O)N(R_SR_S')$, $-N(R_S)C(O)R_S'$, $-N(R_S)C(O)OR_S'$, $-N(R_S)SO_2R_S'$, $-SO_2R_S$, $-SR_S$, or $-P(O)(OR_S)_2$, wherein R_S and R_S' can be, for example, each independently selected at each occurrence from (1) hydrogen or (2) C_1-C_6alkyl optionally substituted at each occurrence with one or more halogen, hydroxy, $-O-C_1$-C_6alkyl or 3- to 6-membered heterocycle; or R_M is C_1-C_6alkyl, C_2-C_6alkenyl or C_2-C_6alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl or cyano; or R_M is C_3-C_6carbocycle or 3- to 6-membered heterocycle, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6haloalkyl, C_2-C_6haloalkenyl, C_2-C_6haloalkynyl, $-C(O)OR_S$, or $-N(R_SR_S')$. More preferably, R_M is halogen (e.g., fluoro, chloro, bromo, iodo), hydroxy, mercapto, amino, carboxy, or C_1-C_6alkyl (e.g., methyl, isopropyl, tert-butyl), C_2-C_6alkenyl or C_2-C_6alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, cyano, or carboxy. For example R_M is CF_3, $-C(CF_3)_2-OH$, $-C(CH_3)_2-CN$, $-C(CH_3)_2-CH_2OH$, or $-C(CH_3)_2-CH_2NH_2$. Also preferably R_M is $-L_S-R_E$ where L_S is a bond and R_E is $-N(R_SR_S')$, $-O-R_S$, $-N(R_S)C(O)OR_S'$, $-N(R_S)SO_2R_S'$, $-SO_2R_S$, or $-SR_S$. For example where L_S is a bond, R_E is $-N(C_1$-C_6alkyl$)_2$ (e.g., $-NMe_2$); $-N(C_1$-C_6alkylene$-O-C_1$-C_6alkyl$)_2$ (e.g. $-N(CH_2CH_2OMe)_2$); $-N(C_1$-C_6alkyl$)(C_1$-C_6alkylene$-O-C_1$-C_6alkyl) (e.g. $-N(CH_3)(CH_2CH_2OMe)$);—$O-C_1$-C_6alkyl (e.g., –O–Me, –O–Et, –O–isopropyl, –O–tert-butyl, –O–n-hexyl); $-O-C_1$-C_6haloalkyl (e.g., $-OCF_3$, $-OCH_2CF_3$); $-O-C_1$-C_6alkylene–piperidine (e.g., $-O-CH_2CH_2$–1-piperidyl); $-N(C_1$-C_6alkyl$)C(O)OC_1$-C_6alkyl (e.g., $-N(CH_3)C(O)O-CH_2CH(CH_3)_2$), $-N(C_1$-C_6alkyl$)SO_2C_1$-C_6alkyl (e.g., $-N(CH_3)SO_2CH_3$); $-SO_2C_1$-C_6alkyl (e.g., $-SO_2Me$); $-SO_2C_1$-C_6haloalkyl (e.g., $-SO_2CF_3$); or $-S-C_1$-C_6haloalkyl (e.g., SCF_3). Also preferably R_M is $-L_S-R_E$ where L_S is C_1-C_6alkylene (e.g., $-CH_2-$, $-C(CH_3)_2-$, $-C(CH_3)_2-CH_2-$) and R_E is $-O-R_S$, $-C(O)OR_S$, $-N(R_S)C(O)OR_S'$, or $-P(O)(OR_S)_2$. For example R_M is $-C_1$-C_6alkylene$-O-R_S$ (e.g., $-C(CH_3)_2-CH_2-OMe$); $-C_1$-C_6alkylene$-C(O)OR_S$ (e.g., $-C(CH_3)_2-C(O)OMe$); $-C_1$-C_6alkylene$-N(R_S)C(O)OR_S'$ (e.g., $-C(CH_3)_2-CH_2-NHC(O)OCH_3$); or $-C_1$-C_6alkylene$-P(O)(OR_S)_2$ (e.g., $-CH_2-P(O)(OEt)_2$). Also more preferably R_M is C_3-C_6carbocycle or 3- to 6-membered heterocycle, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, C_1-

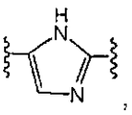
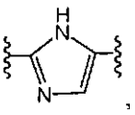
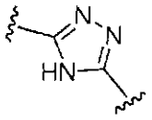
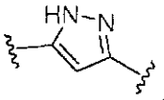
C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6haloalkyl, C_2-C_6haloalkenyl, C_2-C_6haloalkynyl, –C(O)OR_S, or –N($R_S$$R_S$'). For example R_M is cycloalkyl (e.g., cyclopropyl, 2,2-dichloro-1-methylcycloprop-1-yl, cyclohexyl), phenyl, heterocyclyl (e.g., morpholin-4-yl, 1,1-dioxidothiomorpholin-4-yl, 4-methylpiperazin-1-yl, 4-methoxycarbonylpiperazin-1-yl, pyrrolidin-1-yl, piperidin-1-yl, 4-methylpiperidin-1-yl, 3,5-dimethylpiperidin-1-yl, 4,4-difluoropiperidin-1-yl, tetrahydropyran-4-yl, pyridinyl, pyridin-3-yl, 6-(dimethylamino)pyridin-3-yl). Highly preferably, R_M is C_1-C_6alkyl which is optionally substituted with one or more substituents selected from halogen, hydroxy, mercapto, amino or carboxy (e.g., tert-butyl, CF_3).

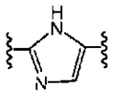
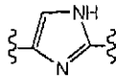
X preferably is C_5-C_6carbocycle, 5- to 6-membered heterocycle, or 6- to 12-membered bicycles (e.g.,  or  , wherein X_3 is N and is directly linked to –L_3–D), and is optionally substituted with one or more R_A. Non-limiting examples of X are described hereinabove.

L_1 and L_2 are preferably independently bond or C_1-C_6alkylene, L_3 is preferably selected from bond, C_1-C_6alkylene or –C(O)–, and L_1, L_2, and L_3 are each independently optionally substituted with one or more R_L. More preferably, L_1, L_2 and L_3 are each independently bond or C_1-C_6alkylene (e.g., –CH_2– or –CH_2CH_2–), and are each independently optionally substituted with one or more R_L. Highly preferably, L_1, L_2 and L_3 are bond.

R_2 and R_5, taken together with the atoms to which they are attached, preferably form a 5- to 6-membered heterocycle or 6- to 12-membered bicycle (e.g.,  or ), which is optionally substituted with one or more R_A.

R_9 and R_{12}, taken together with the atoms to which they are attached, preferably form a 5- to 6-membered heterocycle or 6- to 12-membered bicycle (e.g.,  or ), which is optionally substituted with one or more R_A.

G_1 and G_2 preferably are each independently selected from  ,  ,  or  , and are each independently optionally substituted with one or more

R_A (e.g., one or more chloro or bromo). More preferably, G_1 is  (including any tautomer thereof), and G_2 is  (including any tautomer thereof), and each G_1 and G_2 is independently optionally substituted with one or more R_A (e.g., one or more chloro or bromo).

-T-R_D' can be, without limitation, independently selected at each occurrence from –C(O)–L_Y'–, –C(O)O–L_Y'–R_D', –C(O)–L_Y'–N(R_B)C(O)–L_S''–R_D', –C(O)–L_Y'–N(R_B)C(O)O–L_S''–R_D', –N(R_B)C(O)–L_Y'–N(R_B)C(O)–L_S''–R_D', –N(R_B)C(O)–L_Y'—N(R_B)C(O)O–L_S''–R_D', or –N(R_B)C(O)–L_Y'—N(R_B)–L_S''–R_D', wherein L_Y' is each independently L_S' and, preferably, is each independently C_1-C_6alkylene (e.g., -CH_2-) and optionally substituted with one or more substituents selected from R_L. Preferably, -T-R_D' is independently selected at each occurrence from –C(O)–L_Y'–M'–L_S''–R_D' or –N(R_B)C(O)–L_Y'–M'–L_S''–R_D'. More preferably, -T-R_D' is independently selected at each occurrence from –C(O)–L_Y'–N(R_B)C(O)–L_S''–R_D' or –C(O)–L_Y'–N(R_B)C(O)O–L_S''–R_D'. Highly preferably, -T-R_D' is independently selected at each occurrence from –C(O)–L_Y'–N(R_B)C(O)–R_D' or –C(O)–L_Y'–N(R_B)C(O)O–R_D', wherein L_Y' preferably is each independently C_1-C_6alkylene (e.g., -CH_2-) and optionally substituted with one or more substituents selected from R_L.

R_C' is preferably hydrogen, and R_D' preferably is independently selected at each occurrence from R_E. More preferably, R_D' is independently selected at each occurrence from C_1-C_6alkyl, C_2-C_6alkenyl or C_2-C_6alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, C_3-C_6carbocycle or 3- to 6-membered heterocycle; or C_3-C_6carbocycle or 3- to 6-membered heterocycle, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6haloalkyl, C_2-C_6haloalkenyl or C_2-C_6haloalkynyl.

R_A preferably is halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, cyano; or C_1-C_6alkyl, C_2-C_6alkenyl or C_2-C_6alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl or cyano; or C_3-C_6carbocycle or 3- to 6-membered heterocycle, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6haloalkyl, C_2-C_6haloalkenyl or C_2-C_6haloalkynyl; or –L_A–O–R_S, –L_A–S–R_S, –L_A–C(O)R_S, –L_A–OC(O)R_S, –L_A–C(O)OR_S, –L_A–N($R_S$$R_S$'), –$L_A$–S(O)$R_S$, –$L_A$–$SO_2R_S$, –$L_A$–C(O)N($R_S$$R_S$'), –$L_A$–N($R_S$)C(O)$R_S$', –$L_A$–N($R_S$)C(O)N($R_S$'$R_S$''), –$L_A$–N($R_S$)$SO_2R_S$', –$L_A$–$SO_2$N($R_S$$R_S$'), –$L_A$–N($R_S$)$SO_2$N($R_S$'$R_S$''), –$L_A$–N($R_S$)S(O)N($R_S$'$R_S$''), –$L_A$–OS(O)–$R_S$, –$L_A$–

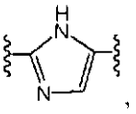
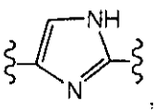
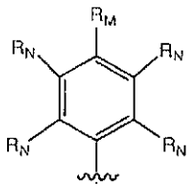
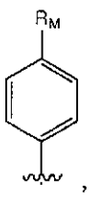
$OS(O)_2–R_S$, $–L_A–S(O)_2OR_S$, $–L_A–S(O)OR_S$, $–L_A–OC(O)OR_S$, $–L_A–N(R_S)C(O)OR_S'$, $–L_A–OC(O)N(R_SR_S')$, $–L_A–N(R_S)S(O)–R_S'$, $–L_A–S(O)N(R_SR_S')$ or $–L_A–C(O)N(R_S)C(O)–R_S'$, wherein L_A is bond, C_1-C_6alkylene, C_2-C_6alkenylene or C_2-C_6alkynylene.

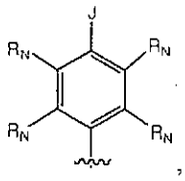
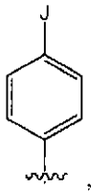
More preferably, R_A is halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, cyano; or C_1-C_6alkyl, C_2-C_6alkenyl or C_2-C_6alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl or cyano; or C_3-C_6carbocycle or 3- to 6-membered heterocycle, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6haloalkyl, C_2-C_6haloalkenyl or C_2-C_6haloalkynyl.

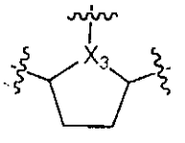
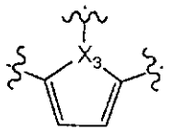
Highly preferably, R_A is halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, cyano; or C_1-C_6alkyl, C_2-C_6alkenyl or C_2-C_6alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl or cyano.

L_S, L_S' and L_S'' preferably are each independently selected at each occurrence from bond; or C_1-C_6alkylene, C_2-C_6alkenylene or C_2-C_6alkynylene.

A and B can be the same or different. Likewise, L_1 and L_2 can be the same or different.

In one embodiment of this aspect, A, B, and D are each independently phenyl, and are each independently optionally substituted with one or more R_A; and G_1 is  , G_2 is  , and each G_1 and G_2 is independently optionally substituted with one or more R_A (e.g., one or more chloro or bromo). Preferably, D is  or  , wherein R_M and R_N are as defined above. L_1 and L_2 are each independently bond or C_1-C_6alkylene, and L_3 is bond, C_1-C_6alkylene or -C(O)-, and L_1, L_2, and L_3 are each independently optionally substituted with one or more R_L. Preferably, L_1, L_2, and L_3 are bond. $-T-R_D'$ is independently selected at each occurrence from $–C(O)–L_Y'–N(R_B)C(O)–L_S''–R_D'$ or $–C(O)–L_Y'–N(R_B)C(O)O–L_S''–R_D'$, wherein L_Y' is C_1-C_6alkylene (e.g., $-CH_2-$) and optionally substituted with one or more substituents selected from R_L, and L_S'' preferably is bond. $–T-R_D'$ can also be, without limitation, selected from $–C(O)–L_Y'–L_S''–R_D'$, $–C(O)–L_Y'–O–L_S''–R_D'$, $–C(O)–L_Y'–N(R_B)–L_S''–R_D'$, or $–C(O)–L_Y'–N(R_B)S(O)_2–L_S''–R_D'$.

The present invention also features the compounds of Formulae I, I_A, I_B, I_C and I_D as described herein (including each embodiment described herein) or salts thereof, except that D is C_3-C_{12}carbocycle or 3- to 12-membered heterocycle which is substituted with J and optionally substituted with one or more R_A, where J is C_3-C_{12}carbocycle or 3- to 12-membered heterocycle and is optionally substituted with one or more R_A, or J is $-SF_5$. Preferably, D is C_5-C_6carbocycle, 5- to 6-membered heterocycle or 6- to 12-membered bicycle and is optionally substituted with one or more R_A, and J is C_3-C_6carbocycle or 3- to 6-membered heterocycle and is optionally substituted with one or more R_A. More preferably, D is C_5-C_6carbocycle or 5- to 6-membered heterocycle and is optionally substituted with one or more R_A, and J is C_3-C_6carbocycle or 3- to 6-membered heterocycle and is optionally substituted with one or more R_A. Highly preferably, D is phenyl substituted with J and optionally substituted with one or more R_A, where J is C_3-C_6carbocycle or 3- to 6-membered heterocycle and is optionally substituted with one or more R_A. Preferred R_As are as described above. In one embodiment, D is  , wherein each R_N is independently selected from R_D and preferably is hydrogen, and J is as defined above and preferably is C_3-C_6carbocycle or 3- to 6-membered heterocycle optionally substituted with one or more R_A. In another embodiment, D is  , and J is C_3-C_6carbocycle or 3- to 6-membered heterocycle and is optionally substituted with one or more R_A.

Moreover, the present invention features the compounds of Formulae I, I_A, I_B, I_C and I_D as described herein (including each embodiment described herein, as well as where D is C_3-C_{12}carbocycle or 3- to 12-membered heterocycle substituted with J and optionally substituted with one or more R_A as described hereinabove) or salts thereof, except that X is optionally substituted with one or more R_A'. Specific examples of X are as described above, such as  or  wherein X_3 is N and is directly linked to $-L_3-D$. Each R_A' is independently R_A; or C_1-C_{10}alkyl, C_2-C_{10}alkenyl or C_2-C_{10}alkynyl, each of which contains 0, 1, 2, 3, 4 or 5 heteroatoms selected from O, S or N and is optionally substituted with one or more R_L. R_A is as defined above. In one embodiment, each R_A' is independently R_A; or C_1-C_{10}alkyl, C_2-C_{10}alkenyl or C_2-C_{10}alkynyl, each of which contains 0, 1, 2, 3, 4 or 5 heteroatoms selected from O, S or N and is optionally substituted

with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl or cyano. In another embodiments, each R_A' is independently selected from R_A; or C_1-C_{10}alkyl, C_2-C_{10}alkenyl or C_2-C_{10}alkynyl, each of which contains 0, 1, 2, 3, 4 or 5 O and is optionally substituted with one or more R_L. In a further embodiment, each R_A' is independently selected from C_1-C_{10}alkyl, C_2-C_{10}alkenyl or C_2-C_{10}alkynyl, each of which contains 0, 1, 2 or 3 O and is optionally substituted with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl or cyano.

In another aspect of the invention, each R_A' is independently R_A or $-(R_X-R_Y)_N-(R_X-R_Y')$, wherein N is 0, 1, 2, 3, 4; each R_X is independently O, S or $N(R_B)$; each R_Y is independently C_1-C_6alkylene, C_2-C_6alkenylene or C_2-C_6alkynylene each of which is optionally substituted with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl or cyano; and R_Y' is independently C_1-C_6alkyl, C_2-C_6alkenyl or C_2-C_6alkynyl each of which is optionally substituted with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl or cyano. R_A and R_B are as defined above. In one embodiment, each R_X is O. For example, each R_A' is selected from $-(O-C_1$-C_6alkylene$)_N-(O-C_1$-C_6alkyl), wherein N preferably is 0, 1, 2 or 3.

In addition, the present invention features the compounds of Formulae I, I_A, I_B, I_C and I_D as described herein (including each embodiment described herein, as well as where D is C_3-C_{12}carbocycle or 3- to 12-membered heterocycle substituted with J and optionally substituted with one or more R_A as described hereinabove, or where X is optionally substituted with one or more R_A' as described herein above), wherein:

R_E is independently selected at each occurrence from $-O-R_S$, $-S-R_S$, $-C(O)R_S$, $-OC(O)R_S$, $-C(O)OR_S$, $-N(R_SR_S')$, $-S(O)R_S$, $-SO_2R_S$, $-C(O)N(R_SR_S')$, $-N(R_S)C(O)R_S'$, $-N(R_S)C(O)N(R_S'R_S'')$, $-N(R_S)SO_2R_S'$, $-SO_2N(R_SR_S')$, $-N(R_S)SO_2N(R_S'R_S'')$, $-N(R_S)S(O)N(R_S'R_S'')$, $-OS(O)-R_S$, $-OS(O)_2-R_S$, $-S(O)_2OR_S$, $-S(O)OR_S$, $-OC(O)OR_S$, $-N(R_S)C(O)OR_S'$, $-OC(O)N(R_SR_S')$, $-N(R_S)S(O)-R_S'$, $-S(O)N(R_SR_S')$, $-P(O)(OR_S)_2$, or $-C(O)N(R_S)C(O)-R_S'$; or C_1-C_6alkyl, C_2-C_6alkenyl or C_2-C_6alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl or cyano; or C_3-C_6carbocycle or 3- to 6-membered heterocycle, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, C_1-C_6alkyl, C_2-C_6alkenyl,

C_2-C_6alkynyl, C_1-C_6haloalkyl, C_2-C_6haloalkenyl, C_2-C_6haloalkynyl, C(O)OR_S, or –$N(R_SR_S')$; and

R_S, R_S' and R_S'' are each independently selected at each occurrence from hydrogen; C_1-C_6alkyl, C_2-C_6alkenyl or C_2-C_6alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, –O–C_1-C_6alkyl, –O–C_1-C_6alkylene–O–C_1-C_6alkyl, or 3- to 6-membered carbocycle or heterocycle; or 3- to 6-membered carbocycle or heterocycle; wherein each 3- to 6-membered carbocycle or heterocycle in R_S , R_S' or R_S' is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6haloalkyl, C_2-C_6haloalkenyl or C_2-C_6haloalkynyl.

The compounds of the present invention can be used in the form of salts. Depending on the particular compound, a salt of a compound may be advantageous due to one or more of the salt's physical properties, such as enhanced pharmaceutical stability under certain conditions or desired solubility in water or oil. In some instances, a salt of a compound may be useful for the isolation or purification of the compound.

Where a salt is intended to be administered to a patient, the salt preferably is pharmaceutically acceptable. Pharmaceutically acceptable salts include, but are not limited to, acid addition salts, base addition salts, and alkali metal salts.

Pharmaceutically acceptable acid addition salts may be prepared from inorganic or organic acids. Examples of suitable inorganic acids include, but are not limited to, hydrochloric, hydrobromic, hydroionic, nitric, carbonic, sulfuric, and phosphoric acid. Examples of suitable organic acids include, but are not limited to, aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclyl, carboxylic, and sulfonic classes of organic acids. Specific examples of suitable organic acids include acetate, trifluoroacetate, formate, propionate, succinate, glycolate, gluconate, digluconate, lactate, malate, tartaric acid, citrate, ascorbate, glucuronate, maleate, fumarate, pyruvate, aspartate, glutamate, benzoate, anthranilic acid, mesylate, stearate, salicylate, p-hydroxybenzoate, phenylacetate, mandelate, embonate (pamoate), methanesulfonate, ethanesulfonate, benzenesulfonate, pantothenate, toluenesulfonate, 2-hydroxyethanesulfonate, sufanilate, cyclohexylaminosulfonate, algenic acid, b-hydroxybutyric acid, galactarate, galacturonate, adipate, alginate, bisulfate, butyrate, camphorate, camphorsulfonate, cyclopentanepropionate, dodecylsulfate, glycoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, nicotinate, 2-naphthalesulfonate, oxalate, palmoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, thiocyanate, tosylate, and undecanoate.

Pharmaceutically acceptable base addition salts include, but are not limited to, metallic salts and organic salts. Non-limiting examples of suitable metallic salts include alkali metal (group Ia) salts, alkaline earth metal (group IIa) salts, and other pharmaceutically acceptable metal salts. Such salts may be made, without limitation, from aluminum, calcium, lithium, magnesium, potassium, sodium, or zinc. Non-limiting examples of suitable organic salts can be made from tertiary amines and quaternary amine, such as tromethamine, diethylamine, N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine), and procaine. Basic nitrogen-containing groups can be quaternized with agents such as alkyl halides (e.g., methyl, ethyl, propyl, butyl, decyl, lauryl, myristyl, and stearyl chlorides/bromides/iodides), dialkyl sulfates (e.g., dimethyl, diethyl, dibuytl, and diamyl sulfates), aralkyl halides (e.g., benzyl and phenethyl bromides), and others.

The compounds or salts of the present invention may exist in the form of solvates, such as with water (i.e., hydrates), or with organic solvents (e.g., with methanol, ethanol or acetonitrile to form, respectively, methanolate, ethanolate or acetonitrilate).

The compounds or salts of the present invention may also be used in the form of prodrugs. Some prodrugs are aliphatic or aromatic esters derived from acidic groups on the compounds of the invention. Others are aliphatic or aromatic esters of hydroxyl or amino groups on the compounds of the invention. Phosphate prodrugs of hydroxyl groups are preferred prodrugs.

The compounds of the invention may comprise asymmetrically substituted carbon atoms known as chiral centers. These compounds may exist, without limitation, as single stereoisomers (e.g., single enantiomers or single diastereomer), mixtures of stereoisomers (e.g. a mixture of enantiomers or diastereomers), or racemic mixtures. Compounds identified herein as single stereoisomers are meant to describe compounds that are present in a form that is substantially free from other stereoisomers (e.g., substantially free from other enantiomers or diastereomers). By "substantially free," it means that at least 80% of the compound in a composition is the described stereoisomer; preferably, at least 90% of the compound in a composition is the described stereoisomer; and more preferably, at least 95%, 96%, 97%, 98% or 99% of the compound in a composition is the described stereoisomer. Where the stereochemistry of a chiral carbon is not specified in the chemical structure of a compound, the chemical structure is intended to encompass compounds containing either stereoisomer of the chiral center.

Individual stereoisomers of the compounds of this invention can be prepared using a variety of methods known in the art. These methods include, but are not limited to, stereospecific synthesis, chromatographic separation of diastereomers, chromatographic resolution of enantiomers, conversion of enantiomers in an enantiomeric mixture to diastereomers followed by chromatographically separation of the diastereomers and regeneration of the individual enantiomers, and enzymatic resolution.

Stereospecific synthesis typically involves the use of appropriate optically pure (enantiomerically pure) or substantial optically pure materials and synthetic reactions that do not cause racemization or inversion of stereochemistry at the chiral centers. Mixtures of stereoisomers of compounds, including racemic mixtures, resulting from a synthetic reaction may be separated, for example, by chromatographic techniques as appreciated by those of ordinary skill in the art. Chromatographic resolution of enantiomers can be accomplished by using chiral chromatography resins, many of which are commercially available. In a non-limiting example, racemate is placed in solution and loaded onto the column containing a chiral stationary phase. Enantiomers can then be separated by HPLC.

Resolution of enantiomers can also be accomplished by converting enantiomers in a mixture to diastereomers by reaction with chiral auxiliaries. The resulting diastereomers can be separated by column chromatography or crystallization/re-crystallization. This technique is useful when the compounds to be separated contain a carboxyl, amino or hydroxyl group that will form a salt or covalent bond with the chiral auxiliary. Non-limiting examples of suitable chiral auxiliaries include chirally pure amino acids, organic carboxylic acids or organosulfonic acids. Once the diastereomers are separated by chromatography, the individual enantiomers can be regenerated. Frequently, the chiral auxiliary can be recovered and used again.

Enzymes, such as esterases, phosphatases or lipases, can be useful for the resolution of derivatives of enantiomers in an enantiomeric mixture. For example, an ester derivative of a carboxyl group in the compounds to be separated can be treated with an enzyme which selectively hydrolyzes only one of the enantiomers in the mixture. The resulting enantiomerically pure acid can then be separated from the unhydrolyzed ester.

Alternatively, salts of enantiomers in a mixture can be prepared using any suitable method known in the art, including treatment of the carboxylic acid with a suitable optically pure base such as alkaloids or phenethylamine, followed by precipitation or crystallization/re-crystallization of the enantiomerically pure salts. Methods suitable for the resolution/separation of a mixture of stereoisomers, including racemic mixtures, can be found in ENANTIOMERS, RACEMATES, AND RESOLUTIONS (Jacques *et al.*, 1981, John Wiley and Sons, New York, NY).

A compound of this invention may possess one or more unsaturated carbon-carbon double bonds. All double bond isomers, such as the cis (Z) and trans (E) isomers, and mixtures thereof are intended to be encompassed within the scope of a recited compound unless otherwise specified. In addition, where a compound exists in various tautomeric forms, a recited compound is not limited to any one specific tautomer, but rather is intended to encompass all tautomeric forms.

Certain compounds of the invention may exist in different stable conformational forms which may be separable. Torsional asymmetry due to restricted rotations about an asymmetric single bond,

for example because of steric hindrance or ring strain, may permit separation of different conformers. The invention encompasses each conformational isomer of these compounds and mixtures thereof.

Certain compounds of the invention may also exist in zwitterionic form and the invention encompasses each zwitterionic form of these compounds and mixtures thereof.

The compounds of the present invention are generally described herein using standard nomenclature. For a recited compound having asymmetric center(s), it should be understood that all of the stereoisomers of the compound and mixtures thereof are encompassed in the present invention unless otherwise specified. Non-limiting examples of stereoisomers include enantiomers, diastereomers, and cis-transisomers. Where a recited compound exists in various tautomeric forms, the compound is intended to encompass all tautomeric forms. Certain compounds are described herein using general formulas that include variables (e.g., A, B, D, X, L_1, L_2, L_3, Y, Z, T, R_A or R_B). Unless otherwise specified, each variable within such a formula is defined independently of any other variable, and any variable that occurs more than one time in a formula is defined independently at each occurrence. If moieties are described as being "independently" selected from a group, each moiety is selected independently from the other. Each moiety therefore can be identical to or different from the other moiety or moieties.

The number of carbon atoms in a hydrocarbyl moiety can be indicated by the prefix "C_x-C_y," where x is the minimum and y is the maximum number of carbon atoms in the moiety. Thus, for example, "C_1-C_6alkyl" refers to an alkyl substituent containing from 1 to 6 carbon atoms. Illustrating further, C_3-C_6cycloalkyl means a saturated hydrocarbyl ring containing from 3 to 6 carbon ring atoms. A prefix attached to a multiple-component substituent only applies to the first component that immediately follows the prefix. To illustrate, the term "carbocyclylalkyl" contains two components: carbocyclyl and alkyl. Thus, for example, C_3-C_6carbocyclylC_1-C_6alkyl refers to a C_3-C_6carbocyclyl appended to the parent molecular moiety through a C_1-C_6alkyl group.

Unless otherwise specified, when a linking element links two other elements in a depicted chemical structure, the leftmost-described component of the linking element is bound to the left element in the depicted structure, and the rightmost-described component of the linking element is bound to the right element in the depicted structure. To illustrate, if the chemical structure is $-L_S-M-L_S'-$ and M is $-N(R_B)S(O)-$, then the chemical structure is $-L_S-N(R_B)S(O)-L_S'-$.

If a linking element in a depicted structure is a bond, then the element left to the linking element is joined directly to the element right to the linking element via a covalent bond. For example, if a chemical structure is depicted as $-L_S-M-L_S'-$ and M is selected as bond, then the chemical structure will be $-L_S-L_S'-$. If two or more adjacent linking elements in a depicted structure are bonds, then the element left to these linking elements is joined directly to the element right to these linking elements via a covalent bond. For instance, if a chemical structure is depicted as $-L_S-M-L_S'-M'-L_S''-$, and M and L_S' are selected as bonds, then the chemical structure will be $-L_S-M'-$

L_S''–. Likewise, if a chemical structure is depicted as –L_S–M–L_S'–M'–L_S''–, and M, L_S' and M' are bonds, then the chemical structure will be –L_S–L_S''–.

When a chemical formula is used to describe a moiety, the dash(s) indicates the portion of the moiety that has the free valence(s).

If a moiety is described as being "optionally substituted", the moiety may be either substituted or unsubstituted. If a moiety is described as being optionally substituted with up to a particular number of non-hydrogen radicals, that moiety may be either unsubstituted, or substituted by up to that particular number of non-hydrogen radicals or by up to the maximum number of substitutable positions on the moiety, whichever is less. Thus, for example, if a moiety is described as a heterocycle optionally substituted with up to three non-hydrogen radicals, then any heterocycle with less than three substitutable positions will be optionally substituted by up to only as many non-hydrogen radicals as the heterocycle has substitutable positions. To illustrate, tetrazolyl (which has only one substitutable position) will be optionally substituted with up to one non-hydrogen radical. To illustrate further, if an amino nitrogen is described as being optionally substituted with up to two non-hydrogen radicals, then a primary amino nitrogen will be optionally substituted with up to two non-hydrogen radicals, whereas a secondary amino nitrogen will be optionally substituted with up to only one non-hydrogen radical.

The term "alkenyl" means a straight or branched hydrocarbyl chain containing one or more double bonds. Each carbon-carbon double bond may have either cis or trans geometry within the alkenyl moiety, relative to groups substituted on the double bond carbons. Non-limiting examples of alkenyl groups include ethenyl (vinyl), 2-propenyl, 3-propenyl, 1,4-pentadienyl, 1,4-butadienyl, 1-butenyl, 2-butenyl, and 3-butenyl.

The term "alkenylene" refers to a divalent unsaturated hydrocarbyl chain which may be linear or branched and which has at least one carbon-carbon double bond. Non-limiting examples of alkenylene groups include —C(H)=C(H)—, —C(H)=C(H)—CH_2—, —C(H)=C(H)—CH_2—CH_2—, —CH_2—C(H)=C(H)—CH_2—, —C(H)=C(H)—CH(CH_3)—, and —CH_2—C(H)=C(H)—CH(CH_2CH_3)—.

The term "alkyl" means a straight or branched saturated hydrocarbyl chain. Non-limiting examples of alkyl groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, t-butyl, pentyl, iso-amyl, and hexyl.

The term "alkylene" denotes a divalent saturated hydrocarbyl chain which may be linear or branched. Representative examples of alkylene include, but are not limited to, -CH_2-, -CH_2CH_2-, -$CH_2CH_2CH_2$-, -$CH_2CH_2CH_2CH_2$-, and -$CH_2CH(CH_3)CH_2$-.

The term "alkynyl" means a straight or branched hydrocarbyl chain containing one or more triple bonds. Non-limiting examples of alkynyl include ethynyl, 1-propynyl, 2-propynyl, 3-propynyl, decynyl, 1-butynyl, 2-butynyl, and 3-butynyl.

The term "alkynylene" refers to a divalent unsaturated hydrocarbon group which may be linear or branched and which has at least one carbon-carbon triple bonds. Representative alkynylene groups include, by way of example, —C≡C—, —C≡C—CH_2—, —C≡C—CH_2—CH_2—, —CH_2—C≡C—CH_2—, —C≡C—$CH(CH_3)$—, and —CH_2—C≡C—$CH(CH_2CH_3)$—.

The term "carbocycle" or "carbocyclic" or "carbocyclyl" refers to a saturated (e.g., "cycloalkyl"), partially saturated (e.g., "cycloalkenyl" or "cycloalkynyl") or completely unsaturated (e.g., "aryl") ring system containing zero heteroatom ring atom. "Ring atoms" or "ring members" are the atoms bound together to form the ring or rings. A carbocyclyl may be, without limitation, a single ring, two fused rings, or bridged or spiro rings. A substituted carbocyclyl may have either cis or trans geometry. Representative examples of carbocyclyl groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclopentenyl, cyclopentadienyl, cyclohexadienyl, adamantyl, decahydro-naphthalenyl, octahydro-indenyl, cyclohexenyl, phenyl, naphthyl, indanyl, 1,2,3,4-tetrahydro-naphthyl, indenyl, isoindenyl, decalinyl, and norpinanyl. A carbocycle group can be attached to the parent molecular moiety through any substitutable carbon ring atom. Where a carbocycle group is a divalent moiety linking two other elements in a depicted chemical structure (such as A in Formula I), the carbocycle group can be attached to the two other elements through any two substitutable ring atoms. Likewise, where a carbocycle group is a trivalent moiety linking three other elements in a depicted chemical structure (such as X in Formula I), the carbocycle group can be attached to the three other elements through any three substitutable ring atoms, respectively.

The term "carbocyclylalkyl" refers to a carbocyclyl group appended to the parent molecular moiety through an alkylene group. For instance, C_3-C_6carbocyclylC_1-C_6alkyl refers to a C_3-C_6carbocyclyl group appended to the parent molecular moiety through C_1-C_6alkylene.

The term "cycloalkenyl" refers to a non-aromatic, partially unsaturated carbocyclyl moiety having zero heteroatom ring member. Representative examples of cycloalkenyl groups include, but are not limited to, cyclobutenyl, cyclopentenyl, cyclohexenyl, and octahydronaphthalenyl.

The term "cycloalkyl" refers to a saturated carbocyclyl group containing zero heteroatom ring member. Non-limiting examples of cycloalkyls include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, decalinyl and norpinanyl.

The prefix "halo" indicates that the substituent to which the prefix is attached is substituted with one or more independently selected halogen radicals. For example, "C_1-C_6haloalkyl" means a C_1-C_6alkyl substituent wherein one or more hydrogen atoms are replaced with independently selected halogen radicals. Non-limiting examples of C_1-C_6haloalkyl include chloromethyl, 1-bromoethyl, fluoromethyl, difluoromethyl, trifluoromethyl, and 1,1,1-trifluoroethyl. It should be recognized that if a substituent is substituted by more than one halogen radical, those halogen radicals may be identical or different (unless otherwise stated).

The term "heterocycle" or "heterocyclo" or "heterocyclyl" refers to a saturated (e.g., "heterocycloalkyl"), partially unsaturated (e.g., "heterocycloalkenyl" or "heterocycloalkynyl") or completely unsaturated (e.g., "heteroaryl") ring system where at least one of the ring atoms is a heteroatom (i.e., nitrogen, oxygen or sulfur), with the remaining ring atoms being independently selected from the group consisting of carbon, nitrogen, oxygen and sulfur. A heterocycle may be, without limitation, a single ring, two fused rings, or bridged or spiro rings. A heterocycle group can be linked to the parent molecular moiety via any substitutable carbon or nitrogen atom(s) in the group. Where a heterocycle group is a divalent moiety that links two other elements in a depicted chemical structure (such as A in Formula I), the heterocycle group can be attached to the two other elements through any two substitutable ring atoms. Likewise, where a heterocycle group is a trivalent moiety that links three other elements in a depicted chemical structure (such as X in Formula I), the heterocycle group can be attached to the three other elements through any three substitutable ring atoms, respectively.

A heterocyclyl may be, without limitation, a monocycle which contains a single ring. Non-limiting examples of monocycles include furanyl, dihydrofuranyl, tetrahydrofuranyl, pyrrolyl, isopyrrolyl, pyrrolinyl, pyrrolidinyl, imidazolyl, isoimidazolyl, imidazolinyl, imidazolidinyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, triazolyl, tetrazolyl, dithiolyl, oxathiolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, thiazolinyl, isothiazolinyl, thiazolidinyl, isothiazolidinyl, thiodiazolyl, oxathiazolyl, oxadiazolyl (including 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl (also known as "azoximyl"), 1,2,5-oxadiazolyl (also known as "furazanyl"), and 1,3,4-oxadiazolyl), oxatriazolyl (including 1,2,3,4-oxatriazolyl and 1,2,3,5-oxatriazolyl), dioxazolyl (including 1,2,3-dioxazolyl, 1,2,4-dioxazolyl, 1,3,2-dioxazolyl, and 1,3,4-dioxazolyl), oxathiolanyl, pyranyl (including 1,2-pyranyl and 1,4-pyranyl), dihydropyranyl, pyridinyl, piperidinyl, diazinyl (including pyridazinyl (also known as "1,2-diazinyl"), pyrimidinyl (also known as "1,3-diazinyl"), and pyrazinyl (also known as "1,4-diazinyl")), piperazinyl, triazinyl (including s-triazinyl (also known as "1,3,5-triazinyl"), as-triazinyl (also known 1,2,4-triazinyl), and v-triazinyl (also known as "1,2,3-triazinyl), oxazinyl (including 1,2,3-oxazinyl, 1,3,2-oxazinyl, 1,3,6-oxazinyl (also known as "pentoxazolyl"), 1,2,6-oxazinyl, and 1,4-oxazinyl), isoxazinyl (including o-isoxazinyl and p-isoxazinyl), oxazolidinyl, isoxazolidinyl, oxathiazinyl (including 1,2,5-oxathiazinyl or 1,2,6-oxathiazinyl), oxadiazinyl (including 1,4,2-oxadiazinyl and 1,3,5,2-oxadiazinyl), morpholinyl, azepinyl, oxepinyl, thiepinyl, thiomorpholinyl, and diazepinyl.

A heterocyclyl may also be, without limitation, a bicycle containing two fused rings, such as, for example, naphthyridinyl (including [1,8] naphthyridinyl, and [1,6] naphthyridinyl), thiazolpyrimidinyl, thienopyrimidinyl, pyrimidopyrimidinyl, pyridopyrimidinyl, pyrazolopyrimidinyl, indolizinyl, pyrindinyl, pyranopyrrolyl, 4H-quinolizinyl, purinyl, pyridopyridinyl (including pyrido[3,4-b]-pyridinyl, pyrido[3,2-b]-pyridinyl, and pyrido[4,3-b]-pyridinyl), pyridopyrimidine, and pteridinyl. Other non-limiting examples of fused-ring heterocycles include benzo-fused

heterocyclyls, such as indolyl, isoindolyl, indoleninyl (also known as "pseudoindolyl"), isoindazolyl (also known as "benzpyrazolyl" or indazolyl), benzazinyl (including quinolinyl (also known as "1-benzazinyl") and isoquinolinyl (also known as "2-benzazinyl")), benzimidazolyl, phthalazinyl, quinoxalinyl, benzodiazinyl (including cinnolinyl (also known as "1,2-benzodiazinyl") and quinazolinyl (also known as "1,3-benzodiazinyl")), benzopyranyl (including "chromenyl" and "isochromenyl"), benzothiopyranyl (also known as "thiochromenyl"), benzoxazolyl, indoxazinyl (also known as "benzisoxazolyl"), anthranilyl, benzodioxolyl, benzodioxanyl, benzoxadiazolyl, benzofuranyl (also known as "coumaronyl"), isobenzofuranyl, benzothienyl (also known as "benzothiophenyl", "thionaphthenyl", and "benzothiofuranyl"), isobenzothienyl (also known as "isobenzothiophenyl", "isothionaphthenyl", and "isobenzothiofuranyl"), benzothiazolyl, 4,5,6,7-tetrahydrobenzo[d]thiazolyl, benzothiadiazolyl, benzimidazolyl, benzotriazolyl, benzoxazinyl (including 1,3,2-benzoxazinyl, 1,4,2-benzoxazinyl, 2,3,1-benzoxazinyl, and 3,1,4-benzoxazinyl), benzisoxazinyl (including 1,2-benzisoxazinyl and 1,4-benzisoxazinyl), and tetrahydroisoquinolinyl.

A heterocyclyl may also be, without limitation, a spiro ring system, such as, for example, 1,4-dioxa-8-azaspiro[4.5]decanyl.

A heterocyclyl may comprise one or more sulfur atoms as ring members; and in some cases, the sulfur atom(s) is oxidized to SO or SO_2. The nitrogen heteroatom(s) in a heterocyclyl may or may not be quaternized, and may or may not be oxidized to N-oxide. In addition, the nitrogen heteroatom(s) may or may not be N-protected.

⋯ in a chemical formula refers to a single or double bond.

The term "pharmaceutically acceptable" is used adjectivally to mean that the modified noun is appropriate for use as a pharmaceutical product or as a part of a pharmaceutical product.

The term "therapeutically effective amount" refers to the total amount of each active substance that is sufficient to show a meaningful patient benefit, e.g. a reduction in viral load.

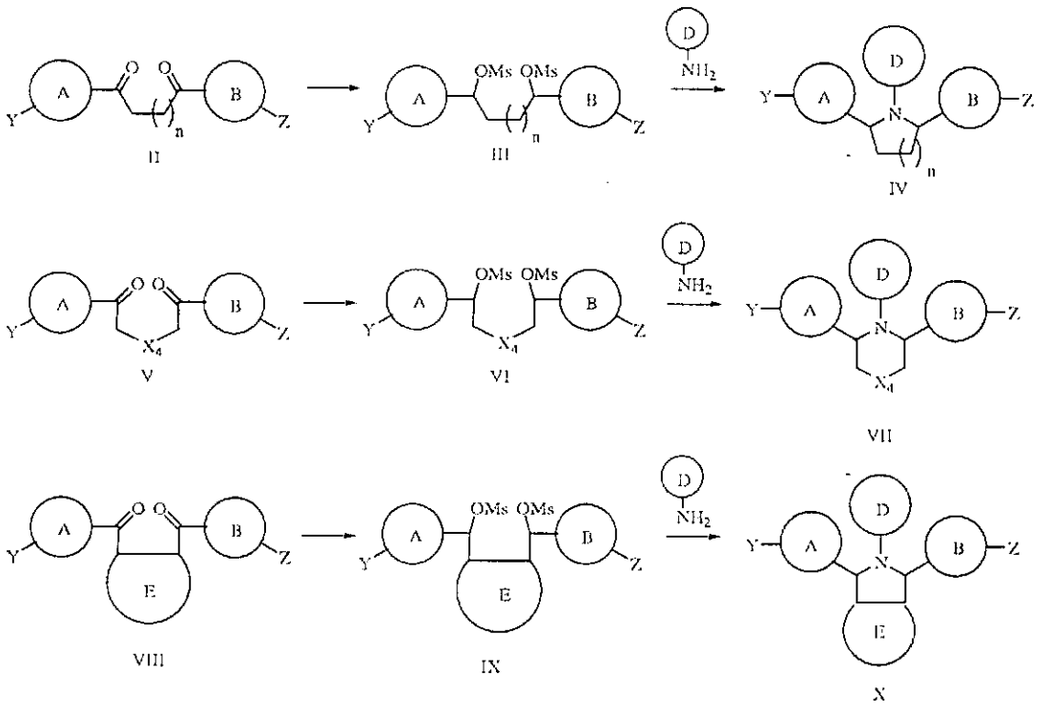
The term "prodrug" refers to derivatives of the compounds of the invention which have chemically or metabolically cleavable groups and become, by solvolysis or under physiological conditions, the compounds of the invention which are pharmaceutically active *in vivo*. A prodrug of a compound may be formed in a conventional manner by reaction of a functional group of the compound (such as an amino, hydroxy or carboxy group). Prodrugs often offer advantages of solubility, tissue compatibility, or delayed release in mammals (see, Bungard, H., DESIGN OF PRODRUGS, pp. 7-9, 21-24, Elsevier, Amsterdam 1985). Prodrugs include acid derivatives well known to practitioners of the art, such as, for example, esters prepared by reaction of the parent acidic compound with a suitable alcohol, or amides prepared by reaction of the parent acid compound with a suitable amine. Examples of prodrugs include, but are not limited to, acetate, formate, benzoate or other acylated derivatives of alcohol or amine functional groups within the compounds of the invention.

The term "solvate" refers to the physical association of a compound of this invention with one or more solvent molecules, whether organic or inorganic. This physical association often includes hydrogen bonding. In certain instances the solvate will be capable of isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. "Solvate" encompasses both solution-phase and isolable solvates. Exemplary solvates include, but are not limited to, hydrates, ethanolates, and methanolates.

The term "N-protecting group" or "N-protected" refers to those groups capable of protecting an amino group against undesirable reactions. Commonly used N-protecting groups are described in Greene and Wuts, PROTECTING GROUPS IN CHEMICAL SYNTHESIS (3rd ed., John Wiley & Sons, NY (1999). Non-limiting examples of N-protecting groups include acyl groups such as formyl, acetyl, propionyl, pivaloyl, t-butylacetyl, 2-chloroacetyl, 2-bromoacetyl, trifluoroacetyl, trichloroacetyl, phthalyl, o-nitrophenoxyacetyl, benzoyl, 4-chlorobenzoyl, 4-bromobenzoyl, or 4-nitrobenzoyl; sulfonyl groups such as benzenesulfonyl or p-toluenesulfonyl; sulfenyl groups such as phenylsulfenyl (phenyl-S-) or triphenylmethylsulfenyl (trityl-S-); sulfinyl groups such as p-methylphenylsulfinyl (p-methylphenyl-S(O)-) or t-butylsulfinyl (t-Bu-S(O)-); carbamate forming groups such as benzyloxycarbonyl, p-chlorobenzyloxycarbonyl, p-methoxybenzyloxycarbonyl, p-nitrobenzyloxycarbonyl, 2-nitrobenzyloxycarbonyl, p-bromobenzyloxycarbonyl, 3,4-dimethoxybenzyloxycarbonyl, 3,5-dimethoxybenzyloxycarbonyl, 2,4-dimethoxybenzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 2-nitro-4,5-dimethoxybenzyloxycarbonyl, 3,4,5-trimethoxybenzyloxycarbonyl, 1-(p-biphenylyl)-1-methylethoxycarbonyl, dimethyl-3,5-dimethoxybenzyloxycarbonyl, benzhydryloxycarbonyl, t-butyloxycarbonyl, diisopropylmethoxycarbonyl, isopropyloxycarbonyl, ethoxycarbonyl, methoxycarbonyl, allyloxycarbonyl, 2,2,2-trichloro-ethoxy-carbonyl, phenoxycarbonyl, 4-nitro-phenoxycarbonyl, cyclopentyloxycarbonyl, adamantyloxycarbonyl, cyclohexyloxycarbonyl, or phenylthiocarbonyl; alkyl groups such as benzyl, p-methoxybenzyl, triphenylmethyl, or benzyloxymethyl; p-methoxyphenyl; and silyl groups such as trimethylsilyl. Preferred N-protecting groups include formyl, acetyl, benzoyl, pivaloyl, t-butylacetyl, phenylsulfonyl, benzyl, t-butyloxycarbonyl (Boc) and benzyloxycarbonyl (Cbz).

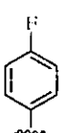
The compounds of the present invention can be prepared using a variety of methods. As a non-limiting example, the compounds of the present invention can be prepared according to Scheme I starting from compounds of Formula II (e.g., n = 0 to 8), Formula V (X_4 can be, for example, O or NR_A, where R_A is as described hereinabove and is preferably H or R_E as defined above such as C1-C6alkyl, 3- to 12-membered carbocycle or heterocycle, $-C(O)R_S$, $-C(O)OR_S$, $-C(O)N(R_SR_S')$, $-SO_2N(R_SR_S')$, $-S(O)_2OR_S$, $-S(O)OR_S$, $-S(O)N(R_SR_S')$, or a suitable protecting group such as Boc or Fmoc), or Formula VIII (E can be, for example, 3- to 7-membered carbocycle or heterocycle and is optionally substituted with one or more R_A), wherein A, B, D, Y, Z and R_A are as described above.

The 1,4-diketones II, V, and VIII can be reduced to the 1,4-diols using the methods described below, and the resultant racemic, enantiomerically enriched, or meso 1,4-diols may be converted to the dimesylates III, VI, or IX, or alternatively to ditriflates, ditosylates, or dihalides by the methods described below. The dimesylates III, VI, and IX, ditriflates, ditosylates, or dihalides may be reacted with an amine, including but not limited to, aniline, 3,5-difluoroaniline, 3,4-difluoroaniline, 4-fluoroaniline, 3-fluoroaniline, 4-trifluoromethylaniline, 4-chloroaniline, heteroaryl amines, alkyl amines, cycloalkyl amines, substituted benzylamines, or allylamine, under the conditions described below to give the compounds of the invention. L_1 and L_2 can be readily introduced to Formulae II, V and VIII, as appreciated by those skilled in the art in light of the present invention. Likewise, D-L_3-NH_2 can be used instead of D-NH_2, as appreciated by those skilled in the art.

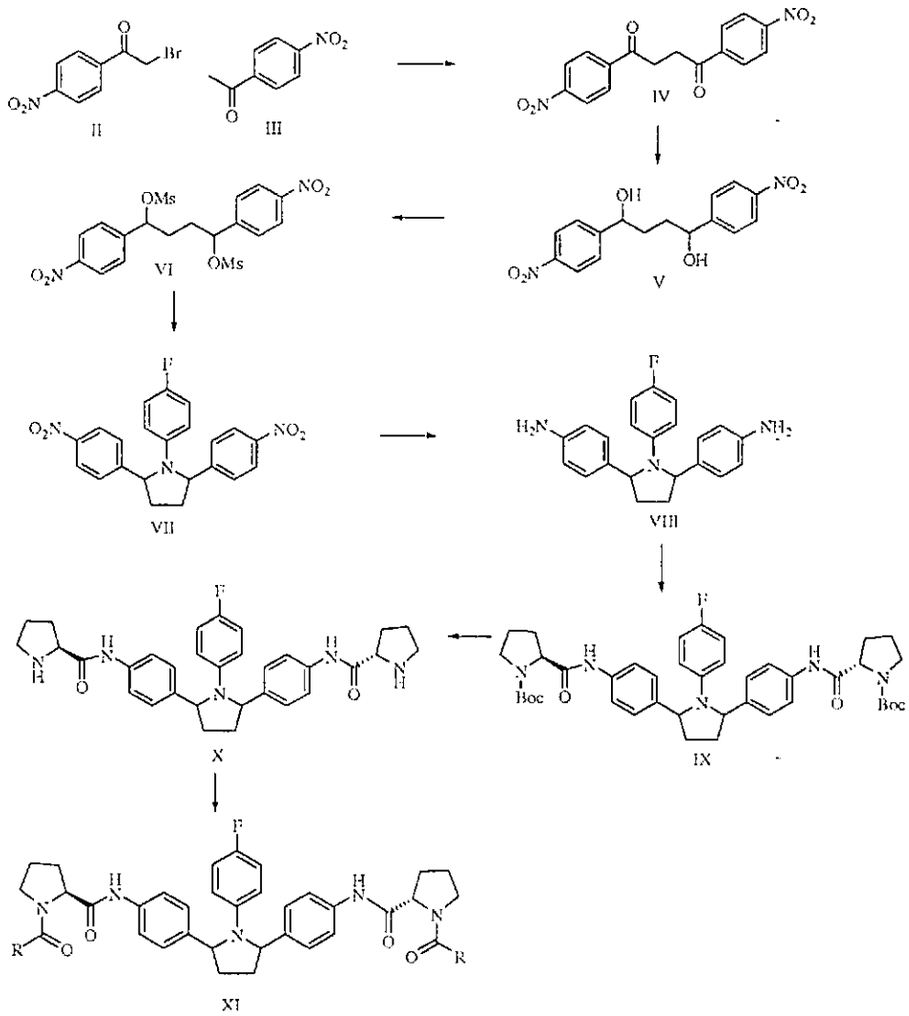


Scheme I

As another non-limiting example, the compounds of the present invention can be prepared starting from compounds of Formula II and Formula III as shown in Scheme II. The 1,4-diketones such as Formula IV may be prepared using known methods (see Nevar, et al., Synthesis:1259-1262 (2000), such as the reaction of α-bromoketones such as Formula II with methyl ketones such as Formula III in the presence of a suitable Lewis acid such as $ZnCl_2$ or $Ti(OiPr)_4$. The 1,4-diketones IV may be reduced to the 1,4-diols such as V by the action of $NaBH_4$, $LiAlH_4$, or DIBAL. Alternatively, enantioselective reduction of 1,4-diketones such as Formula IV can be accomplished by analogy with reported methods (see Chong, et al., Tetrahedron: Asymmetry 6:409-418 (1995), Li, et al., Tetrahedron 63:8046-8053 (2007), Aldous, et al., Tetrahedron: Asymmetry 11:2455-2462 (2000),

Masui, et al., Synlett:273-274 (1997), Jing, et al., Adv. Synth. Catal. 347:1193-1197 (2005), Sato, et al., Synthesis:1434-1438 (2004)), such as reduction with (-) or (+)-diisopinocamheylchloroborane (DIP-chloride), with borane and an oxazaborolidine catalyst, or with asymmetric hydrogenation in the presence of a suitable Ruthenium (II) catalyst, such as [RuCl2{(R)-BINAP}{(R,R)-DPEN}] (BINAP=2,2'-bis(diarylphosphino)-1,1'-binaphthyl; DPEN=1,2-diphenylethylenediamine). The resultant racemic, enantiomerically enriched, or meso 1,4-diols V may be reacted with methanesulfonyl chloride to provide the dimesylate Formula VI. Alternatively Formula V may be converted to a ditriflate or ditosylate by the action of p-toluenesulfonyl chloride or triflic anhydride, or to a dihalide such as a dibromide or dichloride by the action of PPh_3 in the presence of CCl_4 or CBr_4, or by the action of $SOCl_2$, $POCl_3$, or PBr_3. The dimesylate, ditriflate, ditosylate, or dihalide may be reacted with an amine, such as 4-fluoroaniline (as shown for illustration in Scheme II), with or without a co-solvent such as DMF at room temperature to 100 °C, to give the pyrrolidines such as Formula VII. In addition to 4-fluoroaniline, alternative amines may be reacted with the dimesylate Formula VI, including but not limited to aniline, 3,5-difluoroaniline, 3,4-difluoroaniline, 3-fluoroaniline, 4-trifluoromethylaniline, 4-chloroaniline, heteroaryl amines, alkyl amines, cycloalkyl amines, substituted benzylamines, or allylamine. The dinitro Formula VII may be reduced to the diamino Formula VIII using Fe in the presence of NH_4Cl, HCl, or acetic acid, or by treatment with a hydride reducing agent, such as sodium borohydride (with or without the addition of a transition metal salt, such as $BiCl_3$, $SbCl_3$, $NiCl_2$, Cu_2Cl_2, or $CoCl_2$) in a solvent such as ethanol or THF. Alternatively, Formula VII can be reduced to the product Formula VIII by hydrogenation in the presence of a suitable catalyst, such as a palladium or platinum catalyst or Raney nickel. The diamine Formula VIII may be reacted with a suitably protected proline acid (Boc is shown, although Cbz, Troc, or Fmoc may be substituted) in the presence of a peptide coupling reagent, such as EDAC/HOBT, PyBOP, HATU, or DEBPT, in a solvent such as THF, DMF, dichloromethane, or DMSO, with or without the addition of an amine base such as Hunig's base, pyridine, 2,6-lutidine, or triethylamine, to give Formula IX. Removal of the Boc protecting groups to give X may be accomplished by treatment with an acid, such as TFA, HCl, or formic acid. Compounds of the present invention may be prepared by coupling of Formula X with an acid of choice using the standard peptide coupling reagents and conditions described above. Alternately, diamine VIII may be reacted with an N-substituted proline in the presence of a peptide coupling reagent such as EDAC/HOBT, PyBOP, HATU, T_3P, or DEBPT, in a solvent such as THF, DMF, dichloromethane, or DMSO, with or without the addition of an amine base such as Hunig's base, pyridine, 2,6-lutidine, or triethylamine, to directly give compounds of the present invention (Formula XI).  in each Formula within

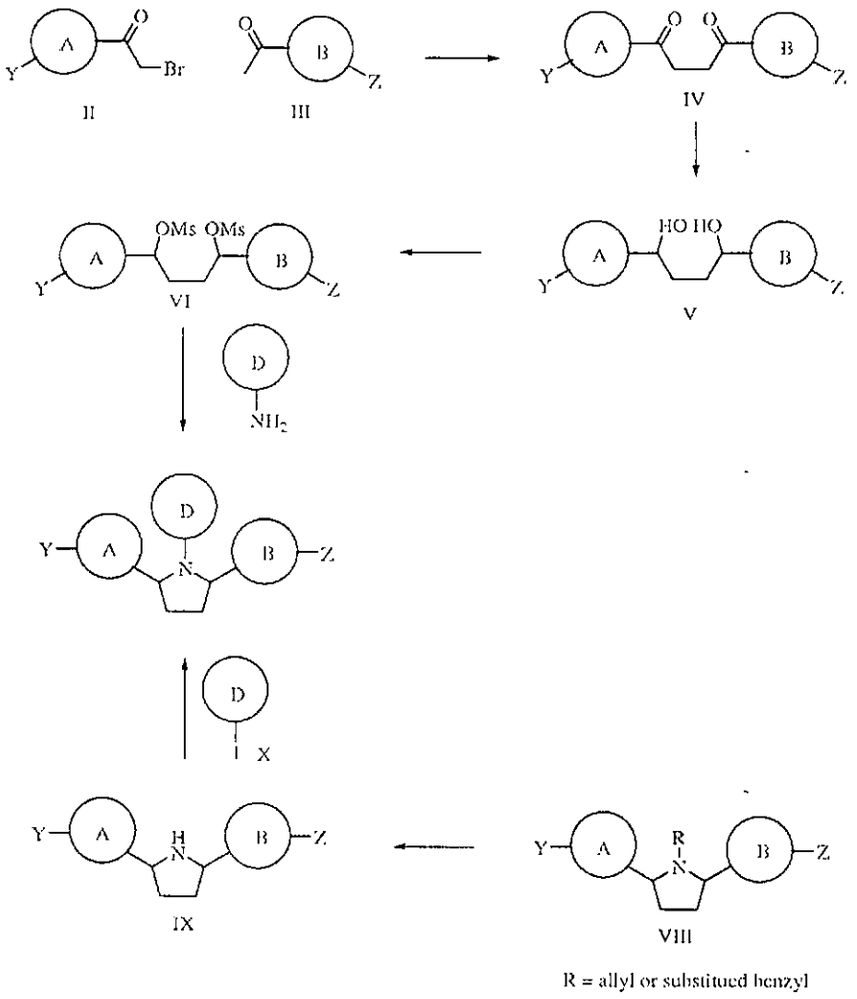
Scheme II can be replaced with  where D is defined above, and such compounds can be readily prepared according to the process described in Scheme II (including making compound XI directly from compound VIII).



Scheme II

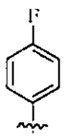
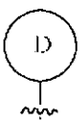
As yet another non-limiting example, the compounds of the present invention can be prepared starting from compounds of Formula II and Formula III as shown in Scheme III, where A, B, D, Y, and Z are as described above, using conditions similar to those described above for the preparation of IV in Scheme II. Similarly, the resulting 1,4-diketone IV may be reduced to the 1,4-diols V using the methods described above for Scheme II. The resultant racemic, enantiomerically enriched, or meso 1,4-diols V may be converted to the dimesylate VI or alternatively to a ditriflate, ditosylate, or dihalide by the methods described above. The dimesylate VI, ditriflate, ditosylate, or dihalide may be

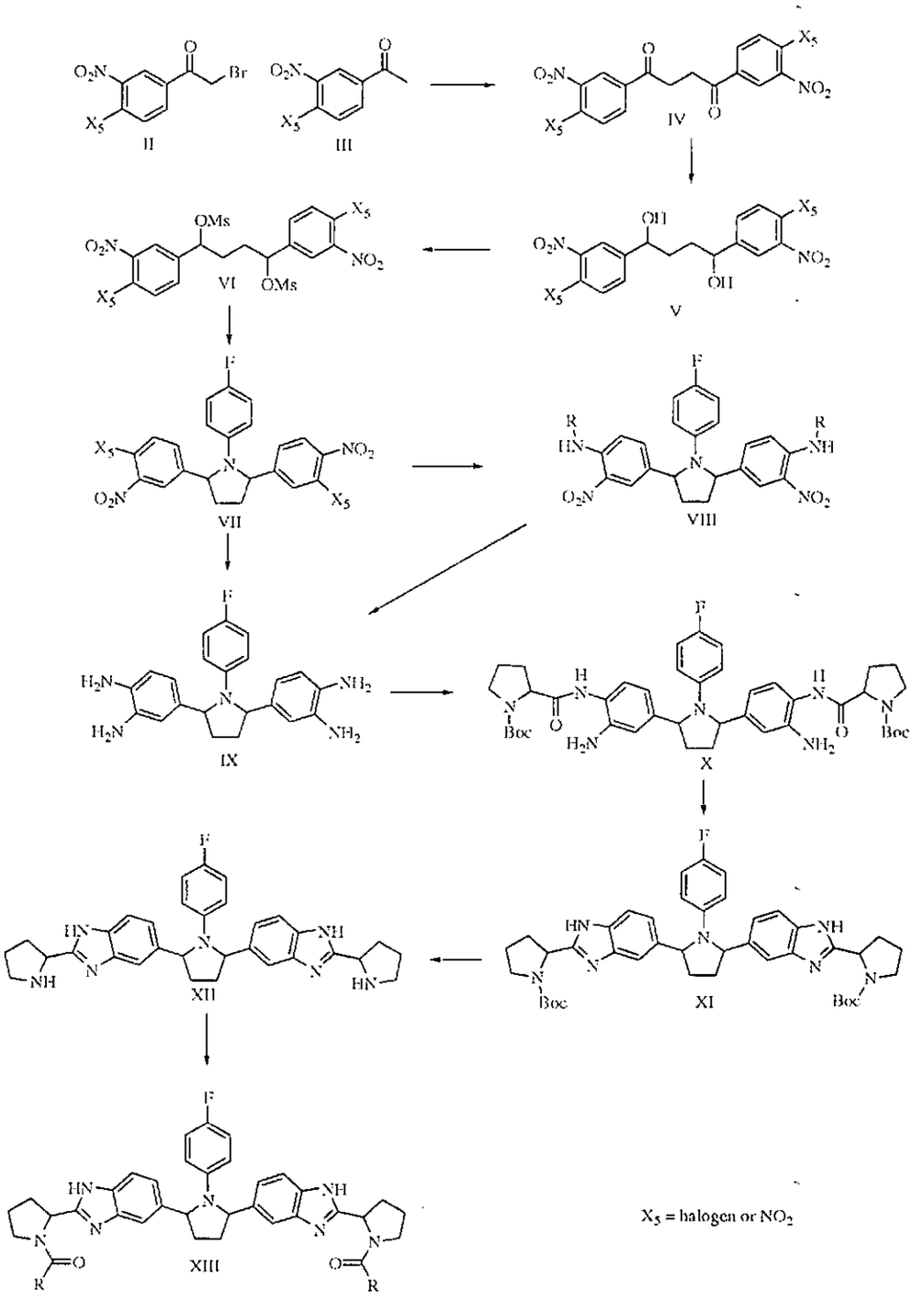
reacted with an amine, including but not limited to, aniline, 3,5-difluoroaniline, 3,4-difluoroaniline, 4-fluoroaniline, 3-fluoroaniline, 4-trifluoromethylaniline, 4-chloroaniline, heteroaryl amines, alkyl amines, cycloalkyl amines, substituted benzylamines, or allylamine, under the conditions described above the give the compounds of the invention. Alternatively, compounds such as VIII, where R is a group such as allyl, 4-methoxybenzyl, or 2,4-dimethoxybenzyl, may be treated with reagents useful for the removal of the R group (rhodium catalyst such as $Rh(Ph_3P)_3Cl$ for R = allyl, treatment with an acid such as TFA or HCl for R = 4-methoxybenzyl or 2,4-dimethoxybenzyl, hydrogenolysis with a Pd catalyst for R = substituted benzyl) to generate compounds such as IX. Amine IX may be reacted with an aryl halide or triflate such as X (iodide shown for illustration) employing the Buchwald-Hartwig reaction in the presence of a palladium catalyst (such as $Pd(OAc)_2$ or $Pd_2(dba)_3$) and a phosphine ligand (such as triphenylphosphine or XantPhos) and a base (such as sodium bis(trimethylsilyl)amide, potassium tert-butoxide, or K_3PO_4) to give the compounds of the present invention. Alternatively, the compounds of the present invention may be obtained by reaction of IX with an aldehyde or ketone through reductive amination in the presence of a hydride reducing agent, such as sodium borohydride or sodium cyanoborohydride (with or without the addition of an acid, such as acetic acid) in a solvent such as ethanol, toluene, THF, or dichloromethane. Alternatively the reductive amination may be conducted through the use of hydrogenation in the presence of a suitable catalyst, such as a palladium or platinum catalyst or Raney nickel. Alternatively, amine IX may react with electrophilic reagents, such as alkyl halides, or with aryl electrophiles (suitably electron deficient aryl and heteroaryl halides and triflates) through nucleophilic aromatic substitution reactions to give the compounds of the present invention.



Scheme III

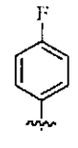
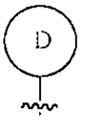
As a further non-limiting example, the compounds of the present invention can be prepared starting from compounds of Formula II and Formula III as shown in Scheme IV, where X_5 in Formula II and Formula III represents a halogen (e.g., Cl, Br, or F) or a nitro group. The 1,4-diketones such as IV may be prepared using known methods described above for the preparation of IV for Scheme II. The 1,4-diketones IV may be reduced to the 1,4-diols such as V by the action of $NaBH_4$, $LiAlH_4$, or DIBAL. Alternatively, enantioselective reduction of 1,4-diketone such as IV can be accomplished by the methods described above for the preparation of V for Scheme II. The resultant racemic, enantiomerically enriched, or meso 1,4-diols V may be reacted with methansulfonyl chloride to provide the dimesylate VI. Alternatively V may be converted to a ditriflate or ditosylate by the methods described above for Scheme II. The dimesylate, ditriflate, ditosylate, or dihalide may be reacted with an amine including but not limited to aniline, 3,5-difluoroaniline, 3,4-difluoroaniline, 4-fluoroaniline, 3-fluoroaniline, 4-trifluoromethylaniline, 4-chloroaniline, heteroaryl amines, alkyl

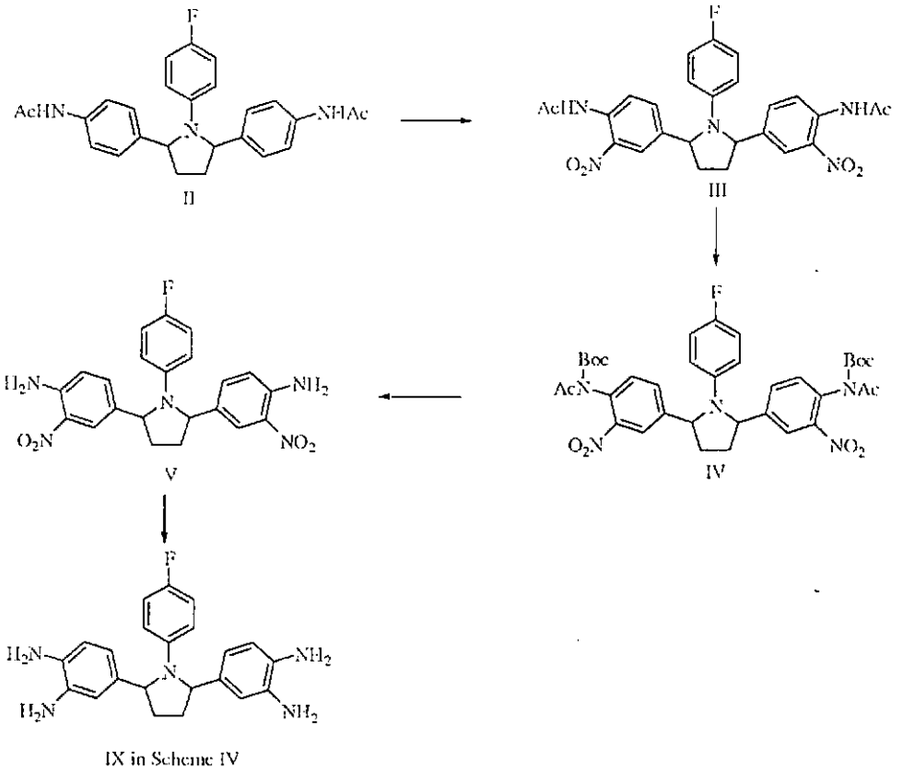
amines, cycloalkyl amines, substituted benzylamines, or allylamine to give VII. When X_5 in Formula VII is nitro, the nitro groups may be reduced to the tetraamino product IX using Fe in the presence of NH_4Cl, HCl, or acetic acid, or with a hydride reducing agent, such as sodium borohydride (with or without the addition of a transition metal salt, such as $BiCl_3$, $SbCl_3$, $NiCl_2$, Cu_2Cl_2, or $CoCl_2$) in a solvent such as ethanol or THF. Alternatively, VII (X_5 = nitro) can be reduced to the product IX by hydrogenation in the presence of a suitable catalyst, such as a palladium or platinum catalyst or Raney nickel. Alternatively, compounds VII where X_5 = halogen may be reacted with ammonia (R = H) or an amine bearing a suitable protecting group (R = substituted benzyl such as 4-methoxybenzyl or 2,4 dimethoxybenzyl or R = allyl). The resulting products VIII may be treated with a reagent useful for the removal of the R protecting group (rhodium catalyst such as $Rh(Ph_3P)_3Cl$ for R = allyl, treatment with an acid such as TFA or HCl for R = 4-methoxybenzyl or 2,4-dimethoxybenzyl, hydrogenolysis with a Pd catalyst for R = substituted benzyl) to give the product IX. Formula IX may be reacted with a suitably protected proline acid (Boc is shown, although Cbz, Troc, or Fmoc may be substituted) in the presence of a peptide coupling reagent, such as EDAC/HOBT, PyBOP, HATU, or DEBPT, in a solvent such as THF, DMF, dichloromethane, or DMSO, with or without the addition of an amine base, such as Hunig's base, pyridine, 2,6-lutidine, or triethylamine, to give X as a mixture of the amide products. Conversion to the benzimidazole compound XI may be accomplished by heating X in acetic acid (50-100 °C). Alternatively, XI may be prepared by reaction of IX with an aldehyde, followed by treatment with an oxidant, such as $Cu(OAc)_2$ or MnO_2 (see Penning, et al., Bioorg. Med. Chem. 16:6965-6975 (2008). After removal of the Boc protecting groups from XI (accomplished by treatment with an acid, such as TFA, HCl, or formic acid), the compounds of the present invention may be prepared by coupling of the resulting diamine XII with an acid of choice using the standard peptide coupling reagents and conditions described above for Scheme II.  in each Formula within Scheme IV can be replaced with  where D is defined above, and such compounds can be readily prepared according to the process described in Scheme IV.



Scheme IV

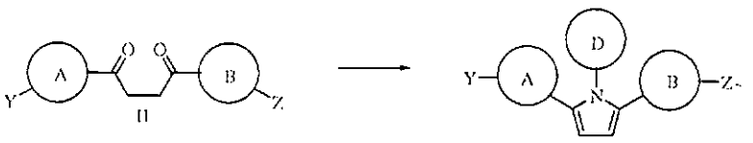
Alternatively IX in Scheme IV may be prepared from a compound of Formula II as shown in Scheme V. Compound VIII from Scheme II may be treated with an acylating agent such as acetyl chloride or acetic anhydride to give compound II (Scheme V). Nitration of compound II to provide III may be accomplished using known methods, such as treatment with nitric acid or potassium nitrate in the presence of an acid such as sulfuric acid or treatment with NO_2BF_4. Removal of the acetamide protecting group may be accomplished by treatment with Boc anhydride in the presence of DMAP to

give IV, followed by sequential treatment of IV with hydroxide (such as NaOH, KOH, or LiOH) to remove the acetyl group and a strong acid such as TFA or HCl to remove the Boc protecting group. The nitro groups in V may be reduced to amino groups using the methods described above for Scheme IV.  in each Formula within Scheme V can be replaced with  where D is defined above, and such compounds can be readily prepared according to the process described in Scheme V.



Scheme V

As still another non-limiting example, the compounds of the present invention can be prepared starting from compounds of Formula II as shown in Scheme VI, where A, B, D, Y, and Z are as described above. A 1,4-diketone compound of Formula II (prepared as described in Scheme III) may be reacted with an amine, including but not limited to, aniline, 3,5-difluoroaniline, 3,4-difluoroaniline, 4-fluoroaniline, 3-fluoroaniline, 4-trifluoromethylaniline, 4-chloroaniline, heteroaryl amines, alkyl amines, cycloalkyl amines, substituted benzylamines, or allylamine, under acid catalyzed conditions, such as acetic acid, TFA, formic acid or HCl, to give the compounds of the invention.



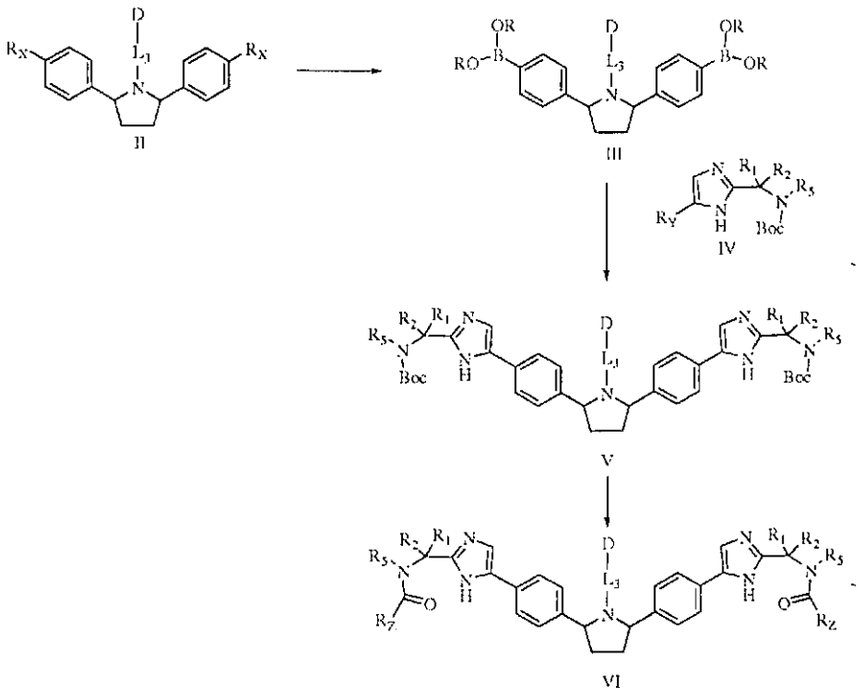
Scheme VI

As a further non-limiting example, the compounds of the present invention can be prepared from a compound of Formula II as shown in Scheme VII. A compound of Formula II, where R_X is a halogen, such as bromo, chloro, or iodo, or a triflate or a nonaflate may be converted to a boronic acid or ester such as Formula III, where R is hydrogen, methyl, ethyl, or a cyclic pinacolate ester. For example a compound of Formula II can be transformed to a compound of III by treatment with pinacol-borane in the presence of a catalyst such as, for example, tris(dibenzylidineacetone)palladium (0), and a ligand such as, for example, tri-t-butylphosphine, in solvents such as, for example, tetrahydrofuran, dioxane, or toluene at temperatures ranging from ambient to about 130°C. Alternatively, compound II can be reacted with bis(pinacolato)diboron in the presence of a catalyst such as, for example, Combiphos-Pd6 (CombiPhos Catalysts, Inc. (NJ, USA), dichloro[1,1'-bis(diphenylphosphino)ferrocene] palladium (II) dichloromethane adduct, or palladium acetate in the presence of a ligand such as, for example, 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (XPhos), and a base such as, for example, potassium acetate in solvents such as, for example, toluene, dioxane, tetrahydrofuran, dimethylformamide or dimethyl sulfoxide at temperatures from about 60 to about 130°C to give compound III. Alternatively, a compound of Formula II may be reacted with an organolithium reagent, such an n-BuLi, sec-BuLi, or t-BuLi, followed by reaction with trimethyl borate or triethyl borate, to give a compound of Formula III.

A compound of Formula III in Scheme VII can be coupled with a compound of Formula IV, where R_Y is a halogen, such as bromo, chloro or iodo, under Suzuki reaction conditions to provide a compound of Formula V. Such conditions include, for example, use of a palladium catalyst such as, for example, tris(dibenzylidineacetone)palladium (0), palladium acetate, bis(triphenylphosphine)palladium (II) chloride, tetrakis(triphenylphosphine)palladium, or dichloro[1,1'-bis(diphenylphosphino)ferrocene] palladium (II) dichloromethane adduct; base such as, for example, potassium carbonate, potassium phosphate, potassium t-butoxide, sodium carbonate, cesium carbonate, or cesium fluoride; and solvent such as, for example, toluene, ethanol, water, or tetrahydrofuran, or mixtures thereof heated in the temperature range from about 40 to about 130°C.

Removal of the Boc protecting groups from V may be accomplished by treatment with an acid, such as TFA, HCl, or formic acid. Compounds of the present invention such as VI may be prepared by coupling the resulting amino compounds with an acid of choice using the standard peptide coupling reagents, such as EDAC/HOBT, PyBOP, HATU, or DEBPT, in a solvent such as

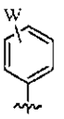
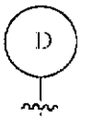
THF, DMF, dichloromethane, or DMSO, with or without the addition of an amine base such as Hunig's base, pyridine, 2,6-lutidine, or triethylamine. Each R_Z is independently $-L_Y'-M'-R_D$ (e.g., $-L_Y-N(R_B'')C(O)-L_S-R_E$), and D, L_3, R_1, R_2, R_5, L_Y, R_B'', L_S, R_E, L_Y', M' and R_D are as defined above.

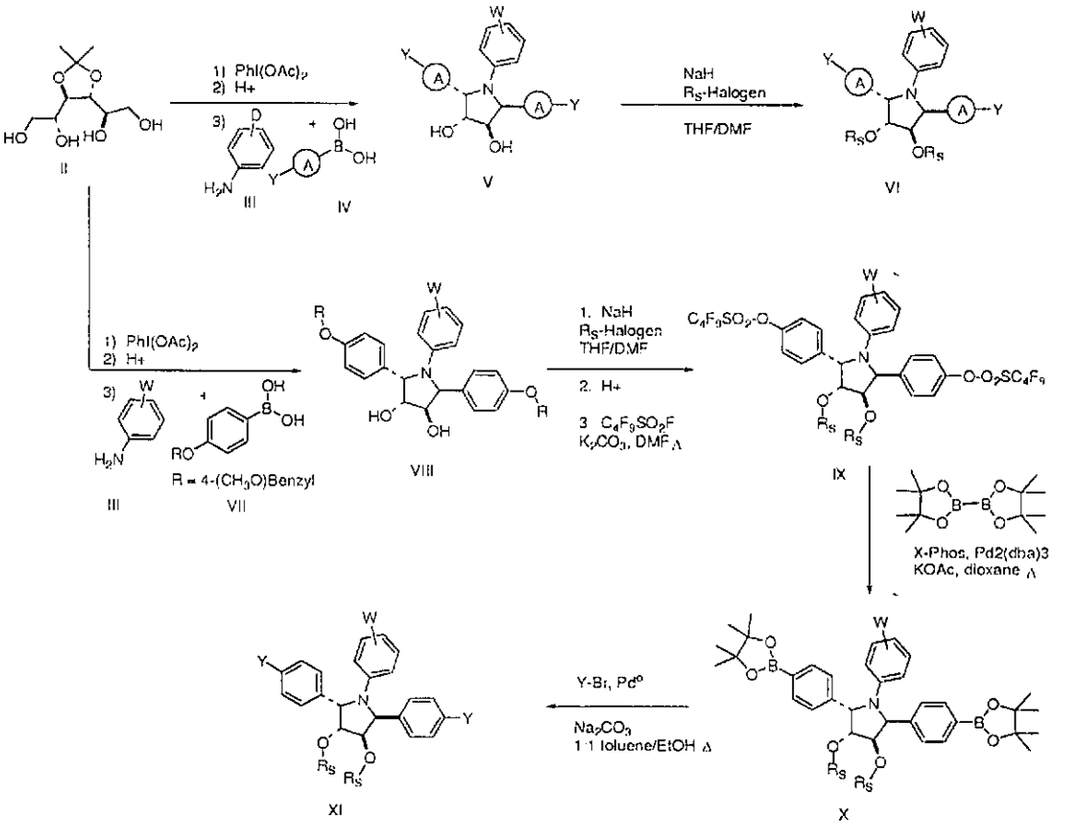


Scheme VII

As another non-limiting example, the compounds of the present invention can be prepared according to Scheme VIII starting from the compound of Formula II, initially cleaving the diol in oxidative fashion followed by subsequent acid hydrolysis of the acetonide. This dialdehyde intermediate is then treated with an aryl boronate or aryl boronic acid (compound IV where A and Y are as described previously, or compound VII) and aniline III (where W is R_M or J, and R_M and J are as defined above) resulting in the formation of Formula V or Formula VIII respectively. Formula V can be derivatized by deprotonating the hydroxyl groups with a strong base such as sodium hydride, butyl lithium, or potassium hydride, followed by alkylation with R_S-halogen. Alternatively Formula VIII can be deprotonated with a strong base (e.g., sodium hydride) and alkylated with R_S-halogen as well, followed by acid hydrolysis of the phenol protecting groups. The sulfonylation of the phenols with nonafluorobutylsulfonyl fluoride in the presence of a neutralizing agent such as potassium carbonate in a polar aprotic solvent such as DMF, followed by heating provides a compound of Formula IX. Boronate of Formula X is produced by heating Formula IX with bis(pinacolato)diboron in the presence of X-phos and a palladium catalyst, such as Pd2(dba)3 and a base such as potassium acetate in an organic solvent such as dioxane. Formula X is further derivatized to final product by heating a suitably substituted heteroarylhalide in the presence of a palladium catalyst such as

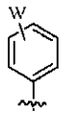
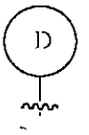
PdCl2(dppf) in the presence of a base such as sodium carbonate in a mixture of toluene and ethanol.

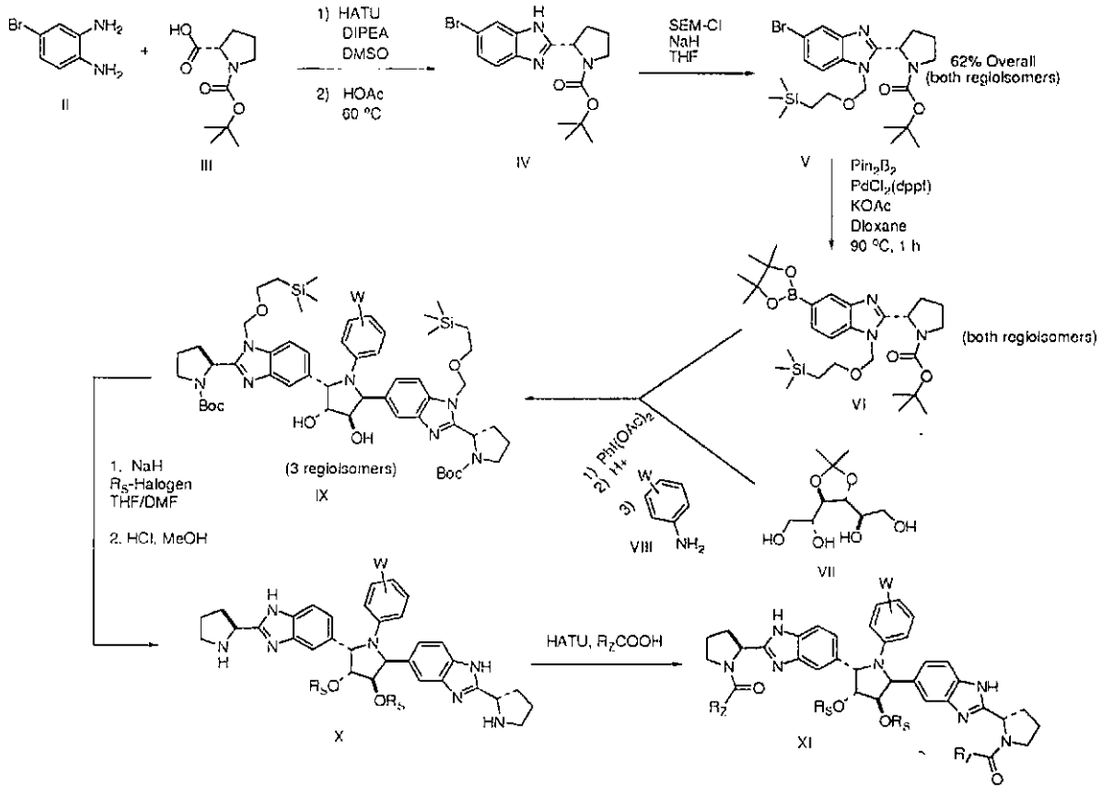
R_S is as defined above.  in each Formula within Scheme VIII can be replaced with  where D is defined above, and such compounds can be readily prepared according to the process described in Scheme VIII.



Scheme VIII

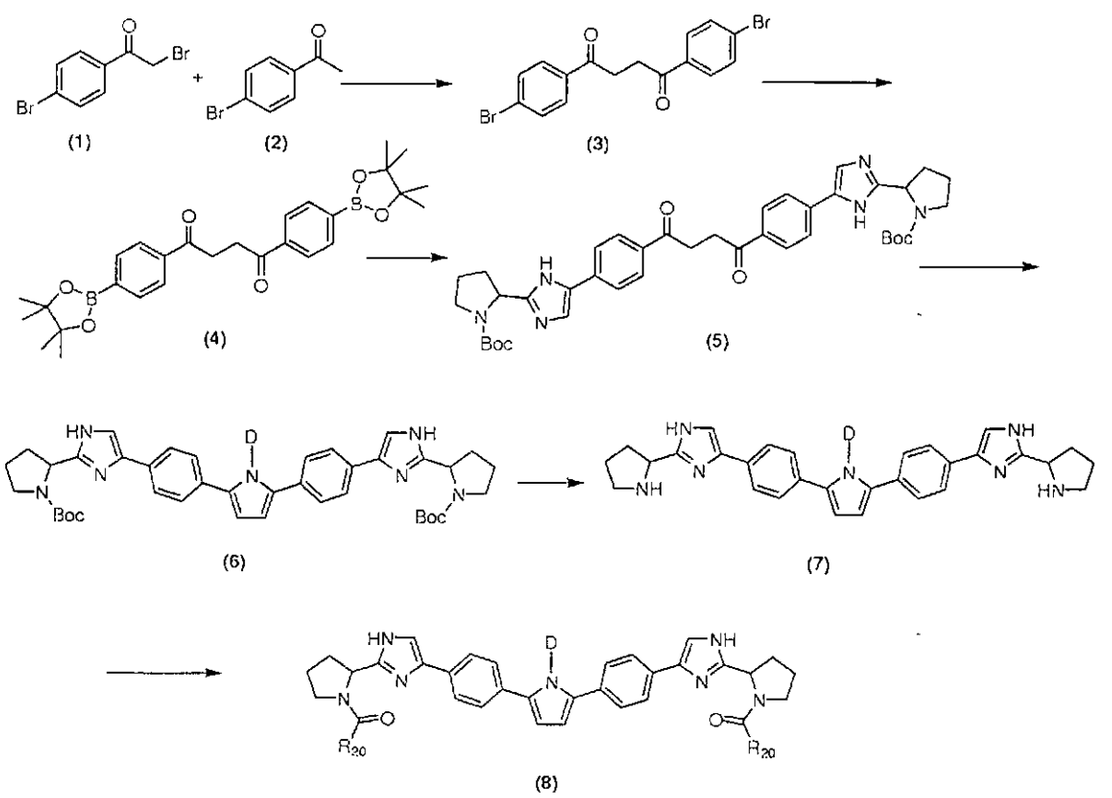
As yet another non-limiting example, the compounds of the present invention can be prepared according to Scheme IX starting from the compounds of Formula II and Formula III. Formula III carboxylic acid is activated towards coupling using reagents such as isobutylchloroformate, DCC, EDAC, or HATU in the presence of an organic base, such as diisopropylethylamine. Upon activation, dianiline of Formula II is added to the reaction, with the isolation of an intermediate amide, which is heated in acetic acid, preferably at 60 °C, to yield the compound of Formula IV. The benzimidazole of Formula IV is treated with SEM-Cl in the presence of a base in an aprotic solvent such as THF, yielding two protected benzimidazole regioisomers V. The boronate esters VI are produced by heating Formula V with bis(pinacolato)diboron in the presence of a palladium catalyst, such as PdCl2(dppf), X-Phos, and a base such as potassium acetate in an organic solvent such as dioxane. Heating yields both benzimidazole regioisomers VI. Diol VII

is cleaved in oxidative fashion followed by subsequent acid hydrolysis of the acetonide. This dialdehyde intermediate is then treated with an aryl boronate VI and aniline VIII (where W is R_M or J, and R_M and J are as defined above) resulting in the formation of the 3 benzimidazole regioisomers of Formula IX. Formula X is produced by deprotonating the hydroxyl groups with a strong base such as sodium hydride, butyl lithium, or potassium hydride, followed by alkylation with R_S-halogen, followed by acid hydrolysis of the pyrollidine and benzimidazole protecting groups, preferably by treatment with mineral acid, such as hydrochloric acid in an alcoholic solvent such as methanol. The carboxylic acid R_Z-COOH is activated towards coupling using reagents such as isobutylchloroformate, DCC, EDAC, or HATU in the presence of an organic base, such as diisopropylethylamine. Upon activation, Formula X is added to the reaction, with the isolation of Formula XI.  in each Formula within Scheme IX can be replaced with  where D is defined above, and such compounds can be readily prepared according to the process described in Scheme IX.



Scheme IX

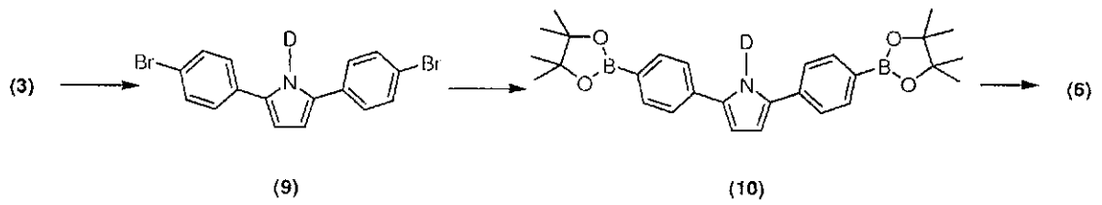
Compounds of the invention of general formula (8), where R_{20} is $-L_S'-M'-L_S''-R_D$ and D is as described above, can be prepared according to the methods of Scheme X. The bromoalkylketone (1) can be reacted with an arylalkylketone (2) using the Lewis acid mediated conditions, described above in Scheme II, to give the diaryldiketone (3). The diketone (3) can be converted to the bisboronate (4) by reaction with bis(pinacolato)diborane in the presence of a base such as potassium acetate, a catalyst such as $PdCl_2(dppf)$-CH_2Cl_2, in a solvent such as DMSO, dimethoxyethane or dioxane with heating to between 60-100 °C. Bisboronate (4) can be converted to the intermediate (5) by Suzuki reaction using, in analogous fashion, the Suzuki conditions described in Scheme VII. The intermediate (5) can be converted to (6) by reaction with an amine $D-NH_2$ under the analogous conditions described in Scheme VI. For example, reaction of (5) with $D-NH_2$ in the presence of an acid such as, but not limited to, TFA, in a solvent such as, but not limited to, toluene and with heating up to 110 °C can provide intermediates of general structure (6). Compounds (6) can be converted to compounds of general formulas (7) and then (8) using, in analogous fashion, the methods described in Scheme VII.



Scheme X

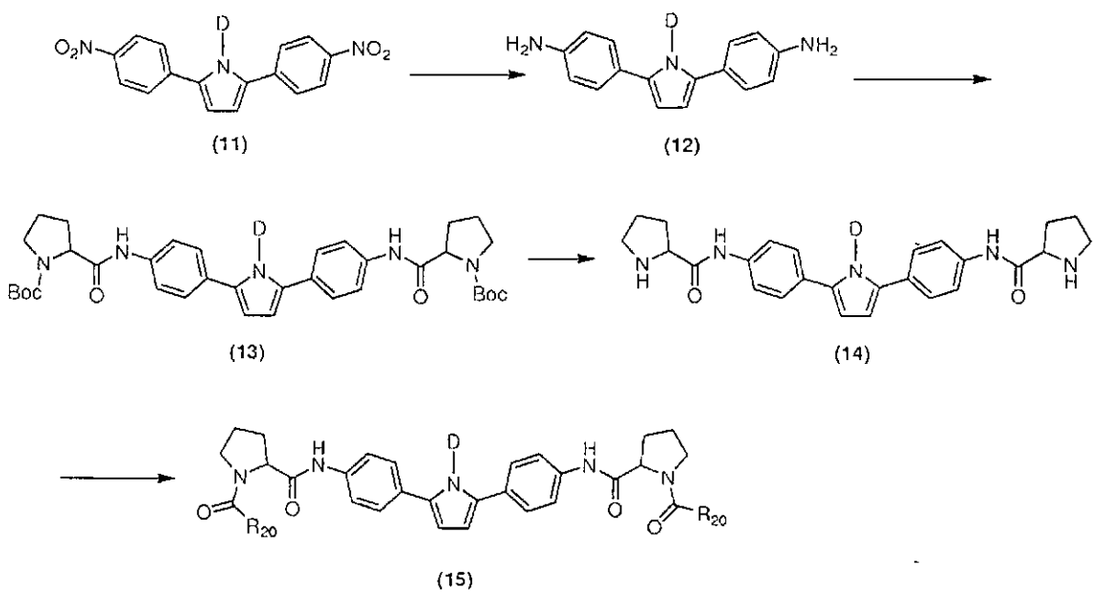
The intermediates (6) can also be prepared using the route depicted in Scheme XI. The intermediate (3) can be reacted with an amine $D-NH_2$ using, in analogous fashion, the conditions described in Schemes VI and X to provide intermediates (9), which can be converted to (10) using,

analogously, conditions as described above in Scheme X; and (10),in turn, can be converted to compounds (6) using the Suzuki reaction conditions described in Scheme VII.



Scheme XI

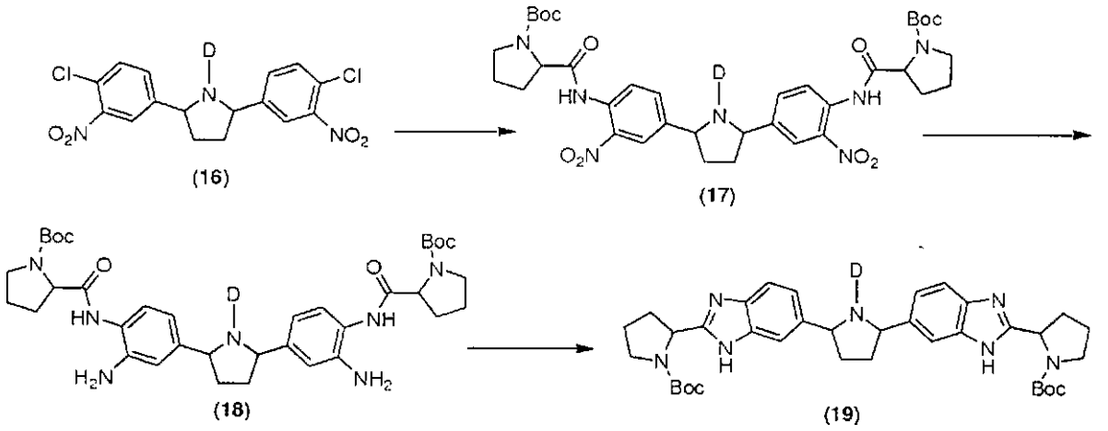
Compounds of the invention of general formula (15), where R_{20} is $-L_S'-M'-L_S''-R_D$ and D is as described above, can be prepared according to the methods of Scheme XII. Compounds (11) can prepared according to the procedures to convert (3) to (9), using general conditions as described in Scheme VI, such as by reacting an appropriate nitrophenyldiketone with an amine $D-NH_2$ with heating in acetic acid to temperature of about 70 °C. The compounds (11) can be converted to (12) using the reduction conditions described in Scheme II. Compounds (12) can be converted sequentially to compounds of general formulae (13), (14) and (15) by using, in analogous fashion, the methods described above in Scheme II.



Scheme XII

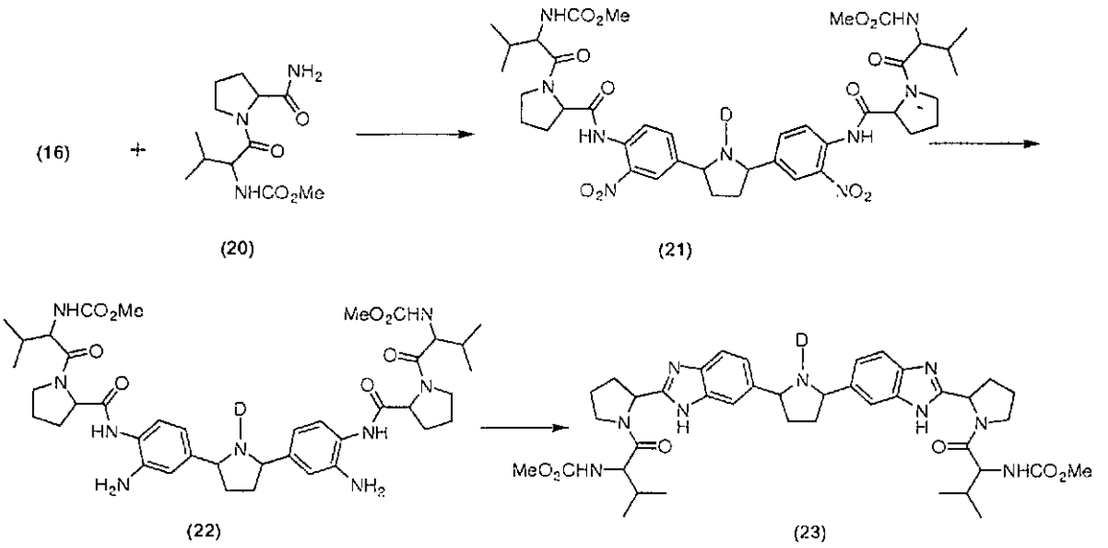
Compounds of general formula (19), where D is as described above, can be prepared according to the methods of Scheme XIII. Compounds of general formula (16) can be converted to compounds of general formula (17) using a Buchwald reaction with tert-butyl-2-carbamoylpyrrolidine-1-carboxylate. This Buchwald reaction can be conducted in the presence of a base (e.g., cesium carbonate), a palladium catalyst (e.g., tris(dibenzylideneacetone)dipalladium(0)), a

phosphine ligand (e.g., 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene) in solvent such as dioxane with heating to about 80-120 °C. The intermediate (17) can be reduced to (18) and cyclized to (19) using, in analogous fashion, the conditions described generally in Scheme IV. Compounds (19) can be further reacted as illustrated in Scheme IV to provide compounds of the invention.



Scheme XIII

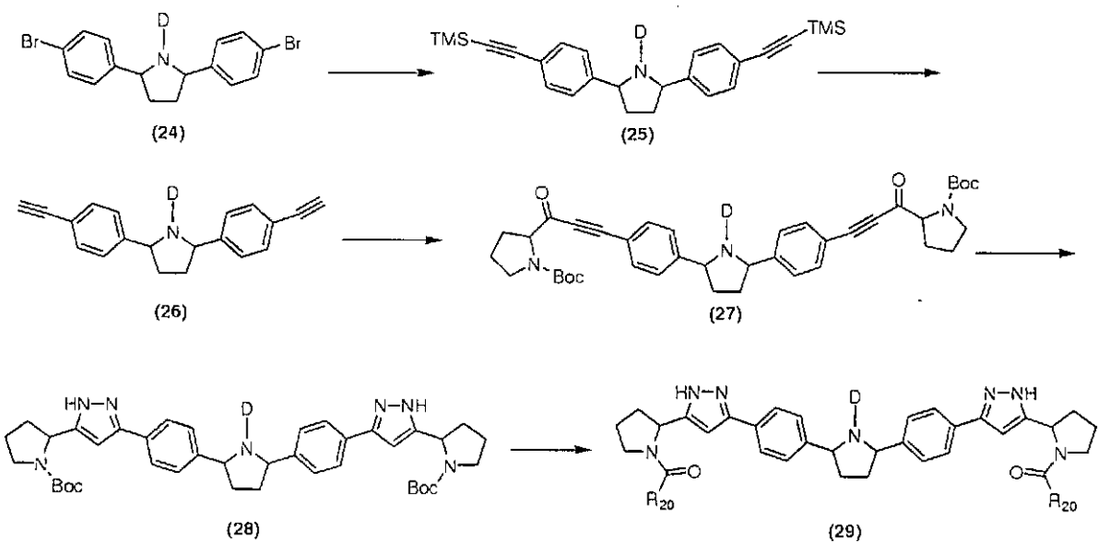
Compounds of the invention of general formula (23), where D is as described above, can be prepared according to the methods of Scheme XIV. Compounds (16) can be reacted with compound (20) using a Buchwald reaction as described generally in Scheme XIII to provide compounds (21). Compounds (21) can be reduced to compounds (22) and cyclized to (23) using, in analogous fashion, the conditions described generally in the foregoing Schemes.



Scheme XIV

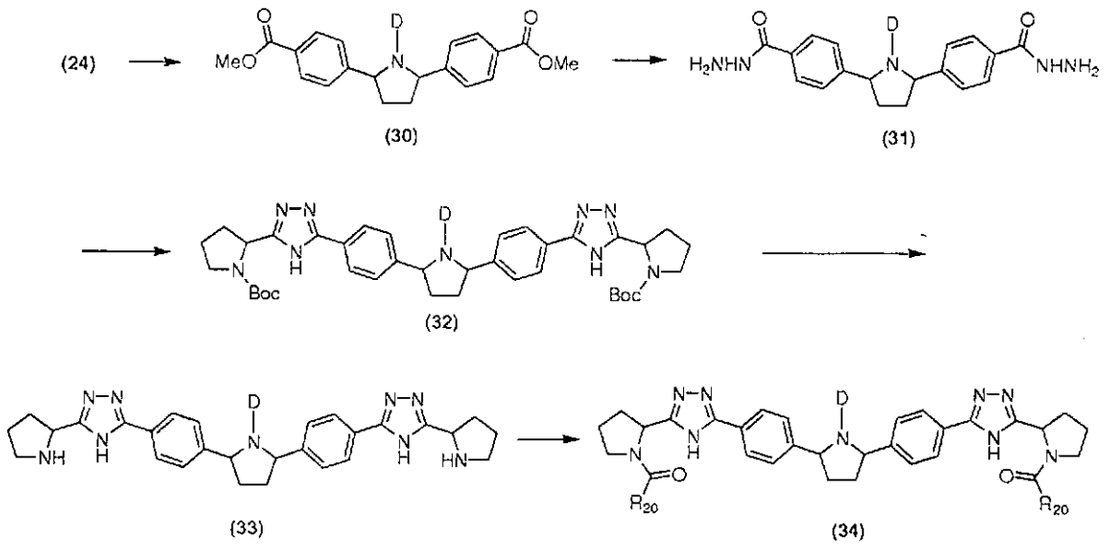
Compounds of the invention of general formula (29), where R_{20} is $-L_S'-M'-L_S''-R_D$ and D is as described above, can be prepared according to the methods of Scheme XV. Compounds of formula

(24) can be converted to compounds of formula (25) (Sonogashira reaction) by reaction with trimethylsilylacetylene, a palladium catalyst (e.g., bis(triphenylphosphine)palladium(II)chloride), a copper catalyst (e.g., copper(I)iodide), and a base (e.g., triethylamine) wherein an amine base can also be used as solvent. The compounds (25) can be desilylated to compounds (26) by reaction with a fluoride source (e.g., tetrabutylammonium fluoride) in a solvent such as THF. Compounds (26) can be converted to compounds (27) by formation of the dianion of (26) with n-butyllithium and subsequent reaction with a Weinreb amide (e.g., N-(tert-butoxycarbonyl)-L-proline-N'-methoxy-N'methylamide). This reaction can be conducted in an appropriate solvent such as THF or dimethoxyethane. Compounds (27) can be converted to compounds (28) by reaction with hydrazine in a solvent such as ethanol. The compounds (28) can be converted to compounds (29) using the methods described generally in the foregoing Schemes.



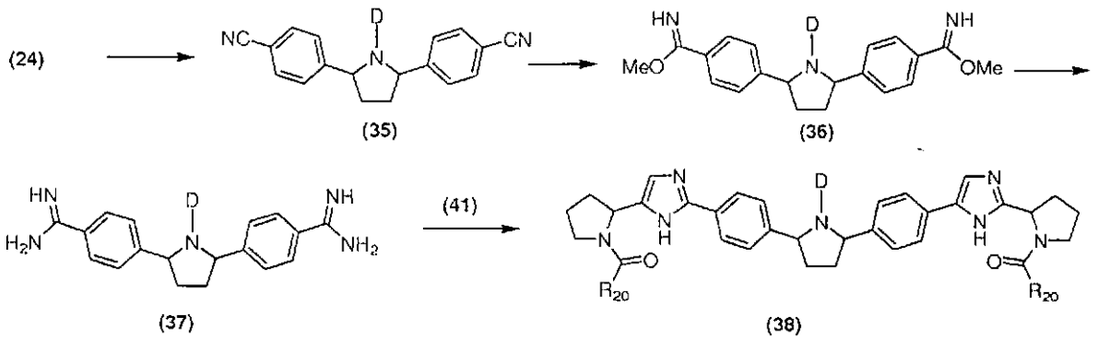
Scheme XV

Compounds of the invention of general formula (34), where R_{20} is $-L_S'-M'-L_S''-R_D$ and D is as described above, can be prepared according to the methods of Scheme XVI. Compounds (24) can be converted to compounds (30) by reaction of (24) with CO(g) under pressure (ca. 60 psi) in the presence of a palladium catalyst (e.g., $PdCl_2(dppf)$) in methanol as solvent and with heating to around 100 °C. Compounds (30) can be converted to compounds (31) by reaction with hydrazine in a solvent such as methanol with heating to about 60-80 °C. Compounds (31) can be converted to compounds (32) by reaction withN-Boc-2-cyano-pyrrolidine in the presence of a base (e.g, potassium carbonate) in a solvent such as butanol and with heating to around 150 °C with irradiation in a microwave reactor. Compounds (32) can be deprotected to compounds (33) and acylated to (34) using, in analogous fashion, the conditions described generally in the foregoing Schemes.



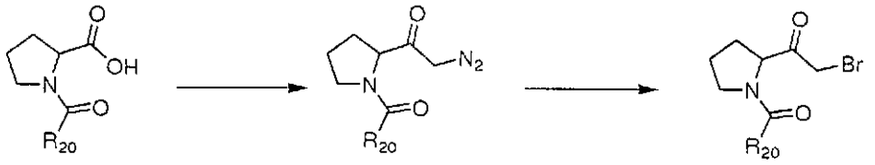
Scheme XVI

Compounds of the invention of general formula (38), where R_{20} is $-L_S'-M'-L_S''-R_D$ and D is as described above, can be prepared according to the methods of Scheme XVII. Compounds of formula (24) can be converted to compounds (35) by reaction with CuCN in a solvent such as DMF and with heating to about 160 °C with microwave irradiation. Compounds (35) can be converted to compounds (36) by reaction with HCl(g) in anhydrous methanol at 0 °C with warming to room temperature. Compounds (36) can be converted to compounds (37) by reaction with NH_3(g) in anhydrous methanol at 0 °C with warming to room temperature. Compounds (37) can be converted to compounds (38) by reaction with (41) in THF in the presence of a base (e.g., potassium carbonate).



Scheme XVII

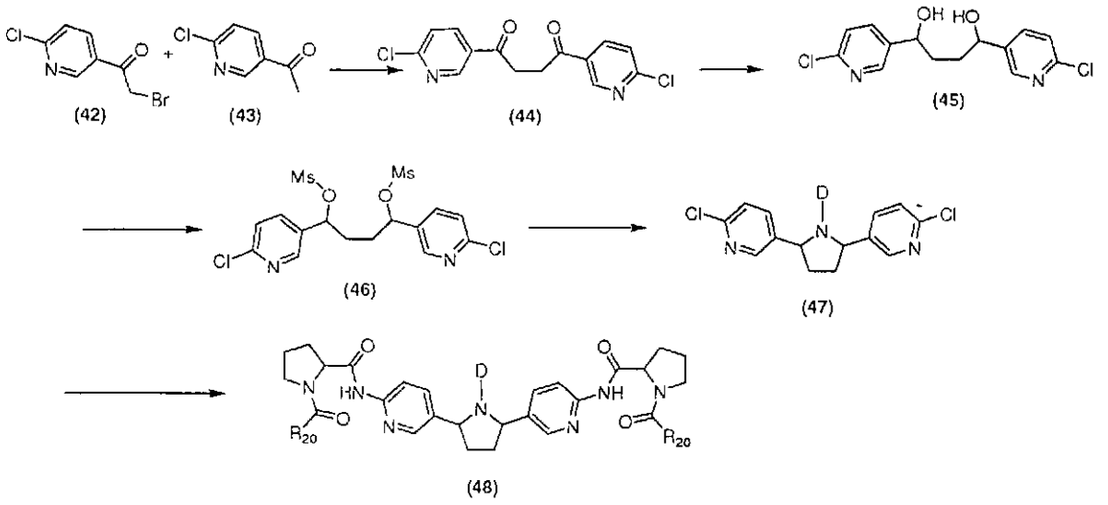
Compounds of formula (41), where R_{20} is $-L_S'-M'-L_S''-R_D$, can be prepared using the methods of Scheme XVIII. Compounds (39) can be converted to compounds (40) by sequential reaction of (39) with isobutylchloroformate in THF at 0 °C followed by diazomethane. Compounds (40) can be converted to compounds (41) by reaction with HBr in acetic acid.



(39) (40) (41)

Scheme XVIII

Compounds of the invention of general formula (48), where R_{20} is $-L_S'-M'-L_S''-R_D$ and D is as described above, can be prepared according to the methods of Scheme XIX. Compound (42) can be reacted with compound (43) using, in analogous fashion, the Lewis acid mediated conditions described above in Scheme II to provide compound (44). Compound (44) can be converted sequentially to the diol (45), the mesylate (46) and the cyclic intermediate (47) using, in analogous fashion, the conditions of Scheme II. Compounds (47) can be converted to compounds (48) by reaction with (20) under Buchwald conditions such as those referred to Scheme XIV and described in Scheme XIII.

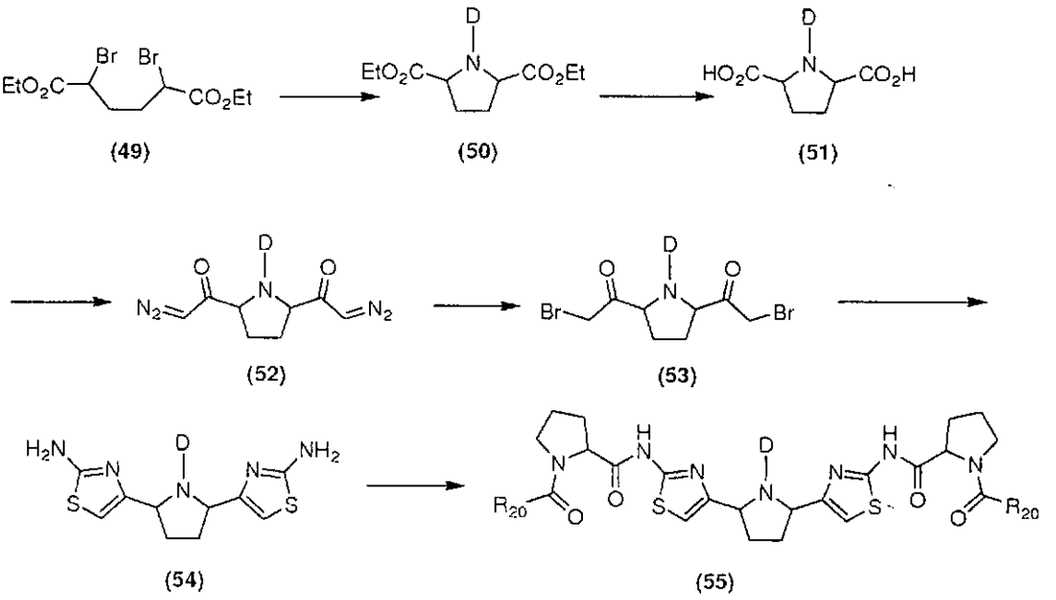


(42) (43) (44) (45) (46) (47) (48)

Scheme XIX

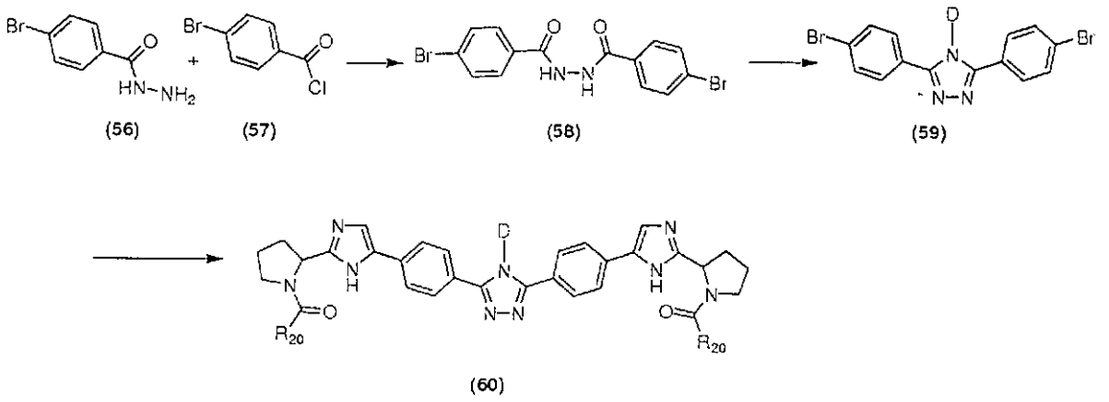
Compounds of the invention of general formula (55), where R_{20} is $-L_S'-M'-L_S''-R_D$ and D is as described above, can be prepared according to the methods of Scheme XX. Diethyl meso-2,5-dibromoadipate (49) can be reacted with an amine $D-NH_2$ in a solvent such as THF, dioxane, or dimethoxyethane with heating from 50-100 °C to give compounds (50). Compounds (50) can be converted to (51) by alkaline hydrolysis with a base (e.g., NaOH, KOH) in an alcohol (e.g., methanol, ethanol) and water mixture for solvent. Compounds (51) can be converted to (52) by reaction first with oxalylchloride, and treatment of the intermediate acid chloride with diazomethane at 0 °C. Compounds (52) can be converted to (53) by reaction with aqueous HBr. Compounds (53) can be

converted to compounds (54) by reaction with thiourea in ethanol or like solvent. Compounds (54) can be converted to compounds (55) using, in analogous fashion, the conditions described above in Scheme II.



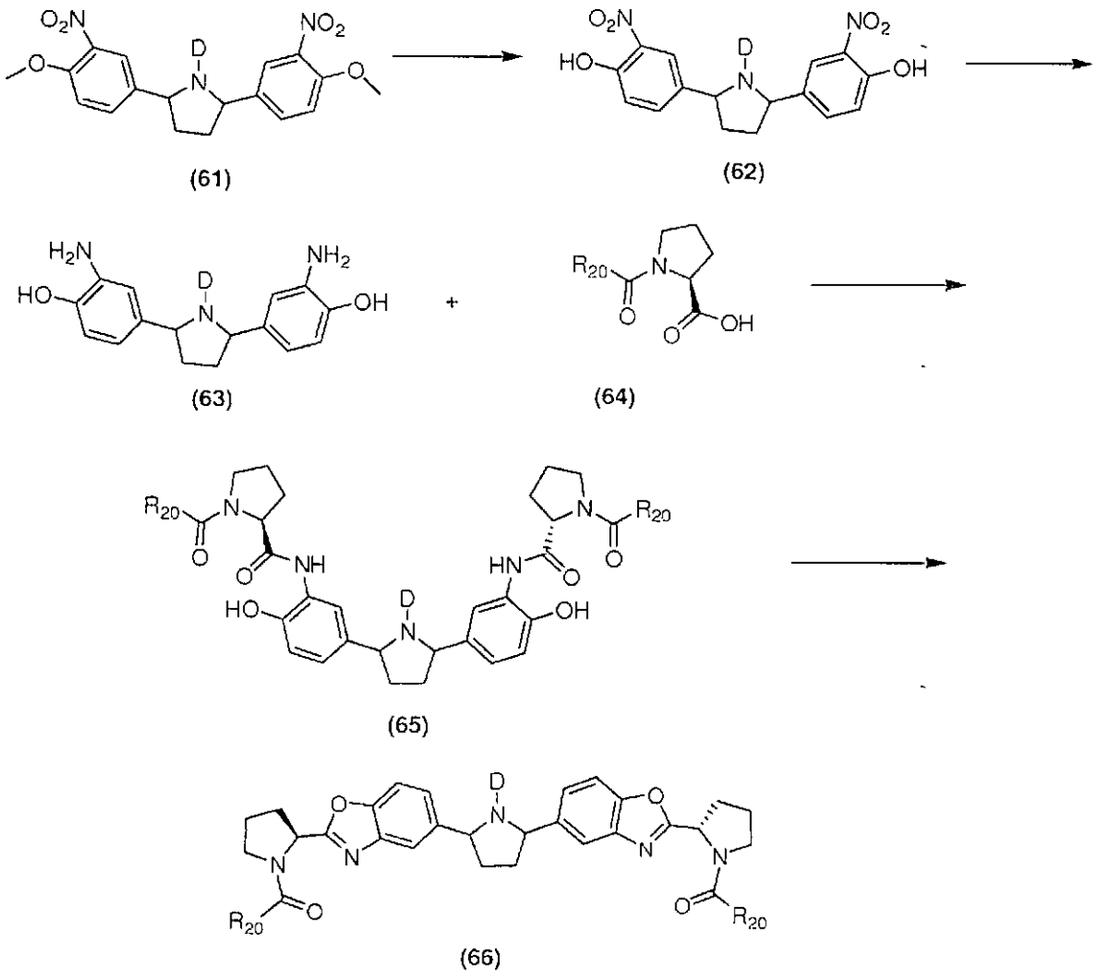
Scheme XX

Compounds of the invention of general formula (60), where R_{20} is $-L_S'-M'-L_S''-R_D$ and D is as described above, can be prepared according to the methods of Scheme XXI. Compound (56) can be reacted with compound (57) in pyridine with heating to about 135 °C to form compound (58). Compound (58) can be converted to compounds (59) by reaction of an amine D-NH_2 with $POCl_3$ followed by addition of (58) and heating at about 200 °C in 1,2-dichlorobenzene. Compounds (59) can be converted to compounds (60) using, in analogous fashion, the conditions described above in Scheme VII.



Scheme XXI

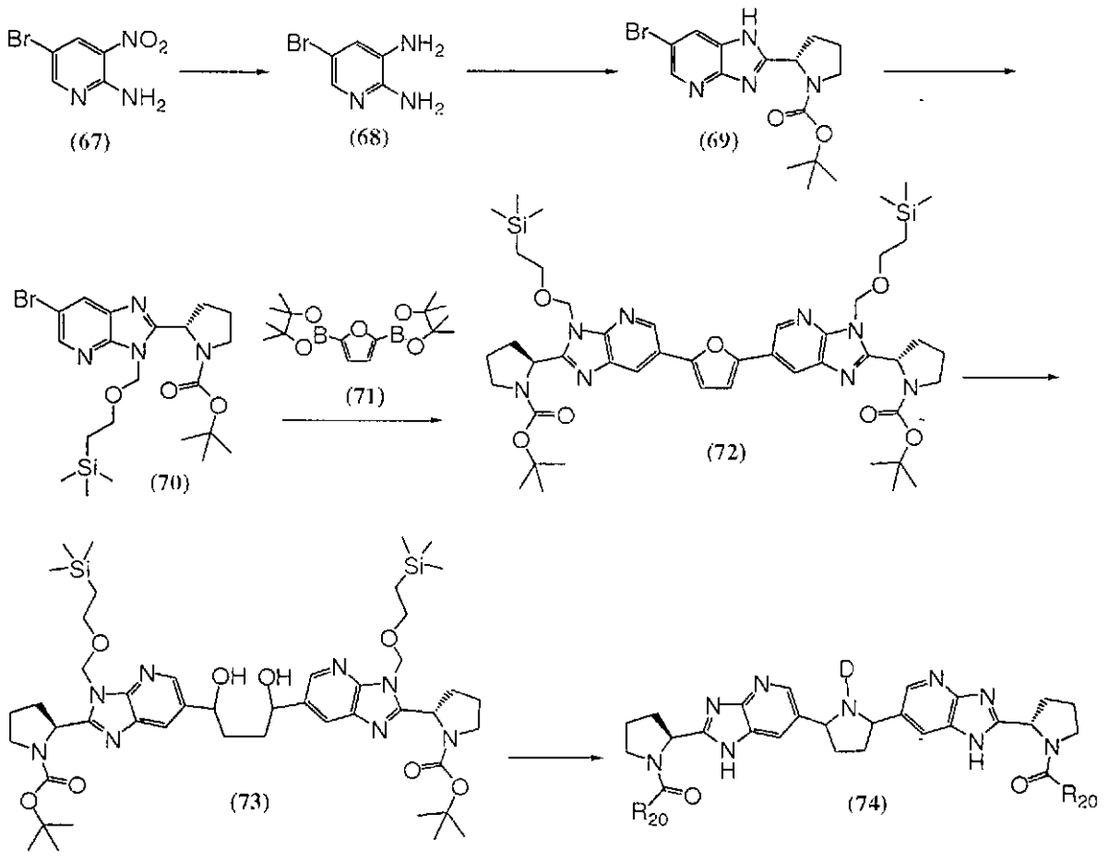
Compounds of the invention of general formula (66), where R_{20} is $-L_S'-M'-L_S''-R_D$ and D are as described above, can be prepared according to the methods of Scheme XXII. Compounds of general formula (61) can be reacted with borontribromide in dichloromethane at 0 °C to give compounds (62), which can be subjected to hydrogenation conditions using platinum(II) oxide to give compounds (63). Coupling between compounds (63) and proline derivatives (64) can be carried out using standard coupling conditions described above to give compounds (65), which can be converted to (66) by the action of diethylazodicarboxylate and triphenylphosphine in THF.



Scheme XXII

Compounds of the invention of general formula (74), where R_{20} is $-L_S'-M'-L_S''-R_D$ and D is as described above, can be prepared according to the methods of Scheme XXIII. Compound (67) can be converted to (68) by reduction of the nitro group using tin(II) chloride in ethanol. Compound (69) can be made from (68) by peptide coupling with Boc-proline, followed by heating of the resulting amide in acetic acid at 80 °C. Compound (69) can be reacted with SEM-Cl and diisopropylethylamine in dichloromethane to give (70), which can be coupled with (71) using a palladium catalyst such as PXPd using a base such as cesium fluoride in a solvent such as N,N-

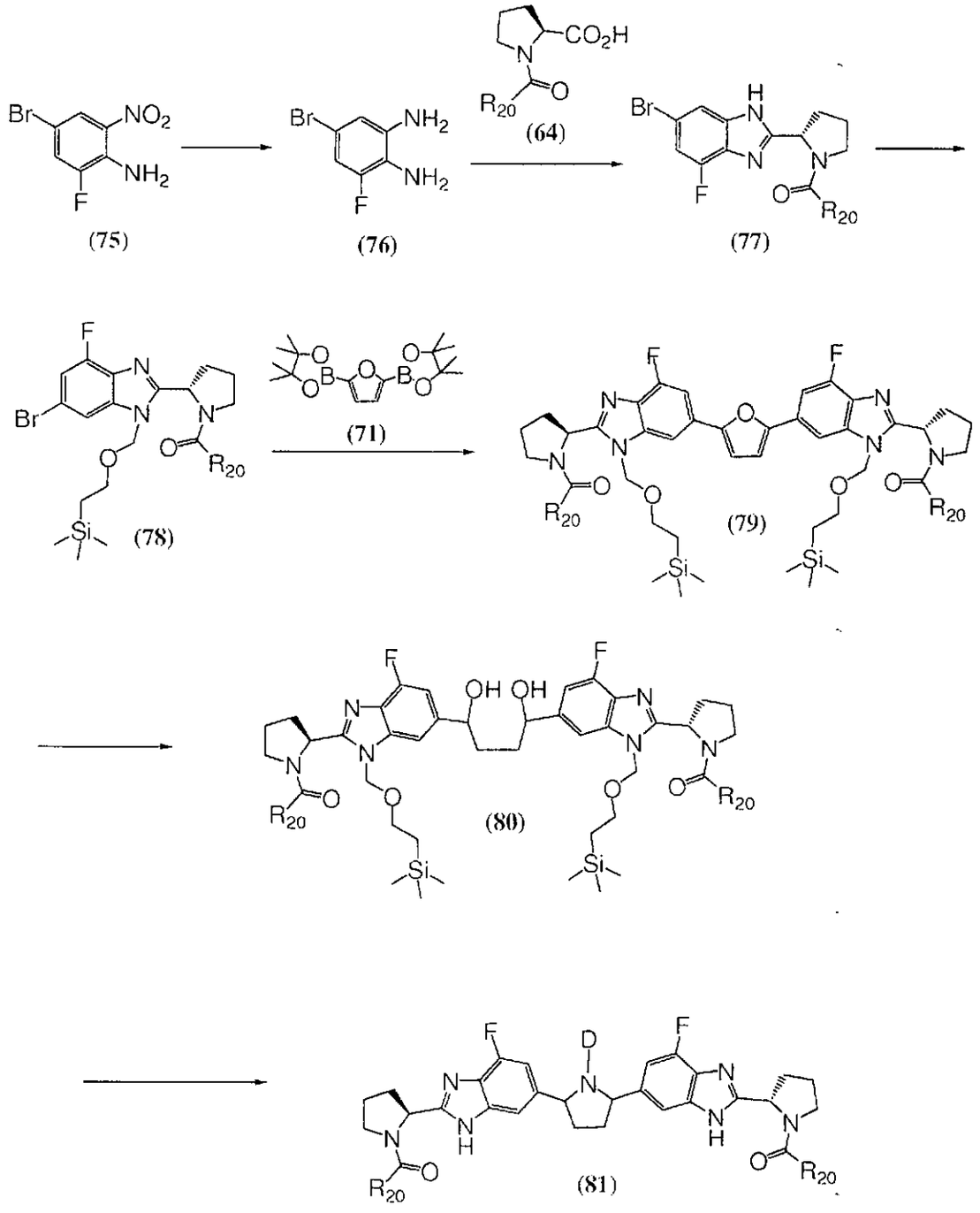
dimethylformamide at 100 °C to give (72). Compound (72) can be converted to (73) by reaction with Selectfluor® in a mixture of THF and water, followed by hydrogenation using 3% Pt on carbon in ethylacetate and then reduction using sodium borohydride in methanol. Compound (73) can be reacted with methanesulfonyl chloride and triethylamine in dichloromethane at -10 °C, followed by addition of an amine (H_2N-D) to give an intermediate that can be converted to (74) by deprotection using 4N HCl in 1,4-dioxane and then coupling with $R_{20}CO_2H$ using peptide coupling procedures described above.



Scheme XXIII

Compounds of the invention of general formula (81), where R_{20} is $-L_S'-M'-L_S''-R_D$ and D is as described above, can be prepared according to the methods of Scheme XXIV. Compound (75) can be converted to (76) using $SnCl_2$ in ethanol. Coupling of (76) with (64) using peptide coupling procedures described above to give an amide that can be heated in acetic acid at 100 °C to give (77). Compound (77) can be reacted with SEM-Cl and diisopropylethylamine in dichloromethane to give (78), which can be reacted with (71) as described above to give (79). Compound (79) can be converted to (80) using Selectfluor® in a mixture of THF and water, followed by hydrogenation with Pt on carbon in ethylacetate and reduction with sodium borohydride in methanol. Compound (80) can be converted to compounds (81) by mesylation with methanesulfonyl chloride and triethylamine at

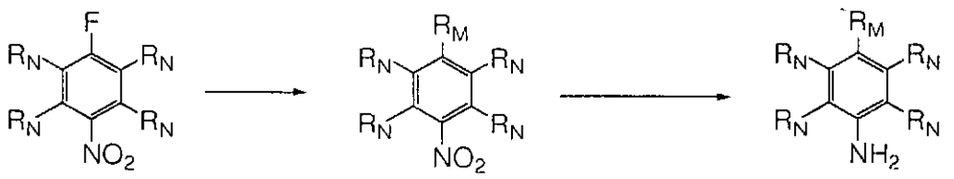
temperatures less than 0 °C, followed by reaction with primary amine H_2N-D and deprotection using 4N HCl in 1,4-dioxane.



Scheme XXIV

Certain amines, D–NH_2, in the foregoing Schemes are represented by formula (84), and may be prepared according to the general method shown in Scheme XXV, wherein R_N is as defined above (e.g., halogen, alkyl, haloalkyl) and R_M is –$N(R_SR_S)$ (e.g., –NEt_2), heterocyclyl (e.g., pyrrolidin-1-yl,

piperidin-1-yl, etc.), or $-OR_S$ (e.g., –O–t-butyl, –O–isopropyl, etc.). Fluoronitrobenzenes (82) can be reacted with an appropriate amine in the presence of dibasic potassium phosphate in a solvent such as DMSO optionally with heating to give intermediates (83), wherein R_M is $-N(R_SR_S)$ (e.g., $-NEt_2$) or heterocyclyl (e.g., pyrrolidin-1-yl, piperidin-1-yl, etc.). Fluoronitrobenzenes (82) can also be reacted with alkali metal alkoxides (e.g., potassium tert-butoxide) to give intermediates (83), wherein R_M is $-OR_S$ (e.g., –O–t-butyl, –O–isopropyl, etc.). Intermediates (83) may be converted to (84) using well-known nitro reduction conditions. For example, (83) can be converted to (84) by catalytic hydrogenation using palladium on carbon. Alternatively, (83) can be converted to (84) by reaction with iron/ammonium chloride in THF/methanol/water as solvent. Other conditions for effecting nitro reduction include those described in the foregoing schemes and those generally known to one skilled in the art.



(82) (83) (84)

Scheme XXV

In the foregoing Schemes, compounds are shown wherein an aromatic ring (e.g., phenyl) is substituted with groups in a particular regiochemistry (e.g., para). A starting material or intermediate with para-substitution provides a final product with para-substitution in the foregoing Schemes. It is understood by one of skill in the art that substitution in the foregoing Schemes of a starting material or intermediate with a different regiochemistry (e.g., meta) would provide a final product with a different regiochemistry. For example, replacement of a para-substituted starting material or intermediate in the foregoing Schemes with a meta substituted starting material or intermediate would lead to a meta-substituted product.

If a moiety described herein (e.g., $-NH_2$ or –OH) is not compatible with the synthetic methods, the moiety may be protected with a suitable protecting group that is stable to the reaction conditions used in the methods. The protecting group may be removed at a suitable point in the reaction sequence to provide a desired intermediate or target compound. Suitable protecting groups and methods for protecting or deprotecting moieties are well know in the art, examples of which can be found in Greene and Wuts, *supra*. Optimum reaction conditions and reaction times for each individual step may vary depending on the particular reactants employed and substituents present in the reactants used. Solvents, temperatures and other reaction conditions may be readily selected by one of ordinary skill in the art based on the present invention.

Other compounds of the invention can be similarly prepared according to the above-described schemes as well as the procedures described in following examples, as appreciated by those skilled in the art. It should be understood that the above-described embodiments and schemes and the following examples are given by way of illustration, not limitation. Various changes and modifications within the scope of the present invention will become apparent to those skilled in the art from the present description.

Example compounds below were named using either ChemDraw version 9.0 or ACD version 12 (ACD v12). Final compounds for Examples 1-50 were named using ChemDraw unless otherwise indicated as being named using ACD v12. Final compounds after Example 50 were named using ACD v12. Intermediates were named using ChemDraw, unless otherwise indicated as being named using ACD v12.

Certain compounds in the Examples below were purified using reverse-phase HPLC. Purification was conducted using either a C18 or C8 reverse-phase column. Compounds were eluted using a gradient of about 10-100% acetonitrile in 0.1% aqueous TFA; about 60-100% methanol in 10 mM aqueous ammonium acetate; or about 10-95% methanol in 10 mM aqueous ammonium acetate. For purifications conducted with TFA, the product thus obtained may be in the form of a TFA salt. Compounds may be characterized as the TFA salt or as the free base following neutralization, extraction and isolation.

Certain compounds in the Examples below were purified using normal phase silica gel chromatography including traditional flash chromatography or an automated purification system (e.g., Isco Combi-Flash, Analogix Intelliflash) using pre-packed silica gel columns (55 or 35 μm silica gel, Isco gold columns)

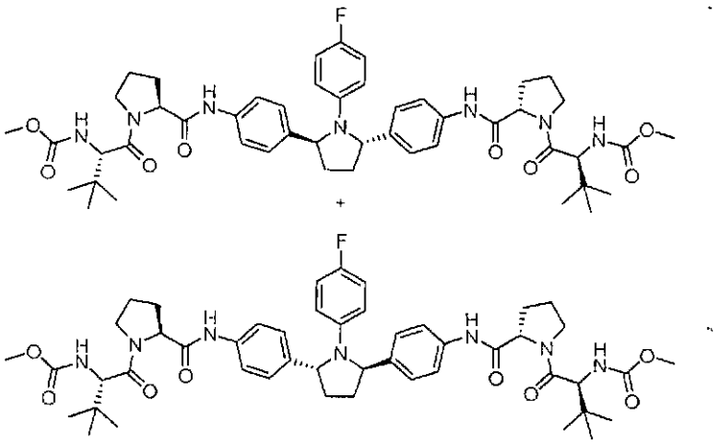
Typical solvents for silica gel chromatography include: Ethyl acetate in hexanes, Diethyl ether in hexanes, THF in hexanes, Ethyl acetate in methylene chloride, Methanol in methylene chloride, Methanol in methylene chloride with NH_4OH, Acetone in hexanes, and Methylene chloride in hexanes.

Example 1

Dimethyl (2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-((2S,5S)-1-(4-fluorophenyl)pyrrolidine-2,5-diyl)bis(4,1-phenylene))bis(azanediyl)bis(oxomethylene)bis(pyrrolidine-2,1-diyl))bis(3,3-dimethyl-1-oxobutane-2,1-diyl)dicarbamate

and

Dimethyl (2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-((2R,5R)-1-(4-fluorophenyl)pyrrolidine-2,5-diyl)bis(4,1-phenylene))bis(azanediyl)bis(oxomethylene)bis(pyrrolidine-2,1-diyl))bis(3,3-dimethyl-1-oxobutane-2,1-diyl)dicarbamate



Example 1A

1,4-Bis(4-nitrophenyl)butane-1,4-dione

Anhydrous zinc(II) chloride (2.73 g, 20.00 mmol) was stirred in dry benzene (15 ml) while diethylamine (1.558 ml, 15.00 mmol) and t-butanol (1.435 ml, 15.00 mmol) were added, and the resulting mixture was stirred at room temperature for 90 min to give a cloudy solution. To this mixture was added 2-bromo-1-(4-nitrophenyl)ethanone (2.44 g, 10.00 mmol) and 1-(4-nitrophenyl)ethanone (2.477 g, 15.00 mmol), and the resulting mixture was stirred at room temperature overnight. The mixture was poured into water (50 mL) and extracted with ethyl acetate (3 x 50 ml). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The resulting residue was triturated with dichloromethane to give an orange solid that was collected by filtration and dried to give the title compound (2.0 gm, 61% yield).

Example 1B

1,4-Bis(4-nitrophenyl)butane-1,4-diol

To a solution of the product from Example 1A (1.0 g, 3.05 mmol) in anhydrous THF (30 ml) at 0°C was added sodium borohydride (0.357 g, 9.44 mmol). The resulting mixture was stirred at 50°C overnight. The cooled mixture was poured into water, extracted with ethyl acetate, dried over Na_2SO_4, filtered and concentrated in vacuo. The resulting solid was triturated with dichloromethane to give a tan solid that was collected by filtration and dried to give the title compound ((0.82 gm, 81% yield).

Example 1C

1,4-Bis(4-nitrophenyl)butane-1,4-diyl dimethanesulfonate

To a solution of the product from Example 1B (0.80 g, 2.407 mmol) in dry CH_2Cl_2 (25 ml) at 0°C was added triethylamine (1.007 ml, 7.22 mmol), followed by dropwise addition of methanesulfonyl chloride (0.469 ml, 6.02 mmol). The resulting mixture was stirred at 0°C for 30 min,

during which time the starting material slowly went into solution. After stirring an additional 1 h at 0°C, a precipitate began to form. Saturated aq NH_4Cl (4 ml) was added, and stirring was continued at room temperature for 20 min. The mixture was washed with water (2 x 10 ml), and the organic layer was treated with hexanes (10 ml) to give an orange solid that was collected by filtration to give the title compound (0.75 gm, 64% yield).

Example 1D

1-(4-Fluorophenyl)-2,5-bis(4-nitrophenyl)pyrrolidine

The product from Example 1C (0.6 gm, 1.228 mmol) and 4-fluoroaniline (2.0 ml, 20.82 mmol) were combined and stirred at 50°C overnight. The resulting mixture was partitioned between 0.2 N HCl (50 ml) and ethyl acetate (3 x 50 ml), and the combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by chromatography on silica gel.using a solvent gradient of 0-40% ethyl acetate in hexane to give the title compound as a mixture of cis and trans isomers (0.5 gm, 100% yield).

Example 1E

4,4'-(1-(4-Fluorophenyl)pyrrolidine-2,5-diyl)dianiline

To a solution of the product from Example 1D (0.501 g, 1.23 mmol) in ethanol (5 ml) and THF (5.00 ml) was added iron powder (0.412 g, 7.38 mmol) and a solution of ammonium chloride (0.197 g, 3.69 mmol) in water (1.0 ml). The resulting mixture was stirred at 80°C for 45 min. The mixture was cooled, filtered through celite, washed with ethanol, and concentrated in vacuo. The crude product was purified by chromatography on silica gel using a solvent gradient of 0-100% ethyl acetate in hexanes to give the title compound as a mixture of cis and trans isomers (0.135 gm, 32%).

Example 1F

(2S,2'S)-tert-Butyl 2,2'-(4,4'-(1-(4-fluorophenyl)pyrrolidine-2,5-diyl)bis(4,1-phenylene))bis(azanediyl)bis(oxomethylene)dipyrrolidine-1-carboxylate

To a mixture of the product from Example 1E (0.13 gm, 0.374 mmol), (S)-1-(tert-butoxycarbonyl)pyrrolidine-2-carboxylic acid (0.201 gm, 0.935 mmol) and HATU (0.356 gm, 0.935 mmol) in DMSO (3 ml) was added Hunig's base (0.196 ml, 1.123 mmol), and reaction mixture was stirred at room tempertaure for 90 min. The mixture was poured into water and extracted by ethyl acetate. The organic extract was dried over Na_2SO_4, filtered and concentrated in vacuo to give a crude product that was purified by column chromatography on silica gel, eluting with a solvent gradient of 5-100% ethyl acetate in hexane to give title compound (0.28 gm, 100%).

Example 1G

(2S,2'S)-N,N'-(4,4'-(1-(4-Fluorophenyl)pyrrolidine-2,5-diyl)bis(4,1-phenylene))dipyrrolidine-2-carboxamide

To the product from Example 1F (0.28 gm, 0.377 mmol) in CH_2Cl_2 (2.0 ml) was added TFA (2.0 ml). The reaction mixture was stirred at room temperature for 45 min and concentrated in vacuo. The residue was partitioned between into 3:1 CH_2Cl_2:2-PrOH and saturated aq. $NaHCO_3$. The organic layer was dried over Na_2SO_4, filtered and concentrated to give the title compound (0.195 gm, 95% yield).

Example 1H

Dimethyl (2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-((2S,5S)-1-(4-fluorophenyl)pyrrolidine-2,5-diyl)bis(4,1-phenylene))bis(azanediyl)bis(oxomethylene)bis(pyrrolidine-2,1-diyl))bis(3,3-dimethyl-1-oxobutane-2,1-diyl)dicarbamate

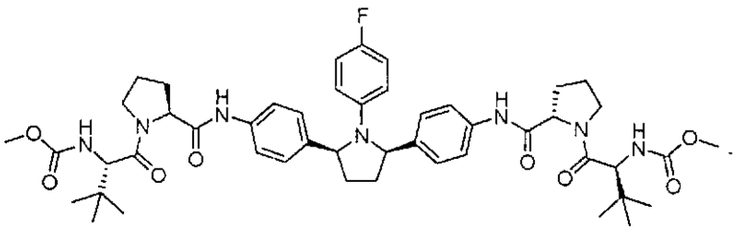
and

Dimethyl (2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-((2R,5R)-1-(4-fluorophenyl)pyrrolidine-2,5-diyl)bis(4,1-phenylene))bis(azanediyl)bis(oxomethylene)bis(pyrrolidine-2,1-diyl))bis(3,3-dimethyl-1-oxobutane-2,1-diyl)dicarbamate

To a mixture of the product from Example 1G (0.03 gm, 0.055 mmol), (S)-2-(methoxycarbonylamino)-3,3-dimethylbutanoic acid (0.0262 gm, 0.138 mmol) and HATU (0.0526 gm, 0.138 mmol) in DMSO (0.5 ml) was added Hunig's base (0.029 ml, 0.166 mmol), and the resulting mixture was stirred at room temperature for 90 min. The mixture was poured into water (2 ml) and extracted by ethyl acetate (2 x 2 ml), and the combined organic layers were concentrated and subjected to HPLC purification on a semi-prep C18 reverse-phased column using a gradient of 10-100% acetonitrile in 0.1% aq TFA. The trans-substituted pyrrolidine isomer was the first of 2 stereoisomers to elute, providing the title compound as a 1:1 mixture of diastereomers (0.014 gm, 29% yield): 1H NMR (TFA salt) (400 MHz, DMSO-D6) δ ppm 0.93 – 1.01 (m, *J*=4.99 Hz, 18 H) 1.62 – 1.68 (m, 2 H) 1.81 – 1.93 (m, 6 H) 1.94 – 2.04 (m, 2 H) 2.09 – 2.20 (m, 2 H) 3.54 (s, 6 H) 3.59 – 3.69 (m, 2 H) 3.73 – 3.81 (m, 2 H) 4.18 – 4.24 (m, 2 H) 4.43 (dd, *J*=7.81, 5.42 Hz, 2 H) 5.16 (d, 2 H) 6.20 (dd, *J*=9.05, 4.39 Hz, 2 H) 6.78 (t, *J*=8.89 Hz, 2 H) 7.09 (d, *J*=8.89 Hz, 2 H) 7.12 (d, 4 H) 7.50 (d, *J*=8.02 Hz, 4 H) 9.99 (s, 2 H). The title compound showed an EC_{50} value of less than about 0.1 nM in HCV 1b-Con1 replicon assays in the presence of 5% FBS. The 1b-Con1 replicon assay is described below.

Example 2

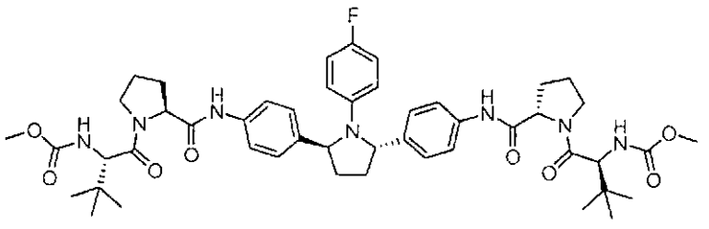
Dimethyl (2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-((2S,5R)-1-(4-fluorophenyl)pyrrolidine-2,5-diyl)bis(4,1-phenylene))bis(azanediyl)bis(oxomethylene)bis(pyrrolidine-2,1-diyl))bis(3,3-dimethyl-1-oxobutane-2,1-diyl)dicarbamate



To a mixture of the product from Example 1G (0.03 gm, 0.055 mmol), (S)-2-(methoxycarbonylamino)-3,3-dimethylbutanoic acid (0.0262 gm, 0.138 mmol) and HATU (0.0526 gm, 0.138 mmol) in DMSO (0.5 ml) was added Hunig's base (0.029 ml, 0.166 mmol), and the resulting mixture was stirred at room temperature for 90 min. The mixture was poured into water (2 ml) and extracted by ethyl acetate (2 x 2 ml), and the combined organic layers were concentrated and subjected to HPLC purification on a semi-prep C18 reverse-phased column using a gradient of 10-100% acetonitrile in 0.1% aq TFA. The cis-substituted pyrrolidine isomer was the second of 2 stereoisomers to elute, providing the title compound (0.018 gm, 37% yield): 1H NMR (TFA salt) (400 MHz, DMSO-D6) δ ppm 0.93 – 1.01 (m, *J*=3.04 Hz, 18 H) 1.75 – 1.94 (m, 6 H) 1.94 – 2.05 (m, 2 H) 2.11 – 2.22 (m, 2 H) 2.31 – 2.35 (m, 1 H) 3.54 (s, 6 H) 3.61 – 3.70 (m, 2 H) 3.74 – 3.83 (m, 2 H) 4.22 (d, *J*=8.78 Hz, 2 H) 4.46 (dd, *J*=8.02, 5.42 Hz, 2 H) 4.65 (t, 2 H) 6.34 (dd, 2 H) 6.86 (t, *J*=8.89 Hz, 2 H) 7.08 (d, 2 H) 7.43 (d, *J*=7.81 Hz, 4 H) 7.60 (d, *J*=8.57 Hz, 4 H) 10.05 (s, 2 H). The title compound showed an EC_{50} value of less than about 0.1 nM in HCV 1b-Con1 replicon assays in the presence of 5% FBS.

Example 3

Dimethyl (2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-((2S,5S)-1-(4-fluorophenyl)pyrrolidine-2,5-diyl)bis(4,1-phenylene))bis(azanediyl)bis(oxomethylene)bis(pyrrolidine-2,1-diyl))bis(3,3-dimethyl-1-oxobutane-2,1-diyl)dicarbamate

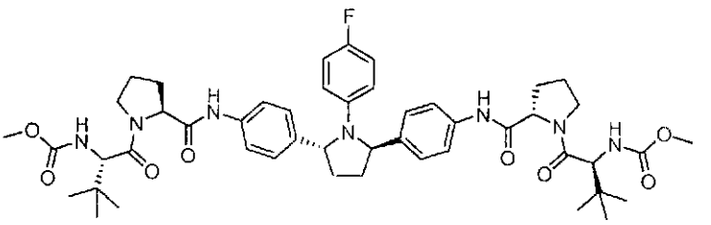


The product from Example 1H was purified by chiral chromatography on a Chiralpak AD-H semi-prep column eluting with a 1:1 mixture of hexanes:(2:1 IPA:EtOH). The title compound was the first of 2 stereoisomers to elute. 1H NMR (400 MHz, DMSO-D6) δ ppm 0.97 (s, 18 H) 1.61 – 1.67 (m, *J*=5.64 Hz, 2 H) 1.79 – 1.92 (m, 6 H) 1.93 – 2.04 (m, *J*=5.86 Hz, 2 H) 2.07 – 2.20 (m, *J*=6.51 Hz, 2 H) 3.54 (s, 6 H) 3.59 – 3.69 (m, 2 H) 3.71 – 3.83 (m, 2 H) 4.21 (d, *J*=8.89 Hz, 2 H) 4.43 (dd,

J=7.97, 5.37 Hz, 2 H) 5.15 (d, *J*=6.51 Hz, 2 H) 6.20 (dd, 2 H) 6.78 (t, *J*=8.95 Hz, 2 H) 7.13 (d, *J*=8.57 Hz, 4 H) 7.50 (d, *J*=8.57 Hz, 4 H) 9.99 (s, 2 H). The title compound showed an EC_{50} value of less than about 0.1 nM in HCV 1b-Con1 replicon assays in the presence of 5% FBS.

Example 4

Dimethyl (2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-((2R,5R)-1-(4-fluorophenyl)pyrrolidine-2,5-diyl)bis(4,1-phenylene))bis(azanediyl)bis(oxomethylene)bis(pyrrolidine-2,1-diyl))bis(3,3-dimethyl-1-oxobutane-2,1-diyl)dicarbamate



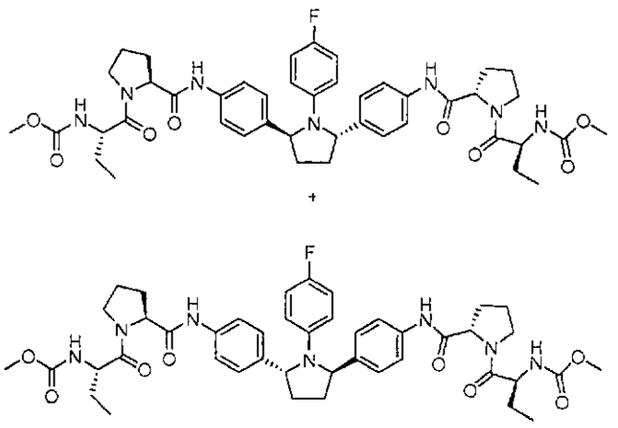
The product from Example 1H was separated by chiral chromatography on a Chiralpak AD-H semi-prep column eluting with a 1:1 mixture of hexanes:(2:1 IPA:EtOH). The title compound was the second of 2 stereoisomers to elute. 1H NMR (400 MHz, DMSO-D6) δ ppm 0.96 (s, 18 H) 1.64 (d, *J*=5.53 Hz, 2 H) 1.78 – 1.93 (m, 6 H) 1.94 – 2.06 (m, 2 H) 2.09 – 2.21 (m, 2 H) 3.54 (s, 6 H) 3.59 – 3.69 (m, 2 H) 3.72 – 3.83 (m, 2 H) 4.20 (d, *J*=8.89 Hz, 2 H) 4.43 (dd, *J*=7.92, 5.42 Hz, 2 H) 5.16 (d, *J*=6.29 Hz, 2 H) 6.20 (dd, *J*=9.16, 4.39 Hz, 2 H) 6.77 (t, *J*=8.95 Hz, 2 H) 7.12 (d, *J*=8.57 Hz, 4 H) 7.50 (d, *J*=8.57 Hz, 4 H) 9.99 (s, 2 H). The title compound showed an EC_{50} value of less than about 0.1 nM in HCV 1b-Con1 replicon assays in the presence of 5% FBS.

Example 5

Dimethyl (2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-((2S,5S)-1-(4-fluorophenyl)pyrrolidine-2,5-diyl)bis(4,1-phenylene))bis(azanediyl)bis(oxomethylene)bis(pyrrolidine-2,1-diyl))bis(1-oxobutane-2,1-diyl)dicarbamate

and

Dimethyl (2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-((2R,5R)-1-(4-fluorophenyl)pyrrolidine-2,5-diyl)bis(4,1-phenylene))bis(azanediyl)bis(oxomethylene)bis(pyrrolidine-2,1-diyl))bis(1-oxobutane-2,1-diyl)dicarbamate



Example 5A

4,4'-((2S,5S)-1-(4-Fluorophenyl)pyrrolidine-2,5-diyl)dianiline and 4,4'-((2R,5R)-1-(4-Fluorophenyl)pyrrolidine-2,5-diyl)dianiline

The product from Example 1E was purified by column chromatography on silica gel, eluting with a solvent gradient of 0-100% ethyl acetate in hexanes. The title compound eluted as the first of 2 stereoisomers and was obtained as a racemic mixture of trans diastereomers. 1H NMR (400 MHz, DMSO-D6) δ ppm 1.57 (d, *J*=5.64 Hz, 2 H) 2.36 - 2.42 (m, 2 H) 4.86 - 4.91 (m, 4 H) 4.96 (d, *J*=6.61 Hz, 2 H) 6.17 - 6.25 (m, 2 H) 6.47 (d, *J*=8.35 Hz, 4 H) 6.74 (t, 2 H) 6.82 (d, *J*=8.35 Hz, 4 H).

Example 5B

(2S,2'S)-tert-Butyl 2,2'-(4,4'-((2S,5S)-1-(4-fluorophenyl)pyrrolidine-2,5-diyl)bis(4,1-phenylene))bis(azanediyl)bis(oxomethylene)dipyrrolidine-1-carboxylate and (2S,2'S)-tert-Butyl 2,2'-(4,4'-((2R,5R)-1-(4-fluorophenyl)pyrrolidine-2,5-diyl)bis(4,1-phenylene))bis(azanediyl)bis(oxomethylene)dipyrrolidine-1-carboxylate

The product from Example 5A (50 mg, 0.144 mmol) was subjected to the conditions described in Example 1F to give the title compound as a 1:1 mixture of diastereomers (105 mg, 98%): 1H NMR (400 MHz, DMSO-D6) δ ppm 1.34 (d, 18 H) 1.66 (d, *J*=5.10 Hz, 2 H) 1.74 - 1.89 (m, 6 H) 2.07 - 2.23 (m, 2 H) 4.15 - 4.25 (m, 2 H) 5.18 (d, *J*=3.47 Hz, 2 H) 6.18 - 6.25 (m, 2 H) 6.78 (t, *J*=8.95 Hz, 2 H) 7.14 (d, *J*=8.24 Hz, 4 H) 7.51 (t, *J*=8.29 Hz, 4 H) 9.92 (d, 2 H).

Example 5C

(2S,2'S)-N,N'-(4,4'-((2S,5S)-1-(4-Fluorophenyl)pyrrolidine-2,5-diyl)bis(4,1-phenylene))dipyrrolidine-2-carboxamide and (2S,2'S)-N,N'-(4,4'-((2R,5R)-1-(4-Fluorophenyl)pyrrolidine-2,5-diyl)bis(4,1-phenylene))dipyrrolidine-2-carboxamide

The product from Example 5B was subjected to the conditions described in Example 1G to give the title compound as a 1:1 mixture of diastereomers.

Example 5D

Dimethyl (2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-((2S,5S)-1-(4-fluorophenyl)pyrrolidine-2,5-diyl)bis(4,1-phenylene))bis(azanediyl)bis(oxomethylene)bis(pyrrolidine-2,1-diyl))bis(1-oxobutane-2,1-diyl)dicarbamate and Dimethyl (2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-((2R,5R)-1-(4-fluorophenyl)pyrrolidine-2,5-diyl)bis(4,1-phenylene))bis(azanediyl)bis(oxomethylene)bis(pyrrolidine-2,1-diyl))bis(1-oxobutane-2,1-diyl)dicarbamate

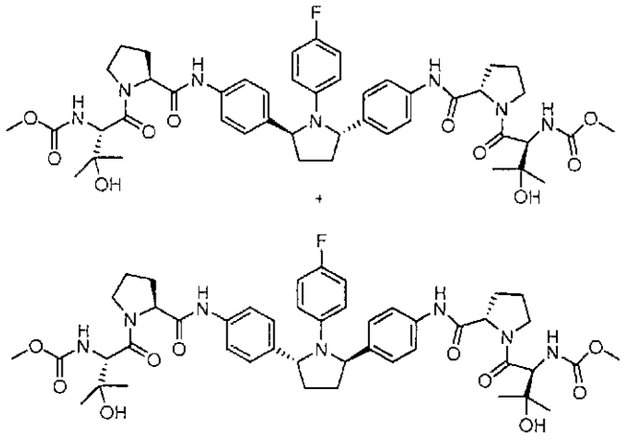
To a mixture of the product from Example 5C (0.102 g, 0.188 mmol), (S)-2-(methoxycarbonyl amino)butanoic acid (0.064 g, 0.395 mmol) and HATU (0.150 g, 0.395 mmol) in DMSO (2 ml) was added Hunig's base (0.099 ml, 0.565 mmol), and the reaction was stirred at room temperature for 45 min. The reaction mixture was partitioned between water and ethyl acetate, and the organic layer was dried over Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by column chromatography on silica gel using a solvent gradient of 0-4% MeOH in dichloromethane to give the title compound as a 1:1 mixture of stereoisomers (0.158 gm, 94% yield): 1H NMR (400 MHz, DMSO-D6) δ ppm 0.86 - 0.96 (m, 6 H) 1.53 (d, *J*=4.34 Hz, 2 H) 1.59 - 1.73 (m, 2 H) 1.80 - 1.96 (m, *J*=6.29 Hz, 4 H) 1.96 - 2.06 (m, 2 H) 2.08 - 2.20 (m, 2 H) 3.52 (s, 6 H) 3.67 - 3.79 (m, 2 H) 4.12 - 4.23 (m, 2 H) 4.42 (dd, *J*=8.13, 4.66 Hz, 2 H) 5.16 (d, *J*=6.40 Hz, 2 H) 6.20 (dd, *J*=9.22, 4.45 Hz, 2 H) 6.77 (t, *J*=8.89 Hz, 2 H) 7.12 (d, *J*=7.59 Hz, 4 H) 7.30 (dd, *J*=7.59, 3.25 Hz, 2 H) 7.50 (d, *J*=8.24 Hz, 4 H) 8.16 (s, 2 H) 9.95 (s, 2 H). The title compound showed an EC_{50} value of from about 0.1 to about 1 nM in HCV 1b-Con1 replicon assays in the presence of 5% FBS.

Example 6

Dimethyl (2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-((2S,5S)-1-(4-fluorophenyl)pyrrolidine-2,5-diyl)bis(4,1-phenylene))bis(azanediyl)bis(oxomethylene)bis(pyrrolidine-2,1-diyl))bis(3-hydroxy-3-methyl-1-oxobutane-2,1-diyl)dicarbamate

and

Dimethyl (2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-((2R,5R)-1-(4-fluorophenyl)pyrrolidine-2,5-diyl)bis(4,1-phenylene))bis(azanediyl)bis(oxomethylene)bis(pyrrolidine-2,1-diyl))bis(3-hydroxy-3-methyl-1-oxobutane-2,1-diyl)dicarbamate



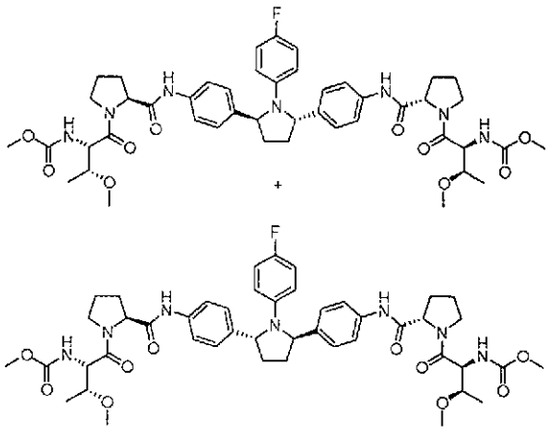
To a mixture of the product from Example 5C (0.1 g, 0.185 mmol), (S)-3-hydroxy-2-(methoxycarbonyl amino)-3-methylbutanoic acid (0.074 g, 0.388 mmol) and HATU (0.147 g, 0.388 mmol) in DMSO (2 ml) was added Hunig's base (0.097 ml, 0.554 mmol), and the reaction mixture was stirred at room temperature for 45 min. The reaction mixture was partitioned between water and ethyl acetate, and the organic layer was dried over Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by column chromatography on silica gel using a solvent gradient of 0-4% MeOH in dichloromethane to give the title compound as a 1:1 mixture of stereoisomers (0.162 gm, 97% yield): ^{1}H NMR (400 MHz, DMSO-D6) δ ppm 1.15 (d, *J*=10.19 Hz, 12 H) 1.64 (d, *J*=5.64 Hz, 2 H) 1.87 - 1.98 (m, 6 H) 2.09 – 2.22 (m, 2 H) 3.55 (s, 6 H) 3.58 – 3.66 (m, 2 H) 3.66 – 3.74 (m, 2 H) 3.83 – 3.92 (m, 2 H) 4.37 (s, 2 H) 4.44 – 4.50 (m, 2 H) 5.07 (s, 2 H) 5.11 (s, 2 H) 5.17 (d, *J*=6.18 Hz, 2 H) 6.15 – 6.28 (m, 2 H) 6.78 (t, *J*=8.89 Hz, 2 H) 7.13 (d, *J*=8.13 Hz, 4 H) 7.51 (d, *J*=7.81 Hz, 4 H) 8.11 – 8.23 (m, 2 H) 9.67 (d, *J*=9.11 Hz, 2 H). The title compound showed an EC_{50} value of less than about 0.1 nM in HCV 1b-Con1 replicon assays in the presence of 5% FBS.

Example 7

Dimethyl (2S,2'S,3R,3'R)-1,1'-((2S,2'S)-2,2'-(4,4'-((2S,5S)-1-(4-fluorophenyl)pyrrolidine-2,5-diyl)bis(4,1-phenylene))bis(azanediyl)bis(oxomethylene)bis(pyrrolidine-2,1-diyl))bis(3-methoxy-1-oxobutane-2,1-diyl)dicarbamate

and

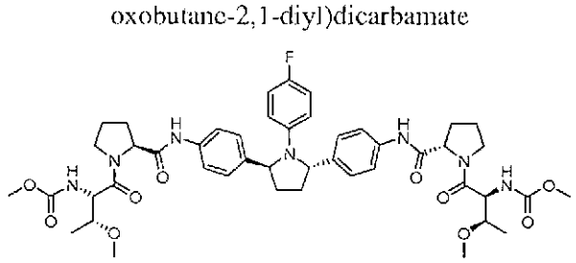
Dimethyl (2S,2'S,3R,3'R)-1,1'-((2S,2'S)-2,2'-(4,4'-((2R,5R)-1-(4-fluorophenyl)pyrrolidine-2,5-diyl)bis(4,1-phenylene))bis(azanediyl)bis(oxomethylene)bis(pyrrolidine-2,1-diyl))bis(3-methoxy-1-oxobutane-2,1-diyl)dicarbamate



To a mixture of the product from Example 5C (0.025 gm, 0.046 mmol), (2S,3R)-3-methoxy-2-(methoxycarbonylamino)butanoic acid (0.01941 gm, 0.102 mmol) and HATU (0.0439 gm, 0.115 mmol) in DMSO (0.2 ml) was added Hunig's base (0.024 ml, 0.138 mmol). The mixture was stirred at room temperature for 2 hr, and was then poured into water and extracted with ethyl acetate. The organic phase was dried over Na_2SO_4, filtered and concentrated in vacu, and the crude product was purified by chromatography on silica gel using a solvent gradient of 0-5%MeOH in CH_2Cl_2 to give the title compound (0.040 gm, 93% yield): ^{1}H NMR (400 MHz, DMSO-D6) δ ppm 1.09 - 1.31 (m, 6 H) 1.64 (d, *J*=5.10 Hz, 2 H) 1.83 - 1.93 (m, *J*=12.42, 12.42 Hz, 4 H) 1.93 - 2.03 (m, 2 H) 2.11 - 2.19 (m, 2 H) 3.10 - 3.18 (m, *J*=6.94 Hz, 2 H) 3.24 (d, *J*=4.99 Hz, 6 H) 3.42 - 3.49 (m, *J*=10.84, 6.72 Hz, 2 H) 3.53 (s, 6 H) 3.58 - 3.70 (m, 2 H) 3.79 - 3.89 (m, 2 H) 4.26 (t, *J*=7.10 Hz, 2 H) 4.41 (dd, *J*=7.97, 4.93 Hz, 2 H) 5.16 (d, *J*=6.29 Hz, 2 H) 6.20 (dd, *J*=9.11, 4.34 Hz, 2 H) 6.78 (t, *J*=8.95 Hz, 2 H) 7.12 (d, 4 H) 7.33 (dd, *J*=7.70, 3.47 Hz, 2 H) 7.50 (d, *J*=8.13 Hz, 4 H) 9.95 (s, 2 H). The title compound showed an EC_{50} value of from about 0.1 to about 1 nM in HCV 1b-Con1 replicon assays in the presence of 5% FBS.

Example 8

dimethyl (2S,2'S,3R,3'R)-1,1'-((2S,2'S)-2,2'-(4,4'-((2S,5S)-1-(4-fluorophenyl)pyrrolidine-2,5-diyl)bis(4,1-phenylene))bis(azanediyl)bis(oxomethylene)bis(pyrrolidine-2,1-diyl))bis(3-methoxy-1-oxobutane-2,1-diyl)dicarbamate

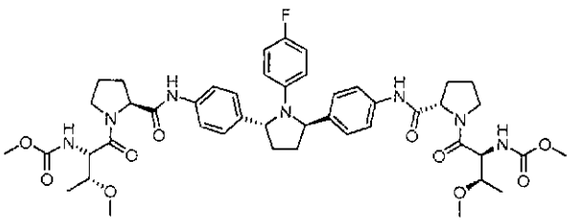


The product from Example 7 was purified by chiral chromatography on a Chiralpak AD-H semi-prep column eluting with a 1:3 mixture of hexanes:(1:1 IPA:EtOH). The title compound was the

first of 2 stereoisomers to elute. 1H NMR (400 MHz, DMSO-D6) δ ppm 1.13 (d, *J*=6.18 Hz, 6 H) 1.64 (d, *J*=5.64 Hz, 2 H) 1.82 - 1.93 (m, 4 H) 1.95 - 2.04 (m, 2 H) 2.10 - 2.19 (m, 2 H) 3.25 (s, 6 H) 3.44 - 3.48 (m, 2 H) 3.53 (s, 6 H) 3.62 - 3.71 (m, 2 H) 3.79 - 3.87 (m, 2 H) 4.26 (t, *J*=7.75 Hz, 2 H) 4.41 (dd, *J*=7.92, 4.99 Hz, 2 H) 5.16 (d, *J*=6.51 Hz, 2 H) 6.20 (dd, *J*=9.16, 4.39 Hz, 2 H) 6.78 (t, *J*=8.89 Hz, 2 H) 7.13 (d, *J*=8.57 Hz, 4 H) 7.34 (d, *J*=7.92 Hz, 2 H) 7.50 (d, *J*=8.57 Hz, 4 H) 9.95 (s, 2 H). The title compound showed an EC_{50} value of less than about 0.1 nM in HCV 1b-Con1 replicon assays in the presence of 5% FBS.

Example 9

dimethyl (2S,2'S,3R,3'R)-1,1'-((2S,2'S)-2,2'-(4,4'-((2R,5R)-1-(4-fluorophenyl)pyrrolidine-2,5-diyl)bis(4,1-phenylene))bis(azanediyl)bis(oxomethylene)bis(pyrrolidine-2,1-diyl))bis(3-methoxy-1-oxobutane-2,1-diyl)dicarbamate



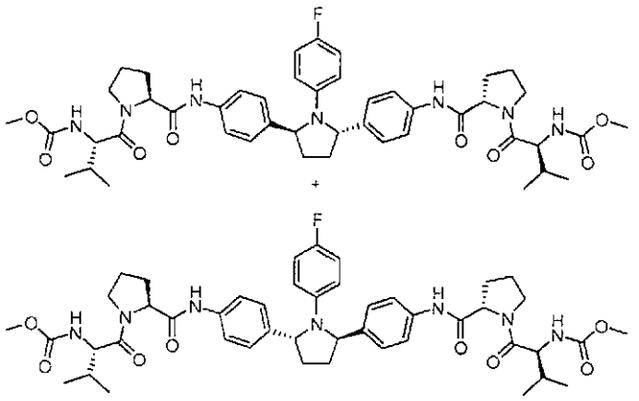
The product from Example 7 was purified by chiral chromatography on a Chiralpak AD-H semi-prep column eluting with a 1:3 mixture of hexanes:(1:1 IPA:EtOH). The title compound was the second of 2 stereoisomers to elute. 1H NMR (400 MHz, DMSO-D6) δ ppm 1.12 (d, *J*=6.18 Hz, 6 H) 1.64 (d, *J*=5.64 Hz, 2 H) 1.82 - 1.93 (m, 4 H) 1.95 - 2.06 (m, 2 H) 2.10 - 2.21 (m, 2 H) 3.24 (s, 6 H) 3.42 - 3.48 (m, 2 H) 3.53 (s, 6 H) 3.61 - 3.73 (m, 2 H) 3.78 - 3.88 (m, 2 H) 4.26 (t, *J*=7.75 Hz, 2 H) 4.41 (dd, *J*=7.92, 4.99 Hz, 2 H) 5.16 (d, *J*=6.18 Hz, 2 H) 6.20 (dd, 2 H) 6.78 (t, *J*=8.89 Hz, 2 H) 7.13 (d, *J*=8.46 Hz, 4 H) 7.33 (d, *J*=7.81 Hz, 2 H) 7.49 (d, *J*=8.46 Hz, 4 H) 9.95 (s, 2 H). The title compound showed an EC_{50} value of from about 0.1 to about 1 nM in HCV 1b-Con1 replicon assays in the presence of 5% FBS.

Example 10

Dimethyl (2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-((2S,5S)-1-(4-fluorophenyl)pyrrolidine-2,5-diyl)bis(4,1-phenylene))bis(azanediyl)bis(oxomethylene)bis(pyrrolidine-2,1-diyl))bis(3-methyl-1-oxobutane-2,1-diyl)dicarbamate

and

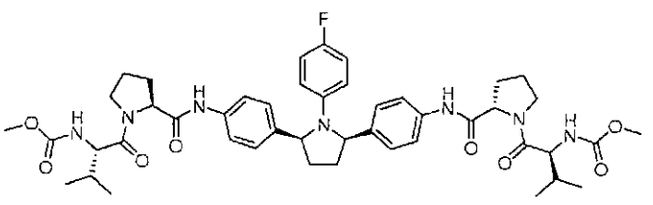
Dimethyl (2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-((2R,5R)-1-(4-fluorophenyl)pyrrolidine-2,5-diyl)bis(4,1-phenylene))bis(azanediyl)bis(oxomethylene)bis(pyrrolidine-2,1-diyl))bis(3-methyl-1-oxobutane-2,1-diyl)dicarbamate



To a mixture of the product from Example 1G (0.030 g, 0.055 mmol), (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (0.024 g, 0.14 mmol) and HATU (0.052 g, 0.14 mmol) in DMSO (0.3 ml) was added Hunig's base (0.024 ml, 0.166 mmol), and the resulting mixture was stirred at room temperature for 90 min. The mixture was partitioned between water and ethyl acetate, and the organic layer was concentrated and subjected to HPLC purification on a semi-prep C18 reverse-phased column using a gradient of 10-100% acetonitrile in 0.1% aq TFA. The trans-substituted pyrrolidine isomer was the first of 2 stereoisomers to elute, providing the title compound as a 1:1 mixture of diastereomers (9 mg, 16%): 1H NMR (TFA salt) (400 MHz, DMSO-D6) δ ppm 0.85 - 0.96 (m, 12 H) 1.64 (d, *J*=5.75 Hz, 2 H) 1.82 - 1.92 (m, 6 H) 1.95 - 2.06 (m, 2 H) 2.08 - 2.20 (m, 2 H) 3.52 (s, 6 H) 3.57 - 3.68 (m, 2 H) 3.74 - 3.86 (m, *J*=5.86 Hz, 2 H) 4.02 (t, *J*=8.35 Hz, 2 H) 4.42 (dd, *J*=7.92, 4.88 Hz, 2 H) 5.16 (d, *J*=6.18 Hz, 2 H) 6.20 (dd, *J*=9.16, 4.39 Hz, 2 H) 6.77 (t, *J*=8.89 Hz, 2 H) 7.12 (dd, *J*=8.51, 1.68 Hz, 4 H) 7.31 (dd, *J*=8.24, 3.36 Hz, 2 H) 7.50 (d, *J*=7.26 Hz, 4 H) 9.99 (s, 2 H). The title compound showed an EC_{50} value of less than about 0.1 nM in HCV 1b-Con1 replicon assays in the presence of 5% FBS.

Example 11

Dimethyl (2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-((2S,5R)-1-(4-fluorophenyl)pyrrolidine-2,5-diyl)bis(4,1-phenylene))bis(azanediyl)bis(oxomethylene)bis(pyrrolidine-2,1-diyl))bis(3-methyl-1-oxobutane-2,1-diyl)dicarbamate

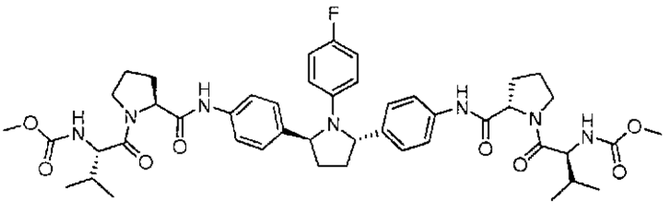


To a mixture of the product from Example 1G (0.030 g, 0.055 mmol), (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (0.024 g, 0.14 mmol) and HATU (0.052 g, 0.14 mmol) in DMSO (0.3 ml) was added Hunig's base (0.024 ml, 0.166 mmol), and the resulting mixture

was stirred at room temperature for 90 min. The mixture was partitioned between water and ethyl acetate, and the organic layer was concentrated and subjected to HPLC purification on a semi-prep C18 reverse-phased column using a gradient of 10-100% acetonitrile in 0.1% aq TFA. The cis-substituted pyrrolidine isomer was the second of 2 stereoisomers to elute, providing the title compound (11 mg, 20%): 1H NMR (TFA salt) (400 MHz, DMSO-D6) δ ppm 9.35 (s, 2 H) 8.26 (s, 2 H) 7.77 - 7.83 (m, 4 H) 7.68 - 7.73 (m, 4 H) 7.01 (t, *J*=8.95 Hz, 2 H) 6.61 - 6.71 (m, 2 H) 6.23 (d, *J*=8.35 Hz, 2 H) 4.87 - 4.97 (m, 2 H) 4.67 - 4.78 (m, 2 H) 4.42 - 4.52 (m, 2 H) 3.99 - 4.09 (m, 2 H) 3.87 - 3.97 (m, 2 H) 3.84 (s, 6 H) 1.22 (dd, *J*=6.78, 2.11 Hz, 6 H) 1.15 (dd, *J*=6.72, 2.06 Hz, 6 H). The title compound showed an EC_{50} value of less than about 0.1 nM in HCV 1b-Con1 replicon assays in the presence of 5% FBS.

Example 12

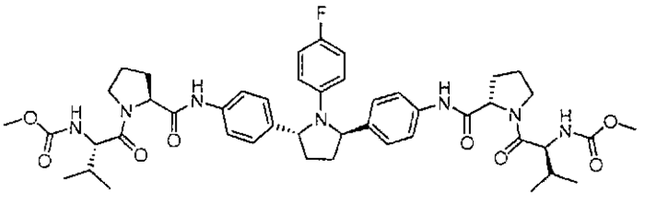
Dimethyl (2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-((2S,5S)-1-(4-fluorophenyl)pyrrolidine-2,5-diyl)bis(4,1-phenylene))bis(azanediyl)bis(oxomethylene)bis(pyrrolidine-2,1-diyl))bis(3-methyl-1-oxobutane-2,1-diyl)dicarbamate



The product from Example 10 was separated by chiral chromatography on a Chiralpak AD-H semi-prep column eluting with a 1:1 mixture of hexanes:(2:1 2-PrOH:EtOH). The title compound eluted as the first of 2 stereoisomers. 1H NMR (400 MHz, DMSO-D6) δ ppm 0.84 – 0.97 (m, 12 H) 1.64 (d, *J*=5.64 Hz, 2 H) 1.88 (s, 6 H) 1.95 – 2.05 (m, 2 H) 2.08 – 2.19 (m, 2 H) 3.52 (s, 6 H) 3.58 – 3.66 (m, 2 H) 3.76 – 3.85 (m, 2 H) 4.02 (t, *J*=8.51 Hz, 2 H) 4.42 (dd, *J*=8.02, 4.88 Hz, 2 H) 5.15 (d, *J*=6.51 Hz, 2 H) 6.20 (dd, *J*=9.16, 4.39 Hz, 2 H) 6.78 (t, *J*=8.89 Hz, 2 H) 7.13 (d, *J*=8.46 Hz, 4 H) 7.31 (d, *J*=8.35 Hz, 2 H) 7.50 (d, *J*=8.46 Hz, 4 H) 9.99 (s, 2 H). The title compound showed an EC_{50} value of less than about 0.1 nM in HCV 1b-Con1 replicon assays in the presence of 5% FBS.

Example 13

Dimethyl (2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-((2R,5R)-1-(4-fluorophenyl)pyrrolidine-2,5-diyl)bis(4,1-phenylene))bis(azanediyl)bis(oxomethylene)bis(pyrrolidine-2,1-diyl))bis(3-methyl-1-oxobutane-2,1-diyl)dicarbamate



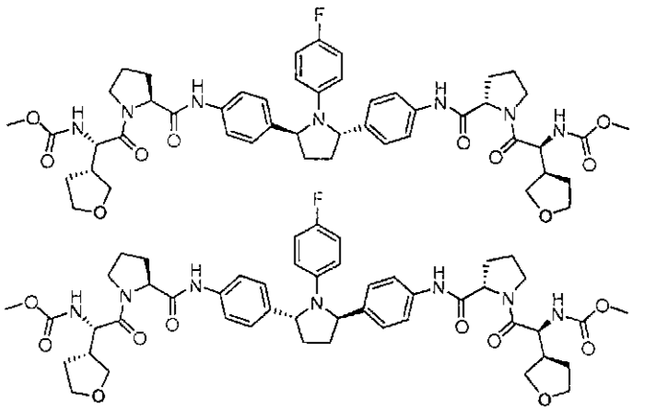
The product from Example 10 was separated by chiral chromatography on a Chiralpak AD-H semi-prep column eluting with a 1:1 mixture of hexanes:(2:1 2-PrOH:EtOH). The title compound eluted as the second of 2 stereoisomers. 1H NMR (400 MHz, DMSO-D6) δ ppm 0.82 – 0.97 (m, 12 H) 1.65 (d, 2 H) 1.80 – 2.05 (m, 8 H) 2.08 – 2.20 (m, 2 H) 3.52 (s, 6 H) 3.57 – 3.68 (m, 2 H) 3.76 – 3.87 (m, 2 H) 4.01 (t, 2 H) 4.42 (dd, 2 H) 5.16 (d, *J*=6.40 Hz, 2 H) 6.20 (dd, *J*=9.22, 4.45 Hz, 2 H) 6.77 (t, *J*=8.95 Hz, 2 H) 7.12 (d, *J*=8.57 Hz, 4 H) 7.30 (d, *J*=8.35 Hz, 2 H) 7.50 (d, *J*=8.46 Hz, 4 H) 9.98 (s, 2 H). The title compound showed an EC_{50} value of less than about 0.1 nM in HCV 1b-Con1 replicon assays in the presence of 5% FBS.

Example 14

Dimethyl (1S,1'S)-2,2'-((2S,2'S)-2,2'-(4,4'-((2S,5S)-1-(4-fluorophenyl)pyrrolidine-2,5-diyl)bis(4,1-phenylene))bis(azanediyl)bis(oxomethylene)bis(pyrrolidine-2,1-diyl))bis(2-oxo-1-((R)-tetrahydrofuran-3-yl)ethane-2,1-diyl)dicarbamate

and

Dimethyl (1S,1'S)-2,2'-((2S,2'S)-2,2'-(4,4'-((2R,5R)-1-(4-fluorophenyl)pyrrolidine-2,5-diyl)bis(4,1-phenylene))bis(azanediyl)bis(oxomethylene)bis(pyrrolidine-2,1-diyl))bis(2-oxo-1-((R)-tetrahydrofuran-3-yl)ethane-2,1-diyl)dicarbamate

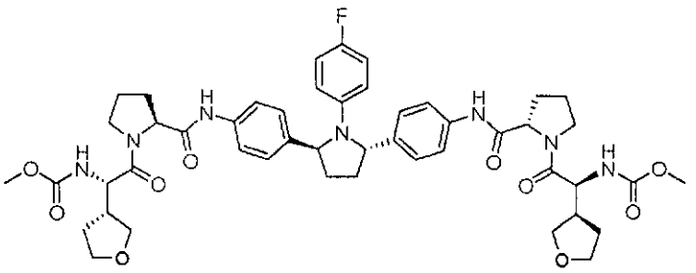


To a mixture of the product from Example 5C (0.013 g, 0.024 mmol), HATU (0.02275 gm, 0.060 mmol), and (S)-2-(methoxycarbonylamino)-2-((R)-tetrahydrofuran-3-yl)acetic acid (0.0107 gm, 0.053 mmol) in DMSO (0.200 ml) was added Hunig's Base (0.013 ml, 0.072 mmol). The reaction was stirred at room temperature for 2 hr, poured into water, and extracted with ethyl acetate. The organic extract was dried over Na_2SO_4, filtered and concentrated in vacuo, and the crude material was

purified on a semi-prep C18 reverse-phased column using a gradient of 10-100% acetonitrile in 0.1% aq TFA to give the title compound (6.9 mg, 28% yield): 1H NMR (TFA salt) (400 MHz, DMSO-D6) δ ppm 1.61 - 1.77 (m, 4 H) 1.80 - 1.94 (m, 6 H) 1.93 - 2.06 (m, 2 H) 2.08 - 2.21 (m, 2 H) 3.44 (dd, *J*=8.46, 6.29 Hz, 2 H) 3.53 (s, 6 H) 3.56 - 3.68 (m, 8 H) 3.68 - 3.77 (m, 2 H) 3.80 - 3.90 (m, 2 H) 4.23 (t, *J*=8.84 Hz, 2 H) 4.43 (dd, *J*=8.02, 4.77 Hz, 2 H) 5.16 (d, *J*=6.29 Hz, 2 H) 6.20 (dd, *J*=9.11, 4.45 Hz, 2 H) 6.77 (t, *J*=8.95 Hz, 2 H) 7.13 (d, *J*=8.57 Hz, 4 H) 7.50 (d, *J*=8.57 Hz, 4 H) 7.60 (d, *J*=7.92 Hz, 2 H) 9.98 (s, 2 H). The title compound showed an EC_{50} value of from about 0.1 to about 1 nM in HCV 1b-Con1 replicon assays in the presence of 5% FBS.

Example 15

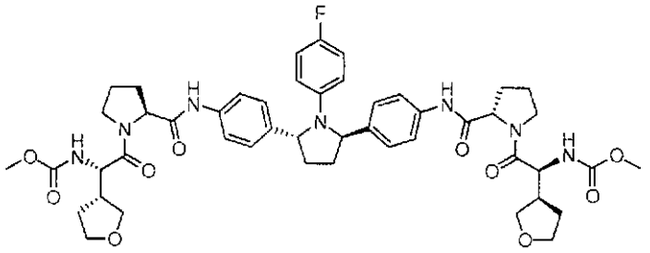
Dimethyl (1S,1'S)-2,2'-((2S,2'S)-2,2'-(4,4'-((2S,5S)-1-(4-fluorophenyl)pyrrolidine-2,5-diyl)bis(4,1-phenylene))bis(azanediyl)bis(oxomethylene)bis(pyrrolidine-2,1-diyl))bis(2-oxo-1-((R)-tetrahydrofuran-3-yl)ethane-2,1-diyl)dicarbamate



The product from Example 14 was separated by chiral chromatography on a Chiralpak AD-H semi-prep column eluting with a 2:3 mixture of hexanes:(1:1 2-PrOH:EtOH). The title compound eluted as the first of 2 stereoisomers. 1H NMR (400 MHz, DMSO-D6) δ ppm 1.59 - 1.78 (m, 4 H) 1.79 - 1.94 (m, 6 H) 1.94 - 2.05 (m, 2 H) 2.09 - 2.23 (m, *J*=5.10 Hz, 2 H) 3.44 (dd, *J*=8.35, 6.40 Hz, 2 H) 3.53 (s, 6 H) 3.57 - 3.73 (m, 8 H) 3.71 - 3.80 (m, 2 H) 3.81 - 3.89 (m, 2 H) 4.23 (t, *J*=8.78 Hz, 2 H) 4.43 (dd, *J*=7.97, 4.83 Hz, 2 H) 5.16 (d, *J*=6.07 Hz, 2 H) 6.16 - 6.24 (m, 2 H) 6.78 (t, *J*=8.89 Hz, 2 H) 7.13 (d, *J*=8.57 Hz, 4 H) 7.50 (d, *J*=8.46 Hz, 4 H) 7.60 (d, *J*=8.02 Hz, 2 H) 9.98 (s, 2 H). The title compound showed an EC_{50} value of less than about 0.1 nM in HCV 1b-Con1 replicon assays in the presence of 5% FBS.

Example 16

Dimethyl (1S,1'S)-2,2'-((2S,2'S)-2,2'-(4,4'-((2R,5R)-1-(4-fluorophenyl)pyrrolidine-2,5-diyl)bis(4,1-phenylene))bis(azanediyl)bis(oxomethylene)bis(pyrrolidine-2,1-diyl))bis(2-oxo-1-((R)-tetrahydrofuran-3-yl)ethane-2,1-diyl)dicarbamate

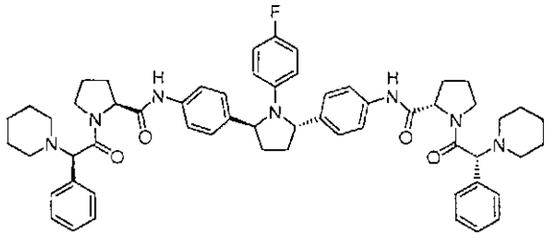


The product from Example 14 was separated by chiral chromatography on a Chiralpak AD-H semi-prep column eluting with a 2:3 mixture of hexanes:(1:1 2-PrOH:EtOH). The title compound eluted as the second of 2 stereoisomers. 1H NMR (400 MHz, DMSO-D6) δ ppm 1.61 - 1.77 (m, 4 H) 1.80 - 1.94 (m, 6 H) 1.93 - 2.06 (m, 2 H) 2.08 - 2.21 (m, 2 H) 3.44 (dd, *J*=8.46, 6.29 Hz, 2 H) 3.53 (s, 6 H) 3.56 - 3.68 (m, 8 H) 3.68 - 3.77 (m, 2 H) 3.80 - 3.90 (m, 2 H) 4.23 (t, *J*=8.84 Hz, 2 H) 4.43 (dd, *J*=8.02, 4.77 Hz, 2 H) 5.16 (d, *J*=6.29 Hz, 2 H) 6.20 (dd, *J*=9.11, 4.45 Hz, 2 H) 6.77 (t, *J*=8.95 Hz, 2 H) 7.13 (d, *J*=8.57 Hz, 4 H) 7.50 (d, *J*=8.57 Hz, 4 H) 7.60 (d, *J*=7.92 Hz, 2 H) 9.98 (s, 2 H). The title compound showed an EC_{50} value of from about 0.1 to about 1 nM in HCV 1b-Con1 replicon assays in the presence of 5% FBS.

Example 17

(R,2S,2'S)-N,N'-(4,4'-((2S,5S)-1-(4-Fluorophenyl)pyrrolidine-2,5-diyl)bis(4,1-phenylene))bis(1-((R)-2-phenyl-2-(piperidin-1-yl)acetyl)pyrrolidine-2-carboxamide) and

(R,2S,2'S)-N,N'-(4,4'-((2R,5R)-1-(4-Fluorophenyl)pyrrolidine-2,5-diyl)bis(4,1-phenylene))bis(1-((R)-2-phenyl-2-(piperidin-1-yl)acetyl)pyrrolidine-2-carboxamide)

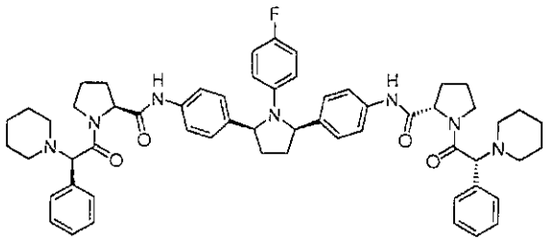


To a mixture of (R)-2-phenyl-2-(piperidin-1-yl)acetic acid TFA salt (0.0455 mg, 0.137 mmol), the product from Example 1G (0.030 gm, 0.055 mmol), and HATU (0.0526 gm, 0.138 mmol) in DMSO (0.300 ml) was added Hunig's base (0.029.0 ml, 0.166 mmol), and the resulting mixture was stirred at rt for 2 hr. The mixture was partitioned between water and ethyl acetate, the organic layer was dried over Na_2SO_4, filtered and concentrated in vacuo. The crude product was subjected to HPLC purification on a semi-prep C18 reverse-phased column using a gradient of 10-100% acetonitrile in 0.1% aq TFA (8.3 mg, 11%): 1H NMR (TFA salt) (400 MHz, DMSO-D6) δ ppm 1.20 - 1.42 (m, 4 H) 1.61 - 2.02 (m, 16 H) 2.62 - 2.81 (m, 4 H) 3.01 - 3.23 (m, *J*=9.32 Hz, 4 H) 3.87 - 3.98

(m, 2 H) 4.40 - 4.47 (m, *J*=8.24 Hz, 2 H) 5.14 - 5.24 (m, 2 H) 5.50 (d, *J*=8.78 Hz, 2 H) 6.23 (dd, *J*=8.89, 4.34 Hz, 2 H) 6.75 - 6.84 (m, 2 H) 7.16 (d, *J*=7.81 Hz, 4 H) 7.48 - 7.59 (m, 12 H) 7.62 (d, *J*=3.69 Hz, 4 H) 9.89 (s, 2 H) 10.17 (s, 2 H). The title compound showed an EC_{50} value of from about 0.1 to about 1 nM in HCV 1b-Con1 replicon assays in the presence of 5% FBS.

Example 18

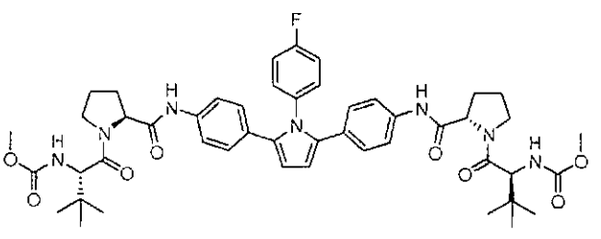
(R,2S,2'S)-N,N'-(4,4'-((2S,5R)-1-(4-fluorophenyl)pyrrolidine-2,5-diyl)bis(4,1-phenylene))bis(1-((R)-2-phenyl-2-(piperidin-1-yl)acetyl)pyrrolidine-2-carboxamide)



To a mixture of (R)-2-phenyl-2-(piperidin-1-yl)acetic acid TFA salt (0.0455 mg, 0.137 mmol), the product from Example 1G (0.030 gm, 0.055 mmol), and HATU (0.0526 gm, 0.138 mmol) in DMSO (0.300 ml) was added Hunig's base (0.029.0 ml, 0.166 mmol), and the resulting mixture was stirred at rt for 2 hr. The mixture was partitioned between water and ethyl acetate, the organic layer was dried over Na_2SO_4, filtered and concentrated in vacuo. The crude product was subjected to HPLC purification on a semi-prep C18 reverse-phased column using a gradient of 10-100% acetonitrile in 0.1% aq TFA (8.7 mg, 12%): 1H NMR (TFA salt) (400 MHz, DMSO-D6) δ ppm 1.22 - 1.43 (m, 4 H) 1.62 - 2.03 (m, *J*=80.02 Hz, 16 H) 2.08 - 2.18 (m, 2 H) 2.62 - 2.85 (m, 4 H) 3.04 - 3.24 (m, 4 H) 3.88 - 3.99 (m, 2 H) 4.41 - 4.52 (m, 2 H) 4.64 - 4.72 (m, 2 H) 5.52 (d, *J*=8.24 Hz, 2 H) 6.36 (dd, *J*=9.05, 4.50 Hz, 2 H) 6.88 (t, *J*=8.89 Hz, 2 H) 7.41 - 7.68 (m, 18 H) 9.89 (s, 2 H) 10.23 (s, 2 H). The title compound showed an EC_{50} value of less than about 0.1 nM in HCV 1b-Con1 replicon assays in the presence of 5% FBS.

Example 19

Dimethyl (2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-(1-(4-fluorophenyl)-1H-pyrrole-2,5-diyl)bis(4,1-phenylene))bis(azanediyl)bis(oxomethylene)bis(pyrrolidine-2,1-diyl))bis(3,3-dimethyl-1-oxobutane-2,1-diyl)dicarbamate



Example 19A

1-(4-Fluorophenyl)-2,5-bis(4-nitrophenyl)-1H-pyrrole

To a slurry of the product from Example 1A (1.5 g, 4.57 mmol) in acetic acid (22.85 mL) was added 4-fluoroaniline (4.33 ml, 45.7 mmol). The mixture was heated to 70 °C for 24 h. After cooling to rt the mixture was diluted with water and ether and stirred vigourously, filtered and dried to provide 1.67 g (91%) of the title compound.

Example 19B

4,4'-(1-(4-Fluorophenyl)-1H-pyrrole-2,5-diyl)dianiline

To a solution of example 19A (1.017 g, 2.496 mmol) in ethanol (15 mL) and THF (15 mL) was added iron powder (0.836 g, 14.98 mmol) followed by ammonium chloride (0.401 g, 7.49 mmol) and water (3.75 mL). Reaction mixture was refluxed for 45 minutes. Slurry filtered through celite, washed with ethanol, combined filtrate was concentrated and the residue purified by column chromatography (gradient elution from 30% to 50% EtOAc:hexanes) to provide 1.09 g (77%) of the title compound.

Example 19C

(2S,2'S)-tert-Butyl 2,2'-(4,4'-(1-(4-fluorophenyl)-1H-pyrrole-2,5-diyl)bis(4,1-phenylene))bis(azanediyl)bis(oxomethylene)dipyrrolidine-1-carboxylate

To a solution of Example 19B (1.09 g, 3.17 mmol) in DMF (15.87 mL) at rt was added HATU (2.66 g, 6.98 mmol), (S)-1-(tert-butoxycarbonyl)pyrrolidine-2-carboxylic acid (1.503 g, 6.98 mmol), and Hunig's base (2.218 mL, 12.70 mmol). Stirring was continued overnight. The mixture was partitioned between water and EtOAc added. Organic phase washed with brine, dried (Na_2SO_4) and concentrated. Residue purified by column chromatography (gradient elution from 20% to 50% EtOAc/ hexanes). MS (ESI; M+H) m/z = 738.

Example 19D

(2S,2'S)-N,N'-(4,4'-(1-(4-Fluorophenyl)-1H-pyrrole-2,5-diyl)bis(4,1-phenylene))dipyrrolidine-2-carboxamide

To the product from Example 19C (100 mg, 0.136 mmol) in CH_2Cl_2 (2.0 mL) was added TFA (1.0 mL) and the reaction was stirred 1 h. Mixture concentrated, the residue was partitioned between water and 25% IPA-$CHCl_3$ and neutralized with $NaHCO_3$. The organic layer was dried over Na_2SO_4, filtered and concentrated to give the title compound as a white solid used without further purification. MS (DCI; M+H) m/z = 538.

Example 19E

Dimethyl (2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-(1-(4-fluorophenyl)-1H-pyrrole-2,5-diyl)bis(4,1-phenylene))bis(azanediyl)bis(oxomethylene)bis(pyrrolidine-2,1-diyl))bis(3,3-dimethyl-1-oxobutane-2,1-diyl)dicarbamate

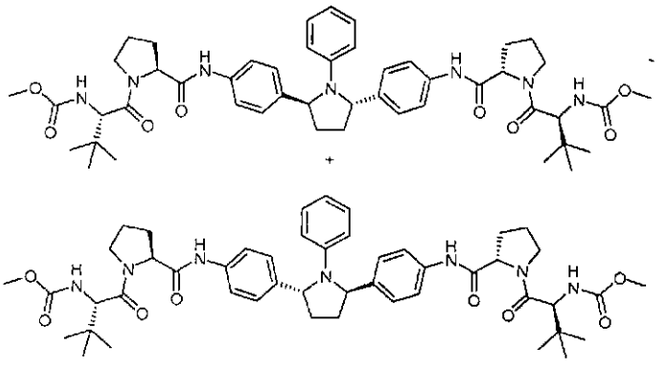
To a mixture of the product from Example 19D (0.073 g, 0.136 mmol) in CH_2Cl_2 (10 mL) at rt was added Hunig's base (0.070 mL, 0.407 mmol). To this was then added (S)-2-methoxycarbonylamino-3,3-dimethyl-butyric acid (0.054 g, 0.285 mmol) followed by HATU (0.114 g, 0.299 mmol). Mixture stirred for 2 hrs then washed with saturated $NaHCO_3$ and the organic phase concentrated and the residue purified by column chromatography (1% gradient elution from 0% to 3% MeOH-CH_2Cl_2) to provide the desired compound as a light tan solid. MS (ESI; M+H) m/z = 881; 1H NMR (400 MHz, DMSO-D6) δ ppm 0.96 (s, 18 H), 1.81-1.89 (m, 4 H), 1.95-2.00 (m, 2 H), 2.11-2.16 (m, 2 H), 3.53 (s, 6 H), 3.61-3.65 (m, 2 H), 3.75-3.79 (m, 2 H), 4.20 (d, J=8.85 Hz, 2 H), 4.39-4.42 (m, 2 H), 6.39 (s, 2 H), 6.96 (d, J=8.69 Hz, 4 H), 7.07-7.10 (m, 4 H), 7.17 (dd, J=8.70, 8.70 Hz, 2 H), 7.41 (d, J=8.70 Hz, 4 H), 10.01 (br s, 2 H). The title compound showed an EC_{50} value of less than about 0.1 nM in HCV 1b-Con1 replicon assays in the presence of 5% FBS.

Example 20

Dimethyl (2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-((2S,5S)-1-phenylpyrrolidine-2,5-diyl)bis(4,1-phenylene))bis(azanediyl)bis(oxomethylene)bis(pyrrolidine-2,1-diyl))bis(3,3-dimethyl-1-oxobutane-2,1-diyl)dicarbamate

and

Dimethyl (2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-((2R,5R)-1-phenylpyrrolidine-2,5-diyl)bis(4,1-phenylene))bis(azanediyl)bis(oxomethylene)bis(pyrrolidine-2,1-diyl))bis(3,3-dimethyl-1-oxobutane-2,1-diyl)dicarbamate



Example 20A

2,5-Bis(4-nitrophenyl)-1-phenylpyrrolidine

A mixture of the product from Example 1C (50 mg, 0.102 mmol) and aniline (0.2 ml, 2.19 mmol) were stirred at rt for 48h. The mixture was partitioned between 1N aq. HCl and ethyl acetate, and the organic layer was dried over Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by column chromatography on silica gel using a solvent gradient of 0-50% ethyl acetate in hexanes. The title compound was obtained as a yellow solid (19 mg, 48%).

Example 20B

(2S,2'S)-tert-Butyl 2,2'-(4,4'-(1-phenylpyrrolidine-2,5-diyl)bis(4,1-phenylene))bis(azanediyl)bis(oxomethylene)dipyrrolidine-1-carboxylate

The product from Example 20A (19 mg, 0.049 mmol) was subjected to the conditions described in Example 1E. The crude product was subjected to the conditions described in Example 1F to give the title compound (33 mg, 93%).

Example 20C

Dimethyl (2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-((2S,5S)-1-phenylpyrrolidine-2,5-diyl)bis(4,1-phenylene))bis(azanediyl)bis(oxomethylene)bis(pyrrolidine-2,1-diyl))bis(3,3-dimethyl-1-oxobutane-2,1-diyl)dicarbamate

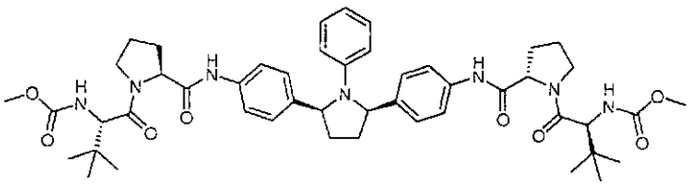
and

Dimethyl (2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-((2R,5R)-1-phenylpyrrolidine-2,5-diyl)bis(4,1-phenylene))bis(azanediyl)bis(oxomethylene)bis(pyrrolidine-2,1-diyl))bis(3,3-dimethyl-1-oxobutane-2,1-diyl)dicarbamate

The product from Example 20B (30 mg, 0.041 mmol) was subjected to the conditions described in Example 1G, and the crude product was subjected to the conditions described in Example 1H. The crude product was subjected to HPLC purification on a semi-prep C18 reverse-phased column using a gradient of 10-100% acetonitrile in 0.1% aq TFA. The trans-substituted pyrrolidine isomer was the first of 2 stereoisomers to elute, providing the title compound as a 1:1 mixture of diastereomers (7 mg, 19%): 1H NMR (TFA salt) (400 MHz, DMSO-D6) δ ppm 0.95 (d, *J*=5.31 Hz, 18 H) 1.59 - 1.67 (m, 2 H) 1.79 - 1.91 (m, 4 H) 1.91 - 2.02 (m, 2 H) 2.08 - 2.17 (m, 2 H) 3.52 (s, 6 H) 3.58 - 3.68 (m, 2 H) 3.71 - 3.82 (m, 2 H) 4.19 (d, *J*=9.00 Hz, 2 H) 4.42 (dd, 2 H) 5.17 (d, *J*=5.64 Hz, 2 H) 6.24 (d, *J*=8.35 Hz, 2 H) 6.39 (t, *J*=7.37 Hz, 2 H) 6.90 (t, *J*=7.92 Hz, 2 H) 7.07 (d, 2 H) 7.11 (d, 4 H) 7.48 (d, *J*=8.24 Hz, 4 H) 9.98 (s, 2 H). The title compound showed an EC_{50} value of less than about 0.1 nM in HCV 1b-Con1 replicon assays in the presence of 5% FBS.

Example 21

Dimethyl (2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-((2S,5R)-1-phenylpyrrolidine-2,5-diyl)bis(4,1-phenylene))bis(azanediyl)bis(oxomethylene)bis(pyrrolidine-2,1-diyl))bis(3,3-dimethyl-1-oxobutane-2,1-diyl)dicarbamate



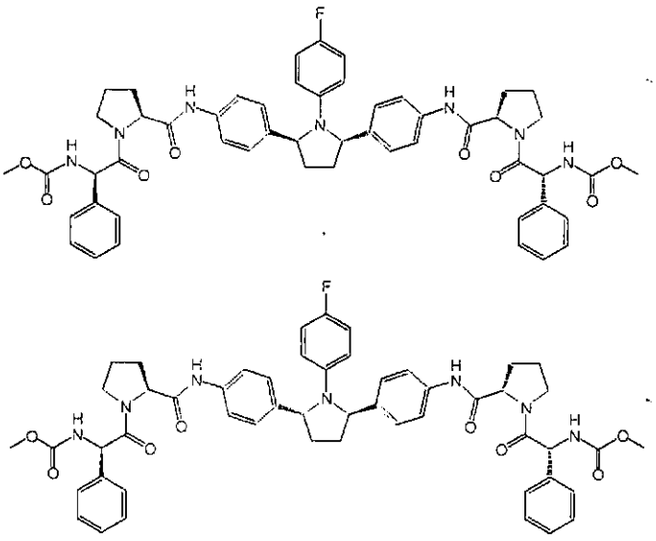
The product from Example 20B (30 mg, 0.041 mmol) was subjected to the conditions described in Example 1G, and the crude product was subjected to the conditions described in Example 1H. The crude product was subjected to HPLC purification on a semi-prep C18 reverse-phased column using a gradient of 10-100% acetonitrile in 0.1% aq TFA. The cis-substituted pyrrolidine isomer was the second of 2 stereoisomers to elute, providing the title compound (8.5 mg, 24%): 1H NMR (TFA salt) (400 MHz, DMSO-D6) δ ppm 0.96 (d, *J*=3.25 Hz, 18 H) 1.74 - 1.91 (m, 6 H) 1.93 - 2.03 (m, 2 H) 2.10 - 2.20 (m, 2 H) 3.53 (s, 6 H) 3.58 - 3.69 (m, 2 H) 3.72 - 3.83 (m, 2 H) 4.20 (d, *J*=8.89 Hz, 2 H) 4.45 (dd, *J*=7.97, 5.37 Hz, 2 H) 4.68 (t, *J*=5.20 Hz, 2 H) 6.37 (d, *J*=8.24 Hz, 2 H) 6.56 (t, *J*=7.26 Hz, 2 H) 6.98 (t, *J*=7.92 Hz, 2 H) 7.07 (d, 2 H) 7.42 (d, *J*=8.02 Hz, 4 H) 7.58 (d, *J*=8.57 Hz, 4 H) 10.03 (s, 2 H). The title compound showed an EC_{50} value of less than about 0.1 nM in HCV 1b-Con1 replicon assays in the presence of 5% FBS.

Example 22

Dimethyl (1R,1'R)-2,2'-((2S,2'S)-2,2'-(4,4'-((2S,5S)-1-(4-fluorophenyl)pyrrolidine-2,5-diyl)bis(4,1-phenylene))bis(azanediyl)bis(oxomethylene)bis(pyrrolidine-2,1-diyl))bis(2-oxo-1-phenylethane-2,1-diyl)dicarbamate

and

Dimethyl (1R,1'R)-2,2'-((2S,2'S)-2,2'-(4,4'-((2R,5R)-1-(4-fluorophenyl)pyrrolidine-2,5-diyl)bis(4,1-phenylene))bis(azanediyl)bis(oxomethylene)bis(pyrrolidine-2,1-diyl))bis(2-oxo-1-phenylethane-2,1-diyl)dicarbamate



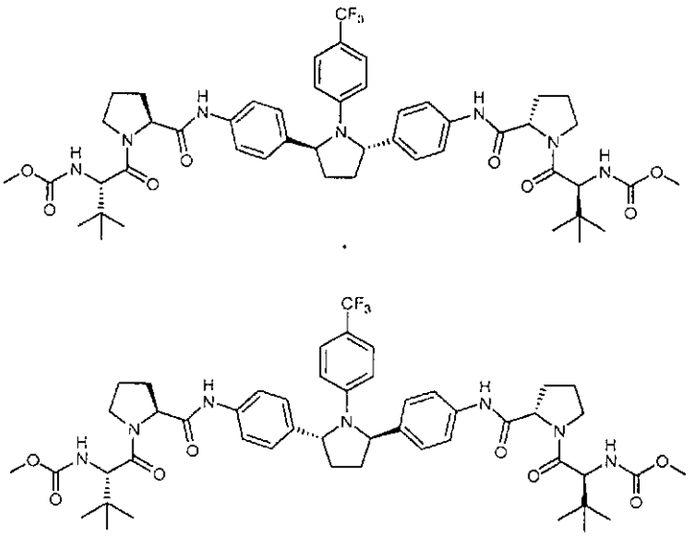
The product from Example 5C (25 mg, 0.046 mmol) was subjected to the conditions described in Example 5D, substituting (R)-2-(methoxycarbonylamino)-2-phenylacetic acid for (S)-2-(methoxycarbonyl amino)butanoic acid, to give the title compound as a 1:1 mixture of diastereomers (42 mg, 48%): 1H NMR (400 MHz, DMSO-D6) δ ppm 9.83 (s, 2 H) 7.67 (d, *J*=7.81 Hz, 2 H) 7.51 - 7.57 (m, 4 H) 7.29 - 7.44 (m, 8 H) 7.15 (d, *J*=8.46 Hz, 4 H) 6.74 - 6.83 (m, 2 H) 6.17 - 6.28 (m, *J*=9.00, 4.34 Hz, 2 H) 5.48 (d, *J*=7.81 Hz, 2 H) 5.12 - 5.24 (m, 1 H) 4.33 - 4.43 (m, *J*=8.13 Hz, 2 H) 3.75 - 3.87 (m, 2 H) 3.54 (s, 6 H) 1.73 - 2.05 (m, 8 H) 1.62 - 1.70 (m, 2 H). The title compound showed an EC_{50} value of less than about 0.1 nM in HCV 1b-Con1 replicon assays in the presence of 5% FBS.

Example 23

Dimethyl (2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-((2S,5S)-1-(4-(trifluoromethyl)phenyl)pyrrolidine-2,5-diyl)bis(4,1-phenylene))bis(azanediyl)bis(oxomethylene)bis(pyrrolidine-2,1-diyl))bis(3,3-dimethyl-1-oxobutane-2,1-diyl)dicarbamate

and

Dimethyl (2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-((2R,5R)-1-(4-(trifluoromethyl)phenyl)pyrrolidine-2,5-diyl)bis(4,1-phenylene))bis(azanediyl)bis(oxomethylene)bis(pyrrolidine-2,1-diyl))bis(3,3-dimethyl-1-oxobutane-2,1-diyl)dicarbamate



Example 23A

4,4'-((2S,5S)-1-(4-(Trifluoromethyl)phenyl)pyrrolidine-2,5-diyl)dianiline and 4,4'-((2R,5R)-1-(4-(Trifluoromethyl)phenyl)pyrrolidine-2,5-diyl)dianiline

The product from Example 1C (0.74 g, 1.5 mmol) was subjected to the conditions described in Example 1D, substituting 4-(trifluoromethyl)aniline for 4-fluoroaniline. The product thus obtained was subjected to the conditions described in Example 1E to give the title compound as a racemic mixture of trans-substituted pyrrolidine stereoisomers (0.10 g, 17%).

Example 23B

(2S,2'S)-N,N'-(4,4'-((2S,5S)-1-(4-(Trifluoromethyl)phenyl)pyrrolidine-2,5-diyl)bis(4,1-phenylene))dipyrrolidine-2-carboxamide and (2S,2'S)-N,N'-(4,4'-((2R,5R)-1-(4-(Trifluoromethyl)phenyl)pyrrolidine-2,5-diyl)bis(4,1-phenylene))dipyrrolidine-2-carboxamide

The product from Example 23A (0.95 g, 0.24 mmol) was subjected to the conditions described in Example 1F to give a solid (0.166 g, 88%), which was dissolved in 4M HCl in 1,4-dioxane (2 ml), and the resulting mixture was stirred at rt for 30 min. The resulting mixture was concentrated and dried in vacuo to give an HCl salt of the title compound as a 1:1 mixture of stereoisomers.

Example 23C

Dimethyl (2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-((2S,5S)-1-(4-(trifluoromethyl)phenyl)pyrrolidine-2,5-diyl)bis(4,1-phenylene))bis(azanediyl)bis(oxomethylene)bis(pyrrolidine-2,1-diyl))bis(3,3-dimethyl-1-oxobutane-2,1-diyl)dicarbamate

and

Dimethyl (2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-((2R,5R)-1-(4-(trifluoromethyl)phenyl)pyrrolidine-2,5-diyl)bis(4,1-phenylene))bis(azanediyl)bis(oxomethylene)bis(pyrrolidine-2,1-diyl))bis(3,3-dimethyl-1-oxobutane-2,1-diyl)dicarbamate

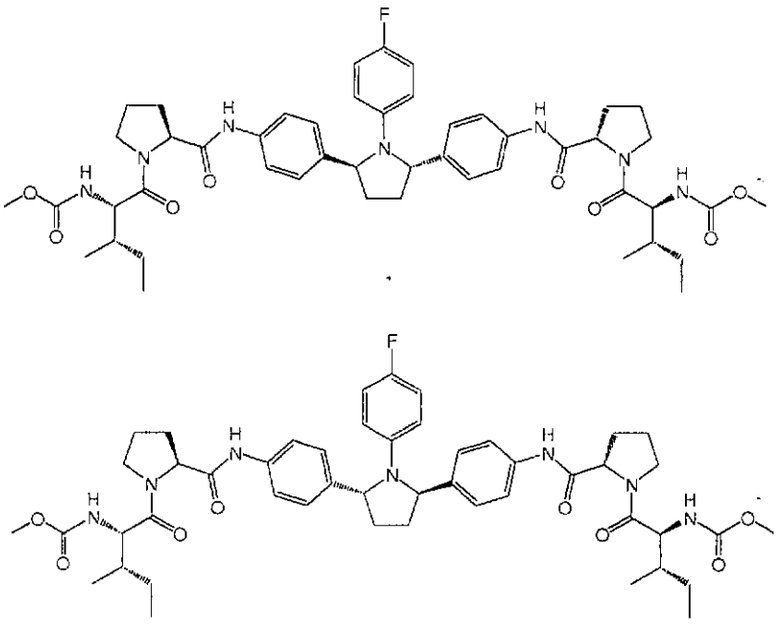
The product from Example 23B (58 mg, 0.083 mmol) was subjected to the conditions described in Example 1H to give the title compound as a colorless solid (30 mg, 39%): 1H NMR (free base) (400 MHz, DMSO-D6) δ ppm 10.03 (s, 2 H) 7.52 (d, *J*=8.46 Hz, 4 H) 7.25 (d, *J*=8.89 Hz, 2 H) 7.14 (d, *J*=7.48 Hz, 4 H) 7.06 - 7.11 (m, 2 H) 6.36 (d, *J*=8.35 Hz, 2 H) 5.23 - 5.33 (m, 2 H) 4.39 - 4.48 (m, 2 H) 4.21 (d, *J*=8.46 Hz, 2 H) 3.71 - 3.82 (m, 2 H) 3.58 - 3.69 (m, 2 H) 3.54 (s, 6 H) 2.08 - 2.21 (m, 2 H) 1.93 - 2.06 (m, 2 H) 1.76 - 1.94 (m, 4 H) 1.61 - 1.73 (m, 2 H) 0.96 (m, 18 H). The title compound showed an EC_{50} value of less than about 0.1 nM in HCV 1b-Con1 replicon assays in the presence of 5% FBS.

Example 24

Dimethyl (2S,2'S,3S,3'S)-1,1'-((2S,2'S)-2,2'-(4,4'-((2S,5S)-1-(4-fluorophenyl)pyrrolidine-2,5-diyl)bis(4,1-phenylene))bis(azanediyl)bis(oxomethylene)bis(pyrrolidine-2,1-diyl))bis(3-methyl-1-oxopentane-2,1-diyl)dicarbamate

and

Dimethyl (2S,2'S,3S,3'S)-1,1'-((2S,2'S)-2,2'-(4,4'-((2R,5R)-1-(4-fluorophenyl)pyrrolidine-2,5-diyl)bis(4,1-phenylene))bis(azanediyl)bis(oxomethylene)bis(pyrrolidine-2,1-diyl))bis(3-methyl-1-oxopentane-2,1-diyl)dicarbamate



The product from Example 1G (20 mg, 0.037 mmol) was subjected to the conditions described in Example 1H, substituting (2S,3S)-2-(methoxycarbonylamino)-3-methylpentanoic acid

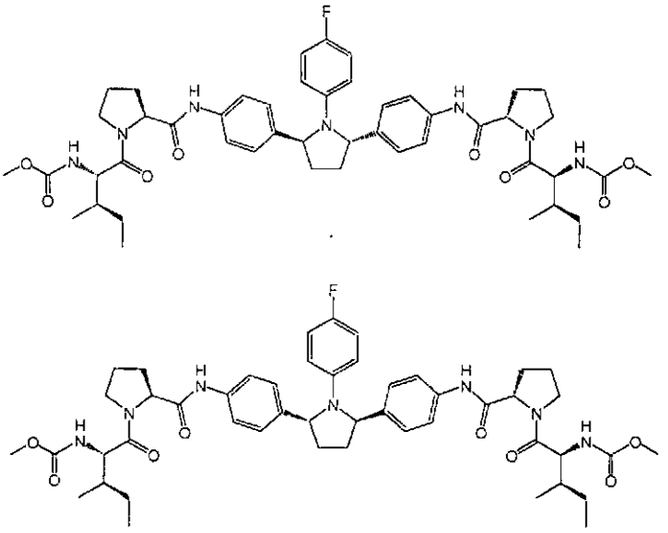
(15.4 mg, 0.081 mmol) for (S)-2-(methoxycarbonylamino)-3,3-dimethylbutanoic acid. The title compound was obtained as a 1:1 mixture of diastereomers (13.5 mg, 41%) after silica gel chromatography (0-5% MeOH/CH_2Cl_2): 1H NMR (free base) (400 MHz, DMSO-D6) δ ppm 9.99 (s, 2 H) 7.50 (dd, *J*=8.46, 1.52 Hz, 4 H) 7.36 (dd, *J*=8.35, 3.04 Hz, 2 H) 7.13 (dd, *J*=8.62, 1.79 Hz, 4 H) 6.78 (t, *J*=8.89 Hz, 2 H) 6.20 (dd, *J*=9.16, 4.39 Hz, 2 H) 5.16 (d, *J*=6.29 Hz, 2 H) 4.43 (dd, *J*=7.92, 4.77 Hz, 2 H) 4.02 - 4.13 (m, 2 H) 3.77 - 3.89 (m, 2 H) 3.57 - 3.67 (m, 2 H) 3.52 (s, 6 H) 2.08 - 2.21 (m, *J*=14.96 Hz, 2 H) 1.94 - 2.05 (m, 2 H) 1.81 - 1.93 (m, *J*=5.42 Hz, 4 H) 1.60 - 1.79 (m, 4 H) 1.42 - 1.57 (m, 2 H) 1.04 - 1.18 (m, 2 H) 0.89 (t, *J*=6.51 Hz, 6 H) 0.76 - 0.85 (m, 6 H). The title compound showed an EC_{50} value of less than about 0.1 nM in HCV 1b-Con1 replicon assays in the presence of 5% FBS.

Example 25

Dimethyl (2S,2'S,3R,3'R)-1,1'-((2S,2'S)-2,2'-(4,4'-((2S,5S)-1-(4-fluorophenyl)pyrrolidine-2,5-diyl)bis(4,1-phenylene))bis(azanediyl)bis(oxomethylene)bis(pyrrolidine-2,1-diyl))bis(3-methyl-1-oxopentane-2,1-diyl)dicarbamate

and

Dimethyl (2S,2'S,3R,3'R)-1,1'-((2S,2'S)-2,2'-(4,4'-((2R,5R)-1-(4-fluorophenyl)pyrrolidine-2,5-diyl)bis(4,1-phenylene))bis(azanediyl)bis(oxomethylene)bis(pyrrolidine-2,1-diyl))bis(3-methyl-1-oxopentane-2,1-diyl)dicarbamate

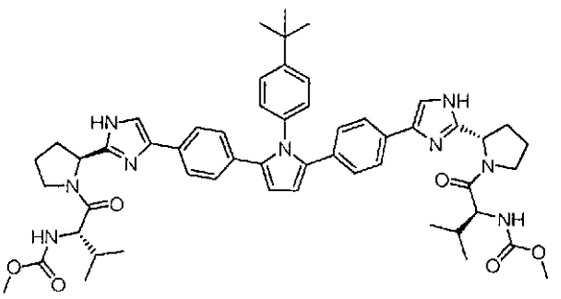


The product from Example 1G (25 mg, 0.046 mmol) was subjected to the conditions described in Example 1H, substituting (2S,3R)-2-(methoxycarbonylamino)-3-methylpentanoic acid (19.2 mg, 0.102 mmol) for (S)-2-(methoxycarbonylamino)-3,3-dimethylbutanoic acid. The title compound was obtained as a 1:1 mixture of diastereomers (20.5 mg, 50%) after silica gel chromatography (0-5% MeOH/CH_2Cl_2): 1H NMR (free base) (400 MHz, DMSO-D6) δ ppm 9.96 (s,

2 H) 7.49 (d, *J*=8.35 Hz, 4 H) 7.14 (t, *J*=7.43 Hz, 4 H) 6.77 (t, *J*=8.89 Hz, 2 H) 6.20 (dd, *J*=9.11, 4.45 Hz, 2 H) 5.16 (d, *J*=6.40 Hz, 2 H) 4.38 - 4.48 (m, 2 H) 4.18 - 4.28 (m, 2 H) 3.69 - 3.82 (m, 2 H) 3.55 - 3.64 (m, 2 H) 3.52 (s, 6 H) 2.09 - 2.20 (m, 2 H) 1.95 - 2.05 (m, 2 H) 1.72 - 1.95 (m, 6 H) 1.58 - 1.70 (m, *J*=5.64 Hz, 2 H) 1.40 - 1.55 (m, 2 H) 1.06 - 1.18 (m, 2 H) 0.79 - 0.91 (m, 12 H). The title compound showed an EC_{50} value of less than about 0.1 nM in HCV 1b-Con1 replicon assays in the presence of 5% FBS.

Example 26

dimethyl (2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-(4,4'-(1-(4-tert-butylphenyl)-1H-pyrrole-2,5-diyl)bis(4,1-phenylene))bis(1H-imidazole-4,2-diyl))bis(pyrrolidine-2,1-diyl))bis(3-methyl-1-oxobutane-2,1-diyl)dicarbamate



Example 26A

(S)-tert-butyl 2-formylpyrrolidine-1-carboxylate

To an oven-dried 500-mL 3-neck flask purged with nitrogen was added oxalyl chloride (5.32 mL, 60.8 mmol) and anhydrous dichloromethane (125 mL), and the solution cooled to -78 °C. A solution of anhydrous DMSO (7.30 mL, 103 mmol) in anhydrous dichloromethane (25 mL) was added dropwise from a constant-pressure addition funnel over 20-min period. A solution of (S)-tert-butyl 2-(hydroxymethyl)pyrrolidine-1-carboxylate (9.41 g, 46.8 mmol) in anhydrous dichloromethane (50 mL) was added dropwise from a constant-pressure addition funnel over 20-min period, then stirred reaction mixture at -78 °C for 30 min. Added triethylamine (32.6 mL, 234 mmol) dropwise via syringe over a 5-min period and stirred the thick white mixture in an ice-water bath for 30 min. Quenched reaction with 10% (w/v) aq. citric acid (30 mL), poured reaction into a separatory funnel with Et_2O (550 mL) and 10% (w/v) aq citric acid, separated layers, and washed organic phase with water and brine. Dried the organic phase over anhydrous Na_2SO_4, filtered, and concentrated to afford a yellow oil (9.4 g), which was used directly in the next reaction.

Example 26B

(S)-tert-butyl 2-(1H-imidazol-2-yl)pyrrolidine-1-carboxylate

The product from Example 26A (20 g, 100 mmol) was dissolved in methanol (50.2 mL) and ammonium hydroxide (50.2 mL) was added. To this solution glyoxal (40% in water; 24.08 mL, 211

mmol) was added, dropwise, over 10 min. The reaction was stirred at room temperature overnight. Reaction was concentrated under reduced pressure, diluted with 50 mL of water, and then extracted with ethyl acetate. Washed organic layer with brine, dried (Na_2SO_4) and concentrated to a tan solid. Solid was treated with ether and concentrated. The solid was then triturated with 2:1 diethyl ether:hexanes (150 mL) to afford 17 g of solid, which was used directly in the next reaction.

Example 26C

(S)-tert-butyl 2-(4,5-dibromo-1H-imidazol-2-yl)pyrrolidine-1-carboxylate

N-bromosuccinimide (108 mmol) was added to a cold (0 °C) solution of the product from Example 26B (12.05 g, 50.8 mmol) in dichloromethane (200 mL). Let stir in ice bath for 2 h and then concentrated, dissolved in ethyl acetate (250 mL) washed with water (3 x 150 mL), brine (1 x 100 mL), dried ($MgSO_4$) and concentrated to very dark residue, chased with dichloromethane/hexanes (1:1) to get brown solid (~19 g). Triturated solid with ether (~100 mL), filtered to isolate a tan solid (13.23 g, 65% yield).

Example 26D

(S)-tert-butyl 2-(5-bromo-1H-imidazol-2-yl)pyrrolidine-1-carboxylate or (S)-tert-butyl 2-(4-bromo-1H-imidazol-2-yl)pyrrolidine-1-carboxylate

Dissolved the product from Example 26C (6.25 g, 15.82 mmol) in dioxane (200 mL) and water (200 mL) in a 1 L round bottom flask equipped with a condenser and glass stopper, added a solution of sodium sulfite (22.38 g, 174 mmol) in water (200 mL), and heated at reflux with heating mantle for 16 h. Reaction was reddish-amber homogeneous solution. Cooled reaction to room temperature, removed dioxane and some water by rotary evaporation, extracted with dichloromethane, washed the combined organic extracts with brine (50 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated by rotary evaporation, co-evaporating with 2:1 hexanes/dichloromethane (100 mL) to give a beige foam (4.38 g). Dissolved foam in dichloromethane (2 mL), added hexanes (2 mL), applied solution to column, and purified by silica gel flash chromatography eluting with 30% to 80% ethyl acetate/hexanes to afford the title compound as a white solid (3.48 g).

Example 26E

1,4-bis(4-bromophenyl)butane-1,4-dione

To a solution of zinc(II) chloride (19.62 g, 144 mmol) in benzene (108 mL) were added diethylamine (11.16 mL, 108 mmol) and 2-methylpropan-2-ol (10.32 mL, 108 mmol) and the mixture was stirred at room temperature for 2 h. 2-bromo-1-(4-bromophenyl)ethanone (20.0 g, (72 mmol) and 1-(4-bromophenyl)ethanone (21.48 g, 108 mmol) were added in one portion, and the mixture was stirred overnight (18 h). Quenched with 5% H_2SO_4 (500 mL) and stirred vigorously to induce

precipitation of the product, which was collected by vacuum filtration and washed with benzene, water, methanol, then dichloromethane, successively. The product was dried under vacuum to give the title compound as a white solid (11.15 g, 39.1% yield).

Example 26F

2,5-bis(4-bromophenyl)-1-(4-tert-butylphenyl)-1H-pyrrole

To a solution of the product from Example 26E (4.00 g, 10.10 mmol) in toluene (40 mL) was added 4-tert-butylaniline (1.81 g, 12.12 mmol) followed by TFA (2.30 g, 20.20 mmol). Mixture heated to 110 °C for 2 h. Mixture cooled to room temperature and water and diethyl ether were added. Stirred for 15 min, filtered, washed with water and diethyl ether and dried to provide the title compound as a white solid (4.61 g; 90% yield).

Example 26G

1-(4-tert-butylphenyl)-2,5-bis(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1H-pyrrole

To a solution of the product from Example 26F (2.32 g, 4.56 mmol) in DMSO (26 mL) at room temperature were added bis(pinacolato)diborane (2.54 g, 10.02 mmol), potassium acetate (5.00 g, 36.4 mmol) and $PdCl_2$(dppf) (744 mg, 0.91 mmol). The mixture was degassed and heated to 85 °C. After 4 h, the mixture was cooled to room temperature, diluted with dichloromethane and washed with water followed by brine. The organic phase was dried (Na_2SO_4) and concentrated. The residue was taken up in 20% ethyl acetate:hexanes and filtered through a short plug of silica gel (elution with 20% ethyl acetate:hexanes) and concentrated to afford the title compound as a light yellow solid (1.62 g; 59% yield).

Example 26H

(2S,2'S)-tert-butyl 2,2'-(4,4'-(4,4'-(1-(4-tert-butylphenyl)-1H-pyrrole-2,5-diyl)bis(4,1-phenylene))bis(1H-imidazole-4,2-diyl))dipyrrolidine-1-carboxylate

A mixture of the product from Example 26D (664 mg, 2.10 mmol), the product from Example 26G (1.48 g, 2.45 mmol), 2 M sodium carbonate (1400 µL, 2.80 mmol), and Pd(dppf)Cl2 (51.2 mg, 0.070 mmol) in DME (2800 µL) was subjected to microwave irradiation at 140 °C for 20 min. The mixture was diluted with ethyl acetate, then washed with water and brine, and dried over Na_2SO_4. The product was purified on silica gel eluted with 30 to 70% ethyl acetate:hexanes to provide the title compound (140 mg; 24% yield).

Example 26I

(2S,2'S)-4,4'-(4,4'-(1-(4-tert-butylphenyl)-1H-pyrrole-2,5-diyl)bis(4,1-phenylene))bis(2-(pyrrolidin-2-yl)-1H-imidazole)

To a solution of the product from Example 26H (135 mg, 0.164 mmol) in dichloromethane (2 mL) at room temperature was added TFA (0.60 mL). After 3 h, the solvent was removed and the residue partitioned between water and 25% isopropyl alcohol:$CHCl_3$; neutralized with $NaHCO_3$. The organic phase was dried (Na_2SO_4), filtered and concentrated. Residue used directly in the next reaction (98 mg; 96% yield).

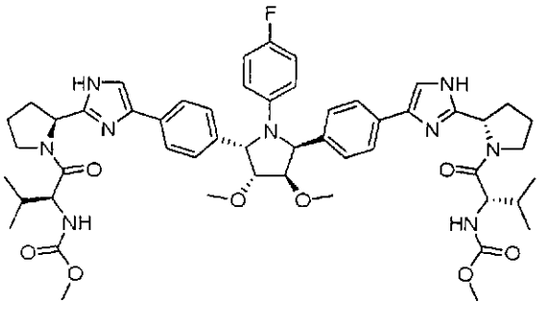
Example 26J

Dimethyl (2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-(4,4'-(1-(4-tert-butylphenyl)-1H-pyrrole-2,5-diyl)bis(4,1-phenylene))bis(1H-imidazole-4,2-diyl))bis(pyrrolidine-2,1-diyl))bis(3-methyl-1-oxobutane-2,1-diyl)dicarbamate

To a solution of the product from Example 26I (98 mg, 0.158 mmol) in DMF (2 mL) at room temperature was added (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (61 mg, 0.347 mmol), EDAC (66 mg, 0.347 mmol) and 1-hydroxybenzotriazole hydrate (53 mg, 0.347 mmol). After 3 h, the mixture was transferred to a separatory funnel with ethyl acetate and water. The organic phase was concentrated and the residue purified by chromatography (1% gradient elution from 0% to 4% methanol:dichloromethane) to provide the desired material as a light yellow solid (70 mg; 30% yield). ^{1}HNMR (MeOH-d4; 400 MHz): δ 7.55-7.30 (m, 6H), 7.25-6.96 (m, 8H), 6.45 (s, 2H), 5.12 (dd, J=5.43, 5.43 Hz, 2H), 4.20 (d, J=7.26 Hz, 2H), 4.02-3.90 (m, 2H), 3.85-3.80 (m, 2H), 3.64 (s, 6H), 2.36-1.93 (m, 10H), 1.31 (s, 9H), 0.97-0.86 (m, 12H). The title compound showed an EC_{50} value of less than about 0.1 nM in HCV 1b-Con1 replicon assays in the presence of 5% FBS.

Example 27

dimethyl (2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-(4,4'-((2S,3R,4R,5S)-1-(4-fluorophenyl)-3,4-dimethoxypyrrolidine-2,5-diyl)bis(4,1-phenylene))bis(1H-imidazole-4,2-diyl))bis(pyrrolidine-2,1-diyl))bis(3-methyl-1-oxobutane-2,1-diyl)dicarbamate



Example 27A

(2S,3R,4R,5S)-2,5-bis(4-bromophenyl)-1-(4-fluorophenyl)pyrrolidine-3,4-diol

A solution of 3,4-O-isopropylidene-D-mannitol (2.24 g, 10.08 mmol) in 2:1 methanol-dichloromethane (45 mL) was treated with iodobenzene diacetate (7.95 g, 24.19 mmol) followed by stirring at room temperature for 5 h. The mixture was concentrated by rotary evaporation and the

residue was dissolved in 0.1M aq. sulfuric acid solution (20.6 mL) followed by stirring at room temperature for 18 h. The mixture was adjusted to pH 6 by addition of solid sodium bicarbonate. The mixture was then sequentially treated with 4-fluoroaniline (1.96 mL, 20.16 mmol), 4-bromophenylboronic acid (3.64 g, 18.14 mmol), and absolute ethanol (40 mL). The mixture was then heated in an oil bath (110 °C) at reflux for 20 h. The dark brown mixture was cooled to room temperature and concentrated in vacuo. The residue was taken up in ethyl acetate (100 mL), washed with water (50 mL), 0.33M aq. potassium phosphate tribasic solution (2 x 50 mL), and brine (50 mL). The organic phase was dried over anhydrous sodium sulfate, filtered, and the filtrate concentrated by rotary evaporation to a dark reddish-brown oil. Dissolved oil in dichloromethane-hexanes, concentrated in vacuo, and dried in vacuo to give a dark brown foam. Purification by silica gel flash chromatography eluting with a step gradient of 10% to 15% ethyl acetate/dichloromethane afforded pure product as a yellow solid (1.216 g, 24%).

Example 27B

(2S,3R,4R,5S)-2,5-bis(4-bromophenyl)-1-(4-fluorophenyl)-3,4-dimethoxypyrrolidine

Dissolved the product of Example 27A (237 mg, 0.467 mmol) in a mixture of THF (3 mL) and DMF (1 mL) under a nitrogen atmosphere and cooled to 0 °C. Added 60% sodium hydride dispersion in mineral oil (56.1 mg, 1.402 mmol) in portions and stirred the mixture at 0 °C for 15 min. Then added neat iodomethane (65 µL, 1.028 mmol), removed the cooling bath, and stirred the reaction at room temperature for 14.5 h. Diluted the reaction in ethyl acetate (50 mL), washed with saturated aq. ammonium chloride solution (25 mL), water (2 x 25 mL), and brine (25 mL). Dried the organic phase over anhydrous sodium sulfate, filtered, and concentrated the filtrate by rotary evaporation. The yellow residue was purified by silica gel flash chromatography eluting with 30% hexanes/dichloromethane to afford the title compound as a white foam (206 mg, 82%).

Example 27C

(2S,3R,4R,5S)-1-(4-fluorophenyl)-3,4-dimethoxy-2,5-bis(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)pyrrolidine

Charged a nitrogen-purged flask with the product of Example 27B (204 mg, 0.381 mmol), bis(pinacalato)diboron (242 mg, 0.953 mmol), potassium acetate (112 mg, 1.143 mmol), and anhydrous dioxane (2 mL). Sparged the mixture with nitrogen for 30 min, added 1,1'-bis(diphenylphosphino)ferrocene-palladium (II) dichloride dichloromethane complex (31.1 mg, 0.038 mmol), sparged the mixture again with nitrogen for 5 min, and heated in an oil bath at 85 °C for 6 h. The reaction was vacuum filtered through a small bed of celite 545, the collected solids were thoroughly washed with 5% methanol/dichloromethane, and the filtrate concentrated in vacuo, chasing the residue with dichloromethane/hexanes to give a tan solid. Purification by silica gel flash

chromatography eluting with 5% ethyl acetate/dichloromethane afforded the title compound as a salmon-colored solid (238 mg, 99%).

Example 27D

(2S,2'S)-tert-butyl 2,2'-(4,4'-(4,4'-((2S,3R,4R,5S)-1-(4-fluorophenyl)-3,4-dimethoxypyrrolidine-2,5-diyl)bis(4,1-phenylene))bis(1H-imidazole-4,2-diyl))dipyrrolidine-1-carboxylate

A nitrogen-purged 5-mL microwave tube was charged with the product of Example 27C (237 mg, 0.377 mmol), the product from Example 26D (298 mg, 0.941 mmol), and a mixture of absolute ethanol (1.5 mL) and toluene (1.5 mL). Sonicated to obtain a cloudy orange mixture, added 1M aq sodium carbonate (0.941 mL, 0.941 mmol), and sparged with nitrogen for 20 min. Added 1,1'-bis(diphenylphosphino)ferrocene-palladium (II) dichloride dichloromethane complex (30.8 mg, 0.038 mmol), sparged the mixture again with nitrogen for 5 min, sealed the reaction tube with an aluminum crimp cap, and heated in a microwave reactor with stirring at 100 °C for 1 h. Cooled reaction to room temperature, diluted in ethyl acetate (75 mL), washed with water (2 x 25 mL) and brine (25 mL), dried the organic phase over anhydrous magnesium sulfate, filtered, and concentrated the filtrate by rotary evaporation to a dark yellow solid. Purification by silica gel flash chromatography eluting with 4% methanol/dichloromethane afforded the title compound as a yellow solid (221 mg, 69%).

Example 27E

(S)-4,4'-(4,4'-((2S,3R,4R,5S)-1-(4-fluorophenyl)-3,4-dimethoxypyrrolidine-2,5-diyl)bis(4,1-phenylene))bis(2-((S)-pyrrolidin-2-yl)-1H-imidazole)

A solution of the product of Example 27D (147.5 mg, 0.174 mmol) in anhydrous dichloromethane (2 mL) under nitrogen was treated with TFA (1 mL) and stirred at room temperature for 30 min. The solvent was removed in vacuo and chased with 1:10 dichloromethane-hexanes (3 x 50 mL) to afford a pale yellow solid (193 mg). The solid TFA salt was dissolved in anhydrous methanol (15 mL), treated with dry Amberlite IRA-400(OH) resin (1.66 g, previously washed 10 g of wet resin (Supelco) with deionized water (3 x 25 mL) and methanol (3 x 25 mL), then dried in vacuo), and stirred for 2 h at room temperature. The mixture was then vacuum filtered, the collected resin washed thoroughly with methanol, the filtrate concentrated by rotary evaporation, and the residue chased with 1:10 dichloromethane-hexanes to afford the title compound as a light yellow solid (94 mg, 0.145 mmol, 83%).

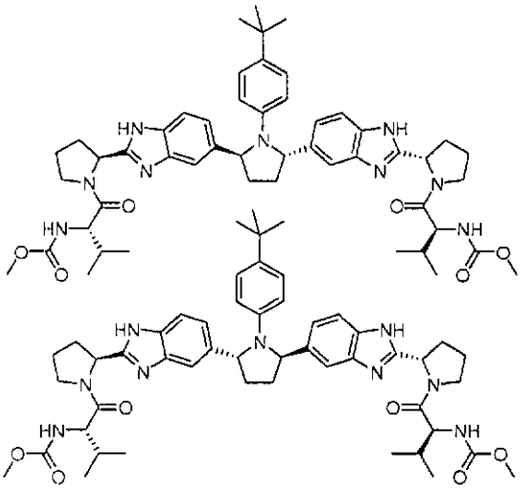
Example 27F

dimethyl (2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-(4,4'-((2S,3R,4R,5S)-1-(4-fluorophenyl)-3,4-dimethoxypyrrolidine-2,5-diyl)bis(4,1-phenylene))bis(1H-imidazole-4,2-diyl))bis(pyrrolidine-2,1-diyl))bis(3-methyl-1-oxobutane-2,1-diyl)dicarbamate

In an oven-dried round bottom flask, dissolved the product of Example 27E (92 mg, 0.142 mmol) in a mixture of DMF (1 mL) and DMSO (1 mL) under nitrogen and cooled the solution to 0 °C. Added sequentially (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (53.5 mg, 0.305 mmol), EDAC (61.1 mg, 0.312 mmol), 1-hydroxybenzotriazole hydrate (47.8 mg, 0.312 mmol), and N-methylmorpholine (47 µL, 0.426 mmol). Removed the cooling bath and stirred at room temperature for 15 h. Diluted the reaction with ethyl acetate (50 mL), washed with saturated aq. sodium bicarbonate solution (25 mL), water (2 x 25 mL), and brine (25 mL). The organic phase was dried over anhydrous magnesium sulfate, filtered, and the filtrate concentrated by rotary evaporation. Purification by silica gel flash chromatography eluting with 5% methanol/dichloromethane afforded the title compound as a pale yellow solid (78 mg, 56%). ^{1}H NMR (400 MHz, DMSO-d6) δ ppm 0.86 (dd, J=17.67, 6.72 Hz, 12 H), 0.97 - 1.37 (m, 3 H), 1.41 - 2.29 (m, 11 H), 3.53 (s, 6 H), 3.69 - 3.86 (m, 4 H), 4.04 (q, J=8.02 Hz, 2 H), 4.12 - 4.23 (m, 2 H), 5.07 (d, J=3.80 Hz, 2 H), 5.35 - 5.48 (m, 2 H), 6.31 (dd, J=9.16, 4.39 Hz, 2 H), 6.74 (t, J=8.89 Hz, 2 H), 7.12 - 7.71 (m, 12 H), 11.53 - 12.31 (m, 2 H); MS (ESI+) m/z 963 (M+H)+. The title compound showed an EC_{50} value of less than about 0.1 nM in HCV 1b-Con1 replicon assays in the presence of 5% FBS.

Example 28

dimethyl (2S,2'S)-1,1'-((2S,2'S)-2,2'-(5,5'-((2R,5R)-1-(4-tert-butylphenyl)pyrrolidine-2,5-diyl)bis(1H-benzo[d]imidazole-5,2-diyl))bis(pyrrolidine-2,1-diyl))bis(3-methyl-1-oxobutane-2,1-diyl)dicarbamate and dimethyl (2S,2'S)-1,1'-((2S,2'S)-2,2'-(5,5'-((2S,5S)-1-(4-tert-butylphenyl)pyrrolidine-2,5-diyl)bis(1H-benzo[d]imidazole-5,2-diyl))bis(pyrrolidine-2,1-diyl))bis(3-methyl-1-oxobutane-2,1-diyl)dicarbamate



Example 28A

1,4-bis(4-chloro-3-nitrophenyl)butane-1,4-dione

Zinc chloride (27.4g, 201 mmol), diethylamine (15.6 mL, 151 mmol) and t-butanol (14.4 mL, 151 mmol) were combined in benzene (151 mL) at room temperature under a nitrogen atmosphere and stirred for 2 h. 1-(4-chloro-3-nitrophenyl)ethanone (30.1 g, 151 mmol) and 2-bromo-1-(4-chloro-3-nitrophenyl)ethanone (28 g, 101 mmol) were added. The mixture was stirred vigorously for 20 h, and the solid product was collected by filteration and rinsed with benzene, water, methanol, and dichloromethane. The solid was dried in a vacuum oven.

Example 28B

1,4-bis(4-chloro-3-nitrophenyl)butane-1,4-diol

The product of Example 28A (5.75 g, 14.48 mmol) was dissolved in ethanol (150 mL) at room temperature and treated with sodium borohydride (1.21 g, 31.9 mmol) portionwise over 5 minutes. The solution was heated at 70 °C for 1 h and then cooled to room temperature, quenched with water, extracted into ethyl acetate, dried over sodium sulfate, and concentrated to dryness to give 4.81g (83%) of an off-white solid.

Example 28C

1,4-bis(4-chloro-3-nitrophenyl)butane-1,4-diyl dimethanesulfonate

The product of Example 28B (4.81 g, 11.99 mmol) and triethylamine (5.85 mL, 42.0 mmol) were dissolved in dichloromethane (80 mL) at room temperature and treated with methanesulfonyl chloride (2.34 mL, 30.0 mmol) dropwise over 10 minutes. The resulting solution was stirred for 2 h then concentrated to dryness and used directly in the next step.

Example 28D

1-(4-tert-butylphenyl)-2,5-bis(4-chloro-3-nitrophenyl)pyrrolidine

The product from Example 28C (6.6 g, 11.84 mmol) was slurried in DMF (30 mL) and 4-t-butyl aniline (18.7 mL, 118 mmol) was added and the solution was heated at 55 °C for 2 h then cooled and poured into water and extracted into dichloromethane. The organics were concentrated and the residue was purified by chromatography on silica gel 120g column, eluting with 0-5%ethyl acetate/hexanes to give 4.41g (72%) of a thick oil.

Example 28E

4,4'-(1-(4-tert-butylphenyl)pyrrolidine-2,5-diyl)bis(N-(4-methoxybenzyl)-2-nitroaniline)

The product from Example 28D (4.41 g, 8.57 mmol) was combined, neat, with p-methoxy benzylamine (8.93 mL, 68.6 mmol) and heated at 145 °C for 1 h. The mixture was diluted with dichloromethane and filtered. The filtrate was washed with 0.5 M HCl, then $NaHCO_3$ soln, then

brine, concentrated and purified by chromatography on silica gel with an 80g column, eluting with 0-50% ethyl acetate/hexanes to give 4.13g (67%) of an orange foamy solid.

Example 28F

4,4'-(1-(4-tert-butylphenyl)pyrrolidine-2,5-diyl)bis(N1-(4-methoxybenzyl)benzene-1,2-diamine)

The product from Example 28E (2 g, 2.79 mmol) was dissolved in a mixture of THF (15 mL), ethanol (15 mL), and ethyl acetate (5 mL) then platinum oxide (0.254 g, 1.12 mmol) was added via THF slurry. The flask was evacuated and purged with nitrogen twice, then evacuated and opened to hydrogen balloon. The mixture was stirred at room temperature for 20 h, then filtered through celite, concentrated, and purified by chromatography on silica gel with an 80g column, eluting with 0-40% ethyl acetate/dichloromethane to give the first peak of trans product 0.508 g (28%).

Example 28G

(2S,2'S)-tert-butyl 2,2'-(5,5'-(1-(4-tert-butylphenyl)pyrrolidine-2,5-diyl)bis(2-(4-methoxybenzylamino)-5,1-phenylene)bis(azanediyl)bis(oxomethylene))dipyrrolidine-1-carboxylate

The product from Example 28F (0.422 g, 0.643 mmol) and diisopropylethylamine (0.674 mL, 3.86 mmol) were dissolved in DMSO (6 mL) at room temperature and treated with S-Boc-proline (0.319 g, 1.48 mmol) followed by HATU (0.514 g, 1.35 mmol). The solution was stirred for 1 h at room temperature then diluted with water and the solid product was filtered off and purified by chromatography on silica gel with a 40g column, eluting with 0-50% ethyl acetate in dichloromethane to give 0.565 g (84%) of a yellow solid.

Example 28H

(2S,2'S)-tert-butyl 2,2'-(5,5'-(1-(4-tert-butylphenyl)pyrrolidine-2,5-diyl)bis(2-amino-5,1-phenylene)bis(azanediyl)bis(oxomethylene))dipyrrolidine-1-carboxylate

The product from Example 28G (0.565 g, 0.538 mmol) was dissolved in dichloromethane (5 mL) and water (0.25 mL) at room temperature and treated with DDQ (0.244 g, 1.076 mmol) portionwise over 2 minutes. The mixture was diluted with sodium bicarbonate solution, extracted into dichloromethane, concentrated and purified by chromatography on silica gel with a 40g column, eluting with 0-15% methanol/dichloromethane to give 0.355 g (81%) of a yellow solid.

Example 28I

(2S,2'S)-tert-butyl 2,2'-(5,5'-(1-(4-tert-butylphenyl)pyrrolidine-2,5-diyl)bis(1H-benzo[d]imidazole-5,2-diyl))dipyrrolidine-1-carboxylate

The product from Example 28H was dissolved in neat acetic acid (3 mL) and heated at 72 °C for 2 h. The solution was concentrated and then poured into water and adjusted pH to ~7-8 with

sodium bicarbonate. The product was extracted into dichloromethane, concentrated and purified by chromatography on silica gel with a 40g column, eluting with 0-5%methanol/dichloromethane to give 0.185 g (55%) of a light yellow solid.

Example 28J

(S)-5,5'-(1-(4-tert-butylphenyl)pyrrolidine-2,5-diyl)bis(2-((S)-pyrrolidin-2-yl)-1H-benzo[d]imidazole)

The product from Example 28I (0.204 g, 0.264 mmol) was dissolved in THF (2 mL) at room temperature and treated with 4 M hydrochloric acid in dioxane (2 mL). The mixture was concentrated to dryness and used directly in the next step.

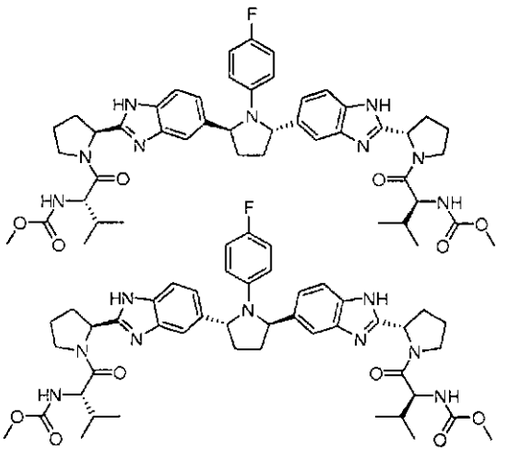
Example 28K

dimethyl (2S,2'S)-1,1'-((2S,2'S)-2,2'-(5,5'-((2R,5R)-1-(4-tert-butylphenyl)pyrrolidine-2,5-diyl)bis(1H-benzo[d]imidazole-5,2-diyl))bis(pyrrolidine-2,1-diyl))bis(3-methyl-1-oxobutane-2,1-diyl)dicarbamate and dimethyl (2S,2'S)-1,1'-((2S,2'S)-2,2'-(5,5'-((2S,5S)-1-(4-tert-butylphenyl)pyrrolidine-2,5-diyl)bis(1H-benzo[d]imidazole-5,2-diyl))bis(pyrrolidine-2,1-diyl))bis(3-methyl-1-oxobutane-2,1-diyl)dicarbamate

The product from Example 28J (0.150 g, 0.261 mmol) and diisopropylethylamine (0.365 mL, 2.09 mmol) were dissolved in DMSO (3 mL) at room temperature and treated with (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (0.105 g, 0.601 mmol) followed by HATU (0.204 g, 0.536 mmol). The solution was stirred for 1 h at room temperature then diluted with water and the solid product was filtered off and purified by chromatography on silica gel with a 12g column, eluting with 0-8% methanol in dichloromethane to give 0.143 g (60%) of a yellow solid. ^{1}H NMR (400 MHz, DMSO-D6) δ ppm 0.75 - 0.92 (m, 12 H) 1.07 (s, 9 H) 1.64 - 1.76 (m, 2 H) 1.85 - 2.04 (m, 6 H) 2.12 - 2.26 (m, 4 H) 2.43 (dd, J=7.75, 4.07 Hz, 2 H) 3.53 (s, 6 H) 3.76 - 3.87 (m, 4 H) 4.04 (dd, J=11.49, 6.51 Hz, 2 H) 5.12 (t, J=7.59 Hz, 2 H) 5.35 (d, J=3.25 Hz, 2 H) 6.25 (d, J=8.46 Hz, 2 H) 6.85 - 6.96 (m, 2 H) 7.07 (t, J=7.97 Hz, 2 H) 7.19 (s, 1 H) 7.28 (d, J=8.35 Hz, 3 H) 7.38 (dd, J=8.19, 1.90 Hz, 1 H) 7.46 (d, J=8.13 Hz, 1 H) 11.97 - 12.09 (m, 2 H). The title compound showed an EC_{50} value of less than about 0.1 nM in HCV 1b-Con1 replicon assays in the presence of 5% FBS.

Example 29

dimethyl (2S,2'S)-1,1'-((2S,2'S)-2,2'-(5,5'-((2R,5R)-1-(4-fluorophenyl)pyrrolidine-2,5-diyl)bis(1H-benzo[d]imidazole-5,2-diyl))bis(pyrrolidine-2,1-diyl))bis(3-methyl-1-oxobutane-2,1-diyl)dicarbamate and dimethyl (2S,2'S)-1,1'-((2S,2'S)-2,2'-(5,5'-((2S,5S)-1-(4-fluorophenyl)pyrrolidine-2,5-diyl)bis(1H-benzo[d]imidazole-5,2-diyl))bis(pyrrolidine-2,1-diyl))bis(3-methyl-1-oxobutane-2,1-diyl)dicarbamate



Example 29A

2,5-bis(4-chloro-3-nitrophenyl)-1-(4-fluorophenyl)pyrrolidine

The product from Example 28C (2.9 g, 5.2 mmol) and 4-fluoroaniline (5.0 mL, 52.0 mmol) were combined, neat, and heated at 45 °C for 20 h then cooled and poured into water and extracted into dichloromethane. The organics were concentrated the residue was purified by chromatography on silica gel with a 120g column, eluting with 0-5% ethyl acetate/hexanes to give 0.59g (24%) of a thick oil.

Example 29B

4,4'-(1-(4-fluorophenyl)pyrrolidine-2,5-diyl)bis(N-(4-methoxybenzyl)-2-nitroaniline)

The product from Example 29A (0.88 g, 1.86 mmol) was combined with 4-methoxy benzylamine (3.64 mL, 28.0 mmol) and heated at 145 °C for 1 h in a microwave reactor. The mixture was diluted with dichloromethane and filtered. The filtrate was concentrated and purified by chromatography on silica gel with a 330g column, eluting with 0-60% ethyl acetate/hexanes to give 0.79g (62%) of an orange foam solid.

Example 29C

4,4'-(1-(4-fluorophenyl)pyrrolidine-2,5-diyl)bis(2-nitroaniline)

The product from Example 29B (0.78 g, 1.15 mmol) was dissolved in dichloromethane (10 mL) at room temperature and treated with TFA (1.8 mL, 23.0 mmol) for 3 h. The residue was concentrated and partitioned between dichloromethane and sodium bicarbonate solution. The organics were concentrated and purified by chromatography on silica gel with a 40g column, eluting with dichloromethane to give 0.218 g (43%) of the trans isomer.

Example 29D

4,4'-(1-(4-fluorophenyl)pyrrolidine-2,5-diyl)dibenzene-1,2-diamine

The product from Example 29C (0.218 g, 0.50 mmol) was dissolved in DMF (5 mL) then platinum oxide (0.226 g, 0.99 mmol) was added via THF slurry. The flask was evacuated and purged with nitrogen twice, then evacuated and opened to hydrogen balloon. The mixture was stirred at room temperature for 20 h. The solution was taken on to the next step without purification.

Example 29E

(2S,2'S)-tert-butyl 2,2'-(5,5'-(1-(4-fluorophenyl)pyrrolidine-2,5-diyl)bis(2-amino-5,1-phenylene))bis(azanediyl)bis(oxomethylene)dipyrrolidine-1-carboxylate

The crude DMF solution of the product from Example 29D was treated with diisopropylethylamine (0.296 mL, 1.70 mmol) and S-Boc-proline (0.192 g, 0.89 mmol) followed by HATU (0.322 g, 0.85 mmol). The solution was stirred for 1.5 h at room temperature then diluted with water and the solid product was filtered off and purified by chromatography on silica gel with a 12g column, eluting with 0-3% methanol in dichloromethane to give 0.235 g (72%) of a yellow solid.

Example 29F

(2S,2'S)-tert-butyl 2,2'-(5,5'-(1-(4-fluorophenyl)pyrrolidine-2,5-diyl)bis(1H-benzo[d]imidazole-5,2-diyl))dipyrrolidine-1-carboxylate

The product from Example 29E was dissolved in neat acetic acid (2 mL) and heated at 60 °C for 1 h. The solution was concentrated then poured into water and adjusted pH to ~7-8 with sodium bicarbonate. The product was extracted into dichloromethane, concentrated and purified by chromatography on silica gel with a 12g column, eluting with 0-20% ethyl acetate in dichloromethane to give 0.124 g (55%) of a light yellow solid.

Example 29G

(S)-5,5'-(1-(4-fluorophenyl)pyrrolidine-2,5-diyl)bis(2-((S)-pyrrolidin-2-yl)-1H-benzo[d]imidazole)

The product from Example 29F (0.120 g, 0.163 mmol) was dissolved in dichloromethane (2 mL) at room temperature and treated with TFA (1 mL). The mixture was concentrated to dryness, dissolved in 25%ISOPROPYL ALCOHOL/dichloromethane and washed with sodium bicarbonate solution. The resulting solids were filtered off and dried and the organics were concentrated and dried to give the title compound (0.062 g 72% yield) of an off-white solid.

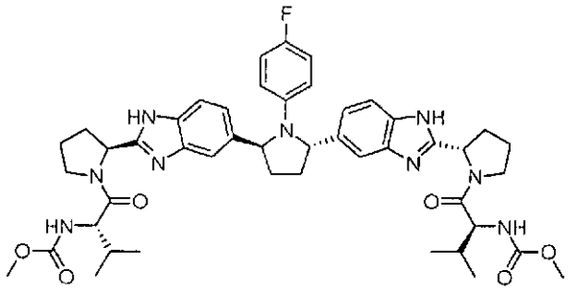
Example 29H

dimethyl (2S,2'S)-1,1'-((2S,2'S)-2,2'-(5,5'-((2R,5R)-1-(4-fluorophenyl)pyrrolidine-2,5-diyl)bis(1H-benzo[d]imidazole-5,2-diyl))bis(pyrrolidine-2,1-diyl))bis(3-methyl-1-oxobutane-2,1-diyl)dicarbamate and dimethyl (2S,2'S)-1,1'-((2S,2'S)-2,2'-(5,5'-((2S,5S)-1-(4-fluorophenyl)pyrrolidine-2,5-diyl)bis(1H-benzo[d]imidazole-5,2-diyl))bis(pyrrolidine-2,1-diyl))bis(3-methyl-1-oxobutane-2,1-diyl)dicarbamate

The product from Example 29G (0.062 g, 0.116 mmol) and diisopropylethylamine (0.101 mL, 0.58 mmol) were dissolved in DMSO (2 mL) at room temperature and treated with (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (0.051 g, 0.289 mmol) followed by HATU (0.092 g, 0.243 mmol). The solution was stirred for 1 h at room temperature then diluted with water and the solid product was filtered off and purified by chromatography on silica gel with a 12g column, eluting with 0-7% methanol in dichloromethane to give 0.021 g (21%) of a yellow solid. ^{1}H NMR (400 MHz, DMSO-D6) δ ppm 0.78 - 0.90 (m, 12 H) 1.70 (s, 2 H) 1.87 - 2.03 (m, 6 H) 2.13 - 2.26 (m, 4 H) 2.54 - 2.62 (m, 2 H) 3.54 (s, 6 H) 3.82 (s, 4 H) 4.03 - 4.11 (m, 2 H) 5.09 - 5.18 (m, 2 H) 5.32 - 5.42 (m, 2 H) 6.28 (dd, J=8.89, 4.34 Hz, 2 H) 6.70 - 6.80 (m, 2 H) 7.01 - 7.10 (m, 2 H) 7.20 (d, J=9.32 Hz, 1 H) 7.27 - 7.34 (m, 3 H) 7.38 (dd, J=8.13, 2.71 Hz, 1 H) 7.45 (d, J=8.02 Hz, 1 H) 12.03 (s, 2 H). The title compound showed an EC_{50} value of less than about 0.1 nM in HCV 1b-Con1 replicon assays in the presence of 5% FBS.

Example 30

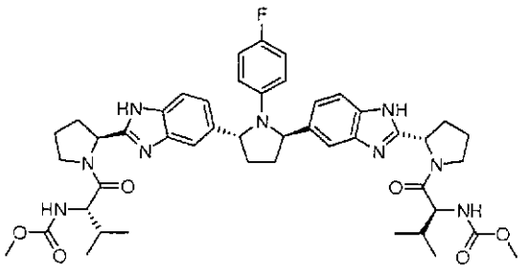
dimethyl (2S,2'S)-1,1'-((2S,2'S)-2,2'-(5,5'-((2S,5S)-1-(4-fluorophenyl)pyrrolidine-2,5-diyl)bis(1H-benzo[d]imidazole-5,2-diyl))bis(pyrrolidine-2,1-diyl))bis(3-methyl-1-oxobutane-2,1-diyl)dicarbamate



The product from Example 29H was purified by chiral chromatography on a Chirapak IA column eluting with a mixture of hexane/EtOH/MeOH/1,2 Dichloroethane/diethylamine (25/25/25/25/0.1). ^{1}H NMR (400 MHz, DMSO-D6) δ ppm 0.75 - 0.89 (m, 12 H) 1.64 - 1.73 (m, 2 H) 1.85 - 2.03 (m, 6 H) 2.12 - 2.24 (m, 4 H) 2.81 - 2.90 (m, 2 H) 3.52 (s, 6 H) 3.76 - 3.87 (m, 4 H) 4.01 - 4.09 (m, 2 H) 5.08 - 5.16 (m, 2 H) 5.34 (q, J=6.65 Hz, 2 H) 6.26 (dd, J=9.05, 4.50 Hz, 2 H) 6.67 - 6.78 (m, 2 H) 7.03 (t, J=8.02 Hz, 2 H) 7.20 (s, 1 H) 7.24 - 7.32 (m, 3 H) 7.36 (d, J=8.13 Hz, 1 H) 7.44 (d, J=7.92 Hz, 1 H) 12.01 - 12.07 (m, 2 H). The title compound showed an EC_{50} value of less than about 0.1 nM in HCV 1b-Con1 replicon assays in the presence of 5% FBS.

Example 31

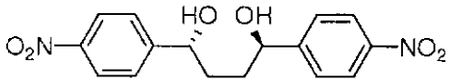
dimethyl (2S,2'S)-1,1'-((2S,2'S)-2,2'-(5,5'-((2R,5R)-1-(4-fluorophenyl)pyrrolidine-2,5-diyl)bis(1H-benzo[d]imidazole-5,2-diyl))bis(pyrrolidine-2,1-diyl))bis(3-methyl-1-oxobutane-2,1-diyl)dicarbamate



The product from Example 29H was purified by chiral chromatography on a Chirapak IA column eluting with a mixture of hexane/EtOH/MeOH/1,2 Dichloroethane/diethylamine (25/25/25/25/0.1). ^{1}H NMR (400 MHz, DMSO-D6) δ ppm 0.74 - 0.93 (m, 12 H) 1.69 (t, J=9.65 Hz, 2 H) 1.82 - 2.06 (m, 6 H) 2.09 - 2.26 (m, 4 H) 3.04 - 3.23 (m, 2 H) 3.52 (s, 6 H) 3.73 - 3.90 (m, 4 H) 4.06 (t, J=8.46 Hz, 2 H) 5.05 - 5.21 (m, 2 H) 5.29 - 5.44 (m, 2 H) 6.21 - 6.32 (m, 2 H) 6.67 - 6.86 (m, 2 H) 7.05 (t, J=8.78 Hz, 2 H) 7.18 (s, 1 H) 7.23 - 7.33 (m, 3 H) 7.37 (d, J=8.13 Hz, 1 H) 7.45 (d, J=8.02 Hz, 1 H) 12.04 (d, J=14.96 Hz, 2 H). The title compound showed an EC_{50} value of less than about 0.1 nM in HCV 1b-Con1 replicon assays in the presence of 5% FBS.

Example 32

(1R,4R)-1,4-bis(4-nitrophenyl)butane-1,4-diol

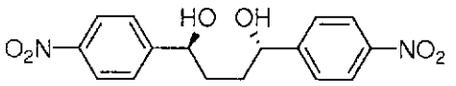


To (S)-(-)-α,α-diphenyl-2-pyrrolidinemethanol (2.71 g, 10.70 mmol) was added THF (80 mL) at 23 °C. The very thin suspension was treated with trimethyl borate (1.44 g, 13.86 mmol) over 30 seconds, and the resulting solution was mixed at 23 °C for 1 h. The solution was cooled to 16-19 °C, and N,N-diethylaniline borane (21.45 g, 132 mmol) was added dropwise via syringe over 3-5 min (caution: vigorous H_2 evolution), while the internal temperature was maintained at 16-19 °C. After 15 min, the H_2 evolution had ceased. To a separate vessel was added the product from Example 1A (22.04 g, 95 wt%, 63.8 mmol), followed by THF (80 mL), to form an orange slurry. After cooling the slurry to 11 °C, the borane solution was transferred via cannula into the dione slurry over 3-5 min. During this period, the internal temperature of the slurry rose to 16 °C. After the addition was complete, the reaction was maintained at 20-27 °C for an additional 2.5 h. After reaction completion, the mixture was cooled to 5 °C and methanol (16.7 g, 521 mmol) was added dropwise over 5-10 min, maintaining an internal temperature <20 °C (note: vigorous H_2 evolution). After the exotherm had ceased (ca. 10 min), the temperature was adjusted to 23 °C, and the reaction was mixed until complete dissolution of the solids had occurred. Ethyl acetate (300 mL) and 1 M HCl (120 mL) were added, and the phases were partitioned. The organic phase was then washed successively with 1 M HCl (2 x 120 mL), H_2O (65 mL), and 10% aq. NaCl (65 mL). The organics were dried over $MgSO_4$, filtered, and concentrated in vacuo. Crystallization of the product occurred during the concentration. The

slurry was warmed to 50 °C, and heptane (250 mL) was added over 15 min. The slurry was then allowed to mix at 23 °C for 30 min and filtered. The wet cake was washed with 3:1 heptane:ethyl acetate (75 mL), and the orange, crystalline solids were dried at 45 °C for 24 h to provide the title compound (15.35 g, 99.3% ee, 61% yield), which was contaminated with 11% of the meso isomer (vs. dl isomer).

Example 33

(1S,4S)-1,4-bis(4-nitrophenyl)butane-1,4-diol



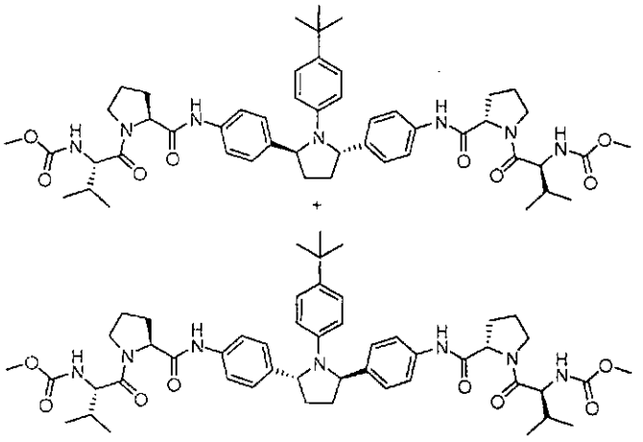
The product from Example 1A (30 g, 95 wt%, 91.4 mmol) was subjected to the conditions described in Example 32, substituting (R)-(-)-α,α-diphenyl-2-pyrrolidinemethanol for (S)-(-)-α,α-diphenyl-2-pyrrolidinemethanol, to give the title compound (20.14 g, >99.55 ee, 61% yield) which was contaminated with 9.7% of the meso isomer (vs. dl isomer).

Example 34

Dimethyl (2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-((2S,5S)-1-(4-*tert*-butylphenyl)pyrrolidine-2,5-diyl)bis(4,1-phenylene))bis(azanediyl)bis(oxomethylene)bis(pyrrolidine-2,1-diyl))bis(3-methyl-1-oxobutane-2,1-diyl)dicarbamate

and

Dimethyl (2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-((2R,5R)-1-(4-*tert*-butylphenyl)pyrrolidine-2,5-diyl)bis(4,1-phenylene))bis(azanediyl)bis(oxomethylene)bis(pyrrolidine-2,1-diyl))bis(3-methyl-1-oxobutane-2,1-diyl)dicarbamate



Example 34A

1-(4-*tert*-butylphenyl)-2,5-bis(4-nitrophenyl)pyrrolidine

The product from Example 1C (3.67 g, 7.51 mmol) and 4-*tert*-butylaniline (11.86 ml, 75 mmol) in DMF (40 ml) was stirred under nitrogen at 50 °C for 4 h. The resulting mixture was diluted

into ethyl acetate, treated with 1M HCl, stirred for 10 minutes and filtered to remove solids. The filtrate organic layer was washed twice with brine, dried with sodium sulfate, filtered and evaporated. The residue was purified by chromatography on silica gel eluting with ethyl acetate in hexane (5% to 30%) to give a solid. The solid was triturated in a minimal volume of 1:9 ethyl acetate/hexane to give a light yellow solid as a mixture of trans and cis isomers (1.21 g, 36%).

Example 34B

4,4'-((2S,5S)-1-(4-*tert*-butylphenyl)pyrrolidine-2,5-diyl)dianiline and 4,4'-((2R,5R)-1-(4-*tert*-butylphenyl)pyrrolidine-2,5-diyl)dianiline

To a solution of the product from Example 34A (1.1 g, 2.47 mmol) in ethanol (20 ml) and THF (20 ml) was added PtO_2 (0.22 g, 0.97 mmol) in a 50 ml pressure bottle and stirred under 30 psi hydrogen at room temperature for 1 h. The mixture was filtered through a nylon membrane and evaporated. The residue was purified by chromatography on silica gel eluting with ethyl acetate in hexane (20% to 60%). The title compound eluted as the first of 2 stereoisomers (trans isomer, 0.51 g, 54%).

Example 34C

(2S,2'S)-tert-Butyl 2,2'-(4,4'-((2S,5S)-1-(4-*tert*-butylphenyl)pyrrolidine-2,5-diyl)bis(4,1-phenylene))bis(azanediyl)bis(oxomethylene)dipyrrolidine-1-carboxylate and (2S,2'S)-tert-Butyl 2,2'-(4,4'-((2R,5R)-1-(4-*tert*-butylphenyl)pyrrolidine-2,5-diyl)bis(4,1-phenylene))bis(azanediyl)bis(oxomethylene)dipyrrolidine-1-carboxylate

To a mixture of the product from Example 34B (250 mg, 0.648 mmol), (S)-1-(tert-butoxycarbonyl)pyrrolidine-2-carboxylic acid (307 mg, 1.427 mmol) and HATU (542 mg, 1.427 mmol) in DMSO (10 ml) was added Hunig's base (0.453 ml, 2.59 mmol). The reaction mixture was stirred at room temperature for 1 h. The mixture was partitioned with ethyl acetate and water. The organic layer was washed with brine, dried with sodium sulfate, filtered and evaporated. The residue was purified by chromatography on silica gel eluting with ethyl acetate in hexane (10% to 50%) to give the title compound (500 mg, 99%).

Example 34D

(2S,2'S)-N,N'-(4,4'-((2S,5S)-1-(4-*tert*-butylphenyl)pyrrolidine-2,5-diyl)bis(4,1-phenylene))dipyrrolidine-2-carboxamide and (2S,2'S)-N,N'-(4,4'-((2R,5R)-1-(4-*tert*-butylphenyl)pyrrolidine-2,5-diyl)bis(4,1-phenylene))dipyrrolidine-2-carboxamide

To the product from Example 34C (498 mg, 0.638 mmol) in dichloromethane (4 ml) was added TFA (6 ml). The reaction mixture was stirred at room temperature for 1 h and concentrated in vacuo. The residue was partitioned between 3:1 $CHCl_3$:isopropyl alcohol and saturated aq. $NaHCO_3$.

The aqueous layer was extracted by 3:1 $CHCl_3$:isopropyl alcohol again. The combined organic layers were dried over Na_2SO_4, filtered and concentrated to give the title compound (345 mg, 93%).

Example 34E

Dimethyl (2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-((2S,5S)-1-(4-*tert*-butylphenyl)pyrrolidine-2,5-diyl)bis(4,1-phenylene))bis(azanediyl)bis(oxomethylene)bis(pyrrolidine-2,1-diyl))bis(3-methyl-1-oxobutane-2,1-diyl)dicarbamate

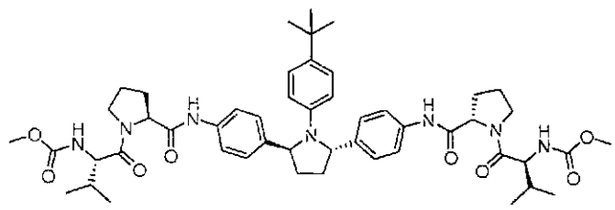
and

Dimethyl (2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-((2R,5R)-1-(4-*tert*-butylphenyl)pyrrolidine-2,5-diyl)bis(4,1-phenylene))bis(azanediyl)bis(oxomethylene)bis(pyrrolidine-2,1-diyl))bis(3-methyl-1-oxobutane-2,1-diyl)dicarbamate

The product from Example 34D (29.0 mg, 0.050 mmol), (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (19.27 mg, 0.110 mmol), EDAC (21.09 mg, 0.110 mmol), HOBT (16.85 mg, 0.110 mmol) and N-methylmorpholine (0.027 ml, 0.250 mmol) were combined in DMF (2 ml). The reaction mixture was stirred at room temperature for 3 h. The mixture was partitioned with ethyl acetate and water. The organic layer was washed with brine twice, dried with sodium sulfate, filtered and evaporated. The residue was purified by chromatography on silica gel eluting with ethyl acetate in hexane (50% to 80%) to give a solid. The solid was triturated with ethyl acetate/hexane to give the title compound (13 mg, 29%). ^{1}H NMR (400 MHz, DMSO-D6) δ ppm 0.85 - 0.95 (m, 12 H) 1.11 (s, 9 H) 1.59 - 1.65 (m, 2 H) 1.79 - 2.04 (m, 8 H) 2.10 - 2.18 (m, 2 H) 2.41-2.46 (m, 2H) 3.52 (s, 6 H) 3.57 - 3.67 (m, 2 H) 3.76 - 3.86 (m, 2 H) 4.00 (t, J=7.56 Hz, 2 H) 4.39 - 4.46 (m, 2 H) 5.15 (d, J=7.00 Hz, 2 H) 6.17 (d, J=7.70 Hz, 2 H) 6.94 (d, J=8.78 Hz, 2 H) 7.13 (d, J=7.37 Hz, 4 H) 7.30 (d, J=8.20 Hz, 2 H) 7.50 (d, J=8.24 Hz, 4 H) 9.98 (s, 2 H); (ESI+) m/z 895 (M+H)+. The title compound showed an EC_{50} value of less than about 0.1 nM in HCV 1b-Con1 replicon assays in the presence of 5% FBS.

Example 35

Dimethyl (2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-((2S,5S)-1-(4-*tert*-butylphenyl)pyrrolidine-2,5-diyl)bis(4,1-phenylene))bis(azanediyl)bis(oxomethylene)bis(pyrrolidine-2,1-diyl))bis(3-methyl-1-oxobutane-2,1-diyl)dicarbamate

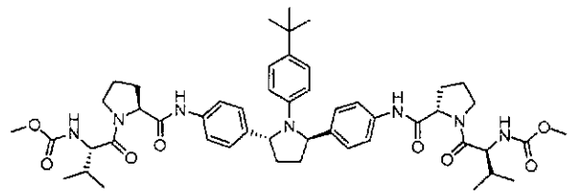


The product from Example 34E was purified by chiral chromatography on a Chiralpak AD-H semi-prep column eluting with a 2:1 mixture of hexane:(2:1 isopropyl alcohol:EtOH). The title

compound was the first of the 2 diastereomers to elute. ^{1}H NMR (400 MHz, DMSO-D6) δ ppm 0.88 (d, J=6.61 Hz, 6 H) 0.93 (d, J=6.72 Hz, 6 H) 1.11 (s, 9 H) 1.63 (d, J=5.42 Hz, 2 H) 1.80 - 2.04 (m, 8 H) 2.09 - 2.19 (m, 2 H) 2.44 - 2.47 (m, 2 H) 3.52 (s, 6 H) 3.59 - 3.66 (m, 2 H) 3.77 - 3.84 (m, 2 H) 4.02 (t, J=8.40 Hz, 2 H) 4.42 (dd, J=7.86, 4.83 Hz, 2 H) 5.14 (d, J=6.18 Hz, 2 H) 6.17 (d, J=8.67 Hz, 2 H) 6.94 (d, J=8.78 Hz, 2 H) 7.13 (d, J=8.46 Hz, 4 H) 7.31 (d, J=8.35 Hz, 2 H) 7.50 (d, J=8.35 Hz, 4 H) 9.98 (s, 2 H). The title compound showed an EC_{50} value of less than about 0.1 nM in HCV 1b-Con1 replicon assays in the presence of 5% FBS.

Example 36

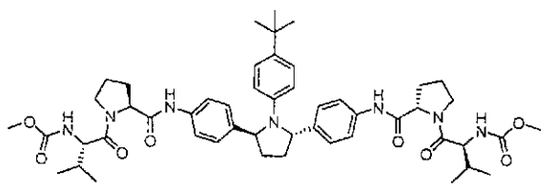
Dimethyl (2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-((2R,5R)-1-(4-*tert*-butylphenyl)pyrrolidine-2,5-diyl)bis(4,1-phenylene))bis(azanediyl)bis(oxomethylene)bis(pyrrolidine-2,1-diyl))bis(3-methyl-1-oxobutane-2,1-diyl)dicarbamate



The product from Example 34E was purified by chiral chromatography on a Chiralpak AD-H semi-prep column eluting with a 2:1 mixture of hexane:(2:1 isopropyl alcohol:EtOH). The title compound was the second of 2 diastereomers to elute. ^{1}H NMR (400 MHz, DMSO-D6) δ ppm 0.87 (d, J=6.51 Hz, 6 H) 0.92 (d, J=6.72 Hz, 6 H) 1.11 (s, 9 H) 1.63 (d, J=5.53 Hz, 2 H) 1.82 - 2.04 (m, 8 H) 2.09-2.18 (m, 2 H) 2.41 - 2.47 (m, 2 H) 3.52 (s, 6 H) 3.58 - 3.67 (m, 2 H) 3.75 - 3.84 (m, 2 H) 4.02 (t, J=7.26 Hz, 2 H) 4.43 (dd, J=7.92, 4.88 Hz, 2 H) 5.14 (d, J=6.18 Hz, 2 H) 6.17 (d, J=8.78 Hz, 2 H) 6.94 (d, J=8.67 Hz, 2 H) 7.12 (d, J=8.46 Hz, 4 H) 7.31 (d, J=8.35 Hz, 2 H) 7.49 (d, J=8.46 Hz, 4 H) 9.98 (s, 2 H). The title compound showed an EC_{50} value of less than about 0.1 nM in HCV 1b-Con1 replicon assays in the presence of 5% FBS.

Example 37

Dimethyl (2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-((2S,5S)-1-(4-*tert*-butylphenyl)pyrrolidine-2,5-diyl)bis(4,1-phenylene))bis(azanediyl)bis(oxomethylene)bis(pyrrolidine-2,1-diyl))bis(3-methyl-1-oxobutane-2,1-diyl)dicarbamate



Example 37A

(S)-2,5-dioxopyrrolidin-1-yl 2-(methoxycarbonylamino)-3-methylbutanoate

To a mixture of (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (19.66 g, 112 mmol) and N-hydroxysuccinimide (13.29g, 116 mmol) was added ethyl acetate (250 ml), and the mixture was cooled to 0-5 °C. Diisopropylcarbodiimide (13.88 g, 110 mmol) was added and the reaction mixture was stirred at 0-5 °C for about 1 hour. The reaction mixture was warmed to room temperature. The solids (diisopropylurea by-product) were filtered and rinsed with ethyl acetate. The filtrate was concentrated in vacuo to an oil. Isopropyl alcohol (200 ml) was added to the oil and the mixture was heated to about 50 °C to obtain a homogeneous solution. Upon cooling, crystalline solids formed. The solids were filtered and washed with isopropyl alcohol (3 x 20 ml) and dried to give the title compound as a white solid (23.2 g, 77% yield).

Example 37B

(S)-1-((S)-2-(methoxycarbonylamino)-3-methylbutanoyl)pyrrolidine-2-carboxylic acid

To a mixture of L-proline (4.44g, 38.6 mmol), water (20 ml), acetonitrile (20 ml) and DIEA (9.5 g, 73.5 mmol) was added a solution of the product from Example 37A (10g, 36.7 mmol) in acetonitrile (20 mL) over 10 minutes. The reaction mixture was stirred overnight at room temperature. The solution was concentrated under vacuum to remove the acetonitrile. To the resulting clear water solution was added 6N HCl (9 ml) until pH ~ 2 .The solution was transferred to a separatory funnel and 25% NaCl (10 ml) was added and the mixture was extracted with ethyl acetate (75 ml), and then again with ethyl acetate (6 x 20 ml), and the combined extracts were washed with 25% NaCl (2 x 10ml). The solvent was evaporated to give a thick oil. Heptane was added and the solvent was evaporated to give a foam, which was dried under high vacuum. Diethyl ether was added and the solvent was evaporated to give a foam, which was dried under high vacuum to give the title compound (10.67g) as a white solid.

The compound of Example 37B can also be prepreared according to the following procedure:

To a flask was charged *L*-valine (35 g, 299 mmol), 1N sodium hydroxide solution (526 ml, 526 mmol) and sodium carbonate (17.42 g, 164 mmol). The mixture was stirred for 15 min to dissolve solids and then cooled to 15 °C. Methyl chloroformate (29.6 g, 314 mmol) was added slowly to the reaction mixture. The mixture was then stirred at rt for 30 min. The mixture was cooled to 15 °C and pH adjusted to ~5.0 with concentrated HCl solution. 100 mL of 2-methytetrahydrofuran (2-MeTHF) was added and the adjustment of pH continued until the pH reached ~ 2.0. 150 mL of 2-MeTHF was added and the mixture was stirred for 15 min. Layers were separated and the aqueous layer extracted with 100 mL of 2-MeTHF. The combined organic layer was dried over anhyd Na_2SO_4 and filtered, and Na_2SO_4 cake was washed with 50 mL of 2-MeTHF. The product solution was concentrated to ~ 100 mL, chased with 120 mL of IPAc twice. 250 mL of heptanes was charged slowly and then the volume of the mixture was concentrated to 300 mL. The mixture was heated to 45 °C and 160 mL of heptanes charged. The mixture was cooled to rt in 2h, stirred for 30 min,

filtered and washed with 2-MeTHF/heptanes mixture (1:7, 80 mL). The wetcake was dried at 55 °C for 24 h to give 47.1 g of Moc-*L*-Val-OH product as a white solid (90%).

Moc-*L*-Val-OH (150 g, 856 mmol), HOBt hydrate (138 g, 899 mmol) and DMF (1500 ml) were charged to a flask. The mixture was stirred for 15 min to give a clear solution. EDC hydrochloride (172 g, 899 mmol) was charged and mixed for 20 min. The mixture was cooled to 13 °C and (*L*)-proline benzyl ester hydrochloride (207 g, 856 mmol) charged. Triethylamine (109 g, 1079 mmol) was then charged in 30 min. The resulting suspension was mixed at rt for 1.5 h. The reaction mixture was cooled to 15 °C and 1500 mL of 6.7% $NaHCO_3$ charged in 1.5 h, followed by the addition of 1200 mL of water over 60 min. The mixture was stirred at rt for 30 min, filtered and washed with water/DMF mixture (1:2, 250 mL) and then with water (1500 mL). The wetcake was dried at 55 °C for 24 h to give 282 g of product as a white solid (90%).

The resulting solids (40 g) and 5% Pd/Alumina were charged to a Parr reactor followed by THF (160 mL). The reactor was sealed and purged with nitrogen (6 × 20 psig) followed by a hydrogen purge (6 × 30 psig). The reactor was pressurized to 30 psig with hydrogen and agitated at room temperature for approximately 15 hours. The resulting slurry was filtered through a GF/F filter and concentrated to approximately 135 g solution. Heptane was added (120 mL), and the solution was stirred until solids formed. After an addition 2 – 3 hours additional heptane was added drop-wise (240 mL), the slurry was stirred for approximately 1 hour, then filtered. The solids were dried to afford the title compound.

Example 37C

(1R,4R)-1,4-bis(4-nitrophenyl)butane-1,4-diyl dimethanesulfonate

The product from Example 32 (5.01 g, 13.39 mmol) was combined with 2-methyltetrahydrofuran (70 mL) and cooled to -5 °C, and N,N-diisopropylethylamine (6.81 g, 52.7 mmol) was added over 30 seconds. Separately, a solution of methanesulfonic anhydride (6.01 g, 34.5 mmol) in 2-methyltetrahydrofuran (30 mL) was prepared and added to the diol slurry over 3 min., maintaining the internal temperature between -15 °C and -25 °C. After mixing for 5 min at -15 °C, the cooling bath was removed and the reaction was allowed to warm slowly to 23 °C and mixed for 30 minutes. After reaction completion, the crude slurry was carried immediately into the next step.

Example 37D

(2S,5S)-1-(4-tert-butylphenyl)-2,5-bis(4-nitrophenyl)pyrrolidine

To the crude product solution from Example 37C (7.35 g, 13.39 mmol) was added 4-tert-butylaniline (13.4 g, 90 mmol) at 23 °C over 1 minute. The reaction was heated to 65 °C for 2 h. After completion, the reaction mixture was cooled to 23 °C and diluted with 2-methyltetrahydrofuran (100 mL) and 1 M HCl (150 mL). After partitioning the phases, the organic phase was treated with 1 M

HCl (140 mL), 2-methyltetrahydrofuran (50 mL), and 25 wt% aq. NaCl (100 mL), and the phases were partitioned. The organic phase was washed with 25 wt% aq. NaCl (50 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo to approximately 20 mL. Heptane (30 mL) and additional 2-methyltetrahydrofuran were added in order to induce crystallization. The slurry was concentrated further, and additional heptane (40 mL) was slowly added and the slurry was filtered, washing with 2-methyltetrahydrofuran:heptane (1:4, 20 mL). The solids were suspended in MeOH (46 mL) for 3 h, filtered, and the wet solid was washed with additional MeOH (18 mL). The solid was dried at 45 °C in a vacuum oven for 16 h to provide the title compound (3.08 g, 51% 2-step yield).

Example 37E

4,4'-((2S,5S)-1-(4-tert-butylphenyl)pyrrolidine-2,5-diyl)dianiline

To a 160 ml Parr stirrer hydrogenation vessel was added the product from Example 37D (2 g, 4.49 mmol), followed by 60 ml of THF, and Raney Nickel Grace 2800 (1 g, 50 wt% (dry basis)) under a stream of nitrogen. The reactor was assembled and purged with nitrogen (8 x 20 psig) followed by purging with hydrogen (8 x 30 psig). The reactor was then pressurized to 30 psig with hydrogen and agitation (700 rpm) began and continued for a total of 16 h at room temperature. The slurry was filtered by vacuum filtration using a GF/F Whatman glass fiber filter. Evaporation of the filtrate to afford a slurry followed by the addition heptane and filtration gave the crude title compound, which was dried and used directly in the next step.

Example 37F

dimethyl (2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-((2S,5S)-1-(4-tert-butylphenyl)pyrrolidine-2,5-diyl)bis(4,1-phenylene)bis(azanediyl)bis(oxomethylene))bis(pyrrolidine-2,1-diyl))bis(3-methyl-1-oxobutane-2,1-diyl)dicarbamate

To a solution of the product from Example 37E (1.64 g, 4.25 mmol) in DMF (20 ml), the product from Example 37B (2.89 g, 10.63 mmol), and HATU (4.04 g, 10.63 mmol) in DMF (150mL) was added triethylamine (1.07 g, 10.63 mmol), and the solution was stirred at room temperature for 90 min. To the reaction mixture was poured 20 mL of water, and the white precipitate obtained was filtered, and the solid was washed with water (3x5 mL). The solid was blow dried for 1h. The crude material was loaded on a silica gel column and eluted with a gradient starting with ethyl acetate/ heptane (3/7), and ending with pure ethyl acetate. The desired fractions were combined and solvent distilled off to give a very light yellow solid, which was dried at 45 °C in a vacuum oven with nitrogen purge for 15 h to give the title compound (2.3 g, 61% yield). ^{1}H NMR (400 MHz, DMSO-D6) δ ppm 0.88 (d, J=6.61 Hz, 6 H) 0.93 (d, J=6.72 Hz, 6 H) 1.11 (s, 9 H) 1.63 (d, J=5.42 Hz, 2 H) 1.80 - 2.04 (m, 8 H) 2.09 - 2.19 (m, 2 H) 2.44 - 2.47 (m, 2 H) 3.52 (s, 6 H) 3.59 - 3.66 (m, 2 H) 3.77 - 3.84 (m, 2 H) 4.02 (t, J=8.40 Hz, 2 H) 4.42 (dd, J=7.86, 4.83 Hz, 2 H) 5.14 (d, J=6.18 Hz, 2 H) 6.17

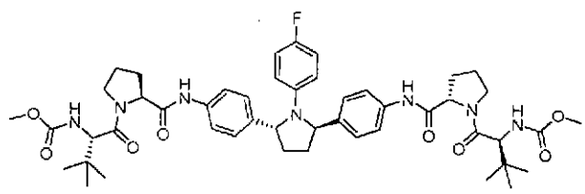
(d, J=8.67 Hz, 2 H) 6.94 (d, J=8.78 Hz, 2 H) 7.13 (d, J=8.46 Hz, 4 H) 7.31 (d, J=8.35 Hz, 2 H) 7.50 (d, J=8.35 Hz, 4 H) 9.98 (s, 2 H).

Alternately, the product from example 37E (11.7 g, 85 wt%, 25.8 mmol) and the product from example 37B (15.45 g, 56.7 mmol) are suspended in EtOAc (117 mL), diisopropylethylamine (18.67 g, 144 mmol) is added and the solution is cooled to 0 °C. In a separate flask, 1-propanephosphonic acid cyclic anhydride (T3P®) (46.0 g, 50 wt% in EtOAc, 72.2 mmol) was dissolved in EtOAc (58.5 mL), and charged to an addition funnel. The T_3P solution is added to the reaction mixture drop-wise over 3-4 h and stirred until the reaction is complete. The reaction is warmed to room temperature,and washed with 1M HCl/7.5 wt% NaCl (100 mL), then washed with 5% $NaHCO_3$ (100-mL), then washed with 5% NaCl solution (100 mL). The solution was concentrated to approximately 60 mL, EtOH (300 mL) was added, and the solution was concentrated to 84 g solution.

A portion of the EtOH solution of product (29 g) was heated to 40 °C, and added 134 g 40 w% EtOH in H_2O. A slurry of seeds in 58 wt/wt% EtOH/H_2O was added, allowed to stir at 40 °C for several hours, then cooled to 0 °C. The slurry is then filtered, and washed with 58wt/wt% EtOH/H_2O. The product is dried at 40 - 60 °C under vacuum, and then rehydrated by placing a tray of water in the vacuum oven to give the title compound. The title compound showed an EC_{50} value of less than about 0.1 nM in HCV 1b-Con1 replicon assays in the presence of 5% FBS.

Example 38

Dimethyl (2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-((2R,5R)-1-(4-fluorophenyl)pyrrolidine-2,5-diyl)bis(4,1-phenylene))bis(azanediyl)bis(oxomethylene)bis(pyrrolidine-2,1-diyl))bis(3,3-dimethyl-1-oxobutane-2,1-diyl)dicarbamate



Example 38A

(1S,4S)-1,4-bis(4-nitrophenyl)butane-1,4-diyl dimethanesulfonate

The title compound was prepared using the methods from Example 37C, substituting the product from Example 33 for the product from Example 32.

Example 38B

(2R,5R)-1-(4-fluorophenyl)-2,5-bis(4-nitrophenyl)pyrrolidine

The title compound was prepared using the methods from Example 37D, substituting 4-fluoroaniline for 4-*tert*-butylaniline.

Example 38C

4,4'-((2R,5R)-1-(4-fluorophenyl)pyrrolidine-2,5-diyl)dianiline

To a solution of the product from Example 38B (2.34 g, 5.74 mmol) in 1:1 ethanol:THF (60 ml) in a 250 mL stainless steel pressure bottle was added PtO_2 (0.47 g, 2.06 mmol) and the resulting mixture was placed under H_2 pressure (30 psi) and stirred at rt. for 90 min. The mixture was filtered through a nylon membrane and the filtrate was concentrated in vacuo. The crude product was purified by column chromatography on silica gel using a solvent gradient of 0-65% ethyl acetate in hexanes to give the title compound as a solid (0.736 g, 37%).

Example 38D

(2S,2'S)-tert-butyl 2,2'-(4,4'-((2R,5R)-1-(4-fluorophenyl)pyrrolidine-2,5-diyl)bis(4,1-phenylene))bis(azanediyl)bis(oxomethylene)dipyrrolidine-1-carboxylate

To a solution of the product from Example 38C (3.54 g, 10.19 mmol), (S)-1-(tert-butoxycarbonyl)pyrrolidine-2-carboxylic acid (5.48 g, 25.5 mmol), and HATU (9.69 g, 25.5 mmol) in anhydrous NMP (50mL) was added N,N-diisopropylethylamine (5.29 ml, 30.6 mmol), and reaction mixture was stirred at room temperature for 30-45 minutes. The reaction mixture diluted with water (500mL). The precipitated product was filtered and washed with water (3x100mL), sodium bicarbonate solution (50mL), and water (50mL). The product dried at 40 °C for 15 h. This material (8.5g) was passed through a pad of silica gel and eluted with ethyl acetate to afford the white solid product (7.9g, 99%).

Example 38E

(2S,2'S)-N,N'-(4,4'-((2R,5R)-1-(4-fluorophenyl)pyrrolidine-2,5-diyl)bis(4,1-phenylene))dipyrrolidine-2-carboxamide

To a solution of the product from Example 38D (7.9 g, 10.65 mmol) in dichloromethane (50mL), was added 5M HCl solution in isopropyl alcohol (50mL) and the reaction mixture was stirred at room temperature for 16 h. The solvent was evaporated by rotavap under vacuum and crude material taken in dichloromethane containing 20% methanol (200mL). The solution was washed with 5% ammonium hydroxide solution (90mL), brine (50mL) and dried over $MgSO_4$. The solution was filtered and concentrated to give 6.5g of crude product. This material was recrystallized from ethyl acetate /heptane (8/2) to give the title compound (5.0 g, 87% yield).

Example 38F

Dimethyl (2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-((2R,5R)-1-(4-fluorophenyl)pyrrolidine-2,5-diyl)bis(4,1-phenylene))bis(azanediyl)bis(oxomethylene)bis(pyrrolidine-2,1-diyl))bis(3,3-dimethyl-1-oxobutane-2,1-diyl)dicarbamate

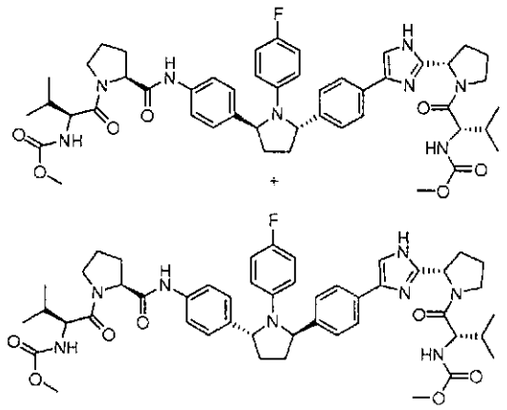
To a solution of the product from Example 38E (4.14 g, 7.64 mmol), (S)-2-methoxycarbonylamino-3,3-dimethyl-butyric acid (3.62 g, 19.11 mmol), and EDAC (3.66 g, 19.11 mmol) in anhydrous DMF (80mL) was added N,N-diisopropylethylamine (2.96 g, 22.93 mmol) and the solution was stirred at room temperature for 4 h. The reaction mixture poured into 400 mL of water, and the white precipitate obtained was filtered and washed with water (3x50mL), sodium bicarbonate (50mL), water (50ML), and dried at 45 ^{0}C in a vacuum oven with nitrogen purge for 15 h to give 7.0 g of the crude product. The crude material was loaded on silica gel column (150g silica) and eluted with a gradient starting with ethyl acetate/ heptane (7/3), and ending with ethyl acetate. Desired fractions were combined and solvent distilled off to give very light yellow oil, which was triturated MTBE /heptane(1:9) for 1h. The white solid thus obtained was filtered and dried in a vacuum oven with nitrogen purge to afford 6.1g of product. The solid 5.5 g was dissolved in 16mL of methanol and this solution was added into water (220 mL) in a 500mL flask. The slurry was stirred for 30 minutes, and the solid was collected by filtration, dried at 45 ^{0}C with nitrogen purge for 15 h to give the title compound (5.4 g). ^{1}H NMR (400 MHz, DMSO-D6) δ ppm 0.96 (s, 18 H) 1.64 (d, *J*=5.53 Hz, 2 H) 1.78 – 1.93 (m, 6 H) 1.94 – 2.06 (m, 2 H) 2.09 – 2.21 (m, 2 H) 3.54 (s, 6 H) 3.59 – 3.69 (m, 2 H) 3.72 – 3.83 (m, 2 H) 4.20 (d, *J*=8.89 Hz, 2 H) 4.43 (dd, *J*=7.92, 5.42 Hz, 2 H) 5.16 (d, *J*=6.29 Hz, 2 H) 6.20 (dd, *J*=9.16, 4.39 Hz, 2 H) 6.77 (t, *J*=8.95 Hz, 2 H) 7.12 (d, *J*=8.57 Hz, 4 H) 7.50 (d, *J*=8.57 Hz, 4 H) 9.99 (s, 2 H). The title compound showed an EC_{50} value of less than about 0.1 nM in HCV 1b-Con1 replicon assays in the presence of 5% FBS.

Example 39

N-(methoxycarbonyl)-L-valyl-*N*-(4-{(2*S*,5*S*)-1-(4-fluorophenyl)-5-[4-(2-{(2*S*)-1-[*N*-(methoxycarbonyl)-L-valyl]pyrrolidin-2-yl}-1*H*-imidazol-4-yl)phenyl]pyrrolidin-2-yl}phenyl)-L-prolinamide (ACD v12)

and

N-(methoxycarbonyl)-L-valyl-*N*-(4-{(2*R*,5*R*)-1-(4-fluorophenyl)-5-[4-(2-{(2*S*)-1-[*N*-(methoxycarbonyl)-L-valyl]pyrrolidin-2-yl}-1*H*-imidazol-4-yl)phenyl]pyrrolidin-2-yl}phenyl)-L-prolinamide (ACD v12)



Example 39A

1-(4-bromophenyl)-4-(4-nitrophenyl)butane-1,4-dione

Added benzene (108 mL) to anhydrous zinc(II) chloride (19.62 g, 144 mmol), followed by the addition of diethylamine (11.16 mL, 108 mmol) and 2-methylpropan-2-ol (10.32 mL, 108 mmol) and stirred at room temperature for 2 h. Added 2-bromo-1-(4-bromophenyl)ethanone (20 g, 72.0 mmol) and 1-(4-nitrophenyl)ethanone (17.83 g, 108 mmol) together and stirred mixture for 18 h. Added 5% aq. sulfuric acid (50 mL) and stirred vigorously, then the product was collected by filtration, rinsed with benzene, water, methanol, dichloromethane and dried under vacuum to provide the product (15.0 g, 58% yield, colorless powder).

Example 39B

1-(4-bromophenyl)-4-(4-nitrophenyl)butane-1,4-diol

Dissolved the product from Example 39A (3.64 g, 10.05 mmol) in ethanol (67 mL) and added sodium borohydride (0.837 g, 22.11 mmol) portionwise. After stirring for 1 h at room temperature, the mixture was filtered through celite and washed with methanol and ethyl acetate and the filtrate concentrated to a solid. The solid was dissolved in ethyl acetate (200 mL) and extracted with 1N aq. HCl (200 mL), then brine and the organic layer dried and concentrated to a colorless oil (3.68 g, 100%) that was used directly in the next reaction.

Example 39C

1-(4-bromophenyl)-4-(4-nitrophenyl)butane-1,4-diyl dimethanesulfonate

Dissolved the product from Example 39B (3.68 g, 10.05 mmol) in dichloromethane (167 mL) and cooled the solution in an ice bath followed by the addition of triethylamine (4.20 mL, 30.1 mmol) and methanesulfonyl chloride (1.96 mL, 25.1 mmol) dropwise. After stirring for 15 min, the solution was concentrated to a solid (5.25 g, 100%) that was used directly in the next reaction.

Example 39D

2-(4-bromophenyl)-1-(4-fluorophenyl)-5-(4-nitrophenyl)pyrrolidine

Dissolved the product from Example 39C (5.25 g, 10.05 mmol) in DMF (31 mL) and then added 4-fluoroaniline (9.65 mL, 101 mmol) and heated solution at 50 °C for 18 h. Solution was cooled to room temperature and 1N aq. HCl added (100 mL) then extracted with ethyl acetate (2 x 200 mL), then combined organic extracts washed with brine, dried and concentrated to an amber oil to which methanol (10 mL) was added and after 3 h a yellow solid (1.05 g, 24%) resulted as the title compound as a 1/1 mixture of trans pyrrolidine isomers.

Example 39E

1-(4-fluorophenyl)-2-(4-nitrophenyl)-5-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)pyrrolidine

Dissolved the product from Example 39D (1.05 g, 2.38 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (0.725 g, 2.86 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.194 g, 0.238 mmol), and potassium acetate (0.35 g, 3.57 mmol) in dioxane (20 mL) and then bubbled nitrogen gas through the solution for 10 min, then heated at 100 °C for 1.5 h. Solution was cooled to room temperature then filtered through celite and washed with ethyl acetate (20 mL). The filtrate was dried, concentrated and the residue purified by column chromatography on silica gel, eluting with a solvent gradient of 10-50% ethyl acetate in hexane to give the title compound (1.09 g, 94%) as a yellow solid and a 1/1 mixture of trans stereoisomers.

Example 39F

(2S)-tert-butyl 2-(4-(4-(1-(4-fluorophenyl)-5-(4-nitrophenyl)pyrrolidin-2-yl)phenyl)-1H-imidazol-2-yl)pyrrolidine-1-carboxylate

Dissolved the product from Example 39E (1.05 g, 2.15 mmol), the product from Example 26D (0.748 g, 2.365 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.176 g, 0.215 mmol) in a mixture of toluene (10 mL), ethanol (10 mL) and a 1N aq. sodium bicarbonate solution (2.58 mL, 2.58 mmol) and bubbled nitrogen gas through the solution for 10 min, then heated at 90°C for 3 h. Solution was cooled to room temperature and water (20 mL) added then extracted with dichloromethane (50 mL), then dried, concentrated and the residue purified by column chromatography on silica gel, eluting with a solvent gradient of 0-100% ethyl acetate in hexane to give the title compound (0.28 g, 72%) as a yellow solid and a 1/1 mixture of trans stereoisomers.

Example 39G

(2S)-tert-butyl 2-(4-(4-(5-(4-aminophenyl)-1-(4-fluorophenyl)pyrrolidin-2-yl)phenyl)-1H-imidazol-2-yl)pyrrolidine-1-carboxylate

Dissolved the product from Example 39F (300 mg, 0.502 mmol) in ethanol (5 mL) and THF (5 mL) then added platinum(IV) oxide (22.8 mg, 0.1 mmol) and a hydrogen balloon and stirred the solution at room temperature for 2.5 h. Solution was filtered through celite and washed with

methanol (10 mL), then concentrated to give the title compound (285 mg, 100%) as a colorless semi-solid and a 1/1 mixture of stereoisomers.

Example 39H

(2S)-tert-butyl 2-(4-(5-(4-(2-((S)-1-(tert-butoxycarbonyl)pyrrolidin-2-yl)-1H-imidazol-4-yl)phenyl)-1-(4-fluorophenyl)pyrrolidin-2-yl)phenylcarbamoyl)pyrrolidine-1-carboxylate

Dissolved the product from Example 39G (285 mg, 0.502 mmol), (S)-1-(tert-butoxycarbonyl)pyrrolidine-2-carboxylic acid (162 mg, 0.753 mmol), HATU (305 mg, 0.803 mmol) and Hunig's base (0.263 mL, 1.506 mmol) in DMSO (5 mL) and stirred at room temperature for 1 h. Dichloromethane (50 mL) was added followed by extraction with water (2 x 50 mL), the organic extract dried, concentrated and the residue dissolved in methanol (10 mL) followed by the addition of potassium carbonate (400 mg, 2.89 mmol) and stirred the bright yellow solution at room temperature for 30 min. The solution was then filtered and the filtrate concentrated to an oil, which was dissolved in a 95/5 dichloromethane/methanol mixture (50 mL) and extracted with water (20 mL). The organic extract was dried and concentrated to give the title product (350 mg, 91%) as a light yellow solid and a 1/1 mixture of stereoisomers.

Example 39I

(2S)-N-(4-(1-(4-fluorophenyl)-5-(4-(2-((S)-pyrrolidin-2-yl)-1H-imidazol-4-yl)phenyl)pyrrolidin-2-yl)phenyl)pyrrolidine-2-carboxamide hydrochloride salt

Dissolved the product from Example 39H (350 mg, 0.458 mmol) in 4M hydrochloric acid in dioxane solution (6 mL) and stirred the solution at room temperature for 30 min then concentrated the mixture under high vacuum to a solid (approx. 310 mg) as a hydrochloride salt that was used directly in the next reaction.

Example 39J

N-(methoxycarbonyl)-L-valyl-*N*-(4-{(2*S*,5*S*)-1-(4-fluorophenyl)-5-[4-(2-{(2*S*)-1-[*N*-(methoxycarbonyl)-L-valyl]pyrrolidin-2-yl}-1*H*-imidazol-4-yl)phenyl]pyrrolidin-2-yl}phenyl)-L-prolinamide (ACD v12)

and

N-(methoxycarbonyl)-L-valyl-*N*-(4-{(2*R*,5*R*)-1-(4-fluorophenyl)-5-[4-(2-{(2*S*)-1-[*N*-(methoxycarbonyl)-L-valyl]pyrrolidin-2-yl}-1*H*-imidazol-4-yl)phenyl]pyrrolidin-2-yl}phenyl)-L-prolinamide (ACD v12)

To a mixture of the product from Example 39I (300 mg, 0.45 mmol), (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (173 mg, 0.99 mmol), and HATU (428 mg, 1.125 mmol) in DMSO (5 ml) was added Hunig's base (0.786 mL, 4.5 mmol), and the reaction was stirred at room temperature for 1 h. Dichloromethane (50 mL) was added followed by extraction with water (2 x 25 mL), the organic extract dried, concentrated and the residue dissolved in methanol (15 mL)

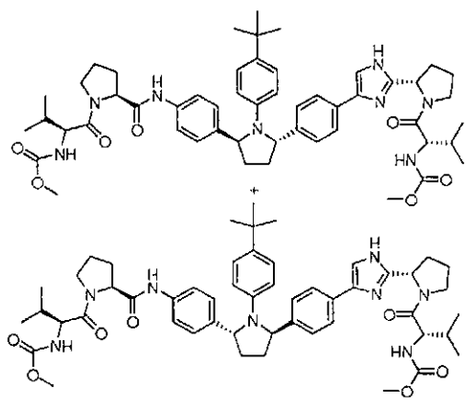
followed by the addition of potassium carbonate (300 mg, 2.17 mmol) and stirred at room temperature for 20 min. The solution was then filtered and the filtrate concentrated to an oil, which was dissolved in a 95/5 dichloromethane/methanol mixture (50 mL) and extracted with water (20 mL). The organic extract was dried and concentrated, and the residue purified by column chromatography on silica gel, eluting with a solvent gradient of 0-25% methanol in dichloromethane to give the title compounds (0.13 g, 33%) as a colorless solid and as a 1/1 mixture of diastereomers. ^{1}H NMR (400 MHz, DMSO-D6) δ ppm 11.64 (s, 1H), 9.94 (s, 1H), 7.57 (d, J=8.1 Hz, 2H), 7.47 (m, 3H), 7.33 (d, J=1.7 Hz, 1H), 7.24 (m, 2H), 7.08 (m, 4H), 6.72 (m, 2H), 6.17 (m, 2H), 5.15 (m, 2H), 5.01 (m, 1H), 4.38 (m, 1H), 4.0 (m, 2H), 3.75 (m, 2H), 3.56 (m, 1H), 3.48 (s, 3H), 3.47 (s, 3H), 2.06 (m, 2H), 1.87 (m, 8H), 1.63 (m, 2H), 0.82 (m, 12H). The title compound showed an EC_{50} value of less than about 0.1 nM in HCV 1b-Con1 replicon assays in the presence of 5% FBS.

Example 40

N-(methoxycarbonyl)-L-valyl-*N*-(4-{(2*S*,5*S*)-1-(4-*tert*-butylphenyl)-5-[4-(2-{(2*S*)-1-[*N*-(methoxycarbonyl)-L-valyl]pyrrolidin-2-yl}-1*H*-imidazol-4-yl)phenyl]pyrrolidin-2-yl}phenyl)-L-prolinamide (ACD v12)

and

N-(methoxycarbonyl)-L-valyl-*N*-(4-{(2*R*,5*R*)-1-(4-*tert*-butylphenyl)-5-[4-(2-{(2*S*)-1-[*N*-(methoxycarbonyl)-L-valyl]pyrrolidin-2-yl}-1*H*-imidazol-4-yl)phenyl]pyrrolidin-2-yl}phenyl)-L-prolinamide (ACD v12)



Example 40A

2-(4-bromophenyl)-1-(4-tert-butylphenyl)-5-(4-nitrophenyl)pyrrolidine

The product from Example 39C (10.86 g, 20.79 mmol), DMF (65 mL) and 4-tert-butylaniline (26.5 mL, 166 mmol) was reacted according to the procedure in Example 39D to provide the title compound (5.0 g, 50%, yellow solid) as a mixture of cis and trans pyrrolidine stereoisomers.

Example 40B

1-(4-tert-butylphenyl)-2-(4-nitrophenyl)-5-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)pyrrolidine

The product from Example 40A (2.0 g, 4.17 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (1.27 g, 5.01 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.681 g, 0.834 mmol), and potassium acetate (0.614 g, 6.26 mmol) in dioxane (35 mL) was reacted according to the procedure in Example 39E to provide the title compound (1.5 g, 68%, yellow solid) as a mixture of stereoisomers.

Example 40C

(2S)-tert-butyl 2-(4-(4-(1-(4-tert-butylphenyl)-5-(4-nitrophenyl)pyrrolidin-2-yl)phenyl)-1H-imidazol-2-yl)pyrrolidine-1-carboxylate

The product from Example 40B (0.7 g, 1.33 mmol), (S)-tert-butyl 2-(4-bromo-1H-imidazol-2-yl)pyrrolidine-1-carboxylate (0.462 g, 1.463 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.109 g, 0.133 mmol) in a mixture of toluene (6 mL), ethanol (6 mL) and a 1N aq. sodium bicarbonate solution (1.6 mL, 1.6 mmol) was reacted according to the procedure in Example 39F to provide the title compound (0.66 g, 78%, yellow solid) as a mixture of stereoisomers.

Example 40D

(2S)-tert-butyl 2-(4-(4-(5-(4-aminophenyl)-1-(4-tert-butylphenyl)pyrrolidin-2-yl)phenyl)-1H-imidazol-2-yl)pyrrolidine-1-carboxylate

The product from example 40C (1.37 g, 2.153 mmol), in ethanol (10 mL) and THF (10 mL) then added platinum(IV) oxide (196 mg, 0.862 mmol) and a hydrogen balloon and stirred the solution at room temperature for 48 h. The reaction was then treated according to the procedure in Example 39G to provide the title compound (1.3 g, 100%) as a mixture of stereoisomers.

Example 40E

(2R)-tert-butyl 2-(4-(5-(4-(2-((S)-1-(tert-butoxycarbonyl)pyrrolidin-2-yl)-1H-imidazol-4-yl)phenyl)-1-(4-tert-butylphenyl)pyrrolidin-2-yl)phenylcarbamoyl)pyrrolidine-1-carboxylate

The product from Example 40D (1.3 g, 2.146 mmol), (S)-1-(tert-butoxycarbonyl)pyrrolidine-2-carboxylic acid (1.386 g, 6.44 mmol), HATU (1.305 g, 3.43 mmol) and Hunig's base (1.124 mL, 6.44 mmol) in DMSO (20 mL) was reacted according to the procedure in Example 39H to provide the title compound (1.01 g, 59%) as a mixture of stereoisomers.

Example 40F

(2R)-N-(4-(1-(4-tert-butylphenyl)-5-(4-(2-((S)-pyrrolidin-2-yl)-1H-imidazol-4-yl)phenyl)pyrrolidin-2-yl)phenyl)pyrrolidine-2-carboxamide hydrochloride salt

The product from Example 40E (610 mg, 0.76 mmol), in 2M hydrochloric acid in dioxane solution (10 mL) was reacted according to the procedure in Example 39I to provide the title compound (495 mg) as a hydrochloride salt and a mixture of stereoisomers.

Example 40G

N-(methoxycarbonyl)-L-valyl-*N*-(4-{(2*S*,5*S*)-1-(4-*tert*-butylphenyl)-5-[4-(2-{(2*S*)-1-[*N*-(methoxycarbonyl)-L-valyl]pyrrolidin-2-yl}-1*H*-imidazol-4-yl)phenyl]pyrrolidin-2-yl}phenyl)-L-prolinamide (ACD v12)

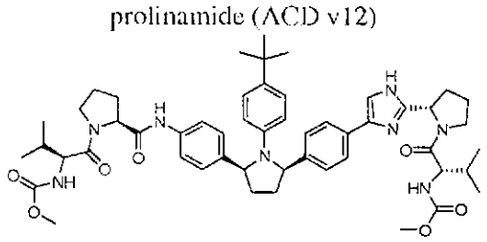
and

N-(methoxycarbonyl)-L-valyl-*N*-(4-{(2*R*,5*R*)-1-(4-*tert*-butylphenyl)-5-[4-(2-{(2*S*)-1-[*N*-(methoxycarbonyl)-L-valyl]pyrrolidin-2-yl}-1*H*-imidazol-4-yl)phenyl]pyrrolidin-2-yl}phenyl)-L-prolinamide (ACD v12)

The product from Example 40F (372 mg, 0.617 mmol), (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (324 mg, 1.851 mmol), HATU (821 mg, 2.16 mmol) in DMSO (6 ml) and Hunig's base (1.078 ml, 6.17 mmol) was reacted according to the procedure in Example 39J then the reaction was diluted with acetonitrile and water (0.1% TFA) and purified by reversed phase chromatography (C18), eluting with 10-100% acetonitrile in water (0.1% TFA) to give the title compounds (68 mg, 12% yield, white solid) as a 1/1 mixture of diastereomers . ^{1}H NMR (free base) (400 MHz, DMSO-D6) δ ppm 0.80 - 0.96 (m, 12 H), 1.10 (s, 9 H), 1.65 (d, *J*=6.07 Hz, 2 H), 1.82 - 2.04 (m, 8 H), 2.07 - 2.20 (m, 3 H), 3.52 (s, 3 H), 3.53 (s, 3 H), 3.58 - 3.66 (m, 2 H), 3.73 - 3.85 (m, 3 H), 3.99 - 4.08 (m, 2 H), 4.43 (dd, *J*=7.97, 4.93 Hz, 1 H), 5.06 (dd, *J*=6.99, 2.87 Hz, 1 H), 5.17 (d, *J*=6.40 Hz, 2 H), 6.20 (d, *J*=8.89 Hz, 2 H), 6.93 (d, *J*=8.89 Hz, 2 H), 7.14 (dd, *J*=8.51, 2.87 Hz, 4 H), 7.30 (t, *J*=9.11 Hz, 2 H), 7.37 (d, *J*=1.84 Hz, 1 H), 7.50 (d, *J*=8.02 Hz, 2 H), 7.61 (d, *J*=8.13 Hz, 2 H), 9.98 (s, 1 H), 11.68 (s, 1 H). The title compound showed an EC_{50} value of less than about 0.1 nM in HCV 1b-Con1 replicon assays in the presence of 5% FBS.

Example 41

N-(methoxycarbonyl)-L-valyl-*N*-(4-{(2*S*,5*R*)-1-(4-*tert*-butylphenyl)-5-[4-(2-{(2*S*)-1-[*N*-(methoxycarbonyl)-L-valyl]pyrrolidin-2-yl}-1*H*-imidazol-4-yl)phenyl]pyrrolidin-2-yl}phenyl)-L-prolinamide (ACD v12)



To the product from Example 40F (493 mg, 0.818 mmol), (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (430 mg, 2.454 mmol), HATU (1088 mg, 2.86 mmol) in DMSO (8.2 mL) and Hunig's base (1.5 mL, 8.59 mmol) was reacted according to the procedure in Example 39J then the

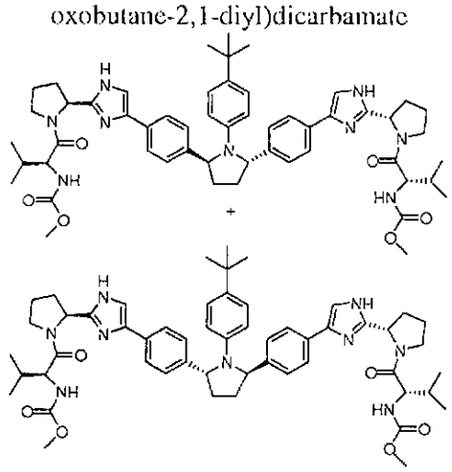
residue was diluted with acetonitrile and water (0.1% TFA) and purified by reversed phase chromatography (C18), eluting with 10-100% acetonitrile in water (0.1% TFA) to give the title compound (80 mg, 11% yield, white solid). ^{1}H NMR (free base) (400 MHz, DMSO-D6) δ ppm 0.89 - 1.04 (m, 12 H), 1.20 (s, 9 H), 1.86 - 2.12 (m, 10 H), 2.15 - 2.27 (m, 3 H), 2.43 - 2.49 (m, 2 H), 3.60 (s, 3 H), 3.61 (s, 3 H), 3.66 - 3.74 (m, 1 H), 3.81 - 3.93 (m, 2 H), 4.06 - 4.15 (m, 2 H), 4.52 (dd, *J*=7.86, 4.61 Hz, 1 H), 4.74 (d, *J*=5.20 Hz, 2 H), 5.14 (dd, *J*=6.99, 3.31 Hz, 1 H), 6.40 (d, *J*=8.78 Hz, 2 H), 7.06 - 7.11 (m, 2 H), 7.32 - 7.41 (m, 2 H), 7.47 (d, *J*=1.73 Hz, 1 H), 7.51 (d, *J*=7.81 Hz, 4 H), 7.65 (d, *J*=8.46 Hz, 2 H), 7.77 (d, *J*=8.24 Hz, 2 H), 10.10 (s, 1 H) ,11.76 (s, 1 H). The title compound showed an EC_{50} value of less than about 0.1 nM in HCV 1b-Con1 replicon assays in the presence of 5% FBS.

Example 42

dimethyl (2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-(4,4'-((2S,5S)-1-(4-tert-butylphenyl)pyrrolidine-2,5-diyl)bis(4,1-phenylene))bis(1H-imidazole-4,2-diyl))bis(pyrrolidine-2,1-diyl))bis(3-methyl-1-oxobutane-2,1-diyl)dicarbamate

and

dimethyl (2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-(4,4'-((2R,5R)-1-(4-tert-butylphenyl)pyrrolidine-2,5-diyl)bis(4,1-phenylene))bis(1H-imidazole-4,2-diyl))bis(pyrrolidine-2,1-diyl))bis(3-methyl-1-oxobutane-2,1-diyl)dicarbamate



Example 42A

1,4-bis(4-bromophenyl)butane-1,4-diol

The product from Example 26E (3.42 g, 8.63 mmol) was subjected to the conditions described in Example 39B to provide the title product (3.45 g, 100% yield, colorless oil).

Example 42B

1,4-bis(4-bromophenyl)butane-1,4-diyl dimethanesulfonate

The product from Example 42A (3.45 g, 8.63 mmol) was subjected to the conditions described in Example 39C to provide the title product (4.8 g, 100%).

Example 42C

2,5-bis(4-bromophenyl)-1-(4-tert-butylphenyl)pyrrolidine

The product from Example 42B (5.2 g, 9.35 mmol) was subjected to the conditions described in Example 39D, substituting 4-tert-butylaniline (11.91 mL, 74.8 mmol) for 4-fluoroaniline to provide the title product (3.89 g, 81%) as a mixture of isomers.

Example 42D

1-(4-tert-butylphenyl)-2,5-bis(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)pyrrolidine

Dissolved the product from Example 42C (3.88 g, 7.56 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (6.72 g, 26.5 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.617 g, 0.756 mmol), and potassium acetate (3.34 g, 34.0 mmol) in dimethoxyethane (70 mL) and bubbled nitrogen gas through the solution for 10 min, then heated at 85 °C for 1 h. Solution was cooled to room temperature then filtered through celite and washed with ethyl acetate (20 mL), the filtrate dried, then concentrated and the residue purified by column chromatography on silica gel, eluting with a solvent gradient of 0-10% ethyl acetate in hexane followed by trituration of the resultant solid with diethyl ether to give the title compound (1.14 g, 25%) as a 1/1 mixture of trans stereoisomers.

Example 42E

(2S,2'S)-tert-butyl 2,2'-(4,4'-(4,4'-(1-(4-tert-butylphenyl)pyrrolidine-2,5-diyl)bis(4,1-phenylene))bis(1H-imidazole-4,2-diyl))dipyrrolidine-1-carboxylate

Dissolved the products from Example 42D (0.915 g, 1.506 mmol), the product from Example 26D (1.429 g, 4.52 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.123 g, 0.151 mmol) in a mixture of toluene (7 mL), ethanol (7 mL) and a 2N aq. sodium bicarbonate solution (2.64 mL, 5.28 mmol) and bubbled nitrogen gas through the solution for 10 min, then heated at 100 °C for 3 h. Solution was cooled to room temperature and water (20 mL) added then extracted with dichloromethane (50 mL), then dried, concentrated and the residue purified by column chromatography on silica gel, eluting with a solvent gradient of 0-80% ethyl acetate in hexane to give the title compound (0.93 g, 75%) as a 1/1 mixture of trans stereoisomers.

Example 42F

(S)-4,4'-(4,4'-(1-(4-tert-butylphenyl)pyrrolidine-2,5-diyl)bis(4,1-phenylene))bis(2-((S)-pyrrolidin-2-yl)-1H-imidazole) hydrochloride salt

To the product from Example 42E (1.11 g, 1.344 mmol), in 4M hydrochloric acid in dioxane solution (5 mL) was reacted according to the procedure in Example 39I to provide the title compound (1.12 g) as a hydrochloride salt and a mixture of stereoisomers.

Example 42G

dimethyl (2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-(4,4'-((2S,5S)-1-(4-tert-butylphenyl)pyrrolidine-2,5-diyl)bis(4,1-phenylene))bis(1H-imidazole-4,2-diyl))bis(pyrrolidine-2,1-diyl))bis(3-methyl-1-oxobutane-2,1-diyl)dicarbamate

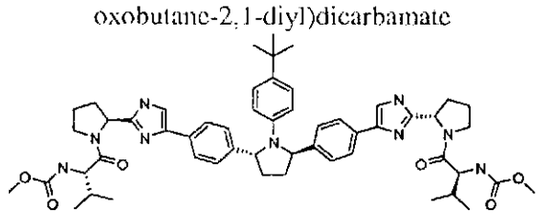
and

dimethyl (2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-(4,4'-((2R,5R)-1-(4-tert-butylphenyl)pyrrolidine-2,5-diyl)bis(4,1-phenylene))bis(1H-imidazole-4,2-diyl))bis(pyrrolidine-2,1-diyl))bis(3-methyl-1-oxobutane-2,1-diyl)dicarbamate

To a mixture of the products from Example 42F (1.04 g, 1.662 mmol), (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (0.728 g, 4.15 mmol), and HATU (1.295 g, 3.41 mmol) in DMSO (20 mL) was added Hunig's base (2.322 mL, 13.29 mmol), and the reaction was stirred at room temperature for 1 h. Water (20 mL) was added to form a solid that was dissolved in dichloromethane and purified by column chromatography on silica gel, eluting with a solvent gradient of 0-5% methanol in dichloromethane to give a solid that was diluted with acetonitrile and water (0.1% TFA) and further purified by reversed phase chromatography (C18), eluting with 10-100% acetonitrile in water (0.1% TFA) to give the title compound (92 mg, 6% yield, white solid) as a 1/1 mixture of diastereomers. ^{1}H NMR (free base) (400 MHz, DMSO-D6) δ ppm 0.78 - 0.92 (m, 12 H), 1.09 (s, 9 H), 1.63 - 1.74 (m, 2 H), 1.85 - 2.00 (m, 6 H), 2.05 - 2.16 (m, 2 H), 3.44 - 3.50 (m, 4 H), 3.52 (s, 6 H), 3.70 - 3.82 (m, 4 H), 4.02 - 4.09 (m, 2 H), 5.04 (dd, J=6.67, 3.20 Hz, 2 H), 5.19 (t, J=6.18 Hz, 2 H), 6.21 (d, J=8.57 Hz, 2 H), 6.91 (dd, J=7.16, 1.63 Hz, 2 H), 7.14 (dd, J=8.19, 2.22 Hz, 4 H), 7.20 - 7.30 (m, 2 H), 7.36 (d, J=1.19 Hz, 2 H), 7.61 (d, J=8.13 Hz, 4 H), 11.67 (d, J=4.01 Hz, 2 H). The title compound showed an EC_{50} value of less than about 0.1 nM in HCV 1b-Con1 replicon assays in the presence of 5% FBS.

Example 43

dimethyl (2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-(4,4'-((2R,5R)-1-(4-tert-butylphenyl)pyrrolidine-2,5-diyl)bis(4,1-phenylene))bis(1H-imidazole-4,2-diyl))bis(pyrrolidine-2,1-diyl))bis(3-methyl-1-oxobutane-2,1-diyl)dicarbamate

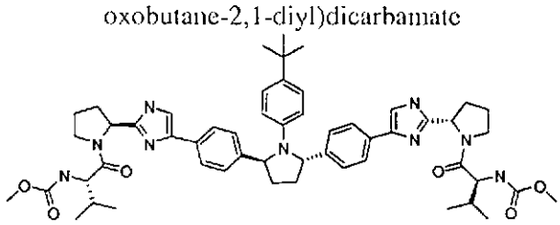


The product from Example 42G was purified by chiral chromatography on a Chirapak IB column eluting with a mixture of hexane/THF/MeOH (80/10/10). The title compound was the first of 2 diastereomers to elute. ^{1}H NMR (400 MHz, DMSO-D6) δ ppm 0.78 - 0.92 (m, 12 H), 1.09 (s, 9 H), 1.63 - 1.74 (m, 2 H), 1.85 - 2.00 (m, 6 H), 2.05 - 2.16 (m, 2 H), 3.44 - 3.50 (m, 4 H), 3.52 (s, 6 H), 3.70 - 3.82 (m, 4 H), 4.02 - 4.09 (m, 2 H), 5.04 (dd, J=6.67, 3.20 Hz, 2 H), 5.19 (t, J=6.18 Hz, 2 H), 6.21 (d, J=8.57 Hz, 2 H), 6.91 (dd, J=7.16, 1.63 Hz, 2 H), 7.14 (dd, J=8.19, 2.22 Hz, 4 H), 7.20 - 7.30

(m, 2 H), 7.36 (d, J=1.19 Hz, 2 H), 7.61 (d, J=8.13 Hz, 4 H), 11.67 (d, J=4.01 Hz, 2 H). The title compound showed an EC_{50} value of less than about 0.1 nM in HCV 1b-Con1 replicon assays in the presence of 5% FBS.

Example 44

dimethyl (2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-(4,4'-((2S,5S)-1-(4-tert-butylphenyl)pyrrolidine-2,5-diyl)bis(4,1-phenylene))bis(1H-imidazole-4,2-diyl))bis(pyrrolidine-2,1-diyl))bis(3-methyl-1-oxobutane-2,1-diyl)dicarbamate



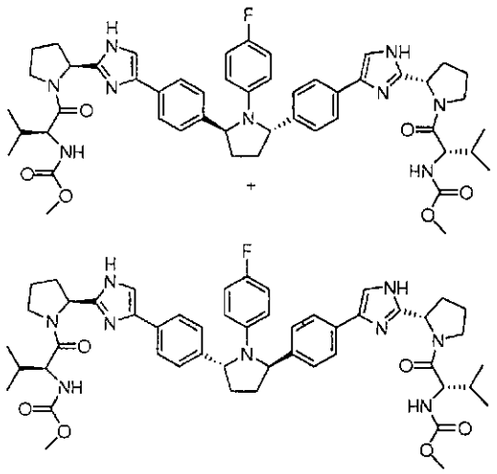
The product from Example 42G was purified by chiral chromatography on a Chirapak IB column eluting with a mixture of hexane/THF/MeOH (80/10/10). The title compound was the second of 2 diastereomers to elute. ^{1}H NMR (400 MHz, DMSO-D6) δ ppm 0.78 - 0.92 (m, 12 H), 1.09 (s, 9 H), 1.63 - 1.74 (m, 2 H), 1.85 - 2.00 (m, 6 H), 2.05 - 2.16 (m, 2 H), 3.44 - 3.50 (m, 4 H), 3.52 (s, 6 H), 3.70 - 3.82 (m, 4 H), 4.02 - 4.09 (m, 2 H), 5.04 (dd, J=6.67, 3.20 Hz, 2 H), 5.19 (t, J=6.18 Hz, 2 H), 6.21 (d, J=8.57 Hz, 2 H), 6.91 (dd, J=7.16, 1.63 Hz, 2 H), 7.14 (dd, J=8.19, 2.22 Hz, 4 H), 7.20 - 7.30 (m, 2 H), 7.36 (d, J=1.19 Hz, 2 H), 7.61 (d, J=8.13 Hz, 4 H), 11.67 (d, J=4.01 Hz, 2 H). The title compound showed an EC_{50} value of less than about 0.1 nM in HCV 1b-Con1 replicon assays in the presence of 5% FBS.

Example 45

dimethyl (2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-(4,4'-((2S,5S)-1-(4-fluorophenyl)pyrrolidine-2,5-diyl)bis(4,1-phenylene))bis(1H-imidazole-4,2-diyl))bis(pyrrolidine-2,1-diyl))bis(3-methyl-1-oxobutane-2,1-diyl)dicarbamate

and

dimethyl (2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-(4,4'-((2R,5R)-1-(4-fluorophenyl)pyrrolidine-2,5-diyl)bis(4,1-phenylene))bis(1H-imidazole-4,2-diyl))bis(pyrrolidine-2,1-diyl))bis(3-methyl-1-oxobutane-2,1-diyl)dicarbamate



Example 45A

2,5-bis(4-bromophenyl)-1-(4-fluorophenyl)pyrrolidine

The product from Example 42B (5.2 g, 9.35 mmol) was subjected to the conditions described in Example 39D to provide the title product (6.41 g, 48%) as a mixture of cis and trans isomers.

Example 45B

1-(4-fluorophenyl)-2,5-bis(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)pyrrolidine

The product from Example 45A (2.17 g, 4.57 mmol) was subjected to the conditions described in Example 42D and purified by column chromatography on silica gel, eluting with a solvent gradient of 0-15% ethyl acetate in hexane to give the title compound (1.65 g, 64%) as a mixture of cis and trans stereoisomers.

Example 45C

(2S,2'S)-tert-butyl 2,2'-(4,4'-(4,4'-(1-(4-fluorophenyl)pyrrolidine-2,5-diyl)bis(4,1-phenylene))bis(1H-imidazole-4,2-diyl))dipyrrolidine-1-carboxylate

The product from Example 45B (1.0 g, 1.756 mmol) was subjected to the conditions described in Example 42E to provide the title product (1.0 g, 72%) as a mixture of cis and trans isomers.

Example 45D

(S)-4,4'-(4,4'-(1-(4-fluorophenyl)pyrrolidine-2,5-diyl)bis(4,1-phenylene))bis(2-((S)-pyrrolidin-2-yl)-1H-imidazole)

Dissolved the product from Example 45C (150 mg, 0.19 mmol) in dichloromethane (1 mL) and TFA (1 mL) and stirred the solution at room temperature for 1 h then concentrated the mixture under high vacuum to give a solid that was diluted with acetonitrile and water (0.1% TFA) and purified by reversed phase chromatography (C18), eluting with 10-100% acetonitrile in water (0.1% TFA) to give the title compound (62 mg, 55% yield) as a 1/1 mixture of trans diastereomers that eluted before the cis isomer.

Example 45E

dimethyl (2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-(4,4'-((2S,5S)-1-(4-fluorophenyl)pyrrolidine-2,5-diyl)bis(4,1-phenylene))bis(1H-imidazole-4,2-diyl))bis(pyrrolidine-2,1-diyl))bis(3-methyl-1-oxobutane-2,1-diyl)dicarbamate

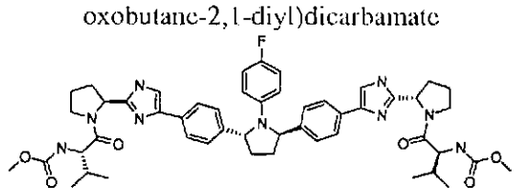
and

dimethyl (2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-(4,4'-((2R,5R)-1-(4-fluorophenyl)pyrrolidine-2,5-diyl)bis(4,1-phenylene))bis(1H-imidazole-4,2-diyl))bis(pyrrolidine-2,1-diyl))bis(3-methyl-1-oxobutane-2,1-diyl)dicarbamate

To a mixture of the product from Example 45D (47 mg, 0.08 mmol), (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (29 mg, 0.168 mmol), and HATU (61 mg, 0.16 mmol) in DMSO (0.8 mL) was added Hunig's base (0.035 mL, 0.2 mmol) was reacted according to the procedure in Example 39J then the residue was diluted with acetonitrile and water (0.1% TFA) and purified by reversed phase chromatography (C18), eluting with 10-100% acetonitrile in water (0.1% TFA) to give the title compound (54 mg, 75% yield, white solid) as a 1/1 mixture of diastereomers . ^{1}H NMR (free base) (400 MHz, DMSO-D6) δ ppm 11.62 - 12.13 (m, 2 H), 7.59 - 7.71 (m, *J*=8.13 Hz, 3 H), 7.46 - 7.57 (m, *J*=8.24 Hz, 1 H), 7.38 (d, *J*=1.84 Hz, 2 H), 7.10 - 7.32 (m, 6 H), 6.72 - 6.83 (m, 2 H), 6.19 - 6.31 (m, 2 H), 5.17 - 5.28 (m, 2 H), 5.02 - 5.11 (m, *J*=6.72 Hz, 2 H), 4.05 (t, *J*=8.40 Hz, 2 H), 3.71 - 3.85 (m, 4 H), 3.53 (s, 6 H), 2.05 - 2.21 (m, 4 H), 1.94 (s, 6 H), 1.64 - 1.78 (m, 2 H), 0.77 - 0.95 (m, 12 H). The title compound showed an EC_{50} value of less than about 0.1 nM in HCV 1b-Con1 replicon assays in the presence of 5% FBS.

Example 46

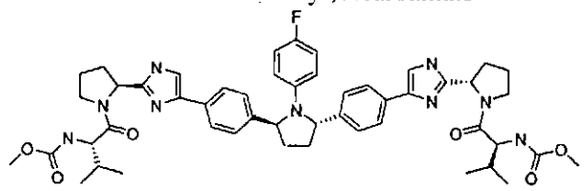
dimethyl (2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-(4,4'-((2R,5R)-1-(4-fluorophenyl)pyrrolidine-2,5-diyl)bis(4,1-phenylene))bis(1H-imidazole-4,2-diyl))bis(pyrrolidine-2,1-diyl))bis(3-methyl-1-oxobutane-2,1-diyl)dicarbamate



The product from Example 45E was purified by chiral chromatography on a Chirapak IB column eluting with a mixture of hexane/THF/MeOH (85/7.5/7.5). ^{1}H NMR (400 MHz, DMSO-D6) δ ppm 11.62 - 12.13 (m, 2 H), 7.59 - 7.71 (m, *J*=8.13 Hz, 3 H), 7.46 - 7.57 (m, *J*=8.24 Hz, 1 H), 7.38 (d, *J*=1.84 Hz, 2 H), 7.10 - 7.32 (m, 6 H), 6.72 - 6.83 (m, 2 H), 6.19 - 6.31 (m, 2 H), 5.17 - 5.28 (m, 2 H), 5.02 - 5.11 (m, *J*=6.72 Hz, 2 H), 4.05 (t, *J*=8.40 Hz, 2 H), 3.71 - 3.85 (m, 4 H), 3.53 (s, 6 H), 2.05 - 2.21 (m, 4 H), 1.94 (s, 6 H), 1.64 - 1.78 (m, 2 H), 0.77 - 0.95 (m, 12 H). The title compound showed an EC_{50} value of less than about 0.1 nM in HCV 1b-Con1 replicon assays in the presence of 5% FBS.

Example 47

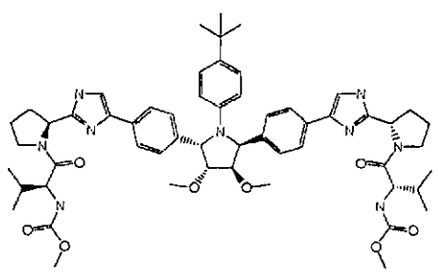
dimethyl (2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-(4,4'-((2S,5S)-1-(4-fluorophenyl)pyrrolidine-2,5-diyl)bis(4,1-phenylene))bis(1H-imidazole-4,2-diyl))bis(pyrrolidine-2,1-diyl))bis(3-methyl-1-oxobutane-2,1-diyl)dicarbamate



The product from Example 45E was purified by chiral chromatography on a Chirapak IB column eluting with a mixture of hexane/THF/MeOH (85/7.5/7.5). ^{1}H NMR (400 MHz, DMSO-D6) δ ppm 11.62 - 12.13 (m, 2 H), 7.59 - 7.71 (m, *J*=8.13 Hz, 3 H), 7.46 - 7.57 (m, *J*=8.24 Hz, 1 H), 7.38 (d, *J*=1.84 Hz, 2 H), 7.10 - 7.32 (m, 6 H), 6.72 - 6.83 (m, 2 H), 6.19 - 6.31 (m, 2 H), 5.17 - 5.28 (m, 2 H), 5.02 - 5.11 (m, *J*=6.72 Hz, 2 H), 4.05 (t, *J*=8.40 Hz, 2 H), 3.71 - 3.85 (m, 4 H), 3.53 (s, 6 H), 2.05 - 2.21 (m, 4 H), 1.94 (s, 6 H), 1.64 - 1.78 (m, 2 H), 0.77 - 0.95 (m, 12 H). The title compound showed an EC_{50} value of less than about 0.1 nM in HCV 1b-Con1 replicon assays in the presence of 5% FBS.

Example 48

dimethyl (2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-(4,4'-((2S,3R,4R,5S)-1-(4-tert-butylphenyl)-3,4-dimethoxypyrrolidine-2,5-diyl)bis(4,1-phenylene))bis(1H-imidazole-4,2-diyl))bis(pyrrolidine-2,1-diyl))bis(3-methyl-1-oxobutane-2,1-diyl)dicarbamate



Example 48A

(2S,3R,4R,5S)-2,5-bis(4-(benzyloxy)phenyl)-1-(4-tert-butylphenyl)pyrrolidine-3,4-diol

To a solution of (1R,1'R)-1,1'-((4R,5R)-2,2-dimethyl-1,3-dioxolane-4,5-diyl)diethane-1,2-diol (200 mg, 0.90 mmol) in methanol (6 ml) and dichloromethane (3 ml) was added iodobenzene diacetate (696 mg, 2.16 mmol) and the solution was stirred at room temperature for 5 h. Solution was concentrated and to the residue was added 0.1M H_2SO_4 (4 ml) and stirring was continued at room temperature for 18 h. The pH was adjusted to ~6 with solid $NaHCO_3$, and 4-tert-butylaniline (287 µl, 1.80 mmol) was added followed by 4-benzyloxyphenylboronic acid (369 mg, 1.62 mmol) and hexafluoroisopropyl alcohol (4 ml) and stirred at 60 °C for 2 h. Solvent was concentrated and the residue dissolved in ethyl acetate, washed with H_2O, 0.33M K_3PO_4, brine, dried (Na_2SO_4), filtered and

concentrated to give crude product which was purified by chromatography on silica gel eluting with 0-20% ethyl acetate/dichloromethane to give title compound (249 mg, 46%).

Example 48B

(2S,3R,4R,5S)-2,5-bis(4-(benzyloxy)phenyl)-1-(4-tert-butylphenyl)-3,4-dimethoxypyrrolidine

To a solution of the product from Example 48A (200 mg, 0.33 mmol) in THF (2.1 ml) and DMF (0.7 ml) at 0 °C was added, in portions, sodium hydride, 60% in mineral oil (40.0 mg, 1.0 mmol) and stirring continued at 0 °C for 20 min. Iodomethane (0.046 ml, 0.734 mmol) was added and stirring continued at room temperature overnight. Diluted with ethyl acetate, washed with saturated NH_4Cl, H_2O, brine, dried (Na_2SO_4), filtered and concentrated to give crude product which was purified by chromatography on silica gel eluting with 0-20% ethyl acetate/dichloromethane to give title compound (170 mg, 80%).

Example 48C

4,4'-((2S,3R,4R,5S)-1-(4-tert-butylphenyl)-3,4-dimethoxypyrrolidine-2,5-diyl)diphenol

To a solution of the product from Example 48B (168 mg, 0.268mmol) in ethyl acetate (3 ml) was added 10% palladium on carbon (17 mg) and the flask was evacuated and back-filled with H_2 gas. The solution was stirred under a balloon of H_2 gas for 20 h, filtered through Celite, and washed with ethyl acetate and methanol. The filtrate was concentrated and the residue was azeotroped with ether to give title compound (120 mg, 100%) as a white solid.

Example 48D

4,4'-((2S,3R,4R,5S)-1-(4-tert-butylphenyl)-3,4-dimethoxypyrrolidine-2,5-diyl)bis(4,1-phenylene) bis(1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonate)

To a solution of the product from Example 48C (117 mg, 0.261 mmol) in DMF (1.3 ml) was added K_2CO_3 (81 mg, 0.588 mmol) and 1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonyl fluoride (0.101 ml, 0.575 mmol) and the solution was stirred at 100 °C for 1 h. The cooled solution was diluted with ethyl acetate, washed with H_2O, brine, dried (Na_2SO_4), filtered and concentrated to give an oil which was purified by chromatography on silica gel eluting with 0-20% ethyl acetate/hexane to give title compound (195 mg, 73.7 % yield).

Example 48E

(2S,3R,4R,5S)-1-(4-tert-butylphenyl)-3,4-dimethoxy-2,5-bis(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)pyrrolidine

To a pressure tube was added the product from Example 48D (193 mg, 0.191 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (102 mg, 0.401 mmol), dicyclohexyl(2',4',6'-

triisopropylbiphenyl-2-yl)phosphine (X-Phos) (14.55 mg, 0.031 mmol), potassium acetate (112 mg, 1.145 mmol), and dioxane (1.5 ml) and the solution was degassed with N_2 gas for 30 min. Tris(dibenzylideneacetone)dipalladium(0) (6.99 mg, 7.63 μmol) was added and degassing was continued another 10 min. The tube was sealed and heated with stirring at 100 °C overnight. The cooled solution was diluted with ethyl acetate, washed with H_2O, brine, dried (Na_2SO_4), filtered and the filtrate treated with 3-(mercaptopropyl) silica gel for 1 h. The solution was filtered and solvent removed to give a yellow solid which was purified by chromatography on silica gel eluting with 0-20% ethyl acetate/hexane to give title compound (99 mg, 78 % yield) as a white solid.

Example 48F

(2S,2'S)-tert-butyl 2,2'-(4,4'-(4,4'-((2S,3R,4R,5S)-1-(4-tert-butylphenyl)-3,4-dimethoxypyrrolidine-2,5-diyl)bis(4,1-phenylene))bis(1H-imidazole-4,2-diyl))dipyrrolidine-1-carboxylate

In a sealed tube was combined the product from Example 48E (97 mg, 0.145 mmol), the product from Example 26D (115 mg, 0.363 mmol), 1 M Na_2CO_3 (0.363 ml, 0.363 mmol), EtOH (1.0 ml) and toluene (1.0 ml) and the solution was degassed with N2 gas for 30 min. 1,1'-Bis(diphenylphosphino)ferrocenedichloro palladium(II) dichloromethane complex (10.63 mg, 0.015 mmol) was added and degassing was continued an additional 10 min. The tube was sealed and heated at 100 °C for 3 h. The cooled solution was diluted with ethyl acetate, filtered through Celite and the residue washed with ethyl acetate. The filtrate was concentrated in vacuo and the resulting material was purified chromatography on silica gel using a 12g silica gel column eluting with 0-2% methanol/dichloromethane to give title compound (85 mg, 66.1 % yield).

Example 48G

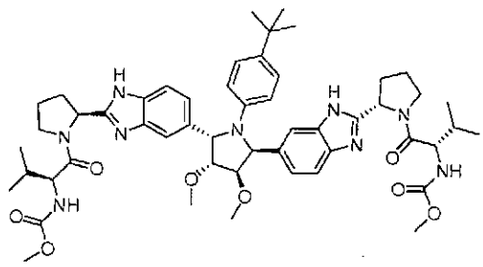
dimethyl (2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-(4,4'-((2S,3R,4R,5S)-1-(4-tert-butylphenyl)-3,4-dimethoxypyrrolidine-2,5-diyl)bis(4,1-phenylene))bis(1H-imidazole-4,2-diyl))bis(pyrrolidine-2,1-diyl))bis(3-methyl-1-oxobutane-2,1-diyl)dicarbamate

To a solution of the product from Example 48F (83 mg, 0.094 mmol) in dichloromethane (1.0 ml) was added TFA (1.0 ml, 12.98 mmol) and the solution was stirred at room temperature for 1 h. Solvent was concentrated and the residue was azeotroped 2 times with dichloromethane. The residue was placed under vacuum for 1 h to remove final traces of TFA. To this residue (64.2 mg, 0.094 mmol) was added DMSO (500 μl) followed by (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (41.1 mg, 0.234 mmol), HATU (89 mg, 0.234 mmol) and hunig's base (82 μl, 0.469 mmol). pH was checked and additional Hunig's base was added to adjust pH to ~9. Stirring was continued at room temperature for 1 h. The solution was diluted with ethyl acetate, washed with H_2O, brine, dried (Na_2SO_4), filtered and concentrated to give crude residue. Purification was run by chromatography on silica gel eluting with 0-4% methanol/dichloromethane over 60 min to give title compound (7.5 mg,

8.01 % yield). 1H NMR (400 MHz, CDCl3) δ ppm 0.86 (s, 12H) 1.13 (s, 9H) 1.86-2.02 (m, 2H) 2.02-2.12 (m, 2H) 2.12-2.25 (m, 2H) 2.25-2.41 (m, 1H) 2.90-3.17 (m, 2H) 3.43 (s, 6H) 3.53-3.65 (m, 2H) 3.70 (s, 6H) 3.74-3.89 (m, 2H) 4.16-4.26 (m, 2H) 4.26-4.37 (m, 1H) 5.18-5.26 (m, 2H) 5.26-5.32 (m, 2H) 5.33-5.41 (m, 2H) 6.28 (d, J=8.78 Hz, 2H) 6.89-6.99 (m, 2H) 7.16 (s, 2H) 7.20 (s, 2H) 7.22 (s, 2H) 7.26 (s, 4H) 7.30-7.48 (br s, 1H) 7.58-7.82 (br s, 2H) 10.08-10.42 (br s, 1H). The title compound showed an EC_{50} value of less than about 0.1 nM in HCV 1b-Con1 replicon assays in the presence of 5% FBS.

Example 49

dimethyl (2S,2'S)-1,1'-((2S,2'S)-2,2'-(5,5'-((2S,3R,4R,5S)-1-(4-tert-butylphenyl)-3,4-dimethoxypyrrolidine-2,5-diyl)bis(1H-benzo[d]imidazole-5,2-diyl))bis(pyrrolidine-2,1-diyl))bis(3-methyl-1-oxobutane-2,1-diyl)dicarbamate



Example 49A

(S)-tert-butyl 2-(2-amino-5-bromophenylcarbamoyl)pyrrolidine-1-carboxylate

A solution of the 2-amino-4-bromoaniline (6.0 g, 32.1 mmol), Boc-Pro-OH (6.90 g, 32.1 mmol) and HATU (13.42 g, 35.3 mmol) in dry DMSO (160 mL) was treated with diisopropylethylamine (14.0 mL, 10.4 g, 80 mmol) followed by stirring at room temperature for 18 h. The mixture was diluted with ethyl acetate and extracted with water (3 x) and saturated sodium chloride solution. Drying (Na_2SO_4) and concentration in vacuo afforded a brown solid which was used directly in the next step.

Example 49B

(S)-tert-butyl 2-(5-bromo-1H-benzo[d]imidazol-2-yl)pyrrolidine-1-carboxylate

A solution of the compound of Example 49A in glatial acetic acid (75 mL) was warmed at 60 °C for 3 h. The mixture was cooled and diluted with toluene and concentrated in vacuo. The remainder of the acetic acid was removed by azeotroping with toluene (2 x) and the residue was chromatographed over a 360 g silica gel cartridge, eluting with 25-75% ethyl acetate in dichloromethane. These procedures afforded the product (10.0 g, 85%) as a light beige rigid foam.

Example 49C

(S)-tert-butyl 2-(6-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-benzo[d]imidazol-2-yl)pyrrolidine-1-carboxylate

A solution of the compound of Example 49B (2.25 g, 6.14 mmol) in dry THF (25 mL) was treated with sodium hydride (295 mg of 60% in oil, 177 mg, 7.37 mmol) followed by stirring at room temperature for 1 h. The solution was then treated with SEM-Chloride (1.20 mL, 1.13 g, 6.76 mmol) followed by stirring at room temperature for 18 h. The mixture was quenched by addition of water and the mixture was diluted with ethyl acetate. The mixture was extracted with water and saturated sodium chloride solution. Drying (Na_2SO_4) and concentration in vacuo afforded an oil, which was chromatographed over a 100 g silica gel cartridge, eluting with 20-75% ethyl acetate in hexanes. These procedures afforded the product (2.24 g, 73%) as a heavy oil, which solidified after setting for several days. This mixture of both regioisomeric SEM derivatives was not separated for use in the next step.

Example 49D

(S)-tert-butyl 2-(6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-benzo[d]imidazol-2-yl)pyrrolidine-1-carboxylate

In a resealable pressure tube, a solution of the compound of Example 49C (2.24 g, 4.51 mmol), bis(pinacolato)diboron (1.26 g, 4.96 mmol), and potassium acetate (1.33 g, 13.53 mmol) in dry dioxane (23 mL) was degassed by nitrogen sparge for 30 min. The solution was treated with 1,1'-bis(diphenylphosphino)ferrocene palladium (II) chloride dichloromethane complex (111 mg, 0.14 mmol) followed by degassing for another 5 min. The pressure tube was sealed and warmed at 90 °C for 4 h. The mixture was cooled and diluted with ethyl acetate, followed by extraction with water and saturated sodium chloride solution. The solution was dried (Na_2SO_4) and stirred for 1 h with 3-mercaptopropyl) silica gel. After filtration and concentration in vacuo the brown oil was chromatographed over a 100 g silica gel cartridge, eluting with 15-70% ethyl acetate in dichloromethane. These procedures afforded the product (1.99 g, 81%) as a white rigid foam.

Example 49E

(S)-tert-butyl 2-(6-((2S,3R,4R,5S)-5-(2-((S)-1-(tert-butoxycarbonyl)pyrrolidin-2-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-benzo[d]imidazol-5-yl)-1-(4-tert-butylphenyl)-3,4-dihydroxypyrrolidin-2-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-benzo[d]imidazol-2-yl)pyrrolidine-1-carboxylate

A solution of 2,3-O-isopropylidene-D-mannitol (144 mg, 0.65 mmol) and iodobenzenediacetate (501 mg, 1.56 mmol) in 2:1 methanol-dichloromethane (3 mL) was stirred at room temperature for 5 h. The mixture was concentrated in vacuo to a white paste and then suspended in 0.1 M sulfuric acid solution (1.0 mL) followed by stirring at room temperature for 18 h.

The solution was adjusted to pH 6 by addition of solid sodium bicarbonate followed by addition of 4-tert-butylaniline (206 μL, 193 mg, 1.30 mmol) the product from Example 49D (634 mg, 1.17 mmol) and hexafluoroisopropyl alcohol (2.6 mL). The solution was then warmed at 70 °C for 5 h. The solution was cooled and concentrated in vacuo. The residue was dissolved in ethyl acetate and extracted with 0.33 M tribasic potassium phosphate solution and saturated sodium chloride solution. Drying (Na_2SO_4) and concentration in vacuo afforded a brown oil, which was chromatographed over a 50 g silica gel cartridge, eluting with 15-85% ethyl acetate in dichloromethane. These procedures afforded the recovered boronate (208 mg) as a viscous brown oil. The column was then re-eluted with 0-20% methanol in dichloromethane to afford the product (159 mg, 23%) as a brown solid.

Example 49F

(S)-tert-butyl 2-(6-((2S,3R,4R,5S)-5-(2-((S)-1-(tert-butoxycarbonyl)pyrrolidin-2-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-benzo[d]imidazol-5-yl)-1-(4-tert-butylphenyl)-3,4-dimethoxypyrrolidin-2-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-benzo[d]imidazol-2-yl)pyrrolidine-1-carboxylate

A solution of the product from Example 49E (154 mg, 0.14 mol) in dry THF was treated with sodium hydride (13 mg of 60% in oil, 8 mg, 0.33 mmol) followed by stirring at room temperature for 30 min. The mixture was treated with methyl iodide (19 μL, 43 mg, 0.30 mmol) followed by stirring at room temperature for 2 h. The mixture was diluted with ethyl acetate and quenched by addition of water. The mixture was extracted with water and saturated sodium chloride solution. Drying (Na_2SO_4) and concentration in vacuo afforded a brown oil, which was chromatographed over a 25 g silica gel cartridge, eluting with 0-15% methanol in dichloromethane. These procedures afforded the product (121 mg, 77%) as a beige foam.

Example 49G

(S)-5,5'-((2S,3R,4R,5S)-1-(4-tert-butylphenyl)-3,4-dimethoxypyrrolidine-2,5-diyl)bis(2-((S)-pyrrolidin-2-yl)-1H-benzo[d]imidazole)

A solution of the compound of Example 49F (111 mg, 0.10 mmol) in ethanol (1 mL) was treated with 4 N hydrochloric acid solution (2.0 mL) followed by warming at 60 °C for 18 h. The solution was cooled and concentrated in vacuo with ethanol-toluene mixtures (2 x) to afford the tetrahydrochloride as a light yellow solid. This material was dissolved in methanol (3 mL) and stirred with Amberlyte IRA 400 (OH- form, 1.4 mequiv/g, 577 mg, 0.81 mequiv) for 1 h. The resin was removed by filtration and the filtrate was concentrated in vacuo to afford the product (29 mg, 45%) as a light amber glass.

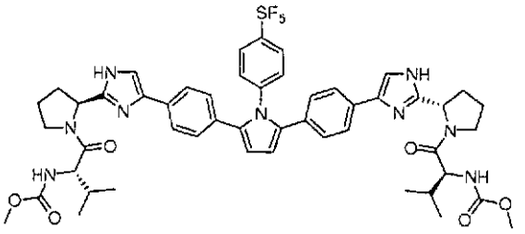
Example 49H

dimethyl (2S,2'S)-1,1'-((2S,2'S)-2,2'-(5,5'-((2S,3R,4R,5S)-1-(4-tert-butylphenyl)-3,4-dimethoxypyrrolidine-2,5-diyl)bis(1H-benzo[d]imidazole-5,2-diyl))bis(pyrrolidine-2,1-diyl))bis(3-methyl-1-oxobutane-2,1-diyl)dicarbamate

A solution of the compound of Example 49G (29 mg, 0.046 mmol), HOBt hydrate (18 mg, 0.114 mmol), EDAC (22 mg, 0.114 mmol) and (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (20 mg, 0.114 mmol) in dry DMF (0.5 mL) at 0 °C was treated with N-methylmorpholine (15 µL, 14 mg, 0.137 mmol) followed by stirring at 0 °C for 30 min and warming to room temperature for 2 h. The mixture was diluted with ethyl acetate and extracted with water (3 x) and saturated sodium chloride solution. Drying (Na_2SO_4) and concentration in vacuo afforded an oil which was dissolved in methanol and treated with a small amount of potassium carbonate. After stirring 1 h, the mixture was filtered and concentrated in vacuo to afford a yellow oil, which was chromatographed over a 25 g silica gel cartridge, eluting with 0-15% methanol in dichloromethane to give the product (14 mg, 32%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d6) δ 7.39 (m, 4 H), 7.30 (m, 4 H), 7.07 (t, J = 9.1 Hz, 2 H), 6.87 (m, 2 H), 6.31 (d, J = 8.9 Hz, 1 H), 5.54 (m, 2 H), 5.14 (dd, J = 7.6, 4.6 Hz, 2 H), 4.14 (m, 2 H), 3.77 (m, 4 H), 3.51 (m, 6 H), 3.28 (m, 6 H), 2.15 (m, 4 H), 1.04 (s, 9 H), 0.86 (m, 12 H). The title compound showed an EC_{50} value of from about 0.1 to about 1 nM in HCV 1b-Con1 replicon assays in the presence of 5% FBS.

Example 50

dimethyl (2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-(4,4'-(1-(4-(pentafluorothio)phenyl)-1H-pyrrole-2,5-diyl)bis(4,1-phenylene))bis(1H-imidazole-4,2-diyl))bis(pyrrolidine-2,1-diyl))bis(3-methyl-1-oxobutane-2,1-diyl)dicarbamate



Example 50A

2,5-bis(4-bromophenyl)-1-(4-(pentafluorothio)phenyl)-1H-pyrrole

Title compound was prepared from the product from Example 26E using the methods from Example 26F substituting 4-aminophenylsulfur pentafluoride for 4-tert-butylaniline to provide the desired compound.

Example 50B

1-(4-(pentafluorothio)phenyl)-2,5-bis(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1H-pyrrole

Title compound was prepared using the methods from Example 26G substituting the product from Example 50A for the product from Example 26F to provide the desired compound.

Example 50C

tert-butyl 2,2'-(4,4'-(4,4'-(1-(4-(pentafluorothio)phenyl)-1H-pyrrole-2,5-diyl)bis(4,1-phenylene))bis(1H-imidazole-4,2-diyl))dipyrrolidine-1-carboxylate

Title compound was prepared using the methods from Example 26H substituting the product from Example 50B for the product from Example 26G to provide the desired compound.

Example 50D

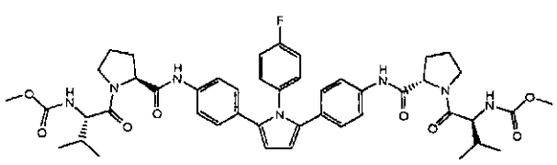
4,4'-(4,4'-(1-(4-(pentafluorthio)phenyl)-1H-pyrrole-2,5-diyl)bis(4,1-phenylene))bis(2-(pyrrolidin-2-yl)-1H-imidazole)

Title compound was prepared using the methods from Example 26I substituting the product from Example 50C for the product from Example 26H to provide the desired compound.

Example 50E

Dimethyl (2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-(4,4'-(1-(4-(pentafluorothio)phenyl)-1H-pyrrole-2,5-diyl)bis(4,1-phenylene))bis(1H-imidazole-4,2-diyl))bis(pyrrolidine-2,1-diyl))bis(3-methyl-1-oxobutane-2,1-diyl)dicarbamate

Title compound was prepared using the methods from Example 26I substituting the product from Example 50D for the product from Example 26I to provide the desired compound. ^{1}HNMR (DMSO-d6; 400 MHz): δ 11.75 (br s, 2H), 7.88 (m, 2H), 7.56 (app d, J=8.35 Hz, 4H), 7.45 (br s, 2H), 7.27 (m, 4H), 6.96 (app d, J=8.35 Hz, 4H), 6.50 (s, 2H), 5.04 (m, 2H), 4.03 (m, 2H), 3.78 (m, 4H), 3.53 (s, 6H), 2.11-1.85 (m, 10H), 0.86 (d, J=6.72 Hz, 6H), 0.82 (d, J=6.72 Hz, 6H). The title compound showed an EC_{50} value of less than about 0.1 nM in HCV 1b-Con1 replicon assays in the presence of 5% FBS.

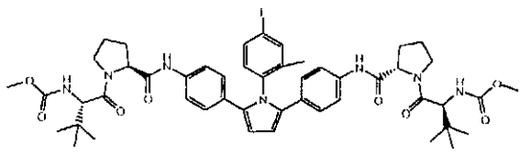


Example 51

dimethyl ([1-(4-fluorophenyl)-1H-pyrrole-2,5-diyl]bis{benzene-4,1-diylcarbamoyl(2S)pyrrolidine-2,1-diyl[(2S)-3-methyl-1-oxobutane-1,2-diyl]})biscarbamate

Example 19D (150 mg) and (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid were processed using the method of Example 19E (substituting DMF as solvent) to provide the title compound which was purified using gradient silica gel chromatography (30-70% EtOAc in

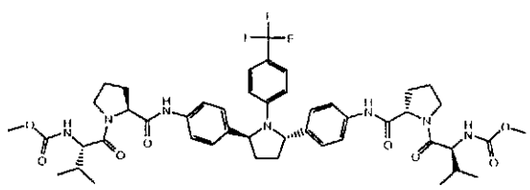
hexanes)(70 mg). ^{1}H NMR (500 MHz, DMSO-D6) δ 9.76 (s, 2H), 7.16 (d, *J* = 8.7, 4H), 7.06 (d, *J* = 8.4, 2H), 6.92 (t, *J* = 8.7, 2H), 6.83 (dd, *J* = 5.0, 8.9, 2H), 6.71 (d, *J* = 8.7, 4H), 6.14 (s, 2H), 4.15 (dd, *J* = 5.1, 7.9, 2H), 3.77 (t, *J* = 8.5, 2H), 3.59 – 3.50 (m, 2H), 3.40 – 3.31 (m, 2H), 3.27 (s, 6H), 1.95 – 1.82 (m, 2H), 1.79 – 1.52 (m, 8H), 0.67 (d, *J* = 6.8, 6H), 0.62 (d, *J* = 6.7, 6H). MS (ESI; M+H) m/z = 853.



Example 52

dimethyl ([1-(4-fluoro-2-methylphenyl)-1H-pyrrole-2,5-diyl]bis{benzene-4,1-diylcarbamoyl(2S)pyrrolidine-2,1-diyl[(2S)-3,3-dimethyl-1-oxobutane-1,2-diyl]})biscarbamate

Example 1A was processed using 4-fluoro-2-methylaniline and the methods from Examples 19A, 19B, 19C, 19D, and 51 ((S)-2-(methoxycarbonylamino)-3,3-dimethylbutanoic acid was used) to provide the title compound. ^{1}H NMR (400 MHz, DMSO-D6) δ 9.98 (s, 2H), 7.44 – 7.36 (m, 5H), 7.09 – 6.96 (m, 8H), 6.42 (s, 2H), 4.39 (dd, *J* = 5.5, 8.1, 2H), 4.19 (d, *J* = 8.7, 2H), 3.80 – 3.70 (m, 2H), 3.65 – 3.56 (m, 2H), 3.52 (s, 6H), 2.20 – 2.06 (m, 2H), 1.97 – 1.91 (m, 2H), 1.90 – 1.76 (m, 4H), 1.63 (s, 3H), 0.94 (s, 18H). MS (ESI; M+H) m/z = 895.



Example 53

dimethyl ({(2S,5S)-1-[4-(trifluoromethyl)phenyl]pyrrolidine-2,5-diyl}bis{benzene-4,1-diylcarbamoyl(2S)pyrrolidine-2,1-diyl[(2S)-3-methyl-1-oxobutane-1,2-diyl]})biscarbamate

Example 53A

dimethyl ({(2*S*,5*S*)-1-[4-(trifluoromethyl)phenyl]pyrrolidine-2,5-diyl}bis{benzene-4,1-diylcarbamoyl(2*S*)pyrrolidine-2,1-diyl[(2*S*)-3-methyl-1-oxobutane-1,2-diyl]})biscarbamate and dimethyl ({(2*R*,5*R*)-1-[4-(trifluoromethyl)phenyl]pyrrolidine-2,5-diyl}bis{benzene-4,1-diylcarbamoyl(2*S*)pyrrolidine-2,1-diyl[(2*S*)-3-methyl-1-oxobutane-1,2-diyl]})biscarbamate

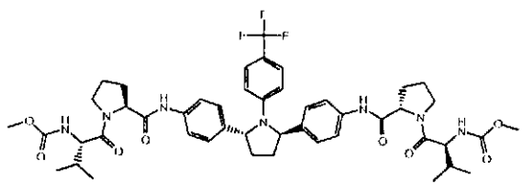
To a solution of the product from Example 23B (84 mg, 0.142 mmol) in DMSO (1.5 mL) was added (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (62.2 mg, 0.355 mmol), HATU (135 mg, 0.355 mmol), and Hunig'sBase (0.074 mL, 0.426 mmol), and the resulting mixture was stirred at rt for 90 min and then partitioned between H_2O (1 mL) and EtOAc (2 x 2 mL). The combined organic

layers were dried over Na_2SO_4, filtered and concentrated in vacuo. The drying agent was filtered off, and the crude product was purified by column chromatography on silica gel using a solvent gradient of 1-3% MeOH in CH_2Cl_2 to give the title compounds as a 1:1 mixture.

Example 53B

dimethyl ({(2S,5S)-1-[4-(trifluoromethyl)phenyl]pyrrolidine-2,5-diyl}bis{benzene-4,1-diylcarbamoyl(2S)pyrrolidine-2,1-diyl[(2S)-3-methyl-1-oxobutane-1,2-diyl]})biscarbamate

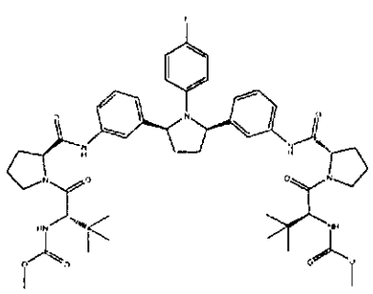
The product from Example 53A was separated on a Chiralpak AD-H column using 1:1 hexanes:(1:1 EtOH:2-PrOH). The title compound was the first component to elute. ^{1}H NMR (400 MHz, DMSO-D6) δ ppm 0.88 (d, *J*=6.61 Hz, 6 H), 0.93 (d, *J*=6.61 Hz, 6 H), 1.63 - 1.72 (m, 2 H), 1.78 - 2.06 (m, 8 H), 2.06 - 2.20 (m, 2 H), 3.52 (s, 6 H), 3.56 - 3.67 (m, 2 H), 3.73 - 3.86 (m, 2 H), 4.03 (t, *J*=8.51 Hz, 2 H), 4.42 (dd, *J*=7.92, 4.88 Hz, 2 H), 5.27 (d, *J*=6.61 Hz, 2 H), 6.36 (d, *J*=8.67 Hz, 2 H), 7.14 (d, *J*=8.57 Hz, 4 H), 7.25 (d, *J*=8.89 Hz, 2 H), 7.31 (d, *J*=8.35 Hz, 2 H), 7.52 (d, *J*=8.57 Hz, 4 H), 10.01 (s, 2 H); MS (ESI) m/z 906.3 $(M+H)^+$.



Example 54

dimethyl ({(2R,5R)-1-[4-(trifluoromethyl)phenyl]pyrrolidine-2,5-diyl}bis{benzene-4,1-diylcarbamoyl(2S)pyrrolidine-2,1-diyl[(2S)-3-methyl-1-oxobutane-1,2-diyl]})biscarbamate

The product from Example 53A was separated on a Chiralpak AD-H column using 1:1 hexanes:(1:1 EtOH:2-PrOH). The title compound was the second component to elute. ^{1}H NMR (400 MHz, DMSO-D6) δ ppm 0.87 (d, *J*=6.61 Hz, 6 H), 0.92 (d, *J*=6.72 Hz, 6 H), 1.64 - 1.74 (m, 2 H), 1.78 - 2.06 (m, 8 H), 2.06 - 2.22 (m, 2 H), 3.52 (s, 6 H), 3.56 - 3.67 (m, 2 H), 3.75 - 3.86 (m, 2 H), 3.97 - 4.08 (m, 2 H), 4.37 - 4.48 (m, 2 H), 5.28 (d, *J*=6.51 Hz, 2 H), 6.36 (d, *J*=8.78 Hz, 2 H), 7.14 (d, *J*=8.57 Hz, 4 H), 7.25 (d, *J*=8.89 Hz, 2 H), 7.30 (d, *J*=8.24 Hz, 2 H), 7.52 (d, *J*=8.57 Hz, 4 H), 10.01 (s, 2 H); MS (ESI) m/z 906.3 $(M+H)^+$.



Example 55

dimethyl ([(2R,5S)-1-(4-fluorophenyl)pyrrolidine-2,5-diyl]bis{benzene-3,1-diylcarbamoyl(2S)pyrrolidine-2,1-diyl[(2S)-3,3-dimethyl-1-oxobutane-1,2-diyl]})biscarbamate

Example 55A

1,4-bis(3-nitrophenyl)butane-1,4-dione

Anhydrous zinc(II) chloride (5.42 g, 39.7 mmol) was stirred in dry benzene (50 mL) under nitrogen while diethylamine (3.10 mL, 29.8 mmol) and t-butanol (2.85 mL, 29.8 mmol) were added. The resulting mixture was stirred at room temperature for 90 min to give a cloudy solution. To this was added 1-(3-nitrophenyl)ethanone (4.97g, 29.8mmol) followed by 2-bromo-1-(3-nitrophenyl)ethanone (5.00g, 19.87mmol) and the resulting mixture allowed to stir at room temperature overnight. A large portion of the benzene was subsequently removed by decantation. The resulting mixture was then treated with 5% sulfuric acid (25mL) in a separatory funnel and the aqueous phase drawn off. The organic phase was washed with water (2x25mL). A third washing resulted in an emulsion. The contents of the funnel were emptied into a large volume of water (750mL) to which was added sodium chloride and the oil in water mixture rapidly stirred. Methanol was added (75mL) in portions to try and disperse the oil and promote solidification of the product. After nearly forty eight hours of stirring the product solidified and was collected by vacuum filtration. The filter cake was water washed, dried first in air and then a vacuum oven at 55 °C to provide the title compound (5.85g, 90% yield) as a pale yellow solid that was used directly in the next step.

Example 55B

1,4-bis(3-nitrophenyl)butane-1,4-diol

Sodium borohydride (0.6173 g, 17.74 mmol) was added to a suspension of Example 55A (2.71 g, 8.26 mmol) in ethanol (150 mL) and stirred at ambient temperature for 3 hours. The reaction was quenched with water (~50 mL) and concentrated to a paste which was taken up in 1:1 MeOH:THF. This suspension was filtered through a celite plug and concentrated. The residue was taken up in toluene and heated with stirring to form a white paste which was then sonicated and scraped until a filterable solid formed. This was filtered, rinsed with toluene and dried under vacuum to afford 2.84 g (100%) of the title compound as an off white solid. MS (DCI) *m/z* 350 $(M+NH_4)^+$.

Example 55C

1,4-bis(3-nitrophenyl)butane-1,4-diyl dimethanesulfonate

Methanesulfonyl chloride (0.3 mL, 3.87 mmol) was added dropwise to a cold (0 °C) solution of Example 55B (0.5089 g, 1.531 mmol) and triethylamine (0.65 mL, 4.66 mmol) in THF (10 mL). The reaction was removed from the ice bath and stirred at ambient temperature for 30 minutes.

Solvent was removed under vacuum to provide the title compound as a solid that was used without purification.

Example 55D

1-(4-fluorophenyl)-2,5-bis(3-nitrophenyl)pyrrolidine

Example 55C (0.733 g, 1.5 mmol) was mixed with 4-fluoroaniline (1.5 mL, 15.63 mmol) and DMF (3 mL). The reaction was stirred at 50 °C for 24 hours. The reaction mixture was partioned between EtOAc and water. The organic portion was washed with water (2 x), brine (1 x), dried ($MgSO_4$), concentrated. Purification by flash chromatography (silica gel, 0-50% EtOAc/Hexanes). The material was dissolved in EtOAc and washed with 1 M HCl (2 x) to remove residual aniline, water (1 x), sat aqueous NaHCO3 (1 x) and brine (1 x) dried ($MgSO_4$) and concentrated to afford the title compound as a mixture of trans and cis isomers (0.45 g, 73%).

Example 55E

3,3'-(1-(4-fluorophenyl)pyrrolidine-2,5-diyl)dianiline

A suspension of Pd/C (0.0527 g, 0.050 mmol) in THF (2 mL) was added to a solution of Example 55D (0.45 g, 1.105 mmol) in THF (7 mL)/EtOH (7 mL) under N_2. The flask was flushed with H_2 and stirred under 1 atm H_2 for 20 hours. The reaction was filtered through a celite plug, rinsed with ~100 mL (1:1 EtOH:THF) and solvent was removed under vacuum. The material was used without purification. MS (DCI) *m/z* 348 $(M+H)^+$.

Example 55F

(2S,2'S)-tert-butyl 2,2'-(3,3'-((2S,5R)-1-(4-fluorophenyl)pyrrolidine-2,5-diyl)bis(3,1-phenylene))bis(azanediyl)bis(oxomethylene)dipyrrolidine-1-carboxylate

Diisopropylethylamine (0.8 mL, 4.58 mmol) was added to a mixture of Example 55E (0.382 g, 1.1 mmol), (S)-1-(tert-butoxycarbonyl)pyrrolidine-2-carboxylic acid (0.5950 g, 2.76 mmol) and HATU (0.9196 g, 2.419 mmol) in dichloromethane (12 mL). The reaction was stirred at rt for 1 hr, diluted with dichloromethane, washed with water (2 x), brine (1 x), dried ($MgSO_4$) and concentrated to give a brown residue. The residue was taken up in ether, sonicated and filtered to afford the title compound as a tan solid. The trans isomers remained in the ether solution and are described further in Example 83. LC/MS Rt 2.27 *m/z* 742 $(M+H)^+$.

Example 55G

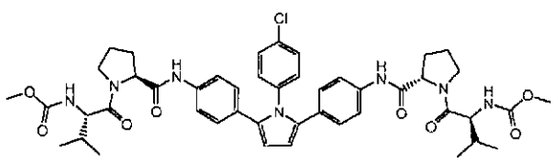
(2S,2'S)-N,N'-(3,3'-((2S,5R)-1-(4-fluorophenyl)pyrrolidine-2,5-diyl)bis(3,1-phenylene))dipyrrolidine-2-carboxamide

TFA (3 mL, 38.9 mmol) was added to a solution of Example 55F (0.4033 g, 0.544 mmol) in dichloromethane (10 mL). After 90 minutes the reaction was concentrated. The residue was sequentially dissolved in and concentrated in vacuo from the following solvents: dichloromethane (2x), methanol (2x), and ether (1x). This semi-solid was taken up in dicholormethane and washed with sat aq $NaHCO_3$ (2 x) water (1x) brine (1x) dried ($MgSO_4$) and filtered to provide the title compound. LC/MS Rt 1.31 *m/z* 542 $(M+H)^+$.

Example 55H

dimethyl ([(2R,5S)-1-(4-fluorophenyl)pyrrolidine-2,5-diyl]bis{benzene-3,1-diylcarbamoyl(2S)pyrrolidine-2,1-diyl[(2S)-3,3-dimethyl-1-oxobutane-1,2-diyl]})biscarbamate

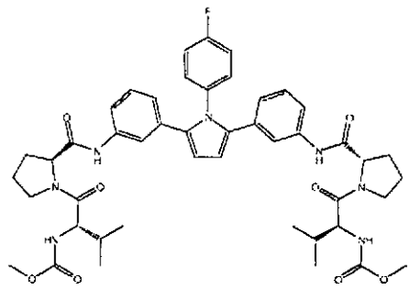
Diisopropylethylamine (0.5 mL, 2.86 mmol) was added to a mixture of Example 55G, (S)-2-methoxycarbonylamino-3,3-dimethyl-butyric acid (0.2600 g, 1.374 mmol) and HATU (0.4527 g, 1.191 mmol) in dichloromethane(15 mL). The reaction was stirred at ambient temperature for 18 hours. The reaction was diluted with dichloromethane, washed with water (2x), brine (1x), dried ($MgSO_4$), concentrated and purified by flash chromatography (silica gel, 0-30% EtOAc/dichloromethane) to afford 0.14 g (30%) of the title compound. ^1H NMR (400 MHz, DMSO-d6) δ 0.96 (s, 9H), 0.98 (s, 9H), 2.06 - 1.71 (m, 8H), 2.25 - 2.07 (m, 2H), 2.42 (t, J = 7.1, 2H), 3.54 (d, J = 3.2, 6H), 3.72 - 3.59 (m, 2H), 3.86 - 3.72 (m, 2H), 4.22 (d, J = 8.9, 2H), 4.51 - 4.37 (m, 2H), 4.69 (t, J = 11.9, 2H), 6.42 - 6.28 (m, 2H), 6.96 - 6.83 (m, 2H), 7.08 (t, J = 8.5, 2H), 7.39 - 7.18 (m, 4H), 7.76 - 7.54 (m, 4H), 10.03 (d, J = 9.8, 2H). MS (ESI) *m/z* 884 $(M+H)^+$, 882 $(M-H)^+$.



Example 56

dimethyl ([1-(4-chlorophenyl)-1H-pyrrole-2,5-diyl]bis{benzene-4,1-diylcarbamoyl(2S)pyrrolidine-2,1-diyl[(2S)-3-methyl-1-oxobutane-1,2-diyl]})biscarbamate

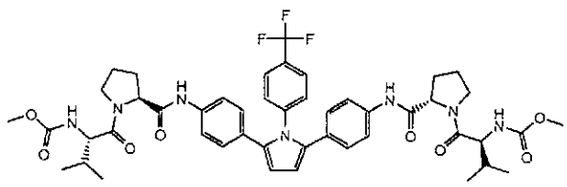
Example 1A was processed using 4-chloroaniline and the methods from Examples 19A, 19B, 19C, 19D, and 51 to provide the title compound (72 mg). ^1H NMR (400 MHz, DMSO-d6) δ 10.00 (s, 2H), 7.45 – 7.36 (m, 6H), 7.31 (d, *J* = 8.3, 2H), 7.04 (d, *J* = 8.4, 2H), 6.96 (d, *J* = 8.6, 4H), 6.39 (s, 2H), 4.44 – 4.37 (m, 2H), 4.06 – 3.99 (m, 2H), 3.85 – 3.74 (m,2H), 3.67 – 3.56 (m, 2H), 3.52 (s, 6H), 2.20 – 2.06 (m, 2H), 2.04 – 1.79 (m, 8H), 0.92 (d, *J* = 6.7, 6H), 0.88 (d, *J* = 6.7, 6H). MS (ESI; M+H) m/z = 869.



Example 57

dimethyl ([1-(4-fluorophenyl)-1H-pyrrole-2,5-diyl]bis{benzene-3,1-diylcarbamoyl(2S)pyrrolidine-2,1-diyl[(2S)-3-methyl-1-oxobutane-1,2-diyl]})biscarbamate

Example 55A was processed using the methods of Example 19A, 19B, 19C, 19D, and 19E to provide the title compound. ^{1}H NMR (400 MHz, DMSO-d6) δ 0.99 - 0.84 (m, 12H), 2.05 - 1.76 (m, 8H), 2.22 - 2.05 (m, 2H), 3.53 (s, 6H), 3.70 - 3.56 (m, 2H), 3.88 - 3.71 (m, 2H), 4.11 - 3.93 (m, 2H), 4.42 (dd, J = 4.9, 7.9, 2H), 6.40 (s, 2H), 6.54 (d, J = 7.9, 2H), 7.18 - 6.98 (m, 6H), 7.34 (dd, J = 8.3, 15.4, 4H), 7.55 (s, 2H), 9.96 (d, J = 11.2, 2H). MS (ESI) *m/z* 852 $(M+H)^+$.



Example 58

dimethyl ({1-[4-(trifluoromethyl)phenyl]-1H-pyrrole-2,5-diyl}bis{benzene-4,1-diylcarbamoyl(2S)pyrrolidine-2,1-diyl[(2S)-3-methyl-1-oxobutane-1,2-diyl]})biscarbamate

Example 58A

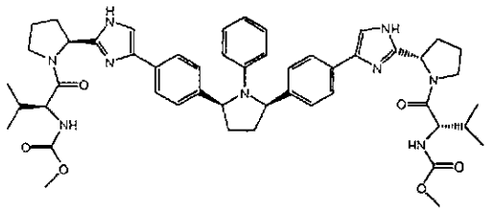
2,5-bis(4-nitrophenyl)-1-(4-(trifluoromethyl)phenyl)-1H-pyrrole

To a slurry of the product from Example 1A (1.00 g, 3.05 mmol) in acetic acid (30 mL) was added 4-(trifluoromethyl)aniline (1.9 mL, 15 mmol). The mixture was heated to 170 °C for 15 minutes under microwave irradiation. The cooled mixture was diluted with water and diethyl ether and stirred vigorously for 15 minutes and then filtered. The crude product was purified by chromatography on silica gel eluting with a solvent gradient of 0-30% ethyl acetate in hexane. Product containing fractions were combined and concentrated under reduced pressure and then triturated with diethyl ether to give the title compound (110 mg, 8% yield).

Example 58B

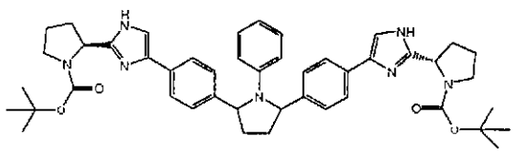
dimethyl ({1-[4-(trifluoromethyl)phenyl]-1H-pyrrole-2,5-diyl}bis{benzene-4,1-diylcarbamoyl(2S)pyrrolidine-2,1-diyl[(2S)-3-methyl-1-oxobutane-1,2-diyl]})biscarbamate

Example 58A was processed using the methods of Examples 19B, 19C, 19D, and 51 to provide the title compound (44 mg). ^{1}H NMR (400 MHz, DMSO-d6) δ 10.01 (s, 2H), 7.71 (d, *J* = 8.6, 2H), 7.42 (d, *J* = 8.7, 4H), 7.31 (d, *J* = 8.2, 2H), 7.22 (d, *J* = 8.3, 2H), 6.95 (d, *J* = 8.6, 4H), 6.43 (s, 2H), 4.39 (dd, *J* = 5.2, 8.1, 2H), 4.03 (d, *J* = 8.3, 2H), 3.85 – 3.75 (m, 2H), 3.66 – 3.56 (m, 2H), 3.52 (s, 6H), 2.18 – 2.08 (m, 2H), 2.01 – 1.79 (m, 8H), 0.92 (d, *J* = 6.7, 6H), 0.87 (d, *J* = 6.6, 6H). MS (ESI; M+H) m/z = 903.



Example 59

methyl {(2S)-1-[(2S)-2-(4-{4-[(2R,5S)-5-(4-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-4-yl}phenyl)-1-phenylpyrrolidin-2-yl]phenyl}-1H-imidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate



Example 59A

(2S,2'S)-tert-butyl 2,2'-(4,4'-(4,4'-(1-phenylpyrrolidine-2,5-diyl)bis(4,1-phenylene))bis(1H-imidazole-4,2-diyl))dipyrrolidine-1-carboxylate

Example 42B and aniline were processed using the methods of Examples 39D, 42D, and 42E to provide the title compound as a mixture of stereoisomers. MS (ESI) m/z 770 (M+H)+.

Example 59B

4,4'-{[(2*R*,5*S*)-1-phenylpyrrolidine-2,5-diyl]dibenzene-4,1-diyl}bis{2-[(2*S*)-pyrrolidin-2-yl]-1*H*-imidazole} (ACD v12)

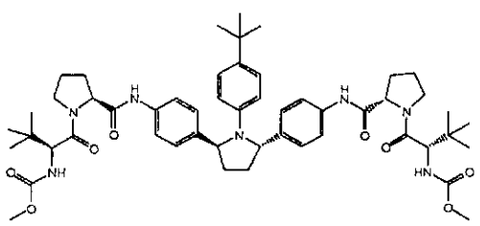
To the product of Example 59A (30 mg, 0.039 mmol) was added dimethoxyethane (1.5 mL) and a solution of 4N hydrochloric acid in dioxane (3 mL) and the resultant solution stirred at room temperature for 1.5 hr. The solvent was then removed under vacuum and the resultant residue was diluted with acetonitrile and water (0.1% TFA) and purified by reversed phase chromatography (C18), eluting with 10-100% acetonitrile in water (0.1% TFA) to afford 9.8 mg (44%) of the title compound

and 8.5 mg of a mixture of the trans diastereomers (MS (ESI) m/z 570 (M+H)+) that were processed further as described in Example 89. For the title compound: MS (ESI) m/z 570 (M+H)+.

Example 59C

methyl {(2S)-1-[(2S)-2-(4-{4-[(2R,5S)-5-(4-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-4-yl}phenyl)-1-phenylpyrrolidin-2-yl]phenyl}-1H-imidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

The product from Example 59B (9.8 mg, 0.012 mmol), (S)-2-(methoxycarbonylamino)-3,3-dimethylbutanoic acid (5.4 mg, 0.031 mmol) and HATU (10.3 mg, 0.027 mmol) in DMSO (1 mL) was added Hunig's base (0.017 mL, 0.098 mmol), and the reaction mixture was stirred at room temperature for 1 hr. The reaction mixture was partitioned between water and ethyl acetate, and the organic layer was dried over $MgSO_4$, filtered and concentrated in vacuo. The crude product was purified by reversed phase chromatography (C18), eluting with 10-100% acetonitrile in water (0.1% TFA) to afford 4.5 mg (41%) of the title compound. 1H NMR (TFA salt) (400 MHz, DMSO-D6) δ ppm 14.50 (bs, 2 H), 7.99 (s, 2 H), 7.78 (m, 4 H), 7.65 (m, 4H), 7.32 (m, 2H), 7.02 (t, *J*=8.0 Hz, 2 H), 6.63 (t, *J*=7.4 Hz, 1 H), 6.40 (d, *J*=8.2 Hz, 2 H), 5.11 (t, *J*=6.9 Hz, 2 H), 4.83 (m, 2H), 4.10 (t, *J*=7.7 Hz, 2 H), 3.82 (m, 6 H), 3.48 (s, 6 H), 2.40 (m, 2 H), 2.08 (m, 2 H), 2.00 (m, 6 H), 1.85 (m, 2 H), 0.85 (m, 2 H), 0.80 (m, 12 H); MS (ESI) m/z 884 (M+H)+.



Example 60

dimethyl ([(2S,5S)-1-(4-tert-butylphenyl)pyrrolidine-2,5-diyl]bis{benzene-4,1-diylcarbamoyl(2S)pyrrolidine-2,1-diyl[(2S)-3,3-dimethyl-1-oxobutane-1,2-diyl]})biscarbamate

Example 60A

dimethyl ([(2S,5S)-1-(4-tert-butylphenyl)pyrrolidine-2,5-diyl]bis{benzene-4,1-diylcarbamoyl(2S)pyrrolidine-2,1-diyl[(2S)-3,3-dimethyl-1-oxobutane-1,2-diyl]})biscarbamate

and

dimethyl ([(2R,5R)-1-(4-tert-butylphenyl)pyrrolidine-2,5-diyl]bis{benzene-4,1-diylcarbamoyl(2S)pyrrolidine-2,1-diyl[(2S)-3,3-dimethyl-1-oxobutane-1,2-diyl]})biscarbamate

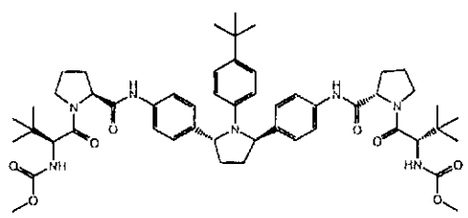
The product from Example 34D (29.0 mg, 0.05 mmol), (S)-2-(methoxycarbonylamino)-3,3-dimethylbutanoic acid (20.81 mg, 0.110 mmol), EDC (21.09 mg, 0.110 mmol), HOBT (16.85 mg,

0.110 mmol) and N-methylmorpholine (0.027 mL, 0.250 mmol) were combined in DMF (2 mL). The mixture was stirred at room temperature for 3 hours. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was washed with brine twice, dried with sodium sulfate, filtered and evaporated. The residue was purified by chromatography on silica gel eluting with ethyl acetate/hexane (50% to 80%) to give the title compound (32 mg, 69%) as a mixture of trans diastereomers.

Example 60B

dimethyl ([(2S,5S)-1-(4-tert-butylphenyl)pyrrolidine-2,5-diyl]bis{benzene-4,1-diylcarbamoyl(2S)pyrrolidine-2,1-diyl[(2S)-3,3-dimethyl-1-oxobutane-1,2-diyl]})biscarbamate

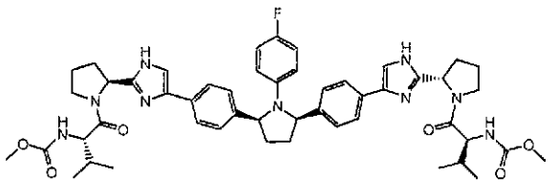
The product from Example 60A was purified by chiral chromatography on a Chiralpak AD-H semi-prep column eluting with a 3:1 mixture of hexane:(2:1 IPA:EtOH). The title compound was the first of the 2 diastereomers to elute. ^{1}H NMR (400 MHz, DMSO-D6) δ ppm 0.97 (s, 18 H) 1.11 (s, 9 H) 1.60 - 1.65 (m, 2 H) 1.79 - 1.91 (m, 4 H) 1.94 - 2.03 (m, 2 H) 2.10 - 2.18 (m, 2 H) 2.44 - 2.50 (m, 2 H) 3.54 (s, 6 H) 3.59 - 3.67 (m, 2 H) 3.71 - 3.82 (m, 2 H) 4.21 (d, J=8.89 Hz, 2 H) 4.43 (dd, J=7.92, 5.42 Hz, 2 H) 5.14 (d, J=6.40 Hz, 2 H) 6.18 (d, J=8.89 Hz, 2 H) 6.94 (d, J=8.78 Hz, 2 H) 7.08 (d, J=8.78 Hz, 2 H) 7.13 (d, J=8.57 Hz, 4 H) 7.50 (d, J=8.46 Hz, 4 H) 9.99 (s, 2 H); MS (ESI+) m/z 923 (M+H)+.



Example 61

dimethyl ([(2R,5R)-1-(4-tert-butylphenyl)pyrrolidine-2,5-diyl]bis{benzene-4,1-diylcarbamoyl(2S)pyrrolidine-2,1-diyl[(2S)-3,3-dimethyl-1-oxobutane-1,2-diyl]})biscarbamate

The product from Example 60A was purified by chiral chromatography on a Chiralpak AD-H semi-prep column eluting with a 3:1 mixture of hexane:(2:1 IPA:EtOH). The title compound was the second of the 2 diastereomers to elute. ^{1}H NMR (400 MHz, DMSO-D6) δ ppm 0.96 (s, 18 H) 1.11 (s, 9 H) 1.60 - 1.66 (m, 2 H) 1.78 - 1.92 (m, 4 H) 1.94 - 2.04 (m, 2 H) 2.08 - 2.19 (m, 2 H) 2.42 - 2.50 (m, 2 H) 3.54 (s, 6 H) 3.59 - 3.67 (m, 2 H) 3.74 - 3.81 (m, 2 H) 4.20 (d, J=8.89 Hz, 2 H) 4.43 (dd, J=7.97, 5.37 Hz, 2 H) 5.15 (d, J=6.29 Hz, 2 H) 6.17 (d, J=8.89 Hz, 2 H) 6.94 (d, J=8.89 Hz, 2 H) 7.07 (d, J=8.89 Hz, 2 H) 7.13 (d, J=8.46 Hz, 4 H) 7.50 (d, J=8.57 Hz, 4 H) 9.99 (s, 2 H); MS (ESI+) m/z 923 (M+H)+.



Example 62

methyl {(2S)-1-[(2S)-2-(4-{4-[(2R,5S)-1-(4-fluorophenyl)-5-(4-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-4-yl}phenyl)pyrrolidin-2-yl]phenyl}-1H-imidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

Example 62A

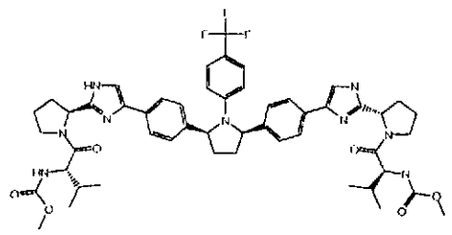
4,4'-{[(2*R*,5*S*)-1-(4-fluorophenyl)pyrrolidine-2,5-diyl]dibenzene-4,1-diyl}bis{2-[(2*S*)-pyrrolidin-2-yl]-1*H*-imidazole} (ACD v12)

The product from Example 45C (0.15 g, 0.190 mmol) in CH_2Cl_2 (1 mL) was treated with TFA (1 mL), and the resulting mixture was stirred at rt for 1h and then concentrated in vacuo. The crude product was purified by column chromatography on C18 silica using a solvent gradient of 10-100% CH_3CN in 0.1% aq TFA. The desired cis-pyrrolidine isomer was the second of 2 components to elute. Fractions containing pure cis-isomer were pooled and concentrated in vacuo. The residue was partitioned between saturated aq. $NaHCO_3$ and a 3:1 mixture of CH_2Cl_2:2-PrOH (3x). The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo to give the title compound (32 mg, 28%).

Example 62B

methyl {(2S)-1-[(2S)-2-(4-{4-[(2R,5S)-1-(4-fluorophenyl)-5-(4-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-4-yl}phenyl)pyrrolidin-2-yl]phenyl}-1H-imidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

The product from Example 62A (32 mg, 54 mmol) was subjected to the method described in Example 5D, substituting (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid for (S)-2-(methoxycarbonyl amino)butanoic acid, to give the title compound (34 mg, 69%). ^{1}H NMR (400 MHz, DMSO-D6) δ ppm 0.78 - 0.93 (m, 12 H), 1.78 - 2.24 (m, 12 H), 2.37 - 2.46 (m, 2 H), 3.54 (s, 6 H), 3.68 - 3.87 (m, 4 H), 4.66 - 4.79 (m, 2 H), 5.02 - 5.13 (m, 2 H), 6.39 (dd, *J*=9.16, 4.50 Hz, 2 H), 6.81 - 6.92 (m, 2 H), 7.23 - 7.34 (m, 2 H), 7.39 - 7.80 (m, 12 H), 11.67 - 12.12 (m, 2 H); MS (ESI) m/z 902.7 $(M+H)^+$.



Example 63

methyl [(2S)-1-{(2S)-2-[4-(4-{(2R,5S)-5-(4-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-4-yl}phenyl)-1-[4-(trifluoromethyl)phenyl]pyrrolidin-2-yl}phenyl)-1H-imidazol-2-yl]pyrrolidin-1-yl}-3-methyl-1-oxobutan-2-yl]carbamate

Example 63A

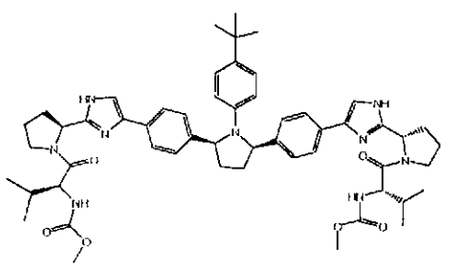
(2R,5S)-2,5-bis(4-bromophenyl)-1-(4-(trifluoromethyl)phenyl)pyrrolidine

The product from Example 42B (11.13 g, 20.0 mmol) and 4-(trifluoromethyl)aniline (Aldrich, 32.2 g, 200 mmol) were combined in DMF (50 mL), stirred at 50 °C under nitrogen for 16 hours, cooled and concentrated. The residue was diluted with ethyl acetate, treated with 1M HCl, stirred for 10 minutes and filtered to remove solids. The organic layer of the filtrate was washed with brine, dried (Na_2SO_4), filtered and concentrated. The residue was purified by flash chromatography (silica gel, 0 to 1% ethyl acetate/hexane) to give the title compound (1.0 g, 10 %) as the second eluting stereoisomer. MS (ESI+) m/z 526 $(M+H)^+$.

Example 63B

methyl [(2S)-1-{(2S)-2-[4-(4-{(2R,5S)-5-(4-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-4-yl}phenyl)-1-[4-(trifluoromethyl)phenyl]pyrrolidin-2-yl}phenyl)-1H-imidazol-2-yl]pyrrolidin-1-yl}-3-methyl-1-oxobutan-2-yl]carbamate

The product from Example 63A (1.0 g, 1.90 mmol) was processed using the methods described in Example 42D, 42E, 42F, and 42G to afford the title compound. ^1H NMR (free base) (400 MHz, DMSO-d_6) δ 0.80 - 0.95 (m, 12 H) 1.83 - 2.18 (m, 14 H) 3.54 (s, 6 H) 3.79 (d, J=6.18 Hz, 3 H) 3.97 - 4.15 (m, 3 H) 4.87 (d, J=4.88 Hz, 2 H) 5.02 - 5.14 (m, 2 H) 6.54 (d, J=8.67 Hz, 2 H) 7.15 - 7.80 (m, 14 H) 11.56 - 12.30 (m, 2 H); MS (ESI+) m/z 953 $(M+H)^+$.



Example 64

methyl {(2S)-1-[(2S)-2-(4-{4-[(2R,5S)-1-(4-tert-butylphenyl)-5-(4-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-4-yl}phenyl)pyrrolidin-2-yl]phenyl}-1H-imida

zol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

Example 64A

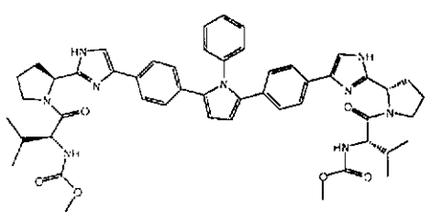
(2S,2'R)-2,2'-(4,4'-(4,4'-(1-(4-tert-butylphenyl)pyrrolidine-2,5-diyl)bis(4,1-phenylene))bis(1H-imidazole) bis trifluoroacetate salt

Example 42C was processed using the methods of Examples 42D, 42E, and 42F to provide a mixture of cis/trans pyrrolidine isomers. The mixture of stereoisomers was dissolved in 10 ml of 80% (0.1% TFA/water):20% CH_3CN and applied to a 13 g C18 silica column. The column was eluted with a gradient of 0.1% TFA(aq):CH3CN; 80/20 to 50:50 over 25 minutes, giving the cis steroisomer of the title compound as a light yellow solid trifluoroacetate salt, 88.6 mg, 58%.

Example 64B

methyl {(2S)-1-[(2S)-2-(4-{4-[(2R,5S)-1-(4-tert-butylphenyl)-5-(4-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-4-yl}phenyl)pyrrolidin-2-yl]phenyl}-1H-imidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

The product from Example 64A was dissolved in 1 ml DMF and added dropwise to a chilled (0-5 °C) solution containing (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (0.41g, 0.232 mmole), HOBt (0.036g, 0.232 mmole), EDAC (0.045 g, 0.232 mmole) and 4-methylmorpholine (0.138g, 0.150 ml, 1.364 mmole) in 0.5 ml DMF. The pH of the solution was measured and found to be 8. The reaction was stirred a total of 3.5 hr in the ice bath. The reaction mixture was diluted with 50 ml EtOAc and washed with 10% $NaHCO_3$, 10% NaCl, dried over anhydrous Na_2SO_4(s), filtered and solvent removed in vacuo leaving a pinkish oil. The oil was dissolved in 5 ml CH_2Cl_2 and applied to a 12 g silica gel column. The column was eluted with a gradient of CH_2Cl_2/MeOH, 99/1 to 94/6 over 25 minutes giving the title compound as a white solid, 12.5 mg, 11%. 1H NMR (400 MHz, DMSO-D6) d ppm 0.85 (s, 12 H) 1.13 (s, 9 H) 1.95 (s, 6 H) 2.15 (s, 4 H) 2.50 (s, 3 H) 3.43 (s, 1 H) 3.54 (s, 5 H) 3.80 (s, 4 H) 4.05 (s, 2 H) 4.70 (s, 2 H) 5.07 (s, 1 H) 6.36 (d, J=8.78 Hz, 2 H) 7.01 (s, 2 H) 7.28 (s, 2 H) 7.47 (s, 6 H) 7.70 (s, 4 H) 11.71 (s, 2 H) 12.09 (s, 2 H)ESI+:940.8



Example 65

methyl {(2S)-1-[(2S)-2-(4-{4-[5-(4-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-4-yl}phenyl)-1-phenyl-1H-pyrrol-2-yl]phenyl}-1H-imidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

Example 65A

(2S,2'R)-tert-butyl 2,2'-(4,4'-(4,4'-(1-phenyl-1H-pyrrole-2,5-diyl)bis(4,1-phenylene))bis(1H-imidazole-4,2-diyl))dipyrrolidine-1-carboxylate

Example 26E and aniline were processed using the methods of Examples 19A, 26G, and 26H to provide the title compound (150 mg).

Example 65B

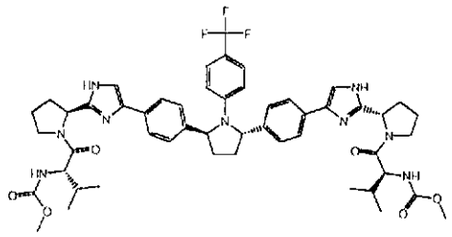
(S)-4,4'-(4,4'-(1-phenyl-1H-pyrrole-2,5-diyl)bis(4,1-phenylene))bis(2-((S)-pyrrolidin-2-yl)-1H-imidazole)

To a suspension of the product from Example 65A (186 mg, 0.243 mmol) in dioxane (5 mL) was added HCl/dioxane (5 mL, 20 mmol). The mixture was stirred for 30 minutes and then concentrated under reduced pressure to provide the title compound as a hydrochloride salt.

Example 65C

methyl {(2S)-1-[(2S)-2-(4-{4-[5-(4-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-4-yl}phenyl)-1-phenyl-1H-pyrrol-2-yl]phenyl}-1H-imidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

A solution consisting of N1-((ethylimino)methylene)-N3,N3-dimethylpropane-1,3-diamine hydrochloride (90 mg, 0.47 mmol), 1H-benzo[d][1,2,3]triazol-1-ol hydrate (72 mg, 0.47 mmol), (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (82 mg, 0.47 mmol) and 4-methylmorpholine (0.28 mL, 2.6 mmol) in DMF (1.6 mL) was cooled in an icebath. To this mixture was added dropwise a solution of the product from Example 65B (150 mg, 0.23 mmol) in DMF (0.5 mL). Additional 4-methylmorpholine was added to the mixture until the pH was adjusted to 8. The reaction was stirred for 3.5 hours and then the icebath was removed and the reaction was stirred for an additional 16 hours. Water was then added to the reaction mixture and the resulting precipitate was recovered by filtration. The residue was washed with copious amounts of water followed by diethyl ether. The crude product was purified by chromatography on silica gel eluting with a solvent gradient of 0-5% methanol in CH_2Cl_2 to provide the title compound. ^{1}H NMR (400 MHz, DMSO-d6) δ 12.12 – 11.64 (m, 2H), 7.57 – 7.45 (m, 4H), 7.42 – 7.36 (m, 2H), 7.36 – 7.29 (m, 3H), 7.29 – 7.05 (m,4H), 7.04 – 6.91 (m, 4H), 6.54 – 6.43 (m, 2H), 5.06 – 4.96 (m, 2H), 4.06 – 3.96 (m, 2H), 3.84 – 3.67 (m, 4H), 3.52 (s, 6H), 2.17 – 1.80 (m, 10H), 0.91 – 0.76 (m, 12H). MS (ESI; M+H) m/z = 881.



Example 66

methyl [(2S)-1-{(2S)-2-[4-(4-{(2S,5S)-5-(4-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-4-yl}phenyl)-1-[4-(trifluoromethyl)phenyl]pyrrolidin-2-yl}phenyl)-1H-imidazol-2-yl]pyrrolidin-1-yl}-3-methyl-1-oxobutan-2-yl]carbamate

Example 66A

(2R,5R)-2,5-bis(4-bromophenyl)-1-(4-(trifluoromethyl)phenyl)pyrrolidine

and

(2S,5S)-2,5-bis(4-bromophenyl)-1-(4-(trifluoromethyl)phenyl)pyrrolidine

The product from Example 42B (11.13 g, 20.0 mmol) and 4-(trifluoromethyl)aniline (32.2 g, 200 mmol) were combined in DMF (50 mL). The mixture was stirred at 50 °C under nitrogen overnight. The reaction mixture was evaporated and the residue was diluted with ethyl acetate, treated with 1M HCl, stirred for 10 minutes, and filtered to remove the solid. The organic layer of filtrate was washed with brine, dried with sodium sulfate, filtered and evaporated. The residue was purified by chromatography on silica gel eluting with ethyl acetate/hexane (0 to 1%). The title compounds (500 mg, 5%) were eluted as the first of 2 stereoisomers and were obtained as a mixture of trans diastereomers.

Example 66B

(2R,5R)-2,5-bis(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1-(4-(trifluoromethyl)phenyl)pyrrolidine

and

(2S,5S)-2,5-bis(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1-(4-(trifluoromethyl)phenyl)pyrrolidine

The products from Example 66A (500 mg, 0.952 mmol), bis(pinacolato)diboron (725 mg, 2.86 mmol), potassium acetate (374 mg, 3.81 mmol) and bis(triphenylphosphine)palladium(II) chloride (66.8 mg, 0.095 mmol) were combined in 1,2-dimethoxyethane (10 mL). The mixture was purged with nitrogen for 15 minutes and stirred at 85 °C for 2 hours. The reaction mixture was partitioned between ethyl acetate and 1M HCl. The organic layer was washed with saturated sodium bicarbonate, brine, dried with sodium sulfate, filtered and evaporated. The residue was purified by

chromatography on silica gel eluting with hexane to ethyl acetate/hexane (10%) to give a solid which was triturated with dichloromethane/hexane (1:3) to give the title compounds (370 mg, 63%).

Example 66C

(2S,2'S)-tert-butyl 2,2'-(4,4'-(4,4'-((2R,5R)-1-(4-(trifluoromethyl)phenyl)pyrrolidine-2,5-diyl)bis(4,1-phenylene))bis(1H-imidazole-4,2-diyl))dipyrrolidine-1-carboxylate

and

(2S,2'S)-tert-butyl 2,2'-(4,4'-(4,4'-((2S,5S)-1-(4-(trifluoromethyl)phenyl)pyrrolidine-2,5-diyl)bis(4,1-phenylene))bis(1H-imidazole-4,2-diyl))dipyrrolidine-1-carboxylate

The products from Example 66B (257 mg, 0.415 mmol), the product from Example 26D (341 mg, 1.079 mmol), potassium phosphate tribasic (352 mg, 1.660 mmol) and 1,1'-bis(di-tert-butylphosphine)ferrocene palladium dichloride (27.0 mg, 0.041 mmol) were combined in THF (4.5 mL)/ water (1.5 mL). The mixture was purged with nitrogen for 15 minutes and stirred at 70 °C for 6 hours. The reaction mixture was partitioned between ethyl acetate and saturated sodium bicarbonate. The organic layer was washed with brine, dried with sodium sulfate, filtered and evaporated. The residue was purified by chromatography on silica gel eluting with methanol/dichloromethane (1% to 3%) to give the title compounds (286 mg, 82%) as a solid.

Example 66D

(S)-4,4'-(4,4'-((2R,5R)-1-(4-(trifluoromethyl)phenyl)pyrrolidine-2,5-diyl)bis(4,1-phenylene))bis(2-((S)-pyrrolidin-2-yl)-1H-imidazole)

and

(S)-4,4'-(4,4'-((2S,5S)-1-(4-(trifluoromethyl)phenyl)pyrrolidine-2,5-diyl)bis(4,1-phenylene))bis(2-((S)-pyrrolidin-2-yl)-1H-imidazole)

To the products from Example 66C (385 mg, 0.459 mmol) in dioxane (6 mL) was added 4M hydrochloric acid in dioxane (10 mL, 40.0 mmol) and the reaction stirred at room temperature for 1 hour. The solvent was evaporated under high vacuum to give the title compounds (approx. 360 mg) as hydrochloride salts.

Example 66E

methyl [(2S)-1-{(2S)-2-[4-(4-{(2S,5S)-5-(4-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-4-yl}phenyl)-1-[4-(trifluoromethyl)phenyl]pyrrolidin-2-yl}phenyl)-1H-imidazol-2-yl]pyrrolidin-1-yl}-3-methyl-1-oxobutan-2-yl]carbamate

and

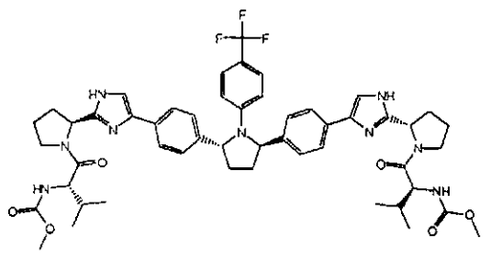
methyl [(2S)-1-{(2S)-2-[4-(4-{(2R,5R)-5-(4-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-4-yl}phenyl)-1-[4-(trifluoromethyl)phenyl]pyrrolidin-2-yl}phenyl)-1H-imidazol-2-yl]pyrrolidin-1-yl}-3-methyl-1-oxobutan-2-yl]carbamate

The product from Example 66D (360 mg, 0.459 mmol), (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (161 mg, 0.919 mmol), 4-methylmorpholine (0.404 mL, 3.68 mmol), N1-((ethylimino)methylene)-N3,N3-dimethylpropane-1,3-diamine hydrochloride (194 mg, 1.011 mmol) and 1H-benzo[d][1,2,3]triazol-1-ol hydrate (155 mg, 1.011 mmol) were combined in DMF (10 mL). The mixture was stirred at room temperature for 20 hours. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was washed with saturated sodium bicarbonate, brine twice, dried with sodium sulfate, filtered and evaporated. The residue was purified by chromatography on silica gel eluting with methanol/dichloromethane (1% to 6%) to give the title compounds (223 mg, 51%) as a solid.

Example 66F

methyl [(2S)-1-{(2S)-2-[4-(4-{(2S,5S)-5-(4-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-4-yl}phenyl)-1-[4-(trifluoromethyl)phenyl]pyrrolidin-2-yl}phenyl)-1H-imidazol-2-yl]pyrrolidin-1-yl}-3-methyl-1-oxobutan-2-yl]carbamate

The product from Example 66E was purified by chiral chromatography on a Chiralpak IB column eluting with a mixture of hexane/THF/methanol (8/1/1). The title compound was the first of the 2 diastereomers to elute. ^{1}H NMR (400 MHz, DMSO-D6) δ ppm 0.78 - 0.90 (m, 12 H) 1.71 - 1.77 (m, 2 H) 1.86 - 2.02 (m, 6 H) 2.09 - 2.18 (m, 4 H) 2.51 - 2.54 (m, 2 H) 3.53 (s, 6 H) 3.74 - 3.84 (m, 4 H) 4.04 (t, J=8.35 Hz, 2 H) 5.06 (dd, J=6.83, 3.14 Hz, 2 H) 5.28 - 5.41 (m, 2 H) 6.41 (d, J=8.67 Hz, 2 H) 7.12 - 7.33 (m, 8 H) 7.36 - 7.72 (m, 6 H) 11.62 - 12.13 (m, 2 H); MS (ESI+) m/z 953 (M+H)+.

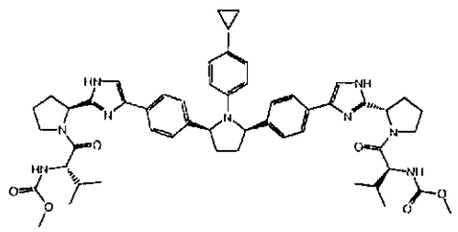


Example 67

methyl [(2S)-1-{(2S)-2-[4-(4-{(2R,5R)-5-(4-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-4-yl}phenyl)-1-[4-(trifluoromethyl)phenyl]pyrrolidin-2-yl}phenyl)-1H-imidazol-2-yl]pyrrolidin-1-yl}-3-methyl-1-oxobutan-2-yl]carbamate

The product from Example 66E was purified by chiral chromatography on a Chiralpak IB column eluting with a mixture of hexane/THF/methanol (8/1/1). The title compound was the second of the 2 diastereomers to elute. ^{1}H NMR (400 MHz, DMSO-D6) δ ppm 0.79 - 0.91 (m, 12 H) 1.71 -

1.77 (m, 2 H) 1.88 - 2.01 (m, 6 H) 2.08 - 2.17 (m, 4 H) 2.51 - 2.54 (m, 2 H) 3.53 (s, 6 H) 3.74 - 3.82 (m, 4 H) 4.05 (t, J=8.40 Hz, 2 H) 5.00 - 5.13 (m, 2 H) 5.29 - 5.40 (m, 2 H) 6.40 (d, J=8.57 Hz, 2 H) 7.12 - 7.31 (m, 8 H) 7.36 - 7.72 (m, 6 H) 11.52 - 12.15 (m, 2 H); MS (ESI+) m/z 953 (M+H)+.



Example 68

methyl {(2S)-1-[(2S)-2-(4-{4-[(2R,5S)-1-(4-cyclopropylphenyl)-5-(4-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-4-yl}phenyl)pyrrolidin-2-yl]phenyl}-1H-imidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

Example 68A

2,5-bis(4-bromophenyl)-1-(4-cyclopropylphenyl)pyrrolidine

The product from Example 42B (3.14 g, 5.64 mmol) and 4-cyclopropylaniline (6.01 g, 45.2 mmol) were combined in DMF (20 mL). The mixture was stirred at 50 °C under nitrogen for 3 hours. The reaction mixture was partitioned between 1M HCl and ethyl acetate. The organic layer was washed with brine three times, dried with sodium sulfate, filtered and evaporated. The residue was purified by chromatography on silica gel eluting with ethyl acetate/hexane (0.5% to 1%) to give the title compound (2.12g, 76%) as a mixture of stereoisomers as a sticky solid.

Example 68B

1-(4-cyclopropylphenyl)-2,5-bis(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)pyrrolidine

The product from Example 68A (2.12 g, 4.26 mmol), bis(pinacolato)biboron (3.25 g, 12.79 mmol), potassium acetate (1.674 g, 17.05 mmol) and bis(triphenylphosphine)palladium(II) chloride (0.299 g, 0.426 mmol) were combined in 1,2-dimethoxyethane (40 mL). The mixture was purged with nitrogen for 15 minutes and stirred at 85 °C for 2 hours. The reaction mixture was partitioned between ethyl acetate and 1M HCl. The organic layer was washed with saturated sodium bicarbonate, brine, dried with sodium sulfate, filtered and evaporated. The residue was purified by chromatography on silica gel eluting with hexane to ethyl acetate/hexane (10%) to give a solid that was triturated with diethyl ether/hexane (1/3) to give the title compound (1.05, 42%) as a mixture of stereoisomers as a white solid.

Example 68C

(2S,2'S)-tert-butyl 2,2'-(4,4'-(4,4'-(1-(4-cyclopropylphenyl)pyrrolidine-2,5-diyl)bis(4,1-phenylene))bis(1H-imidazole-4,2-diyl))dipyrrolidine-1-carboxylate

The product from Example 68B (1.04 g, 1.759 mmol), the product from Example 26D (1.446 g, 4.57 mmol), $PdCl_2(dppf)$ (0.129g, 0.176 mmol) and 1.0 M sodium carbonate (4.57 mL, 4.57 mmol) were combined in the mixed solvent of ethanol (5 mL)/toluene (5 mL). The mixture was purged with nitrogen for 15 minutes and stirred at 80 °C for 2 hours. The reaction mixture was partitioned between ethyl acetate and saturated sodium bicarbonate, brine, dried with sodium sulfate, filtered and evaporated. The residue was purified by chromatography on silica gel eluting with methanol/dichloromethane (1% to 3%) to give the title compound (1.28 g, 90%) as a mixture of stereoisomers as a solid.

Example 68D

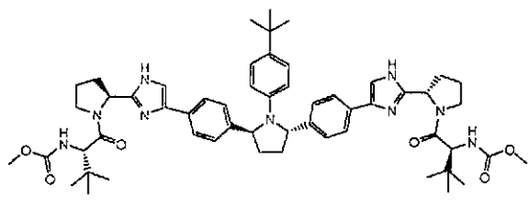
(S)-4,4'-(4,4'-((2R,5S)-1-(4-cyclopropylphenyl)pyrrolidine-2,5-diyl)bis(4,1-phenylene))bis(2-((S)-pyrrolidin-2-yl)-1H-imidazole)

The product from Example 68C (1.27 g, 1.568 mmol) was dissolved in dichloromethane (12 mL). The mixture was cooled to 0 °C and trifluoroacetic acid (8 mL, 104 mmol) was added slowly. The mixture was warmed to room temperature and stirred for 1h. The solvent was evaporated and the residue was purified by chromatography on silica gel eluting with methanol/dichloromethane (1% to 10%). The title compound (310 mg, 32%) eluted as the second of 2 stereoisomers.

Example 68E

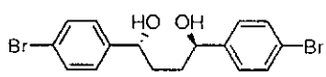
methyl {(2S)-1-[(2S)-2-(4-{4-[(2R,5S)-1-(4-cyclopropylphenyl)-5-(4-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-4-yl}phenyl)pyrrolidin-2-yl]phenyl}-1H-imidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

The product of Example 68D (90 mg, 0.148 mmol), (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (51.7 mg, 0.295 mmol), 4-methylmorpholine (0.130 mL, 1.181 mmol), N1-((ethylimino)methylene)-N3,N3-dimethylpropane-1,3-diamine hydrochloride (62.2 mg, 0.325 mmol) and 1H-benzo[d][1,2,3]triazol-1-ol hydrate (49.7 mg, 0.325 mmol) were combined in DMF (10 mL). The mixture was stirred at room temperature for 2 hours. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was washed with saturated sodium bicarbonate, brine twice, dried with sodium sulfate, filtered and evaporated. The residue was purified by chromatography on silica gel eluting with methanol/dichloromethane (1% to 4%) to give the title compound (40 mg, 29%) as a solid. ^1H NMR (400 MHz, DMSO-D6) δ ppm 0.39-0.47 (m, 2 H) 0.71 - 0.78 (m, 2 H) 0.82 - 0.92 (m, 12 H) 1.65 - 1.72 (m, 1 H) 1.82 - 2.03 (m, 8 H) 2.09 - 2.17 (m, 4 H) 2.40 - 2.45 (m, 2 H) 3.54 (s, 6 H) 3.75 - 3.83 (m, 4 H) 4.02 - 4.09 (m, 2 H) 4.64 - 4.75 (m, 2 H) 5.03 - 5.11 (m, 2 H) 6.32 (d, J=8.67 Hz, 2 H) 6.73 (d, J=8.35 Hz, 2 H) 7.29 (d, J=8.02 Hz, 2 H) 7.37 - 7.81 (m, 10 H) 11.47 - 12.17 (m, 2 H); MS (ESI+) m/z 924.7 (M+H)+.



Example 69

methyl {(2S)-1-[(2S)-2-(4-{4-[(2S,5S)-1-(4-tert-butylphenyl)-5-(4-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3,3-dimethylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-4-yl}phenyl)pyrrolidin-2-yl]phenyl}-1H-imidazol-2-yl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl}carbamate



Example 69A

(1R,4R)-1,4-bis(4-bromophenyl)butane-1,4-diol

To (S)-(-)-alpha, alpha-diphenyl-2-pyrrolidinemethanol (3.81 g, 15.04 mmol) was added THF (140 mL) at 23 °C. The thin slurry was treated with trimethyl borate (2.189 mL, 19.63 mmol) to form a clear solution. After stirring for 1.5 h, the solution was cooled to 10-15 °C, and N,N-diethylaniline borane (33.1 mL, 186 mmol) was added over 5-10 min via a syringe. A slight exotherm and H_2 evolution were observed. To a separate vessel was charged Example 26E (35.045 g, 88 mmol), followed by THF (140 mL), to form a slurry. The slurry was cooled to 10 °C. The cooled borane solution was transferred via cannula into the dione slurry over approximately 5 minutes, maintaining the internal temperature <25 °C. After the transfer was complete, the slurry was held at 15 °C for 5 min and then the temperature was maintained at 23 °C for 3 h. After reaction completion, the solution was cooled to 5 °C, and methanol (31.6 mL, 780 mmol) was added slowly to maintain a temperature <20 °C (*note: vigorous evolution of hydrogen).* The hazy solution was mixed for an additional 1 h in order to ensure complete quenching. The hazy solution was diluted with EtOAc (500 mL) and 1 M HCl (220 mL). The phases were partitioned, and the organic phase was washed successively with 1 M HCl (2 x 220 mL), H_2O (110 mL), and 25% aq. NaCl (110 mL). The organic layer was concentrated in vacuo, then dissolved in EtOAc, filtered, concentrated and crystallized from EtOAc/hexane to provide the title compound (16.92 g; 100% ee; 47% isolated yield).

Example 69B

(2S,5S)-2,5-bis(4-bromophenyl)-1-(4-tert-butylphenyl)pyrrolidine

To a mixture of the product from Example 69A (0.60 g, 1.500 mmol) in anhydrous CH_2Cl_2 (15 mL) at 0 °C was added Et_3N (0.627 mL, 4.50 mmol), and the resulting mixture was stirred at 0 °C for 10 min until a homogenous solution was obtained. To the cooled solution was added methanesulfonyl chloride (0.292 mL, 3.75 mmol) dropwise, and the resulting mixture was stirred at 0 °C for 1.5 h until the reaction was complete as determined by TLC (1:1 EtOAc:hexanes). Solvent was removed in vacuo to give a solid, which was dried in vacuo. The solid was dissolved in anhydrous DMF (5 mL), and 4-tert-butylaniline (2.39 mL, 15 mmol) was added. The resulting mixture was stirred at 40 °C for 4h and then was partitioned between 1N aq. HCl (30 mL) and EtOAc (30 mL). The organic layer was washed with H_2O and dried over Na_2SO_4. The drying agent was filtered off, the solvent was removed in vacuo, and the crude product was purified by column chromatography on silica gel using a solvent gradient of 0-20% EtOAc in hexanes. The title compound was obtained as a colorless solid (0.71 g, 92%). ^1H NMR indicated this material was a 87:13 mixture of trans:cis pyrrolidine isomers.

Example 69C

(2S,5S)-1-(4-tert-butylphenyl)-2,5-bis(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)pyrrolidine

The product from Example 69B (0.71 g, 1.38 mmol) was subjected to the conditions described in Example 42D to give the title compound as a colorless solid (0.56 g, 66%).

Example 69D

(2S,2'S)-tert-butyl 2,2'-(4,4'-(4,4'-((2S,5S)-1-(4-tert-butylphenyl)pyrrolidine-2,5-diyl)bis(4,1-phenylene))bis(1H-imidazole-4,2-diyl))dipyrrolidine-1-carboxylate

The product from Example 69C (0.55 g, 0.91 mmol) was subjected to the conditions described in Example 42E to give the title compound (0.27 g, 36%).

Example 69E

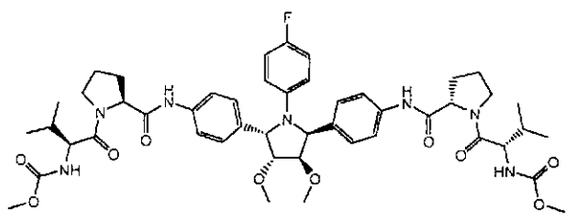
(S)-4,4'-(4,4'-((2S,5S)-1-(4-tert-butylphenyl)pyrrolidine-2,5-diyl)bis(4,1-phenylene))bis(2-((S)-pyrrolidin-2-yl)-1H-imidazole)

A solution of the product from Example 69D (0.27 g, 0.33 mmol) in a 1:1 mixture of CH_2Cl_2:TFA (4 mL) was stirred at rt for 40 min and then concentrated in vacuo. The residue was partitioned between saturated aq $NaHCO_3$ and a 3:1 mixture of CH_2Cl_2:2-PrOH (2x), and the combined organic layers were dried over Na_2SO_4. The drying agent was filtered off, and the solvent was removed in vacuo to give the title compound as an amorphous solid (0.18 g, 87%).

Example 69F

methyl {(2S)-1-[(2S)-2-(4-{4-[(2S,5S)-1-(4-tert-butylphenyl)-5-(4-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3,3-dimethylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-4-yl}phenyl)pyrrolidin-2-yl]phenyl}-1H-imidazol-2-yl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl}carbamate

To a mixture of the product from Example 69E (0.10 g, 0.16 mmol) and (S)-2-(methoxycarbonylamino)-3,3-dimethylbutanoic acid (76 mg, 0.40 mmol) in anhydrous DMSO (1.6 mL) was added HATU (152 mg, 0.40 mmol) and Hunig's base (84 µL, 0.48 mmol). The resulting mixture was stirred at rt for 90 min, and was then partitioned between H_2O (5 mL) and EtOAc (2 x 5mL). The combined organic layers were concentrated in vacuo, and the residue was dissolved in MeOH (1 mL). To the solution was added solid K_2CO_3 (1-2 mg) and the resulting mixture was stirred at rt for 30 min. The mixture was filter and concentrated in vacuo, and the crude product was purified by column chromatography on silica gel using a solvent gradient of 0-5% MeOH in CH_2Cl_2 to give the title compound (0.12 g, 78%). ^{1}H NMR (400 MHz, DMSO-D6) δ ppm 0.94 (s, 18 H), 1.10 (s, 9 H), 1.63 - 1.77 (m, 2 H), 1.84 - 2.25 (m, 10 H), 3.55 (s, 6 H), 3.66 - 3.87 (m, 2 H), 4.16 - 4.28 (m, 2 H), 5.03 - 5.12 (m, 2 H), 5.15 - 5.28 (m, 2 H), 6.22 (d, *J*=8.46 Hz, 2 H), 6.93 (d, *J*=8.67 Hz, 2 H), 7.07 (d, 2 H), 7.15 (d, *J*=8.13 Hz, 4 H), 7.23 (d, 1 H), 7.38 (d, *J*=1.41 Hz, 2 H), 7.52 (d, 1 H), 7.62 (d, *J*=8.02 Hz, 4 H), 11.66 - 12.10 (m, 2 H). MS (ESI) m/z 969.1 $(M+H)^+$.



Example 70

dimethyl ([(2S,3R,4R,5S)-1-(4-fluorophenyl)-3,4-dimethoxypyrrolidine-2,5-diyl]bis{benzene-4,1-diylcarbamoyl(2S)pyrrolidine-2,1-diyl[(2S)-3-methyl-1-oxobutane-1,2-diyl]})biscarbamate

Example 70A

Tert-butyl 4,4'-((2S,3R,4R,5S)-1-(4-fluorophenyl)-3,4-dihydroxypyrrolidine-2,5-diyl)bis(4,1-phenylene)dicarbamate

A solution of 3,4-O-isopropylidene-D-mannitol (444 mg, 2.0 mmol) in 2:1 methanol-dichloromethane (8 mL) was treated with iodobenzene diacetate (1.54 g, 4.79 mmol) followed by stirring at RT for 5 h. The mixture was concentrated in vacuo to remove organic solvents, and the residue was suspended in 0.1 M sulfuric acid solution (4 mL) followed by stirring at RT for 18 h. The mixture was adjusted to pH 6 by addition of solid sodium bicarbonate. The mixture was then sequentially treated with 4-fluoroaniline (383 µL, 444 mg, 4.00 mmol), 4-(tert-

butoxycarbonylamino)phenylboronic acid (853 mg, 3.60 mmol) and hexafluoroisopropyl alcohol (8 mL). The mixture was warmed at 50 °C for 2 h. The solution was cooled and concentrated in vacuo. The mixture was dissolved in ethyl acetate and extracted with water, 0.33 M tribasic potassium phosphate solution, and saturated sodium chloride solution. Drying (Na_2SO_4) and concentration in vacuo afforded a brown solid, which was chromatographed over a 100 g silica gel cartridge, eluting with 5-70% ethyl acetate in dichloromethane. These procedures afforded the title compound (770 mg, 67%) as a nearly white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, J = 8.3 Hz, 4 H), 7.11 (d, J = 8.4 Hz, 4 H), 6.67 (t, J = 8.8 Hz, 2 H), 6.51 (s, 2 H), 6.22 (dd, J = 9.1, 4.3 Hz, 2 H), 5.15 (d, J = 6.3 Hz, 2 H), 4.26 (d, J = 5.7 Hz, 2 H), 1.51 (s, 18 H). MS +ESI m/z (rel abundance) 580 (100, M+H), 602 (15, M+Na), 1159 (18, 2M+H).

Example 70B

(2S,3R,4R,5S)-2,5-bis(4-(tert-butoxycarbonylamino)phenyl)-1-(4-fluorophenyl)pyrrolidine-3,4-diyl diacetate

A solution of the compound of Example 70A (314 mg, 0.54 mmol), triethylamine (227 µL, 164 mg, 1.65 mmol), and DMAP (13 mg, 0.11 mmol) in 1:1 ethyl acetate-tetrahydrofuran (2.8 mL) was treated with acetic anhydride (128 µL, 138 mg, 1.35 mmol) followed by stirring at RT for 1 h. The mixture was treated with water followed by stirring at RT for 30 min. The mixture was diluted with ethyl acetate and extracted with water, saturated sodium bicarbonate solution and saturated sodium chloride solution. Drying (Na_2SO_4) and concentration in vacuo afforded the title compound (330 mg, 92%) as a cream-colored solid, sufficiently pure for further use. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, J = 8.4 Hz, 4 H), 7.07 (d, J = 8.5 Hz, 4 H), 6.66 (t, J = 8.8 Hz, 2 H), 6.47 (s, 2 H), 6.25 (dd, J = 9.2, 4.3 Hz, 2 H), 5.53 (dd, J = 5.5, 1.9 Hz, 2 H), 5.46 (d, J = 7.2 Hz, 2 H), 1.83 (s, 6 H), 1.51 (s, 18 H). MS +ESI m/z (rel abundance) 664 (100, M+H).

Example 70C

(2S,3R,4R,5S)-2,5-bis(4-aminophenyl)-1-(4-fluorophenyl)pyrrolidine-3,4-diyl diacetate dihydrochloride

A solution of 4 N hydrogen chloride in dioxane (8 mL) was treated with the compound of Example 70B (136 mg, 0.21 mmol) followed by stirring at RT for 2 h. (During this time, the mono-deprotection product started precipitating, and ca. 4 mL of dichloromethane was added to speed the reaction by solublizing the mono-hydrochloride) The mixture was added to excess ether and the product collected by filtration and washed with ether. After drying in a vacuum oven at 50 °C for 18 h, these procedures afforded the title compound (92 mg, 84%) as an off-white powder. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.28 (m, 8 H), 6.81 (t, J = 8.9 Hz, 2 H), 6.33 (m, 2 H), 5.63 (m, 2 H), 5.51 (dd, J = 5.5, 1.9 Hz, 2 H), 1.79 (s, 6 H).

Example 70D

(2S,3R,4R,5S)-2,5-bis(4-aminophenyl)-1-(4-fluorophenyl)pyrrolidine-3,4-diol

In a 25-mL round bottom flask, was dissolved Example 70C(160.5 mg, 0.299 mmol) in MeOH (3 mL), added potassium carbonate (165 mg, 1.197 mmol), and stirred at 25 °C for 1.5 hr. Filtered off the solids, washed with MeOH, and concentrated the filtrate by rotary evaporation to dryness. Purified by flash chromatography (silica gel, Alltech Extract-Clean 10g column, 8% MeOH/CH_2Cl_2) to afford the title compound as a yellow solid (85 mg, 75%). ^{1}H NMR (400 MHz, DMSO-D6) δ ppm 4.10 - 4.19 (m, 2 H), 4.73 (d, *J*=2.71 Hz, 2 H), 4.80 - 4.88 (m, 2 H), 4.84 (s, 4 H), 6.21 (dd, *J*=9.22, 4.55 Hz, 2 H), 6.45 (d, *J*=8.35 Hz, 4 H), 6.72 (t, *J*=8.95 Hz, 2 H), 6.77 (d, *J*=8.24 Hz, 4 H); MS (DCI+) 380 $(M+H)^+$.

Example 70E

4,4'-((2S,3R,4R,5S)-1-(4-fluorophenyl)-3,4-dimethoxypyrrolidine-2,5-diyl)dianiline

In an oven-dried 25-mL round bottom flask, dissolved the product of Example 70D (83.6 mg, 0.220 mmol) in anhydrous THF (3 mL) under nitrogen, cooled to 0 °C in an ice water bath, added 60 wt% NaH dispersion in mineral oil (18.51 mg, 0.463 mmol), and stirred at 0 °C for 15 min. Then added iodomethane (0.028 mL, 0.441 mmol) via microsyringe and stirred at 0 °C for 1 hr, then at 25 °C for 3 hr. Removed the solvent by rotary evaporation and dried the residue *in vacuo*. Purified by flash chromatography (silica gel, Alltech Extract-Clean 10g column, gradient of 1% to 2% MeOH/CH_2Cl_2) to afford the title compound as a yellow solid (59 mg, 66%). ^{1}H NMR (400 MHz, DMSO-D6) δ ppm 3.25 (s, 6 H), 3.92 - 4.17 (m, 2 H), 4.91 (s, 4 H), 5.07 - 5.24 (m, 2 H), 6.28 (dd, *J*=9.16, 4.50 Hz, 2 H), 6.47 (d, *J*=8.46 Hz, 4 H), 6.73 (t, *J*=8.95 Hz, 2 H), 6.86 (d, *J*=8.35 Hz, 4 H); MS (DCI+) m/z 408 $(M+H)^+$.

Example 70F

(2S,2'S)-*tert*-butyl 2,2'-(4,4'-((2S,3R,3R,5S)-1-(4-fluorophenyl)-3,4-dimethoxypyrrolidine-2,5-diyl)bis(4,1-phenylene))bis(azanediyl)bis(oxomethylene)dipyrrolidine-1-carboxylate

In a 10-mL round bottom flask, dissolved the product of Example 70E (57 mg, 0.140 mmol) in anhydrous DMSO (1.2 mL) under nitrogen, added (S)-1-(tert-butoxycarbonyl)pyrrolidine-2-carboxylic acid (76 mg, 0.350 mmol), HATU (137 mg, 0.350 mmol), and diisopropylethylamine (0.073 mL, 0.420 mmol), and stirred the bright yellow solution at 25 °C for 1 hr. Diluted the reaction with EtOAc (50 mL), washed with H_2O (3 x 25 mL) and brine (15 mL), dried the organic phase over anhydrous $MgSO_4$, filtered, and concentrated by rotary evaporation to a yellow residue. Purified by flash chromatography (silica gel, Alltech Extract-Clean 10g column, 3% MeOH/CH_2Cl_2) to afford the title compound as a yellow solid (118 mg). ^{1}H NMR (400 MHz, DMSO-D6) δ ppm 1.29 (s, 11 H),

1.39 (s, 7 H), 1.72 - 1.95 (m, 6 H), 2.08 - 2.25 (m, 2 H), 3.29 (s, 6 H), 3.35 - 3.49 (m, 3 H), 4.12 (d, J=0.87 Hz, 2 H), 4.15 - 4.29 (m, 2 H), 5.30 - 5.45 (m, 2 H), 6.28 (dd, *J*=9.22, 4.45 Hz, 2 H), 6.75 (t, *J*=8.89 Hz, 2 H), 7.19 (d, *J*=8.35 Hz, 4 H), 7.50 (t, *J*=8.89 Hz, 4 H), 9.70 - 10.14 (m, 2 H); MS (APCI+) m/z 802 $(M+H)^+$.

Example 70G

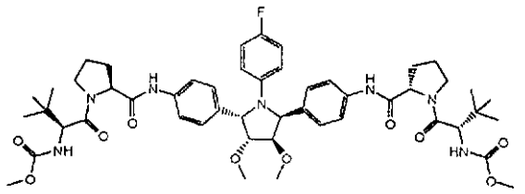
(2S,2'S)-N,N'-(4,4'-((2S,3R,4R,5S)-1-(4-fluorophenyl)-3,4-dimethoxypyrrolidine-2,5-diyl)bis((4,1-phenylene))dipyrrolidine-2-carboxamide

Dissolved the product of Example 70F (112 mg, 0.140 mmol) in anhydrous CH_2Cl_2 (1 mL) under nitrogen, added TFA (1 mL), and stirred at 25 °C for 30 min. Removed the solvent by rotary evaporation, redissolved in 1:5 v/v CH_2Cl_2/hexanes, and concentrated *in vacuo*. Took up the residue in EtOAc (50 mL), washed with sat'd aq $NaHCO_3$ (2 x 15 mL), dried the organic phase over anhydrous $MgSO_4$, filtered, and concentrated by rotary evaporation to afford the title compound as a yellow solid (72 mg, 84%). ^1H NMR (400 MHz, DMSO-D6) δ ppm 1.57 - 1.69 (m, 4 H), 1.70 - 1.85 (m, 2 H), 1.96 - 2.10 (m, 2 H), 2.82 - 2.95 (m, 4 H), 3.28 (s, 6 H), 3.66 (dd, *J*=8.84, 5.58 Hz, 2 H), 4.07 - 4.17 (m, 2 H), 5.30 - 5.49 (m, 2 H), 6.28 (dd, *J*=9.16, 4.39 Hz, 2 H), 6.75 (t, *J*=8.89 Hz, 2 H), 7.18 (d, *J*=8.57 Hz, 4 H), 7.56 (d, *J*=8.57 Hz, 4 H), 9.90 (s, 2 H); MS (ESI+) m/z 602 $(M+H)^+$.

Example 70H

dimethyl ([(2S,3R,4R,5S)-1-(4-fluorophenyl)-3,4-dimethoxypyrrolidine-2,5-diyl]bis{benzene-4,1-diylcarbamoyl(2S)pyrrolidine-2,1-diyl[(2S)-3-methyl-1-oxobutane-1,2-diyl]})biscarbamate

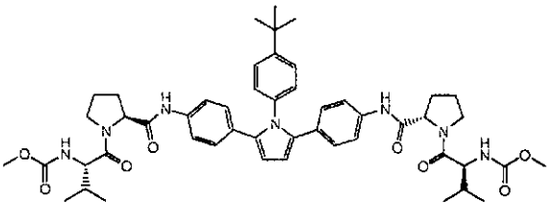
Dissolved the product of Example 70G (69.3 mg, 0.115 mmol) in anhydrous DMF (1.2 mL) under nitrogen, cooled to 0 °C, then sequentially added (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (50.4 mg, 0.288 mmol), HOBT monohydrate (44.1 mg, 0.288 mmol), EDAC (56.3 mg, 0.288 mmol), and N-methylmorpholine (0.038 mL, 0.346 mmol). Removed the cooling bath and stirred at 25 °C for 13 hr. Diluted the reaction with EtOAc (50 mL), washed with sat'd aq $NaHCO_3$ (25 mL), H_2O (2 x 25 mL), and brine (25 mL). Dried the organic phase over anhydrous $MgSO_4$, filtered, and concentrated by rotary evaporation. Purified by flash chromatography (silica gel, 2.5 cm x 15 cm, 6% MeOH/CH_2Cl_2) to afford the title compound as a white solid (48 mg, 85%). ^1H NMR (400 MHz, DMSO-D6) δ ppm 0.88 (d, *J*=6.61 Hz, 6 H), 0.93 (d, *J*=6.72 Hz, 6 H), 1.80 - 2.05 (m, 8 H), 2.08 - 2.22 (m, 2 H), 3.28 (s, 6 H), 3.52 (s, 6 H), 3.56 - 3.69 (m, 2 H), 3.77 - 3.88 (m, 2 H), 4.03 (t, *J*=8.51 Hz, 2 H), 4.07 - 4.16 (m, 2 H), 4.43 (dd, *J*=7.97, 4.83 Hz, 2 H), 5.29 - 5.44 (m, 2 H), 6.27 (dd, *J*=9.22, 4.45 Hz, 2 H), 6.75 (t, *J*=8.89 Hz, 2 H), 7.17 (d, *J*=8.46 Hz, 4 H), 7.31 (d, *J*=8.46 Hz, 2 H), 7.49 (d, *J*=8.57 Hz, 4 H), 9.99 (s, 2 H); MS (ESI+) m/z 408 $(M+H)^+$.



Example 71

dimethyl ([(2S,3R,4R,5S)-1-(4-fluorophenyl)-3,4-dimethoxypyrrolidine-2,5-diyl]bis{benzene-4,1-diylcarbamoyl(2S)pyrrolidine-2,1-diyl[(2S)-3,3-dimethyl-1-oxobutane-1,2-diyl]})biscarbamate

Dissolved the product of Example 70D (58.5 mg, 0.097 mmol) in anhydrous DMF (1 mL) under nitrogen, cooled to 0 °C, then sequentially added (S)-2-(methoxycarbonylamino)-3,3-dimethylbutanoic acid (46.0 mg, 0.243 mmol), HOBt monohydrate (37.2 mg, 0.243 mmol), EDAC (47.5 mg, 0.243 mmol), and 4-methylmorpholine (0.032 mL, 0.292 mmol). Removed the cooling bath and stirred overnight at 25 °C for 16 hr . Diluted the reaction with EtOAc (50 mL), washed with sat'd aq $NaHCO_3$ (25 mL), H_2O (2 x 25 mL), and brine (25 mL). Dried the organic phase over anhydrous $MgSO_4$, filtered, and concentrated by rotary evaporation. Purified by flash chromatography (silica gel, 2.5 cm x 15 cm, 4% MeOH/CH_2Cl_2) to afford the title compound as a cream-colored solid (66 mg, 72%). ^1H NMR (400 MHz, DMSO-D6) δ ppm 0.96 (s, 18 H), 1.79 - 1.94 (m, 4 H), 1.94 - 2.06 (m, 2 H), 2.10 - 2.22 (m, 2 H), 3.28 (s, 6 H), 3.54 (s, 6 H), 3.58 - 3.70 (m, 2 H), 3.71 - 3.86 (m, 2 H), 4.06 - 4.15 (m, 2 H), 4.21 (d, *J*=8.89 Hz, 2 H), 4.44 (dd, *J*=7.92, 5.31 Hz, 2 H), 5.31 - 5.39 (m, 2 H), 6.27 (dd, *J*=9.22, 4.45 Hz, 2 H), 6.75 (t, *J*=8.89 Hz, 2 H), 7.08 (d, *J*=8.78 Hz, 2 H), 7.17 (d, *J*=8.57 Hz, 4 H), 7.49 (d, *J*=8.57 Hz, 4 H), 9.99 (s, 2 H); MS (ESI+) m/z 945 $(M+H)^+$.



Example 72

dimethyl ([1-(4-tert-butylphenyl)-1H-pyrrole-2,5-diyl]bis{benzene-4,1-diylcarbamoyl(2S)pyrrolidine-2,1-diyl[(2S)-3-methyl-1-oxobutane-1,2-diyl]})biscarbamate

Example 72A

4,4'-(1-(4-tert-butylphenyl)-1H-pyrrole-2,5-diyl)dianiline

Example 1A was processed using the methods described generally in Examples 26F and 19B to provide the title compound. MS (ESI; M+H) m/z = 382.

Example 72B

(2S,2'S)-tert-butyl 2,2'-(4,4'-(1-(4-tert-butylphenyl)-1H-pyrrole-2,5-diyl)bis(4,1-phenylene)bis(azanediyl)bis(oxomethylene))dipyrrolidine-1-carboxylate

To a solution of the product from Example 72A (0.310 g, 0.813 mmol) in DMF (5 mL) was added (S)-1-(tert-butoxycarbonyl)pyrrolidine-2-carboxylic acid (0.385 g, 1.79 mmol) 1-hydroxybenzotriazole hydrate (0.274 g; 1.79 mmol) and N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (0.343 g, 1.79 mmol) and the mixture stirred overnight. The mixture was poured into water and extracted CH_2Cl_2. The organic extract was dried (Na_2SO_4), filtered and concentrated to give a crude product that was purified by trituration with ether to give 325 mg (51%) of the title compound. ^1H NMR (400 MHz, DMSO-D6) δ 1.25 (s, 24 H) 1.83 (s, 6 H) 2.15 (s, 2 H) 3.45 (m, 4 H) 4.18 (s, 2 H) 6.40 (s, 2 H) 6.98 (s, 6 H) 7.37 (s, 6 H) 9.98 (s, 2 H).

Example 72C

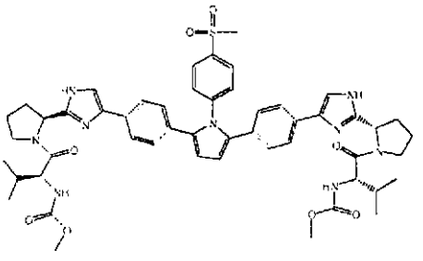
(2S,2'S)-N,N'-(4,4'-(1-(4-tert-butylphenyl)-1H-pyrrole-2,5-diyl)bis(4,1-phenylene))dipyrrolidine-2-carboxamide

To a solution of the product from Example 72B (0.325 g, 0.419 mmol) in CH_2Cl_2 (5 mL) at rt was added TFA (1.0 mL) and stirring continued for 5 h. The reaction was concentrated and the residue partitioned between water and 25% isopropyl alcohol-$CHCl_3$. The organic phase was dried (Na_2SO_4), filtered and concentrated to provide the title compound used directly in the next reaction. MS (DCI; M+H) m/z = 576.

Example 72D

dimethyl ([1-(4-tert-butylphenyl)-1H-pyrrole-2,5-diyl]bis{benzene-4,1-diylcarbamoyl(2S)pyrrolidine-2,1-diyl[(2S)-3-methyl-1-oxobutane-1,2-diyl]})biscarbamate

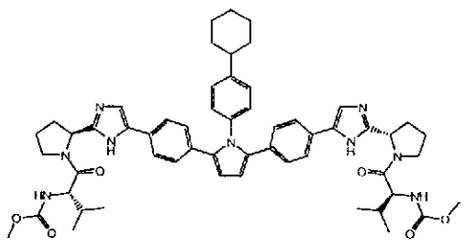
The product from Example 72C and the product from (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid were processed using the method described in Example 72B. The crude residue was purified by silica gel chromatography (1% gradient elution from 0% to 4% MeOH:CH_2Cl_2) to provide 129 mg (35%) of the title compound. ^1H NMR (400 MHz, DMSO-D6) δ0.89 (s, 12 H) 1.25 (s, 9 H) 1.89 (s, 6 H) 1.98 (s, 2 H) 2.13 (s, 2 H) 3.52 (s, 6 H) 3.61 (s, 2 H) 3.80 (s, 2 H) 4.00 (s, 2 H) 4.39 (s, 2 H) 6.38 (s, 2 H) 6.95 (s, 6 H) 7.34 (s, 8 H) 9.96 (s, 2 H).



Example 73

methyl [(2S)-1-{(2S)-2-[4-(4-{5-(4-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-4-yl}phenyl)-1-[4-(methylsulfonyl)phenyl]-1H-pyrrol-2-yl}phenyl)-1H-imidazol-2-yl]pyrrolidin-1-yl}-3-methyl-1-oxobutan-2-yl]carbamate

Example 26E and 4-(methylsulfonyl)aniline were processed using the methods of Examples 26F, 26G, 26H, 65B, and 65C to provide the title compound (78 mg). ^{1}H NMR (400 MHz, DMSO-d6) δ 12.17 – 11.67 (m, 2H), 7.92 – 7.82 (m, 2H), 7.62 – 7.49 (m, 4H), 7.48 – 7.40 (m, 2H), 7.39 – 7.15 (m, 4H), 7.08 – 6.92 (m, 4H), 6.59 – 6.47 (m, 2H), 5.08 – 4.99 (m, 2H), 4.08 – 3.98 (m, 2H), 3.84 – 3.69 (m, 4H), 3.53 (s, 6H), 3.24 (d, *J* = 1.9, 3H), 2.20 – 1.81 (m, 10H), 0.91 – 0.77 (m, 12H). MS (ESI; M+H) m/z = 959.



Example 74

methyl {(2S)-1-[(2S)-2-(5-{4-[1-(4-cyclohexylphenyl)-5-(4-{2-[(2S)-1-{(2S)-2-{(methoxycarbonyl)amino}-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-5-yl}phenyl)-1H-pyrrol-2-yl]phenyl}-1H-imidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

Example 74A

2,5-bis(4-bromophenyl)-1-(4-cyclohexylphenyl)-1H-pyrrole

The product from Example 26E and 4-cyclohexylaniline (Alfa) were processed using the method described in Example 26F to provide 1.23 g (91%) of the title compound. ^{1}H NMR (400 MHz, benzene-D6) δ1.09 (s, 5 H) 1.60 (s, 5 H) 2.14 (s, 1 H) 6.52 (s, 2 H) 6.67 (s, 4 H) 6.84 (s, 4 H) 7.11 (s, 4 H).

Example 74B

1-(4-cyclohexylphenyl)-2,5-bis(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1H-pyrrole

The product from Example 74A was processed using the method described in Example 26G to provide 1.58 g (60%) of the title compound. MS (ESI; M+H) m/z = 630.

Example 74C

(2S,2'S)-tert-butyl 2,2'-(5,5'-(4,4'-(1-(4-cyclohexylphenyl)-1H-pyrrole-2,5-diyl)bis(4,1-phenylene))bis(1H-imidazole-5,2-diyl))dipyrrolidine-1-carboxylate

A solution of the product from Example 74B (0.400 g, 0.635 mmol) and the product from Example 26D (0.442 g, 1.40 mmol) in toluene (3 mL) and ethanol (3 mL) was treated with 1 M sodium carbonate (2 mL) followed by 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex (0.052 g, 0.064 mmol), the mixture degassed (3 x vacuum/purge N_2) and then heated to 90 °C for 4 h. The reaction was concentrated and the residue partitioned between 25% isopropyl alcohol-$CHCl_3$. The organic phase was dried (Na_2SO_4) concentrated and the residue taken up in ether, sonicated, filtered and dried to provide 499 mg (93%) of the title compound. MS (ESI; M+H) m/z = 848.

Example 74D

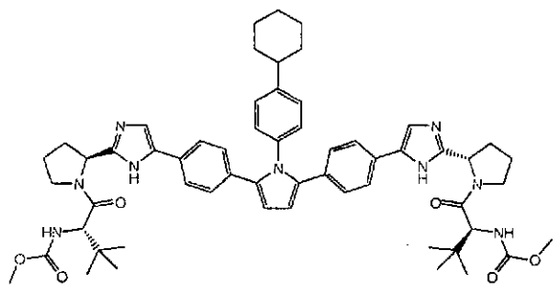
(S)-5,5'-(4,4'-(1-(4-cyclohexylphenyl)-1H-pyrrole-2,5-diyl)bis(4,1-phenylene))bis(2-((S)-pyrrolidin-2-yl)-1H-imidazole)

The product from Example 74C was processed using the method described in Example 19D to provide the title compound. MS (ESI; M+H) m/z = 648.

Example 74E

methyl {(2S)-1-[(2S)-2-(5-{4-[1-(4-cyclohexylphenyl)-5-(4-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-5-yl}phenyl)-1H-pyrrol-2-yl]phenyl}-1H-imidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

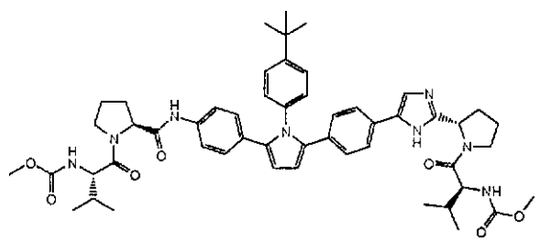
To a solution of the product from Example 74D (0.190 g, 0.293 mmol) in DMF (5 mL) was added (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (0.113 g, 0.645 mmol), 1-hydroxybenzotriazole hydrate (0.099 g; 0.645 mmol) and N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (0.124 g, 0.645 mmol) and the mixture stirred for 3 h. The mixture was poured into water and extracted CH_2Cl_2. The organic layer was concentrated and the residue purified by chromatography (gradient elution from 0% to 4% MeOH-CH_2Cl_2) to provide 100 mg (35%) of the title compound. ^{1}H NMR (400 MHz, DMSO-D6) δ 0.84 (d, J=6.62 Hz, 6 H) 0.87 (d, J=6.72 Hz, 6 H) 1.20 (m, 2 H) 1.35 (m, 4 H) 1.78 (m, 4 H) 1.92 (m, 6 H) 2.10 (m, 4 H) 3.52 (s, 6 H) 3.76 (m, 4 H) 4.02 (m, 2 H) 5.03 (m, 2 H) 6.47 (m, 2 H) 6.99 (m, 6 H) 7.18 (m, 3 H) 7.27 (m, 2 H) 7.41 (m, 2 H) 7.51 (m, 4 H) 11.74 (s, 2 H).



Example 75

methyl {(2S)-1-[(2S)-2-(5-{4-[1-(4-cyclohexylphenyl)-5-(4-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3,3-dimethylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-5-yl}phenyl)-1H-pyrrol-2-yl]phenyl}-1H-imidazol-2-yl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl}carbamate

The product from Example 74D and (S)-2-methoxycarbonylamino-3,3-dimethyl-butyric acid (Org. Process Res. Develop. 2008, 12, 69) was processed using the method described in Example 74E to provide 165 mg (57%) of the title compound. ^{1}H NMR (400 MHz, DMSO-D6) δ 0.86 - 0.96 (m, 18 H) 1.23 (m, 2 H) 1.36 (m, 4 H) 1.78 (m, 4 H) 1.88 - 2.00 (m, 4 H) 2.10 (m, 4 H) 3.54 (s, 6 H) 3.77 (m, 4 H) 4.21 (m, 2 H) 5.05 (m, 2 H) 6.46 (s, 2 H) 6.96 - 7.03 (m, 6 H) 7.19 (m, 2 H) 7.38 - 7.55 (m, 7 H) 7.70 (d, J=8.35 Hz, 1 H) 7.97 (d, J=8.46 Hz, 1 H) 11.76 (s, 2 H).



Example 76

N-(methoxycarbonyl)-L-valyl-N-(4-{1-(4-tert-butylphenyl)-5-[4-(2-{(2S)-1-[N-(methoxycarbonyl)-L-valyl]pyrrolidin-2-yl}-1H-imidazol-5-yl)phenyl]-1H-pyrrol-2-yl}phenyl)-L-prolinamide

Example 76A

2-(4-bromophenyl)-1-(4-tert-butylphenyl)-5-(4-nitrophenyl)-1H-pyrrole

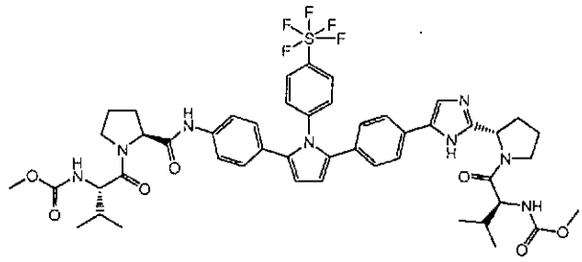
TFA (0.6 mL, 7.79 mmol) was added to a mixture of the product from Example 39A (1.2335 g, 3.41 mmol) and 4-tert-butylaniline (0.8 mL, 5.07 mmol) in toluene (30 mL) and heated at 110 °C for 17 hours. The cooled reaction mixture was poured into ether/water and stirred until nice solid formed. The mixture was filtered to afford the title compound. ^{1}H NMR (400 MHz, BENZENE-D6) δ 1.02 (s, 9H), 6.48 (d, *J* = 3.8, 1H), 6.52 (d, *J* = 3.8, 1H), 6.63 (d, *J* = 8.5, 2H), 6.80 (d, *J* = 8.5, 2H), 6.84 (d, *J* = 8.9, 2H), 6.89 (d, *J* = 8.5, 2H), 7.10 (d, *J* = 8.5, 2H), 7.70 (d, *J* = 8.9, 2H).

Example 76B

N-(methoxycarbonyl)-L-valyl-N-(4-{1-(4-tert-butylphenyl)-5-[4-(2-{(2S)-1-[N-(methoxycarbonyl)-L-valyl]pyrrolidin-2-yl}-1H-imidazol-5-yl)phenyl]-1H-pyrrol-2-yl}phenyl)-L-prolinamide

Example 76A was processed using sequentially the methods of Examples 19B, 55F, 39E (reaction temperature = 85 °C), 39F, 55G, and 26J (reaction solvent = dichloromethane) to provide the title compound (0.14 g). ^{1}H NMR (400 MHz, METHANOL-D4) δ 0.94 (ddd, *J* = 21.1, 19.5, 6.7, 12H), 1.30 (s, 10H), 2.36 - 1.92 (m, 10H), 3.63 (s, 6H), 3.76 - 3.67 (m, 1H), 3.89 - 3.78 (m, 1H), 4.02 - 3.89 (m, 2H), 4.19 (d, *J* = 7.9, 2H), 4.50 (dd, *J* = 8.1, 5.3, 1H), 5.11 (dd, *J* = 7.6, 5.5, 1H), 6.39 (d, *J*

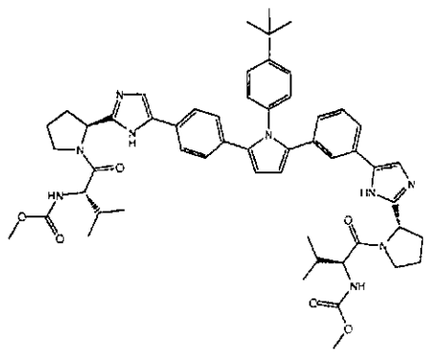
= 3.7, 1H), 6.43 (d, *J* = 3.6, 1H), 7.01 (dt, *J* = 28.2, 8.3, 6H), 7.20 (s, 1H), 7.40 (ddd, *J* = 19.1, 11.9, 5.7, 6H). MS (ESI) *m/z* 913 $(M+H)^+$.



Example 77

N-(methoxycarbonyl)-L-valyl-N-(4-{5-[4-(2-{(2S)-1-[N-(methoxycarbonyl)-L-valyl]pyrrolidin-2-yl}-1H-imidazol-5-yl)phenyl]-1-{4-(pentafluoro-lambda~6~-sulfanyl)phenyl]-1H-pyrrol-2-yl}phenyl)-L-prolinamide

Example 39A and 4-aminophenylsulfurpentafluoridewere processed using sequentially the methods of Examples 76A, 19B, 55F, 39E (reaction temperature = 85 °C), 39F, 55G, and 26J (reaction solvent = DMF) to provide the title compound (0.36 g). ^{1}H NMR (400 MHz, DMSO-D6) δ 0.86 (ddd, J = 6.9, 15.8, 21.6, 12H), 2.04 - 1.76 (m, 7H), 2.24 - 2.04 (m, 3H), 3.53 (d, J = 3.0, 6H), 3.61 (dd, J = 6.7, 16.0, 1H), 3.88 - 3.67 (m, 3H), 4.03 (dd, J = 8.3, 14.1, 2H), 4.40 (dd, J = 5.0, 8.0, 1H), 5.12 - 4.92 (m, 1H), 6.49 (ddd, J = 3.6, 14.2, 18.1, 2H), 7.09 - 6.84 (m, 4H), 7.38 - 7.12 (m, 4H), 7.50 - 7.38 (m, 3H), 7.58 (dd, J = 8.3, 16.7, 2H), 7.89 (t, J = 8.7, 2H), 10.01 (d, J = 20.9, 1H), 12.16 - 11.66 (m, 1H). MS (ESI) *m/z* 983 $(M+H)^+$, 981 $(M-H)^+$.

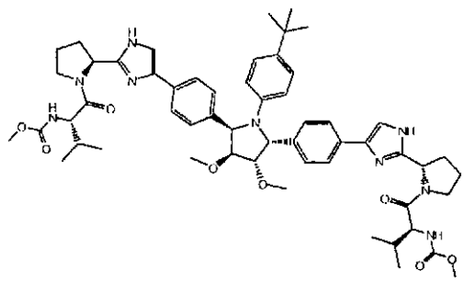


Example 78

methyl {(2S)-1-[(2S)-2-(5-{3-[1-(4-tert-butylphenyl)-5-(4-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-5-yl}phenyl)-1H-pyrrol-2-yl]phenyl}-1H-imidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

2,4'-Dibromoacetophenone and 3'-bromoacetophenone were processed using sequentially the methods of Examples 26E, 26F, 26G, 74C, 19D, and 74E to provide the title compound (232 mg). ^{1}H

NMR (400 MHz, DMSO-D6) δ 0.81 - 0.91 (m, 12 H) 1.25 (s, 9 H) 1.93 (m, 4 H) 2.11 (m, 4 H) 3.53 (s, 6 H) 3.78 (m, 4 H) 4.04 (m, 2 H) 5.03 (m, 2 H) 6.49 (m, 2 H) 6.90 - 7.08 (m, 5 H) 7.11 - 7.21 (m, 1 H) 7.27 - 7.55 (m, 9 H) 7.71 (d, J=8.35 Hz, 1 H) 7.94 - 8.01 (m, 2 H) 11.72 (br s, 2 H).



Example 79

methyl {(2S)-1-[(2S)-2-(4-{4-[(2R,3S,4S,5R)-1-(4-tert-butylphenyl)-3,4-dimethoxy-5-(4-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-4-yl}phenyl)pyrrolidin-2-yl]phenyl}-1H-imidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

Example 79A

1,2:3,4:5,6-Tri-O-isopropylidene-L-mannitol

A solution of L-mannonic acid γ-lactone (9.87 g, 55.4 mmol) in methanol (150 mL) at 0 °C was treated with lithium borohydride (2.1 g, 97 mmol) over 30 min. After addition was complete, the mixture was warmed to RT for 30 min. The mixture was then cautiously treated with a solution of hydrogen chloride in dioxane (4 N, 2 mL). The solution was then concentrated in vacuo, first on the rotary evaporator and then under high vacuum (0.3 mm Hg) while warming with a heat gun to remove the last traces of methanol. The solid obtained was then suspended in acetone (50 mL) and treated with 2,2-dimethoxypropane (41 mL, 34.6 g, 332 mmol) and a solution of hydrogen chloride in dioxane (4 N, 42 mL, 166 mmol) followed by stirring at RT for 18 h. The mixture was concentrated in vacuo to ca. 20% of original volume, and the inhomogeneous mixture was added to saturated sodium bicarbonate solution (200 mL) followed by stirring for 48 h. The precipitate was collected by filtration and washed with water and air dried. The white solid was dissolved in ethanol (200 proof, 175 mL) and filtered through celite to remove particulate matter. The solution was cooled to -78 °C to effect crystallization. The solid was collected by filtration, and the mother liquors concentrated to ca. half volume, and re-cooled to -78 °C. The second crop of crystals was collected by filtration and washed with ethanol. After drying in a vacuum oven at 50 °C for 3 h, these procedures afforded the title compound (9.88 g, 59%) as a fluffy white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.19 (dt, J = 6.0, 3.0 Hz, 2 H), 4.08 (dd, J = 8.3, 6.4 Hz, 2 H), 3.99 (m, 2 H), 3.95 (m, 2 H), 1.43 (s, 6 H), 1.39 (s, 6 H), 1.36 (s, 6 H). MS (+ESI) *m/z* (rel abundance) 303 (100, M+H), 320 (43, M+NH4).

Example 79B

3,4-O-Isopropylidene-L-mannitol

The compound of Example 79A (9.88 g, 32.7 mmol) was suspended in 60% (v/v) acetic acid in water (150 mL) in a 1 L roundbottom and the flask placed on the rotory evaporator and rotated in the heating bath at 45 °C for 1.5 h. The heating bath was reduced in temperature to 40 °C and a line to the vacuum pump was attached to the rotory evaporator. The mixture was concentrated under ca. 1 mm Hg pressure to a wet solid. This material was diluted with dichloromethane (100 mL) and stirred at RT for 10 min. The solution was filtered through celite, and the filtrate concentrated in vacuo. The residue was dissolved in toluene and concentrated in vacuo (2 x) to remove residual acetic acid. The white solid was then triturated with ether (60 mL) and collected by filtration. After drying in a vacuum oven for 18 h, these procedures afforded the title compound (2.46 g, 34%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 5.07 (d, J = 4.5 Hz, 2 H), 4.45 (t, J = 5.7 Hz, 2 H), 3.86 (dd, J = 4.9, 1.5 Hz, 2 H), 3.54 (ddd, J = 10.9, 5.5, 3.1 Hz, 2 H), 3.48 (d, J = 4.6 Hz, 2 H), 3.37 (m, 2 H), 1.28 (s, 6 H).

Example 79C

(2R,3S,4S,5R)-1-(4-tert-butylphenyl)-2,5-bis(4-(4-methoxybenzyloxy)phenyl)-pyrrolidine-3,4-diol

To a solution of Example 79B (1.0g, 4.5 mmol) in CH_3OH (12.0 mL) and CH_2Cl_2 (6.0 mL) was added iodobenzene diacetate (3.48g, 10.8 mmol) and the solution was stirred at room temperature for 5 h. Solvent was removed in vacuo and to the residue was added 0.1 M H_2SO_4 (4 mL) and the solution was stirred at room temperature for 18 h. The pH was adjusted to ~6 with solid $NaHCO_3$, and 4-tert-butylaniline (1.43 mL, 9.0 mmol) was added followed by 4-(4-methoxybenzyloxy)phenylboronic acid (2.09g, 8.1 mmol) and hexafluoroisopropyl alcohol (8 mL). The solution was heated at 50 °C for 2 h, cooled and solvent removed in vacuo leaving the aqueous layer which contained quite a bit of solid material. The mixture was diluted with H_2O and 0.33 M K_3PO_4 was added and the mixture was stirred vigorously. The resulting white solid was collected by filtration and dried in a vacuum oven to give title compound (1.49g, 2.26 mmol, 50%).^{1}H NMR (400 MHz, DMSO-$d6$) δ ppm 1.10 (s, 9H) 3.75 (s, 6H) 4.21 (s, 2H) 4.95 (s, 2H) 5.02 (d, J=6.9 Hz, 2H) 5.75 (s, 2H) 6.20 (d, J=8.9 Hz, 2H) 6.85-6.97 (m, 10H) 7.05 (d, J=8.6 Hz, 4H) 7.37 (d, J=8.7 Hz, 4H).

Example 79D

(2R,3S,4S,5R)-1-(4-tert-butylphenyl)-3,4-dimethoxy-2,5-bis-(4-(4-methoxybenzyloxy)phenyl)pyrrolidine

To a solution of Example 79C (1.49g, 2.26 mmol) in THF (17 mL) and DMF (5.7 mL) at 0 °C was added, in portions, NaH, 60% in mineral oil (0.27g, 6.77 mmol) and the mixture was stirred at 0

°C for 20 min. Iodomethane (0.31 mL, 4.97 mmol) was added and the reaction mixture was stirred at room temperature for 18 h, diluted with EtOAc, washed with saturated NH_4Cl, H_2O, and brine, dried (Na_2SO_4), filtered and solvent removed in vacuo to give an oily product. The oil was diluted with minimal ether and the oil began to solidify and the title compound was isolated as a colorless solid (1.55g, 2.25 mmol, 100%). ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.16 (s, 6H) 3.44 (s, 6H) 3.82 (s, 6H) 4.12-4.17 (m, 2H) 4.94 (s, 4H) 5.22 (dd, J=5.2, 1.63 Hz, 2H) 6.29 (d, J=8.9 Hz, 2H) 6.88-7.00 (m, 10H) 7.12 (d, J=8.6 Hz, 4H) 7.34 (d, J=8.6 Hz, 4H). MS (ESI) m/z 688 $(M+H)^+$.

Example 79E

4,4'-((2R,3S,4S,5R)-1-(4-tert-butylphenyl)-3,4-dimethoxypyrrolidine-2,5-diyl)diphenol

To a solution of Example 79D (1.55g, 2.25 mmol) in CH_2Cl_2 (9 mL) was added trifluoroacetic acid (9 mL, 117 mmol) and stirring was continued at room temperature for 1 h. Solvent was removed and the crude residue was dissolved in 1:1 EtOAc/ saturated $NaHCO_3$. The organic layer was separated, washed with brine, dried (Na_2SO_4), filtered and solvent removed in vacuo to give title compound (1.0 g, 2.23 mmol, 99%). MS (ESI) m/z 448 $(M+H)^+$.

Example 79F

4,4'-((2R,3S,4S,5R)-1-(4-tert-butylphenyl)-3,4-dimethoxypyrrolidine-2,5-diyl)bis(4,1-phenylene)bis(1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonate)

To a solution of Example 79E (1.0g, 2.23 mmol) in DMF (12 mL) was added K_2CO_3 (0.695 g, 5.0 mmol) and 1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonyl fluoride (0.86 mL, 4.9 mmol) and the solution was stirred at 100 °C for 1 h. The cooled solution was diluted with EtOAc, washed with H_2O, brine, dried (Na_2SO_4), filtered and solvent removed in vacuo to give crude product which was purified by flash chromatography on silica gel eluting with 0-20% EtOAc/hexane to give the title compound (1.63 g, 1.61 mmol, 72%). ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.17 (s, 9H) 3.42 (s, 6H) 4.10 (dd, J=5.3, 1.90 Hz, 2H) 5.30 (dd, J=5.2, 1.9 Hz, 2H) 6.19 (d, J=8.8 Hz, 2H) 6.99-7.03 (m, 2H) 7.21-7.29 (m, 8H). MS (ESI) m/z 1012 $(M+H)^+$.

Example 79G

(2R,3S,4S,5R)-1-(4-tert-butylphenyl)-3,4-dimethoxy-2,5-bis(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)pyrrolidine

To a pressure tube was combined Example 79F (216 mg, 0.21 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (114 mg, 0.45 mmol), dicyclohexyl(2',4',6'-triisopropylbiphenyl-2-yl)phosphine (16.3 mg, 0.034 mmol), potassium acetate (126 mg, 1.28 mmol) and dioxane (2 mL) and the mixture was de-gassed with N_2 gas for 30 min. Tris(dibenzylideneacetone)dipalladium(0) (7.8 mg, 8.54 mmol) was added and de-gassing was

continued for 10 min. The tube was sealed and heated at 100 °C for 30 min. The cooled solution was diluted with EtOAc, washed with H_2O, brine, dried (Na_2SO_4), filtered and the filtrate treated with 3-mercaptopropyl functionalized silica gel for 1 h, filtered and solvent removed in vacuo to give the title compound (143 mg, 100%).

Example 79H

(2S,2'S)-tert-butyl 2,2'-(4,4'-(4,4'-((2R,3S,4S,5R)-1-(4-tert-butylphenyl)-3,4-dimethoxypyrrolidine-2,5-diyl)bis(4,1-phenylene)bis(1H-imidazole-4,2-diyl))dipyrrolidine-1-carboxylate

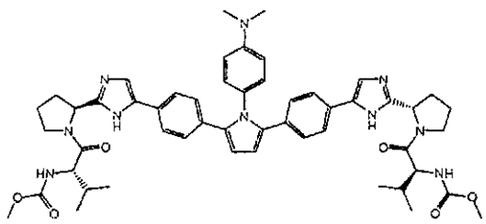
To a pressure tube was combined Example 79G (140 mg, 0.21 mmol), (S)-tert-butyl-2-(4-bromo-1H-imidazol-2-yl)pyrrolidine-1-carboxylate (Example 26D) (166 mg, 0.524 mmol), 1 M Na_2CO_3 (0.524 mL, 0.524 mmol), EtOH (1 mL), and toluene (1 mL) and the mixture was de-gassed with N_2 gas for 30 min. 1,1'-bis(diphenylphosphino)ferrocenedichloro palladium(II) dichloromethane complex (15.3 mg, 0.021 mmol) was added and de-gassing was continued for 10 min. The tube was sealed and heated at 100 °C for 3 h, then stirred at room temperature for 16 h. The solution was diluted with EtOAc, filtered through Celite and the filtrate washed with brine, dried (Na_2SO_4), filtered and solvent removed in vacuo. Purified by flash chromatography on silica gel eluting with 0-100% EtOAc/hexane to give title compound (119 mg, 0.135 mmol, 64%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.13 (s, 9H) 1.49 (s, 18H) 1.88-2.02 (m, 2H) 2.06-2.22 (m, 4H) 2.99 (s, 2H) 3.33-3.48 (m, 4H) 3.43 (s, 6H) 4.23 (s, 2H) 4.96 (d, J=5.3 Hz, 2H) 5.29 (d, J=6.9 Hz, 2H) 6.29 (d, J=8.9 Hz, 2H) 6.94 (d, J=8.4 Hz, 2H) 7.13-7.29 (m, 8H). MS (ESI) m/z 886 $(M+H)^+$.

Example 79I

methyl {(2S)-1-{(2S)-2-(4-{4-[(2R,3S,4S,5R)-1-(4-tert-butylphenyl)-3,4-dimethoxy-5-(4-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-4-yl}phenyl)pyrrolidin-2-yl]phenyl}-1H-imidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

To a solution of Example 79H (30 mg, 0.034 mmol) in CH_2Cl_2 (1 mL) was added trifluoroacetic acid (1 mL) and the solution was stirred at room temperature for 1 h. Solvent was removed in vacuo and then dissolved in DMSO (0.5 mL). N,N-diisopropylethylamine was added until pH 9-10, then (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (14.8 mg, 0.085 mmol) was added followed by HATU (32 mg, 0.085 mmol) and the solution was stirred at room temperature for 1 h. The solution was diluted with EtOAc, washed with H_2O, brine, dried (Na_2SO_4), filtered and solvent removed in vacuo. Dissolved the residue in CH_3OH (2 mL), added solid K_2CO_3 and stirred at room temperature for 30 min. Solid was filtered off and the filtrate was concentrated in vacuo and the residue purified by flash chromatography on silica gel eluting with 0-5% CH_3OH/CH_2Cl_2 to give title compound (21.6 mg, 0.022 mmol, 63%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.85 (s, 12H) 1.13 (s,

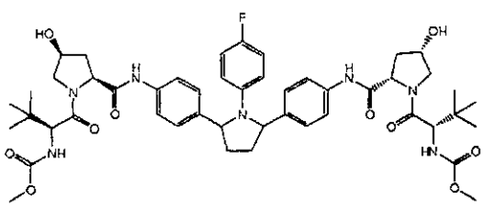
9H) 1.82-2.03 (m, 2H) 2.02-2.24 (m, 4H) 2.32 (br s, 2H) 3.04 (br s, 2H) 3.43 (s, 6H) 3.53-3.65 (m, 2H) 3.70 (s, 6H) 3.75-3.90 (m, 2H) 4.22 (s, 2H) 4.31 (d, J=15.7 Hz, 2H) 5.16-5.33 (m, 4H) 5.37 (d, J=9.1 Hz, 2H) 6.29 (d, J=8.9 Hz, 2H) 6.94 (s, 2H) 7.16 (s, 2H) 7.22 (d, J=8.0 Hz, 4H) 7.31-7.52 (m, 2H) 7.60-7.87 (m, 2H) 10.26 (s, 1H) 10.64 (s, 1H). MS (ESI) m/z 1000 $(M+H)^+$.



Example 80

methyl [(2S)-1-{(2S)-2-[5-(4-{1-[4-(dimethylamino)phenyl]-5-(4-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-5-yl}phenyl)-1H-pyrrol-2-yl}phenyl)-1H-imidazol-2-yl]pyrrolidin-1-yl}-3-methyl-1-oxobutan-2-yl]carbamate

Example 26E and N,N-dimethyl-p-phenylenediamine were processed using sequentially the methods of Examples 76A, 39E, 39F, 55G (25% isopropylalcohol/chloroform used for extraction), and 26J (reaction solvent = dichloromethane) to provide the title compound (5.6 mg). ^{1}H NMR (400 MHz, DMSO-d6) δ 0.94 - 0.75 (m, 12H), 2.04 - 1.78 (m, 6H), 2.21 - 2.03 (m, 4H), 2.89 (s, 6H), 3.38 (s, 1H), 3.53 (s, 6H), 3.84 - 3.68 (m, 3H), 4.10 - 3.96 (m, 2H), 5.04 (dd, J = 2.9, 6.7, 2H), 6.53 - 6.37 (m, 2H), 6.70 - 6.54 (m, 2H), 7.12 - 6.85 (m, 6H), 7.33 - 7.12 (m, 2H), 7.46 - 7.34 (m, 2H), 7.60 - 7.46 (m, 4H), 12.11 - 11.64 (m, 2H). MS (ESI) *m/z* 923 $(M+H)^+$.



Example 81

dimethyl ([(2*S*,5*S*)-1-(4-fluorophenyl)pyrrolidine-2,5-diyl]bis{benzene-4,1-diylcarbamoyl[(2*S*,4*S*)-4-hydroxypyrrolidine-2,1-diyl][(2*S*)-3,3-dimethyl-1-oxobutane-1,2-diyl]})biscarbamate

and

dimethyl ([(2*R*,5*R*)-1-(4-fluorophenyl)pyrrolidine-2,5-diyl]bis{benzene-4,1-diylcarbamoyl[(2*S*,4*S*)-4-hydroxypyrrolidine-2,1-diyl][(2*S*)-3,3-dimethyl-1-oxobutane-1,2-diyl]})biscarbamate

Example 81A

(2S,4S)-1-(tert-butoxycarbonyl)-4-hydroxypyrrolidine-2-carboxylic acid

To a solution of (2S,4S)-4-hydroxypyrrolidine-2-carboxylic acid (3.9 g, 29.7 mmol) in THF (26.7 mL) and water (13.3 mL) was added di-tert-butyl dicarbonate (7.14 g, 32.7 mmol) and sodium hydroxide (2.0 N, 22.9 mL, 45.8 mmol) and the mixture stirred at room temperature overnight. The mixture then had 10% citric acid (50 mL) added followed by EtOAc and extraction with water and brine. The organic extract was dried, filtered and concentrated to afford 5.31 g (77%) of the title compound. MS (ESI) m/z 232 (M+H)+.

Example 81B

(2S,4S)-1-(tert-butoxycarbonyl)-4-(tert-butyldimethylsilyloxy)pyrrolidine-2-carboxylic acid

To a solution of Example 81A (5.31, 22.96 mmol) and imidazole (7.82 g, 115 mmol) in dichloromethane (106 mL) and DMF (21.3 mL) was added *tert*-butyldimethylsilyl chloride (7.61 g, 50.5 mmol) and the mixture stirred at room temperature overnight. The mixture then had water (425 mL) added and the solution was extracted with EtOAc and the organic extract concentrated to a residue that was dissolved in 25% EtOAc and 75% hexanes then extracted with brine and the organic extract concentrated to a solid. The resultant solid was dissolved in methanol (65 mL) and water (85 mL) then lithium hydroxide monohydrate (1.93 g, 46 mmol) added and the solution stirred at room temperature for 2 h. Afterwards water (106 mL) and a solution of 1N aqueous hydrochloric acid was added until a pH of 2 was reached. The mixture was then extracted with a mixture of 25% EtOAc and 75% hexanes, the organic extract dried, filtered and concentrated to a colorless solid. MS (ESI) m/z 346 (M+H)+.

Example 81C

(3S,3'S,5S,5'S)-tert-butyl 5,5'-(4,4'-((2S,5S)-1-(4-fluorophenyl)pyrrolidine-2,5-diyl)bis(4,1-phenylene))bis(azanediyl)bis(oxomethylene)bis(3-(tert-butyldimethylsilyloxy)pyrrolidine-1-carboxylate)

and

(3S,3'S,5S,5'S)-tert-butyl 5,5'-(4,4'-((2R,5R)-1-(4-fluorophenyl)pyrrolidine-2,5-diyl)bis(4,1-phenylene))bis(azanediyl)bis(oxomethylene)bis(3-(tert-butyldimethylsilyloxy)pyrrolidine-1-carboxylate)

The product of Example 81B (149 mg, 0.432 mmol) and the product from Example 5A (50 mg, 0.144 mmol) were processed using the method described in Example 1F to afford 74 mg (51%) of the title compound as a 1:1 mixture of diastereomers. MS (ESI) m/z 1002 (M+H)+.

Example 81D

(2S,2'S,4S,4'S)-N,N'-(4,4'-((2S,5S)-1-(4-fluorophenyl)pyrrolidine-2,5-diyl)bis(4,1-phenylene))bis(4-hydroxypyrrolidine-2-carboxamide)

and

(2S,2'S,4S,4'S)-N,N'-(4,4'-((2R,5R)-1-(4-fluorophenyl)pyrrolidine-2,5-diyl)bis(4,1-phenylene))bis(4-hydroxypyrrolidine-2-carboxamide)

The product of Example 81C (74 mg, 0.074 mmol) was dissolved in trifluoroacetic acid (4 mL), water (0.2 mL) and dichloromethane (0.2 mL) and the mixture stirred at room temperature for 3 hours. Afterwards the mixture was concentrated to an oil which was dissolved in 75% $CHCl_3$ and 25% isopropyl alcohol then extracted with a saturated aqueous sodium bicarbonate solution, the organic extract separated, dried, filtered and concentrated to a colorless solid. MS (ESI) m/z 574 (M+H)+.

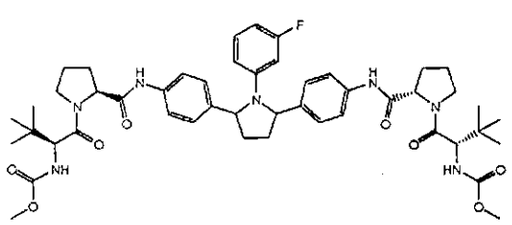
Example 81E

dimethyl ([(2*S*,5*S*)-1-(4-fluorophenyl)pyrrolidine-2,5-diyl]bis{benzene-4,1-diylcarbamoyl[(2*S*,4*S*)-4-hydroxypyrrolidine-2,1-diyl][(2*S*)-3,3-dimethyl-1-oxobutane-1,2-diyl]})biscarbamate

and

dimethyl ([(2*R*,5*R*)-1-(4-fluorophenyl)pyrrolidine-2,5-diyl]bis{benzene-4,1-diylcarbamoyl[(2*S*,4*S*)-4-hydroxypyrrolidine-2,1-diyl][(2*S*)-3,3-dimethyl-1-oxobutane-1,2-diyl]})biscarbamate

To the product from Example 81D (40 mg, 0.072 mmol), (S)-2-(methoxycarbonylamino)-3,3-dimethylbutanoic acid (34.1 mg, 0.18 mmol) and HATU (60.2 mg, 0.158 mmol) in DMSO (3 mL) was added Hunig's base (0.063 mL, 0.36 mmol), and the reaction mixture was stirred at room temperature for 1 hr. The reaction mixture was partitioned between water and ethyl acetate, and the organic layer was dried over $MgSO_4$, filtered and concentrated in vacuo. The crude product was purified by column chromatography on silica gel using a solvent gradient of 0-10% MeOH in dichloromethane to give the title compound as a 1:1 mixture of stereoisomers (21 mg, 32% yield): ^1H NMR (400 MHz, DMSO-D6) δ ppm 9.94 (s, 2 H), 7.44 (d, *J*=8.4 Hz, 4 H), 7.07 (m, 6 H) 6.74 (t, *J*=8.9 Hz, 2 H), 6.15 (dd, *J*=9.1, 4.4 Hz, 2 H), 5.26 (dd, *J*=6.1, 3.3 Hz, 2 H), 5.11 (d, *J*=5.5 Hz, 2 H), 4.33 (t, *J*=7.8 Hz, 2H), 4.19 (m, 2 H), 4.07 (m, 2 H), 3.93 (m, 2 H), 3.48 (s, 6 H), 2.34 (m, 2 H), 1.66 (m, 2 H), 1.59 (m, 2 H), 1.20 (m, 2 H), 0.91 (m, 18 H).



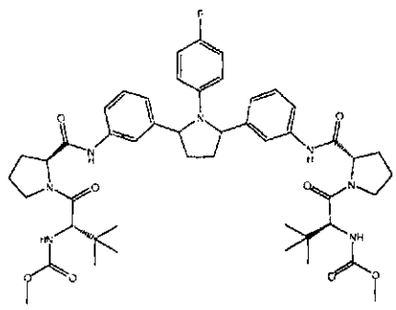
Example 82

dimethyl ([(2*S*,5*S*)-1-(3-fluorophenyl)pyrrolidine-2,5-diyl]bis{benzene-4,1-diylcarbamoyl(2*S*)pyrrolidine-2,1-diyl[(2*S*)-3,3-dimethyl-1-oxobutane-1,2-diyl]})biscarbamate

and

dimethyl ([(2*R*,5*R*)-1-(3-fluorophenyl)pyrrolidine-2,5-diyl]bis{benzene-4,1-diylcarbamoyl(2*S*)pyrrolidine-2,1-diyl[(2*S*)-3,3-dimethyl-1-oxobutane-1,2-diyl]})biscarbamate

Example 1C and 3-fluoroaniline were processed using sequentially the methods of Examples 1D, 1E, 1F, 1G, and 1H to provide the title compounds. The trans diastereomers were separated from the cis diastereomer at the stage of 4,4'-(1-(3-fluorophenyl)pyrrolidine-2,5-diyl)dianiline. Data for the title compounds. ^{1}H NMR (free base) (400 MHz, DMSO-d_6) δ ppm 0.96 (d, *J*=2.17 Hz, 18 H), 1.75 - 1.92 (m, 7 H), 1.93 - 2.05 (m, 2 H), 2.10 - 2.21 (m, 2 H), 2.31 - 2.44 (m, 2 H), 3.43 - 3.51 (m, 4 H), 3.53 (s, 6 H), 3.59 - 3.73 (m, 6 H), 3.73 - 3.82 (m, 2 H), 4.21 (d, *J*=8.89 Hz, 2 H), 4.46 (dd, *J*=7.92, 5.31 Hz, 2 H), 4.70 (t, *J*=4.66 Hz, 2 H), 6.07 (d, *J*=12.90 Hz, 1 H), 6.19 (dd, *J*=8.35, 1.63 Hz, 1 H), 6.37 (dt, *J*=8.35, 2.06 Hz, 1 H), 6.97 - 7.05 (m, 2 H), 7.08 (d, *J*=8.67 Hz, 2 H), 7.41 (d, *J*=7.26 Hz, 4 H), 7.60 (d, *J*=8.57 Hz, 4 H), 10.07 (s, 2 H). MS (ESI) m/z 885 $(M+H)^+$.



Example 83

dimethyl ([(2*S*,5*S*)-1-(4-fluorophenyl)pyrrolidine-2,5-diyl]bis{benzene-3,1-diylcarbamoyl(2*S*)pyrrolidine-2,1-diyl[(2*S*)-3,3-dimethyl-1-oxobutane-1,2-diyl]})biscarbamate

and

dimethyl ([(2*R*,5*R*)-1-(4-fluorophenyl)pyrrolidine-2,5-diyl]bis{benzene-3,1-diylcarbamoyl(2*S*)pyrrolidine-2,1-diyl[(2*S*)-3,3-dimethyl-1-oxobutane-1,2-diyl]})biscarbamate

Example 83A

(2S,2'S)-tert-butyl 2,2'-(3,3'-((2S,5S)-1-(4-fluorophenyl)pyrrolidine-2,5-diyl)bis(3,1-phenylene))bis(azanediyl)bis(oxomethylene)dipyrrolidine-1-carboxylate

and

(2S,2'S)-tert-butyl 2,2'-(3,3'-((2R,5R)-1-(4-fluorophenyl)pyrrolidine-2,5-diyl)bis(3,1-phenylene))bis(azanediyl)bis(oxomethylene)dipyrrolidine-1-carboxylate

The ether fraction from the work up of Example 55F was purified using flash chromatography (silica gel, 0-30%EtOAc/dichloromethane) to afford the title compound as a mixture of trans diastereomers. MS (ESI) *m/z* 742 $(M+H)^+$.

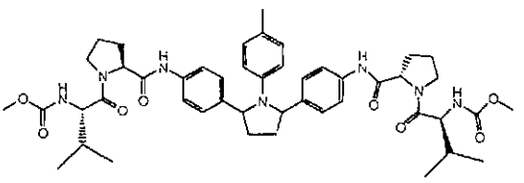
Example 83B

dimethyl ([(2*S*,5*S*)-1-(4-fluorophenyl)pyrrolidine-2,5-diyl]bis{benzene-3,1-diylcarbamoyl(2*S*)pyrrolidine-2,1-diyl[(2*S*)-3,3-dimethyl-1-oxobutane-1,2-diyl]})biscarbamate

and

dimethyl ([(2*R*,5*R*)-1-(4-fluorophenyl)pyrrolidine-2,5-diyl]bis{benzene-3,1-diylcarbamoyl(2*S*)pyrrolidine-2,1-diyl[(2*S*)-3,3-dimethyl-1-oxobutane-1,2-diyl]})biscarbamate

The product from Example 83A was processed using the methods described in Examples 55G and 55H to afford the title compound (0.18 g, 27%). ^{1}H NMR (400 MHz, DMSO-D6) δ 0.97 (d, J = 4.5, 18H), 1.73 - 1.60 (m, 2H), 1.92 - 1.75 (m, 5H), 2.05 - 1.92 (m, 3H), 2.23 - 2.05 (m, 2H), 3.54 (d, J = 1.5, 6H), 3.71 - 3.59 (m, 2H), 3.85 - 3.71 (m, 2H), 4.21 (d, J = 8.9, 2H), 4.50 - 4.37 (m, 2H), 5.14 (d, J = 5.7, 2H), 6.30 - 6.19 (m, 2H), 6.85 - 6.75 (m, 2H), 6.88 (d, J = 7.7, 2H), 7.09 (d, J = 8.7, 2H), 7.23 (t, J = 7.9, 2H), 7.40 - 7.30 (m, 2H), 7.58 (d, J = 8.1, 2H), 10.07 - 9.96 (m, 2H). MS (ESI) *m/z* 884 $(M+H)^+$, 882 $(M-H)^+$.



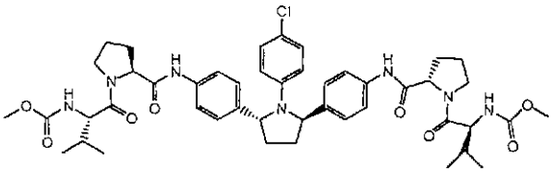
Example 84

dimethyl ([(2S,5S)-1-(4-methylphenyl)pyrrolidine-2,5-diyl]bis{benzene-4,1-diylcarbamoyl(2S)pyrrolidine-2,1-diyl[(2S)-3-methyl-1-oxobutane-1,2-diyl]})biscarbamate

and

dimethyl ([(2R,5R)-1-(4-methylphenyl)pyrrolidine-2,5-diyl]bis{benzene-4,1-diylcarbamoyl(2S)pyrrolidine-2,1-diyl[(2S)-3-methyl-1-oxobutane-1,2-diyl]})biscarbamate

The title compound was prepared using the procedures described for the synthesis of Examples 34A, 34B, 34C, 34D, and 34E, substituting 4-methylaniline for 4-*tert*-butylaniline. ^{1}H NMR (500 MHz, DMSO-D6) δ ppm 0.85 - 0.90 (m, 6 H), 0.90 - 0.95 (m, 6 H), 1.61 - 1.65 (m, 2 H), 1.82 - 2.01 (m, 8 H), 2.03 (s, 3 H), 2.09 - 2.16 (m, 2 H), 3.52 (s, 6 H), 3.58 - 3.66 (m, 2 H), 3.77 - 3.84 (m, 2 H), 4.02 (t, 2 H), 4.40 - 4.45 (m, 2 H), 5.14 (d, *J*=6.6 Hz, 2 H), 6.13 - 6.18 (m, 2 H), 6.72 (d, *J*=8.4 Hz, 2 H), 7.08 - 7.14 (m, 4 H), 7.29 - 7.34 (m, 2 H), 7.46 - 7.51 (m, 4 H), 9.98 (s, 2 H); MS m/z 852.3 $(M+H)^+$.



Example 85

dimethyl ([(2S,5S)-1-(4-chlorophenyl)pyrrolidine-2,5-diyl]bis{benzene-4,1-diylcarbamoyl(2S)pyrrolidine-2,1-diyl[(2S)-3-methyl-1-oxobutane-1,2-diyl]})biscarbamate

and

dimethyl ([(2R,5R)-1-(4-chlorophenyl)pyrrolidine-2,5-diyl]bis{benzene-4,1-diylcarbamoyl(2S)pyrrolidine-2,1-diyl[(2S)-3-methyl-1-oxobutane-1,2-diyl]})biscarbamate

Example 85A

1-(4-chlorophenyl)-2,5-bis(4-nitrophenyl)pyrrolidine

The product of Example 1B (0.50 g, 1.51 mmol) was suspended in CH_2Cl_2 (15 mL). Triethylamine (0.626 mL, 4.51 mmol) was added at 0 °C, the resulting mixture was stirred for 30 min, and methanesulfonyl chloride (0.293 mL, 3.76 mmol) was added. The mixture was stirred at rt for 1 hr and then concentrated in vacuo to give a light yellow solid. The solid was dissolved in DMF (6 mL), 4-chloroaniline (1.92 g, 15.05 mmol) was added, and the resulting mixture was stirred at 50 °C overnight. The mixture was partitioned between EtOAc and 1N aq HCl, and the organic layer was dried over Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by column chromatography on silica gel using a solvent gradient of 0-12% EtOAc in hexane to give the title compound (0.226 g, 35%).

Example 85B

4,4'-(trans-1-(4-chlorophenyl)pyrrolidine-2,5-diyl)dianiline

To a solution of the product of example 85A (0.214 g, 0.505 mmol) in EtOH (2.52 mL) and THF (2.52 mL) was added platinum(IV) oxide (0.115 g, 0.505 mmol), and the resulting mixture was stirred at rt under 1 atm H_2 overnight. The mixture was filtered through celite, and the filtrate was concentrated in vacuo. The crude product was purified by column chromatography on silica gel using a solvent gradient of 0-12% EtOAc in hexane to give a mixture of the title compound and some dechlorinated product (4,4'-(trans-1-phenylpyrrolidine-2,5-diyl)dianiline).

Example 85C

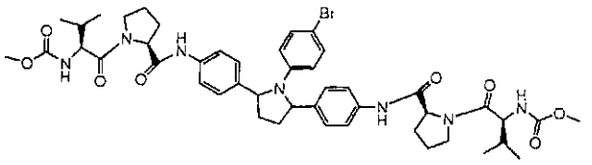
dimethyl ([(2S,5S)-1-(4-chlorophenyl)pyrrolidine-2,5-diyl]bis{benzene-4,1-diylcarbamoyl(2S)pyrrolidine-2,1-diyl[(2S)-3-methyl-1-oxobutane-1,2-diyl]})biscarbamate

and

dimethyl ([(2R,5R)-1-(4-chlorophenyl)pyrrolidine-2,5-diyl]bis{benzene-4,1-diylcarbamoyl(2S)pyrrolidine-2,1-diyl[(2S)-3-methyl-1-oxobutane-1,2-diyl]})biscarbamate

A mixture of the product from Example 85B was subjected to the procedures described in Examples 34C, 34D, and 34E to give the title compounds free of dechlorinated product. 1H NMR

(TFA salt) (400 MHz, DMSO-D6) δ ppm 0.84 - 0.89 (m, 6 H), 0.89 - 0.94 (m, 6 H), 1.61 - 1.66 (m, 2 H), 1.80 - 2.03 (m, 8 H), 2.06 - 2.18 (m, 2 H), 3.51 (s, 6 H), 3.56 - 3.65 (m, 2H), 3.74 - 3.84 (m, 2 H), 4.01 (t, *J*=8.4 Hz, 2 H), 4.36 - 4.44 (m, 2 H), 5.16 (d, *J*=6.3 Hz, 2 H), 6.21 (d, *J*=8.9 Hz, 2 H), 6.93 (d, *J*=9.0 Hz, 2 H), 7.08 - 7.13 (m, 4 H), 7.26 - 7.31 (m, 2 H), 7.46 - 7.51 (m, 4 H), 9.99 (s, 2 H). MS m/z 872.3 $(M+H)^+$.



Example 86

dimethyl ([(2*S*,5*S*)-1-(4-bromophenyl)pyrrolidine-2,5-diyl]bis{benzene-4,1-diylcarbamoyl(2*S*)pyrrolidine-2,1-diyl[(2*S*)-3-methyl-1-oxobutane-1,2-diyl]})biscarbamate

and

dimethyl ([(2*R*,5*R*)-1-(4-bromophenyl)pyrrolidine-2,5-diyl]bis{benzene-4,1-diylcarbamoyl(2*S*)pyrrolidine-2,1-diyl[(2*S*)-3-methyl-1-oxobutane-1,2-diyl]})biscarbamate

Example 86A

1-(4-bromophenyl)-2,5-bis(4-nitrophenyl)pyrrolidine

The product from Example 1C (0.7 g, 1.433 mmol) and 4-bromoaniline (2.54 g, 14.33 mmol) were suspended in DMF (6mL) and stirred at 50 °C overnight. The resulting mixture was partitioned between ethyl acetate (100 mL) and water (50 mL). The organic phase was washed with 1N HCl (2x50mL) followed by a brine wash then dried over $MgSO_4$ filtered and concentrated. The crude product was purified by chromatography on silica gel.using a solvent gradient of 2-50% ethyl acetate in hexane to give the title compound as a mixture of stereoisomers (74.4mg, 11% yield).

Example 86B

(2S,2'S)-N,N'-(4,4'-(1-(4-bromophenyl)pyrrolidine-2,5-diyl)bis(4,1-phenylene))dipyrrolidine-2-carboxamide

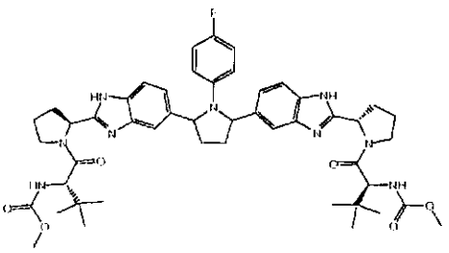
Example 86A was processed using the methods of Examples 1E, 1F, and 1G to provide the title compound as a mixture of stereoisomers.

Example 86C

dimethyl ([1-(4-bromophenyl)pyrrolidine-2,5-diyl]bis{benzene-4,1-diylcarbamoyl(2S)pyrrolidine-2,1-diyl[(2S)-3-methyl-1-oxobutane-1,2-diyl]})biscarbamate

The product from Example 86B (78.0mg, 0.129mmole) was combined with EDAC (67.0mg, 0.347 mmol), 1-hydroxybenzotriazole hydrate (49.0mg, 0.323mmole) and (S)-2-

(methoxycarbonylamino)-3-methylbutanoic acid (61.0mg, 0.346mmole) in dimethylformamide (1.4mL) at room temperature under a nitrogen atmosphere. To this solution was added diisopropylethylamine (0.113 mL, 0.645 mmol). The mixture was allowed to stir overnight at room temperature followed by partition between ethyl acetate (20mL) and water (5mL). The organic phase was washed with water (3x5mL) then dried over $MgSO_4$, filtered and evaporated to dryness. The crude product was chromatographed by reverse phase (C_{18}) HPLC providing the title compound as a 1:1 mixture of (trans) diastereomers (0.045g, 38% yield) as an off white solid. 1H NMR (free base) (400 MHz, DMSO-D6) δ ppm 0.72 - 1.03 (m, 12 H) 1.65 (s, 2 H) 1.79 - 2.19 (m, 11 H) 3.52 (s, 6 H) 3.58 - 3.67 (m, 2 H) 3.75 - 3.86 (m, 2 H) 3.95 - 4.09 (m, 2 H) 4.43 (dd, *J*=7.92, 4.88 Hz, 2 H) 5.08 - 5.25 (m, 2 H) 6.19 (d, *J*=8.89 Hz, 2 H) 7.06 (d, *J*=8.89 Hz, 2 H) 7.12 (d, *J*=7.16 Hz, 4 H) 7.31 (dd, *J*=8.29, 3.96 Hz, 2 H) 7.51 (dd, *J*=8.46, 1.52 Hz, 4 H) 10.00 (s, 2 H). MS ESI(+) m/z@916.6 (M+H)+.



Example 87

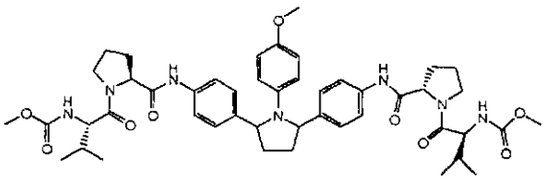
methyl {(2*S*)-1-[(2*S*)-2-{5-[(2*S*,5*S*)-1-(4-fluorophenyl)-5-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3,3-dimethylbutanoyl}pyrrolidin-2-yl]-1*H*-benzimidazol-5-yl}pyrrolidin-2-yl]-1*H*-benzimidazol-2-yl}pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl}carbamate

and

methyl {(2*S*)-1-[(2*S*)-2-{5-[(2*R*,5*R*)-1-(4-fluorophenyl)-5-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3,3-dimethylbutanoyl}pyrrolidin-2-yl]-1*H*-benzimidazol-5-yl}pyrrolidin-2-yl]-1*H*-benzimidazol-2-yl}pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl}carbamate

The product from Example 29G (0.045 g, 0.084 mmol), (S)-2-methoxycarbonylamino-3,3-dimethyl-butyric acid (0.037 g, 0.193 mmol), 4-methylmorpholine (0.037 mL, 0.336 mmol), 1H-benzo[d][1,2,3]triazol-1-ol hydrate (0.028 g, 0.185 mmol) and N1-((ethylimino)methylene)-N3,N3-dimethylpropane-1,3-diamine hydrochloride (0.035 g, 0.185 mmol) were combined in 2 mL DMF and stirred for 2 hours. The reaction mixture was partitioned between EtOAc and water. The organic layer was washed 3 X 20 mL with brine, dried (Na_2SO_4), filtered and concentrated. The crude material was flash chromatographed on a 4 g Isco Gold silica cartridge eluting with 1.5-8% MeOH in methylene chloride. A second reverse phase C-18 preparative chromatography eluting with 9:1 water/acetonitrile --> 100% acetonitrile afforded the title compounds (29 mg, 28%; mix of trans diastereomers) as a light tan powder. ^{1}H NMR (TFA salt) (400 MHz, DMSO-d_6) δ 0.84 - 0.95 (m, 18 H) 1.21 - 1.46 (m, 4

H) 1.75 - 2.27 (m, 8 H) 3.56 (s, 6 H) 3.86 (t, J=5.26 Hz, 4 H) 4.22 (dd, J=8.57, 4.45 Hz, 2 H) 5.15 - 5.24 (m, 2 H) 5.53 (d, J=4.88 Hz, 2 H) 6.30 (dd, J=9.11, 4.34 Hz, 2 H) 6.75 - 6.83 (m, 2 H) 7.29 (d, J=8.57 Hz, 2 H) 7.35 (d, J=8.46 Hz, 2 H) 7.48 (d, J=7.92 Hz, 2 H) 7.69 (d, J=7.37 Hz, 2 H). MS (ESI+) m/z 879 $(M+H)^+$.



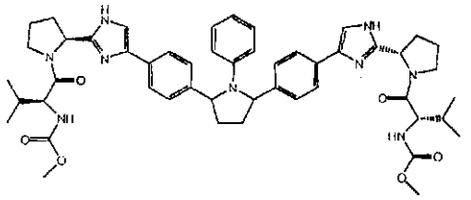
Example 88

dimethyl ([(2S,5S)-1-(4-methoxyphenyl)pyrrolidine-2,5-diyl]bis{benzene-4,1-diylcarbamoyl(2S)pyrrolidine-2,1-diyl[(2S)-3-methyl-1-oxobutane-1,2-diyl]})biscarbamate

and

dimethyl ([(2R,5R)-1-(4-methoxyphenyl)pyrrolidine-2,5-diyl]bis{benzene-4,1-diylcarbamoyl(2S)pyrrolidine-2,1-diyl[(2S)-3-methyl-1-oxobutane-1,2-diyl]})biscarbamate

The title compound was prepared using the procedures described for the synthesis of Examples 34A, 34B, 34C, 34D, and 34E, substituting 4-methoxyaniline for 4-*tert*-butylaniline. ^{1}H NMR (TFA salt) (400 MHz, DMSO-D6) δ ppm 0.85 - 0.90 (m, 6 H), 0.90 - 0.95 (m, 6 H), 1.60 - 1.66 (m, 2 H), 1.81 - 2.04 (m, 8 H), 2.08 - 2.19 (m, 2 H), 3.52 (s, 9 H), 3.57 - 3.66 (m, 2 H), 3.77 - 3.85 (m, 2 H), 4.02 (t, 2 H), 4.39 - 4.46 (m, 2 H), 5.12 (d, *J*=6.3 Hz, 2 H), 6.18 (d, *J*=9.0 Hz, 2 H), 6.56 (d, *J*=9.0 Hz, 2 H), 7.09 - 7.15 (m, 4 H), 7.28 - 7.34 (m, 2 H), 7.46 - 7.52 (m, 4 H), 9.97 (s, 2 H); MS m/z 868.5 $(M+H)^+$.



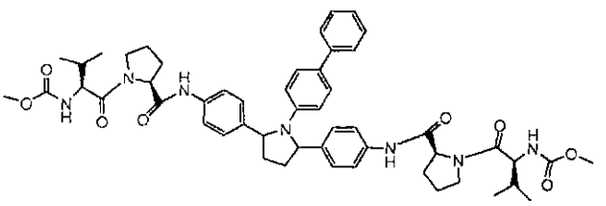
Example 89

methyl {(2*S*)-1-[(2*S*)-2-(4-{4-[(2*S*,5*S*)-5-(4-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1*H*-imidazol-4-yl}phenyl)-1-phenylpyrrolidin-2-yl]phenyl}-1*H*-imidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

and

methyl {(2*S*)-1-[(2*S*)-2-(4-{4-[(2*R*,5*R*)-5-(4-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1*H*-imidazol-4-yl}phenyl)-1-phenylpyrrolidin-2-yl]phenyl}-1*H*-imidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

The trans diastereomers obtained in Example 59B (8.5 mg, 0.0107 mmol), (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (4.67 mg, 0.027 mmol) and HATU (8.9 mg, 0.023 mmol) in DMSO (1 mL) was added Hunig's base (0.015 mL, 0.085 mmol), and the reaction mixture was stirred at room temperature for 1 hr. The reaction mixture was partitioned between water and ethyl acetate, and the organic layer was dried over $MgSO_4$, filtered and concentrated in vacuo. The crude product was purified by reversed phase chromatography (C18), eluting with 10-100% acetonitrile in water (0.1% TFA) to afford 5.0 mg (53%) of the title compound as a mixture of trans diastereomers. 1H NMR (TFA salt) (400 MHz, DMSO-D6) δ ppm 14.45 (bs, 2 H), 7.97 (s, 2 H), 7.66 (m, 4 H), 7.38 (m, 4H), 7.31 (d, *J*=7.4 Hz, 2 H), 6.92 (t, *J*=7.6 Hz, 2 H), 6.43 (m, 1 H), 6.28 (d, *J*=8.1 Hz, 2 H), 5.37 (m, 2H), 5.09 (t, *J*=6.7 Hz, 2 H), 4.09 (t, *J*=7.7 Hz, 2 H), 3.81 (m, 6 H), 3.53 (s, 6 H), 2.40 (m, 2 H), 2.08 (m, 2 H), 2.02 (m, 6 H), 1.85 (m, 2 H), 0.85 (m, 2 H), 0.80 (m, 12 H); MS (ESI) m/z 884 (M+H)+.



Example 90

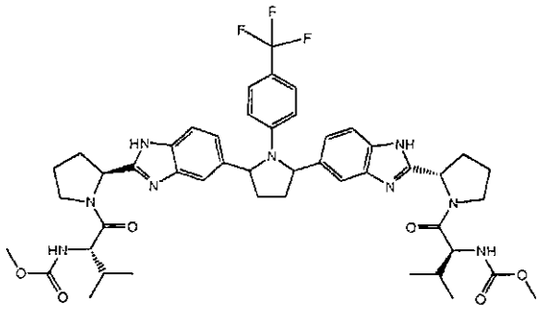
dimethyl ([(2*S*,5*S*)-1-(biphenyl-4-yl)pyrrolidine-2,5-diyl]bis{benzene-4,1-diylcarbamoyl(2*S*)pyrrolidine-2,1-diyl[(2*S*)-3-methyl-1-oxobutane-1,2-diyl]})biscarbamate

and

dimethyl ([(2*R*,5*R*)-1-(biphenyl-4-yl)pyrrolidine-2,5-diyl]bis{benzene-4,1-diylcarbamoyl(2*S*)pyrrolidine-2,1-diyl[(2*S*)-3-methyl-1-oxobutane-1,2-diyl]})biscarbamate

The product from Example 86C (24.9mg, 0.027mmole) dissolved in a THF (1mL) and water (0.3mL) solution was combined in a microwave tube with phenylboronic acid (6.90mg, 0.054mmole), tribasic potassium phosphate (13.37mg, 0.063mmole) and 1,1'-bis(di-tert-butylphosphino)ferrocene palladium dichloride (1.42mg, 2.17μmole). The tube was sealed and nitrogen bubbled through at room temperature for five minutes. All gas lines were subsequently removed and the reaction vessel immersed in a 50 °C oil bath and heated for two and one half hours. The contents of the tube were partitioned between ethylacetate (5mL) and brine (1mL). The organic phase was washed with brine (2 x 1mL) then dried over $MgSO_4$, filtered and concentrated. The crude product was purified by silica gel chromatography eluting with 5% EtOAc – hexane and progressing to (75% EtOAc-hexane) + 3% methanol to provide as a 1:1 mixture of (trans) diastereomers the title compound (18.6mg, 75% yield) as a cream colored solid. 1H NMR (400 MHz, DMSO-D6) δ ppm 0.76 - 0.99 (m, 12 H) 1.67 (s, 2 H) 1.77 - 2.19 (m, 11 H) 3.52 (s, 6 H) 3.58 - 3.65 (m, 2 H) 3.74 - 3.86 (m, 2 H) 3.96 - 4.08 (m, 2 H) 4.44 (d, *J*=4.99 Hz, 2 H) 5.25 (s, 2 H) 6.35 (d, *J*=8.02 Hz, 2 H) 7.17 (d, *J*=7.26 Hz, 5 H) 7.24 - 7.34 (m, 6

H) 7.45 (d, *J*=7.92 Hz, 2 H) 7.52 (d, *J*=7.81 Hz, 4 H) 10.00 (s, 2 H). MS ESI(+) m/z@ 915.1 (M+H)+, m/z@ 972.3 (M+CH_3CN+NH_4)+.



Example 91

methyl {(2*S*)-1-[(2*S*)-2-(5-{(2*S*,5*S*)-5-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1*H*-benzimidazol-5-yl}-1-[4-(trifluoromethyl)phenyl]pyrrolidin-2-yl}-1*H*-benzimidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

and

methyl {(2*S*)-1-[(2*S*)-2-(5-{(2*R*,5*R*)-5-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1*H*-benzimidazol-5-yl}-1-[4-(trifluoromethyl)phenyl]pyrrolidin-2-yl}-1*H*-benzimidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

Example 91A

(2*S*,2'*S*)-2,2'(6,6'-(1-(4-(trifluoromethyl)phenyl)pyrrolidine-2,5-diyl)bis(1H-benzo[d]imidazole-6,2-diyl))dipyrrolidinium chloride

Example 28C and 4-trifluoromethylaniline were processed using the methods of Examples 28D-28J to provide the title compound as a mixture of cis and trans stereoisomers.

Example 91B

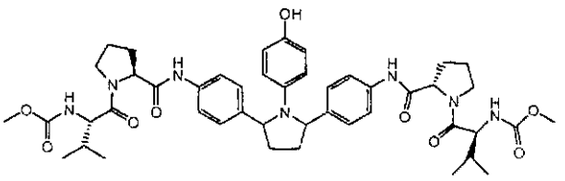
methyl {(2*S*)-1-[(2*S*)-2-(5-{(2*S*,5*S*)-5-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1*H*-benzimidazol-5-yl}-1-[4-(trifluoromethyl)phenyl]pyrrolidin-2-yl}-1*H*-benzimidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

and

methyl {(2*S*)-1-[(2*S*)-2-(5-{(2*R*,5*R*)-5-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1*H*-benzimidazol-5-yl}-1-[4-(trifluoromethyl)phenyl]pyrrolidin-2-yl}-1*H*-benzimidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

The product from Example 91A (1: 1 mixture of cis and trans isomers), 0.018 g, 0.027 mmole), HOBt (0.013 g, 0.082 mmole), EDAC (0.016 g, 0.082 mmole) and (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (0.014 g, 0.082 mmole) were combined in a 20 ml round bottom flask and dissolved in 1 ml DMF at room temperature, added 4-methylmorpholine

(0.015 ml, 0.137 mmole) and the resulting clear slightly brown solution was stirred at room temperature for 2 hr. The reaction mixture was analyzed by LC-MS and determined to be complete. The reaction mixture was diluted with 50 ml EtOAc, washed with 10% $NaHCO_3$ and 10% NaCl, dried over anhydrous Na_2SO_4(s), filtered and solvent removed in vacuo leaving the title compound as a light brown solid. The material was purified by preparative HPLC on a Phenomenex Luna C8(2) 5 um 100Å AXIA column (30mm x 75mm). A gradient of acetonitrile (A) and 0.1% trifluoroacetic acid in water (B) was used, at a flow rate of 50mL/min (0-0.5 min 10% A, 0.5-7.0 min linear gradient 10-95% A, 7.0-10.0 min 95% A, 10.0-12.0 min linear gradient 95-10% A). The product fractions were collected and evaporated to dryness in vacuo leaving the title compound as a tan solid, (11 mg, 44%) and a mixture of diastereomeric trans isomers. 1H NMR (TFA salt) (400 MHz, DMSO-D6) d ppm 0.67 - 0.94 (m, 12 H) 1.95 (m, 18 H) 3.79 - 3.89 (m, 6 H) 4.10 (s, 2 H) 5.19 (s, 1 H) 5.64 (s, 2 H) 6.45 (s, 2 H) 7.28 (s, 4 H) 7.47 (s, 4 H) 7.69 (s, 4 H), 12.1 (b, 2H)ESI+(m/z):900.6, ESI-(m/z):898.8.



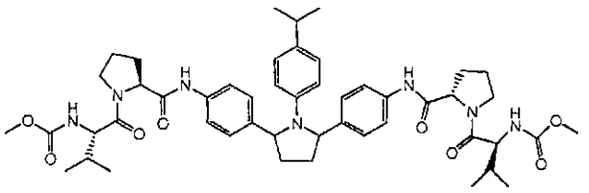
Example 92

dimethyl ([(2S,5S)-1-(4-hydroxyphenyl)pyrrolidine-2,5-diyl]bis{benzene-4,1-diylcarbamoyl(2S)pyrrolidine-2,1-diyl[(2S)-3-methyl-1-oxobutane-1,2-diyl]})biscarbamate

and

dimethyl ([(2R,5R)-1-(4-hydroxyphenyl)pyrrolidine-2,5-diyl]bis{benzene-4,1-diylcarbamoyl(2S)pyrrolidine-2,1-diyl[(2S)-3-methyl-1-oxobutane-1,2-diyl]})biscarbamate

To a solution of the product from Example 88 (0.050 g, 0.058 mmol) in CH_2Cl_2 (1 mL) at –78 °C was added a 1.0 M solution of borontribromide in CH_2Cl_2 (0.29 mL, 0.29 mmol). The resulting dark red color solution was stirred at –78 °C for 4 h, and then warmed to rt and washed with water. The organic layer was dried over sodium sulphate, filtered, and concentrated in vacuo. The crude product was purified by column chromatography on silica gel using a solvent gradient of 0-7.5% MeOH in CH_2Cl_2 to give the title compound (5.5 mg, 12%) as a mixture of trans diastereomers. 1H NMR (400 MHz, DMSO-D6) δ ppm 0.86 - 0.90 (m, 6 H), 0.90 - 0.95 (m, 6 H), 1.58 - 1.63 (m, 2 H), 1.82 - 2.04 (m, 8 H), 2.08 - 2.19 (m, 2 H), 3.52 (s, 6 H), 3.58 - 3.66 (m, 2 H), 3.77 - 3.84 (m, 2 H), 4.02 (t, *J*=8.5 Hz, 2 H), 4.40 - 4.46 (m, 2 H), 5.08 (d, *J*=6.3 Hz, 2 H), 6.08 (d, *J*=8.8 Hz, 2 H), 6.38 (d, *J*=8.8 Hz, 2 H), 7.08 - 7.13 (m, 4 H), 7.29 - 7.34 (m, 2 H), 7.45 - 7.51 (m, 4 H), 8.27 (d, *J*=1.2 Hz, 1 H), 9.96 (s, 2 H); MS m/z 854.4 $(M+H)^+$.



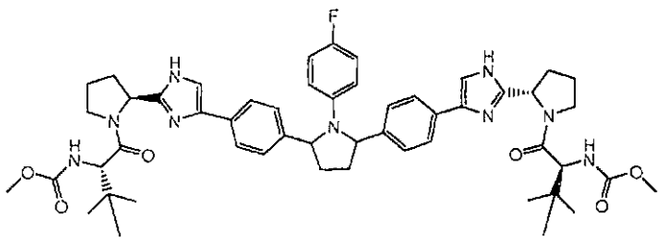
Example 93

dimethyl ({(2S,5S)-1-[4-(propan-2-yl)phenyl]pyrrolidine-2,5-diyl}bis{benzene-4,1-diylcarbamoyl(2S)pyrrolidine-2,1-diyl[(2S)-3-methyl-1-oxobutane-1,2-diyl]})biscarbamate

and

dimethyl ({(2R,5R)-1-[4-(propan-2-yl)phenyl]pyrrolidine-2,5-diyl}bis{benzene-4,1-diylcarbamoyl(2S)pyrrolidine-2,1-diyl[(2S)-3-methyl-1-oxobutane-1,2-diyl]})biscarbamate

The title compound was prepared as a mixture of trans diastereomers using the procedures described for the synthesis of Examples 34A, 34B, 34C, 34D, and 34E, substituting 4-isopropylaniline for 4-*tert*-butylaniline. 1H NMR (TFA salt) (400 MHz, DMSO-D6) δ ppm 0.85 - 0.90 (m, *J*=5.8, 5.8 Hz, 6 H), 0.90 - 0.96 (m, 6 H), 1.02 - 1.06 (m, 6 H), 1.60 - 1.65 (m, 2 H), 1.81 - 2.04 (m, 8 H), 2.08 - 2.19 (m, 2 H), 2.56 - 2.65 (m, 1 H), , 3.52 (s, 6 H), 3.58 - 3.66 (m, 2 H), 3.76 - 3.85 (m, 2 H), 4.02 (t, *J*=8.3 Hz, 2 H), 4.40 - 4.45 (m, 2 H), 5.14 (d, *J*=6.5 Hz, 2 H), 6.15 - 6.20 (m, 2 H), 6.79 (d, *J*=8.7 Hz, 2 H), 7.09 - 7.16 (m, 4 H), 7.29 - 7.34 (m, 2 H), 7.47 - 7.52 (m, 4 H), 9.97 (s, 2 H); MS m/z 880.5 $(M+H)^+$.



Example 94

methyl {(2*S*)-1-[(2*S*)-2-(4-{4-[(2*S*,5*S*)-1-(4-fluorophenyl)-5-(4-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3,3-dimethylbutanoyl}pyrrolidin-2-yl]-1*H*-imidazol-4-yl}phenyl)pyrrolidin-2-yl]phenyl}-1*H*-imidazol-2-yl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl}carbamate

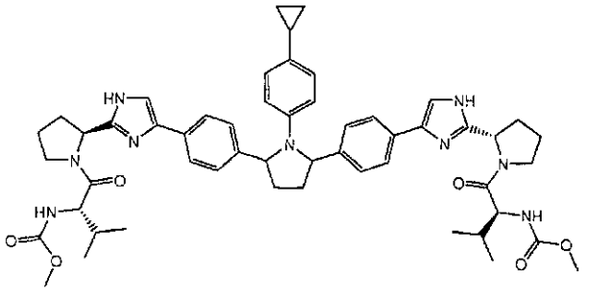
and

methyl {(2*S*)-1-[(2*S*)-2-(4-{4-[(2*R*,5*R*)-1-(4-fluorophenyl)-5-(4-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3,3-dimethylbutanoyl}pyrrolidin-2-yl]-1*H*-imidazol-4-yl}phenyl)pyrrolidin-2-yl]phenyl}-1*H*-imidazol-2-yl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl}carbamate

The product from Example 45D (28 mg, 0.048 mmol) was subjected to the conditions described in example 45E, substituting (S)-2-(methoxycarbonylamino)-3,3-dimethylbutanoic acid for

000222

(S)-2-(methoxycarbonylamino)-3-methylbutanoic acid, to give the title compound (18 mg, 41%) as a mixture of diastereomers. 1H NMR (TFA salt) (400 MHz, DMSO-D6) δ ppm 0.86 (s, 9 H), 0.87 (s, 9 H), 1.70 - 1.81 (m, 2 H), 1.94 - 2.25 (m, 6 H), 2.34 - 2.44 (m, 2 H), 3.55 (s, 6 H), 3.72 - 3.95 (m, 4 H), 4.19 (d, *J*=8.7 Hz, 2 H), 5.09 (t, *J*=7.2 Hz, 2 H), 5.35 (d, *J*=6.1 Hz, 2 H), 6.26 (dd, *J*=9.1, 4.4 Hz, 2 H), 6.81 (t, *J*=8.9 Hz, 2 H), 7.29 (d, *J*=8.0 Hz, 2 H), 7.37 (d, *J*=7.2 Hz, 4 H), 7.68 (dd, *J*=7.8, 5.4 Hz, 4 H), 7.97 (s, 2 H), 14.46 (br s, 2 H); MS m/z 930.8 $(M+H)^+$.



Example 95

methyl {(2*S*)-1-[(2*S*)-2-(4-{4-[(2*S*,5*S*)-1-(4-cyclopropylphenyl)-5-(4-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1*H*-imidazol-4-yl}phenyl)pyrrolidin-2-yl]phenyl}-1*H*-imidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

and

methyl {(2*S*)-1-[(2*S*)-2-(4-{4-[(2*R*,5*R*)-1-(4-cyclopropylphenyl)-5-(4-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1*H*-imidazol-4-yl}phenyl)pyrrolidin-2-yl]phenyl}-1*H*-imidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

Example 95A

(S)-4,4'-(4,4'-((2R,5R)-1-(4-cyclopropylphenyl)pyrrolidine-2,5-diyl)bis(4,1-phenylene))bis(2-((S)-pyrrolidin-2-yl)-1H-imidazole)

and

(S)-4,4'-(4,4'-((2S,5S)-1-(4-cyclopropylphenyl)pyrrolidine-2,5-diyl)bis(4,1-phenylene))bis(2-((S)-pyrrolidin-2-yl)-1H-imidazole)

The product from Example 68C (1.27 g, 1.568 mmol) was dissolved in dichloromethane (12 mL). The mixture was cooled to 0 °C and trifluroacetic acid (8 mL, 104 mmol) was added slowly. The mixture was warmed to room temperature and stirred for 1h. The solvent was evaporated and the residue was purified by chromatography on silica gel eluting with methanol/dichloromethane (1% to 10%). The title compound was eluted as the first of 2 stereoisomers and was obtained as a mixture of trans diastereomers (510 mg, 53%).

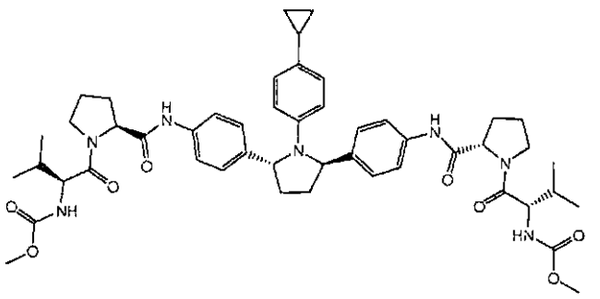
Example 95B

methyl {(2*S*)-1-[(2*S*)-2-(4-{4-[(2*S*,5*S*)-1-(4-cyclopropylphenyl)-5-(4-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1*H*-imidazol-4-yl}phenyl)pyrrolidin-2-yl]phenyl}-1*H*-imidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

and

methyl {(2*S*)-1-[(2*S*)-2-(4-{4-[(2*R*,5*R*)-1-(4-cyclopropylphenyl)-5-(4-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1*H*-imidazol-4-yl}phenyl)pyrrolidin-2-yl]phenyl}-1*H*-imidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

The product from Example 95A (150 mg, 0.246 mmol), (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (86 mg, 0.492 mmol), 4-methylmorpholine (0.216 mL, 1.968 mmol), N1-((ethylimino)methylene)-N3,N3-dimethylpropane-1,3-diamine hydrochloride (104 mg, 0.541 mmol) and 1H-benzo[d][1,2,3]triazol-1-ol hydrate (83 mg, 0.541 mmol) were combined in DMF (10 mL). The mixture was stirred at room temperature for 2 hours. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was washed with saturated sodium bicarbonate, brine twice, dried with sodium sulfate, filtered and evaporated. The residue was purified by chromatography on silica gel eluting with methanol/dichloromethane (1% to 4%) to give the title compound (78 mg, 34%) as a solid. 1H NMR (400 MHz, DMSO-D6) δ ppm 0.35 - 0.41 (m, 2 H) 0.65 - 0.72 (m, 2 H) 0.81 - 0.92 (m, 12 H) 1.58 - 1.64 (m, 1 H) 1.66 - 1.72 (m, 2 H) 1.86 - 2.03 (m, 6 H) 2.07 - 2.17 (m, 4 H) 2.24 - 2.30 (m, 2 H) 3.53 (s, 6 H) 3.74 - 3.82 (m, 4 H) 4.04 (t, J=7.86 Hz, 2 H) 5.06 (dd, J=6.72, 2.93 Hz, 2 H) 5.14 - 5.26 (m, 2 H) 6.19 (d, J=8.67 Hz, 2 H) 6.64 (d, J=8.24 Hz, 2 H) 7.10 - 7.30 (m, 6 H) 7.34 - 7.69 (m, 6 H) 11.64 - 12.11 (m, 2 H); MS (ESI+) m/z 924.8 (M+H)+.

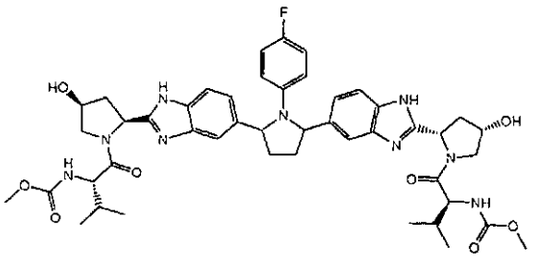


Example 96

dimethyl ([(2R,5R)-1-(4-cyclopropylphenyl)pyrrolidine-2,5-diyl]bis{benzene-4,1-diylcarbamoyl(2S)pyrrolidine-2,1-diyl[(2S)-3-methyl-1-oxobutane-1,2-diyl]})biscarbamate

Example 38A and 4-cyclopropylaniline were processed using sequentially the methods of Examples 34A, 34B, 34C, 66D, and 66E to provide the title compound (62 mg). ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.36 - 0.46 (m, 2 H) 0.63 - 0.77 (m, 2 H) 0.87 (d, J=6.61 Hz, 6 H) 0.92 (d, J=6.72 Hz, 6 H) 1.52 - 2.46 (m, 15 H) 3.52 (s, 6 H) 3.57 - 3.66 (m, 2 H) 3.75 - 3.85 (m, 2 H) 4.02 (t, J=8.46 Hz, 2 H) 4.42 (dd, J=8.02, 4.88 Hz, 2 H) 5.14 (d, J=6.40 Hz, 2 H) 6.14 (d, J=8.78 Hz, 2 H) 6.65 (d, J=8.67

Hz, 2 H) 7.10 (d, J=8.57 Hz, 4 H) 7.30 (d, J=8.35 Hz, 2 H) 7.48 (d, J=8.57 Hz, 4 H) 9.97 (s, 2 H). MS (APCI) m/z 878 $(M+H)^+$.

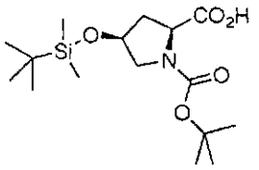


Example 97

methyl {(2*S*)-1-[(2*S*,4*S*)-2-{5-[(2*S*,5*S*)-1-(4-fluorophenyl)-5-{2-[(2*S*,4*S*)-4-hydroxy-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1*H*-benzimidazol-5-yl}pyrrolidin-2-yl]-1*H*-benzimidazol-2-yl}-4-hydroxypyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

and

methyl {(2*S*)-1-[(2*S*,4*S*)-2-{5-[(2*R*,5*R*)-1-(4-fluorophenyl)-5-{2-[(2*S*,4*S*)-4-hydroxy-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1*H*-benzimidazol-5-yl}pyrrolidin-2-yl]-1*H*-benzimidazol-2-yl}-4-hydroxypyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate



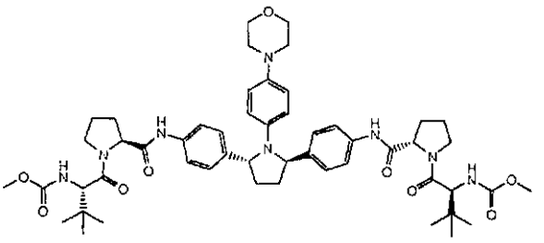
Example 97A

(2S,4S)-1-(tert-butoxycarbonyl)-4-(tert-butyldimethylsilyloxy)pyrrolidine-2-carboxylic acid

(2S,4S)-1-(tert-butoxycarbonyl)-4-hydroxypyrrolidine-2-carboxylic acid (5.31 g, 22.96 mmol) and imidazole (7.82 g, 115 mmol) were combined in dichlorormethane (106 mL) and dimethylformamide (22 mL) at ambient temperature and treated with portionwise addition of tert-butylchlorodimethylsilane (7.61 g, 50.5 mmol). The mixture was stirred for 18 hours then diluted with water and extracted into ethyl acetate and concentrated to provide the title compound.

Example 97B

The product from Example 29D (0.906 g, 2.62 mmol) was processed as in Examples 29E, 29F, 29G, and 29H, substituting Example 97A for S-Boc-proline in step 29E to give the title compounds (0.012 g, 13%).1H NMR (400 MHz, DMSO-D6) δ ppm 0.69 - 0.85 (m, 12 H) 1.27 - 1.39 (m, 1 H) 1.53 (dt, J=21.31, 6.64 Hz, 1 H) 1.71 (s, 4 H) 1.80 - 1.90 (m, 2 H) 2.02 (d, J=7.70 Hz, 2 H) 2.54 - 2.62 (m, 2 H) 3.53 (s, 6 H) 3.68 (t, J=10.63 Hz, 2 H) 3.93 - 4.00 (m, 2 H) 4.39 (s, 2 H) 5.13 (s, 2 H) 5.38 (s, 2 H) 6.19 - 6.38 (m, 4 H) 6.74 (d, J=2.60 Hz, 2 H) 7.08 (s, 2 H) 7.21 - 7.36 (m, 4 H) 7.40 - 7.51 (m, 2 H) 12.21 - 12.38 (m, 2 H); MS TFA+ m/z 882.5 (M+H)+.



Example 98

dimethyl ({(2R,5R)-1-[4-(morpholin-4-yl)phenyl]pyrrolidine-2,5-diyl}bis{benzene-4,1-diylcarbamoyl(2S)pyrrolidine-2,1-diyl[(2S)-3,3-dimethyl-1-oxobutane-1,2-diyl]})biscarbamate

Example 98A

4-(4-((2R,5R)-2,5-bis(4-nitrophenyl)pyrrolidin-1-yl)phenyl)morpholine

The product from Example 38A and 4-morpholinoaniline were processed using the method described in Example 1D using NMP for the solvent to afford the title compound. MS (ESI) *m/z* 475 $(M+H)^+$.

Example 98B

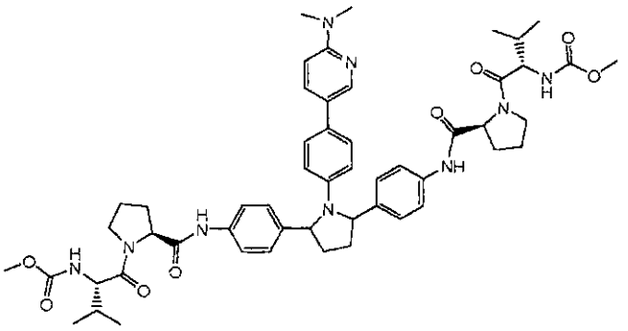
4,4'-((2R,5R)-1-(4-morpholinophenyl)pyrrolidine-2,5-diyl)dianiline

The product from Example 98A in tetrahydrofuran (20 mL) was added to Ra-Ni (water wet, A-7000, 0.8 g, 12.63 mmol) in a 50 mL pressure bottle and stirred for 2 hours at ambient temperature under 30 psi of hydrogen. The mixture was filtered through a nylon membrane and concentrated to afford the title compound (0.31 g, 44%). MS (DCI) *m/z* 415 $(M+H)^+$.

Example 98C

(2S,2'S)-tert-butyl 2,2'-(4,4'-((2R,5R)-1-(4-morpholinophenyl)pyrrolidine-2,5-diyl)bis(4,1-phenylene))bis(azanediyl)bis(oxomethylene)dipyrrolidine-1-carboxylate

The product from Example 98B was processed using sequentially the methods of Examples 55F, 55G, and 26J (with (S)-2-(methoxycarbonylamino)-3,3-dimethylbutanoic acid) to afford the title compound (0.13 g). ^{1}H NMR (400 MHz, DMSO-D6) δ 0.93 (d, *J* = 20.5, 17H), 1.92 - 1.79 (m, 4H), 2.05 - 1.93 (m, 3H), 2.21 - 2.08 (m, 2H), 2.43 (t, *J* = 6.1, 3H), 2.84 - 2.75 (m, 4H), 3.54 (s, 6H), 3.68 - 3.58 (m, 6H), 3.83 - 3.70 (m, 2H), 4.20 (d, *J* = 8.9, 2H), 4.43 (dd, *J* = 7.9, 5.3, 2H), 5.12 (d, *J* = 6.3, 2H), 6.17 (d, *J* = 9.1, 2H), 6.60 (d, *J* = 9.1, 2H), 7.07 (d, *J* = 8.8, 2H), 7.11 (d, *J* = 8.5, 4H), 7.48 (d, *J* = 8.5, 4H), 9.98 (s, 2H). Impurity ^{1}H NMR (400 MHz, DMSO-D6) δ 1.63 (d, *J* = 5.6, 2H), 3.17 (d, *J* = 5.3, 3H), 4.09 (q, *J* = 5.3, 1H). MS (ESI) *m/z* 952 $(M+H^+)$.



Example 99

dimethyl ([(2*S*,5*S*)-1-{4-[6-(dimethylamino)pyridin-3-yl]phenyl}pyrrolidine-2,5-diyl]bis{benzene-4,1-diylcarbamoyl(2*S*)pyrrolidine-2,1-diyl[(2*S*)-3-methyl-1-oxobutane-1,2-diyl]})biscarbamate

and

dimethyl ([(2*R*,5*R*)-1-{4-[6-(dimethylamino)pyridin-3-yl]phenyl}pyrrolidine-2,5-diyl]bis{benzene-4,1-diylcarbamoyl(2*S*)pyrrolidine-2,1-diyl[(2*S*)-3-methyl-1-oxobutane-1,2-diyl]})biscarbamate

Example 99A

5-(4-(2,5-bis(4-nitrophenyl)pyrrolidin-1-yl)phenyl)-N,N-dimethylpyridin-2-amine

The product from Example 86A (25.7mg, 0.055mmole) was combined in a microwave tube with 6-(dimethylamino)pyridine-3-ylboronic acid (17.49mg, 0.105mmole), tribasic potassium phosphate (24.70mg, 0.116mole) and 1,1'-bis(di-tert-butylphosphino)ferrocene palladium dichloride (2.504mg, 3.84μmole). The tube was sealed and a solvent mixture of THF (2mL) and water (0.6mL) added via syringe. The reaction mixture was sparged with nitrogen at room temperature for three minutes during which time the solution turned black in color. Chromatographic analysis indicated that the reaction was complete. The contents of the microwave tube were partitioned between brine (3mL) and ethyl acetate (3mL). The water was drawn off and the organic phase dried over $MgSO_4$, filtered and concentrated. The crude product was purified by chromatography on silica gel from 2 up to 20% ethyl acetate in hexane to provide the title compound (26.8mg, 96% yield) as an orange solid as a mixture of stereoisomers. MS ESI(+) m/z @ 510.4 (M+H)+.

Example 99B

4,4'-(1-(4-(6-(dimethylamino)pyridin-3-yl)phenyl)pyrrolidine-2,5-diyl)dianiline

The product from Example 99A (26.8mg, 0.053mmole) was dissolved in THF (526μL) in a round bottom flask to which was subsequently added ethanol (526μL) resulting in a yellow precipitate. To this suspension was added platinum (IV) oxide (3.16mg, 0.014mmole). The flask was capped with a septum and the contents vacuum degassed three times. Hydrogen was introduced via a balloon and the mixture allowed to stir at room temperature for two and one half hours. The reaction mixture was vacuum filtered through a sand and celite plug, which was rinsed with THF and methanol

until the filtrate was u.v.(-). The filtrate was concentrated in vacuo to provide the title compound in quantitative yield as a white solid as a mixture of stereoisomers. MS ESI(+), m/z @ 450.7 (M+H)+.

Example 99C

(2S,2'S)-tert-butyl 2,2'-(4,4'-(1-(4-(6-(dimethylamino)pyridin-3-yl)phenyl)pyrrolidine-2,5-diyl)bis(4,1-phenylene))bis(azanediyl)bis(oxomethylene)dipyrrolidine-1-carboxylate

The product from Example 99B (23.83mg, 0.053mmole) was reacted with (S)-1-(tert-butoxycarbonyl)pyrrolidine-2-carboxylic acid (27.8mg, 0.129mmole) as described in Example 1F with minor modification. The crude product was recovered by partition of the reaction mixture between ethyl acetate(10mL) and water(3mL). The organic phase was washed with water (3x3mL), dried over $MgSO_4$, filtered and concentrated. Chromatography on silica gel using a solvent gradient of 2-100% ethyl acetate in hexane provided the title compound (32.6mg, 73% yield) as a cream colored solid as a mixture of stereoisomers.

Example 99D

(2S,2'S)-N,N'-(4,4'-(1-(4-(6-(dimethylamino)pyridin-3-yl)phenyl)pyrrolidine-2,5-diyl)bis(4,1-phenylene))dipyrrolidine-2-carboxamide

The product from Example 99C (32.6mg, 0.039mmole) was reacted with trifluoroacetic acid (0.071mL, 0.927mmole) as described in Example 1G to provide the title compound (22.5mg, 90% yield) as a cream colored solid as a mixture of stereoisomers.

Example 99E

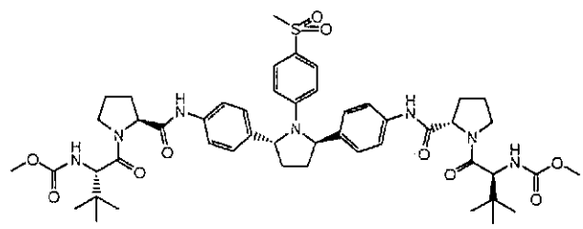
dimethyl ([(2*S*,5*S*)-1-{4-[6-(dimethylamino)pyridin-3-yl]phenyl}pyrrolidine-2,5-diyl]bis{benzene-4,1-diylcarbamoyl(2*S*)pyrrolidine-2,1-diyl[(2*S*)-3-methyl-1-oxobutane-1,2-diyl]})biscarbamate

and

dimethyl ([(2*R*,5*R*)-1-{4-[6-(dimethylamino)pyridin-3-yl]phenyl}pyrrolidine-2,5-diyl]bis{benzene-4,1-diylcarbamoyl(2*S*)pyrrolidine-2,1-diyl[(2*S*)-3-methyl-1-oxobutane-1,2-diyl]})biscarbamate

The product from Example 99D (22.5mg, 0.035mmole) was reacted with (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (19.41mg, 0.111mmole) as described in Example 86C. Chromatography on silica gel (10% ethyl acetate / 90% hexane to 100% ethyl acetate / 4% methanol) provided the title compound (14.5mg, 43.3% yield), an orange yellow solid that darkened somewhat on standing, as a 1:1 mixture of trans diastereomers. 1H NMR (400 MHz, DMSO-D6) δ ppm 0.77 - 0.99 (m, 12 H) 1.67 (s, 2 H) 1.76 - 2.24 (m, 11 H) 2.98 (s, 6 H) 3.52 (s, 6 H) 3.58 - 3.65 (m, 2 H) 3.76 - 3.90 (m, *J*=9.54 Hz, 2 H) 3.95 - 4.11 (m, 2 H) 4.36 - 4.47 (m, 2 H) 5.19 - 5.27 (m, 2 H) 6.30 (s, 2 H) 6.58 (d, *J*=9.00 Hz, 1 H) 7.17 (t, *J*=8.08 Hz, 4 H) 7.30 (d, *J*=8.02 Hz, 3 H) 7.52 (d,

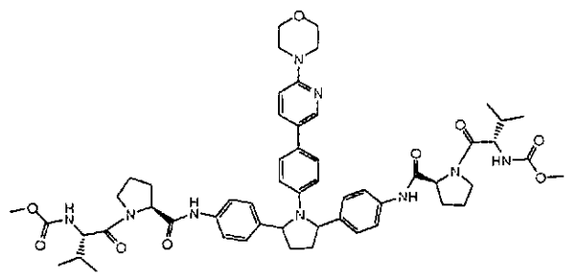
J=7.37 Hz, 4 H) 7.57 - 7.63 (m, 1 H) 7.63 - 7.68 (m, 1 H) 7.91 (s, 1 H) 8.18 - 8.22 (m, 1 H) 10.00 (s, 2 H). MS ESI(+) m/z @ 959.4 (M+H)+.



Example 100

dimethyl ({(2*R*,5*R*)-1-[4-(methylsulfonyl)phenyl]pyrrolidine-2,5-diyl}bis{benzene-4,1-diylcarbamoyl(2*S*)pyrrolidine-2,1-diyl[(2*S*)-3,3-dimethyl-1-oxobutane-1,2-diyl]})biscarbamate

Example 38A and 4-(methylsulfonyl)aniline were processed using sequentially the methods of Examples 98A, 98B, 55F, 55G, and 26J (with (S)-2-(methoxycarbonylamino)-3,3-dimethylbutanoic acid; reaction solvent = dichloromethane) to provide the title compound (55 mg). ^{1}H NMR (400 MHz, DMSO-D6) δ0.96 (d, *J* = 5.1, 18H), 1.24 (s, 1H), 1.69 (d, *J* = 5.7, 2H), 2.04 - 1.74 (m, 7H), 2.22 - 2.07 (m, 2H), 2.98 (s, 3H), 3.54 (s, 6H), 3.70 - 3.58 (m, 2H), 3.83 - 3.70 (m, 2H), 4.20 (d, *J* = 8.9, 2H), 4.43 (dd, *J* = 7.8, 5.4, 2H), 5.32 (d, *J* = 6.1, 2H), 6.39 (d, *J* = 9.0, 2H), 7.08 (d, *J* = 8.8, 2H), 7.15 (d, *J* = 8.6, 4H), 7.43 (d, *J* = 9.0, 2H), 7.53 (d, *J* = 8.6, 4H), 10.03 (s, 2H). MS (ESI) *m/z* 966 $(M+Na)^+$, 943 $(M-H)^+$.



Example 101

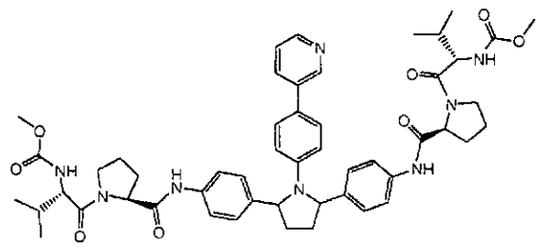
dimethyl ({(2*S*,5*S*)-1-{4-[6-(morpholin-4-yl)pyridin-3-yl]phenyl}pyrrolidine-2,5-diyl]bis{benzene-4,1-diylcarbamoyl(2*S*)pyrrolidine-2,1-diyl[(2*S*)-3-methyl-1-oxobutane-1,2-diyl]})biscarbamate

and

dimethyl ({(2*R*,5*R*)-1-{4-[6-(morpholin-4-yl)pyridin-3-yl]phenyl}pyrrolidine-2,5-diyl]bis{benzene-4,1-diylcarbamoyl(2*S*)pyrrolidine-2,1-diyl[(2*S*)-3-methyl-1-oxobutane-1,2-diyl]})biscarbamate

Example 86A and 4-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)morpholine were processed using sequentially the methods of Examples 99A, 99B, 1F, 1G, and 86C to provide the title compound as a 1:1 mixture of trans diastereomers. 1H NMR (free base) (400 MHz, DMSO-D6) δ ppm 0.78 - 1.00 (m, 12 H) 1.67 (s, 2 H) 1.75 - 2.20 (m, 11 H) 3.36 - 3.41 (m, 4 H) 3.52 (s, 6 H)

3.57 - 3.65 (m, 2 H) 3.65 - 3.72 (m, 4 H) 3.79 (s, 2 H) 4.02 (s, 2 H) 4.36 - 4.48 (m, 2 H) 5.24 (s, 2 H) 6.32 (d, *J*=7.70 Hz, 2 H) 6.78 (d, *J*=9.00 Hz, 1 H) 7.12 - 7.18 (m, 4 H) 7.21 (d, *J*=8.78 Hz, 2 H) 7.31 (d, *J*=8.35 Hz, 2 H) 7.52 (d, *J*=7.48 Hz, 4 H) 7.63 - 7.69 (m, 1 H) 8.22 - 8.27 (m, 1 H) 10.00 (s, 2 H). MS ESI(+) m/z @1000.6 (M+H)+.



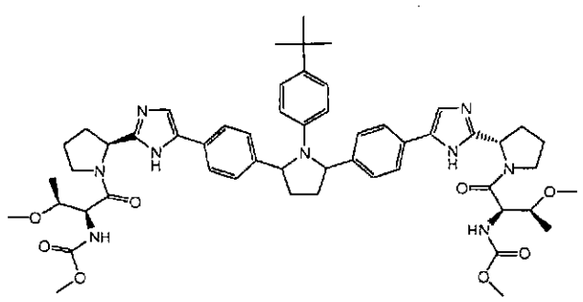
Example 102

dimethyl ({(2*S*,5*S*)-1-[4-(pyridin-3-yl)phenyl]pyrrolidine-2,5-diyl}bis{benzene-4,1-diylcarbamoyl(2*S*)pyrrolidine-2,1-diyl[(2*S*)-3-methyl-1-oxobutane-1,2-diyl]})biscarbamate

and

dimethyl ({(2*R*,5*R*)-1-[4-(pyridin-3-yl)phenyl]pyrrolidine-2,5-diyl}bis{benzene-4,1-diylcarbamoyl(2*S*)pyrrolidine-2,1-diyl[(2*S*)-3-methyl-1-oxobutane-1,2-diyl]})biscarbamate

Example 86A and pyridin-3-ylboronic acid were processed using sequentially the methods of Examples 99A, 99B, 1F, 1G, and 86C to provide the title compound as a 1:1 mixture of trans diastereomers (35.8mg). 1H NMR (free base) (400 MHz, DMSO-D6) δ ppm 0.71 - 1.05 (m, 11 H) 1.68 (s, 2 H) 1.87 (s, 8 H) 2.06 - 2.21 (m, 2 H) 3.52 (s, 6 H) 3.56 - 3.67 (m, 2 H) 3.80 (s, 2 H) 4.02 (d, *J*=1.73 Hz, 2 H) 4.43 (dd, *J*=7.97, 4.93 Hz, 2 H) 5.26 (d, *J*=6.29 Hz, 2 H) 6.37 (d, *J*=7.92 Hz, 2 H) 7.17 (dd, *J*=8.57, 1.95 Hz, 4 H) 7.28 - 7.36 (m, 5 H) 7.52 (d, *J*=7.81 Hz, 4 H) 7.82 - 7.87 (m, 1 H) 8.36 (dd, *J*=4.72, 1.36 Hz, 1 H) 8.69 (s, 1 H) 10.00 (s, 2 H). MS ESI(+) m/z @ 915.6 (M+H)+



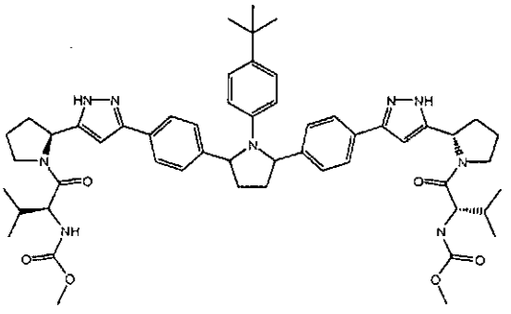
Example 103

methyl [(2*S*,3*S*)-1-{(2*S*)-2-[5-(4-{(2*S*,5*S*)-1-(4-*tert*-butylphenyl)-5-[4-(2-{(2*S*)-1-[*N*-(methoxycarbonyl)-*O*-methyl-D-threonyl]pyrrolidin-2-yl}-1*H*-imidazol-5-yl)phenyl]pyrrolidin-2-yl}phenyl)-1*H*-imidazol-2-yl]pyrrolidin-1-yl}-3-methoxy-1-oxobutan-2-yl]carbamate

and

methyl [(2*S*,3*S*)-1-{(2*S*)-2-[5-(4-{(2*R*,5*R*)-1-(4-*tert*-butylphenyl)-5-[4-(2-{(2*S*)-1-[*N*-(methoxycarbonyl)-*O*-methyl-D-threonyl]pyrrolidin-2-yl}-1*H*-imidazol-5-yl)phenyl]pyrrolidin-2-yl}phenyl)-1*H*-imidazol-2-yl]pyrrolidin-1-yl}-3-methoxy-1-oxobutan-2-yl]carbamate

The product from Example 201A (0.122 g, 0.639 mmol), and HOBt (0.098 g, 0.639 mmole) were combined and dissolved in 2 ml DMF then cooled in an ice bath between 0-5 °C. To this solution was added EDAC (0.123g, 0.639 mmol) followed by 4-methylmorpholine (0.211 ml, 1.917 mmole) and the mixture was stirred 5 minutes, then added dropwise the mixture of the products from Example 42F (0.2 g, 0.320 mmol), in DMF (2 ml) with a DMF wash (1 ml). The pH of the solution was adjusted with additional 4-methylmorpholine (0.1 ml, 0.96 mmole) and the mixture was stirred a total of 90 minutes in the ice bath. The reaction mixture was analyzed by LC-MS at 90 min and determined the reaction to be complete. The reaction mixture was diluted with 100 ml EtOAc and washed with 25 ml water. The layers were separated and the aqueous layer was extracted with another 100 ml EtOAc. The combined organic extracts were washed with 10% $NaHCO_3$ and 10% NaCl, dried over anhydrous Na_2SO_4(s), filtered and solvent removed in vacuo leaving a purple oil. The oil was dissolved in 10 ml CH_2Cl_2 and applied to a 12 g silica gel column. The column was eluted with a gradient of CH_2Cl_2/MeOH, 99/1 to 95/5 over 25 minutes. The title compounds were isolated as a light yellow solid, 60 mg, 19%.1H NMR (400 MHz, DMSO-D6) d ppm 0.86 (m, 2 H) 1.00 - 1.18 (m, 15 H) 1.27 (m, 2 H) 1.70 (m, s H) 1.99 (m, 2H) 2.15 (m, 4 H) 3.18 (d, J=10.08 Hz, 6 H) 3.54 (s, 6 H) 3.81 (m, 4 H) 4.27 (m, 2 H) 5.06 (m, 2 H) 5.21 (d, 2 H) 6.21 (d, 2 H) 6.94 (d, 2 H) 7.17 (d, 2 H) 7.29 (d, 2 H) 7.38 (d, J=1.73 Hz, 2 H) 7.51 (d, 2 H) 7.62 (d, J=8.02 Hz, 2 H) 11.68 (s, 2 H), 12.01 (m, 2H);ESI+:972.6



Example 105

methyl {(2*S*)-1-[(2*S*)-2-(3-{4-[(2*S*,5*S*)-1-(4-*tert*-butylphenyl)-5-(4-{5-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1*H*-pyrazol-3-yl}phenyl)pyrrolidin-2-yl]phenyl}-1*H*-pyrazol-5-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

and

methyl {(2*S*)-1-[(2*S*)-2-(3-{4-[(2*R*,5*R*)-1-(4-*tert*-butylphenyl)-5-(4-{5-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1*H*-pyrazol-3-yl}phenyl)pyrrolidin-2-yl]phenyl}-1*H*-pyrazol-5-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

Example 105A

1-(4-*tert*-butylphenyl)-2,5-bis(4-((trimethylsilyl)ethynyl)phenyl)pyrrolidine

To an oven-dried microwave tube (Size M, 5 mL) purged with nitrogen, added the product of Example 42C (340 mg, 0.662 mmol), bis(triphenylphosphine)palladium(II) dichloride (18.60 mg, 0.026 mmol), THF (2 mL), and triethylamine (2 mL). Stirred at room temperature for 5 min, then added copper(I) iodide (2.52 mg, 0.013 mmol), stirred the yellow mixture for 2 min, then nitrogen bubbled through for 15 min. Added trimethylsilylacetylene (0.374 mL, 2.65 mmol), sealed the tube with an aluminum crimp cap, and heated in an oil bath at 70 °C for 20 hr. Cooled the reaction to room temperature, added fresh bis(triphenylphosphine)palladium(II) dichloride (18.60 mg, 0.026 mmol) and copper(I) iodide (2.52 mg, 0.013 mmol), added additional trimethylsilylacetylene (0.374 mL, 2.65 mmol), and continued heating at 80 °C for 24 hr. Cooled the reaction to room temperature, diluted with Et_2O (50 mL), washed with H_2O (2 x 25 mL) and brine (25 mL), dried the organic phase over anhydrous $MgSO_4$, filtered, and concentrated by rotary evaporation to a light tan foam (470 mg). Purified by flash chromatography (silica gel, 2.5 cm x 10 cm, 2% Et_2O/hexanes) to afford the title product as a yellow foam (324 mg, 89%) as a mixture of stereoisomers. MS (ESI+) m/z 548 $(M+H)^+$.

Example 105B

1-(4-*tert*-butylphenyl)-2,5-bis(4-ethynylphenyl)pyrrolidine

Dissolved the product of Example 105A (322 mg, 0.588 mmol) in anhydrous THF (5 mL) under nitrogen, added 1M TBAF in THF (1.322 mL, 1.322 mmol), and stirred at 25 °C for 30 min. The reaction darkened immediately upon addition and remained a brown color throughout the reaction. Removed solvent by rotary evaporation, dissolved the residue in Et_2O (50 mL), washed with H_2O (2 x 25 mL) and brine (25 mL), dried the organic phase over anhydrous $MgSO_4$, filtered, and concentrated by rotary evaporation to a light tan foam (289 mg). Purified by flash chromatography (silica gel, 3.8 cm x 14 cm, 20% CH_2Cl_2/hexanes) to the title compound as a light yellow foam (176 mg, 74%) as a mixture of stereoisomers. MS (ESI+) m/z 404 $(M+H)^+$.

Example 105C

(S)-3,3'-(4,4'-(1-(4-tert-butylphenyl)pyrrolidine-2,5-diyl)bis(1-(4,1-phenylene))bis(1-(N-Boc-(S)-pyrrolidin-2-yl)prop-2-yn-1-one

In a flame-dried 10-mL round bottom flask, dissolved the product of Example 105B (94.3 mg, 0.234 mmol) in anhydrous THF (2 mL) under nitrogen and cooled to -78 °C, added 1.6 M n-BuLi in hexanes (0.365 mL, 0.584 mmol) slowly in a dropwise manner via gas-tight syringe, and stirred the greenish-yellow solution for 1 hr at -78 °C. In a separate flame-dried 10-mL round bottom flask purged with nitrogen, was prepared a solution of N-(tert-butoxycarbonyl)-L-proline N'-methoxy-N'-

methylamide (166 mg, 0.631 mmol) in anhydrous THF (1 mL), and cooled to -78 °C. Added the dianion mixture dropwise via a gas-tight syringe fitted with a 16G needle to the Weinreb amide solution and stirred at -78 °C for 30 min, replaced the dry ice-acetone bath with an ice-water bath, and stirred at 0 °C for 1 hr. Removed the cooling bath and stirred at room temperature for 1 hr, the cloudy yellow mixture became a dark yellow solution. Quenched the reaction with sat'd aq NH_4Cl (10 mL), extracted with Et_2O (2 x 25 mL), washed the combined ethereal extracts with H_2O (2 x 25 mL) and brine (25 mL), dried the organic phase over anhydrous $MgSO_4$, filtered, and concentrated by rotary evaporation to a yellow oil (214 mg). Purified by flash chromatography (silica gel, Alltech Extract-Clean 10g column, gradient of 5% to 7% EtOAc/CH_2Cl_2) to afford the title compound as a yellow solid (77 mg, 41%) as a mixture of stereoisomers. MS (ESI+) m/z 798 $(M+H)^+$, 1595 $(2M+H)^+$.

Example 105D

(2S,2'S)-*tert*-butyl 2,2'-(3,3'-(4,4'-(1-(4-*tert*-butylphenyl)pyrrolidine-2,5-diyl)bis(4,1-phenylene))bis(1*H*-pyrazole-5,3-diyl))dipyrrolidine-1-carboxylate

Dissolved the product of Example 105C (75 mg, 0.094 mmol) in anhydrous absolute EtOH (1 mL) under nitrogen, added hydrazine hydrate (0.023 mL, 0.235 mmol), and stirred the yellow solution at room temperature for 1 hr. Removed the solvent by rotary evaporation, azeotroped the yellow oil with toluene (2 x 5 mL), redissolved in 1:5 v/v CH_2Cl_2/hexanes, concentrated, and dried the light yellow solid *in vacuo*. Purified by flash chromatography (silica gel, 2.5 cm x 15 cm, 4% MeOH/CH_2Cl_2) to afford the title compound as a white solid (59 mg, 76%) as a mixture of stereoisomers. MS (ESI+) m/z 826 (M+H)+, 848 $(M+Na)^+$.

Example 105E

(S)-3,3'-(4,4'-(1-(4-*tert*-butylphenyl)pyrrolidine-2,5-diyl)bis(4,1-phenylene))bis(5-((S)-pyrrolidin-2-yl)-1*H*-pyrazole

Dissolved the product of Example 105D (57.5 mg, 0.070 mmol) in anhydrous CH_2Cl_2 (2 mL) under nitrogen, added TFA (1 mL, 12.98 mmol), and stirred at 25 °C for 30 min. Removed the solvent by rotary evaporation, took up the residue in 1:5 v/v CH_2Cl_2/hexanes, concentrated to a yellow residue, and dried *in vacuo* (83 mg). The TFA salt was dissolved in anhydrous MeOH (7 mL) under nitrogen, treated with pre-washed (H_2O and MeOH) and dried Amberlite IRA-400(OH) resin (750 mg, ~15 equivs of OH^- based on ~1.4 mequiv/g dry resin) and stirred at 25 °C for 2 hr. Vacuum filtered in a Büchner funnel and washed the resin thoroughly with MeOH. The filtrate was concentrated by rotary evaporation, the residue taken up in 1:5 v/v CH_2Cl_2/hexanes, and concentrated *in vacuo* to give the title compound as a light yellow solid (41 mg, 94%) as a mixture of stereoisomers. MS (ESI+) m/z 626 $(M+H)^+$, 1251 $(2M+H)^+$.

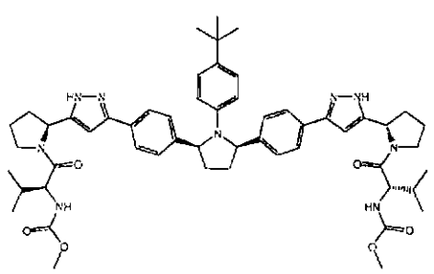
Example 105F

methyl {(2*S*)-1-[(2*S*)-2-(3-{4-[(2*S*,5*S*)-1-(4-*tert*-butylphenyl)-5-(4-{5-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1*H*-pyrazol-3-yl}phenyl)pyrrolidin-2-yl]phenyl}-1*H*-pyrazol-5-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

and

methyl {(2*S*)-1-[(2*S*)-2-(3-{4-[(2*R*,5*R*)-1-(4-*tert*-butylphenyl)-5-(4-{5-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1*H*-pyrazol-3-yl}phenyl)pyrrolidin-2-yl]phenyl}-1*H*-pyrazol-5-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

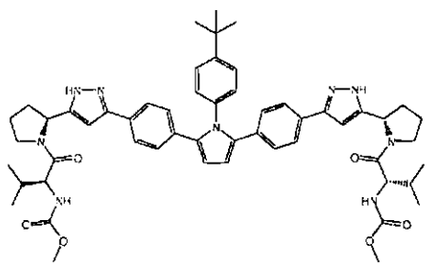
In an oven-dried 10-mL round bottom flask purged with nitrogen, dissolved the product of Example 105E (39.7 mg, 0.063 mmol) in anhydrous DMF (1 mL) and cooled to 0 °C. Added sequentially (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (23.89 mg, 0.136 mmol), HOBt hydrate (21.37 mg, 0.140 mmol), EDAC (27.3 mg, 0.140 mmol), and N-methylmorpholine (0.021 mL, 0.190 mmol). Removed the cooling bath and stirred the dark yellow solution at 25 °C for 1 hr. Diluted the reaction with EtOAc (50 mL), washed with H_2O (3 x 25 mL) and brine (25 mL), dried the organic phase over anhydrous $MgSO_4$, filtered, and concentrated by rotary evaporation to a light peach solid (63 mg). Dissolved the crude material in CH_2Cl_2 and purified by flash chromatography (silica gel, 2.5 cm x 10 cm, 5% MeOH/CH_2Cl_2) to afford a 1:1.25 trans:cis product mixture (34 mg, 94% purity). Dissolved the residue in 1:1 v/v DMSO/MeOH (2 mL) and purified by RP-C_{18} HPLC (Waters Prep LC, 40mm Module with Nova Pak HR C_{18} 6µm 40x100mm Prep Pak cartridge) eluting with a 30 min gradient of 90:10 0.1% TFA in H_2O/AcCN to 100% AcCN at 20 mL/min. Fractions containing a mixture of the trans diastereomers were concentrated by rotary evaporation, the residue taken up in 1:5 v/v CH_2Cl_2/hexanes and evaporated (5 times), and dried *in vacuo* to afford the title compounds as a cream-colored solid (12 mg, 16%). ^{1}H NMR (TFA salt) (400 MHz, DMSO-D6) δ ppm 0.76 - 0.94 (m, 12 H), 1.10 (s, 9 H), 1.13 - 1.31 (m, 3 H), 1.71 (d, *J*=5.42 Hz, 2 H), 1.82 - 2.17 (m, 9 H), 3.53 (s, 6 H), 3.70 - 3.85 (m, 4 H), 4.05 (t, *J*=8.08 Hz, 2 H), 5.09 - 5.19 (m, 2 H), 5.26 (d, *J*=5.96 Hz, 2 H), 6.22 (d, *J*=8.78 Hz, 2 H), 6.39 (d, *J*=1.30 Hz, 2 H), 6.94 (d, *J*=8.67 Hz, 2 H), 7.20 - 7.31 (m, 6 H), 7.62 (d, *J*=7.92 Hz, 4 H); MS (ESI+) m/z 940 $(M+H)^+$.



Example 106

methyl {(2S)-1-[(2S)-2-(3-{4-[(2R,5S)-1-(4-tert-butylphenyl)-5-(4-{5-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-pyrazol-3-yl}phenyl)pyrrolidin-2-yl]phenyl}-1H-pyrazol-5-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

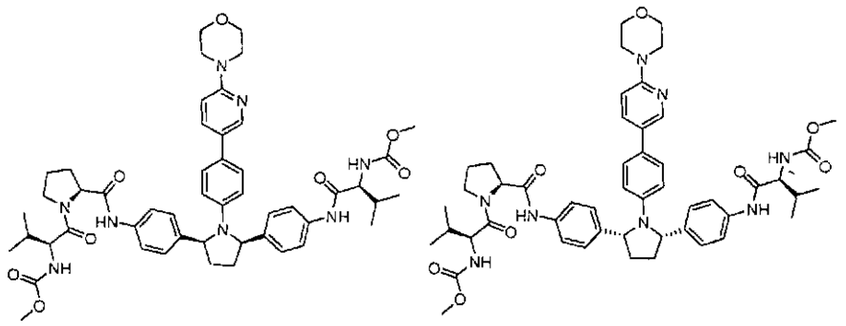
From the preparative HPLC separation of Example 105F was obtained the title compound (cis) as a yellow solid (16 mg, 21%). ^{1}H NMR (TFA salt) (400 MHz, DMSO-D6) δ ppm 0.77 - 0.93 (m, 12 H), 1.14 (s, 9 H), 1.17 - 1.31 (m, 2 H), 1.80 - 2.18 (m, 11 H), 3.35 (d, *J*=8.02 Hz, 1 H), 3.54 (s, 6 H), 3.72 - 3.85 (m, 4 H), 4.06 (t, *J*=8.29 Hz, 2 H), 4.71 - 4.79 (m, 2 H), 5.13 - 5.20 (m, 2 H), 6.35 (d, *J*=8.78 Hz, 2 H), 6.43 (s, 2 H), 7.03 (d, *J*=8.78 Hz, 2 H), 7.28 (d, *J*=8.35 Hz, 2 H), 7.55 (d, *J*=8.24 Hz, 4 H), 7.71 (d, *J*=7.59 Hz, 4 H); MS (ESI+) m/z 940 $(M+H)^+$.



Example 107

methyl {(2S)-1-[(2S)-2-(3-{4-[1-(4-tert-butylphenyl)-5-(4-{5-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-pyrazol-3-yl}phenyl)-1H-pyrrol-2-yl]phenyl}-1H-pyrazol-5-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

In an oven-dried 5-mL round bottom flask purged with nitrogen, dissolved the product of Example 105E (5.1 mg, 8.15 μmol) in anhydrous DMF (400 μL) and cooled to 0 °C. Added sequentially (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (3.07 mg, 0.018 mmol), HOBt hydrate (2.75 mg, 0.018 mmol), EDAC (3.51 mg, 0.018 mmol), and N-methylmorpholine (2.69 μL, 0.024 mmol). Removed the cooling bath and stirred the dark yellow solution at 25 °C for 18 hr. Diluted the reaction in EtOAc (50 mL), washed with H_2O (2 x 10 mL) and brine (10 mL), dried the organic over anhydrous $MgSO_4$, filtered, and concentrated by rotary evaporation to a yellow solid (9.6 mg). Dissolved in 1:1 v/v MeOH/DMSO (1.5 mL) and purified by RP-C_{18} HPLC (Waters Prep LC, 40mm Module with Nova Pak HR C_{18} 6μm 40x100mm Prep Pak cartridge) eluting with a 30 min gradient of 90:10 0.1% TFA in H_2O/AcCN to 100% AcCN at 20 mL/min. Pure fractions were concentrated by rotary evaporation, azeotroped with toluene (25 mL), the residue was taken up in 1:5 v/v CH_2Cl_2/hexanes and evaporated (3 times), then dried *in vacuo* to afford the title compound as an off-white solid (2.5 mg, 25%). ^{1}H NMR (TFA salt) (400 MHz, DMSO-D6) δ ppm 0.76 - 0.92 (m, 12 H), 1.27 (s, 9 H), 1.80 - 2.15 (m, 10 H), 3.53 (s, 6 H), 3.69 - 3.84 (m, 4 H), 4.05 (t, *J*=8.24 Hz, 2 H), 5.08 - 5.16 (m, 2 H), 6.39 (s, 2 H), 6.53 (s, 2 H), 7.06 (dd, *J*=8.29, 2.87 Hz, 6 H), 7.26 (d, *J*=8.35 Hz, 2 H), 7.37 (d, *J*=8.46 Hz, 2 H), 7.44 - 7.55 (m, 4 H), 12.92 (s, 2 H); MS (ESI+) m/z 936 $(M+H)^+$.



Example 108

N-(methoxycarbonyl)-L-valyl-*N*-{4-[(2*S*,5*R*)-5-(4-{[*N*-(methoxycarbonyl)-L-valyl]amino}phenyl)-1-{4-[6-(morpholin-4-yl)pyridin-3-yl]phenyl}pyrrolidin-2-yl]phenyl}-L-prolinamide

and

N-(methoxycarbonyl)-L-valyl-*N*-{4-[(2*R*,5*S*)-5-(4-{[*N*-(methoxycarbonyl)-L-valyl]amino}phenyl)-1-{4-[6-(morpholin-4-yl)pyridin-3-yl]phenyl}pyrrolidin-2-yl]phenyl}-L-prolinamide

Example 108A

4-(5-(4-(2,5-bis(4-nitrophenyl)pyrrolidin-1-yl)phenyl)pyridin-2-yl)morpholine

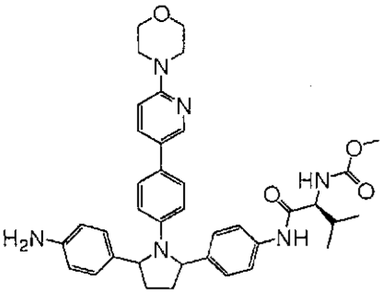
In a microwave tube (size L, 20 mL) purged with nitrogen and sealed with a rubber septum, dissolved the product of Example 86A (160 mg, 0.342 mmol) and 4-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl]morpholine (153 mg, 0.512 mmol) in THF (6 mL), added a solution of potassium phosphate (176 mg, 0.803 mmol) in water (2 mL), and sparged the reaction solution with nitrogen for 5 min. Added 1,1'-bis(di-tert-butylphosphino)ferrocene palladium dichloride (12.02 mg, 0.018 mmol) and stirred at 25 °C for 15 min . During this process, the reaction darkened quickly to a brown color. Diluted the reaction with EtOAc (50 mL), washed with brine (10 mL), dried the organic phase over anhydrous $MgSO_4$, filtered, and concentrated by rotary evaporation. Dissolved the residue in CH_2Cl_2 and purified by flash chromatography (silica gel, Alltech Extract-Clean 10g column, 20% EtOAc/CH_2Cl_2) to afford the title compound as a solid (176 mg, 93%) as a mixture of stereoisomers. ^{1}H NMR (400 MHz, DMSO-D6) δ ppm 1.82 - 1.94 (m, 2 H), 2.53 - 2.62 (m, 2 H), 3.37 - 3.47 (m, 4 H), 3.64 - 3.74 (m, 4 H), 5.03 (t, *J*=5.37 Hz, 2 H), 6.40 (d, *J*=8.89 Hz, 2 H), 6.82 (d, *J*=9.00 Hz, 1 H), 7.34 (d, *J*=8.78 Hz, 2 H), 7.69 (dd, *J*=8.84, 2.55 Hz, 1 H), 7.83 (d, *J*=8.78 Hz, 4 H), 8.28 (d, *J*=8.78 Hz, 4 H), 8.29 - 8.31 (m, 1 H); MS (ESI+) m/z 552 $(M+H)^+$.

Example 108B

4,4'-(1-(4-(6-morpholinopyridin-3-yl)phenyl)pyrrolidine-2,5-diyl)dianiline

Charged a 100-mL round bottom flask with the product of Example 108A (174.7 mg, 0.317 mmol), partially dissolved in THF (12.50 mL) and absolute EtOH (2.50 mL), evacuated on house vacuum and filled flask with nitrogen, then added platinum (IV) oxide (14.38 mg, 0.063 mmol),

evacuated flask on house vacuum and filled with hydrogen from a balloon, repeated evacuation/filling cycle 3 times, and stirred heterogeneous reaction mixture vigorously under hydrogen (1 atm). After 2 hr, charged reaction with additional platinum (IV) oxide (14.38 mg, 0.063 mmol) and continued to vigorously stir under hydrogen at 25 °C. After 5 hr, added additional platinum (IV) oxide (14.38 mg, 0.063 mmol). The reaction mixture was then vacuum filtered through a bed of Celite 545 in a Büchner funnel, the filter pad was washed with $CHCl_3$ (100 mL) and hot $CHCl_3$ (2 x 50 mL), and the filtrate concentrated by rotary evaporation to give the title compound as a yellow solid (101 mg, 65%) as a mixture of stereoisomers. ^{1}H NMR (400 MHz, DMSO-D6) δ ppm 1.71 - 1.87 (m, 2 H), 2.24 - 2.31 (m, 1 H), 3.37 - 3.45 (m, 4 H), 3.64 - 3.74 (m, 4 H), 4.57 (t, *J*=4.99 Hz, 2 H), 4.95 (s, 4 H), 6.42 - 6.53 (m, 3 H), 6.57 (d, *J*=8.35 Hz, 4 H), 6.76 - 6.89 (m, 2 H), 7.15 (d, *J*=8.35 Hz, 4 H), 7.26 (d, *J*=8.78 Hz, 2 H), 7.68 (dd, *J*=8.84, 2.44 Hz, 1 H), 8.29 (d, *J*=2.39 Hz, 1 H); MS (ESI+) m/z 492 $(M+H)^+$.



Example 108C

methyl (2S)-1-(4-(5-(4-aminophenyl)-1-(4-(6-morpholinopyridin-3-yl)phenyl)pyrrolidin-2-yl)phenylamino)-3-methyl-1-oxobutan-2-ylcarbamate

In an oven-dried 5-mL round bottom flask purged with nitrogen, dissolved the product of Example 108B (70 mg, 0.142 mmol) and (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (26.2 mg, 0.150 mmol) in anhydrous DMSO (1.5 mL), added HATU (58.6 mg, 0.150 mmol) and diisopropylethylamine (0.050 mL, 0.285 mmol), and stirred dark yellow solution at 25 °C for 15 min. Diluted the reaction with MeOH (1.5 mL) and purified by RP-C_{18} HPLC (Waters Prep LC, 40mm Module with Nova Pak HR C_{18} 6μm 40x100mm Prep Pak cartridge) eluting with a 30 min gradient of 95:5 0.1% TFA in H_2O/AcCN to 25:75 0.1% TFA in H_2O/AcCN, then 10 min to 100% AcCN at 20 mL/min. Pure fractions were concentrated by rotary evaporation (water bath 35°) to a small volume, partitioned between 20% iPrOH/$CHCl_3$ (50 mL), and sat'd aq $NaHCO_3$ (15 mL), separated layers, dried organic extract over anhydrous $MgSO_4$, filtered, and concentrated by rotary evaporation to afford the title compound as a light yellow solid (48 mg, 52%). 1H NMR showed the material to be ~3:1 trans:cis mixture; MS (ESI+) m/z 649 $(M+H)^+$, 1297 $(2M+H)^+$.

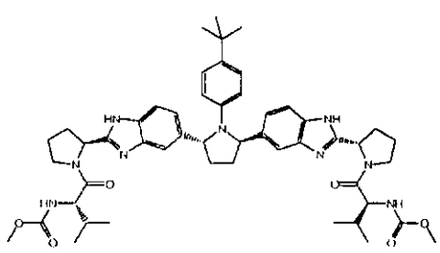
Example 108D

N-(methoxycarbonyl)-L-valyl-*N*-{4-[(2*S*,5*R*)-5-(4-{[*N*-(methoxycarbonyl)-L-valyl]amino}phenyl)-1-{4-[6-(morpholin-4-yl)pyridin-3-yl]phenyl}pyrrolidin-2-yl]phenyl}-L-prolinamide-ACD v12

and

N-(methoxycarbonyl)-L-valyl-*N*-{4-[(2*R*,5*S*)-5-(4-{[*N*-(methoxycarbonyl)-L-valyl]amino}phenyl)-1-{4-[6-(morpholin-4-yl)pyridin-3-yl]phenyl}pyrrolidin-2-yl]phenyl}-L-prolinamide ACD v12

In an oven-dried 5-mL round bottom flask purged with nitrogen, dissolved 3:1 trans/cis mixture of Example 108C (44 mg, 0.068 mmol) and the product of Example 37B (20.31 mg, 0.075 mmol) in anhydrous DMSO (1 mL), added HATU (29.2 mg, 0.075 mmol) and diisopropylethylamine (0.024 mL, 0.136 mmol), and stirred yellow solution at 25 °C for 30 min. Diluted the reaction with MeOH (1 mL) and purified by RP-C_{18} HPLC (Waters Prep LC, 40mm Module with Nova Pak HR C_{18} 6µm 40x100mm Prep Pak cartridge) eluting with a 30 min gradient of 95:5 0.1% TFA in H_2O/AcCN to 25:75 0.1% TFA in H_2O/AcCN, then 10 min to 100% AcCN at 20 mL/min. The earlier eluting compound (18.8 mg, 31%) was determined by ^{1}H NMR to be the trans diastereomers. The fractions of the later eluting peak were concentrated by rotary evaporation (water bath 35 °C) to small volume, partitioned between 20% iPrOH/$CHCl_3$ (50 mL) and sat'd aq $NaHCO_3$ (15 mL), separated layers, dried the organic phase over anhydrous $MgSO_4$, filtered, and concentrated by rotary evaporation to afford a 2:3 trans:cis mixture as an off-white solid (10 mg). The mixture was dissolved in 1:1 v/v MeOH/DMSO (1.5 mL) and purified by RP-C_{18} HPLC (Phenomenex Luna C_8(2) 5 µm 100Å AXIA column (30mm × 75mm)) eluting with a gradient of 90:10 10 mM NH_4OAc:MeOH to 100% MeOH to afford the title cis compounds as a light beige solid (2 mg, 3%). ^{1}H NMR (400 MHz, DMSO-D6) δ ppm 0.85 - 0.98 (m, 12 H), 1.77 - 2.06 (m, 7 H), 2.09 - 2.21 (m, 1 H), 2.36 - 2.45 (m, 1 H), 3.37 - 3.42 (m, 4 H), 3.51 (s, 3 H), 3.53 (s, 3 H), 3.59 - 3.70 (m, 6 H), 3.75 - 3.86 (m, 1 H), 3.95 (t, *J*=8.13 Hz, 1 H), 4.02 (t, *J*=8.57 Hz, 1 H), 4.44 (dd, *J*=8.19, 4.72 Hz, 1 H), 4.73 (s, 2 H), 6.43 (d, *J*=8.89 Hz, 2 H), 6.80 (d, *J*=8.89 Hz, 1 H), 7.27 (d, *J*=8.78 Hz, 2 H), 7.29 - 7.38 (m, 2 H), 7.44 (dd, *J*=8.57, 2.71 Hz, 4 H), 7.54 - 7.64 (m, 4 H), 7.67 (dd, *J*=8.89, 2.49 Hz, 1 H), 8.27 (d, J=2.49 Hz, 1 H), 10.04 (s, 2 H); MS (ESI+) m/z 903 $(M+H)^+$, 920 $(M+NH4)^+$, 961 $(M+AcCN+NH4)^+$.



Example 109

methyl {(2S)-1-[(2S)-2-{5-[(2R,5R)-1-(4-tert-butylphenyl)-5-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-benzimidazol-5-yl}pyrrolidin-2-yl]-1H-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

Example 109A

2-bromo-1-(4-chloro-3-nitrophenyl)ethanone

Method A:

To a flask equipped with a magnetic stir bar and under an atmosphere of N_2 was added 4'-chloro-3'-nitroacetophenone (10.0 g, 50.1 mmol) and THF (100 mL). To this stirring mixture was added portion-wise phenyltrimethylammonium tribromide (19.78 g, 52.6 mmol) over a 15 minutes time period. The resultant mixture was then stirred with monitoring every hour *via* LCMS. After 3 hr the mixture was then filtered and resulting solids washed with EtOAc. The organic solution was then concentrated, H_2O and 10% aq. $NaHCO_3$ added and washed with EtOAc (2 x 300 mL). The combined organic layers were then washed with Brine, dried ($MgSO_4$), filtered and concentrated. The residue material was then subjected to purification *via* crystallization (dissolved material in 100 mL EtOAc and slowly added hexanes until cloudy - let stand for a few hours) to yield 9.81 g (70%) of 2-bromo-1-(4-chloro-3-nitrophenyl)ethanone as an off white colored solid product. 1H NMR (500 MHz, DMSO-D6) δ ppm 5.00 (s, 2 H) 7.98 (d, J=8.54 Hz, 1 H) 8.24 (dd, J=8.54, 2.14 Hz, 1 H) 8.61 (d, J=1.98 Hz, 1 H).

Method B:

In a 500 mL round-bottomed flask was added 1-(4-chloro-3-nitrophenyl)ethanone (11.98 g, 60 mmol) in benzene (75 ml) to give a white suspension. Bromine (9.59 g, 60.0 mmol) was added dropwise over 5 minutes to give a deep red solution. Stirred for 1 hour to give a yellow solution that was concentrated in vacuo to a yellow solid. Recrystallized from 9:1 hexane/ethyl acetate to give 2-bromo-1-(4-chloro-3-nitrophenyl)ethanone as yellow needles.

Example 109B

1,4-bis(4-chloro-3-nitrophenyl)butane-1,4-dione

Zinc (II) chloride (14.68 g, 108 mmol) was added to toluene (81 mL), then diethylamine (8.35 mL, 81 mmol) and tert-butanol (7.73 mL, 81 mmol) were added and the resultant heterogenous solution stirred at rt for approx. 2 h. Afterwards Example 109A (15.0 g, 53.9 mmol) and 4'-chloro-3'-nitroacetophenone (16.13 g, 81 mmol) were added to the solution in one portion, and the resultant mixture stirred at rt for 42 h). The reaction was then quenched with 5% aqueous sulfuric acid (500 mL) and stirred vigorously to induce solid formation. The resultant solid was vacuum filtered, then washed with toluene, water, and methanol successively. Then the solid was added to a solution of hot ethyl acetate and resulting heterogeneous solution was stirred for 30 minutes and then the solid was collected and dried overnight in a vacuum oven to provide 16.6 g (78%) of the title compound. ^1H

NMR (400 MHz, DMSO-d6) δ 8.61 (d, J = 1.9 Hz, 2H), 8.27 (dd, J = 8.4, 1.9 Hz, 2H), 7.96 (d, J = 8.3 Hz, 2H), 3.48 (s, 4H).

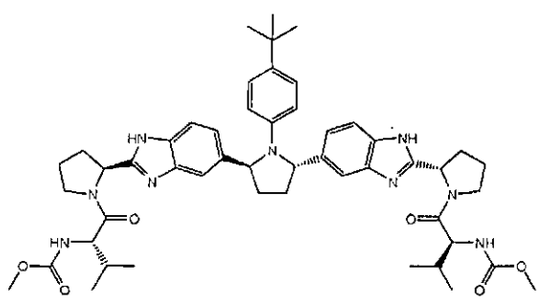
Example 109C

(1S,4S)-1,4-bis(4-chloro-3-nitrophenyl)butane-1,4-diol

(R)-(+)-alpha,alpha-diphenyl-2-pyrrolidinemethanol (1.08g, 4.28mmol) was dissolved in 70 mL of THF at ambient temperature in a dry flask under nitrogen and the timethyl borate (650 uL, 5.54 mmol) was added dropwise. The resulting solution was stirred for 1 hr. The solution was cooled in a cold bath to ~ 10 °C and the N,N-diethylaniline borane (9.18 mL, 51.6 mmol) was added dropwise with some bubbling. After 15 min, this solution was transferred to an addition funnel and added dropwise to 1,4-bis(4-chloro-3-nitrophenyl)butane-1,4-dione (Example 109B) (10.0g, 25.2 mmol) suspended in 200 mL of THF and cooled to ~ 10 °C. Bubbling was observed. After the addition, mixture was stirred at ambient temperature for 4 hours. The mixture was cooled in an ice bath and 30 mL MeOH was added dropwise till bubbling stopped, then the mixture was let stir at ambient temperature for 30 min. The mixture was filtered to get rid of a trace of insoluble unreacted SM. The filtrate was concentrated, poured into 1 M HCl and extracted into ethyl acetate, dried over sodium sulfate; concentrated to give the title compound (9.9g, 99%) as a yellow waxy solid. Chiral HPLC e.e. >99.9% (RR diol was undetectable). ^{1}H NMR (400 MHz, DMSO-d6) δ 7.94 (d, J = 1.9 Hz, 2H), 7.69 (d, J = 8.4 Hz, 2H), 7.60 (dd, J = 8.4, 1.9 Hz, 2H), 4.65 (m, 2H), 1.62 (m, 4H).

Example 109D

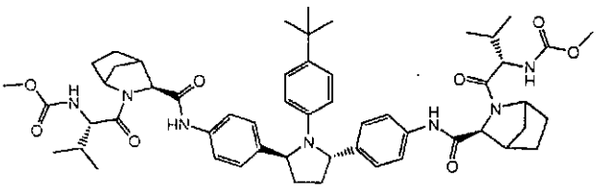
The product of Example 109C was processed as in Example 113A, 113B, 113C, and 113D, substituting 4-t-butylaniline for 4-cyclohexylaniline in the step 113A procedure to give 0.212 g (22%) of the title compound. 1H NMR (400 MHz, DMSO-D6) δ ppm 0.74 - 0.92 (m, 12 H) 1.07 (s, 9 H) 1.69 (d, J=4.01 Hz, 2 H) 1.86 - 2.05 (m, 6 H) 2.13 - 2.24 (m, 4 H) 2.54 (d, J=2.60 Hz, 2 H) 3.51 - 3.56 (m, 6 H) 3.81 (s, 4 H) 4.05 (t, J=8.13 Hz, 2 H) 5.09 - 5.18 (m, 2 H) 5.35 (d, J=3.47 Hz, 2 H) 6.25 (d, J=8.78 Hz, 2 H) 6.86 - 6.96 (m, 2 H) 7.07 (t, J=7.81 Hz, 2 H) 7.20 (s, 1 H) 7.26 - 7.32 (m, 3 H) 7.38 (d, J=8.24 Hz, 1 H) 7.46 (d, J=8.24 Hz, 1 H) 11.98 - 12.08 (m, 2 H); MS TFA+ m/z 889.



Example 110

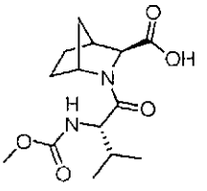
methyl {(2S)-1-[(2S)-2-{5-[(2S,5S)-1-(4-tert-butylphenyl)-5-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-benzimidazol-5-yl}pyrrolidin-2-yl]-1H-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

The product from Example 28K was purified by chiral chromatography on a Chirapak IA column eluting with a mixture of hexane/methanol/tetrahydrofuran (3:1:1) to give the title compound. H1 NMR (400 MHz, DMSO-D6) δ ppm 0.78 - 0.91 (m, 12 H) 1.07 (s, 9 H) 1.64 - 1.73 (m, 2 H) 1.89 - 2.00 (m, 6 H) 2.12 - 2.23 (m, 4 H) 3.14 - 3.24 (m, 2 H) 3.52 (s, 6 H) 3.76 - 3.85 (m, 4 H) 4.05 (td, J=8.38, 2.33 Hz, 2 H) 5.07 - 5.16 (m, 2 H) 5.30 - 5.39 (m, 2 H) 6.23 (d, J=8.78 Hz, 2 H) 6.90 (ddd, J=8.95, 4.72, 4.55 Hz, 2 H) 7.06 (t, J=9.22 Hz, 2 H) 7.17 (s, 1 H) 7.23 - 7.31 (m, 3 H) 7.37 (d, J=8.13 Hz, 1 H) 7.44 (d, J=8.24 Hz, 1 H) 12.02 (d, J=23.42 Hz, 2 H); MS ESI+ m/z 888 (M+H)+.



Example 111

dimethyl ([(2S,5S)-1-(4-tert-butylphenyl)pyrrolidine-2,5-diyl]bis{benzene-4,1-diylcarbamoyl(3S)-2-azabicyclo[2.2.1]heptane-3,2-diyl[(2S)-3-methyl-1-oxobutane-1,2-diyl]})biscarbamate



Example 111A

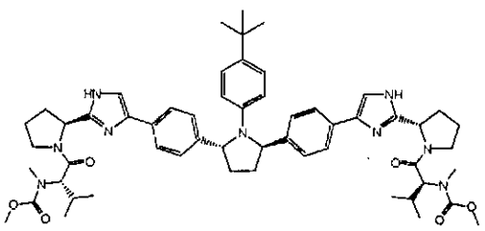
(3S)-2-((S)-2-(methoxycarbonylamino)-3-methylbutanoyl)-2-azabicyclo[2.2.1]heptane-3-carboxylic acid

(3S)-ethyl 2-azabicyclo[2.2.1]heptane-3-carboxylate (1.25 g, 7.39 mmol), (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (1.42 g, 8.13 mmol), diisopropylethylamine (6.45 mL, 36.9 mmol), and HATU (2.95 g, 7.76 mmol) were combined in dimethylformamide (40 mL) at ambient temperature and stirred for 2 hours. The solution was diluted with water and the product filtered and dried. The dried ester (1.0g, 3.06 mmol) was taken up in water (15 mL) and ethanol (15 mL) and treated with sodium hydroxide (0.5 g, 12.5 mmol) at ambient temperature for 17 hours. The solution was washed with ether then the aqueous was neutralized with concentrated HCl to pH 7 and the product extracted into ethyl acetate, dried over sodium sulfate, and concentrated to give the title compound as a waxy solid.

Example 111B

dimethyl ([(2S,5S)-1-(4-tert-butylphenyl)pyrrolidine-2,5-diyl]bis{benzene-4,1-diylcarbamoyl(3S)-2-azabicyclo[2.2.1]heptane-3,2-diyl[(2S)-3-methyl-1-oxobutane-1,2-diyl]})biscarbamate

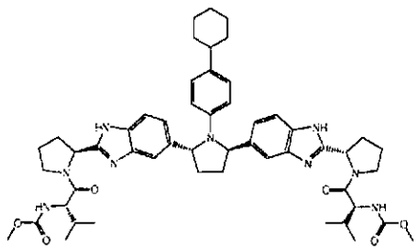
The product from Example 37E (0.05g, 0.13 mmol), the product from example 111A (0.097 g, 0.324 mmol), diisopropylethylamine (0.113 mL, 0.648 mmol), and HATU (0.104 g, 0.272 mmol) were combined in dimethylformamide (2 mL) at ambient temperature and stirred for 3 hours. The solution was poured into brine, extracted into ethyl acetate, concentrated, and purified by combi-flash 12g silica column, eluting with 0-6% methanol in dichloromethane to give the title compound as a solid. 1H NMR (400 MHz, DMSO-D6) δ ppm 0.91 (d, J=6.72 Hz, 6 H) 0.98 (d, J=6.72 Hz, 6 H) 1.11 (s, 9 H) 1.32 (d, J=8.89 Hz, 2 H) 1.36 - 1.46 (m, 2 H) 1.59 - 1.74 (m, 6 H) 1.76 - 1.84 (m, 2 H) 1.90 (td, J=13.88, 6.94 Hz, 2 H) 2.01 - 2.09 (m, 2 H) 2.40 - 2.47 (m, 2 H) 2.60 (d, J=1.19 Hz, 2 H) 3.52 (s, 6 H) 3.94 (s, 2 H) 4.04 - 4.15 (m, 2 H) 4.46 (s, 2 H) 5.15 (d, J=6.51 Hz, 2 H) 6.17 (d, J=8.78 Hz, 2 H) 6.94 (d, J=8.78 Hz, 2 H) 7.13 (d, J=8.57 Hz, 4 H) 7.22 (d, J=8.46 Hz, 2 H) 7.49 (d, J=8.57 Hz, 4 H) 9.95 (s, 2 H)



Example 112

methyl {(2S)-1-{(2S)-2-(4-{4-[(2R,5R)-1-(4-tert-butylphenyl)-5-(4-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)(methyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-4-yl}phenyl)pyrrolidin-2-yl]phenyl}-1H-imidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}methylcarbamate

The product from Example 126H was processed as in Example 42B-42G, substituting (S)-2-(methoxycarbonyl(methyl)amino)-3-methylbutanoic acid for (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid in step 42G, to give 0.07 g (40%) of the title compound as a white solid. 1H NMR (free base) (400 MHz, DMSO-D6) δ ppm 0.76 (d, J=6.61 Hz, 6 H) 0.83 (d, J=6.51 Hz, 6 H) 1.09 (s, 9 H) 1.63 - 1.75 (m, 2 H) 1.86 - 2.00 (m, 4 H) 2.03 - 2.21 (m, 6 H) 2.77 (s, 6 H) 3.10 - 3.22 (m, 4 H) 3.63 (s, 6 H) 3.74 - 3.84 (m, 2 H) 4.98 - 5.07 (m, 2 H) 5.16 - 5.23 (m, 2 H) 6.21 (d, J=8.78 Hz, 2 H) 6.88 - 6.96 (m, 2 H) 7.15 (d, J=8.24 Hz, 4 H) 7.22 (d, J=8.35 Hz, 1 H) 7.36 (d, J=1.52 Hz, 2 H) 7.51 (d, J=8.24 Hz, 1 H) 7.61 (d, J=8.13 Hz, 4 H) 11.70 (s, 2 H); MS ESI+ m/z 968.7 (M+H)+; MS ESI+ m/z 968.7 (M+H)+.



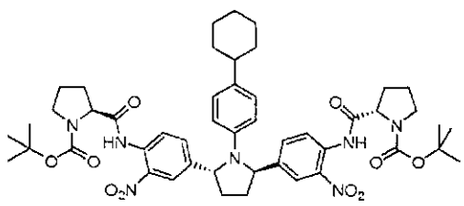
Example 113

methyl {(2S)-1-[(2S)-2-{5-[(2R,5R)-1-(4-cyclohexylphenyl)-5-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-benzimidazol-5-yl}pyrrolidin-2-yl]-1H-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

Example 113A

(2R,5R)-2,5-bis(4-chloro-3-nitrophenyl)-1-(4-cyclohexylphenyl)pyrrolidine

The product of Example 109C (2.0g, 4.99mmol) and triethylamine (1.51 mL, 14.96 mmol) were dissolved in dichloromethane (50 mL) and cooled in an ice bath. Methanesulfonyl chloride (0.855 mL, 10.97 mmol) in dichloromethane (2 mL) was added dropwise and the resulting mixture was stirred at ambient temperature for 2 hours. The solution was concentrated to dryness and dissolved in dimethylformamide (8 mL). 4-Cyclohexylaniline (5.24 g, 29.9 mmol) was added and the solution was heated at 65 °C for 2 hours then poured into 1 M HCl and extracted into dichloromethane, concentrated, and purified by combi-flash 80g silica column, eluting with 0-20% ethyl acetate in hexanes to give 1.38 g (51%) of the title compound.

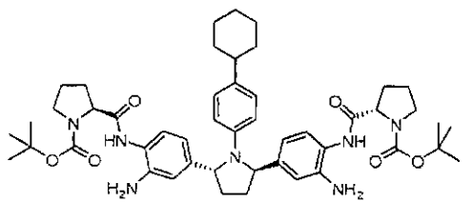


Example 113B

(2S,2'S)-tert-butyl 2,2'-(4,4'-((2R,5R)-1-(4-cyclohexylphenyl)pyrrolidine-2,5-diyl)bis(2-nitro-4,1-phenylene))bis(azanediyl)bis(oxomethylene)dipyrrolidine-1-carboxylate

The product from Example 113A (1.29 g, 2.39 mmol), (S)-tert-butyl 2-carbamoylpyrrolidine-1-carboxylate (1.53 g, 7.16 mmol), cesium carbonate (2.33g, 7.16 mmol), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (0.33 g, 0.573 mmol), and tris(dibenzylideneacetone)dipalladium(0) (0.328 g, 0.358 mmol) were combined in dioxane (18 mL) and nitrogen was bubbled through the solution for 15 min, then the flask was capped with a reflux condenser and the solution heated at 100 °C for 8 hours. After filtering through celite and

concentrating, the residue was purified by combi-flash 80g silica column, eluting with 0-20% ethyl acetate in dichloromethane to give 1.71 g (80%) of the title compound.



Example 113C

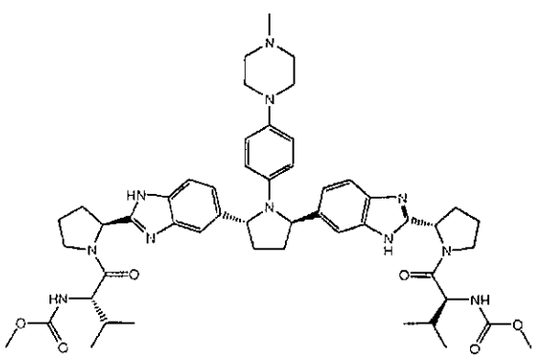
(2S,2'S)-tert-butyl 2,2'-(4,4'-((2R,5R)-1-(4-cyclohexylphenyl)pyrrolidine-2,5-diyl)bis(2-amino-4,1-phenylene))bis(azanediyl)bis(oxomethylene)dipyrrolidine-1-carboxylate

The product from Example 113B (1.71 g, 1.91 mmol) was dissolved in tetrahydrofuran (10 mL) and ethanol (10 mL) at ambient temperature and treated with Platinum (IV) oxide (0.11 g, 0.48 mmol). The flask was evacuated and opened to a hydrogen balloon and stirred for 18 hours then filtered through celite and concentrated to give the title compound.

Example 113D

methyl {(2S)-1-[(2S)-2-{5-[(2R,5R)-1-(4-cyclohexylphenyl)-5-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-benzimidazol-5-yl}pyrrolidin-2-yl]-1H-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

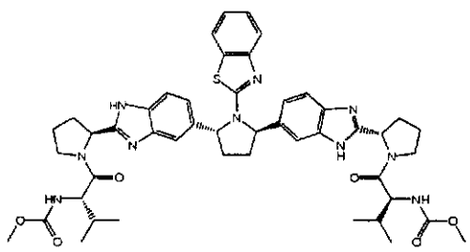
Example 113C was processed using the methods of Examples 28I, 28J, and 28K to provide the title compound. 1H NMR (400 MHz, DMSO-D6) δ ppm 0.76 - 0.91 (m, 12 H) 1.03 - 1.29 (m, 6 H) 1.55 - 1.74 (m, 7 H) 1.84 - 2.06 (m, 6 H) 2.11 - 2.25 (m, 6 H) 3.53 (s, 6 H) 3.81 (s, 4 H) 4.02 - 4.13 (m, 2 H) 5.08 - 5.18 (m, 2 H) 5.32 - 5.38 (m, 2 H) 6.24 (d, J=8.57 Hz, 2 H) 6.68 - 6.77 (m, 2 H) 7.06 (t, J=7.54 Hz, 2 H) 7.19 (s, 1 H) 7.26 - 7.32 (m, 3 H) 7.37 (d, J=8.24 Hz, 1 H) 7.45 (d, J=8.35 Hz, 1 H) 11.98 - 12.05 (m, 2 H); MS ESI+ m/z 914.5.



Example 114

methyl {(2S)-1-[(2S)-2-(6-{(2R,5R)-5-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-benzimidazol-5-yl}-1-[4-(4-methylpiperazin-1-yl)phenyl]pyrrolidin-2-yl}-1H-benzimidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

The product of Example 109C (1.0g, 2.49mmol) was processed as in Examples 113A-113D, substituting 4-(4-methylpiperazin-1-yl)aniline for 4-cyclohexylaniline in the procedure of Example 113A and substituting Raney Nickel in tetrahydrofuran for platinum(IV) oxide in tetrahydrofuran and ethanol in the procedure of Example 113C to give 0.028 g (50%) of the title compound as a solid. 1H NMR (400 MHz, DMSO-D6) δ ppm 0.77 - 0.90 (m, 12 H) 1.65 - 1.72 (m, 2 H) 1.85 - 2.04 (m, 8 H) 2.13 (s, 3 H) 2.15 - 2.23 (m, 4 H) 2.32 (s, 2 H) 2.77 (s, 6 H) 3.54 (s, 6 H) 3.82 (d, J=4.66 Hz, 4 H) 4.02 - 4.08 (m, 2 H) 5.09 - 5.18 (m, 2 H) 5.28 - 5.37 (m, 2 H) 6.23 (d, J=8.78 Hz, 2 H) 6.54 (ddd, J=9.00, 4.66, 4.55 Hz, 2 H) 7.02 - 7.08 (m, 2 H) 7.19 (s, 1 H) 7.26 - 7.31 (m, 3 H) 7.36 (d, J=8.13 Hz, 1 H) 7.44 (d, J=8.35 Hz, 1 H) 12.01 (s, 2 H); MS ESI+ m/z 556 (M+H)+.



Example 115

methyl {(2S)-1-[(2S)-2-{6-[(2R,5R)-1-(1,3-benzothiazol-2-yl)-5-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-benzimidazol-5-yl}pyrrolidin-2-yl]-1H-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

Example 115A

(2R,5R)-1-allyl-2,5-bis(4-chloro-3-nitrophenyl)pyrrolidine

The product from Example 109C (5.0 g , 12.46 mmol) and allylamine were processed as in Example 113A to give 1.5 g (39%) of the title compound as a thick oil.

Example 115B

(2R,5R)-2,5-bis(4-chloro-3-nitrophenyl)pyrrolidine

The product from Example 115A (2.0 g, 4.74 mmol) was dissolved in acetonitrile (40 mL) and water (4 mL) and treated with Tris(triphenylphosphine)rhodium(I) chloride (0.219 g, 0.237 mmol). The mixture was heated at 100 °C and nitrogen was bubbled through the solution for 3 hours. The mixture was partitioned between 5% sodium bicarbonate solution and ethyl acetate, then the

organics were concentrated and the product purified by combiflash 80g silica column eluting with dichloromethane to give 1.33 g (74%) of the title compound.

Example 115C

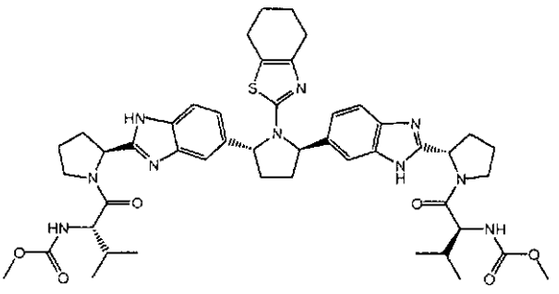
2-((2R,5R)-2,5-bis(4-chloro-3-nitrophenyl)pyrrolidin-1-yl)benzo[d]thiazole

The product from Example 115B (0.335 g, 0.877mmol), 2-bromobenzo[d]thiazole (0.281 g, 1.32 mmol), tris(dibenzylideneacetone)dipalladium(0) 0.08 g (0.088 mmol), BINAP (0.055 g, 0.088 mmol), and sodium tert-butoxide (0.126 g, 1.32 mmol) were combined in dioxane (8 mL) and nitrogen was bubbled through the solution for 10 minuets. The tube was sealed and heated at 100 °C for 18 hours. The reaction mixture was partitioned between brine and dichloromethane and the organics were concentrated and purified by combi-flash 24 g silica column, eluting with 1:1 hexanes: dichloromethane, followed by 100% dichloromethane to give 0.165 g (37%) of the title compound.

Example 115D

methyl {(2S)-1-[(2S)-2-{6-[(2R,5R)-1-(1,3-benzothiazol-2-yl)-5-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-benzimidazol-5-yl}pyrrolidin-2-yl]-1H-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

The product from Example 115C was processed as in Examples 113B, 113C, and 113D to give 0.040 g (38%) of the title compound. 1H NMR (400 MHz, DMSO-D6) δ ppm 0.74 - 0.88 (m, 12 H) 1.76 - 1.84 (m, 2 H) 1.85 - 1.94 (m, 3 H) 1.95 - 2.07 (m, 4 H) 2.14 - 2.26 (m, 4 H) 2.61 - 2.71 (m, 2 H) 3.53 (s, 6 H) 3.76 - 3.85 (m, 4 H) 4.05 (t, J=8.51 Hz, 2 H) 5.10 - 5.18 (m, 2 H) 6.90 (t, J=7.54 Hz, 2 H) 7.07 - 7.16 (m, 3 H) 7.22 - 7.35 (m, 4 H) 7.40 (d, J=8.13 Hz, 2 H) 7.47 (d, J=8.35 Hz, 1 H) 7.52 - 7.59 (m, 1 H) 12.07 (s, 2 H); MS ESI+ m/z 889.



Example 116

methyl {(2S)-1-[(2S)-2-{6-[(2R,5R)-5-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-benzimidazol-5-yl}-1-(4,5,6,7-tetrahydro-1,3-benzothiazol-2-yl)pyrrolidin-2-yl]-1H-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

Example 116A

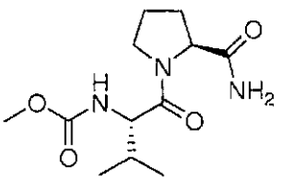
(S)-pyrrolidine-2-carboxamide hydrochloride salt

To (S)-tert-butyl 2-carbamoylpyrrolidine-1-carboxylate (29.8 g, 139 mmol) was added a solution of 4N HCl in dioxane (209 mL, 836 mmol) and the resultant mixture stirred at room temperature for 18 hrs. The mixture was then concentrated and triturated with diethyl ether then vacuum filtered and dried under vacuum to provide 21.6 g (104%) of the title product as a colorless solid.

Example 116B

(S)-2-(methoxycarbonylamino)-3-methylbutanoic acid

To (S)-2-amino-3-methylbutanoic acid (57 g, 487 mmol) dissolved in dioxane (277 mL) was added a 2N aqueous sodium hydroxide solution (803 mL, 1606 mmol) followed by the dropwise addition of methyl chloroformate (75 mL, 973 mmol) over 1 hr which caused warming of the solution to occur. After the addition, the mixture was heated at 60 °C for 22 hrs, then cooled and extracted with dichloromethane (400 mL). The resultant aqueous layer was cooled in an ice bath then 12N hydrochloric acid was added dropwise until the pH was 2. The resultant mixture was stirred at 0 °C for 2 hrs then the resultant solid was vacuum filtered and dried in a vacuum oven to provide 80g (94%) of the title compound as a colorless solid. ^{1}H NMR (400 MHz, DMSO-d6) δ 12.50 (bs, 1H), 7.34 (d, J = 8.6 Hz, 1H), 3.84 (dd, J = 8.6, 6.0 Hz, 1H), 3.54 (s, 3H), 2.03 (m, 1H), 0.86 (t, J = 7.0 Hz, 6H).

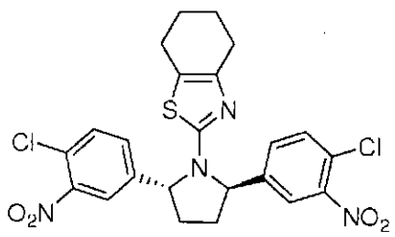


Example 116C

methyl (S)-1-((S)-2-carbamoylpyrrolidin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamate

To the product of Example 116A (21.6 g, 144 mmol), the product of Example 116B (29.1 g, 166 mmol), 1H-benzo[d][1,2,3]triazol-1-ol hydrate (27.6 g, 180 mmol), N1-((ethylimino)methylene)-N3,N3-dimethylpropane-1,3-diamine hydrochloride (34.6 g, 180 mmol) and 4-methylmorpholine (63.5 mL, 578 mmol) was dissolved in dichloromethane (960 mL) and stirred at room temperature for 18 hrs. The resultant solution was then concentrated to a residue, water was then added and the solution extracted with a 25% isopropanol in chloroform solution (2 x 2000 mL) the organic layer washed with brine then the organic extract dried over $MgSO_4$, then concentrated to a yellow oil which was purified by column chromatography eluting with a gradient of 0-10% methanol in dichloromethane to provide 25 g (64%) of the title coompound as a colorless solid. ^{1}H NMR (400 MHz, DMSO-d6) δ 7.28 (m, 2H), 6.81 (s, 1H), 4.24 (dd, J = 8.1, 4.4 Hz, 1H), 4.00 (t, J = 8.4 Hz, 1H),

3.75 (m, 1H), 3.55 (m, 1H), 3.50 (s, 3H), 2.02 (m, 1H), 1.97 (m, 2H), 1.80 (m, 2H), 0.92 (d, J = 6.7 Hz, 3H), 0.86 (d, J = 8.6 Hz, 3H).

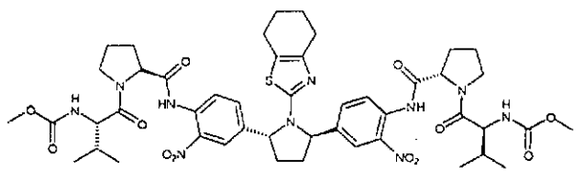


Example 116D

2-((2R,5R)-2,5-bis(4-chloro-3-nitrophenyl)pyrrolidin-1-yl)-4,5,6,7-tetrahydrobenzo[d]thiazole

The product from Example 109C (0.80 g, 1.489mmol) and 4,5,6,7-tetrahydrobenzo[d]thiazol-2-amine were processed using the method of Example 113A to give 0.375 g (50%) of the title compound

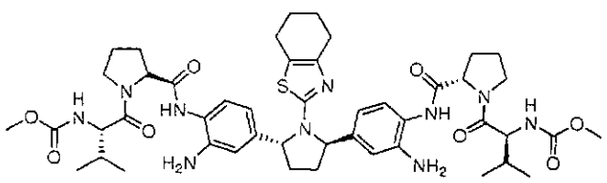
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Example 116E

dimethyl ([(2*R*,5*R*)-1-(4,5,6,7-tetrahydro-1,3-benzothiazol-2-yl)pyrrolidine-2,5-diyl]bis{(2-nitrobenzene-4,1-diyl)carbamoyl(2*S*)pyrrolidine-2,1-diyl[(2*S*)-3-methyl-1-oxobutane-1,2-diyl]})biscarbamate (ACD v12))

The product from Example 116D (0.375 g, 0.722 mmol) was processed as in Example 113B, substituting the product from Example 116C for (S)-tert-butyl 2-carbamoylpyrrolidine-1-carboxylate to give 0.59 g (83%) of the title compound.



Example 116F

dimethyl ([(2*R*,5*R*)-1-(4,5,6,7-tetrahydro-1,3-benzothiazol-2-yl)pyrrolidine-2,5-diyl]bis{(2-aminobenzene-4,1-diyl)carbamoyl(2*S*)pyrrolidine-2,1-diyl[(2*S*)-3-methyl-1-oxobutane-1,2-diyl]})biscarbamate (ACD v12))

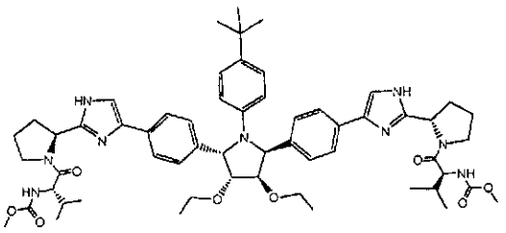
The product from Example 116E (0.59 g, 0.596 mmol) was dissolved in tetrahydrofuran (15 mL) and treated with Raney Nickel slurry in water (0.25 mL). The flask was evacuated and opened to

a hydrogen balloon and stirred at ambient temperature for 1 hour. The solution was filtered through a silica plug and concentrated to dryness to give the title compound.

Example 116G

methyl {(2S)-1-[(2S)-2-{6-[(2R,5R)-5-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-benzimidazol-5-yl}-1-(4,5,6,7-tetrahydro-1,3-benzothiazol-2-yl)pyrrolidin-2-yl]-1H-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

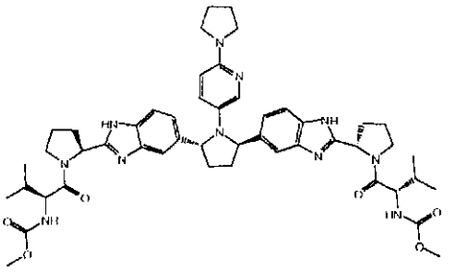
The product from Example 116F (0.55 g, 0.592 mmol) was dissolved in toluene (6 mL) and treated with acetic acid (0.34 mL, 5.92 mmol) and heated to 65 °C for 4 hours. The solution was concentrated to dryness and purified by combi-flash 12g silica column, eluting with 0-6% methanol in dichloromethane to give 0.245 g (48%) of the title compound. 1H NMR (400 MHz, DMSO-D6) δ ppm 0.78 - 0.92 (m, 12 H) 1.53 - 1.61 (m, 4 H) 1.67 - 1.75 (m, 2 H) 1.88 - 2.07 (m, 6 H) 2.15 - 2.27 (m, 6 H) 2.41 - 2.47 (m, 2 H) 2.59 (d, J=1.63 Hz, 2 H) 3.54 (s, 6 H) 3.79 - 3.87 (m, 4 H) 4.07 (t, J=8.57 Hz, 2 H) 5.12 - 5.20 (m, 2 H) 5.38 - 5.46 (m, 2 H) 7.05 (dd, J=12.79, 9.00 Hz, 2 H) 7.22 - 7.33 (m, 4 H) 7.39 (d, J=8.46 Hz, 1 H) 7.46 (d, J=8.46 Hz, 1 H) 12.06 (d, J=6.83 Hz, 2 H); MS ESI+ m/z 893.5.



Example 117

methyl {(2S)-1-[(2S)-2-(4-{4-[(2S,3R,4R,5S)-1-(4-tert-butylphenyl)-3,4-diethoxy-5-(4-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-4-yl}phenyl)pyrrolidin-2-yl]phenyl}-1H-imidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

3,4-O-isopropylidene-D-mannitol was processed using the methods of Examples 79C, 79D, 79E, 79F, 79G, 79H, and 79I to provide the title compound, wherein iodoethane was used in the O-alkylation step (method of Example 79D) instead of iodomethane. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.86 (t, J=7.4 Hz, 12H) 1.04 (t, J=7.0 Hz, 6H) 1.13 (s, 9H) 1.85-2.03 (m, 4H) 2.03-2.13 (m, 2H) 2.13-2.24 (m, 2H) 2.24-2.40 (m, 2H) 3.03 (m, 2H) 3.54-3.89 (m, 9H) 3.69 (d, J=1.7 Hz, 6H) 4.25 (d, J=5.3 Hz, 2H) 4.31 (br s, 2H) 5.19-5.29 (m, 4H) 5.36 (br s, 2H) 6.28 (d, J=8.8 Hz, 2H) 6.90-6.98 (m, 4H) 7.12-7.23 (m, 6H). MS (ESI) m/z 1029 $(M+H)^+$.



Example 118

methyl {(2S)-1-[(2S)-2-(5-{(2R,5R)-5-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-benzimidazol-5-yl}-1-[6-(pyrrolidin-1-yl)pyridin-3-yl]pyrrolidin-2-yl}-1H-benzimidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

Example 118A

5-nitro-2-(pyrrolidin-1-yl)pyridine

To a slurry of 2-chloro-5-nitropyridine (10 g, 63.1 mmol) in EtOH (100 mL) at room temperature was added pyrrolidine (15.72 mL, 189 mmol) and the mixture was heated at 70 °C for 18 h. The cooled solution was concentrated in vacuo and the residue partitioned between CH_2Cl_2 and 1M NaOH. The organic layer was dried (Na_2SO_4), filtered and solvent removed in vacuo to give title compound (9.52g, 78%). MS (ESI) m/z 194 $(M+H)^+$.

Example 118B

6-(pyrrolidin-1-yl)pyridin-3-amine

Material from Example 118A (9.52 g, 49.3 mmol) was dissolved in THF (50 mL) and DMF (40 mL) and added to a pressure bottle containing Raney Nickel 2800, water slurry (45%) (9.52g, 162 mmol) stirred for 2 h at 30 psi under H_2 gas. The solution was filtered through a nylon membrane, washed with CH_3OH and the filtrate concentrated in vacuo to give the title compound (7.78 g, 97%). ^1H NMR (400 MHz, DMSO-*d6*) δ ppm 1.81-1.91 (m, 4H) 3.17-3.29 (m, 4H) 4.30 (s, 2H) 6.25 (d, J=8.7, 1H), 6.90 (dd, J=2.8, 8.7, 1H), 7.55 (d, J=2.6, 1H). MS (ESI) m/z 164 $(M+H)^+$.

Example 118C

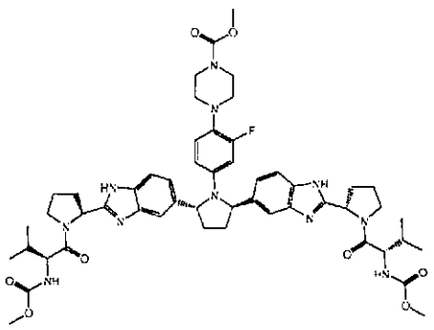
(2S,2'S)-tert-butyl 2,2'-(5,5'-((2R,5R)-1-(6-(pyrrolidin-1-yl)pyridine-3-yl)pyrrolidine-2,5-diyl)bis(1H-benzo[d]imidazole-5,2-diyl)dipyrrolidine-1-carboxylate

Example 118B and Example 109C were processed using sequentially the methods of Examples 113A, 113B, 116F, and 28I to provide the title compound.

Example 118D

methyl {(2S)-1-[(2S)-2-(5-{(2R,5R)-5-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-benzimidazol-5-yl}-1-[6-(pyrrolidin-1-yl)pyridin-3-yl]pyrrolidin-2-yl}-1H-benzimidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

To a solution of Example 118C (741 mg, 0.94 mmol) in dioxane (4 mL) was added 4 M HCl in dioxane (4.0 mL) and the solution was stirred at room temperature for 30 min. Solvent is removed in vacuo and the residue is dissolved in DMF (9.4 mL). Added N,N-diisopropyethylamine (0.99 mL, 5.65 mmol) followed by (S)-2-(methoxycarbonyl-amino)-3-methylbutanoic acid (379 mg, 2.16 mmol), HOBT (331 mg, 2.16 mmol), and EDC (415 mg, 2.16 mmol) and stirred at room temperature for 18 h. Poured into EtOAc, washed with H_2O, brine, dried (Na_2SO_4), filtered and removed solvent in vacuo to give crude product which was purified by flash chromatography on silica gel eluting with 0-6% CH_3OH/CH_2Cl_2 to give the title compound (165 mg, 0.183 mmol, 19%). ^1H NMR (400 MHz, DMSO-d6) δ 0.73-0.95 (m, 12H) 1.66-2.27 (m, 12H) 3.09 (br s, 5H) 3.53 (s, 6H) 3.81 (br s, 4H) 4.06 (t, J=8.4 Hz, 2H) 5.13 (br s, 2H) 5.33 (br s, 2H) 6.12 (br s, 1H) 6.64 (br s, 1H) 7.00-7.47 (m, 10H) 12.02 (s, 2H). MS (ESI) m/z 903 $(M+H)^+$.



Example 119

methyl 4-{4-[(2R,5R)-2,5-bis(2-{(2S)-1-[N-(methoxycarbonyl)-L-valyl]pyrrolidin-2-yl}-1H-benzimidazol-5-yl)pyrrolidin-1-yl]-2-fluorophenyl}piperazine-1-carboxylate

Example 119A

1-(2-fluoro-4-nitrophenyl)piperazine

To a warm solution of piperazine (7.78 g, 90 mmol) in DMSO (40 mL) was added dropwise 1,2-difluoro-4-nitrobenzene (2.0 mL, 18.07 mmol). The solution was stirred at 70 °C for 2 h, cooled to room temperature, diluted with EtOAc, washed with H_2O, brine, dried (Na_2SO_4), filtered and solvent removed in vacuo to give the title compound (4.05 g, 17.98 mmol, 100%). ^1H NMR (400 MHz, $CDCl_3$) δ ppm 3.03-3.09 (m, 4H) 3.26-3.29 (m, 4H) 6.91 (t, J=8.8 Hz, 1H) 7.91 (dd, J=13.1, 2.6 Hz, 1H) 7.96-8.01 (m, 1H). MS (ESI) m/z 226 $(M+H)^+$.

Example 119B

Methyl 4-(2-fluoro-4-nitrophenyl)piperazine-1-carboxylate

To a solution of Example 119A (4.0 g, 17.76 mmol) in dioxane (40 mL) at 0 °C was added 2 M NaOH (29.3 mL, 58.6 mmol) followed by dropwise addition of methyl chloroformate (2.75 mL, 35.5 mmol). The solution was warmed to room temperature and stirred for 2 h. Diluted with EtOAc and added 1 N HCl until all solid had dissolved, separated the phases and washed the organic phase with 1 N HCl, H_2O, brine, dried (Na_2SO_4), filtered and removed solvent in vacuo to give the title compound (4.69 g, 16.56 mmol, 93%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.20-3.31 (m, 4H) 3.62-3.71 (m, 4H) 3.75 (s, 3H) 6.92 (t, J=8.8 Hz, 1H) 7.93 (dd, J=12.9, 2.6 Hz, 1H) 7.98-8.02 (m, 1H). MS (ESI) m/z 284 $(M+H)^+$.

Example 119C

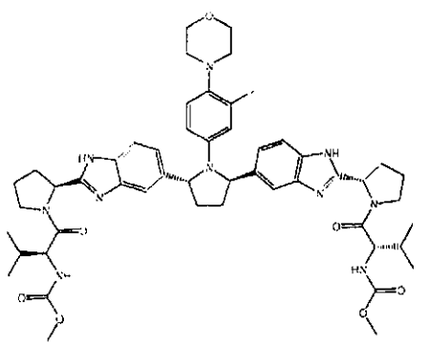
Methyl 4-(4-amino-2-fluorophenyl)piperazine-1-carboxylate

To a solution of Example 119B (3.0 g, 10.59 mmol) in EtOAc (40 mL) was added 10% palladium on carbon (300 mg) and the solution was stirred under a balloon of H_2 gas for 1.5 h. The solution was filtered through Celite, the catalyst washed with EtOAc, and the filtrate concentrated in vacuo to give the title compound (2.68g, 10.59 mmol, 100%).

Example 119D

methyl 4-{4-[(2R,5R)-2,5-bis(2-{(2S)-1-[N-(methoxycarbonyl)-L-valyl]pyrrolidin-2-yl}-1H-benzimidazol-5-yl)pyrrolidin-1-yl]-2-fluorophenyl}piperazine-1-carboxylate

Example 119C and Example 109C were processed using sequentially the methods of Examples 113A-113C, 26I, and 118D to provide the title compound. ^{1}H NMR (400 MHz, DMSO-*d6*) δ ppm 0.75-0.93 (m, 12H) 1.69 (br s, 2H) 1.82-2.07 (m, 7H) 2.10-2.28 (m, 4H) 2.61-2.73 (m, 5H) 3.54 (s, 6H) 3.56 (s, 3H) 3.82 (br s, 4H) 3.99-4.11 (m, 2H) 5.09-5.19 (m, 2H) 5.29-5.41 (m, 2H) 6.01-6.13 (m, 2H) 6.61-6.72 (m, 1H) 7.06 (s, 2H) 7.20 (s, 1H) 7.29 (d, J=9.1 Hz, 3H) 7.38 (d, J=8.1 Hz, 1H) 7.46 (d, 1H) 12.04 (s, 2H). MS (ESI) m/z 993 $(M+H)^+$.



Example 120

methyl {(2S)-1-[(2S)-2-{5-[(2R,5R)-1-[3-fluoro-4-(morpholin-4-yl)phenyl]-5-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-benzimidazol-5-yl}pyrrolidin-2-yl]-1H-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

Example 120A

4-(2-Fluoro-4-nitrophenyl)morpholine

A suspension of morpholine (4.72 mL, 4.72 g, 54.2 mmol) and dibasic potassium phosphate (9.44 g, 54.2 mmol) in DMSO (27 mL) was treated with 3,4-difluoronitrobenzene (3.0 mL, 4.31 g, 27.1 mmol) was warmed at 60 °C for 18 h. The solution was cooled and diluted with ethyl acetate and extracted with water (3 x) and saturated sodium chloride solution. Drying (Na_2SO_4) and concentration in vacuo afforded the title compound (6.32 g, ca. 100%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (ddd, J = 9.0, 2.6, 0.9 Hz, 1 H), 7.92 (dd, J = 13.1, 2.6 Hz, 1 H), 6.92 (t, J = 8.8 Hz, 1 H), 3.88 (m, 4 H), 3.29 (dd, J = 5.5, 4.0 Hz, 4 H). MS +DCI m/z (rel abundance) 227 (10, M+H), 244 (100, M+NH4).

Example 120B

3-Fluoro-4-morpholinoaniline

A solution of the compound of Example 120A (2.26 g, 10.00 mmol) in ethyl acetate (35 mL) was treated with 10% palladium on carbon (300 mg) followed by hydrogenation under one atmosphere pressure for 6 h. The mixture was filtered through celite and concentrated in vacuo to afford the title compound as a white solid.

Example 120C

4-(4-((2*R*,5*R*)-2,5-bis(4-chloro-3-nitrophenyl)pyrrolidin-1-yl)-2-fluorophenyl)morpholine

A solution of the compound of Example 109C (2.00 g, 4.99 mmol) and triethylamine (4.17 mL, 3.03 g, 29.9 mmol) in dry dichloromethane (25 mL) at 0 °C was treated with methanesulfonyl chloride (1.17 mL, 1.71 g, 14.96 mmol) followed by stirring at 0 °C for 30 min. The solution was warmed to RT and then concentrated in vacuo. The residue was combined with the compound of Example 120B and N,N-dimethylaniline (1.26 mL, 1.21 g, 9.98 mmol) and dissolved in dry DMF (14 mL) followed by warming at 50 °C for 2 h. The solution was cooled and diluted with ethyl acetate, followed by extraction with water (3 x) and 1 N hydrochloric acid solution (2 x) and saturated sodium chloride solution. Drying (Na_2SO_4) and concentration in vacuo afforded an orange oil, which was chromatographed over a 340 g silica gel cartridge, eluting with 10-80% ethyl acetate in hexanes. These procedures afforded the title compound (1.39 g, 50%) as an orange rigid foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (m, 2 H), 7.58 (m, 9 H), 7.31 (dd, *J* = 8.3, 2.1 Hz, 2 H), 6.69 (s, 1 H), 5.99 (m, 2 H), 5.20 (d, *J* = 7.1 Hz, 2 H), 3.79 (m, 4 H), 2.92 (m, 6 H), 2.54 (m, 2 H), 1.88 (m, 2 H).

Example 120D

Dimethyl *(2R,2'R)*-1,1'-((*2S,2'S)*-2,2'-(4,4'-((*2R,5R)*-1-(3-fluoro-4-morpholinophenyl)pyrrolidin-2,5-diyl)bis(2-nitro-4,1-phenylene))bis(azanediyl)bis(oxomethylene)bis(pyrrolidine-2,1-diyl))bis(3-methyl-1-oxobutane-2,1-diyl)dicarbamate

In a microwave tube, a suspension of the Example 120C (1.39 g, 2.48 mmoL), the compound of Example 116C (2.02 g, 7.43 mmol), XantPhos (129 mg, 0.22 mmol) and cesium carbonate (2.42 g, 7.43 mmoL) in dioxane (14 mL) was degassed by nitrogen sparge for 30 min. The mixture was treated with tris(dibenzylideneacetone)dipalladium (0) (68 mg, 0.074 mmol) followed by degassing for another 5 min. The microwave tube was sealed and the mixture was warmed at 100 °C for 2 h. The mixture was cooled and diluted with ethyl acetate and extracted with water (3 x) and saturated sodium chloride solution. The solution was dried (Na_2SO_4) and stirred overnight with 3-(mercaptopropyl) silica gel. Filtration and concentration in vacuo afforded a solid, which was chromatographed over a 340 g silica gel cartridge, eluting with 0-10% methanol in dichloromethane. These procedures afforded the title compound as an orange solid. ^{1}H NMR (400 MHz, DMSO-*d6*) δ ppm 0.80-0.90 (m, 12H) 1.74 (br s, 2H) 1.82-2.03 (m, 10H) 2.08-2.20 (m, 2H) 2.71-2.81 (m, 4H) 3.52 (s, 6H) 3.62 (m, 4H) 3.76 (s, 2H) 4.02 (m, 2H) 4.50 (d, J=4.4 Hz, 2H) 5.39 (s, 2H) 6.04-6.19 (m, 2H) 6.72-6.81 (m, 1H) 7.32 (d, J=8.4 Hz, 2H) 7.47-7.60 (m, 4H) 7.80 (d, J=1.5 Hz, 2H) 10.41 (s, 2H). MS (ESI) m/z 1031 $(M+H)^+$.

Example 120E

Dimethyl (2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-((2R,5R)-1-(3-fluoro-4-morpholinophenyl)pyrrolidine-2,5-diyl)bis(2-amino-4,1-phenylene)bis(azanediyl)bis(oxomethylene)bis(pyrrolidine-2,1diyl)bis(3-methyl-1-oxobutane-2,1-diyl)dicarbamate

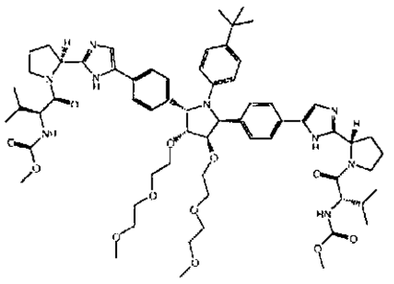
To a solution of Example 120D (640 mg, 0.621 mmol) in EtOH (4 mL) and THF (4 mL) was added PtO_2 (35 mg) and the solution was stirred under a balloon of H_2 gas for 16 h. The solution was filtered through Celite and washed with EtOAc. The filtrate was concentrated in vacuo to give the title compound (322 mg, 0.332 mmol, 53%).

Example 120F

methyl {(2S)-1-[(2S)-2-{5-[(2R,5R)-1-[3-fluoro-4-(morpholin-4-yl)phenyl]-5-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-benzimidazol-5-yl}pyrrolidin-2-yl]-1H-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

To a solution of Example 120E (320 mg, 0.33 mmol) in toluene (1.5 mL) was added glacial acetic acid (0.057 mL, 0.99 mmol) and the solution was stirred at 50 °C for 3 h. The cooled solution was concentrated in vacuo and azeotroped 2 times with toluene. The crude product was purified by

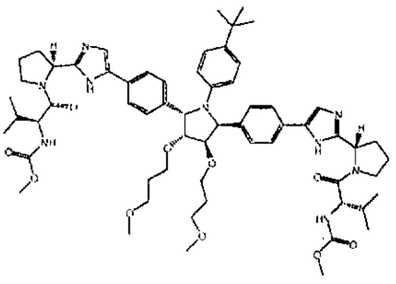
flash chromatography on silica gel eluting with 0-4% CH_3OH/CH_2Cl_2 to give the title compound (100 mg, 0.107 mmol, 32%). ^1H NMR (400 MHz, DMSO-*d6*) δ ppm 0.72-0.92 (m, 12H) 1.69 (br s, 2H) 1.81-2.10 (m, 8H) 2.11-2.28 (m, 4H) 2.64-2.78 (m, 4H) 3.54 (s, 6H) 3.59 (s, 4H) 3.73-3.92 (m, 4H) 4.06 (s, 2H) 5.02-5.21 (m, 2H) 5.36 (s, 2H) 6.03-6.14 (m, 2H) 6.60-6.73 (m, 1H) 7.00-7.15 (m, 2H) 7.15-7.37 (m, 4H) 7.36-7.61 (m, 2H) 12.06 (br s, 2H). MS (ESI) m/z 935 $(M+H)^+$.



Example 121

methyl [(2S)-1-{(2S)-2-[5-(4-{(2S,3R,4R,5S)-1-(4-tert-butylphenyl)-5-(4-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-5-yl}phenyl)-3,4-bis[2-(2-methoxyethoxy)ethoxy]pyrrolidin-2-yl}phenyl)-1H-imidazol-2-yl]pyrrolidin-1-yl}-3-methyl-1-oxobutan-2-yl]carbamate

3,4-O-isopropylidene-D-mannitol was processed using sequentially the methods of Examples 79C, 79D (1-bromo-2-(2-methoxyethoxy)ethane as the alkyating agent with added sodium iodide), 79E-79G, 79H (18 hour reaction time), 66D, and 66E to provide the title compound (46 mg) as a light yellow solid. ^1H NMR (400 MHz, DMSO-d_6) δ 7.60 (d, J = 7.9 Hz, 4 H), 7.50 (d, J = 8.4 Hz, 2 H), 7.38 (s, 2 H), 7.29 (d, J = 8.6 Hz, 2 H), 7.19 (s, 4 H), 6.90 (m, 2 H), 6.27 (d, J = 8.6 Hz, 2 H), 5.37 (s, 2 H), 5.07 (d, J = 3.6 Hz, 2 H), 4.32 (s, 2 H), 4.06 (m, 2 H), 3.78 (d, J = 6.0 Hz, 2 H), 3.66 (d, J = 4.2 Hz, 4 H), 3.53 (s, 6 H), 3.17 (s, 6 H), 2.10 (m, 4 H), 1.93 (m,4 H), 1.07 (s, 9 H), 0.86 (m, 12 H). MS (+ESI) *m/z* (rel abundance) 1177 (100, M+H), 1199 (5, M+Na).

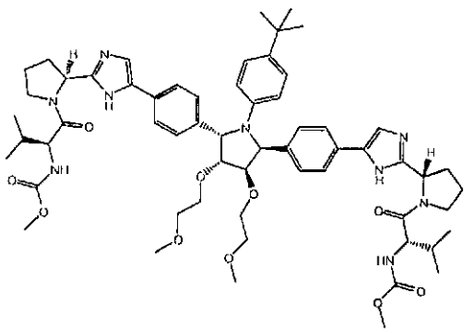


Example 122

methyl {(2S)-1-[(2S)-2-(5-{4-[(2S,3R,4R,5S)-1-(4-tert-butylphenyl)-5-(4-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-5-yl}phenyl)-3,4-bis(3-

methoxypropoxy)pyrrolidin-2-yl]phenyl}-1H-imidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

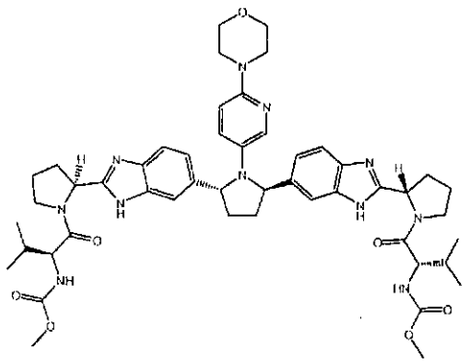
3,4-O-isopropylidene-D-mannitol was processed using sequentially the methods of Examples 79C, 79D (1-bromo-3-methoxypropane as the alkyating agent with added sodium iodide), 79E-79H, 66D, and 66E to provide the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.60 (s, 4 H), 7.52 (m, 2 H), 7.37 (m, 2 H), 7.30 (m, 4 H), 7.18 (d, J = 7.1 Hz, 4 H), 6.91 (m, 2 H), 6.24 (m, 2 H), 5.40 (m, 2 H), 5.06 (m, 2 H), 4.31 (m, 2 H), 4.11 (m, 2 H), 3.78 (s, 4 H), 3.66 (m, 4 H), 3.56 (m, 10 H), 3.14 (m, 14 H), 2.14 (m, 6 H), 1.94 (d, J = 3.5 Hz, 8 H), 1.43 (m, 6 H), 1.07 (s, 10 H), 0.89 (d, J = 6.1 Hz, 6 H), 0.84 (d, J = 5.9 Hz, 6H).



Example 123

methyl [(2S)-1-[(2S)-2-(5-{4-[(2S,3R,4R,5S)-1-(4-tert-butylphenyl)-5-(4-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-5-yl}phenyl)-3,4-bis(2-methoxyethoxy)pyrrolidin-2-yl]phenyl}-1H-imidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

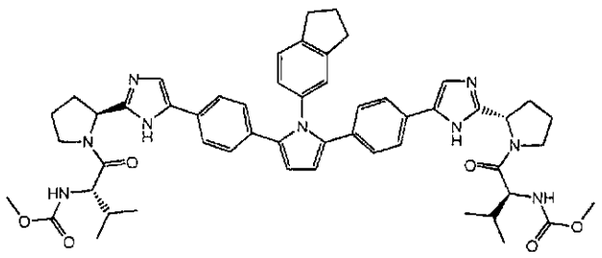
3,4-O-isopropylidene-D-mannitol was processed using sequentially the methods of Examples 79C, 79D (1-bromo-2-methoxyethane as the alkyating agent with added sodium iodide), 79E, 79F, 79G, and 79H, wherein Example 126G replaced (S)-tert-butyl-2-(4-bromo-1H-imidazol-2-yl)pyrrolidine-1-carboxylate in applying the method of Example 79H, to provide the title compound (43 mg) as a light beige solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.60 (d, J = 8.0 Hz, 4 H), 7.47 (m, 2 H), 7.37 (m, 2 H), 7.27 (m, 4 H), 7.19 (s, 4 H), 6.90 (d, J = 8.6 Hz, 2 H), 6.26 (d, J = 8.7 Hz, 2 H), 5.37 (s, 2 H), 5.06 (d, J = 3.7 Hz, 2 H), 4.30 (s, 2 H), 4.03 (m, 2 H), 3.79 (s, 4 H), 3.66 (m, 6 H), 3.53 (s, 6 H), 3.25 (m, 6 H), 3.12 (s, 6 H), 2.13 (m, 4 H), 1.94 (m, 6 H), 1.07 (s, 9 H), 0.89 (d, J = 6.6 Hz, 6 H), 0.84 (d, J = 6.6 Hz, 6 H). MS +ESI m/z (rel abundance) 1088 (100, M+H).



Example 124

methyl {(2S)-1-[(2S)-2-(6-{(2R,5R)-5-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-benzimidazol-6-yl}-1-[6-(morpholin-4-yl)pyridin-3-yl]pyrrolidin-2-yl}-1H-benzimidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

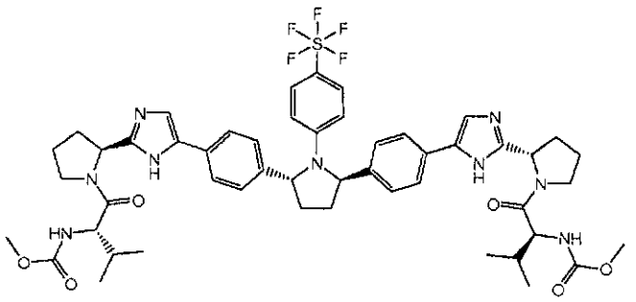
Example 109C and Example 154B were processed using the methods of Examples 113A, 113B, 116F, 28I (reaction conducted at 50 °C for 4 h), 66D, and 66E to provide the title compound (120 mg) as a light beige solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.03 (s, 1 H), 7.46 (d, J = 8.2 Hz, 1 H), 7.45 (s, 1 H), 7.31 (d, J = 6.4 Hz, 3 H), 7.21 (s, 1 H), 7.06 (t, J = 8.0 Hz, 2 H), 6.64 (m, 1 H), 6.49 (m, 1 H), 5.36 (d, J = 6.2 Hz, 2 H), 5.13 (s, 2 H), 4.04 (m, 2 H), 3.77 (m, 3 H), 3.55 (m, 9 H), 3.04 (s, 4 H), 2.19 (s, 3 H), 1.95 (m, 5 H), 1.73 (s, 3 H), 0.82 (m, 12 H). MS +ESI m/z (rel abundance) 918 (100, M+H).



Example 125

methyl {(2S)-1-[(2S)-2-(5-{4-[1-(2,3-dihydro-1H-inden-5-yl)-5-(4-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-5-yl}phenyl)-1H-pyrrol-2-yl]phenyl}-1H-imidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

Example 26E and 5-aminoindan were processed using the methods of Examples 76A, 39E, 39F, 55G, and 26J (reaction solvent = dichloromethane) to provide the title compound (0.1446 g). ^{1}H NMR (400 MHz, DMSO-D6) δ 0.91 - 0.79 (m, 12H), 2.18 - 1.87 (m, 12H), 2.74 (t, J = 6.7, 2H), 2.86 (t, J = 6.8, 2H), 3.53 (s, 6H), 3.84 - 3.68 (m, 4H), 4.10 - 3.98 (m, 2H), 5.03 (dd, J = 6.8, 2.9, 2H), 6.54 - 6.40 (m, 2H), 7.10 - 6.86 (m, 5H), 7.22 - 7.13 (m, 2H), 7.33 - 7.22 (m, 2H), 7.45 - 7.35 (m, 2H), 7.53 (dd, J = 13.7, 8.5, 4H), 11.70 (s, 1H), 12.07 - 11.96 (m, 1H). MS (ESI) m/z 920 $(M+H)^+$, 918 $(M-H)^+$.



Example 126

methyl [(2S)-1-{(2S)-2-[5-(4-{(2R,5R)-5-(4-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-5-yl}phenyl)-1-[4-(pentafluoro-lambda~6~-sulfanyl)phenyl]pyrrolidin-2-yl}phenyl)-1H-imidazol-2-yl]pyrrolidin-1-yl}-3-methyl-1-oxobutan-2-yl]carbamate

Example 126A

(S)-2-(methoxycarbonylamino)-3-methylbutanoic acid

A mixture of (S)-2-amino-3-methylbutanoic acid (10.0 g, 85.0 mmol), NaOH (3.41 g, 85.0 mmol) and $NaHCO_3$ (4.7 g, 44.4 mmol) in H_2O (85 mL) was cooled to 0 °C. A mixture of methyl chloroformate (7.3 mL, 94.0 mmol) dissolved in Et_2O (40 mL) was slowly added to the aqueous mixture and stirred for 20 hours coming to ambient temperature. Mixture was adjusted to pH 2.0 with HCl (*conc*). The mixture was extracted with CH_2Cl_2 (3 x 100 mL) and then dried ($MgSO_4$), filtered and concentrated to afford 7.5 g (50%) of the title compound. MS (ESI) m/z 176 $(M+H)^+$.

Example 126B

(S)-tert-butyl 2-formylpyrrolidine-1-carboxylate

A mixture of oxalyl chloride (14.1 mL, 161 mmol) in CH_2Cl_2 (331 mL) was cooled to -75 °C. Dimethylsulfoxide (19.4 mL, 273 mmol) in CH_2Cl_2 (70 mL) was slowly added over 30 minutes followed by stirring at -75 °C for an additional 15 minutes. At -75 °C (S)-tert-butyl 2-(hydroxymethyl)pyrrolidine-1-carboxylate (25.0 g, 124 mmol) in CH_2Cl_2 (132 mL) was added slowly over one hour, followed by a further 15 minutes of stirring. Then, still at -75 °C, Et_3N (87 mL, 621 mmol) was added over 30 minutes followed by another 15 minutes of stirring. Mixture was then allowed to stir at 0 °C for 90 minutes. Mixture was quenched with 10% aqueous Citric acid at 0 °C. The mixture was diluted with 10% aqueous Citric acid and partitioned. Organic was washed with H_2O (5 x 150 mL) and Brine. The organic was then dried ($MgSO_4$), filtered and concentrated to afford 24.7g (100%) of the title compound. MS (ESI) m/z 200 $(M+H)^+$.

Example 126C

(S)-tert-butyl 2-(1H-imidazol-2-yl)pyrrolidine-1-carboxylate

A mixture of Example 126B (24.7g, 124.0 mmol) and NH_4OH (62.0 mL, 497 mmol) in methanol (62 mL) was stirred at 0 °C followed by slow addition of glyoxal hydrate (29.9 mL, 262 mmol) over 10 minutes. Mixture was stirred for 16 hours at ambient temperature. The mixture was concentrated, diluted with H_2O and extracted with EtOAc (3 x 200 mL). The organic was then dried ($MgSO_4$), filtered and concentrated. Purification by trituration with *t*BuOMe afforded 15.5g (53%) of the title compound. MS (ESI) m/z 238 $(M+H)^+$.

Example 126D

(S)-tert-butyl 2-(4,5-dibromo-1H-imidazol-2-yl)pyrrolidine-1-carboxylate

A mixture of Example 126C (15.5 g, 65.4 mmol) in CH_2Cl_2 (260 mL) was stirred at 0 °C followed by portion-wise addition of 1-bromopyrrolidine-2,5-dione (24.5, 137.0 mmol) over 10 minutes. Mixture was stirred 0 °C for 90 minutes. Mixture was concentrated, diluted with EtOAc (600 mL) and washed with H_2O (3 x 200 mL) and brine. The organic was then dried ($MgSO_4$), filtered and concentrated. Purification by trituration with Et_2O afforded 24.9 g (96%) of the title compound. MS (ESI) m/z 396 $(M+H)^+$.

Example 126E

(S)-tert-butyl 2-(5-bromo-1H-imidazol-2-yl)pyrrolidine-1-carboxylate

A mixture of Example 126D (12.5 g, 31.5 mmol) in dioxane (400 mL) and H_2O (400 mL) had a solution of Na_2SO_3 (43.7 g, 347 mmol) in H_2O (400 mL) added and was heated to reflux for 21 hours. The mixture was concentrated to half volume and extracted with CH_2Cl_2 (3 x 200 mL). The organic was then washed with brine, dried ($MgSO_4$), filtered and concentrated. Purification by trituration (CH_2Cl_2, *t*BuOMe, and Hexanes) afforded 5.2 g (52%) of the title compound. MS (ESI) m/z 317 $(M+H)^+$.

Example 126F

(S)-5-bromo-2-(pyrrolidin-2-yl)-1H-imidazole hydrochloride

A mixture of Example 126E (5.0g, 15.8 mmol) in 4M HCl/Dioxane (40 mL) was allowed to stir for one hour. The mixture was concentrated to afford 3.99g (100%) of the title compound. MS (ESI) m/z 217 $(M+H)^+$.

Example 126G

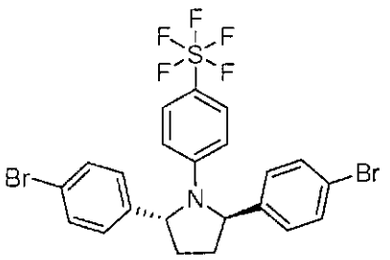
methyl (S)-1-((S)-2-(5-bromo-1H-imidazol-2-yl)pyrrolidin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamate

A mixture of Example 126F (3.99g, 15.8 mmol), Example 126A (2.77 g, 15.8 mmol), N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (3.63 g, 19.0 mmol), 1-Hydroxy-benzotriazole hydrate (2.90 g, 19.0 mmol) and N-methylmorpholine (12.2 mL, 111.0 mmol) in DMF (150 mL) were allowed to stir overnight. Mixture was diluted with H_2O and extracted with EtOAc (3 x 300 mL). The organic was washed with H_2O and Brine. The organic was then dried ($MgSO_4$), filtered and concentrated. Purification by chromatography (silica gel, 75% EtOAc in Hexanes) afforded 5.2 g (88%) of the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.79 (dd, J=6.67, 3.63 Hz, 6 H), 1.84 - 1.96 (m, 3 H), 2.02 - 2.14 (m, 2 H), 3.51 (s, 3 H), 3.66 - 3.80 (m, 2 H), 3.96 - 4.03 (m, 1 H), 4.91 - 4.99 (m, 1 H), 7.06 (d, J=1.52 Hz, 1 H), 7.26 (d, J=8.46 Hz, 1 H), 12.01 (s, 1 H). MS (ESI) m/z 373 $(M+H)^+$.

Example 126H

(1S,4S)-1,4-bis(4-bromophenyl)butane-1,4-diol

(1S,4S)-1,4-bis(4-bromophenyl)butane-1,4-diol was prepared using the method of Example 69A and (R)-alpha, alpha-diphenyl-2-pyrrolidinemethanol).



Example 126I

(2R,5R)-2,5-bis(4-bromophenyl)-1-(4-sulfur pentafluoride phenyl)pyrrolidine

A solution of methanesulfonic anhydride (2.95 mL, 23.02 mmol) in 2-Me THF (15 mL) was cooled in ice/salt bath to ~0°C. To this cold solution a solution of Example 126H (4.0524 g, 10.13 mmol) and N,N-diisopropylethylamine (5.5 mL, 31.8 mmol) in 2-Me THF (40 mL) was added dropwise over 40 minutes. The reaction was slowly warmed to 20 °C. At this time 4-aminophenylsulfur pentafluoride (7.1238 g, 32.5 mmol) was added and the mixture was warmed to 38 °C for 17 hours. The reaction was cooled and partioned between EtOAc and water. The organic fraction was washed with water (2 x) brine (1 x) and concentrated. Purification by flash chromatography (silica gel, EtOAc/hexane) afforded the title compound (1.95 g, 33%). LC/MS Rt 2.38 *m/z* 584 $(M+H)^+$.

Example 126J

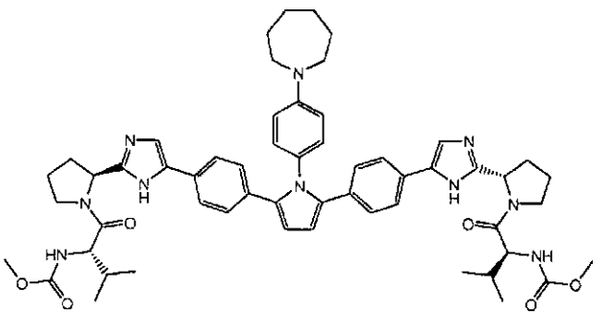
(2R,5R)-1-(4-sulfur pentafluoride phenyl)-2,5-bis(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)pyrrolidine

The product from Example 126I was processed using the method described in Example 39E to afford the title compound (1.67 g, 74%). MS (ESI) *m/z* 678 $(M+H)^+$.

Example 126K

methyl [(2S)-1-{(2S)-2-[5-(4-{(2R,5R)-5-(4-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-5-yl}phenyl)-1-[4-(pentafluoro-lambda~6~-sulfanyl)phenyl]pyrrolidin-2-yl}phenyl)-1H-imidazol-2-yl]pyrrolidin-1-yl}-3-methyl-1-oxobutan-2-yl]carbamate

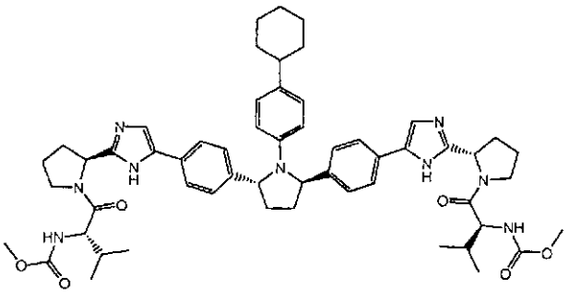
The product from Example 126J and Example 126G were processed using the method described in Example 39F to afford the title compound (0.75 g, 30%). ^{1}H NMR (400 MHz, DMSO-d6) δ 0.85 (dd, *J* = 6.7, 15.8, 12H), 2.26 – 1.66 (m, 14H), 3.53 (s, 6H), 3.87 – 3.63 (m, 4H), 4.14 – 3.91 (m, 2H), 5.06 (dd, *J* = 3.0, 6.7, 2H), 5.34 (s, 2H), 6.34 (d, *J* = 9.1, 2H), 7.17 (d, *J* = 8.2, 4H), 7.26 (dd, *J* = 8.4, 17.3, 2H), 7.75 – 7.34 (m, 8H), 12.22 – 11.46 (m, 2H). MS (ESI) *m/z* 1010 $(M+H)^+$, 1008 $(M-H)^+$.



Example 127

methyl [(2S)-1-{(2S)-2-[5-(4-{1-[4-(azepan-1-yl)phenyl]-5-(4-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-5-yl}phenyl)-1H-pyrrol-2-yl}phenyl)-1H-imidazol-2-yl]pyrrolidin-1-yl}-3-methyl-1-oxobutan-2-yl]carbamate

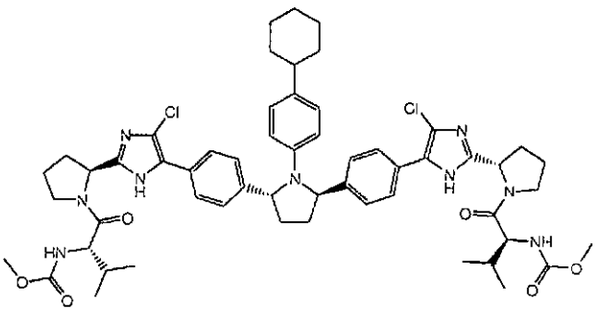
Example 26E and 4-(1-azepanyl)aniline were processed using the methods of Examples 76A, 39E, 39F, 55G, and 26J (reaction solvent = dichloromethane) to provide the title compound (6.1 mg). MS (ESI) *m/z* 977 $(M+H)^+$.



Example 128

methyl {(2S)-1-[(2S)-2-(5-{4-[(2R,5R)-1-(4-cyclohexylphenyl)-5-(4-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-5-yl}phenyl)pyrrolidin-2-yl]phenyl}-1H-imidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

Example 126H and 4-cyclohexylaniline were processed using the methods of Examples 126I, 126J, and 126K to provide the title compound (0.14 g). ^{1}H NMR (400 MHz, DMSO-D6) δ 0.85 (dd, *J* = 16.6, 6.9, 12H), 1.32 - 1.06 (m, 8H), 1.65 (dd, *J* = 19.1, 6.2, 7H), 2.27 - 1.82 (m, 13H), 3.53 (s, 6H), 3.78 (d, *J* = 6.8, 2H), 4.10 - 3.95 (m, 2H), 5.06 (dd, *J* = 6.9, 3.1, 2H), 5.19 (t, *J* = 6.7, 2H), 6.21 (d, *J* = 8.7, 2H), 6.76 (dd, *J* = 8.6, 3.7, 2H), 7.19 - 7.08 (m, 4H), 7.34 - 7.19 (m, 2H), 7.37 (d, *J* = 1.8, 1H), 7.50 (t, *J* = 11.3, 1H), 7.65 - 7.57 (m, 3H), 11.68 (s, 1H), 12.10 - 11.93 (m, 1H). MS (ESI) *m/z* 966 $(M+H)^+$.

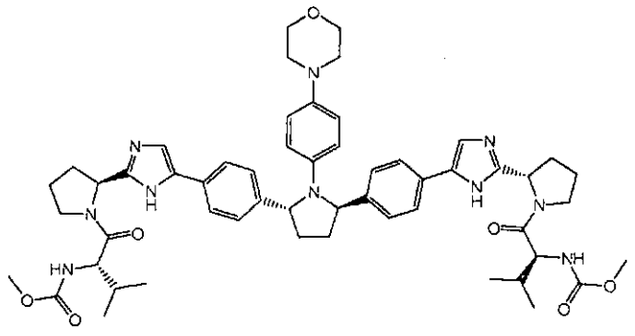


Example 129

methyl {(2S)-1-[(2S)-2-(4-chloro-5-{4-[(2R,5R)-5-(4-{4-chloro-2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-5-yl}phenyl)-1-(4-cyclohexylphenyl)pyrrolidin-2-yl]phenyl}-1H-imidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

N-Chlorosuccinimide (0.046 g, 0.342 mmol) was added to a solution of the product from Example 128 (0.1435 g, 0.149 mmol) in dichloromethane (7 mL) and stirred at ambient temperature for 17 hours. The reaction was diluted with dichloromethane and washed with sat aq NaHCO3 (2 x) and concentrated. The residue was purified by flash chromatography (silica gel, MeOH/dichloromethane) then by prep HPLC to afford the title compound (20.4 mg, 13%). ^{1}H NMR (free base) (400 MHz, DMSO-D6) δ 0.94 - 0.73 (m, 12H), 1.39 - 0.99 (m, 8H), 1.75 - 1.41 (m, 6H),

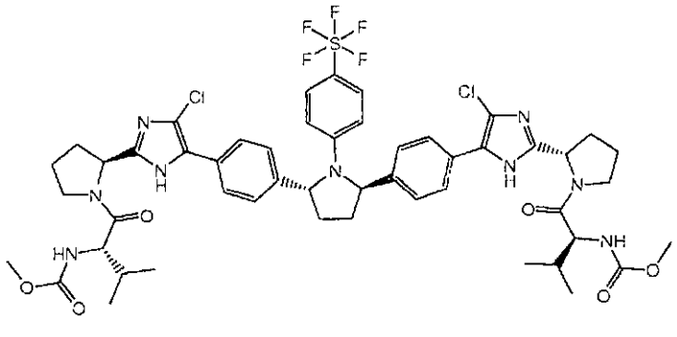
2.27 - 1.77 (m, 12H), 3.53 (s, 6H), 3.86 - 3.66 (m, 3H), 4.08 - 3.96 (m, 2H), 5.11 - 4.89 (m, 2H), 5.30 - 5.12 (m, 1H), 5.55 - 5.33 (m, 1H), 6.21 (d, J = 8.7, 1H), 6.88 - 6.67 (m, 2H), 6.94 (dd, J = 4.3, 8.4, 1H), 7.42 - 7.02 (m, 6H), 7.56 - 7.42 (m, 3H), 7.61 (t, J = 8.5, 1H), 11.68 (d, J = 10.7, 1H), 12.49 - 12.26 (m, 1H). MS (ESI) *m/z* 1034 $(M+H)^+$.



Example 130

methyl [(2S)-1-{(2S)-2-[5-(4-{(2R,5R)-5-(4-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-5-yl}phenyl)-1-[4-(morpholin-4-yl)phenyl]pyrrolidin-2-yl}phenyl)-1H-imidazol-2-yl]pyrrolidin-1-yl}-3-methyl-1-oxobutan-2-yl]carbamate

Example 126H and 4-morpholinoaniline were processed using sequentially the methods of Examples 126I, 39E, 39F, 39I, and 26J (reaction solvent = dichloromethane) to provide the title compound (0.16 g). ^{1}H NMR (300 MHz, DMSO-D6) δ 0.86 (dd, *J* = 12.2, 6.6, 12H), 1.77 - 1.55 (m, 2H), 2.03 - 1.77 (m, 6H), 2.21 - 2.03 (m, 4H), 2.45 - 2.39 (m, 1H), 2.58 - 2.54 (m, 1H), 2.82 - 2.74 (m, 4H), 3.53 (s, 6H), 3.67 - 3.57 (m, 4H), 3.77 (d, *J* = 6.1, 3H), 4.04 (t, *J* = 8.3, 2H), 5.06 (dd, *J* = 6.7, 3.0, 2H), 5.18 (t, *J* = 5.0, 2H), 6.22 (d, *J* = 9.0, 2H), 6.58 (dd, *J* = 9.0, 1.9, 2H), 7.14 (d, *J* = 8.4, 4H), 7.32 - 7.17 (m, 3H), 7.37 (d, *J* = 1.8, 2H), 7.55 - 7.41 (m, 1H), 7.63 (t, *J* = 10.0, 4H), 11.68 (s, 1H), 12.15 - 11.90 (m, 1H). MS (ESI) *m/z* 969 $(M+H)^+$.

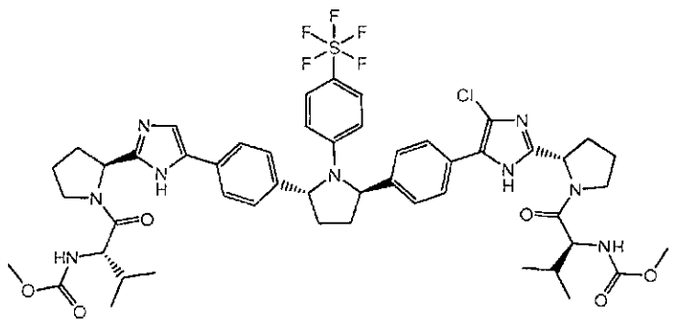


Example 131

methyl [(2S)-1-{(2S)-2-[4-chloro-5-(4-{(2R,5R)-5-(4-{4-chloro-2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-5-yl}phenyl)-1-[4-

(pentafluoro-lambda~6~-sulfanyl)phenyl]pyrrolidin-2-yl}phenyl)-1H-imidazol-2-yl]pyrrolidin-1-yl}-3-methyl-1-oxobutan-2-yl]carbamate

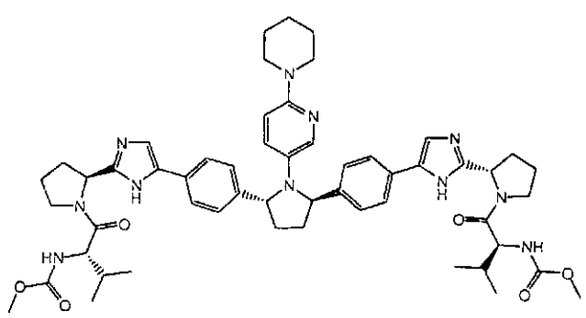
The product from Example 126K was processed using the method described in Example 129. The mixture of mono and dichlorinated products was purified via reverse phase HPLC to afford the title compound (90.9 mg, 19%). ^{1}H NMR (free base) (500 MHz, DMSO-D6) δ 0.84 (dd, *J* = 6.8, 16.1, 12H), 2.23 – 1.70 (m, 13H), 3.53 (s, 6H), 3.85 – 3.66 (m, 4H), 4.02 (ddd, *J* = 4.8, 10.8, 16.1, 3H), 5.05 – 4.91 (m, 2H), 5.43 (d, *J* = 5.8, 2H), 6.36 (d, *J* = 9.1, 2H), 7.28 (d, *J* = 8.4, 2H), 7.34 (d, *J* = 8.3, 4H), 7.46 (d, *J* = 9.4, 2H), 7.72 – 7.58 (m, 4H), 12.43 (s, 2H). MS(ESI) *m/z* 1078 $(M+H)^+$.



Example 132

methyl [(2S)-1-{(2S)-2-[4-chloro-5-(4-{(2R,5R)-5-(4-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-5-yl}phenyl)-1-[4-(pentafluoro-lambda~6~-sulfanyl)phenyl]pyrrolidin-2-yl}phenyl)-1H-imidazol-2-yl]pyrrolidin-1-yl}-3-methyl-1-oxobutan-2-yl]carbamate

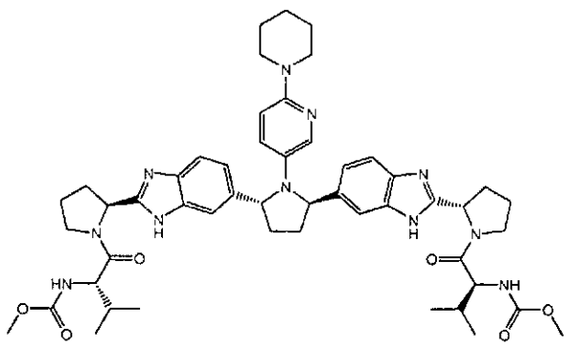
The product from Example 126K was processed using the method described in Example 129. The mixture of mono and dichlorinated products was purified via reverse phase HPLC to afford the title compound (33.3 mg, 7%). ^{1}H NMR (free base) (500 MHz, DMSO-D6) δ 0.94 – 0.76 (m, 12H), 2.24 – 1.63 (m, 13H), 3.53 (d, *J* = 1.2, 6H), 3.86 – 3.68 (m, 4H), 4.10 – 3.98 (m, 2H), 5.02 – 4.93 (m, 1H), 5.06 (dd, *J* = 3.2, 7.1, 1H), 5.48 – 5.30 (m, 2H), 6.35 (d, *J* = 9.1, 2H), 7.21 – 7.10 (m, 2H), 7.36 – 7.21 (m, 4H), 7.58 – 7.38 (m, 4H), 7.73 – 7.59 (m, 4H), 12.50 – 11.65 (m, 2H). MS (ESI) *m/z* 1044 $(M+H)^+$, 1042 $(M-H)^+$.



Example 133

methyl [(2S)-1-{(2S)-2-[5-(4-{(2R,5R)-5-(4-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-5-yl}phenyl)-1-[6-(piperidin-1-yl)pyridin-3-yl]pyrrolidin-2-yl}phenyl)-1H-imidazol-2-yl]pyrrolidin-1-yl}-3-methyl-1-oxobutan-2-yl]carbamate

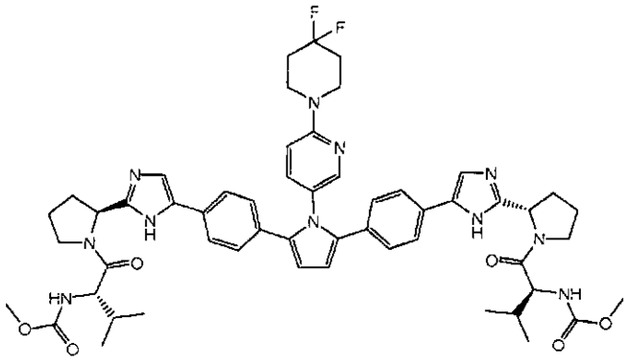
Example 126H and 6-(piperidin-1-yl)pyridine-3-amine were processed using sequentially the methods of Examples 126I, 39E, 39F, 39I, and 26J (reaction solvent = dichloromethane) to provide the title compound (91.4 mg). ^{1}H NMR (400 MHz, DMSO-D6) δ 0.85 (dt, *J* = 7.1, 14.3, 12H), 1.24 (s, 2H), 1.44 (s, 6H), 1.70 (d, *J* = 5.2, 2H), 2.04 – 1.82 (m, 6H), 2.23 – 2.04 (m, 4H), 3.21 – 3.03 (m, 4H), 3.53 (s, 6H), 3.87 – 3.67 (m, 4H), 4.12 – 3.96 (m, 2H), 5.06 (dd, *J* = 3.2, 7.0, 2H), 5.20 (t, *J* = 6.8, 2H), 6.49 (dd, *J* = 3.1, 9.1, 1H), 6.60 (dd, *J* = 2.9, 9.2, 1H), 7.20 – 7.10 (m, 4H), 7.33 – 7.20 (m, 3H), 7.38 (d, *J* = 1.8, 2H), 7.51 (t, *J* = 10.4, 1H), 7.64 (dd, *J* = 8.1, 15.7, 3H), 11.69 (s, 1.4H), 12.06 (t, *J* = 32.1, 0.6H).



Example 134

methyl {(2S)-1-[(2S)-2-(6-{(2R,5R)-5-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-benzimidazol-6-yl}-1-[6-(piperidin-1-yl)pyridin-3-yl]pyrrolidin-2-yl}-1H-benzimidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

Example 109C and 6-(piperidin-1-yl)pyridine-3-amine were processed using sequentially the methods of Examples 113A, 113B, 116F (Ra-Ni reduction conducted in an SS pressure bottle for 120 min at 30 psi at room temperature), 28I (reaction conducted at 50 °C for 4 hours), 39I, and 26J (reaction solvent = dichloromethane) to provide the title compound (71 mg). ^{1}H NMR (400 MHz, METHANOL-D4) δ 0.89 (ddd, *J* = 6.5, 20.7, 26.0, 12H), 1.62 – 1.43 (m, 6H), 2.48 – 1.80 (m, 13H), 2.72 – 2.60 (m, 2H), 3.10 – 2.97 (m, 4H), 3.64 (s, 6H), 3.93 – 3.78 (m, 2H), 4.09 – 3.94 (m, 2H), 4.22 (d, *J* = 7.3, 2H), 5.21 (dd, *J* = 5.2, 7.6, 1H), 5.44 – 5.30 (m, 2H), 6.50 (d, *J* = 9.1, 1H), 6.83 – 6.71 (m, 1H), 7.59 – 7.15 (m, 7H). MS (ESI) *m/z* 916 $(M+H)^+$, 914 $(M-H)^+$.



Example 135

methyl [(2S)-1-{(2S)-2-[5-(4-{1-[6-(4,4-difluoropiperidin-1-yl)pyridin-3-yl]-5-(4-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-5-yl}phenyl)-1H-pyrrol-2-yl}phenyl)-1H-imidazol-2-yl]pyrrolidin-1-yl}-3-methyl-1-oxobutan-2-yl]carbamate

Example 135A

2-(4,4-difluoropiperidin-1-yl)-5-nitropyridine

To a slurry of 2-chloro-5-nitropyridine (5 g, 31.5 mmol) and 4,4-difluoropiperidine hydrochloride (4.97 g) in ethanol (40 mL) at ambient temperature was added N,N-diisopropylethylamine (12.00 mL, 69.4 mmol) and the mixture heated to 70 °C for 18 hours. The reaction was concentrated, partitioned between CH2Cl2 and 1M NaOH. The organic phase concentrated and purified by chromatography (elution with 2% MeOH-CH2Cl2 then 3% MeOH-CH2Cl2) to provide the title compound as a yellow oil. MS (DCI) *m/z* 261 $(M+NH_4)^+$.

Example 135B

6-(4,4-difluoropiperidin-1-yl)pyridin-3-amine

The product from Example 135A (4.56 g, 18.75 mmol) and solvent THF (20 mL)/DMF were added to Ra-Ni 2800, water slurry (4.56 g, 78 mmol) in a 250 mL SS pressure bottle and stirred for 2 hr at 30 psi and ambient temperature. The mixture was filtered through a nylon membrane and washed with MeOH. The filtrate was concentrated and dried under vacuum to afford the title compound (3.40 g, 85%). ^{1}H NMR (400 MHz, DMSO-D6) δ 2.03 – 1.88 (m, 4H), 3.49 – 3.38 (m, 4H), 4.61 (s, 2H), 6.73 (d, *J* = 8.8, 1H), 6.93 (dd, *J* = 2.9, 8.8, 1H), 7.61 (d, *J* = 2.6, 1H). MS (ESI) *m/z* 214 ($M+H^+$).

Example 135C

5-(2,5-bis(4-(2-((S)-pyrrolidin-2-yl)-1H-imidazol-5-yl)phenyl)-1H-pyrrol-1-yl)-2-(4,4-difluoropiperidin-1-yl)pyridine

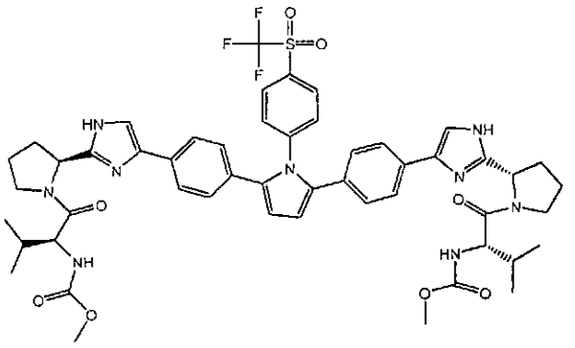
TFA (0.046 mL, 0.596 mmol) was added to a mixture of the product from Example 138B (0.2114 g, 0.298 mmol) and the product from Example 135B (0.095 g, 0.447 mmol) in toluene (2.98

mL). The mixture was heated at 110 °C for 18 hours. The reaction was cooled and additional TFA (0.023 mL, 0.298 mmol) was added and stirred for another hour. The solvent was removed under reduced pressure and azatroped with toluene to afford the title compound.

Example 135D

methyl [(2S)-1-{(2S)-2-[5-(4-{1-[6-(4,4-difluoropiperidin-1-yl)pyridin-3-yl]-5-(4-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-5-yl}phenyl)-1H-pyrrol-2-yl}phenyl)-1H-imidazol-2-yl]pyrrolidin-1-yl}-3-methyl-1-oxobutan-2-yl]carbamate

The product from Example 135C was processed using the method described in Example 26J to afford the title compound. ^{1}H NMR (400 MHz, DMSO-D6) δ 0.94 - 0.73 (m, 12H), 2.03 - 1.82 (m, 10H), 2.20 - 2.04 (m, 4H), 3.53 (s, 6H), 3.64 (s, 4H), 3.86 - 3.69 (m, 4H), 4.04 (dd, 2H), 5.04 (dd, *J* = 3.0, 7.0, 2H), 6.53 - 6.39 (m, 2H), 6.93 - 6.79 (m, 1H), 7.06 (d, *J* = 8.4, 3H), 7.13 (dd, *J* = 10.9, 19.3, 1H), 7.30 - 7.21 (m, 2H), 7.39 - 7.30 (m, 1H), 7.42 (d, *J* = 1.7, 1H), 7.48 - 7.43 (m, 1H), 7.66 - 7.49 (m, 4H), 7.85 (dd, *J* = 2.7, 9.7, 1H), 12.16 - 11.64 (m, 2H). MS (ESI) *m/z* 1000 $(M+H)^+$, 998 $(M-H)^+$.



Example 136

methyl {(2S)-1-[(2S)-2-(4-{4-[5-(4-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-4-yl}phenyl)-1-{4-[(trifluoromethyl)sulfonyl]phenyl}-1H-pyrrol-2-yl]phenyl}-1H-imidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

Example 136A

2,5-bis(4-bromophenyl)-1-(4-(trifluoromethylsulfonyl)phenyl)-1H-pyrrole

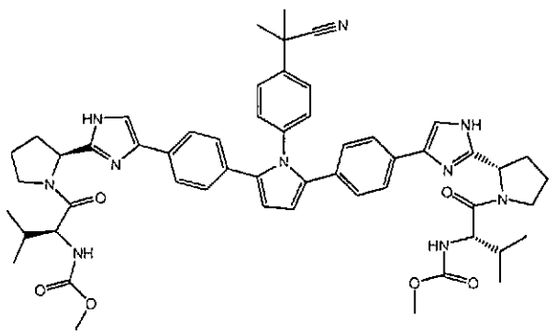
To a slurry of the product from Example 26E (0.60 g, 1.52 mmol) and 4-(trifluoromethylsulfonyl)aniline (0.51 g, 2.27 mmol) in toluene (12 mL) was added a 1N solution of titanium(IV) chloride (1.6 mL, 1.6 mmol) in toluene. The mixture was stirred overnight at room temperature and then heated to reflux for 3 hours. The cooled mixture was filtered and the solid residue was suspended in a mixture of water and diethyl ether. The solid was diluted with water and ether and stirred vigorously for 15 minutes. The mixture was filtered and then washed thoroughly

with diethyl ether to give the title compound as a crude mixture that was used in subsequent reactions without further purification (0.60g, 68% yield crude).

Example 136B

methyl {(2S)-1-[(2S)-2-(4-{4-[5-(4-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-4-yl}phenyl)-1-{4-[(trifluoromethyl)sulfonyl]phenyl}-1H-pyrrol-2-yl]phenyl}-1H-imidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

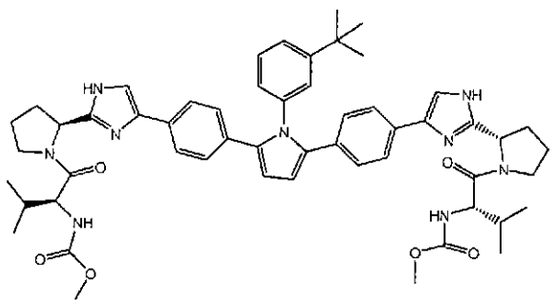
Example 136A was processed using sequentially the methods of Examples 26G, 26H, 65B, and 65C to provide the title compound (90 mg). ^{1}H NMR (400 MHz, DMSO-D6) δ 12.20 – 11.68 (m, 2H), 8.17 – 8.04 (m, 2H), 7.63 – 7.42 (m, 8H), 7.31 – 7.15 (m, 2H), 7.02 – 6.90 (m, 4H), 6.64 – 6.53 (m, 2H), 5.08 – 4.97 (m, 2H), 4.05 – 3.97 (m, 2H), 3.83 – 3.69 (m, 4H), 3.53 (s, 6H), 2.18 – 1.79 (m, 10H), 0.90 – 0.78 (m, 12H). MS (ESI; M+H) m/z = 1013.



Example 137

methyl [(2S)-1-{(2S)-2-{4-(4-{1-[4-(2-cyanopropan-2-yl)phenyl]-5-(4-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-4-yl}phenyl)-1H-pyrrol-2-yl}phenyl)-1H-imidazol-2-yl]pyrrolidin-1-yl}-3-methyl-1-oxobutan-2-yl]carbamate

Example 26E and 2-(4-aminophenyl)-2-methylpropanenitrile were processed using sequentially the methods of Examples 26F, 26G, 26H, 65B, and 65C to provide the title compound (100 mg). ^{1}H NMR (400 MHz, DMSO-D6) δ 12.15 – 11.68 (m, 0H), 7.58 – 7.44 (m, 0H), 7.44 – 7.36 (m, 0H), 7.30 – 7.12 (m, 0H), 7.07 – 6.91 (m, 0H), 6.55 – 6.42 (m, 0H), 5.06 – 4.96 (m, 0H), 4.02 (t, *J* = 8.3, 0H), 3.81 – 3.67 (m, 0H), 3.52 (s, 0H), 2.15 – 1.82 (m, 0H), 1.65 (s, 0H), 0.90 – 0.74 (m, 1H). MS (ESI; M+H) m/z = 948.



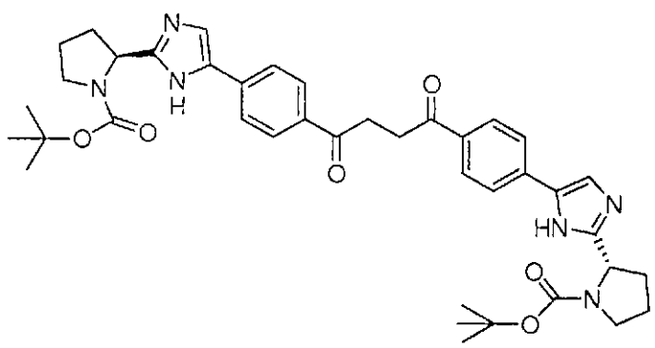
Example 138

methyl {(2S)-1-[(2S)-2-(4-{4-[1-(3-tert-butylphenyl)-5-(4-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-4-yl}phenyl)-1H-pyrrol-2-yl]phenyl}-1H-imidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

Example 138A

1,4-bis(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)butane-1,4-dione

To a solution of the product from Example 26E (2.00 g, 5.05 mmol), bis(pinacolato)diborane (3.85 g, 15.15 mmol), potassium acetate (1.982 g, 20.20 mmol) in dimethoxyethane (50 mL) at room temperature was added $PdCl_2(dppf)$-CH_2Cl_2 adduct (0.412 g, 0.505 mmol) and the mixture degassed (purge with N_2). The mixture was heated to reflux for 1 hour. The cooled mixture was filtered through celite and washed with ethyl acetate. The filtrate was washed with water, brine and dried (Na_2SO_4). After filtration and removal of solvent, the residue was purified by chromatography (80 g column; gradient elution from 0% to 40% ethyl acetate-hexanes) to provide the title compound (2.22 g; 90%) as a white solid. ^{1}HNMR ($CDCl_3$; 400 MHz): δ 8.02 (AA'XX', J=8.24 Hz, 4H), 7.91 (AA'XX', J=8.13 Hz, 4H), 3.47 (s, 4H), 1.36 (s, 24H).



Example 138B

di-*tert*-butyl (2*S*,2'*S*)-2,2'-[(1,4-dioxobutane-1,4-diyl)bis(benzene-4,1-diyl-1*H*-imidazole-5,2-diyl)]dipyrrolidine-1-carboxylate

A solution of the product from Example 138A (2.22 g, 4.53 mmol), $PdCl_2(dppf)$-CH_2Cl_2 adduct (0.37 g, 0.45 mmol), 1 M sodium carbonate (18 mL, 18 mmol) and the product from Example

26D (4.30 g, 13.6 mmol) in ethanol (23 mL)/toluene (23 mL) was degassed (purge N_2) and heated in oil bath at 90 °C overnight. The cooled mixture was concentrated and the residue partitioned between water and ethyl acetate. The organic phase was concentrated and the residue was purified by chromatography (gradient elution from 30% to 100% ethyl acetate-hexane) to provide the title compound (1.90 g, 59%) as a light tan solid. ^{1}HNMR (DMSO-d_6; 400 MHz): δ 12.06 (m, 2H), 8.04-7.96 (m, 4H), 7.89-7.78 (m, 4H), 7.69 (m, 2H), 4.85-4.75 (m, 2H), 3.53 (m, 2H), 3.35 (m, 4H), 2.24-1.87 (m, 10H), 1.39 (br s, 8H), 1.14 (br s, 10H). MS (ESI; M+H) m/z = 709.

Example 138C

(S)-4,4'-(4,4'-(1-(3-tert-butylphenyl)-1H-pyrrole-2,5-diyl)bis(4,1-phenylene))bis(2-((S)-pyrrolidin-2-yl)-1H-imidazole)

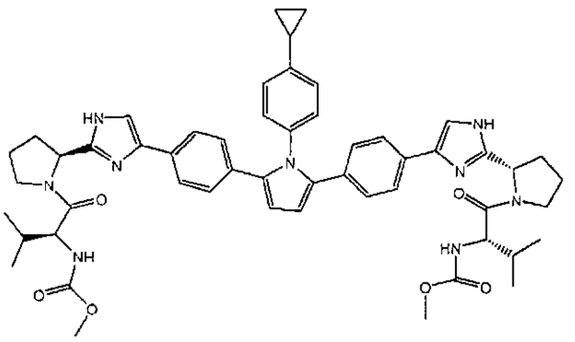
To a solution of the product from Example 138B (180 mg, 0.25 mmol) and 3-tert-butylaniline (57 mg, 0.38 mmol) in toluene (2.0 mL) was added trifluoroacetic acid (39 µL 0.50 mmol). The mixture was heated to 110 °C overnight. To the cooled mixture was added trifluoroacetic acid (0.4 mL) and the mixture was stirred for 1 hour at room temperature. The mixture was concentrated under reduced pressure. The residue was partitioned between 25% isopropyl alcohol in $CHCl_3$ and saturated sodium bicarbonate solution. The organic layer was separated and dried over Na_2SO_4, filtered and concentrated under reduced pressure to provide the title compound.

Example 138D

methyl {(2S)-1-[(2S)-2-(4-{4-[1-(3-tert-butylphenyl)-5-(4-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-4-yl}phenyl)-1H-pyrrol-2-yl]phenyl}-1H-imidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

A solution consisting of N1-((ethylimino)methylene)-N3,N3-dimethylpropane-1,3-diamine hydrochloride (109 mg, 0.57 mmol), 1H-benzo[d][1,2,3]triazol-1-ol hydrate (87 mg, 0.57 mmol), (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (100 mg, 0.57 mmol) and 4-methylmorpholine (0.14 mL, 1.0 mmol) in DMF (2.6 mL) was cooled in an icebath. To this mixture was added the product from Example 138C (161 mg, 0.26 mmol). Additional 4-methylmorpholine was added to the mixture until the pH was adjusted to 8. The reaction was stirred for 3.5 hours and then the icebath was removed and the reaction was stirred for an additional 16 hours. Water was then added to the reaction mixture and the resulting precipitate was recovered by filtration. The residue was washed with copious amounts of water followed by diethyl ether. The crude product was purified by chromatography on silica gel eluted with a solvent gradient of 0-5% methanol in CH_2Cl_2 to provide the title compound (15 mg, 6% yield). ^{1}H NMR (400 MHz, DMSO-D6) δ 12.04 – 11.65 (m, 2H), 7.57 – 7.45 (m, 4H), 7.43 – 7.35 (m, 2H), 7.33 – 7.08 (m, 5H), 7.05 – 6.91 (m, 4H), 6.79 (t, *J* = 7.5, 1H),

6.53 – 6.40 (m, 2H), 5.05 – 4.99 (m, 2H), 4.02 (t, *J* = 8.3, 2H), 3.82 – 3.68 (m, 4H), 3.56 – 3.47 (m, 6H), 2.18 – 1.79 (m, 10H), 1.09 (s, 9H), 0.89 – 0.75 (m, 12H). MS (ESI; M+H) m/z = 937.



Example 139

methyl {(2S)-1-[(2S)-2-(4-{4-[1-(4-cyclopropylphenyl)-5-(4-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-4-yl}phenyl)-1H-pyrrol-2-yl]phenyl}-1H-imidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

Example 139A

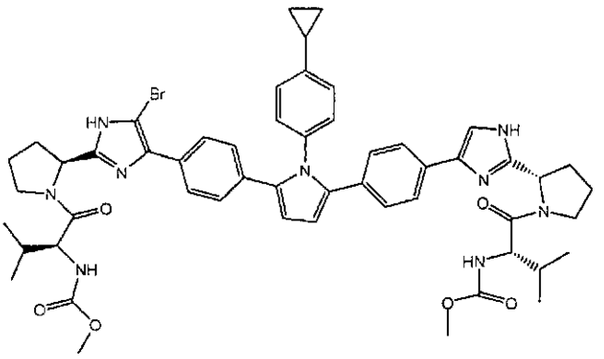
(S)-4,4'-(4,4'-(1-(4-cyclopropylphenyl)-1H-pyrrole-2,5-diyl)bis(4,1-phenylene))bis(2-((S)-pyrrolidin-2-yl)-1H-imidazole) tetrakis(2,2,2-trifluoroacetate)

To a solution of the product from Example 138B (0.30g 0.43 mmol) and 4-cyclopropylaniline (85 mg, 0.64 mmol) in toluene (3.4 mL) was added trifluoroacetic acid (65 µL 0.85 mmol). The mixture was heated to 110 °C overnight. To the cooled mixture was added trifluoroacetic acid (1.0 mL) and the mixture was stirred for 1 hour at room temperature. The mixture was concentrated under reduced pressure and then triturated with diethyl ether to provide the title compound (0.42g, 28% yield).

Example 139B

methyl {(2S)-1-[(2S)-2-(4-{4-[1-(4-cyclopropylphenyl)-5-(4-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-4-yl}phenyl)-1H-pyrrol-2-yl]phenyl}-1H-imidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

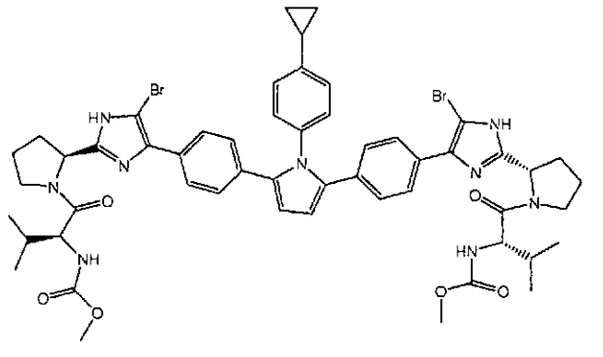
The title compound was prepared using the methods from Example 138D substituting the product from Example 139A for the product from Example 138C to provide the title compound (150 mg, 40% yield). ^{1}H NMR (400 MHz, DMSO-D6) δ 12.09 – 11.63 (m, 2H), 7.56 – 7.46 (m, 4H), 7.44 – 7.35 (m, 2H), 7.30 – 7.11 (m, 2H), 7.07 – 6.88 (m, 8H), 6.54 – 6.39 (m, 2H), 5.07 – 4.97 (m, 2H), 4.03 (t, *J* = 8.3, 2H), 3.83 – 3.66 (m, 4H), 3.52 (s, 6H), 2.18 – 1.79 (m, 10H), 1.26 – 1.19 (m, 1H), 0.98 – 0.90 (m, 2H), 0.90 – 0.74 (m, 12H), 0.69 – 0.60 (m, 2H). MS (ESI; M+H) m/z = 921.



Example 140

methyl [(2S)-1-{(2S)-2-[5-bromo-4-(4-{1-(4-cyclopropylphenyl)-5-[4-(2-{(2S)-1-[N-(methoxycarbonyl)-L-valyl]pyrrolidin-2-yl}-1H-imidazol-4-yl)phenyl]-1H-pyrrol-2-yl}phenyl)-1H-imidazol-2-yl]pyrrolidin-1-yl}-3-methyl-1-oxobutan-2-yl]carbamate

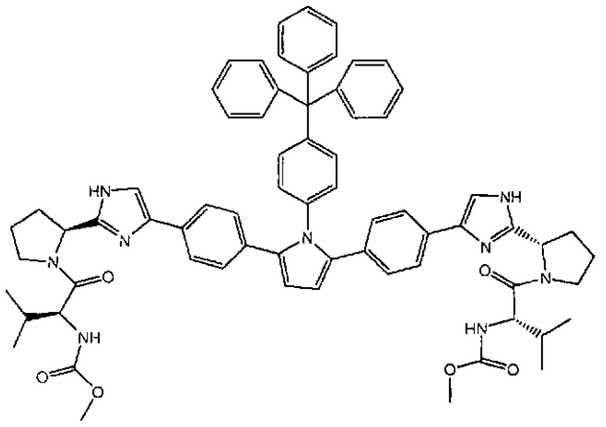
To a suspension of the product from Example 139 (47 mg, 0.051 mmol) in CH_2Cl_2 (0.5 mL) was added a mixture of 1-bromopyrrolidine-2,5-dione (9.1 mg, 0.051 mmol) in CH_2Cl_2 (0.5 mL). The mixture was stirred overnight at room temperature then concentrated under reduced pressure and triturated with diethyl ether to provide a mixture of brominated compounds that was subjected to reverse phase HPLC purification eluted with a gradient of 10-100% CH_3CN in 0.1% aqueous trifluoroacetic acid to afford the title compound (8 mg, 13% yield). ^{1}H NMR (TFA salt) (400 MHz, DMSO-D6) δ 14.32 (s, 1H), 12.44 (s, 1H), 7.97 (s, 1H), 7.62 – 7.48 (m, 4H), 7.31 (d, J = 8.4, 1H), 7.24 (d, J = 8.5, 1H), 7.18 – 7.08 (m, 4H), 7.09 – 7.00 (m, 4H), 6.61 (d, J = 3.7, 1H), 6.57 (d, J = 3.7, 1H), 5.07 (t, J = 7.0, 1H), 4.98 – 4.91 (m, 1H), 4.08 (t, J = 7.9, 1H), 4.02 (t, J = 8.3, 1H), 3.90 – 3.67 (m, 4H), 3.52 (s, 3H), 3.51 (s, 3H), 2.18 – 1.83 (m, 10H), 1.22 (s, 1H), 1.01 – 0.93 (m, 2H), 0.89 – 0.72 (m, 12H), 0.70 – 0.62 (m, 2H). MS (ESI; M+H) m/z = 1000.



Example 141

methyl {(2S)-1-[(2S)-2-(5-bromo-4-{4-[5-(4-{5-bromo-2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-4-yl}phenyl)-1-(4-cyclopropylphenyl)-1H-pyrrol-2-yl]phenyl}-1H-imidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

The title compound was formed as an additional product in Example 140. The mixture of products was subjected to reverse phase HPLC purification eluted with a gradient of 10-100% CH_3CN in 0.1% aqueous trifluoroacetic acid to afford the title compound (15 mg, 23% yield). ^1H NMR (TFA salt) (400 MHz, DMSO-D6) δ 12.43 (s, 2H), 7.54 (dd, 4H), 7.25 (d, J = 8.4, 2H), 7.15 – 7.08 (m, 4H), 7.08 – 7.00 (m, 4H), 6.55 (s, 2H), 4.99 – 4.89 (m, 2H), 4.02 (t, J = 8.3, 2H), 3.82 – 3.68 (m, 4H), 3.51 (s, 6H), 2.22 – 2.03 (m, 4H), 2.00 – 1.81 (m, 6H), 1.27 – 1.19 (m, 1H), 1.02 – 0.92 (m, 2H), 0.90 – 0.77 (m, 12H), 0.70 – 0.61 (m, 2H). MS (ESI; M+H) m/z = 1078.



Example 142

methyl {(2S)-1-[(2S)-2-(4-{4-[5-(4-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-4-yl}phenyl)-1-(4-tritylphenyl)-1H-pyrrol-2-yl]phenyl}-1H-imidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

Example 142A

(S)-4,4'-(4,4'-(1-(4-tritylphenyl)-1H-pyrrole-2,5-diyl)bis(4,1-phenylene))bis(2-((S)-pyrrolidin-2-yl)-1H-imidazole) tetrakis(2,2,2-trifluoroacetate)

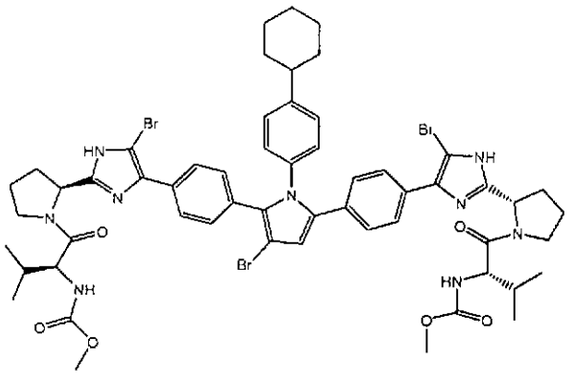
The title compound was prepared using the methods from Example 139A substituting 4-tritylaniline for 4-cyclopropylaniline to provide the title compound.

Example 142B

methyl {(2S)-1-[(2S)-2-(5-bromo-4-{4-[5-(4-{5-bromo-2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-4-yl}phenyl)-1-(4-cyclopropylphenyl)-1H-pyrrol-2-yl]phenyl}-1H-imidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

The title compound was prepared using the methods from Example 138D substituting the product from Example 142A for the product from Example 138C to provide the title compound (71 mg, 43% yield). ^1H NMR (400 MHz, DMSO-D6) δ 12.15 – 11.69 (m, 2H), 7.61 – 7.48 (m, 4H), 7.46

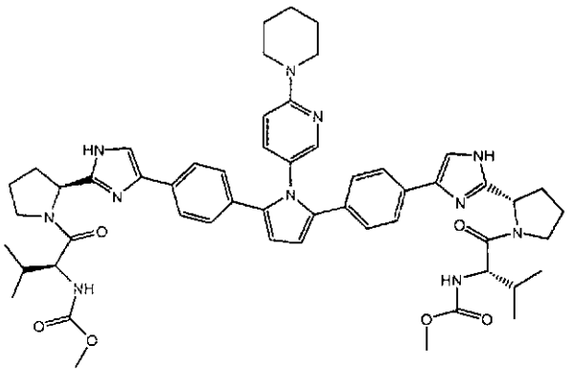
– 7.37 (m, 2H), 7.35 – 7.15 (m, 11H), 7.10 – 6.91 (m, 14H), 6.55 – 6.44 (m, 2H), 5.11 – 5.00 (m, 2H), 4.03 (t, *J* = 8.5, 2H), 3.86 – 3.70 (m, 4H), 3.52 (s, 6H), 2.21 – 1.83 (m, 10H), 0.92 – 0.76 (m, 12H). MS (ESI; M+H) m/z = 1123.



Example 143

methyl {(2S)-1-[(2S)-2-(5-bromo-4-{4-[4-bromo-5-(4-{5-bromo-2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-4-yl}phenyl)-1-(4-cyclohexylphenyl)-1H-pyrrol-2-yl]phenyl}-1H-imidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

To a suspension of the product from Example 74 (100 mg, 0.10 mmol) in CH_2Cl_2 (1.0 mL) at -78 °C was added a mixture of 1-bromopyrrolidine-2,5-dione (59 mg, 0.33 mmol) in CH_2Cl_2 (1.0 mL). The mixture was stirred for 3 hours, warming to room temperature then concentrated under reduced pressure and triturated with diethyl ether to provide the title compound (103 mg, 83% yield). ^{1}H NMR (400 MHz, DMSO-D6) δ 12.47 (s, 1H), 11.02 (s, 1H), 7.54 (d, *J* = 26.1, 4H), 7.29 – 6.98 (m, 10H), 6.71 (s, 1H), 5.01 – 4.90 (m, 2H), 4.02 (t, *J* = 8.1, 2H), 3.86 – 3.67 (m, 4H), 3.52 (s, 6H), 2.18 – 1.58 (m, 16H), 1.35 – 1.20 (m, 5H), 0.90 – 0.76 (m, 12H). MS (ESI; M+H) m/z = 1200.



Example 144

methyl [(2S)-1-{(2S)-2-[4-(4-{5-(4-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-4-yl}phenyl)-1-[6-(piperidin-1-yl)pyridin-3-yl]-1H-pyrrol-2-yl}phenyl)-1H-imidazol-2-yl]pyrrolidin-1-yl}-3-methyl-1-oxobutan-2-yl]carbamate

Example 144A

5-nitro-2-(piperidin-1-yl)pyridine

To a slurry of 2-chloro-5-nitropyridine (100 g, 632 mmol) in ethanol (2000 mL) at room temperature was added piperidine (206 mL, 2.08 mol) and the mixture heated to 60 °C for 30 minutes. The cooled mixture was concentrated and the residue taken up in CH_2Cl_2 then washed with saturated $NaHCO_3$ and brine. The mixture was dried (Na_2SO_4), filtered, and concentrated to provide the title compound as a yellow solid (130.4g, 99% yield). ^{1}H NMR (400 MHz, DMSO-D6) δ 8.94 (d, J = 2.9, 1H), 8.17 (dd, J = 9.6, 2.9, 1H), 6.93 (d, J = 9.6, 1H), 3.79 – 3.73 (m, 4H), 1.69 – 1.64 (m, 2H), 1.61 – 1.51 (m, 4H).

Example 144B

tert-butyl 6-(piperidin-1-yl)pyridin-3-ylcarbamate

To a solution of the product from Example 144A (130.4g, 629 mmol) and di-*tert*-butyl dicarbonate (165g, 755 mmol) in ethanol (750 mL) was added PtO_2 (5.4g, 24 mmol). The mixture was pressurized at 40 psi with H_2 and stirred overnight at room temperature. To ensure complete reaction additional PtO_2 (3.2g, 14 mmol) was added and the pressurized mixture was heated to 50 °C for 1 hour. The mixture was then filtered, concentrated under reduced pressure and absorbed onto silicagel and placed on top of a 4 to 5" plug of silica in a 3000 mL sintered glass funnel. Material was eluted with 15% diethyl ether in CH_2Cl_2 and the filtrate was concentrated under reduced pressure and the residue triturated with boiling hexanes. Additional product was recovered upon concentration of the filtrate, which was then chromatographed on silica gel eluted with 10% diethyl ether in CH_2Cl_2. The appropriate fractions were collected and concentrated then triturated with boiling hexanes. The two lots of lavender solids were combined to provide the title compound (100g, 57% yield). ^{1}H NMR (400 MHz, DMSO) δ 9.02 (bs, 1H), 8.11 (s, 1H), 7.63 – 7.54 (m, 1H), 6.74 (d, J = 9.1, 1H), 3.42 – 3.37 (m, 4H), 1.57 – 1.49 (m, 6H), 1.45 (9, 1H).

Example 144C

6-(piperidin-1-yl)pyridin-3-amine dihydrochloride

The product from Example 144B (1.00 g, 3.62 mmol) was added slowly to 4 M hydrochloric acid (10 mL, 40 mmol) and stirred at room temperature. After stirring overnight, ether was added and the solid filtered. Dried in vacuum oven to a white solid (0.817 g; 84%). ^{1}H NMR (400 MHz,

methanol-d4) δ 1.77 (s, 6H), 3.65 (s, 4H), 7.41 (d, J=9.8 Hz, 1H), 7.70 (d, J=2.6 Hz, 1H), 7.79 (dd, J=2.7, 9.8 Hz, 1H).

Example 144D

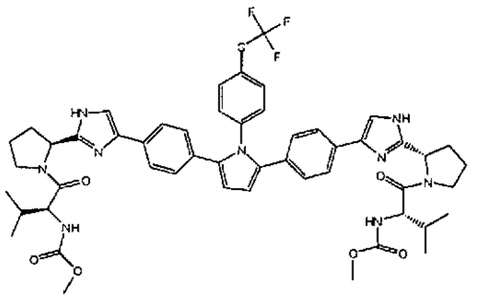
5-(2,5-bis(4-(2-((S)-pyrrolidin-2-yl)-1H-imidazol-4-yl)phenyl)-1H-pyrrol-1-yl)-2-(piperidin-1-yl)pyridine

To a solution of the product from Example 138B (0.20 g, 0.28 mmol) and the product from Example 144C (0.11 g, 0.42 mmol) in toluene (2.8 mL) was added TFA (22 μL, 0.28 mmol). The mixture was stirred at 110 °C for 3 hours. To the cooled mixture was added TFA (0.5 mL) and the mixture was stirred for 1 h at rt. The solvent was then removed under reduced pressure and triturated with diethylether and dried to provide 0.31 g of the desired compound as a TFA salt. ^{1}HNMR (DMSO-d_6; 400 MHz): δ 9.78 (br s, 2H), 7.84 (d, J=2.71 Hz, 1H), 7.75 (s, 2H), 7.67 (AA'XX', J=8.34 Hz, 4H), 7.35 (dd, J=9.11, 2.71 Hz, 1H), 7.18 (AA'XX', J=8.46 Hz, 4H), 6.79 (d, J=9.11 Hz, 1H), 6.53 (s, 2H), 4.79 (app t, J=7.81 Hz, 2H), 3.4-3.2 (m, 4H), 2.44-2.36 (m, 2H), 2.25-1.98 (m, 6H), 1.65-1.45 (m, 6H).

Example 144E

methyl [(2S)-1-{(2S)-2-[4-(4-{5-(4-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-4-yl}phenyl)-1-[6-(piperidin-1-yl)pyridin-3-yl]-1H-pyrrol-2-yl}phenyl)-1H-imidazol-2-yl]pyrrolidin-1-yl}-3-methyl-1-oxobutan-2-yl]carbamate

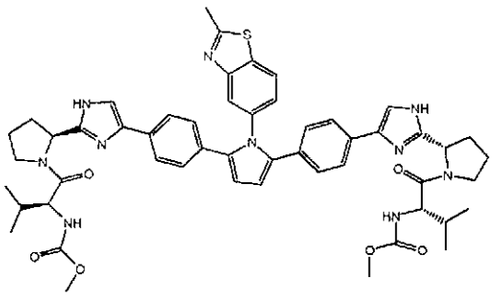
To a solution of N1-((ethylimino)methylene)-N3,N3-dimethylpropane-1,3-diamine hydrochloride (0.17 g, 0.89 mmol), 1H-benzo[d][1,2,3]triazol-1-ol hydrate (0.14 g, 0.89 mmol), (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (0.16 g, 0.89 mmol) in DMF (1.0 mL) was added 4-methylmorpholine (0.3 mL, 2.7 mmol). This mixture was stirred at room temperature for 15 minutes and then added to a solution of the product from Example 144D (0.31 g, 0.25 mmol) and 4-methylmorpholine (0.2 mL, 1.8 mmol) in DMF (0.7 mL). After stirring 4 h, water was added to this mixture and the solid collected by filtration then washed with water and diethylether. The residue was purified on silica gel eluted with 60% THF/Hexanes to provide 100 mg of the title compound. ^{1}H NMR (400 MHz, DMSO) δ 12.17 – 11.70 (m, 2H), 7.84 – 7.76 (m, 1H), 7.64 – 7.50 (m, 4H), 7.49 – 7.40 (m, 2H), 7.31 – 7.02 (m, 7H), 6.76 – 6.69 (m, 1H), 6.52 – 6.41 (m, 2H), 5.09 – 5.01 (m, 2H), 4.04 (t, *J* = 8.3, 2H), 3.83 – 3.71 (m, 4H), 3.53 (s, 6H), 3.50 – 3.44 (m, 4H), 2.18 – 2.04 (m, 4H), 2.03 – 1.86 (m, 6H), 1.61 – 1.46 (m, 6H), 0.90 – 0.79 (m, 12H). MS (ESI; M+H) m/z = 965.



Example 145

methyl {(2S)-1-[(2S)-2-(4-{4-[5-(4-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-4-yl}phenyl)-1-{4-[(trifluoromethyl)sulfanyl]phenyl}-1H-pyrrol-2-yl]phenyl}-1H-imidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

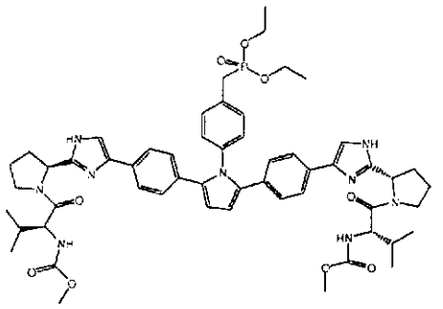
Example 138B and 4-(trifluoromethylthio)aniline were processed using the methods of Examples 139A and 138D to provide the title compound (19 mg). ^{1}H NMR (400 MHz, DMSO-D6) δ 12.18 – 11.65 (m, 2H), 7.73 – 7.63 (m, 2H), 7.60 – 7.48 (m, 4H), 7.45 – 7.39 (m, 2H), 7.31 – 7.15 (m, 4H), 7.06 – 6.92 (m, 4H), 6.58 – 6.46 (m, 2H), 5.08 – 5.00 (m, 2H), 4.03 (t, *J* = 8.4, 2H), 3.85 – 3.69 (m, 4H), 3.53 (s, 6H), 2.23 – 1.79 (m, 10H), 0.93 – 0.77 (m, 12H). MS (ESI; M+H) m/z = 981.



Example 146

methyl {(2S)-1-[(2S)-2-(4-{4-[5-(4-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-4-yl}phenyl)-1-(2-methyl-1,3-benzothiazol-5-yl)-1H-pyrrol-2-yl]phenyl}-1H-imidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

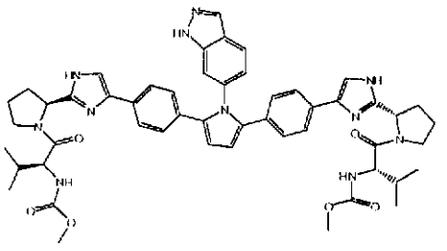
Example 138B and 2-methylbenzo[d]thiazol-5-amine dihydrochloride were processed using the methods of Examples 139A and 138D to provide the title compound (19 mg). ^{1}H NMR (400 MHz, DMSO-D6) δ 12.04 – 11.63 (m, 2H), 8.02 – 6.85 (m, 15H), 6.58 – 6.45 (m, 2H), 5.07 – 4.96 (m, 2H), 4.02 (t, *J* = 8.4, 2H), 3.86 – 3.67 (m, 4H), 3.53 (s, 6H), 2.75 (s, 3H), 2.21 – 1.78 (m, 10H), 0.93 – 0.76 (m, 12H). MS (ESI; M+H) m/z = 952.



Example 147

diethyl (4-{2,5-bis[4-(2-{(2S)-1-[N-(methoxycarbonyl)-L-valyl]pyrrolidin-2-yl}-1H-imidazol-4-yl)phenyl]-1H-pyrrol-1-yl}benzyl)phosphonate

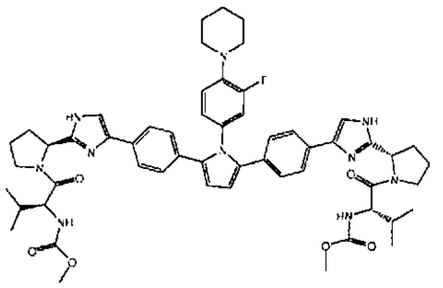
Example 138B and diethyl 4-aminobenzylphosphonate were processed using the methods of Examples 139A and 138D to provide the title compound. ^{1}H NMR (400 MHz, DMSO-D6) δ 12.19 – 11.63 (m, 2H), 7.56 – 7.44 (m, 4H), 7.42 – 7.34 (m, 2H), 7.32 – 7.10 (m, 4H), 7.10 – 6.91 (m, 6H), 6.53 – 6.40 (m, 2H), 5.10 – 4.98 (m, 2H), 4.03 (t, *J* = 8.4, 2H), 3.91 – 3.67 (m, 8H), 3.53 (s, 6H), 3.23 (d, *J* = 21.8, 2H), 2.22 – 1.80 (m, 10H), 1.15 – 1.04 (m, 6H), 0.92 – 0.77 (m, 12H). MS (ESI; M+H) m/z = 1031.



Example 148

methyl {(2S)-1-[(2S)-2-(4-{4-[1-(1H-indazol-6-yl)-5-(4-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-4-yl}phenyl)-1H-pyrrol-2-yl]phenyl}-1H-imidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

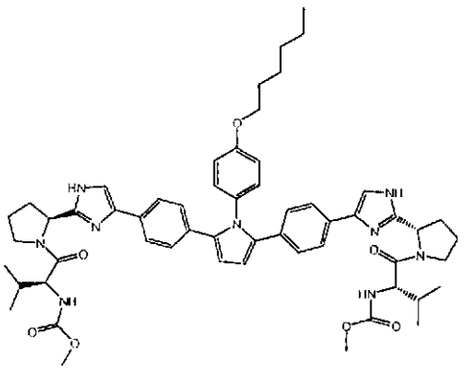
Example 138B and 1H-indazol-6-amine were processed using the methods of Examples 139A and 138D to provide the title compound (24 mg). ^{1}H NMR (400 MHz, DMSO-D6) δ 13.08 – 12.99 (m, 1H), 12.05 – 11.62 (m, 2H), 8.13 – 8.04 (m, 1H), 7.74 – 7.66 (m, 1H), 7.54 – 7.42 (m, 4H), 7.41 – 7.34 (m, 2H), 7.31 – 7.09 (m, 3H), 7.05 – 6.77 (m, 5H), 6.58 – 6.47 (m, 2H), 5.06 – 4.97 (m, 2H), 4.02 (t, *J* = 8.4, 2H), 3.83 – 3.66 (m, 4H), 3.53 (s, 6H), 2.20 – 1.78 (m, 10H), 0.89 – 0.76 (m, 12H). MS (ESI; M+H) m/z = 921.



Example 149

methyl [(2S)-1-{(2S)-2-[4-(4-{1-[3-fluoro-4-(piperidin-1-yl)phenyl]-5-(4-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-4-yl}phenyl)-1H-pyrrol-2-yl}phenyl)-1H-imidazol-2-yl]pyrrolidin-1-yl}-3-methyl-1-oxobutan-2-yl]carbamate

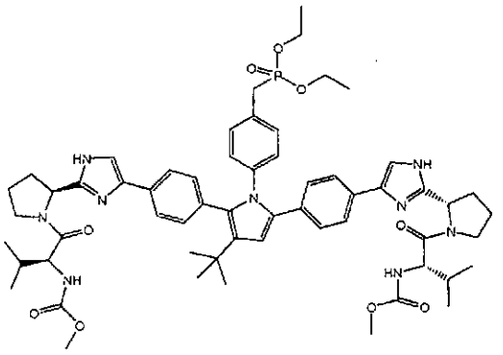
Example 138B and 3-fluoro-4-(piperidin-1-yl)aniline were processed using the methods of Examples 139A and 138D to provide the title compound. ^{1}H NMR (400 MHz, DMSO-D6) δ 12.15 – 11.69 (m, 2H), 7.62 – 7.49 (m, 4H), 7.48 – 7.39 (m, 2H), 7.32 – 7.15 (m, 2H), 7.12 – 6.77 (m, 7H), 6.52 – 6.42 (m, 2H), 5.08 – 4.99 (m, 2H), 4.04 (t, *J* = 8.4, 2H), 3.84 – 3.70 (m, 4H), 3.53 (s, 6H), 3.01 – 2.89 (m, 4H), 2.19 – 1.82 (m, 10H), 1.68 – 1.43 (m, 6H), 0.92 – 0.75 (m, 12H). MS (ESI; M+H) m/z = 982.



Example 150

methyl [(2S)-1-{(2S)-2-[4-(4-{1-[4-(hexyloxy)phenyl]-5-(4-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-4-yl}phenyl)-1H-pyrrol-2-yl}phenyl)-1H-imidazol-2-yl]pyrrolidin-1-yl}-3-methyl-1-oxobutan-2-yl]carbamate

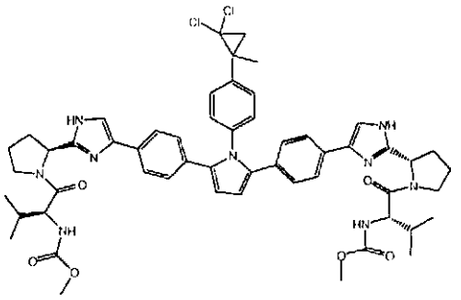
Example 138B and 4-(hexyloxy)aniline were processed using the methods of Examples 139A and 138D to provide the title compound (15 mg). ^{1}H NMR (400 MHz, DMSO-D6) δ 12.12 – 11.67 (m, 2H), 7.59 – 7.48 (m, 4H), 7.45 – 7.39 (m, 2H), 7.30 – 7.13 (m, 2H), 7.08 – 6.96 (m, 6H), 6.90 – 6.83 (m, 2H), 6.52 – 6.42 (m, 2H), 5.07 – 5.01 (m, 2H), 4.04 (t, *J* = 8.5, 2H), 3.92 (t, *J* = 6.4, 2H), 3.83 – 3.70 (m, 4H), 3.53 (s, 6H), 2.19 – 1.83 (m, 10H), 1.73 – 1.63 (m, 2H), 1.45 – 1.21 (m, 6H), 0.92 – 0.77 (m, 15H). MS (ESI; M+H) m/z = 981.



Example 151

diethyl (4-{3-tert-butyl-2,5-bis[4-(2-{(2S)-1-[N-(methoxycarbonyl)-L-valyl]pyrrolidin-2-yl}-1H-imidazol-4-yl)phenyl]-1H-pyrrol-1-yl}benzyl)phosphonate

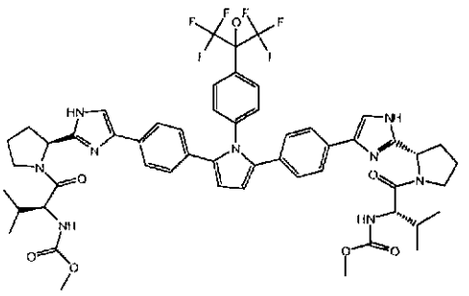
The title compound was formed as an additional product from Example 147. The mixture of products was purified by chromatography on silica gel eluted with a solvent gradient of 0-5% methanol in CH_2Cl_2 to provide the title compound. ^{1}H NMR (400 MHz, DMSO-D6) δ 11.68 (d, J = 13.5, 2H), 7.55 – 7.39 (m, 5H), 7.37 – 7.23 (m, 3H), 7.21 – 6.90 (m, 8H), 6.43 (s, 1H), 5.07 – 4.99 (m, 2H), 4.06 – 3.97 (m, 2H), 3.83 – 3.58 (m, 8H), 3.53 (s, 6H), 3.07 (d, J = 21.5, 2H), 2.20 – 1.81 (m, 10H), 1.15 (s, 9H), 0.98 (t, J = 7.0, 6H), 0.90 – 0.78 (m, 12H). MS (ESI; M+H) m/z = 1087.



Example 152

methyl [(2S)-1-{(2S)-2-[4-(4-{1-[4-(2,2-dichloro-1-methylcyclopropyl)phenyl]-5-(4-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-4-yl}phenyl)-1H-pyrrol-2-yl}phenyl)-1H-imidazol-2-yl]pyrrolidin-1-yl}-3-methyl-1-oxobutan-2-yl]carbamate

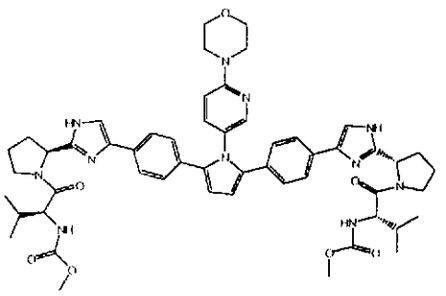
Example 138B and 4-(2,2-dichloro-1-methylcyclopropyl)aniline were processed using the methods of Examples 139A and 138D to provide the title compound (36 mg). ^{1}H NMR (400 MHz, DMSO-D6) δ 12.18 – 11.68 (m, 2H), 7.55 – 7.42 (m, 4H), 7.41 – 7.22 (m, 6H), 7.17 – 6.90 (m, 6H), 6.57 – 6.44 (m, 2H), 5.08 – 5.00 (m, 2H), 4.03 (t, J = 8.3, 2H), 3.86 – 3.69 (m, 4H), 3.53 (s, 6H), 2.22 (t, J = 8.5, 1H), 2.18 – 1.81 (m, 10H), 1.79 – 1.72 (m, 1H), 1.65 (s, 3H), 0.92 – 0.77 (m, 12H). MS (ESI; M+H) m/z = 1003.



Example 153

methyl [(2S)-1-{(2S)-2-[4-(4-{1-[4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)phenyl]-5-(4-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-4-yl}phenyl)-1H-pyrrol-2-yl}phenyl)-1H-imidazol-2-yl]pyrrolidin-1-yl}-3-methyl-1-oxobutan-2-yl]carbamate

Example 138B and 2-(4-aminophenyl)-1,1,1,3,3,3-hexafluoropropan-2-ol were processed using the methods of Examples 139A and 138D to provide the title compound (45 mg). ^{1}H NMR (400 MHz, DMSO-D6) δ 12.08 – 11.71 (m, 2H), 8.80 (s, 1H), 8.01 – 7.37 (m, 8H), 7.33 – 7.13 (m, 4H), 7.06 – 6.89 (m, 4H), 6.57 – 6.47 (m, 2H), 5.03 (d, *J* = 6.8, 2H), 4.03 (t, *J* = 8.4, 2H), 3.77 (d, *J* = 6.2, 4H), 3.53 (s, 6H), 2.21 – 1.80 (m, 10H), 0.92 – 0.76 (m, 12H). MS (ESI; M+H) m/z = 1047.



Example 154 methyl [(2S)-1-{(2S)-2-[4-(4-{5-(4-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-4-yl}phenyl)-1-[6-(morpholin-4-yl)pyridin-3-yl]-1H-pyrrol-2-yl}phenyl)-1H-imidazol-2-yl]pyrrolidin-1-yl}-3-methyl-1-oxobutan-2-yl]carbamate

Example 154A

4-(5-nitropyridin-2-yl)morpholine

The title compound was prepared using the methods from Example 144A substituting morpholine for piperidine to provide the title compound.

Example 154B

6-morpholinopyridin-3-amine

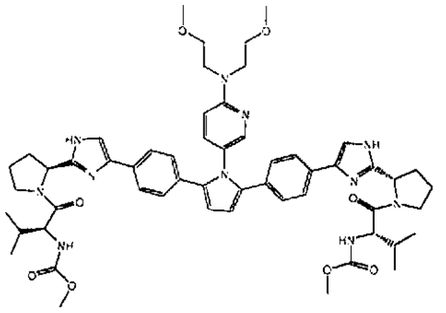
To a solution of the product from Example 154A (12.5, 59.5 mmol) in THF (150 mL) was added to Ra-Ni 2800, water slurry (12.5 g, 212 mmol) in a 500 mL SS pressure bottle. The mixture

was pressurized (H_2, 30 psi) and stirred for 2 hours at room temperature. The mixture was filtered and then concentrated under reduced pressure to provide the title compound.

Example 154C

methyl [(2S)-1-{(2S)-2-[4-(4-{5-(4-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-4-yl}phenyl)-1-[6-(morpholin-4-yl)pyridin-3-yl]-1H-pyrrol-2-yl}phenyl)-1H-imidazol-2-yl]pyrrolidin-1-yl}-3-methyl-1-oxobutan-2-yl]carbamate

Example 138B and Example 154B were processed using the methods of Examples 139A and 138D to provide the title compound. ^{1}H NMR (400 MHz, DMSO-D6) δ 12.16 – 11.69 (m, 2H), 7.89 – 7.80 (m, 1H), 7.63 – 7.50 (m, 4H), 7.50 – 7.40 (m, 2H), 7.39 – 7.02 (m, 7H), 6.80 – 6.71 (m, 1H), 6.52 – 6.41 (m, 2H), 5.10 – 5.00 (m, 2H), 4.04 (t, *J* = 8.7, 2H), 3.85 – 3.72 (m, 4H), 3.69 – 3.59 (m, 4H), 3.53 (s, 6H), 3.45 – 3.37 (m, 4H), 2.20 – 1.82 (m, 10H), 0.94 – 0.77 (m, 12H). MS (ESI; M+H) m/z = 967.



Example 155

methyl {(2S)-1-[(2S)-2-(4-{4-[1-{6-[bis(2-methoxyethyl)amino]pyridin-3-yl}-5-(4-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-4-yl}phenyl)-1H-pyrrol-2-yl]phenyl}-1H-imidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

Example 155A

N,N-bis(2-methoxyethyl)-5-nitropyridin-2-amine

The title compound was prepared using the methods from Example 144A substituting bis(2-methoxyethyl)amine for piperidine to provide the title compound.

Example 155B

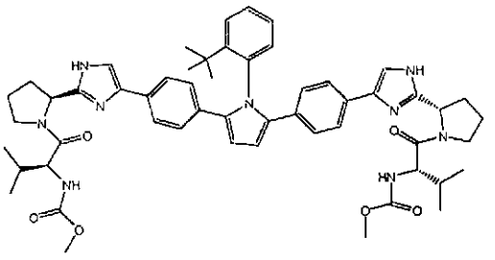
N2,N2-bis(2-methoxyethyl)pyridine-2,5-diamine

Example 155A was processed using the methods of Example 154B to provide the title compound.

Example 155C

methyl {(2S)-1-[(2S)-2-(4-{4-[1-{6-[bis(2-methoxyethyl)amino]pyridin-3-yl}-5-(4-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-4-yl}phenyl)-1H-pyrrol-2-yl]phenyl}-1H-imidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

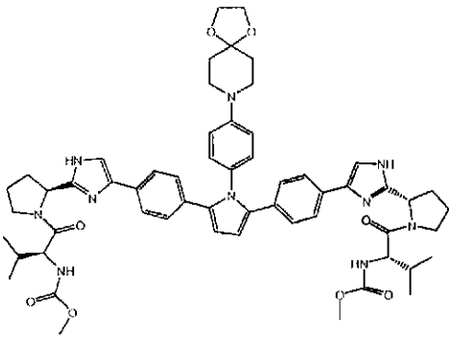
Example 138B and Example 155B were processed using the methods of Examples 139A and 138D to provide the title compound. ^{1}H NMR (400 MHz, DMSO-D6) δ 12.17 – 11.67 (m, 2H), 7.86 – 7.77 (m, 1H), 7.63 – 7.49 (m, 4H), 7.49 – 7.38 (m, 2H), 7.34 – 7.20 (m, 3H), 7.20 – 7.03 (m, 4H), 6.64 – 6.56 (m, 1H), 6.52 – 6.40 (m, 2H), 5.09 – 5.00 (m, 2H), 4.04 (t, *J* = 8.2, 2H), 3.84 – 3.69 (m, 4H), 3.65 – 3.57 (m, 4H), 3.53 (s, 6H), 3.47 – 3.40 (m, 4H), 3.21 (s, 6H), 2.20 – 1.84 (m, 10H), 0.84 (m, 12H). MS (ESI; M+H) m/z = 1013.



Example 156

methyl {(2S)-1-[(2S)-2-(4-{4-[1-(2-tert-butylphenyl)-5-(4-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-4-yl}phenyl)-1H-pyrrol-2-yl]phenyl}-1H-imidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

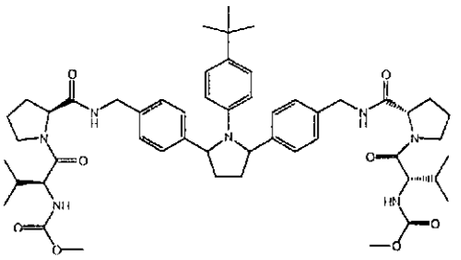
Example 138B and 2-tert-butylaniline were processed using the methods of Examples 139A and 138D to provide the title compound (10 mg). ^{1}H NMR (400 MHz, DMSO-D6) δ 12.07 – 11.64 (m, 2H), 7.61 – 7.11 (m, 12H), 7.06 – 6.93 (m, 4H), 6.65 – 6.49 (m, 2H), 5.08 – 4.97 (m, 2H), 4.04 (t, *J* = 7.2, 2H), 3.82 – 3.69 (m, 4H), 3.53 (s, 6H), 2.17 – 1.83 (m, 10H), 0.92 – 0.77 (m, 21H). MS (ESI; M+H) m/z = 937.



Example 157

methyl [(2S)-1-{(2S)-2-[4-(4-{1-[4-(1,4-dioxa-8-azaspiro[4.5]dec-8-yl)phenyl]-5-(4-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-4-yl}phenyl)-1H-pyrrol-2-yl}phenyl)-1H-imidazol-2-yl]pyrrolidin-1-yl}-3-methyl-1-oxobutan-2-yl]carbamate

Example 138B and 4-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)aniline were processed using the methods of Examples 139A and 138D to provide the title compound (156 mg). ^{1}H NMR (400 MHz, DMSO-D6) δ 12.06 – 11.65 (m, 2H), 7.59 – 7.46 (m, 4H), 7.44 – 7.36 (m, 2H), 7.30 – 7.13 (m, 2H), 7.09 – 6.96 (m, 4H), 6.90 (p, 4H), 6.53 – 6.39 (m, 2H), 5.08 – 4.98 (m, 2H), 4.04 (t, *J* = 8.4, 2H), 3.90 (s, 4H), 3.86 – 3.71 (m, 4H), 3.53 (s, 6H), 3.29 – 3.20 (m, 4H), 2.19 – 1.83 (m, 10H), 1.73 – 1.64 (m, 4H), 0.93 – 0.77 (m, 12H). MS (ESI; M+H) m/z = 1022.



Example 158

dimethyl ([1-(4-tert-butylphenyl)pyrrolidine-2,5-diyl]bis{benzene-4,1-diylmethanediylcarbamoyl(2S)pyrrolidine-2,1-diyl[(2S)-3-methyl-1-oxobutane-1,2-diyl]})biscarbamate

Example 158A

4,4'-(1-(4-tert-butylphenyl)pyrrolidine-2,5-diyl)dibenzonitrile

A solution of Example 42C (2.0 g, 3.9 mmol) and copper(I) cyanide (1.047 g, 11.69 mmol) in DMF (19 mL) was heated in a microwave for 7 hours at 160 °C. Afterwards the mixture was poured in water (700 mL) and then concentrated ammonium hydroxide (40 mL) was added and the solution extracted with EtOAc. The organic extract was dried, filtered, concentrated and the residue purified by flash chromatography (silica gel, EtOAc/hexanes) to afford 1.23 g (78%) of the title compound. MS (ESI) m/z 406 (M+H)+.

Example 158B

4,4'-(1-(4-tert-butylphenyl)pyrrolidine-2,5-diyl)bis(4,1-phenylene)dimethanamine

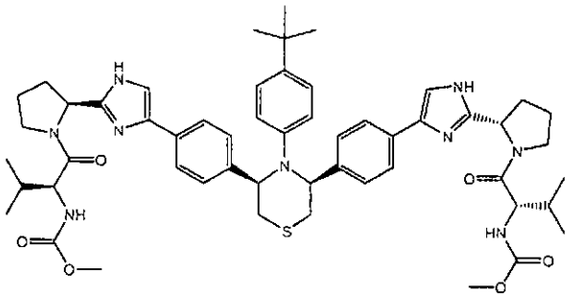
To a solution of Example 158A (0.63 g, 1.554 mmol) in THF (21 mL) was added lithium aluminum hydride (0.236 g, 6.21 mmol) then stirred at room temperature for 20 minutes and at 70 °C for 1 hour. The mixture was then cooled in an ice bath and a solution of saturated aqueous ammonium chloride was added followed by extraction with EtOAc and the organic layer extracted

with Rochelle's solution. The organic solution was then dried, filtered and concentrated to give the title compound. MS (ESI) m/z 414 (M+H)+.

Example 158C

dimethyl ([1-(4-tert-butylphenyl)pyrrolidine-2,5-diyl]bis{benzene-4,1-diylmethanediylcarbamoyl(2S)pyrrolidine-2,1-diyl[(2S)-3-methyl-1-oxobutane-1,2-diyl]})biscarbamate

The product from Example 158B (45 mg, 0.109 mmol), the product from Example 37B (62.2 mg, 0.228 mmol) and HATU (91 mg, 0.239 mmol) in DMSO (3 mL) was added Hunig's base (0.095 mL, 0.544 mmol), and the reaction mixture was stirred at room temperature for 1 hr. The reaction mixture was partitioned between water and dichloromethane, and the organic layer was dried over $MgSO_4$, filtered and concentrated. Purification by flash chromatography (silica gel, 0-10% methanol/dichloromethane) afforded 55 mg (55%) of the title compound as a mixture of stereoisomers. 1H NMR (400 MHz, DMSO-D6) δ ppm 8.11 (m, 2 H), 7.08 (s, 2 H), 6.95 (m, 8 H), 6.74 (d, *J*=8.8 Hz, 2 H), 5.97 (d, *J*=8.7 Hz, 2 H), 5.01 (m, 2H), 4.15 (m, 4H), 4.05 (m, 4 H), 3.80 (m, 2 H), 3.31 (s, 6 H), 2.40 (m, 2 H), 1.90 (m, 2 H), 1.85 (m, 4 H), 1.80 (m, 4 H), 0.95 (s, 9 H), 0.70 (m, 2H), 0.65 (m, 12 H); MS (ESI) m/z 923 (M+H)+.



Example 159

methyl {(2S)-1-[(2S)-2-(4-{4-[(3S,5R)-4-(4-tert-butylphenyl)-5-(4-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-4-yl}phenyl)thiomorpholin-3-yl]phenyl}-1H-imidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

Example 159A

2,2'-thiobis(1-(4-bromophenyl)ethanone)

A solution of 2-bromo-1-(4-bromophenyl)ethanone (27.8 g, 100 mmol) was dissolved in acetone, the solution was cooled in an ice bath then sodium sulfide nonahydrate (12.01 g, 50 mmol) dissolved in water (100 mL) was added dropwise over 45 minutes time. The resultant solution was stirred an additional 2 hours at room temperature, the solid formed in the reaction was collected and

then washed with water then ethanol and dried in a vacuum oven to provide 18.5 g (43%) of the title compound.

Example 159B

2,2'-thiobis(1-(4-bromophenyl)ethanol)

To a solution of Example 159A (5.0 g, 11.68 mmol) in ethanol (78 mL) was added sodium borohydride (0.972 g, 25.7 mmol) portionwise and the mixture was stirred at room temperature for 20 minutes. Afterwards the solution was concentrated, then a solution of 1N aqueous hydrochloric acid (100 mL) was added and extracted with EtOAc. The organic extract was dried, filtered and concentrated to 5.05 g (100%) of a colorless solid as the title compound.

Example 159C

N,N'-(2,2'-thiobis(1-(4-bromophenyl)ethane-2,1-diyl))bis(4-tert-butylaniline)

To a solution of Example 159B (5.05 g, 11.68 mmol) in THF (145 mL) and dichloromethane (145 mL) was added triethylamine (4.86 mL, 35.1 mmol) and the mixture cooled in an ice bath. To this solution was added methanesulfonyl chloride (2.276 mL, 29.2 mmol) dropwise followed by stirring at 0 °C for an additional 30 minutes followed by concentration at room temperature to a residue. The resultant residue was dissolved in DMF (39 mL) followed by the addition of 4-tert-butylaniline (18.62 mL, 117 mmol) and the mixture heated at 50 °C for 5 hours. Afterwards 1N aqueous hydrochloric acid was added followed by extraction with EtOAc. The organic extract was dried, filtered and concentrated. Purification by flash chromatography (silica gel, 0-30% EtOAc/hexanes) afforded 2.67g (42%) of the title compound.

Example 159D

3,5-bis(4-bromophenyl)-4-(4-tert-butylphenyl)thiomorpholine

To a solution of Example 159C (350 mg, 0.504 mmol) in toluene (5 mL) was added silica gel (1.0 g) that had been dehydrated by heating at 180°C in a vacuum oven for 3 hours, and trifluoromethanesulfonic acid (0.045 mL, 0.504 mmol) and heated at 100°C for 3 hours. After cooling to ambient temperature, dichloromethane was added and the silica gel was removed by filtration and the solution extracted with half-saturated aqueous sodium bicarbonate solution. The organic extract was dried, filtered and concentrated to afford 220 mg (80%) of the title compound as a mixture of isomers. MS (ESI) m/z 546 (M+H)+.

Example 159E

4-(4-tert-butylphenyl)-3,5-bis(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)thiomorpholine

The product of Example 159D (200 mg, 0.367 mmol) was processed using the method described in Example 42D to provide 105 mg (45%) of the title compound as a mixture of isomers. MS (ESI) m/z 640 (M+H)+.

Example 159F

(2S,2'S)-tert-butyl 2,2'-(4,4'-(4,4'-(4-(4-tert-butylphenyl)thiomorpholine-3,5-diyl)bis(4,1-phenylene))bis(1H-imidazole-4,2-diyl))dipyrrolidine-1-carboxylate

The product of Example 159E (190 mg, 0.297 mmol) and the product from Example 26D (282 mg, 0.891 mmol) were processed using the method described in Example 42E to provide 110 mg (43%) of the title compound as a mixture of isomers. MS (ESI) m/z 859 (M+H)+.

Example 159G

4-(4-tert-butylphenyl)-3,5-bis(4-(2-((S)-pyrrolidin-2-yl)-1H-imidazol-4-yl)phenyl)thiomorpholine

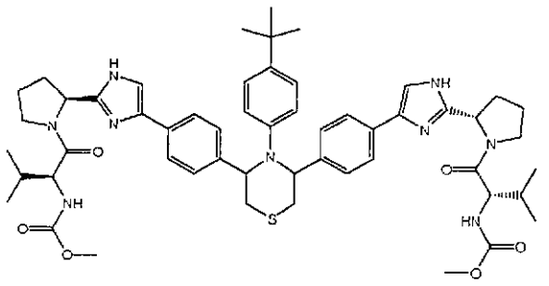
To the product of Example 159F (110 mg, 0.128 mmol) was added dimethoxyethane (5 mL) and a solution of 4N hydrochloric acid in dioxane (5 mL) and the resultant solution stirred at room temperature for 1 hr. The solvent was then removed under vacuum and the resultant residue was diluted with acetonitrile and water (0.1% TFA) and purified by reversed phase chromatography (C18), eluting with 10-100% acetonitrile in water (0.1% TFA) to afford 12 mg (14%) of the title compound as a mixture of stereoisomers. MS (ESI) m/z 658 (M+H)+.

Example 159H

methyl {(2S)-1-[(2S)-2-(4-{4-[(3S,5R)-4-(4-tert-butylphenyl)-5-(4-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-4-yl}phenyl)thiomorpholin-3-yl]phenyl}-1H-imidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

The product from Example 159G (10 mg, 0.015 mmol), (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (5.86 mg, 0.033 mmol) and HATU (12.71 mg, 0.033 mmol) in DMSO (0.5 mL) was added Hunig's base (0.013 mL, 0.076 mmol), and the reaction mixture was stirred at room temperature for 1.5 hr. The reaction mixture was partitioned between water and dichloromethane, and the organic layer was dried over $MgSO_4$, filtered and concentrated in vacuo. The crude product was redissolved in methanol (5 mL) then added potassium carbonate (50 mg) then stirred at room temperature for 20 minutes, the solids removed by filtration, the filtrate concentrated and purified by chromatography (silica gel, 0-10% methanol/dichloromethane) to afford 7 mg (47%) of the title compound. 1H NMR (400 MHz, DMSO-D6) δ ppm 11.65 (m, 2 H), 7.47 (m, 2 H), 7.32 (m, 4 H), 7.23 (m, 4H), 6.85 (m, 4 H), 5.02 (m, 2 H), 4.38 (m, 2H), 4.02 (m, 2 H), 3.75 (m, 4 H), 3.52 (s, 6 H),

3.10 (m, 2 H), 2.66 (m, 2 H), 2.08 (m, 4 H), 1.91 (m, 4 H), 0.97 (s, 9 H), 0.82 (m, 12 H); MS (ESI) m/z 973 (M+H)+.



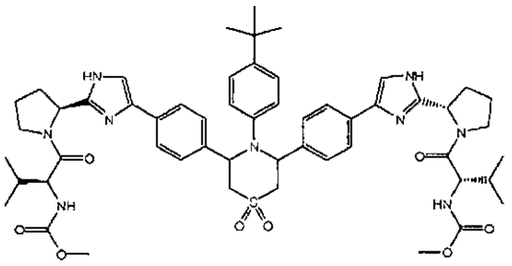
Example 160

methyl {(2*S*)-1-[(2*S*)-2-(4-{4-[(3*S*,5*S*)-4-(4-*tert*-butylphenyl)-5-(4-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1*H*-imidazol-4-yl}phenyl)thiomorpholin-3-yl]phenyl}-1*H*-imidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

and

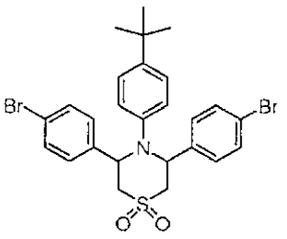
methyl {(2*S*)-1-[(2*S*)-2-(4-{4-[(3*R*,5*R*)-4-(4-*tert*-butylphenyl)-5-(4-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1*H*-imidazol-4-yl}phenyl)thiomorpholin-3-yl]phenyl}-1*H*-imidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

The product from Example 159E (100 mg, 0.156 mmol), the product from Example 126G (146 mg, 0.391 mmol), and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) dichloromethane adduct (25.5 mg, 0.031 mmol) in a mixture of toluene (3 mL), ethanol (3 mL) and a 1N aq. sodium bicarbonate solution (0.469 mL, 4.69 mmol) and bubbled nitrogen gas through the solution for 10 min, then heated at 80 °C for 18 h. Solution was cooled to room temperature and water (20 mL) added then extracted with dichloromethane (50 mL), then dried, concentrated and the residue purified by reversed phase chromatography (C18), eluting with 10-100% acetonitrile in water (0.1% TFA) to afford 8.5 mg (6%) of the title compound as a mixture of stereoisomers. 1H NMR (free base) (400 MHz, DMSO-D6) δ ppm 11.70 (bs, 2 H), 7.64 (m, 4 H), 7.45 (m, 2 H), 7.37 (m, 4H), 7.28 (m, 2 H), 7.01 (m, 2 H), 6.46 (d, *J*=8.7 Hz, 2 H), 5.38 (m, 2 H), 5.07 (m, 2H), 4.03 (m, 2 H), 3.52 (s, 6 H), 3.10 (m, 2 H), 2.12 (m, 4 H), 1.91 (m, 4 H), 1.12 (s, 9 H), 0.86 (m, 12 H); MS (ESI) m/z 973 (M+H)+.



Example 161

methyl {(2S)-1-[(2S)-2-(4-{4-[4-(4-tert-butylphenyl)-5-(4-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-4-yl}phenyl)-1,1-dioxidothiomorpholin-3-yl]phenyl}-1H-imidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate



Example 161A

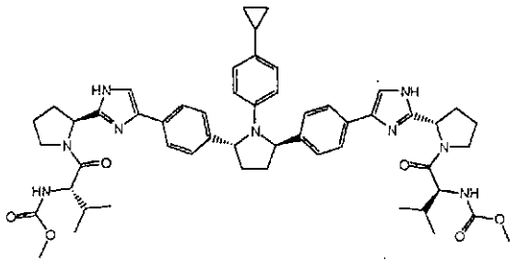
3,5-bis(4-bromophenyl)-4-(4-*tert*-butylphenyl)thiomorpholine 1,1-dioxide (ACD v12)

A solution of Example 159D (850 mg, 1.56 mmol) in mixture of acetone (15 mL), water (5 mL) and THF (5 mL) was added a solution of osmium tetroxide (2.5% in tert-butanol, 0.587 mL, 0.047 mmol) and the mixture was stirred at room temperature for 1.5 hr. The solution was then diluted with water and extracted with EtOAc, the organic extract dried, filtered and concentrated to afford 900 mg (100%) of the title compound. MS (ESI) m/z 578 (M+H)+.

Example 161B

methyl {(2S)-1-[(2S)-2-(4-{4-[4-(4-tert-butylphenyl)-5-(4-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-4-yl}phenyl)-1,1-dioxidothiomorpholin-3-yl]phenyl}-1H-imidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

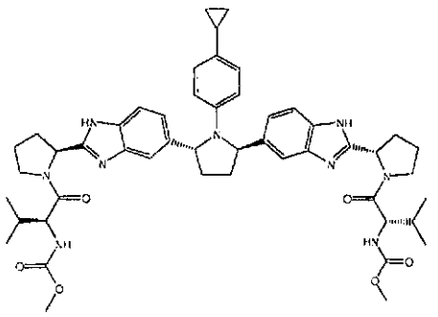
Example 161A was processed using sequentially the methods of Examples 42D, 42E, 159G, and 159H to provide the title compound as a mixture of trans stereoisomers. ^{1}H NMR (400 MHz, DMSO-D6) δ ppm 11.73 (bs, 2 H), 7.64 (m, 4 H), 7.55 (m, 2 H), 7.44 (m, 4H), 7.24 (m, 2 H), 7.04 (m, 2 H), 6.60 (m, 2 H), 5.48 (m, 2 H), 5.06 (m, 2H), 4.04 (m, 2 H), 3.78 (m, 6 H), 3.52 (s, 6 H), 2.11 (m, 4 H), 1.92 (m, 6 H), 1.13 (s, 9 H), 0.92 (m, 12 H); MS (ESI) m/z 1005 (M+H)+.



Example 162

methyl {(2S)-1-[(2S)-2-(4-{4-[(2R,5R)-1-(4-cyclopropylphenyl)-5-(4-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-4-yl}phenyl)pyrrolidin-2-yl]phenyl}-1H-imidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

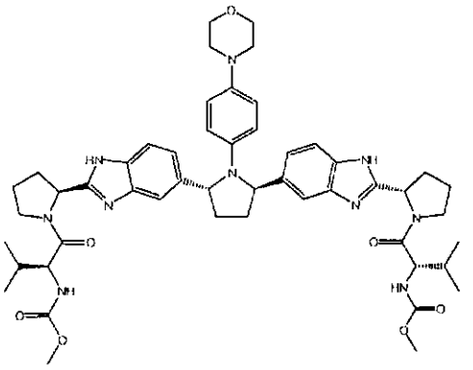
The product from Example 95B was purified by chiral chromatography on a Chiralpak IB column eluting with a mixture of hexane/THF/methanol (85/10/5). The title compound was the first of the 2 diastereomers to elute. 1H NMR (400 MHz, DMSO-D6) δ ppm 0.33 - 0.43 (m, 2 H) 0.65 - 0.72 (m, 2 H) 0.79 - 0.91 (m, 12 H) 1.56 - 1.64 (m, 1 H) 1.66 - 1.72 (m, 2 H) 1.84 - 2.03 (m, 6 H) 2.06 - 2.19 (m, 4 H) 3.53 (s, 6 H) 3.73 - 3.84 (m, 4 H) 4.04 (t, J=8.35 Hz, 2 H) 5.06 (dd, J=6.89, 3.09 Hz, 2 H) 5.14 - 5.23 (m, 2 H) 6.19 (d, J=8.67 Hz, 2 H) 6.60 - 6.67 (m, 2 H) 7.09 - 7.31 (m, 6 H) 7.34 - 7.68 (m, 6 H) 11.62 - 12.11 (m, 2 H); MS (ESI+) m/z 924.6 (M+H).



Example 163

methyl {(2S)-1-[(2S)-2-{5-[(2R,5R)-1-(4-cyclopropylphenyl)-5-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-benzimidazol-5-yl}pyrrolidin-2-yl]-1H-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

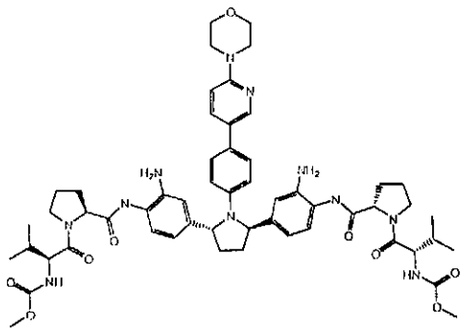
Example 109C and 4-cyclopropylaniline were processed using sequentially the methods of Examples 113A (cyclization reaction conducted at room temperature overnight), 113B, 113C, 28I (reaction conducted at 50 °C for 3 hours), 28J, and 66E to provide the title compound (122 mg) as a solid. 1H NMR (400 MHz, DMSO-D6) δ ppm 0.32 - 0.39 (m, 2 H) 0.63-0.69 (m, 2 H) 0.77 - 0.90 (m, 12 H) 1.53 - 1.61 (m, 1 H) 1.66 - 1.74 (m, 2 H) 1.86 - 2.04 (m, 8 H) 2.14 - 2.23 (m, 4 H) 3.54 (s, 6 H) 3.78 - 3.87 (m, 4 H) 4.00 - 4.07 (m, 2 H) 5.10 - 5.18 (m, 2 H) 5.31 - 5.39 (m, 2 H) 6.22 (d, J=8.67 Hz, 2 H) 6.57 - 6.65 (m, 2 H) 7.00 - 7.07 (m, 2 H) 7.16 - 7.32 (m, 4 H) 7.36 (d, J=8.13 Hz, 1 H) 7.44 (d, J=8.24 Hz, 1 H) 11.97 - 12.27 (m, 2 H); MS (ESI+) m/z 872.5 (M+H)+.



Example 164

methyl {(2S)-1-[(2S)-2-(5-{(2R,5R)-5-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-benzimidazol-5-yl}-1-[4-(morpholin-4-yl)phenyl]pyrrolidin-2-yl}-1H-benzimidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

Example 109C and 4-morpholinoaniline were processed using sequentially the methods of Examples 113A (cyclization reaction conducted at room temperature overnight), 113B, 113C, 28I (reaction conducted at 50 °C for 2 hours), 28J, and 28K to provide the title compound (100 mg) as a solid. 1H NMR (400 MHz, DMSO-D6) δ ppm 0.76 - 0.91 (m, 12 H) 1.66 - 1.72 (m, 2 H) 1.87 - 2.03 (m, 8 H) 2.15 - 2.22 (m, 4 H) 2.72 - 2.78 (m, 4 H) 3.53 (s, 6 H) 3.57 - 3.62 (m, 4 H) 3.78 - 3.86 (m, 4 H) 4.00 - 4.12 (m, 2 H) 5.09 - 5.18 (m, 2 H) 5.30 - 5.37 (m, 2 H) 6.25 (d, J=8.78 Hz, 2 H) 6.52 - 6.59 (m, 2 H) 7.05 (t, J=7.54 Hz, 2 H) 7.18 - 7.32 (m, 4 H) 7.36 (d, J=8.13 Hz, 1 H) 7.44 (d, J=8.24 Hz, 1 H) 11.91 - 12.28 (m, 2 H); MS (ESI+) m/z 917.5 (M+H)+.



Example 165

dimethyl ([(2R,5R)-1-{4-[6-(morpholin-4-yl)pyridin-3-yl]phenyl}pyrrolidine-2,5-diyl]bis{(2-aminobenzene-4,1-diyl)carbamoyl(2S)pyrrolidine-2,1-diyl[(2S)-3-methyl-1-oxobutane-1,2-diyl]})biscarbamate

Example 165A

(2R,5R)-2,5-bis(4-chloro-3-nitrophenyl)-1-(4-iodophenyl)pyrrolidine

Example 109C (3.34 g, 6.0 mmol) and 4-iodoaniline (7.88 g, 36.0 mmol) were processed using the method of Example 113A with the reaction allowed to proceed for 4 days at room temperature to provide the title compound (2.01 g, 57%) as a yellow solid.

Example 165B

4-(5-(4-((2R,5R)-2,5-bis(4-chloro-3-nitrophenyl)pyrrolidin-1-yl)phenyl)pyridin-2-yl)morpholine

The product from 165A (1.869 g, 3.2 mmol), 4-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)morpholine (0.929 g, 3.20 mmol), potassium phosphate (1.359 g, 6.40 mmol), tris(dibenzylideneacetone)dipalladium(0) (0.029 g, 0.032 mmol) and 1,3,5,7-tetramethyl-6-phenyl-2,4,8-trioxa-6-phosphaadamante (0.028 g, 0.096 mmol) were combined in THF (18 mL)/water (6 mL). The mixture was purged with nitrogen for 15 minutes and stirred at room temperature for 24 hours. The reaction mixture was partitioned between ethyl acetate and saturated sodium bicarbonate. The organic layer was washed with brine, dried with sodium sulfate, filtered and evaporated. The residue was purified by chromatography on silica gel eluting with ethyl acetate/hexane (20% to 40%) to give the title compound (1.01 g, 51%) as a solid.

Example 165C

dimethyl (2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-((2R,5R)-1-(4-(6-morpholinopyridin-3-yl)phenyl)pyrrolidine-2,5-diyl)bis(2-nitro-4,1-phenylene))bis(azanediyl)bis(oxomethylene)bis(pyrrolidine-2,1-diyl))bis(3-methyl-1-oxobutane-2,1-diyl)dicarbamate

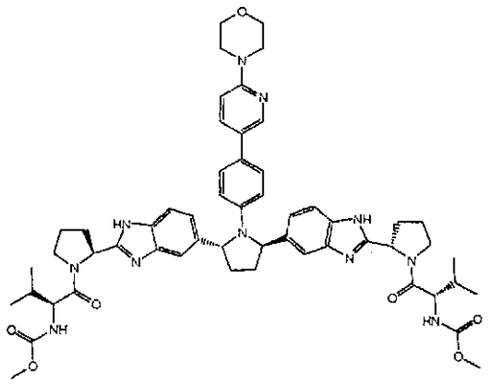
The product from Example 165B (683 mg, 1.10 mmol), the product from Example 116C (895 mg, 3.30 mmol), cesium carbonate (1004 mg, 3.08 mmol), tris(dibenzylideneacetone)dipalladium(0) (60.4 mg, 0.066 mmol) and (9,9-dimethyl-9H-xanthene-4,5-diyl)bis(diphenylphosphine) (115 mg, 0.198 mmol) were combined in dioxane (15 mL). The mixture was purged with nitrogen for 15 minutes and stirred at 100 °C for 3 hours. The mixture was partitioned between ethyl acetate and saturated sodium bicarbonate. The organic layer was washed with brine, dried with sodium sulfate, filtered and evaporated. The residue was purified by chromatography on silica gel eluting with methanol/dichloromethane (1% to 3%) to give the title compound (631 mg, 53%) as a solid.

Example 165D

dimethyl ([(2R,5R)-1-{4-[6-(morpholin-4-yl)pyridin-3-yl]phenyl}pyrrolidine-2,5-diyl]bis{(2-aminobenzene-4,1-diyl)carbamoyl(2S)pyrrolidine-2,1-diyl[(2S)-3-methyl-1-oxobutane-1,2-diyl]})biscarbamate

The product from Example 165C (628 mg, 0.576 mmol) and Ra-Ni 2800 (628 mg) were combined in THF (40 mL). The mixture was hydrogenated at 30psi for 4 hours. The mixture was

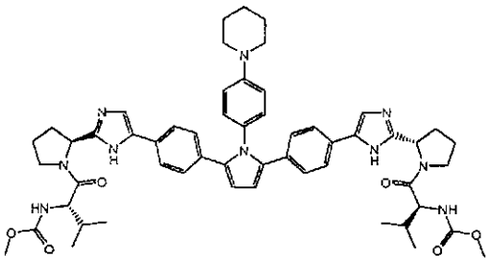
filtered and the filtrate was evaporated. The residue was purified by chromatography on silica gel eluting with methanol/dichloromethane (2% to 5%) to give the title compound (590 g, 99%) as a solid. 1H NMR (400 MHz, DMSO-D6) δ ppm 0.88 (d, J=6.61 Hz, 6 H) 0.91 (d, J=6.72 Hz, 6 H) 1.62 - 1.69 (m, 2 H) 1.82 - 2.04 (m, 8 H) 2.10 - 2.20 (m, 2 H) 2.52 - 2.56 (m, 2 H) 3.37 - 3.41 (m, 4 H) 3.52 (s, 6 H) 3.56 - 3.62 (m, 2 H) 3.65 - 3.70 (m, 4 H) 3.78 - 3.85 (m, 2 H) 3.98 - 4.07 (m, 2 H) 4.36 - 4.44 (m, 2 H) 4.87 (s, 4 H) 5.06 (d, J=6.32 Hz, 2 H) 6.36 (d, J=8.78 Hz, 2 H) 6.42 (d, J=8.02 Hz, 2 H) 6.57 (d, J=1.19 Hz, 2 H) 6.78 (d, J=8.89 Hz, 1 H) 6.96 (d, J=8.02 Hz, 2 H) 7.23 (d, J=8.78 Hz, 2 H) 7.36 (d, J=8.24 Hz, 2 H) 7.68 (dd, J=8.78, 2.49 Hz, 1 H) 8.27 (d, J=2.49 Hz, 1 H) 9.24 (s, 2 H); MS (ESI+) m/z 1030.6 (M+H)+.



Example 166

methyl {(2S)-1-[(2S)-2-{5-[(2R,5R)-5-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-benzimidazol-5-yl}-1-{4-[6-(morpholin-4-yl)pyridin-3-yl]phenyl}pyrrolidin-2-yl]-1H-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

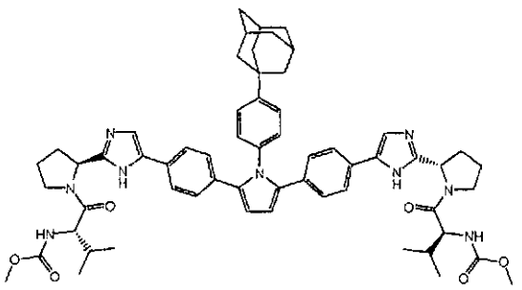
The product from Example 165D (520 g, 0.505 mmol) and acetic acid (0.087 mL, 1.514 mmol) were combined in toluene (10 mL). The mixture was stirred at 50 °C for 4 hours. The solvent was evaporated and the residue was purified by chromatography on silica gel eluting with methanol/dichloromethane (2% to 5%) to give the title compound (309 mg, 62%) as a solid. 1H NMR (400 MHz, DMSO-D6) δ ppm 0.73 - 0.90 (m, 12 H) 1.70 - 1.76 (m, 2 H) 1.84 - 2.05 (m, 8 H) 2.14 - 2.21 (m, 2 H) 2.55 - 2.60 (m, 2 H) 3.34 - 3.39 (m, 4 H) 3.53 (s, 6 H) 3.62 - 3.69 (m, 4 H) 3.75 - 3.87 (m, 4 H) 4.02 - 4.08 (m, 2 H) 5.06 - 5.17 (m, 2 H) 5.40 - 5.47 (m, 2 H) 6.40 (d, J=8.67 Hz, 2 H) 6.75 (d, J=8.89 Hz, 1 H) 7.02 - 7.20 (m, 4 H) 7.25 (s, 1 H) 7.28 (d, J=8.46 Hz, 2 H) 7.34 (s, 1 H) 7.39 (d, J=8.13 Hz, 1 H) 7.47 (d, J=8.24 Hz, 1 H) 7.60 (d, J=8.60 Hz,1 H) 8.21 (s, 1 H) 11.96 - 12.11 (m, 2 H); MS (ESI+) m/z 994.5 (M+H)+.



Example 167

methyl [(2S)-1-{(2S)-2-[5-(4-{5-(4-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-5-yl}phenyl)-1-[4-(piperidin-1-yl)phenyl]-1H-pyrrol-2-yl}phenyl)-1H-imidazol-2-yl]pyrrolidin-1-yl}-3-methyl-1-oxobutan-2-yl]carbamate

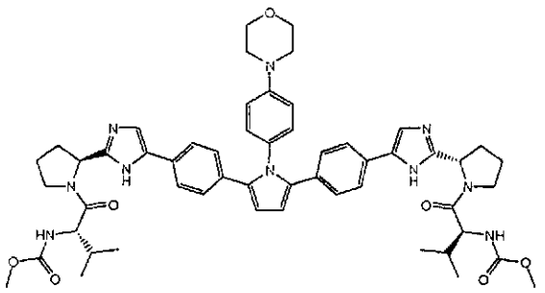
Example 26E and 4-piperidinoaniline (Maybridge) were processed using sequentially the methods of Examples 26F, 26G, 74C, 19D, and 74E to provide the title compound (106 mg). ^{1}H NMR (400 MHz, DMSO-D6) δ 0.83 (d, J=6.73 Hz, 6 H) 0.87 (d, J=6.73 Hz, 6 H) 1.50 – 1.62 (m, 6 H) 1.90 – 2.15 (m, 10 H) 3.13 (m, 4 H) 3.53 (s, 6 H) 3.77 (m, 4 H) 4.04 (m, 2 H) 5.04 (m, 2 H) 6.47 (m, 2 H) 6.80 – 7.35 (m, 10 H) 7.42 (m, 2 H) 7.53 (m, 4 H) 11.73 (s, 2 H).



Example 168

methyl [(2S)-1-{(2S)-2-[5-(4-{5-(4-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-5-yl}phenyl)-1-[4-(tricyclo[3.3.1.1~3,7~]dec-1-yl)phenyl]-1H-pyrrol-2-yl}phenyl)-1H-imidazol-2-yl]pyrrolidin-1-yl}-3-methyl-1-oxobutan-2-yl]carbamate

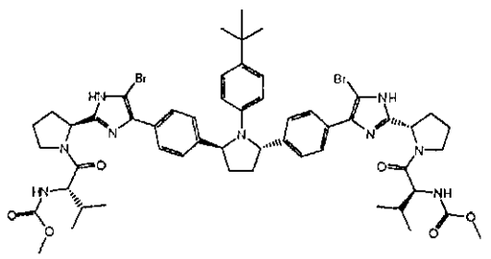
Example 26E and 4-(1-adamantanyl)aniline hydrochloride (Enamine) were processed using sequentially the methods of Examples 26F, 26G, 74C, 19D, and 74E to provide the title compound (320 mg). ^{1}H NMR (400 MHz, methanol-D4) δ 0.91 (m, 12 H) 1.75 – 2.35 (m, 25 H) 3.64 (s, 6 H) 3.84 (m, 2 H) 4.00 (m, 2 H) 4.20 (m, 2 H) 5.12 (m, 2 H) 6.48 (s, 2 H) 7.02 (m, 6 H) 7.31 (m, 4 H) 7.46 (m, 6 H) 7.72 (d, J=8.13 Hz, 1 H) 7.82 (d, J=8.24 Hz, 1 H).



Example 169

methyl [(2S)-1-{(2S)-2-[5-(4-{5-(4-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-5-yl}phenyl)-1-[4-(morpholin-4-yl)phenyl]-1H-pyrrol-2-yl}phenyl)-1H-imidazol-2-yl]pyrrolidin-1-yl}-3-methyl-1-oxobutan-2-yl]carbamate

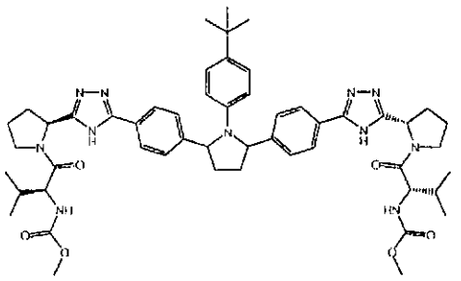
Example 26E and 4-morpholinoaniline (Aldrich) were processed using sequentially the methods of Examples 26F, 26G, 74C, 19D, and 74E to provide the title compound (133 mg). ^{1}H NMR (400 MHz, DMSO-D6) δ 0.83 (d, J=6.83 Hz, 6 H) 0.87 (d, J=6.61 Hz, 6 H) 1.88 - 2.17 (m, 10 H) 3.11 (m, 4 H) 3.53 (s, 6 H) 3.70 – 3.80 (m, 8 H) 3.97 - 4.08 (m, 2 H) 5.04 (m, 2 H) 6.41 - 6.51 (m, 2 H) 6.84 – 7.35 (m, 10 H) 6.93 - 7.02 (m, 6 H) 11.71 – 12.03 (m, 2 H).



Example 170

methyl {(2S)-1-[(2S)-2-(5-bromo-4-{4-[(2S,5S)-5-(4-{5-bromo-2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-4-yl}phenyl)-1-(4-tert-butylphenyl)pyrrolidin-2-yl]phenyl}-1H-imidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

To a solution of Example 44 (0.100 g, 0.106 mmol) in CH_2Cl_2 (5 mL) at rt was added N-bromosuccinimide (0.019 mL, 0.223 mmol). After 15 min, the reaction was washed with saturated $NaHCO_3$ and concentrated. Residue purified by chromatography (1% gradient elution from 0% to 4% MeOH-CH_2Cl_2; 12 g column) to provide 60 mg (51%) of the title compound as a light yellow solid. ^{1}H NMR (400 MHz, DMSO-D6) δ 0.8 (d, J=6.61 Hz, 6 H) 0.87 (d, J=6.56 Hz, 6 H) 1.11 (s, 9 H) 1.72 – 1.75 (m, 2 H) 1.87 - 1.98 (m, 7 H) 2.10 – 2.15 (m, 5 H) 3.53 (s, 6 H) 3.70 -3.75 (m, 4 H) 4.00 = 4.06 (m, 2 H) 4.96 – 5.00 (m, 2 H) 5.27 – 5.35 (m, 2 H) 6.24 (d, J=8.78 Hz, 2 H) 6.97 (d, J=8.78 Hz, 2 H) 7.24 - 7.35 (m, 6 H) 7.60 – 7.65 (m, 4 H) 12.41 (m, 2 H).



Example 171

methyl {(2S)-1-[(2S)-2-(5-{4-[(2S,5S)-1-(4-tert-butylphenyl)-5-(4-{5-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-4H-1,2,4-triazol-3-yl}phenyl)pyrrolidin-2-yl]phenyl}-4H-1,2,4-triazol-3-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

and

methyl {(2S)-1-[(2S)-2-(5-{4-[(2R,5R)-1-(4-tert-butylphenyl)-5-(4-{5-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-4H-1,2,4-triazol-3-yl}phenyl)pyrrolidin-2-yl]phenyl}-4H-1,2,4-triazol-3-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

Example 171A

Dimethyl 4,4'-(1-(4-tert-butylphenyl)pyrrolidine-2,5-diyl)dibenzoate

A mixture of Example 42C (0.5 g, 0.974 mmol), Et_3N (0.407 mL, 2.92 mmol) and [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) (71.3 mg, 0.097 mmol) in methanol (20 mL) was subjected to an atmosphere of carbon monoxide gas (60 psi) for 24 hours at 100 °C. The mixture was filtered through celite and concentrated. Purification by chromatography (silica gel, 25% EtOAc in hexanes) afforded 396 mg (86%) of the title compound. MS (ESI) m/z 472 $(M+H)^+$.

Example 171B

4,4'-(1-(4-tert-butylphenyl)pyrrolidine-2,5-diyl)dibenzohydrazide

A mixture of Example 171A (350 mg, 0.742 mmol) and Hydrazine (0.140 µL, 4.45 mmol) in methanol (10 mL) was refluxed for 72 hours. The mixture was concentrated to afford 350 mg of the title compound as a mixture of stereoisomers. MS (ESI) m/z 472 $(M+H)^+$.

Example 171C

(2S,2'S)-tert-butyl 2,2'-(5,5'-(4,4'-(1-(4-tert-butylphenyl)pyrrolidine-2,5-diyl)bis(4,1-phenylene))bis(4H-1,2,4-triazole-5,3-diyl))dipyrrolidine-1-carboxylate

A mixture of Example 171B (105 mg, 0.223 mmol), (S)-1-N-Boc-2-cyano-pyrrolidine (175 mg, 0.891 mmol), and K_2CO_3 (9.23 mg, 0.067 mmol) in n-butanol (0.5 mL) was heated to 150 °C for

90 minutes in a microwave. The mixture was diluted with EtOAc and then washed with H_2O and Brine. The organic was then dried ($MgSO_4$), filtered and concentrated. Purification by chromatography (silica gel, 90% EtOAc in Hexanes) afforded 59 mg (32%) of the title compound as a mixture of stereoisomers. MS (ESI) m/z 829 $(M+H)^+$.

Example 171D

(S)-5,5'-(4,4'-(1-(4-tert-butylphenyl)pyrrolidine-2,5-diyl)bis(4,1-phenylene))bis(3-((S)-pyrrolidin-2-yl)-4H-1,2,4-triazole) pentahydrochloride

A mixture of Example 171C (59 mg, 0.071 mmol) in 4M HCl/Dioxane (2 mL) was allowed to stir for one hour. The mixture was concentrated to afford 58 mg (100%) of the title compound as a mixture of stereoisomers. MS (ESI) m/z 628 $(M+H)^+$.

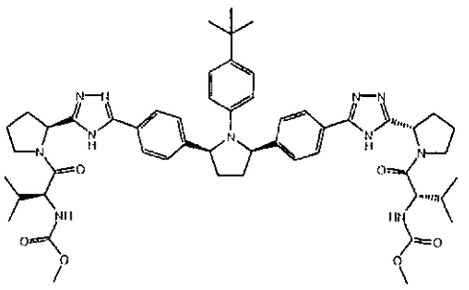
Example 171E

methyl {(2S)-1-[(2S)-2-(5-{4-[(2S,5S)-1-(4-tert-butylphenyl)-5-(4-{5-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-4H-1,2,4-triazol-3-yl}phenyl)pyrrolidin-2-yl]phenyl}-4H-1,2,4-triazol-3-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

and

methyl {(2S)-1-[(2S)-2-(5-{4-[(2R,5R)-1-(4-tert-butylphenyl)-5-(4-{5-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-4H-1,2,4-triazol-3-yl}phenyl)pyrrolidin-2-yl]phenyl}-4H-1,2,4-triazol-3-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

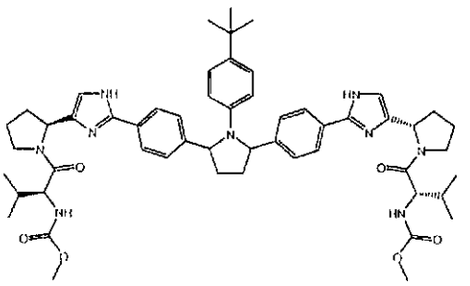
A mixture of Example 171D (58 mg, 0.071 mmol), (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (25 mg, 0.142 mmol), N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (30 mg, 0.157 mmol), 1-Hydroxy-benzotriazole hydrate (24 mg, 0.157 mmol) and N-methylmorpholine (78 µL, 0.712 mmol) in DMF (1 mL) were allowed to stir overnight. Mixture was diluted with EtOAc. The organic was then washed with H_2O and Brine. The organic was then dried ($MgSO_4$), filtered and concentrated. Compound subjected to HPLC purification on a semi-prep C18 reverse-phased column using a gradient of 10-100% acetonitrile in 0.1% aq. TFA to afford both the title compounds of Example 171 (24 mg, 70%) which eluted first (trans isomers) and title compound of Example 172 which eluted second (Cis isomer). ^1H NMR (free base) (400 MHz, DMSO-d_6) δ ppm 0.27 (d, J=6.72 Hz, 2 H), 0.71 (dd, J=6.61, 2.49 Hz, 2 H), 0.78 - 0.95 (m, 9 H), 1.03 (d, J=6.07 Hz, 12 H), 1.09 (s, 9 H), 1.22 (s, 2 H), 1.65 - 1.77 (m, 3 H), 1.82 - 2.30 (m, 10 H), 3.52 (s, 6 H), 3.57 - 3.66 (m, 1 H), 3.71 - 3.92 (m, 3 H), 4.00 - 4.16 (m, 2 H), 5.07 - 5.15 (m, 1 H), 5.25 - 5.34 (m, 2 H), 5.65 (d, J=4.88 Hz, 1 H), 6.21 (dd, J=8.73, 3.20 Hz, 2 H), 6.94 (dd, J=8.78, 2.82 Hz, 2 H), 7.16 - 7.46 (m, 6 H), 7.83 - 7.92 (m, 4 H), 14.01 (s, 1 H); MS (ESI) m/z 943 $(M+H)^+$.



Example 172

methyl {(2S)-1-[(2S)-2-(5-{4-[(2R,5S)-1-(4-tert-butylphenyl)-5-(4-{5-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-4H-1,2,4-triazol-3-yl}phenyl)pyrrolidin-2-yl]phenyl}-4H-1,2,4-triazol-3-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

The title compound, Example 172, was the second eluting compound described in the procedures for Example 171E. The procedure afforded 21 mg (61%) of the title compound (Cis isomer). ^{1}H NMR (free base) (400 MHz, DMSO-d_6) δ ppm 0.27 (d, J=6.29 Hz, 2 H), 0.71 (d, J=6.61 Hz, 2 H), 0.81 - 0.96 (m, 9 H), 1.03 (d, J=6.07 Hz, 12 H), 1.12 (s, 9 H), 1.22 (s, 2 H), 1.82 - 2.30 (m, 12 H), 3.52 (s, 6 H), 3.72 - 3.91 (m, 4 H), 4.03 - 4.17 (m, 2 H), 4.33 (d, J=4.23 Hz, 1 H), 4.73 - 4.83 (m, 2 H), 5.09 - 5.18 (m, 2 H), 6.33 (d, J=8.78 Hz, 2 H), 7.03 (dd, J=8.78, 3.04 Hz, 2 H), 7.29 (d, J=7.70 Hz, 1 H), 7.57 - 7.69 (m, 4 H), 7.92 - 8.01 (m, 4 H), 13.84 (s, 2 H); MS (ESI) m/z 943 $(M+H)^+$.



Example 173

methyl {(2S)-1-[(2S)-2-(2-{4-[(2S,5S)-1-(4-tert-butylphenyl)-5-(4-{4-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-2-yl}phenyl)pyrrolidin-2-yl]phenyl}-1H-imidazol-4-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

and

methyl {(2S)-1-[(2S)-2-(2-{4-[(2R,5R)-1-(4-tert-butylphenyl)-5-(4-{4-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-2-yl}phenyl)pyrrolidin-2-yl]phenyl}-1H-imidazol-4-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

Example 173A

4,4'-(1-(4-tert-butylphenyl)pyrrolidine-2,5-diyl)dibenzonitrile

A mixture of Example 42C (1.0 g, 1.948 mmol) and CuCN (523 mg, 5.84 mmol) in Dimethylformamide (9.5 mL) was heated to 160 °C for 4.5 hours in a microwave. Mixture was poured into a dimethylamine/H_2O mixture (1/10) and extracted with EtOAc (3 x 150 mL). The combined organics were washed with H_2O and Brine. The organic was then dried ($MgSO_4$), filtered and concentrated. Purification by chromatography (silica gel, 20% EtOAc in Hexanes) afforded 395 mg (50%) of the title compound. MS (ESI) m/z 406 $(M+H)^+$.

Example 173B

dimethyl 4,4'-(1-(4-tert-butylphenyl)pyrrolidine-2,5-diyl)dibenzimidate

A mixture of Example 173A (0.5 g, 1.233 mmol) in anhydrous MeOH (12 mL) at 0 °C was bubbled an excess amount of HCl (*g*) for 45 minutes. Mixture was then stirred at ambient temperature for 24 hours and then concentrated to afford the title compound.

Example 173C

4,4'-(1-(4-tert-butylphenyl)pyrrolidine-2,5-diyl)dibenzimidamide

A mixture of Example 173B (0.579 g, 1.233 mmol) in anhydrous MeOH (12 mL) at 0 °C was bubbled an excess amount of NH_3 (*g*) for 45 minutes. Mixture was then stirred at ambient temperature for 24 hours and then concentrated and subjected to purification via chromatography (C18 reverse-phased column using a gradient of 10-100% acetonitrile in 0.1% aq. TFA) to afford the title compound as a mixture of trans isomers; Cis isomer was discarded.. MS (ESI) m/z 440 $(M+H)^+$.

Example 173D

methyl (S)-1-((S)-2-(2-diazoacetyl)pyrrolidin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamate

A mixture of Example 37B (100 mg, 0.367 mmol) and Et_3N (154 µL, 1.102 mmol) in tetrahydrofuran (4 mL) at 0 °C was added Isobutyl chloroformate (50 µL, 0.386 mmol). Mixture was then stirred at 0 °C for 30 minutes followed by addition of excess diazomethane in Et_2O. Mixture was allowed to slowly come to ambient temperature over 3 hours. Mixture was then concentrated and diluted with EtOAc. Organic was then washed with saturated aqueous $NaHCO_3$ and brine. Organic was dried ($MgSO_4$), filtered and concentrated. Purification by chromatography (silica gel, 100% EtOAc) afforded 82 mg (75%) of the title compound. MS (ESI) m/z 297 $(M+H)^+$.

Example 173E

methyl (S)-1-((S)-2-(2-bromoacetyl)pyrrolidin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamate

A mixture of Example 173D (70 mg, 0.236 mmol) in HOAc (0.6 mL) at ambient temperature was added 48%HBr (80 µL, 0.709 mmol). Mixture was stirred at ambient temperature for 1 hour. Mixture was poured into ice/H_2O and extracted with CH_2Cl_2 (3 x 75 mL). Organic was dried (Na_2SO_4), filtered and concentrated afford 63 mg (76%) of the title compound. MS (ESI) m/z 350 $(M+H)^+$.

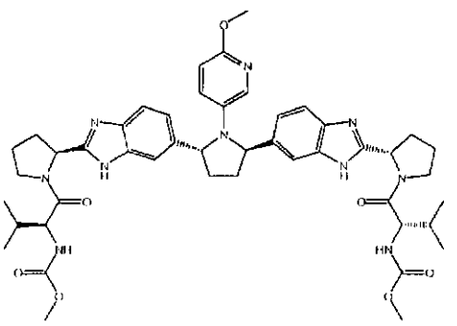
Example 173F

methyl {(2S)-1-[(2S)-2-(2-{4-[(2S,5S)-1-(4-tert-butylphenyl)-5-(4-{4-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-2-yl}phenyl)pyrrolidin-2-yl]phenyl}-1H-imidazol-4-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

and

methyl {(2S)-1-[(2S)-2-(2-{4-[(2R,5R)-1-(4-tert-butylphenyl)-5-(4-{4-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-2-yl}phenyl)pyrrolidin-2-yl]phenyl}-1H-imidazol-4-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

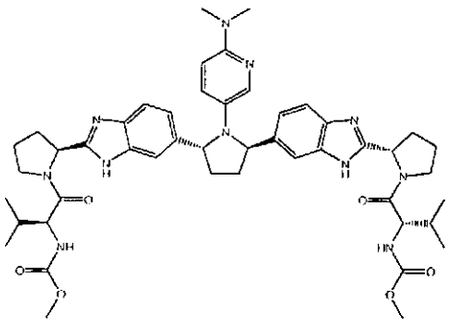
A mixture of Example 173E (59.6 mg, 0.171 mmol), Example 173C (25 mg, 0.057 mmol) and K_2CO_3 (65 mg, 0.470 mmol) in tetrahydrofuran (1 mL) was refluxed for 4 hours. Mixture was diluted with CH_2Cl_2 and washed with H_2O and Brine. The organic was then dried ($MgSO_4$), filtered and concentrated. Compound subjected to HPLC purification on a semi-prep C18 reverse-phased column using a gradient of 10-100% acetonitrile in 0.1% aq. TFA to afford 4.5 mg (6.7%) the title compound Example 173 (Trans isomers). ^1H NMR (free base) (400 MHz, DMSO-d_6) δ ppm 0.78 - 0.89 (m, 12 H), 1.09 (s, 9 H), 1.68 - 1.74 (m, 4 H), 1.88 - 2.04 (m, 8 H), 3.52 (s, 6 H), 3.70 - 3.78 (m, 4 H), 4.04 (t, *J*=8.19 Hz, 2 H), 5.07 (t, *J*=4.61 Hz, 2 H), 5.26 (s, 2 H), 6.21 (d, *J*=8.46 Hz, 2 H), 6.82 (s, 2 H), 6.93 (d, *J*=8.67 Hz, 2 H), 7.22 (d, *J*=8.89 Hz, 2 H), 7.26 (d, *J*=8.13 Hz, 4 H), 7.78 (d, *J*=8.13 Hz, 4 H), 7.82 (d, *J*=7.70 Hz, 2 H), 12.11 - 12.20 (m, 2 H). MS (ESI) m/z 941 $(M+H)^+$.



Example 174

methyl {(2S)-1-[(2S)-2-{6-[(2R,5R)-5-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-benzimidazol-6-yl}-1-(6-methoxypyridin-3-yl)pyrrolidin-2-yl]-1H-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

Example 109C and 6-methoxypyridin-3-amine were processed using sequentially the methods of Examples 113A (dichloromethane used as solvent and cyclization conducted at room temperature overnight), 165C, 113C, and 166 to provide the title compound which was purified by HPLC on a semi-prep C18 reverse-phased column using a gradient of 10-100% acetonitrile in 0.1% aq. TFA to afford 27 mg of the title compound. ^{1}H NMR (free base) (400 MHz, DMSO-d_6) δ ppm 0.76 - 0.86 (m, 12 H), 1.69 - 1.76 (m, 2 H), 1.84 - 2.04 (m, 4 H), 2.13 - 2.22 (m, 4 H), 2.52 - 2.60 (m, 2 H), 3.52 (s, 6 H), 3.55 (s, 3 H), 3.76 - 3.85 (m, 4 H), 4.05 (t, J=8.40 Hz, 2 H), 5.08 - 5.16 (m, 2 H), 5.31 - 5.41 (m, 2 H), 6.36 - 6.45 (m, 2 H), 6.74 (dd, J=9.00, 3.04 Hz, 2 H), 7.05 (t, J=8.57 Hz, 2 H), 7.15 - 7.24 (m, J=17.02 Hz, 3 H), 7.28 (d, J=8.46 Hz, 2 H), 7.31 (s, 1 H), 7.37 (d, J=8.13 Hz, 1 H), 7.45 (d, J=8.13 Hz, 1 H), 12.03 (s, 2 H); MS (ESI) m/z 864 $(M+H)^+$.



Example 175

methyl {(2S)-1-[(2S)-2-{6-[(2R,5R)-1-[6-(dimethylamino)pyridin-3-yl]-5-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-benzimidazol-6-yl}pyrrolidin-2-yl]-1H-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

Example 175A

N,N-dimethyl-5-nitropyridin-2-amine

A mixture of 2-chloro-5-nitropyridine (5.0 g, 31.5 mmol) and 40% solution of Dimethylamine (10.66 g, 95 mmol) in ethanol (40 mL) was heated to 75 °C for 1 hour. The mixture was cooled to ambient temperature, diluted with CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$ (3 x 100 mL) and brine. The organic was dried ($MgSO_4$), filtered and concentrated to afford 5.27 g (100%) of the title compound. MS (ESI) m/z 168 $(M+H)^+$.

Example 175B

N^2,N^2-dimethylpyridine-2,5-diamine

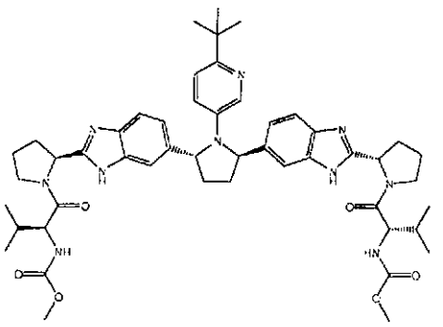
A mixture of Example 175A (5.27 g, 31.5 mmol) and Raney Nickel (5.27 g, 90 mmol) in tetrahydrofuran (60 mL) was subjected to an atmosphere (30 psi) of hydrogen gas for 2 hours at

ambient temperature. Mixture was filtered and concentrated to afford 4.3 g (100%) of the title compound. MS (ESI) m/z 138 $(M+H)^+$.

Example 175C

methyl {(2S)-1-[(2S)-2-{6-[(2R,5R)-1-{6-(dimethylamino)pyridin-3-yl}-5-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl}-1H-benzimidazol-6-yl}pyrrolidin-2-yl]-1H-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

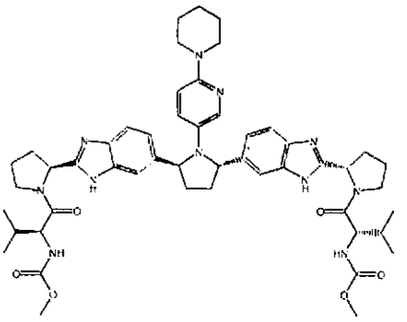
Example 175B was processed using the methods referred to or described in Example 174 to provide the title compound (8.5 mg). ^{1}H NMR (free base) (400 MHz, DMSO-d_6) δ ppm 0.75 - 0.86 (m, 12 H), 1.71 (d, J=4.99 Hz, 2 H), 1.86 - 2.05 (m, 6 H), 2.12 - 2.23 (m, 3 H), 2.55 (s, 2 H), 2.70 (s, 6 H), 3.16 (s, 2 H), 3.52 (s, 6 H), 3.81 (s, 3 H), 4.05 (t, J=8.35 Hz, 2 H), 5.09 - 5.18 (m, 2 H), 5.33 (d, J=5.53 Hz, 2 H), 6.33 (d, J=9.00 Hz, 1 H), 6.63 (dd, J=9.05, 2.98 Hz, 1 H), 7.04 (d, J=7.70 Hz, 2 H), 7.19 - 7.31 (m, 4 H), 7.34 - 7.48 (m, 2 H), 12.02 (s, 2 H); MS (ESI) m/z 877 $(M+H)^+$.



Example 176

methyl {(2S)-1-[(2S)-2-{6-{(2R,5R)-1-(6-tert-butylpyridin-3-yl)-5-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-benzimidazol-6-yl}pyrrolidin-2-yl]-1H-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

6-tert-Butylpyridin-3-amine was processed using the methods referred to or described in Example 174 to provide the title compound (62.5 mg) of the title compound. ^{1}H NMR (free base) (400 MHz, DMSO-d_6) δ ppm 0.74 - 0.88 (m, 12 H), 1.08 (s, 9 H), 1.68 - 1.77 (m, 2 H), 1.83 - 2.04 (m, 7 H), 2.12 - 2.23 (m, 4 H), 2.53 - 2.61 (m, 2 H), 3.16 (d, J=5.20 Hz, 2 H), 3.52 (s, 6 H), 3.76 - 3.85 (m, 4 H), 4.00 - 4.11 (m, 3 H), 5.08 - 5.16 (m, 2 H), 5.37 - 5.46 (m, 2 H), 6.54 - 6.61 (m, 1 H), 6.88 - 6.96 (m, 2 H), 7.08 (t, J=9.00 Hz, 2 H), 7.20 (s, 1 H), 7.25 - 7.31 (m, 3 H), 7.39 (d, J=8.13 Hz, 1 H), 7.47 (d, J=8.24 Hz, 1 H), 7.60 (d, J=3.25 Hz, 1 H), 12.04 (d, J=27.76 Hz, 2 H); MS (ESI) m/z 890 $(M+H)^+$.



Example 177

methyl {(2S)-1-[(2S)-2-(6-{(2S,5S)-5-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-benzimidazol-6-yl}-1-[6-(piperidin-1-yl)pyridin-3-yl]pyrrolidin-2-yl}-1H-benzimidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

Example 177A

5-((2S,5S)-2,5-bis(4-chloro-3-nitrophenyl)pyrrolidin-1-yl)-2-(piperidin-1-yl)pyridine

(1R,4R)-1,4-bis(4-chloro-3-nitrophenyl)butane-1,4-diol (prepared using (S)-(+)-alpha,alpha-diphenyl-2-pyrrolidinemethanol and the method of Example 109C) (0.60 g, 1.5 mmol) was processed using the method described in Example 182A to give the title compound (0.41 g, 50%).

Example 177B

dimethyl (2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-((2S,5S)-1-(6-(piperidin-1-yl)pyridin-3-yl)pyrrolidine-2,5-diyl)bis(2-nitro-4,1-phenylene))bis(azanediyl)bis(oxomethylene)bis(pyrrolidine-2,1-diyl))bis(3-methyl-1-oxobutane-2,1-diyl)dicarbamate

The product from Example 177A (0.20 g, 0.369 mmol) was combined with the product from Example 116C (0.30 g, 1.11 mmol), cesium carbonate (0.336 g, 1.03 mmol), Xantphos (38 mg, 0.066 mmol) and tris(dibenzylideneacetone)dipalladium (20.3 mg, 0.022 mmol). Anhydrous 1,4-dioxane (3.7 mL) was added, and the mixture was bubbled with N_2 gas for 15 min. The resulting mixture was stirred in a sealed tube at 100 °C for 2 h. The mixture was cooled to ambient temperature, diluted with water and extracted with ethyl acetate. The organic extract was washed with brine, dried ($NaSO_4$), filtered and concentrated. Purification by flash chromatography twice (silica gel, 0-10% MeOH/CH_2Cl_2) afforded the title compound (235 mg, 60%).

Example 177C

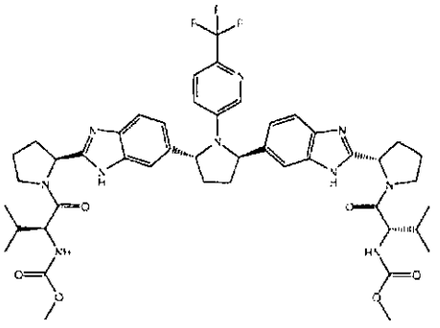
dimethyl (2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-((2S,5S)-1-(6-(piperidin-1-yl)pyridin-3-yl)pyrrolidine-2,5-diyl)bis(2-amino-4,1-phenylene))bis(azanediyl)bis(oxomethylene)bis(pyrrolidine-2,1-diyl))bis(3-methyl-1-oxobutane-2,1-diyl)dicarbamate

To a solution of the product from Example 177B (237mg, 0.234 mmol) in ethanol (1.2 mL) and tetrahydrofuran (1.2 mL) was added platinum(IV) oxide (13.29 mg, 0.059 mmol). The mixture was placed under a hydrogen atmosphere for about 1 hour. The mixture was filtered over celite, washing with methanol and concentrated. Purification by flash chromatography (silica gel, 0-10% MeOH/CH_2Cl_2) afforded the title compound (186 mg, 84%).

Example 177D

methyl {(2S)-1-[(2S)-2-(6-{(2S,5S)-5-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-benzimidazol-6-yl}-1-[6-(piperidin-1-yl)pyridin-3-yl]pyrrolidin-2-yl}-1H-benzimidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

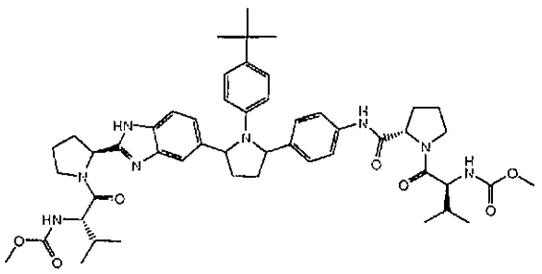
To a solution of the product from Example 177C (113 mg, 0.119 mmol) in toluene (1.2 mL) was added acetic acid (34 μL, 0.593 mmol) and 3A molecular sieves. The mixture was heated to 60 °C for 2 hours. The reaction was cooled to ambient temperature and diluted with ethyl acetate. The organic phase was washed with saturated aqueous $NaHCO_3$, dried (Na_2SO_4), filtered and concentrated. The crude product was purified by reverse-phase HPLC (C18) using a solvent gradient of 10-90% CH_3CN in water (0.1% TFA). Fractions containing the desired product were pooled and concentrated in vacuo, and the residue was partitioned between saturated aq. $NaHCO_3$, and CH_2Cl_2. The organic layer was dried (Na_2SO_4), filtered and concentrated to afford the title compound (9 mg, 8%). ^1H NMR (400 MHz, DMSO-D6) δ ppm 0.78 - 0.85 (m, 7 H), 0.87 (dd, *J*=6.7, 3.0 Hz, 6 H), 1.23 (s, 1 H), 1.43 (s, 6 H), 1.72 (s, 2 H), 1.97 (s, 5 H), 2.18 (s, 3 H), 3.09 (s, 4 H), 3.30 (s, 2 H), 3.53 (d, *J*=1.5 Hz, 6 H), 3.81 (s, 4 H), 4.07 (s, 2 H), 5.13 (s, 2 H), 5.33 (s, 2 H), 6.48 (d, *J*=4.4 Hz, 1 H), 6.59 - 6.64 (m, 1 H), 7.05 (s, 2 H), 7.22 (s, 1 H), 7.25 - 7.34 (m, 4 H), 7.37 (s, 1 H), 7.44 (s, 1 H), 12.06 (s, 2 H); MS (ESI) m/z 916 $(M+H)^+$.



Example 178

methyl {(2S)-1-[(2S)-2-(6-{(2R,5R)-5-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-benzimidazol-6-yl}-1-[6-(trifluoromethyl)pyridin-3-yl]pyrrolidin-2-yl}-1H-benzimidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

Example 109C and 5-amino-2-(trifluoromethyl)pyridine were processed using sequentially the methods of Examples 182A, 177B, 177C, and 177D to provide the title compound. 1H NMR (400 MHz, DMSO-D6) δ ppm 0.79 - 0.89 (m, 15 H), 1.61 (s, 4 H), 1.97 (s, 6 H), 2.19 (s, 5 H), 3.50 - 3.58 (m, 7 H), 3.82 (s, 4 H), 3.99 - 4.10 (m, 2 H), 5.15 (s, 2 H), 6.89 - 6.98 (m, 2 H), 7.19 (s, 1 H), 7.26 - 7.34 (m, 4 H), 7.36 (d, *J*=8.2 Hz, 1 H), 11.94 (d, *J*=12.9 Hz, 2 H). MS m/z 901 $(M+H)^+$.



Example 179

N-(methoxycarbonyl)-L-valyl-N-{4-[(2*S*,5*S*)1-(4-tert-butylphenyl)-5-(2-{(2*S*)-1-[N-(methoxycarbonyl)-L-valyl]pyrrolidin-2-yl}-1H-benzimidazol-5-yl)pyrrolidin-2-yl]phenyl}-L-prolinamide

and

N-(methoxycarbonyl)-L-valyl-*N*-{4-[(2*R*,5*R*)-1-(4-*tert*-butylphenyl)-5-(2-{(2*S*)-1-[*N*-(methoxycarbonyl)-L-valyl]pyrrolidin-2-yl}-1*H*-benzimidazol-5-yl)pyrrolidin-2-yl]phenyl}-L-prolinamide

Example 179A

1-(4-chloro-3-nitrophenyl)-4-(4-nitrophenyl)butane-1,4-dione

To a mixture of zinc chloride (39.1 g, 287 mmol) in benzene (215 mL) was added diethylamine (22.24 mL, 215 mmol) and 2-methylpropan-2-ol (20.57 mL, 215 mmol). The resulting mixture was stirred at rt for 2h, and 2-bromo-1-(4-nitrophenyl)ethanone (35.0 g, 143 mmol) and 1-(4-chloro-3-nitrophenyl)ethanone (42.9 g, 215 mmol) were added in one portion. The resulting mixture was stirred at rt overnight. Added 5% aq. H_2SO_4 (50 mL) and stirred vigorously to induce precipitation. The resulting solid was collected by filtration and washed successively with benzene, water, methanol, and CH_2Cl_2. The solid was dried in vacuo to give the title compound.

Example 179B

1-(4-chloro-3-nitrophenyl)-4-(4-nitrophenyl)butane-1,4-diol

To a solution of the product from Example 179A (10.0 g, 27.6 mmol) in EtOH (220 mL) was added sodium borohydride (2.190 g, 57.9 mmol) in several portions over 1 h. The resulting mixture was stirred at rt for 1 h, filtered through celite, and concentrated in vacuo. The residue was dissolved

in EtOAc and washed by 1N aq. HCl. The organic layer was dried over Na_2SO_4, filtered and concentrated in vacuo to give the title compound (9.29 g, 92%)

Example 179C

1-(4-tert-butylphenyl)-2-(4-chloro-3-nitrophenyl)-5-(4-nitrophenyl)pyrrolidine

To a solution of product from Example 179B (9.29 g, 25.3 mmol) in anhydrous CH_2Cl_2 (200 mL) at 0 °C was added triethylamine (10.53 mL, 76 mmol), followed by dropwise addition of methanesulfonyl chloride (4.93 mL, 63.3 mmol). The resulting mixture was stirred at 0 °C for 2 h, and then concentrated in vacuo. The resulting solid was dissolved in anhydrous DMF (70 mL), 4-tert-butylaniline (40.4 mL, 253 mmol) was added, and the resulting mixture was stirred at 50 °C for 1 h. The resulting mixture was cooled to rt and poured into ice cold 1N aq. HCl (500 mL) to give a yellow precipitate. The precipitate was collected by filtration and dried to give the title compound (13.2 g).

Example 179D

4-(1-(4-tert-butylphenyl)-5-(4-nitrophenyl)pyrrolidin-2-yl)-N-(4-methoxybenzyl)-2-nitroaniline

The product from Example 179C (13.2 g, 27.5 mmol) and 4-methoxybenzylamine (18 mL, 139 mmol) were combined and stirred at 145 °C for 1.5 h. The mixture was cooled to rt, and CH_2Cl_2 was added. The resulting precipitate was filtered off, and the filtrate was washed successively with 1N aq. HCl and saturated aq. $NaHCO_3$. The organic layer was dried over Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by column chromatography on silica gel using a solvent gradient of 0-25% EtOAc in hexane to give the title compound (5.0 g, 31%).

Example 179E

4-(5-(4-aminophenyl)-1-(4-tert-butylphenyl)pyrrolidin-2-yl)-N1-(4-methoxybenzyl)benzene-1,2-diamine

To a solution of the product from Example 179D (2.74 g, 4.72 mmol) in EtOH (25 mL) and THF (25 mL) was added platinum(IV) oxide (0.5 g, 2.2 mmol). The resulting mixture was stirred at rt under 1 atm H_2 overnight. The mixture was filtered through celite, washed with methanol, and the filtrate was concentrated in vacuo. The crude product was purified by column chromatography on silica gel using a solvent gradient of 0-45% EtOAc in hexane to give the title compound (1.74 g, 71%).

Example 179F

(2S)-tert-butyl 2-(4-(5-(3-((S)-1-(tert-butoxycarbonyl)pyrrolidine-2-carboxamido)-4-(4-methoxybenzylamino)phenyl)-1-(4-tert-butylphenyl)pyrrolidin-2-yl)phenylcarbamoyl)pyrrolidine-1-carboxylate

To a mixture of the product from Example 179E (1.74 g, 3.33 mmol), (S)-1-(tert-butoxycarbonyl)pyrrolidine-2-carboxylic acid (1.793 g, 8.33 mmol) and HATU (3.17 g, 8.33 mmol) in DMSO (33 mL) was added Hunig's base (1.746 mL, 10.00 mmol). The resulting mixture was stirred at rt for 1 h and was partitioned between H_2O and CH_2Cl_2. The organic layer was dried over Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by column chromatography on silica gel using a solvent gradient of 0-25% EtOAc in hexane to give the title compound (2.1 g, 69%).

Example 179G

(2S)-tert-butyl 2-(4-(5-(4-amino-3-((S)-1-(tert-butoxycarbonyl)pyrrolidine-2-carboxamido)phenyl)-1-(4-tert-butylphenyl)pyrrolidin-2-yl)phenylcarbamoyl)pyrrolidine-1-carboxylate

To a solution of the product from Example 179F (1.06 g, 1.16 mmol) in CH_2Cl_2 (40 mL) and H_2O (2 mL) was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (0.316 g, 1.393 mmol) in several portions. The mixture was stirred at rt for 20 min and was washed with saturated.aq. $NaHCO_3$. The organic layer was dried over Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by column chromatography on silica gel using a solvent gradient of 0-25% EtOAc in hexane to give the title compound (0.53 g, 57%).

Example 179H

(2S)-tert-butyl 2-(4-(5-(2-((S)-1-(tert-butoxycarbonyl)pyrrolidin-2-yl)-1H-benzo[d]imidazol-5-yl)-1-(4-tert-butylphenyl)pyrrolidin-2-yl)phenylcarbamoyl)pyrrolidine-1-carboxylate

A solution of product from Example 179G (0.526 g, 0.662 mmol) in acetic acid (4.73 mL, 83 mmol) was stirred at 65 °C for 1 h. The resulting mixture was partitioned between CH_2Cl_2 and saturated aq. $NaHCO_3$. The organic layer was dried over Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by column chromatography on silica gel using a solvent gradient of 0-2.5% MeOH in CH_2Cl_2 to give the title compound (0.23 g, 45%).

Example 179I

(S)-N-(4-((2S,5S)-1-(4-tert-butylphenyl)-5-(2-((S)-pyrrolidin-2-yl)-1H-benzo[d]imidazol-5-yl)pyrrolidin-2-yl)phenyl)pyrrolidine-2-carboxamide

and

(S)-N-(4-((2R,5R)-1-(4-tert-butylphenyl)-5-(2-((S)-pyrrolidin-2-yl)-1H-benzo[d]imidazol-5-yl)pyrrolidin-2-yl)phenyl)pyrrolidine-2-carboxamide

To a solution of the product from Example 179H (0.302 g, 0.389 mmol) in CH_2Cl_2 (3 mL) was added TFA (2.5 mL), and the resulting mixture was stirred at rt for 1.5 h. The mixture was concentrated in vacuo, and the crude product was purified by reversed-phase HPLC (C18) using a

solvent gradient of 10-100% acetonitrile in H_2O (0.1% TFA). The trans-pyrrolidine isomer eluted before the cis-pyrrolidine isomer. Fractions containing the trans-isomer were concentrated in vacuo, and the residue was partitioned between CH_2Cl_2 and saturated aq. $NaHCO_3$. The organic layer was dried over Na_2SO_4, filtered and concentrated in vacuo to give the title compound (83 mg, 37%).

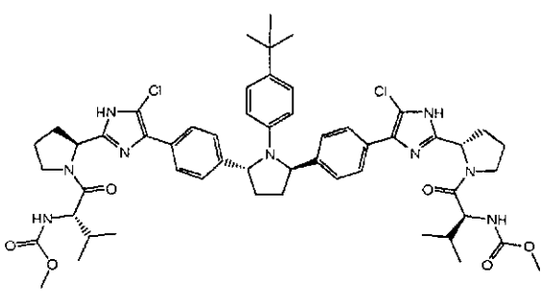
Example 179I

N-(methoxycarbonyl)-L-valyl-N-{4-[(2*S*,5*S*)1-(4-tert-butylphenyl)-5-(2-{(2S)-1-[N-(methoxycarbonyl)-L-valyl]pyrrolidin-2-yl}-1H-benzimidazol-5-yl)pyrrolidin-2-yl]phenyl}-L-prolinamide

and

N-(methoxycarbonyl)-L-valyl-*N*-{4-[(2*R*,5*R*)-1-(4-*tert*-butylphenyl)-5-(2-{(2*S*)-1-[*N*-(methoxycarbonyl)-L-valyl]pyrrolidin-2-yl}-1*H*-benzimidazol-5-yl)pyrrolidin-2-yl]phenyl}-L-prolinamide

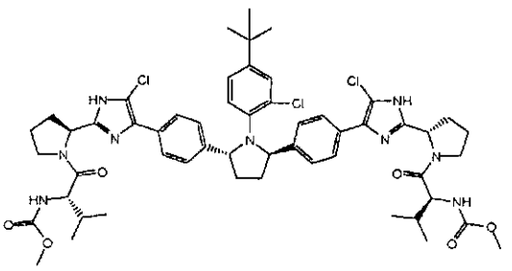
To a mixture of the product from Example 179I (83 mg, 0.144 mmol), (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (63 mg, 0.361 mmol), and HATU (0.137 g, 0.361 mmol) in DMSO (1.5 mL) was added Hunig's base (0.101 mL, 0.578 mmol), and the resulting mixture was stirred at rt for 1 h. The mixture was partitioned between CH_2Cl_2 and H_2O. The organic layer was dried over Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by column chromatography on silica gel using a solvent gradient of 0-3.5% MeOH in CH_2Cl_2 to give the title compounds (80 mg, 60%). 1H NMR (400 MHz, DMSO-D6) δ ppm 0.74 - 0.99 (m, 12 H), 1.09 (s, 9 H), 1.59 - 1.73 (m, 2 H), 1.81 - 2.05 (m, 6 H), 2.07 - 2.24 (m, 2 H), 3.50 - 3.56 (m, 6 H), 3.58 - 3.67 (m, 1 H), 3.76 - 3.85 (m, 2 H), 3.99 - 4.10 (m, 2 H), 4.43 (dd, *J*=8.0, 4.9 Hz, 1 H), 5.08 - 5.16 (m, 1 H), 5.16 - 5.25 (m, 1 H), 5.26 - 5.37 (m, 1 H), 6.21 (d, *J*=8.8 Hz, 2 H), 6.88 - 6.97 (m, 2.5 H), 7.00 - 7.08 (m, 1 H), 7.11 - 7.20 (m, *J*=5.7 Hz, 2.5 H), 7.21 - 7.34 (m, 2 H), 7.37 (dd, *J*=8.2, 2.0 Hz, 0.5 H), 7.45 (d, *J*=8.3 Hz, 0.5 H), 7.50 (d, *J*=8.3 Hz, 2 H), 9.98 (s, 1 H), 12.01 (m, 1 H); MS m/z 891.6 $(M+H)^+$.



Example 180

methyl {(2S)-1-[(2S)-2-(4-{4-[(2R,5R)-1-(4-tert-butylphenyl)-5-(4-{5-chloro-2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-4-yl}phenyl)pyrrolidin-2-yl]phenyl}-5-chloro-1H-imidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

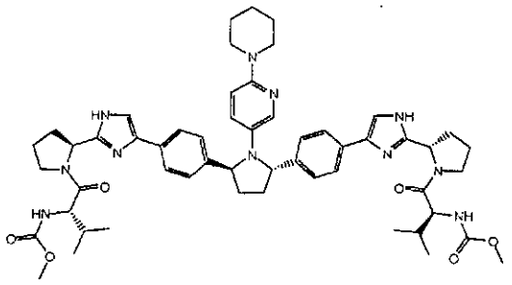
To a solution of the product from Example 43 (114 mg, 0.121 mmol) in CH_2Cl_2 (1.2 mL) was added N-chlorosuccinimide (54 mg, 0.41 mmol), and the resulting mixture was stirred at rt for 9 h. The mixture was diluted by CH_2Cl_2 and washed with saturated aq $NaHCO_3$. The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was subjected to reversed-phase HPLC (C18) using a solvent gradient of 40%-100% acetonitrile in water (0.1% TFA). Fractions containing the desired product were pooled and concentrated in vacuo. The residue was purified on a preparative TLC plate, eluting with 3% MeOH in CH_2Cl_2 to give the title compound (3.5 mg, 3%). 1H NMR (400 MHz, DMSO-D6) δ ppm 0.80 - 0.92 (m, 12 H), 1.11 (s, 9 H), 1.72 (d, *J*=5.0 Hz, 2 H), 1.87 - 2.04 (m, 6 H), 2.05 - 2.23 (m, 2 H), 3.53 (s, 6 H), 3.72 - 3.82 (m, 2 H), 4.04 (t, *J*=8.4 Hz, 2 H), 4.98 (dd, *J*=6.8, 3.5 Hz, 2 H), 5.29 (dd, *J*=3.5, 2.5 Hz, 2 H), 6.23 (d, *J*=8.8 Hz, 2 H), 6.96 (d, *J*=8.8 Hz, 2 H), 7.27 (d, *J*=8.6 Hz, 2 H), 7.32 (d, *J*=8.2 Hz, 4 H), 7.61 (d, *J*=8.1 Hz, 4 H), 12.41 (s, 2 H); MS m/z 1009.1 $(M+H)^+$.



Example 181

methyl {(2S)-1-[(2S)-2-(4-{4-[(2R,5R)-1-(4-tert-butyl-2-chlorophenyl)-5-(4-{5-chloro-2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-4-yl}phenyl)pyrrolidin-2-yl]phenyl}-5-chloro-1H-imidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

The product from Example 43 (114 mg, 0.121 mmol) was subjected to the procedure described in Example 180 to give the title compound (4.7 mg, 4%). 1H NMR (TFA salt) (400 MHz, DMSO-D6) δ ppm 0.78 - 0.89 (m, 12 H), 1.05 (s, 9 H), 1.85 - 1.97 (m, 10 H), 2.04 - 2.18 (m, 4 H), 3.52 (s, 6 H), 3.69 - 3.81 (m, 4 H), 4.03 (t, *J*=8.3 Hz, 2 H), 4.95 (dd, *J*=7.0, 4.0 Hz, 2 H), 5.53 (d, *J*=7.5 Hz, 2 H), 6.91 - 6.95 (m, 1 H), 6.96 - 7.02 (m, 2 H), 7.26 (d, *J*=8.5 Hz, 2 H), 7.30 - 7.41 (m, 4 H), 7.49 (d, *J*=7.6 Hz, 4 H), 12.34 (s, 2 H); MS m/z 1045.1 $(M+H)^+$.



Example 182 methyl [(2S)-1-{(2S)-2-[4-(4-{(2S,5S)-5-(4-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-4-yl}phenyl)-1-[6-(piperidin-1-yl)pyridin-3-yl]pyrrolidin-2-yl}phenyl)-1H-imidazol-2-yl]pyrrolidin-1-yl}-3-methyl-1-oxobutan-2-yl]carbamate

Example 182A

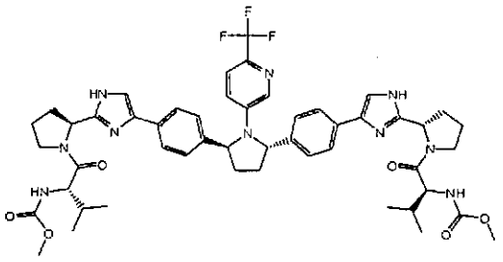
5-((2S,5S)-2,5-bis(4-bromophenyl)pyrrolidin-1-yl)-2-(piperidin-1-yl)pyridine

To a suspension of the product of Example 69A (0.50 g, 1.25 mmol) in anhydrous CH_2Cl_2 (12 mL) at 0 °C was added Et_3N (0.52 mL, 3.75 mmol), followed by methanesulfonyl chloride (0.243 mL, 3.12 mmol). The resulting mixture was stirred and 0 °C for 90 min and then evaporated to dryness. The solid was dissolved in anhydrous DMF (10 mL), and Example 144C (1108 mg, 6.25 mmol) was added. The resulting mixture was stirred at 40 °C overnight, and was partitioned between 0.2 N aq HCl and EtOAc. The organic layer was dried over Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by column chromatography on silica gel using a solvent gradient of EtOAc and hexane to give the title compound (107 mg, 16%).

Example 182B

methyl [(2S)-1-{(2S)-2-[4-(4-{(2S,5S)-5-(4-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-4-yl}phenyl)-1-[6-(piperidin-1-yl)pyridin-3-yl]pyrrolidin-2-yl}phenyl)-1H-imidazol-2-yl]pyrrolidin-1-yl}-3-methyl-1-oxobutan-2-yl]carbamate

The product from Example 182A was subjected to the procedures described in Examples 42D, 42E, 42F, and 42G to give the title compound. 1H NMR (free base) (400 MHz, DMSO-D6) δ ppm 0.80 - 0.94 (m, 12 H), 1.24 (s, 4 H), 1.44 (s, 6 H), 1.89 - 2.04 (m, 6 H), 2.07 - 2.20 (m, 4 H), 3.12 (s, 4 H), 3.53 (s, 6 H), 3.77 (d, *J*=6.7 Hz, 2 H), 4.05 (t, *J*=8.4 Hz, 2 H), 5.06 (dd, *J*=6.7, 3.0 Hz, 2 H), 5.19 (d, *J*=6.4 Hz, 2 H), 6.45 - 6.53 (m, 1 H), 6.56 - 6.63 (m, 1 H), 7.15 (d, *J*=8.2 Hz, 4 H), 7.21 - 7.32 (m, 4 H), 7.38 (d, *J*=1.8 Hz, 2 H), 7.62 (d, *J*=8.0 Hz, 4 H), 11.69 (s, 2 H); MS m/z = 968.8 $(M+H)^+$.



Example 183

methyl [(2S)-1-{(2S)-2-[4-(4-{(2S,5S)-5-(4-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-4-yl}phenyl)-1-[6-(trifluoromethyl)pyridin-3-yl]pyrrolidin-2-yl}phenyl)-1H-imidazol-2-yl]pyrrolidin-1-yl}-3-methyl-1-oxobutan-2-yl]carbamate

Example 183A

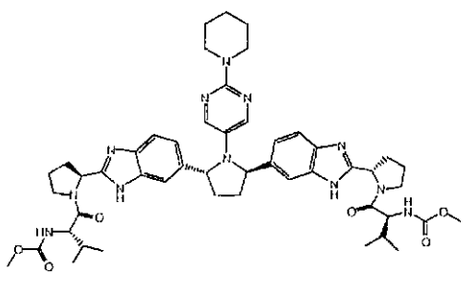
5-((2S,5S)-2,5-bis(4-bromophenyl)pyrrolidin-1-yl)-2-(trifluoromethyl)pyridine

The product from Example 69A (1.0 g, 2.5 mmol) was subjected to the procedure described in Example 182A, substituting 6-(trifluoromethyl)pyridin-3-amine for Example 144C, to give the title compound (0.13 g, 10%).

Example 183B

methyl [(2S)-1-{(2S)-2-[4-(4-{(2S,5S)-5-(4-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-4-yl}phenyl)-1-[6-(trifluoromethyl)pyridin-3-yl]pyrrolidin-2-yl}phenyl)-1H-imidazol-2-yl]pyrrolidin-1-yl}-3-methyl-1-oxobutan-2-yl]carbamate

The product from Example 183A was subjected to the procedures described in Examples 42D, 42E, 42F, and 42G to give the title compound. 1H NMR (TFA salt) (400 MHz, DMSO-D6) δ ppm 0.75 - 0.91 (m, 12 H), 1.84 (d, *J*=5.6 Hz, 2 H), 1.96 - 2.10 (m, 6 H), 2.11 - 2.20 (m, *J*=10.8, 5.5 Hz, 2 H), 3.54 (s, 6 H), 3.76 - 3.91 (m, 4 H), 4.10 (t, *J*=7.9 Hz, 2 H), 5.11 (t, *J*=6.8 Hz, 2 H), 5.56 (d, *J*=5.1 Hz, 2 H), 6.74 (dd, *J*=8.8, 2.5 Hz, 1 H), 7.32 (d, *J*=8.5 Hz, 2 H), 7.41 (d, *J*=7.8 Hz, 4 H), 7.44 - 7.48 (m, *J*=8.8 Hz, 1 H), 7.71 (d, *J*=8.2 Hz, 4 H), 7.76 (d, *J*=2.5 Hz, 1 H), 7.97 (s, 2 H), 14.50 (s, 2 H); MS m/z 953.6 $(M+H)^+$.



Example 184

methyl {(2S)-1-[(2S)-2-(6-{(2R,5R)-5-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-benzimidazol-6-yl}-1-[2-(piperidin-1-yl)pyrimidin-5-yl]pyrrolidin-2-yl}-1H-benzimdazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

Example 184A

2-(piperidin-1-yl)pyrimidin-5-amine

To a suspension of 2-chloro-5-nitropyrimidine (1.5 g, 9.40 mmol) in EtOH (15 mL) was added piperidine (2.79 mL, 28.2 mmol), and the resulting mixture was refluxed for 2 h. The cooled mixture was concentrated in vacuo, and the residue was partitioned between CH_2Cl_2 and saturated aq. $NaHCO_3$. The organic layer was dried over Na_2SO_4, filtered and concentrated in vacuo to give a solid (1.65 g, 84%). The solid was placed in a 250 mL stainless steel pressure bottle and dissolved in THF (20 mL). Raney-Ni 2800 in water slurry (1.650 g, 28.1 mmol) was added, and the mixture was stirred at rt for 2 h under H_2 gas at a pressure of 30 psi. The mixture was filtered through a nylon membrane and concentrated in vacuo to give the title compound (1.4 g, 99%).

Example 184B

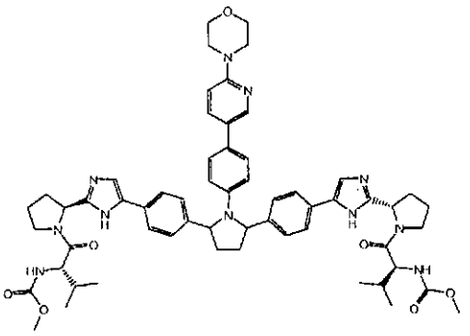
5-((2R,5R)-2,5-bis(4-chloro-3-nitrophenyl)pyrrolidin-1-yl)-2-(piperidin-1-yl)pyrimidine

The product from Example 109C (1.09 g, 2.72 mmol) was subjected to the conditions described in Example 182A, substituting Example 184A for Example 144C, to give the title compound (0.59 g, 40%).

Example 184C

methyl {(2S)-1-[(2S)-2-(6-{(2R,5R)-5-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-benzimidazol-6-yl}-1-[2-(piperidin-1-yl)pyrimidin-5-yl]pyrrolidin-2-yl}-1H-benzimdazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

The product from Example 184B was subjected to the procedures described in Examples 177B, 177C, and 177D to give the title compound. ^{1}H NMR (TFA salt) (400 MHz, DMSO-D6) δ ppm 0.71 - 0.91 (m, 12 H), 1.24 (s, 2 H), 1.32 - 1.41 (m, 4 H), 1.44 - 1.52 (m, 2 H), 1.82 (d, *J*=5.1 Hz, 2 H), 1.92 - 2.26 (m, 12 H), 3.86 (s, 6 H), 4.12 (t, *J*=8.0 Hz, 2 H), 5.20 (dd, *J*=8.0, 5.2 Hz, 2 H), 5.54 (d, *J*=6.2 Hz, 2 H), 7.33 (d, *J*=8.3 Hz, 2 H), 7.40 (d, *J*=7.8 Hz, 2 H), 7.51 (s, 2 H), 7.57 - 7.61 (m, 2 H), 7.72 (d, *J*=8.3 Hz, 2 H); MS m/z 917.5 $(M+H)^+$.



Example 185

methyl {(2*S*)-1-[(2*S*)-2-(5-{4-[(2*S*,5*S*)-5-(4-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1*H*-imidazol-5-yl}phenyl)-1-{4-[6-(morpholin-4-yl)pyridin-3-yl]phenyl}pyrrolidin-2-yl]phenyl}-1*H*-imidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

and

methyl {(2*S*)-1-[(2*S*)-2-(5-{4-[(2*R*,5*R*)-5-(4-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1*H*-imidazol-5-yl}phenyl)-1-{4-[6-(morpholin-4-yl)pyridin-3-yl]phenyl}pyrrolidin-2-yl]phenyl}-1*H*-imidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

Example 185A

2,5-bis(4-bromophenyl)-1-(4-iodophenyl)pyrrolidine

The product from Example 42B (1.39 g, 2.499 mmol) in DMF (6.25 mL) was treated with 4-iodoaniline (Aldrich, 4.38 g, 19.99 mmol), heated at 40-50 °C for two hours, cooled and diluted into EtOAc. The EtOAc layer was washed 3 X 50 mL with 1 M HCl, with water, brine, dried (Na_2SO_4), filtered and concentrated. Purification by flash chromatography on an ISCO 40 g silica cartridge eluting with 0-20% EtOAc in hexane afforded the title compound as a tan foam as a mixture of stereoisomers (0.96 g, 66 %). MS (ESI) m/z 584 $(M+H)^+$.

Example 185B

4-(5-(4-(2,5-bis(4-bromophenyl)pyrrolidin-1-yl)phenyl)pyridin-2-yl)morpholine

The product from Example 185A (0.1 g, 0.171 mmol), 4-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)morpholine (0.050 g, 0.171 mmol), potassium phosphate (0.028 mL, 0.343 mmol), tris(dibenzylideneacetone)dipalladium(0) (1.570 mg, 1.715 μmol) and 1,3,5,7-tetramethyl-6-phenyl-2,4,8-trioxa-6-phosphaadamante (1.504 mg, 5.14 μmol) were combined in THF (1.2 mL) / water (0.4 mL). The mixture was sparged with nitrogen for 15 minutes diluted into EtOAc, washed with 1M sodium bicarbonate, brine, dried (Na_2SO_4), filtered and concentrated. Purification

by flash chromatography on an Isco 12 g silica cartridge eluting with 20-70 % EtOAc in hexane gave the title compound as a cream colored powder (91 mg, 86%). %). MS (ESI) m/z 620 $(M+H)^+$.

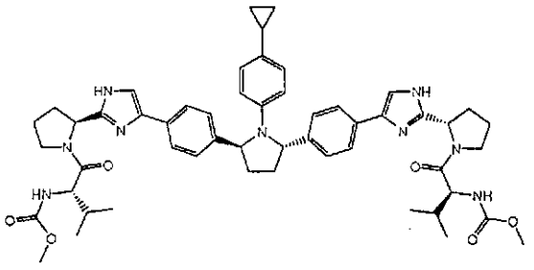
Example 185C

methyl {(2*S*)-1-[(2*S*)-2-(5-{4-[(2*S*,5*S*)-5-(4-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1*H*-imidazol-5-yl}phenyl)-1-{4-[6-(morpholin-4-yl)pyridin-3-yl]phenyl}pyrrolidin-2-yl]phenyl}-1*H*-imidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

and

methyl {(2*S*)-1-[(2*S*)-2-(5-{4-[(2*R*,5*R*)-5-(4-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1*H*-imidazol-5-yl}phenyl)-1-{4-[6-(morpholin-4-yl)pyridin-3-yl]phenyl}pyrrolidin-2-yl]phenyl}-1*H*-imidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

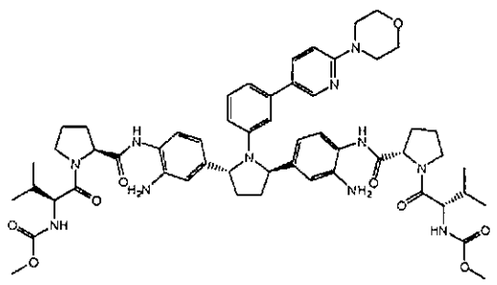
The product from Example 185B was processed as described in Example 42D, 42E, 42F, and 42G to afford the title compounds. ^{1}H NMR (free base) (400 MHz, DMSO-d_6) δ 0.77 - 0.94 (m, 12 H) 1.71 - 2.47 (m, 16 H) 3.36 - 3.42 (m, 4 H) 3.53 (s, 6 H) 3.63 - 3.71 (m, 4 H) 3.74 - 3.84 (m, 3 H) 4.00 - 4.08 (m, 1 H) 4.79 (d, J=4.23 Hz, 1 H) 5.02 - 5.11 (m, 2 H) 5.24 - 5.32 (m, 1 H) 6.37 (d, J=8.89 Hz, 1 H) 6.49 (d, J=8.78 Hz, 1 H) 6.79 (dd, J=14.91, 8.95 Hz, 1 H) 7.12 - 7.78 (m, 15 H) 8.23 - 8.31 (m, 1 H) 11.64 - 12.11 (m, 2 H). MS (ESI) m/z 1046 $(M+H)^+$.



Example 186

methyl {(2S)-1-[(2S)-2-(4-{4-[(2S,5S)-1-(4-cyclopropylphenyl)-5-(4-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-4-yl}phenyl)pyrrolidin-2-yl]phenyl}-1H-imidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

The product from Example 95B was purified by chiral chromatography on a Chiralpak IB column eluting with a mixture of hexane/THF/methanol (85/10/5). The title compound was the second of the 2 diastereomers to elute. 1H NMR (400 MHz, DMSO-D6) δ ppm 0.35 - 0.42 (m, 2 H) 0.65 - 0.73 (m, 2 H) 0.80 - 0.92 (m, 12 H) 1.58 - 1.65 (m, 1 H) 1.67 - 1.71 (m, 2 H) 1.87 - 2.02 (m, 6 H) 2.07 - 2.17 (m, 4 H) 3.53 (s, 6 H) 3.70 - 3.85 (m, 4 H) 4.05 (t, J=8.35 Hz, 2 H) 5.06 (dd, J=6.72, 2.82 Hz, 2 H) 5.16 - 5.25 (m, 2 H) 6.19 (d, J=8.67 Hz,, 2 H) 6.64 (d, J=8.57 Hz, 2 H) 7.09 - 7.32 (m, 6 H) 7.36 - 7.69 (m, 6 H) 11.60 - 12.09 (m, 2 H); MS (ESI+) m/z 924.6 (M+H).



Example 187

dimethyl ([(2R,5R)-1-{3-[6-(morpholin-4-yl)pyridin-3-yl]phenyl}pyrrolidine-2,5-diyl]bis{(2-aminobenzene-4,1-diyl)carbamoyl(2S)pyrrolidine-2,1-diyl[(2S)-3-methyl-1-oxobutane-1,2-diyl]})biscarbamate

Example 187A

(2R,5R)-2,5-bis(4-chloro-3-nitrophenyl)-1-(3-iodophenyl)pyrrolidine

The mesylate of Example 109C (4.17 g, 7.48 mmol) in DMF (15 ml) was treated with 3-iodoaniline (Aldrich, 7.2 mL, 59.8 mmol), stirred at ambient temperature for 48 hours and diluted into EtOAc. The EtOAc layer was washed 3 X 50 mL with 1 M HCl, with water, brine, dried (Na_2SO_4), filtered and concentrated. Purification by flash chromatography on an Isco 300 g silica cartridge eluting with 10-30% EtOAc in hexane afforded the title compound as a bright yellow foam (2.6 g, 60 %). MS (ESI) m/z 584 $(M+H)^+$.

Example 187B

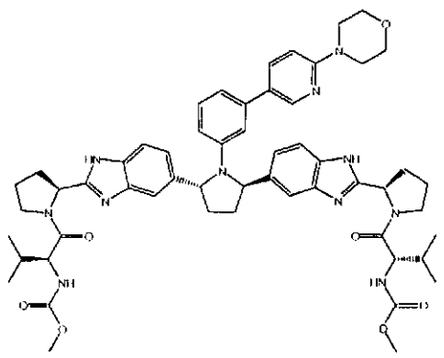
4-(5-(3-((2R,5R)-2,5-bis(4-chloro-3-nitrophenyl)pyrrolidin-1-yl)phenyl)pyridin-2-yl)morpholine

The product from Example 187A (1.4 g, 2.396 mmol), 4-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)morpholine (0.695 g, 2.396 mmol), potassium phosphate (1.017 g, 4.79 mmol), tris(dibenzylideneacetone)dipalladium(0) (0.022 g, 0.024 mmol) and 1,3,5,7-tetramethyl-6-phenyl-2,4,8-trioxa-6-phosphaadamante (0.021 g, 0.072 mmol) were combined in THF (18 mL) / water (6 mL). The mixture was sparged with nitrogen for 15 minutes, stirred for 6-hours diluted into EtOAc, washed with 1M sodium bicarbonate, brine, dried (Na_2SO_4), filtered and concentrated. Purification by flash chromatography on an Isco 120 g silica cartridge eluting with 20-60 % EtOAc in hexane gave the title compound as a yellow glass (1.1 g, 74%). MS (ESI) m/z 620 $(M+H)^+$.

Example 187C

dimethyl ([(2R,5R)-1-{3-[6-(morpholin-4-yl)pyridin-3-yl]phenyl}pyrrolidine-2,5-diyl]bis{(2-aminobenzene-4,1-diyl)carbamoyl(2S)pyrrolidine-2,1-diyl[(2S)-3-methyl-1-oxobutane-1,2-diyl]})biscarbamate

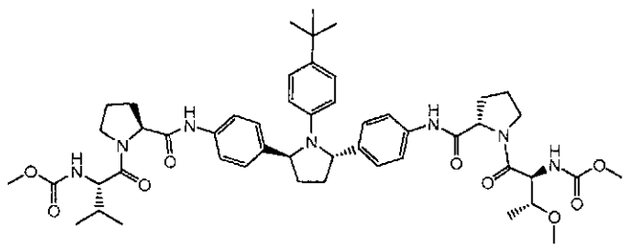
The product from Example 187B (0.5 g, 0.806 mmol), was processed using the methods in Examples 165C and 165D to afford the title compound (400 mg, 45% two steps). ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.89 (dd, *J*=11.82, 6.61 Hz, 12 H) 1.35 - 2.22 (m, 14 H) 3.36 - 3.46 (m, 8 H) 3.52 (s, 6 H) 3.56 - 3.86 (m, 4 H) 3.97 - 4.43 (m, 4 H) 4.85 (s, 4 H) 5.09 (s, 2 H) 6.25 (d, *J*=7.26 Hz, 1 H) 6.42 - 6.51 (m, 3 H) 6.58 (s, 2 H) 6.66 (d, *J*=7.59 Hz, 1 H) 6.81 (d, *J*=8.78 Hz, 1 H) 6.95 - 7.02 (m, 3 H) 7.36 (d, *J*=8.35 Hz, 2 H) 7.51 (dd, *J*=8.73, 2.33 Hz, 1 H) 8.12 (d, *J*=2.06 Hz, 1 H) 9.23 (s, 2 H). MS (ESI) m/z 1031 $(M+H)^+$.



Example 188

methyl {(2S)-1-[(2S)-2-{5-[(2R,5R)-5-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-benzimidazol-5-yl}-1-{3-[6-(morpholin-4-yl)pyridin-3-yl]phenyl}pyrrolidin-2-yl]-1H-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

The product from Example 187C (0.4 g, 0.388 mmol) was treated with acetic acid (0.089 ml, 1.553 mmol) in toluene (7.77 ml) at 50 °C for 4 hours, cooled and concentrated. The residue was dissolved in EtOAc, washed with 10% sodium bicarbonate, brine, dried (Na_2SO_4), filtered and concentrated. Purification by flash chromatography on an Isco Gold 12 g silica cartridge eluting with 1-6% MeOH in dichloromethane afforded the title compound (183 mg, 45%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.71 - 0.90 (m, 12 H) 1.62 - 2.28 (m, 14 H) 3.37 - 3.43 (m, 4 H) 3.53 (s, 6 H) 3.64 - 3.68 (m, 4 H) 3.80 (s, 4 H) 4.05 (t, J=8.35 Hz, 2 H) 5.08 - 5.19 (m, 2 H) 5.48 (s, 2 H) 6.29 (d, J=8.02 Hz, 1 H) 6.54 - 6.64 (m, 2 H) 6.76 (d, J=8.89 Hz, 1 H) 6.93 (d, J=4.66 Hz, 1 H) 7.11 (d, J=8.13 Hz, 2 H) 7.23 - 7.30 (m, 3 H) 7.34 - 7.40 (m, 2 H) 7.46 (s, 2 H) 8.05 (s, 1 H) 12.01 (s, 2 H). MS (ESI) m/z 995 $(M+H)^+$.



Example 189

methyl [(2S,3R)-1-{(2S)-2-[(4-{(2S,5S)-1-(4-tert-butylphenyl)-5-[4-({[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]carbonyl}amino)phenyl]pyrrolidin-2-yl}phenyl)carbamoyl]pyrrolidin-1-yl}-3-methoxy-1-oxobutan-2-yl]carbamate

Example 189A

(S)-tert-butyl 2-(4-((2S,5S)-1-(4-tert-butylphenyl)-5-(4-((S)-1-((S)-2-(methoxycarbonylamino)-3-methylbutanoyl)pyrrolidine-2-carboxamido)phenyl)pyrrolidin-2-yl)phenylcarbamoyl)pyrrolidine-1-carboxylate

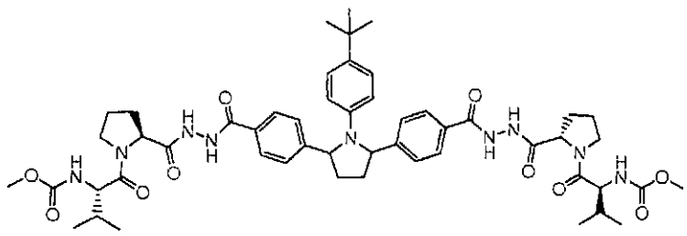
To a solution of the product from Example 213 (33 mg, 0.052 mmol) in anhydrous DMSO (0.5 mL) was added (S)-1-(tert-butoxycarbonyl)pyrrolidine-2-carboxylic acid (13.3 mg, 0.062 mmol), HATU (23.5 mg, 0.062 mmol) and Hunig's base (18 μL, 0.10 mmol). The resulting mixture was stirred at rt for 90 min and then partitioned between H_2O and EtOAc. The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by column chromatography on silica gel using a solvent gradient of 0-10% MeOH in CH_2Cl_2 to give the title compound (33 mg, 76%).

Example 189B

methyl [(2S,3R)-1-{(2S)-2-[(4-{(2S,5S)-1-(4-tert-butylphenyl)-5-[4-({[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]carbonyl}amino)phenyl]pyrrolidin-2-yl}phenyl)carbamoyl]pyrrolidin-1-yl}-3-methoxy-1-oxobutan-2-yl]carbamate

A solution of the product from Example 189A (30 mg, 0.036 mmol) in a 1:1 mixture of CH_2Cl_2:TFA (0.4 mL) was stirred at rt for 45 min. The mixture was concentrated in vacuo, and the residue was partitioned between saturated aq. $NaHCO_3$ and EtOAc (2x). The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo to give a solid. The solid was subjected to the procedure described in Example 189A (27 mg), substituting (2S,3R)-3-methoxy-2-(methoxycarbonylamino)butanoic acid for (S)-1-(tert-butoxycarbonyl)pyrrolidine-2-carboxylic acid, to give the title compound (17 mg, 52%). 1H NMR (400 MHz, DMSO-D6) δ ppm 0.85 - 0.97 (m, 6 H), 1.08 - 1.19 (m, 12 H), 1.60 - 1.66 (m, 2 H), 1.80 - 2.05 (m, 8 H), 2.08 - 2.20 (m, 2 H), 3.25 (s, 3 H), 3.42 - 3.50 (m, 2 H), 3.52 (s, 3 H), 3.53 (s, 3 H), 3.58 - 3.72 (m, 2 H), 3.76 - 3.87 (m, 2 H), 3.98 - 4.06 (m, 1 H), 4.26 (t, *J*=7.81 Hz, 1 H), 4.38 - 4.46 (m, 2 H), 5.15 (d, *J*=6.40 Hz, 2 H), 6.17 (d, *J*=8.78

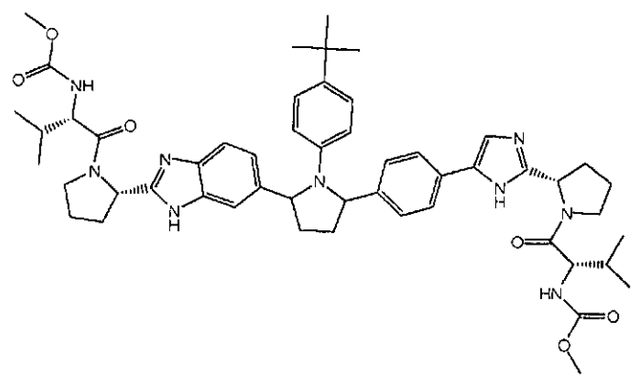
Hz, 2 H), 6.94 (d, *J*=8.89 Hz, 2 H), 7.13 (d, *J*=8.24 Hz, 4 H), 7.32 (t, *J*=8.84 Hz, 2 H), 7.49 (dd, *J*=8.57, 2.06 Hz, 4 H), 9.96 (d, *J*=15.51 Hz, 2 H). MS (ESI) m/z 910.6 $(M+H)^+$.



Example 190

dimethyl ([1-(4-tert-butylphenyl)pyrrolidine-2,5-diyl]bis{benzene-4,1-diylcarbonylhydrazine-2,1-diylcarbonyl(2S)pyrrolidine-2,1-diyl[(2S)-3-methyl-1-oxobutane-1,2-diyl]})biscarbamate)

To a solution of the product from Example 171B (50 mg, 0.106 mmol) and the product from Example 37B (72 mg, 0.27 mmol) in anhydrous DMSO (1 mL) was added HATU (100 mg, 0.27 mmol) and Hunig's base (56 µL, 0.32 mmol). The resulting mixture was stirred at rt for 90 min, and then partitioned between H_2O and EtOAc (2x). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by column chromatography on silica gel using a solvent gradient of 0-10% MeOH in CH_2Cl_2 to give the title compound (68 mg, 65%) as a mixture of cis and trans stereoisomers. 1H NMR (400 MHz, DMSO-D6) δ ppm 0.81 - 0.98 (m, 12 H), 1.08 - 1.17 (m, 9 H), 1.64 - 1.77 (m, 2 H), 1.78 - 2.06 (m, 8 H), 2.07 - 2.22 (m, 2 H), 3.50 - 3.55 (m, 6 H), 3.58 - 3.69 (m, 2 H), 3.70 - 3.83 (m, 2 H), 3.96 - 4.08 (m, 2 H), 4.38 - 4.49 (m, *J*=8.13 Hz, 2 H), 4.76 - 4.87 (m, 0.7 H), 5.28 - 5.40 (m, 1.3 H), 6.14 - 6.33 (m, 2 H), 6.92 - 7.08 (m, 2 H), 7.27 - 7.38 (m, *J*=8.02 Hz, 5 H), 7.62 (d, *J*=8.35 Hz, 1 H), 7.79 - 7.96 (m, 4 H), 9.87 - 9.98 (m, 2 H), 10.31 - 10.44 (m, 2 H); MS (ESI) m/z 981.1 $(M+H)^+$.



Example 191

methyl {(2S)-1-[(2S)-2-(5-{4-[(2S,5S)-1-(4-tert-butylphenyl)-5-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-benzimidazol-6-yl}pyrrolidin-2-yl]phenyl}-1H-imidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

and

methyl {(2S)-1-[(2S)-2-(5-{4-[(2R,5R)-1-(4-tert-butylphenyl)-5-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-benzimidazol-6-yl}pyrrolidin-2-yl]phenyl}-1H-imidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

Example 191A

1-(4-bromophenyl)-4-(4-chloro-3-nitrophenyl)butane-1,4-dione

Zinc chloride (2.73 g, 20 mmole)was treated with anhydrous benzene (10 mL) followed by diethylamine (1.55 mL, 15 mmole) and tert-butanol (1.4 mL, 15 mmole) and the resulting slurry was stirred at room temperature for 1.75 hr until all solids had dissolved. To the cloudy suspension was added 4'-chloro-3'-nitroacetophenone followed by 2,4'-dibromoacetophenone and the resulting light yellow slurry was stirred at room temperature for 68 hours. The resulting thick white slurry was treated with 25 mL 5% aqueous sulfuric acid with stirring and the resulting slurry was filtered. The solid was washed with water (50 mL), MeOH (50 mL)and CH_2Cl_2 (50 mL), then dried in vacuo at room temperature for 1 hr and at 55°C for 5 hr. giving the title compound as a white solid, 3.4 g, 86%.

Example 191B

1-(4-bromophenyl)-4-(4-chloro-3-nitrophenyl)butane-1,4-diol

The product from Example 191A (4.62 g, 11.65 mmole) was mixed with EtOH (100 mL) and the resulting slurry was treated in portions over a five minute period with solid $NaBH_4$ (0.97 g, 25.6 mmole). The resulting foaming slurry was stirred and heated at reflux for 1 hr. The reaction was deemed complete by LC-MS. The reaction mixture was cooled to room temperature and concentrated in vacuo to an oily residue. The residue was dissolved in CH_2Cl_2 and applied to an 80 g silica gel column. The column was eluted with a gradient of hexane/acetone, 90/10 to 20/80 over 32 minutes. The fractions containing product were pooled and concentrated in vacuo giving the title compound as a white solid, 3.14 g, 67%.

Example 191C

1-(4-bromophenyl)-4-(4-chloro-3-nitrophenyl)butane-1,4-diyl dimethanesulfonate

The product from Example 191B (3.14 g, 7.84 mmole) was dissolved in 70 mL CH_2Cl_2 and cooled in an ice-acetone bath to -10 °C. Triethylamine (3.82 mL, 27.4 mmole) was added dropwise to the cold solution, followed by dropwise addition of methanesulfonyl chloride (1.53 mL, 19.59 mmole) in 20 mL CH_2Cl_2 over 10 minutes. The resulting clear solution was stirred in the cold for 90 min. The reaction was deemed complete by LC-MS analysis and the solvent was removed in vacuo leaving a light yellow solid as the title compound, (4.36 g, 100%), that was used directly in the next reaction.

Example 191D

2-(4-bromophenyl)-1-(4-tert-butylphenyl)-5-(4-chloro-3-nitrophenyl)pyrrolidine

The light yellow solid, obtained in Example 191C (4.36 g, 7.84 mmole) was treated with DMF (15 mL) followed by dropwise addition of 4-tert-butylaniline (12.47 mL, 78 mmole), then placed in an oil bath at 52 °C and stirred for a total of 12 hr. The reaction mixture was concentrated in vacuo to an oily residue. The mixture was diluted with 100 mL EtOAc and washed with 50 mL 0.5 M HCl. The aqueous layer was back extracted with 100 mL EtOAc. The combined organic extracts were washed with 10% $NaHCO_3$, 10% NaCl, dried over anhydrous Na_2SO_4(s), filtered and solvent removed in vacuo leaving a reddish oil. The oil was dissolved in CH_2Cl_2 (10 mL) and applied to an 80 g silica gel column. The column was eluted with a gradient of hexane/Acetone, 90/10 to 30/70 over 32 minutes. The title compound was isolated as a 1:1 mixture of cis and trans-pyrrolidine isomers, 3.13 g, 75%.

Example 191E

4-(5-(4-bromophenyl)-1-(4-tert-butylphenyl)pyrrolidin-2-yl)-N-(2,4-dimethoxybenzyl)-2-nitroaniline

The product from Example 191D (1.1 g, 2.14 mmole) was treated with 2,4-dimethoxybenzylamine (3.22 mL, 21.41 mmole) and the resulting slurry was heated at 140 °C (oil bath) for 1 hr. The resulting homogeneous red reaction mixture was concentrated in vacuo leaving a red oil. The oil was diluted with 30 mL CH_2Cl_2, filtered solid and applied the filtrate to a 120 g silica gel column. The column was eluted with CH2Cl2 over a 25 min period. The fractions were pooled and concentrated in vacuo giving the title compound as an orange foamy solid as a mixture of stereoisomers (1.18 g).

Example 191F

4-(5-(4-bromophenyl)-1-(4-tert-butylphenyl)pyrrolidin-2-yl)-N1-(2,4-dimethoxybenzyl)benzene-1,2-diamine

The product from example 191E (1.18 g, 1.831 mmole) was dissolved in a mixture of THF(10 mL):EtOH(10 mL):EtOAc (10 mL), treated with PtO_2 (42 mg)and evacuated 10 minutes, followed by introduction of H_2 (g) via balloon. The reaction mixture was stirred overnight at room temperature. The next day, the reaction mixture was filtered and the solvent removed in vacuo leaving a dark green foamy solid. The solid was dissolved in 10 mL CH_2Cl_2 applied to a 40 g silica gel column and eluted with a gradient of hexane/EtOAc; 90/10 to 30/70 over 20 minutes. The title compound was isolated as a white foamy solid as a mixture of isomers 0.54 g, 48%.

Example 191G

methyl (2S)-1-((2S)-2-(5-(5-(4-bromophenyl)-1-(4-tert-butylphenyl)pyrrolidin-2-yl)-2-(2,4-dimethoxybenzylamino)phenylcarbamoyl)pyrrolidin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamate

(S)-1-((S)-2-(methoxycarbonylamino)-3-methylbutanoyl)pyrrolidine-2-carboxylic acid (0.339g, 1.245 mmole) and HOBt (0.191 g, 1.245 mmole) were dissolved in DMF (4 mL) cooled in an ice bath and treated with EDAC (0.245 g, 1.245 mmole) and N-Methylmorpholine (NMM) (0.55 mL, 4.98 mmole). The resulting solution was stirred 5 minutes in the ice bath, treated dropwise with the product from Example 191F in DMF (4 mL) and the resulting dark mixture was stirred in the ice bath for 1 hr then at room temperature for 18 hr. The next day, the reaction mixture was diluted with EtOAc (50 mL) and the organic layer was washed with 10% $NaHCO_3$ and 10% NaCl, dried over anhydrous Na_2SO_4(s), filtered and the solvent was removed in vacuo leaving an oily residue as the title compound as a mixture of isomers (0.65 g). ESI+ (m/z): 868.2.

Example 191H

methyl (2S)-1-((2S)-2-(2-amino-5-(5-(4-bromophenyl)-1-(4-tert-butylphenyl)pyrrolidin-2-yl)phenylcarbamoyl)pyrrolidin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamate

The product from example 191G (0.65 g, 0.748 mmole) was dissolved in CH_2Cl_2 (10 mL) then added concentrated trifluoroacetic acid (2 mL, 26 mmole)) and the reaction mixture was stirred 10 minutes. The solvent was removed in vacuo and the residue was re-evaporated twice from CH_2Cl_2 and once from toluene. The residue was dissolved in EtOAc (100 mL) washed with 10% $NaHCO_3$, dried over anhydrous Na_2SO_4(s), filtered and solvent removed in vacuo leaving a brown foamy material as the title compound as a mixture of isomers (0.5 g).

Example 191I

methyl (2S)-1-((2S)-2-(6-(5-(4-bromophenyl)-1-(4-tert-butylphenyl)pyrrolidin-2-yl)-1H-benzo[d]imidazol-2-yl)pyrrolidin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamate

The product from Example 191H (0.5 g, 0.696 mmole) was treated with acetic acid (5 mL, 87 mmole) and heated in an oil bath at 75 °C for 70 min. The reaction mixture was cooled to room temperature and concentrated in vacuo leaving an oily residue. The residue was dissolved in EtOAc (100 mL) washed with 10% $NaHCO_3$ (20 mL) and 10% NaCl (20 mL), dried over anhydrous Na_2SO_4(s), filtered and solvent removed in vacuo leaving a brown foamy solid. The residue was dissolved in 10 mL CH_2Cl_2 and applied to a 12 g silica gel column. The column was eluted with a gradient of CH2Cl2/MeOH, 99/1 to 95/5 over 15 minutes and the product was isolated as a tan solid as a mixture of isomers (0.31g). ESI(m/z)+: 702.3.

Example 191J

methyl (2S)-1-((2S)-2-(6-(1-(4-tert-butylphenyl)-5-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)pyrrolidin-2-yl)-1H-benzo[d]imidazol-2-yl)pyrrolidin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamate

The product from Example 191I (0.31g, 0.442 mmole), bis(pinacolato)diboron (0.34 g, 1.327 mmole) and potassium acetate (0.17 g, 1.77 mmole) were combined and dissolved in toluene (5 mL), added 1,1'-bis(diphenylphosphino)ferrocenedichloro palladium(II) dichloromethane complex (32 mg, 0.044 mmole) and the reaction mixture was bubbled with N_2 for 5 minutes, sealed and placed in an oil bath at 95°C for 2 hr. The mixture was cooled to room temperature and diluted with EtOAc (100 mL) washed with water (20 mL) and 10% NaCl (20 mL), dried over anhydrous Na_2SO_4(s), filtered and solvent removed in vacuo leaving a brown oil. The oil was dissolved in CH_2Cl_2 (10 mL), applied to a 12 g silica gel column and the column was eluted with a gradient of hexane:EtOAc, 50:50 to 0:100 over 18 minutes. The title compound was isolated as a white solid as a mixture of isomers (0.23 g).

Example 191K

(2S)-tert-butyl 2-(5-(4-(1-(4-tert-butylphenyl)-5-(2-((S)-1-((S)-2-(methoxycarbonylamino)-3-methylbutanoyl)pyrrolidin-2-yl)-1H-benzo[d]imidazol-6-yl)pyrrolidin-2-yl)phenyl)-1H-imidazol-2-yl)pyrrolidine-1-carboxylate.

The product from example 191J (0.23g, 0.308 mmole) and the product from Example 26D (0.195g, 0.615 mmole) were combined in a 20 mL microwave tube and dissolved in toluene (1.5 mL)/ethanol(1.5 mL) . To this solution was added 1M aqueous sodium carbonate 0.92 mL, 0.92 mmole) followed by 1,1'-bis(diphenylphosphino)ferrocenedichloro palladium(II) dichloromethane complex (23 mg, 0.036 mmole) and the resulting mixture was bubbled with N_2 for 10 minutes, sealed and heated at 100°C for 2 hr. The reaction mixture was cooled to room temperature and diluted with EtOAc (50 mL). The aqueous carbonate layer was separated and the organic layer was washed with water (20 mL) and 10% NaCl (20 mL), dried over anhydrous Na_2SO_4(s), filtered and solvent removed in vacuo leaving a foamy solid. The solid was dissolved in 10 mL CH_2Cl_2 and applied to a 12 g silica gel column. The column was eluted with a gradient of CH2Cl2/MeOH, 99/1 to 95/5 over 20 minutes. The title compound was obtained as a tan solid as a mixture of isomers (0.11g).

Example 191L

(2S)-2-(5-(4-(1-(4-tert-butylphenyl)-5-(2-((S)-1-((S)-2-(methoxycarbonylamino)-3-methylbutanoyl)pyrrolidin-2-yl)-1H-benzo[d]imidazol-6-yl)pyrrolidin-2-yl)phenyl)-1H-imidazol-2-yl)pyrrolidinium chloride

The product from example 191K (0.11 g, 0.28 mmole) was dissolved in dioxane (2 mL), then added 4N HCl/dioxane (1 mL). The resulting solid mass is stirred 30 minutes at room temperature.

The solvent is removed in vacuo leaving a tan solid as the title compound as a mixture of isomers (0.092g) which stored under vacuum overnight.

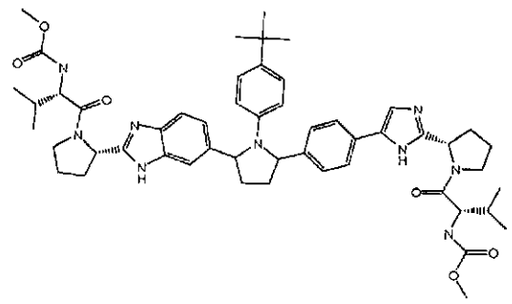
Example 191M

methyl {(2S)-1-[(2S)-2-(5-{4-[(2S,5S)-1-(4-tert-butylphenyl)-5-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-benzimidazol-6-yl}pyrrolidin-2-yl]phenyl}-1H-imidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

and

methyl {(2S)-1-[(2S)-2-(5-{4-[(2R,5R)-1-(4-tert-butylphenyl)-5-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-benzimidazol-6-yl}pyrrolidin-2-yl]phenyl}-1H-imidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

The product from example 191L (0.092g, 0.116 mmole) , (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (0.020 g, 0.116 mmole)and HOBt (000.018g, 0.116 mmole) were combined in a 25 mL RB flask and dissolved in DMF (1 mL). The reaction mixture was placed in an ice bath and treated with EDAC (0.022g, 0.116 mmole) and N-methylmorpholine (0.12 mL, 1.091 mmole. The light yellow reaction mixture was stirred in the ice bath for 1 hr, then stirred at room temperature for 9 hr. The reaction mixture was diluted with EtOAc (100 mL) washed with water (20 mL) and 10% NaCl (20 mL), dried over anhydrous Na_2SO_4(s), filtered and solvent removed in vacuo leaving an oily residue. The residue was dissolved in 5 mL CH2Cl2 and applied to a 12 g silica gel column. The column was eluted with a gradient of CH_2Cl_2/MeOH, 99/1 to 95/5 over 22 minutes. The title compound was isolated from the first fraction eluted from the column as a white solid consisting of a mixture of trans-pyrrolidine isomers, 21 mg, 19%. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.71 - 0.95 (m, 12 H) 1.11 (s, 9 H) 1.99 (m, 6 H) 2.13 (m, 4 H) 3.53 (s, 6 H) 3.81 (m, 4 H) 4.04 (m, 4 H) 5.06 (m, 2 H) 5.11 - 5.15 (m, 1 H) 5.18 - 5.26 (m, 1 H) 5.32 (m, 1 H) 6.25 (m, 2 H) 6.86 - 6.96 (m, 1 H) 7.05 (m, 2 H) 7.33 (m, 6 H) 7.61 (m, 2 H) 11.53 (s, 1 H) 11.68 (s, 1 H) 12.00 (m, 2 H); ESI+: 914.5.



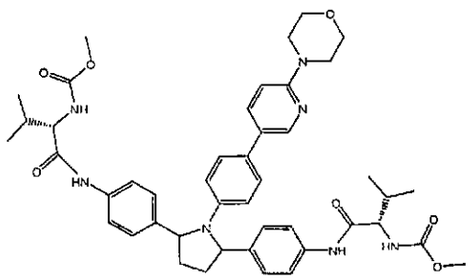
Example 192

methyl {(2*S*)-1-[(2*S*)-2-(5-{4-[(2*R*,5*S*)-1-(4-*tert*-butylphenyl)-5-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1*H*-benzimidazol-6-yl}pyrrolidin-2-yl]phenyl}-1*H*-imidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

and

methyl {(2*S*)-1-[(2*S*)-2-(5-{4-[(2*S*,5*R*)-1-(4-*tert*-butylphenyl)-5-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1*H*-benzimidazol-6-yl}pyrrolidin-2-yl]phenyl}-1*H*-imidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

The title compound was isolated from the late fraction eluted from the column described in Example 191M as a white solid as a mixture of cis pyrrolidine isomers, 18 mg, 17%. ^{1}H NMR (free base) (400 MHz, DMSO-d_6) δppm 0.71 - 0.95 (m, 12 H) 1.11 (s, 9 H) 1.99 (m, 6 H) 2.13 (m, 4 H) 3.53 (s, 6 H) 3.81 (m, 4 H) 4.04 (m, 4 H) 4.72 (m, 1H), 4.83 (m, 1 H) 5.11 - 5.15 (m, 1 H) 5.18 - 5.26 (m, 1 H) 5.32 (m, 1 H) 6.25 (m, 2 H) 6.86 - 6.96 (m, 1 H) 7.05 (m, 2 H) 7.33 (m, 6 H) 7.61 (m, 2 H) 11.53 (s, 1 H) 11.68 (s, 1 H) 12.00 (m, 2 H); ESI+: 914.5.



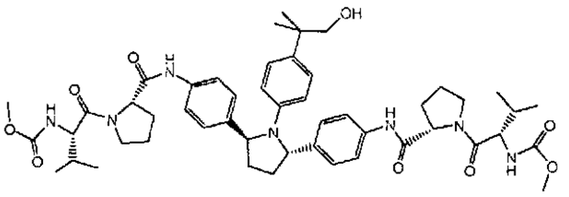
Example 193

dimethyl ([(2*S*,5*S*)-1-{4-[6-(morpholin-4-yl)pyridin-3-yl]phenyl}pyrrolidine-2,5-diyl]bis{benzene-4,1-diylimino[(2*S*)-3-methyl-1-oxobutane-1,2-diyl]})biscarbamate

and

dimethyl ([(2*R*,5*R*)-1-{4-[6-(morpholin-4-yl)pyridin-3-yl]phenyl}pyrrolidine-2,5-diyl]bis{benzene-4,1-diylimino[(2*S*)-3-methyl-1-oxobutane-1,2-diyl]})biscarbamate

Example 86A and 4-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)morpholine were processed using sequentially the methods of Examples 99A, 99B, and 1F (substituting (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (38.2mg, 0.218mmole) for (S)-1-(tert-butoxycarbonyl)pyrrolidine-2-carboxylic acid). Reverse phase (C_{18}) HPLC provided the title compound, a white solid, as a 1:1 mixture of trans diastereomers (40.4mg, 50.6% yield). 1H NMR (free base) (400 MHz, DMSO-D6) δ ppm 0.89 (d, *J*=6.72 Hz, 12 H) 1.67 (d, *J*=5.64 Hz, 2 H) 1.92 - 2.04 (m, 2 H) 3.37 - 3.41 (m, 4 H) 3.53 (d, *J*=2.06 Hz, 6 H) 3.67 (d, *J*=5.10 Hz, 4 H) 3.94 (t, *J*=8.08 Hz, 2 H) 5.25 (s, 2 H) 6.33 (d, *J*=8.67 Hz, 2 H) 6.78 (d, *J*=8.89 Hz, 1 H) 7.14 - 7.23 (m, 6 H) 7.32 (d, *J*=8.67 Hz, 2 H) 7.54 (d, *J*=7.92 Hz, 4 H) 7.66 (dd, *J*=8.84, 2.55 Hz, 1 H) 8.26 (d, *J*=2.49 Hz, 1 H) 10.01 (s, 2 H). MS ESI(+) m/z @ 806.5 (M+H)+.



Example 194

dimethyl ({(2S,5S)-1-[4-(1-hydroxy-2-methylpropan-2-yl)phenyl]pyrrolidine-2,5-diyl}bis{benzene-4,1-diylcarbamoyl(2S)pyrrolidine-2,1-diyl[(2S)-3-methyl-1-oxobutane-1,2-diyl]})biscarbamate)

Example 194A

ethyl 2-methyl-2-(4-nitrophenyl)propanoate

Into a 500mL Morton flask equipped for mechanical stirring was added at room temperature under nitrogen ethyl 2-(4-nitrophenyl)acetate (10.0g, 55.2mmole), anhydrous dimethylformamide (200mL) 18-crown-6 (2.189g, 8.28mmole) and methyl iodide (23.13mL, 370mmole). The flask was cooled in an ice bath and sodium hydride as a 60% mineral oil dispersion (7.73g, 193mmole) was added in portions so as to maintain the internal temperature at or below +10°C. The addition required fifty three minutes. On completion of the addition the reaction mixture was allowed to slowly warm to room temperature and stirred overnight. Subsequent cooling in an ice bath was followed by the drop wise addition of water (200mL) with vigorous stirring. The mixture was partitioned between water (1200mL) and ethyl ether (200mL). The aqueous phase was extracted with ethyl ether (3x200mL each) and the combined organics water washed (3x150mL), dried over $MgSO_4$, filtered and concentrated to provide the title compound in nearly quantitative yield sufficiently pure for use as isolated.

Example 194B

2-methyl-2-(4-nitrophenyl)propan-1-ol

To a solution of the product from Example 194A (12.32g, 55.2mmole) in anhydrous THF (300mL) at room temperature under nitrogen was added dropwise via cannulae 1M BH_3 in THF (200mL) over ten and one half minutes. On completion of the addition the flask was equipped with a condenser and the mixture heated under nitrogen to reflux in an oil bath for ten hours before cooling to room temperature. The reaction was quenched by the cautious drop wise addition of methanol (60mL).The resulting mixture was concentrated to an oil which was then dissolved in ethyl acetate (150mL) and treated with 1N HCl and allowed to stir at room temperature for one hour. The resulting organic phase was washed with brine (4x50mL), dried over $MgSO_4$, filtered and concentrated. The residue was taken up in toluene (25mL) and re-concentrated. The oily solid was suspended in hexane (50mL) and collected by vacuum filtration. The cake was washed with hexane

(50mL) then dried under vacuum to provide the title compound (9.55g, 89% yield) as a light orange solid. MS (DCI+) m/z @ 213.1 $(M+NH_4)+$.

Example 194C

2-(4-aminophenyl)-2-methylpropan-1-ol

The product from Example 194B (0.321g, 1.644mmole) was dissolved in a mixture of THF (10mL) and ethanol (2mL). To this was added platinum(IV)oxide (0.030g, 0.131mmole). The flask was capped with a septum and the contents vacuum degassed three times. Hydrogen was introduced via a balloon and the mixture stirred at room temperature. An additional 38.2mg (0.167mmole) of catalyst was added in two aliquots before chromatographic analysis indicated that the starting material was consumed. After stirring overnight under hydrogen the mixture was filtered through a sand / celite plug followed by an ethyl acetate rinse. The filtrate was concentrated to dryness and the residue purified by chromatography on amine modified silica gel eluting with ethyl acetate – hexane beginning at 8% and advancing to 66% ethyl acetate to provide the title compound (0.3645g, 68% yield) as a clear oil. MS (DCI+) m/z @ 183.1 $(M+NH_4)+$.

Example 194D

2-(4-((2S,5S)-2,5-bis(4-nitrophenyl)pyrrolidin-1-yl)phenyl)-2-methylpropan-1-ol

The product from Example 194C (0.595g, 3.60mmole) was combined in DMF (3mL) with (1R,4R)-1,4-bis(4-nitrophenyl)butane-1,4-diyl dimethanesulfonate (0.259g, 0.530mmole), prepared as described in Example 37C, then heated overnight under nitrogen in an oil bath at 50°C. The reaction mixture was partitioned between ethyl acetate (50mL) and water (50mL). The organic phase was water washed (3x25mL), dried over $MgSO_4$, filtered and concentrated to an oil. Chromatography on silica gel eluting with ethyl acetate – hexane provided the title compound (0.0835g, 34.1% yield) as an orange semi-solid.

Example 194E

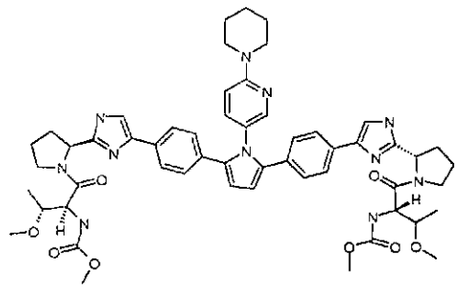
2-(4-((2S,5S)-2,5-bis(4-aminophenyl)pyrrolidin-1-yl)phenyl)-2-methylpropan-1-ol

The product from Example 194D (83.5mg, 0.181mmole) was reacted as described in Example 99B to provide the title compound in quantitative yield as a light yellow solid. MS (DCI+) m/z @ 402.3 (M+H)+.

Example 194F

dimethyl ({(2S,5S)-1-[4-(1-hydroxy-2-methylpropan-2-yl)phenyl]pyrrolidine-2,5-diyl}bis{benzene-4,1-diylcarbamoyl(2S)pyrrolidine-2,1-diyl[(2S)-3-methyl-1-oxobutane-1,2-diyl]})biscarbamate)

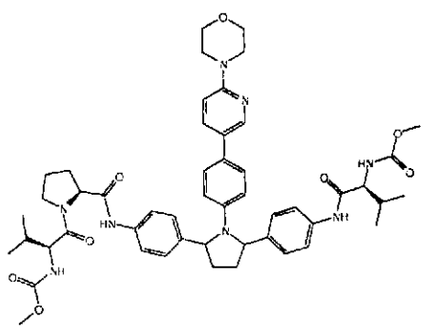
The product from Example 194E (73.0mg, 0.181mmole) was reacted with the product from Example 37B (104.0mg, 0.380mmole) as described in Example 37F. The title compound was isolated after purification by reverse phase (C18) HPLC as an off white solid (97.4mg, 59% yield). H1 NMR (free base) (400 MHz, DMSO-D6) δ ppm 0.79 - 0.96 (m, 12 H) 1.03 (s, 6 H) 1.61 (s, 2 H) 1.76 - 2.04 (m, 8 H) 2.04 - 2.17 (m, 2 H) 3.20 (dd, *J*=5.42, 1.84 Hz, 2 H) 3.51 (s, 6 H) 3.60 (dd, 2 H) 3.78 (s, 2 H) 4.01 (t, *J*=8.46 Hz, 2 H) 4.35 - 4.49 (m, 3 H) 5.14 (s, 2 H) 6.16 (d, *J*=8.78 Hz, 2 H) 6.89 (d, *J*=8.78 Hz, 2 H) 7.12 (d, *J*=8.57 Hz, 4 H) 7.29 (d, *J*=8.35 Hz, 2 H) 7.48 (d, *J*=8.46 Hz, 4 H) 9.97 (s, 2 H). MS ESI(+), m/z @ 910.7 (M+H)+.



Example 195

methyl [(1*S*,2*R*)-2-methoxy-1-({(2*S*)-2-[4-(4-{5-[4-(2-{(2*S*)-1-[*N*-(methoxycarbonyl)-*O*-methyl-L-threonyl]pyrrolidin-2-yl}-1*H*-imidazol-4-yl)phenyl]-1-(6-piperidin-1-ylpyridin-3-yl)-1*H*-pyrrol-2-yl}phenyl)-1*H*-imidazol-2-yl]pyrrolidin-1-yl}carbonyl)propyl]carbamate

The title compound was prepared using the methods from Example 144E substituting (2S,3S)-3-methoxy-2-(methoxycarbonylamino)butanoic acid for (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid to provide the title compound (280 mg, 37% yield). ^{1}H NMR (400 MHz, DMSO-D6) δ 12.12 – 11.70 (m, 2H), 7.85 – 7.76 (m, 1H), 7.63 – 7.49 (m, 4H), 7.49 – 7.39 (m, 2H), 7.34 – 7.03 (m, 7H), 6.77 – 6.69 (m, 1H), 6.54 – 6.41 (m, 2H), 5.08 – 4.99 (m, 2H), 4.27 (t, *J* = 7.6, 2H), 3.86 – 3.75 (m, 4H), 3.54 (s, 6H), 3.50 – 3.43 (m, 4H), 3.17 (s, 6H), 2.19 – 1.88 (m, 10H), 1.61 – 1.44 (m, 6H), 1.12 – 0.99 (m, 6H). MS (ESI; M+H) m/z = 997.

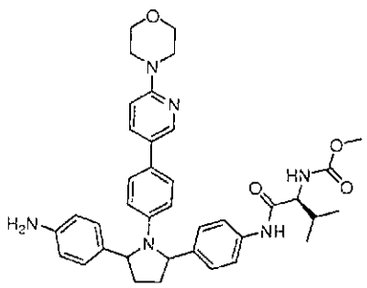


Example 196

N-(methoxycarbonyl)-L-valyl-*N*-{4-[(2*S*,5*S*)-5-(4-{[*N*-(methoxycarbonyl)-L-valyl]amino}phenyl)-1-{4-[6-(morpholin-4-yl)pyridin-3-yl]phenyl}pyrrolidin-2-yl]phenyl}-L-prolinamide

and

N-(methoxycarbonyl)-L-valyl-*N*-{4-[(2*R*,5*R*)-5-(4-{[*N*-(methoxycarbonyl)-L-valyl]amino}phenyl)-1-{4-[6-(morpholin-4-yl)pyridin-3-yl]phenyl}pyrrolidin-2-yl]phenyl}-L-prolinamide



Example 196A

methyl (2S)-1-(4-(5-(4-aminophenyl)-1-(4-(6-morpholinopyridin-3-yl)phenyl)pyrrolidin-2-yl)phenylamino)-3-methyl-1-oxobutan-2-ylcarbamate

In an oven-dried 5-mL round bottom flask purged with nitrogen, dissolved 4,4'-(1-(4-(6-morpholinopyridin-3-yl)phenyl)pyrrolidine-2,5-diyl)dianiline (30 mg, 0.061 mmol; prepared from Example 86A and 4-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)morpholine using the methods of Examples 99A and 99B), and (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (11.22 mg, 0.064 mmol) in anhydrous DMSO (1 mL), added HATU (26.3 mg, 0.067 mmol) and diisopropylethylamine (0.021 mL, 0.122 mmol), and stirred yellow solution at 25 °C for 30 min. Diluted the reaction with MeOH (1 mL) and purified by RP-C_{18} HPLC (Waters Prep LC, 40mm Module with Nova Pak HR C_{18} 6µm 40x100mm Prep Pak cartridge) eluting with a 30 min gradient of 95:5 0.1% TFA in H_2O/AcCN to 25:75 0.1% TFA in H_2O/AcCN, then 10 min to 100% AcCN at 20 mL/min. Pure fractions were concentrated by rotary evaporation (water bath 35°) to a small volume, partitioned between 20% iPrOH/$CHCl_3$ (50 mL) and sat'd aq $NaHCO_3$ (15 mL), separated layers, dried the organic extract over anhydrous $MgSO_4$, filtered, and concentrated by rotary evaporation to afford the title compound as an off-white solid (14.6 mg, 37%) as a mixture of stereoisomers. MS (ESI+) m/z 649 $(M+H)^+$, 707 $(M+AcCN+NH_4)^+$, 1297 $(2M+H)^+$.

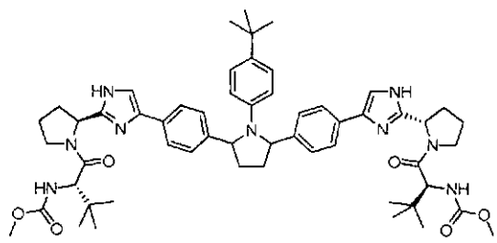
Example 196B

N-(methoxycarbonyl)-L-valyl-*N*-{4-[(2*S*,5*S*)-5-(4-{[*N*-(methoxycarbonyl)-L-valyl]amino}phenyl)-1-{4-[6-(morpholin-4-yl)pyridin-3-yl]phenyl}pyrrolidin-2-yl]phenyl}-L-prolinamide

and

N-(methoxycarbonyl)-L-valyl-*N*-{4-[(2*R*,5*R*)-5-(4-{[*N*-(methoxycarbonyl)-L-valyl]amino}phenyl)-1-{4-[6-(morpholin-4-yl)pyridin-3-yl]phenyl}pyrrolidin-2-yl]phenyl}-L-prolinamide

In a nitrogen-purged 5-mL round bottom flask, dissolved the product of Example 196A (14 mg, 0.022 mmol) in anhydrous DMSO (1 mL), added the product of Example 37B (6.46 mg, 0.024 mmol), HATU (9.30 mg, 0.024 mmol), and diisopropylethylamine (7.54 µL, 0.043 mmol). Stirred at 25 °C for 1 hr, diluted the reaction with MeOH (1 mL) and purified by RP-C_{18} HPLC (Waters Prep LC, 40mm Module with Nova Pak HR C_{18} 6µm 40x100mm Prep Pak cartridge) eluting with a 30 min gradient of 95:5 0.1% TFA in H_2O/AcCN to 25:75 0.1% TFA in H_2O/AcCN, then 10 min to 100% AcCN at 20 mL/min. Pure fractions were concentrated by rotary evaporation (water bath 35°C) to near-dryness, the residue taken up in 1:5 v/v CH_2Cl_2/hexanes and evaporated (3 times), and the residue dried *in vacuo* to give a yellow solid (11mg). The TFA salt was dissolved in 20% iPrOH/$CHCl_3$ (30 mL), washed thoroughly with sat'd aq $NaHCO_3$ (5 mL), extracted the aqueous phase with 20% iPrOH/$CHCl_3$ (20 mL), dried the combined organic extracts over anhydrous MgSO4, filtered, and concentrated by rotary evaporation to afford the title compounds as a white solid (7 mg, 35%). ^{1}H NMR (400 MHz, DMSO-D6) δ ppm 0.83 - 0.96 (m, 12 H), 1.60 - 1.71 (m, 2 H), 1.81 - 2.21 (m, 7 H), 3.36 - 3.43 (m, 4 H), 3.49 - 3.56 (m, 6 H), 3.58 - 3.65 (m, 1 H), 3.65 - 3.70 (m, 4 H), 3.75 - 3.85 (m, 1 H), 3.94 (t, *J*=8.08 Hz, 1 H), 4.02 (t, *J*=8.19 Hz, 1 H), 4.42 (dd, *J*=7.86, 4.93 Hz, 1 H), 5.24 (d, *J*=5.31 Hz, 2 H), 6.32 (d, *J*=8.35 Hz, 2 H), 6.78 (d, *J*=9.00 Hz, 1 H), 7.13 - 7.19 (m, 4 H), 7.21 (d, *J*=8.78 Hz, 2 H), 7.26 - 7.35 (m, 2 H), 7.48 - 7.56 (m, 4 H), 7.66 (dd, *J*=7.86, 1.14 Hz, 1 H), 8.25 (d, *J*=2.17 Hz, 1 H), 10.00 (d, *J*=3.47 Hz, 2 H); MS (ESI+) m/z 903 $(M+H)^+$.



Example 197

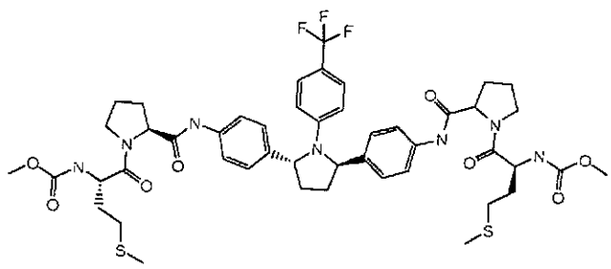
methyl {(2*S*)-1-[(2*S*)-2-(4-{4-[(2*S*,5*S*)-1-(4-*tert*-butylphenyl)-5-(4-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3,3-dimethylbutanoyl}pyrrolidin-2-yl]-1*H*-imidazol-4-yl}phenyl)pyrrolidin-2-yl]phenyl}-1*H*-imidazol-2-yl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl}carbamate

and

methyl {(2*S*)-1-[(2*S*)-2-(4-{4-[(2*R*,5*R*)-1-(4-*tert*-butylphenyl)-5-(4-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3,3-dimethylbutanoyl}pyrrolidin-2-yl]-1*H*-imidazol-4-yl}phenyl)pyrrolidin-2-yl]phenyl}-1*H*-imidazol-2-yl)pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl}carbamate

The product from Example 42F (0.228 g, 0.364 mmol) was processed as in Example 1H to give 0.035 g (10%) of the title compound as a solid as a mixture of trans isomers. ^{1}H NMR (free

base) (400 MHz, DMSO-D6) δ ppm 0.91 (d, J=7.59 Hz, 18 H) 1.08 (s, 9 H) 1.63 - 1.73 (m, 2 H) 1.83 - 2.24 (m, 12 H) 3.54 (s, 6 H) 3.70 - 3.80 (m, 2 H) 4.21 (d, J=7.92 Hz, 2 H) 5.06 (dd, J=6.99, 3.52 Hz, 2 H) 5.15 - 5.25 (m, 2 H) 6.21 (d, J=8.67 Hz, 2 H) 6.92 (dd, J=8.73, 2.44 Hz, 2 H) 7.05 (d, J=8.78 Hz, 2 H) 7.14 (dd, J=8.24, 3.47 Hz, 4 H) 7.37 (s, 2 H) 7.61 (d, J=8.02 Hz, 4 H) 11.69 (s, 2 H); MS ESI+ m/z 968.8 (M+H)+.



Example 198

methyl [(2*S*)-1-{(2*S*)-2-[(4-{(2*R*,5*R*)-5-{4-[({1-[(2*S*)-2-[(methoxycarbonyl)amino]-4-(methylsulfanyl)butanoyl]pyrrolidin-2-yl}carbonyl)amino]phenyl}-1-[4-(trifluoromethyl)phenyl]pyrrolidin-2-yl}phenyl)carbamoyl]pyrrolidin-1-yl}-4-(methylsulfanyl)-1-oxobutan-2-yl]carbamate

Example 198A

(S)-2-(methoxycarbonylamino)-4-(methylthio)butanoic acid

To a solution of (S)-2-amino-4-(methylthio)butanoic acid (1.0 g, 6.7 mmol) in dioxane at 0 °C was added NaOH (11.06 g, 22.12 mmol) followed by dropwise addition of methyl chloroformate (1.04 mL, 13.4 mmol) and the solution was warmed to room temperature with stirring over 2 h. The solution was diluted with EtOAc, washed with 1 N HCl, brine, dried (Na_2SO_4), filtered and solvent removed in vacuo to give the title compound (1.3 g, 6.27 mmol, 94%). ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.95-2.07 (m, 1H) 2.07-2.13 (m, 3H) 2.14-2.28 (m, 1H) 2.59 (t, J=7.4 Hz, 2H) 3.71 (s, 3H) 4.52 (br s, 1H) 5.33 (br s, 1H).

Example 198B

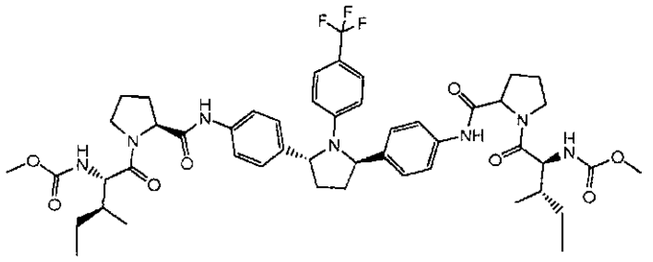
(2S,2'S)-N,N'-(4,4'-((2R,5R)-1-(4-(trifluoromethyl)phenyl)pyrrolidine-2,5-diyl)bis(4,1-phenylene)dipyrrolidine-2-carboxamide

Example 38A and 4-trifluoromethylaniline were processed using the methods of Examples 34A, 34B, 34C, and 34D to provide the title compound.

Example 198C

methyl [(2*S*)-1-{(2*S*)-2-[(4-{(2*R*,5*R*)-5-{4-[({1-[(2*S*)-2-[(methoxycarbonyl)amino]-4-(methylsulfanyl)butanoyl]pyrrolidin-2-yl}carbonyl)amino]phenyl}-1-[4-(trifluoromethyl)phenyl]pyrrolidin-2-yl}phenyl)carbamoyl]pyrrolidin-1-yl}-4-(methylsulfanyl)-1-oxobutan-2-yl]carbamate

Example 198B and Example 198A were processed using the method of Example 1H to provide the title compound which was purified by flash chromatography on silica gel eluting with 10-80% EtOAc/CH_2Cl_2 (29 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.78 (d, J=6.1 Hz, 2H) 1.83-2.00 (m, 6H) 2.02 (s, 6H) 2.04-2.26 (m, 4H) 2.43-2.61 (m, 8H) 3.47-3.83 (m, 4H) 3.69 (s, 6H) 4.75 (dd, J=8.0, 2.0 Hz, 4H) 5.15 (d, J=6.7 Hz, 2H) 5.43 (d, 2H) 6.32 (d, J=8.7 Hz, 2H) 7.09 (d, J=8.5 Hz, 4H) 7.18 (d, J=8.8 Hz, 2H) 7.42 (d, J=8.6 Hz, 4H) 9.05 (s, 2H). MS (ESI) m/z 971 $(M+H)^+$.



Example 199

methyl [(2*S*,3*S*)-1-{(2*S*)-2-[(4-{(2*R*,5*R*)-5-(4-{[(1-{(2*S*,3*S*)-2-[(methoxycarbonyl)amino]-3-methylpentanoyl}pyrrolidin-2-yl)carbonyl]amino}phenyl)-1-[4-(trifluoromethyl)phenyl]pyrrolidin-2-yl}phenyl)carbamoyl]pyrrolidin-1-yl}-3-methyl-1-oxopentan-2-yl]carbamate

Example 199A

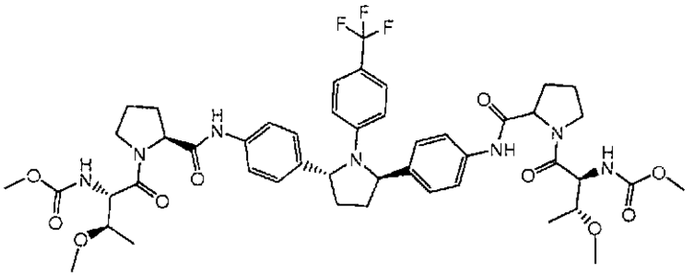
(2S,3S)-2-(methoxycarbonylamino)-3-methylpentanoic acid

To a solution of (2S,3S)-2-amino-3-methylpentanoic acid (1.0 g, 7.62 mmol) in dioxane (10 mL) at 0 °C was added NaOH (12.58 g, 25.2 mmol) followed by dropwise addition of methyl chloroformate (1.18 mL, 15.25 mmol). The solution was warmed to room temperature with stirring over 2 h, diluted with EtOAc, washed with 1 N HCl, brine, dried (Na_2SO_4), filtered and solvent removed in vacuo to give the title compound (1.4 g, 7.4 mmol, 97%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.27-1.39 (m, 1H) 1.38-1.53 (m, 2H) 1.58-1.72 (m, 3H) 1.82-1.94 (m, 2H) 2.04 (d, J=3.8 Hz, 2H) 3.70 (s, 3H) 4.94 (br s, 1H).

Example 199B

methyl [(2*S*,3*S*)-1-{(2*S*)-2-[(4-{(2*R*,5*R*)-5-(4-{[(1-{(2*S*,3*S*)-2-[(methoxycarbonyl)amino]-3-methylpentanoyl}pyrrolidin-2-yl)carbonyl]amino}phenyl)-1-[4-(trifluoromethyl)phenyl]pyrrolidin-2-yl}phenyl)carbamoyl]pyrrolidin-1-yl}-3-methyl-1-oxopentan-2-yl]carbamate

To a solution of Example 198B (60 mg, 0.101 mmol) in DMSO (0.5 mL) was added Example 199A (48 mg, 0.254 mmol), followed by HATU (96 mg, 0.254 mmol) and N,N-diisopropylethylamine (0.089 mL, 0.507 mmol) and the solution was stirred at room temperature for 1 h. Diluted with EtOAc, washed with H_2O, brine, dried (Na_2SO_4), filtered and removed solvent in vacuo to give crude product which was purified by flash chromatography on silica gel eluting with 10-80% EtOAc/CH_2Cl_2 to give the title compound (11 mg, 0.012 mmol, 12%). ^{1}H NMR (400 Hz, $CDCl_3$) δ ppm 0.78-1.00 (m, 12H) 1.69-1.81 (m, 4H) 1.81-1.94 (m, 2H) 1.99-2.10 (m, 2H) 2.09-2.24 (m, 2H) 2.50 (br s, 2H) 2.53-2.61 (m, 2H) 3.63 (br s, 2H) 3.68 (s, 6H) 3.75-3.87 (m, 2H) 4.34 (t, J=8.5 Hz, 2H) 4.79 (d, J=6.3 Hz, 2H) 5.14 (d, J=6.6 Hz, 2H) 5.28 (d, J=9.3 Hz, 2H) 6.32 (d, J=8.7 Hz, 2H) 7.08 (d, J=8.4 Hz, 4H) 7.18 (d, J=8.8 Hz, 2H) 7.41 (d, J=8.5 Hz, 4H) 9.23 (s, 2H). MS (ESI) m/z 935 $(M+H)^+$.



Example 200

methyl [(2*S*,3*R*)-3-methoxy-1-{(2*S*)-2-[(4-{(2*R*,5*R*)-5-(4-{[(1-{(2*S*,3*R*)-3-methoxy-2-[(methoxycarbonyl)amino]butanoyl}pyrrolidin-2-yl)carbonyl]amino}phenyl)-1-[4-(trifluoromethyl)phenyl]pyrrolidin-2-yl}phenyl)carbamoyl]pyrrolidin-1-yl}-1-oxobutan-2-yl]carbamate

Example 200A

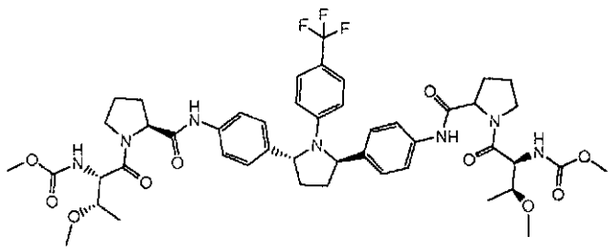
(2S,3R)-3-Methoxy-2-(methoxycarbonylamino)butanoic acid

A solution of O-methyl-L-threonine (1.01 g, 7.59 mmol) in saturated bicarbonate solution (93 mL) was treated dropwise with methyl chloroformate (900 µL, 1.10 g, 11.61 mmol), followed by stirring at RT for 24 h. The mixture was extracted methyl t-butyl ether and cooled to 0 °C. The mixture was adjusted to pH 1-2 by addition of concentrated hydrochloric acid solution. The mixture was extracted with ethyl acetate (3 x) and the combined extracts were extracted with saturated sodium chloride solution and dried (Na_2SO_4). The solution was concentrated in vacuo to afford the title compound (1.31 g, 90%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.44 (d, *J* = 8.7 Hz, 1 H), 4.39 (dd, *J* = 8.7, 2.3 Hz, 1 H), 4.00 (dd, *J* = 6.2, 2.4 Hz, 1 H), 3.71 (s, 3 H), 3.36 (s, 3 H), 1.21 (t, *J* = 7.2 Hz, 3 H). MS (+ESI) *m/z* (rel abundance) 192 (60, M+H), 209 (100, M+NH4).

Example 200B

methyl [(2*S*,3*R*)-3-methoxy-1-{(2*S*)-2-[(4-{(2*R*,5*R*)-5-(4-{[(1-{(2*S*,3*R*)-3-methoxy-2-[(methoxycarbonyl)amino]butanoyl}pyrrolidin-2-yl)carbonyl]amino}phenyl)-1-[4-(trifluoromethyl)phenyl]pyrrolidin-2-yl}phenyl)carbamoyl]pyrrolidin-1-yl}-1-oxobutan-2-yl]carbamate

Example 198B (60 mg, 0.101 mmol) and Example 200A (48.5 mg, 0.254 mmol) were processed in the same manner as Example 199B to give the title compound (10.5 mg, 0.011 mmol, 11%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.19 (s, 3H) 1.21 (s, 3H) 1.78 (d, J=6.1 Hz, 2H) 1.94-2.16 (m, 6H) 2.40-2.57 (m, 4H) 3.36 (s, 6H) 3.66-3.84 (m, 6H) 3.69 (s, 6H) 4.64-4.72 (m, 2H) 4.81 (d, J=8.1 Hz, 2H) 5.14 (d, J=6.7 Hz, 2H) 5.64 (d, J=7.9 Hz, 2H) 6.31 (d, J=8.8 Hz, 2H) 7.08 (d, J=8.6 Hz, 4H) 7.18 (d, J=8.8 Hz, 2H) 7.43(d, J=8.6 Hz, 4H) 8.85 (s, 2H). MS (ESI) m/z 939 $(M+H)^+$.



Example 201

methyl [(2*S*,3*S*)-3-methoxy-1-{(2*S*)-2-[(4-{(2*R*,5*R*)-5-(4-{[(1-{(2*S*,3*S*)-3-methoxy-2-[(methoxycarbonyl)amino]butanoyl}pyrrolidin-2-yl)carbonyl]amino}phenyl)-1-[4-(trifluoromethyl)phenyl]pyrrolidin-2-yl}phenyl)carbamoyl]pyrrolidin-1-yl}-1-oxobutan-2-yl]carbamate

Example 201A

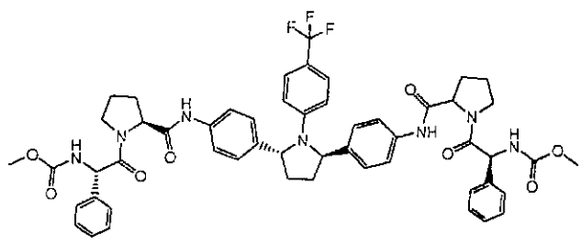
(2S,3S)-3-Methoxy-2-(methoxycarbonylamino)butanoic acid

A solution of allo-O-methyl-L-threonine (519 mg, 3.90 mmol) in saturated sodium bicarbonate solution (47.6 mL) was treated dropwise with methyl chloroformate (453 µL, 553 mg, 5.85 mmol) followed by stirring at RT for 18 h. The mixture was extracted with ether and the aqueous phase was cooled to 0 °C and acidified to pH 2-3 by addition of concentrated hydrochloric acid solution. The mixture was extracted with ethyl acetate (3 x). The combined organic layers were extracted with saturated sodium chloride solution and dried (Na_2SO_4). Concentration in vacuo afforded the title compound (640 mg, 86%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.48 (d, *J* = 7.8 Hz, 1 H), 4.52 (d, *J* = 4.7 Hz, 1 H), 3.71 (s, 3 H), 3.39 (s, 3 H), 1.25 (t, *J* = 7.6 Hz, 3 H).

Example 201B

methyl [(2*S*,3*S*)-3-methoxy-1-{(2*S*)-2-[(4-{(2*R*,5*R*)-5-(4-{[(1-{(2*S*,3*S*)-3-methoxy-2-[(methoxycarbonyl)amino]butanoyl}pyrrolidin-2-yl)carbonyl]amino}phenyl)-1-[4-(trifluoromethyl)phenyl]pyrrolidin-2-yl}phenyl)carbamoyl]pyrrolidin-1-yl}-1-oxobutan-2-yl]carbamate

Example 198B (40 mg, 0.068 mmol) and Example 201A (32.3 mg, 0.169 mmol) were processed in the same manner as Example 199B to give the title compound (22 mg, 0.023 mmol, 35%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.24 (s, 3H) 1.25 (s, 3H) 1.78 (d, J=6.2 Hz, 2H) 1.87-1.99 (m, 2H) 1.99-2.16 (m, 4H) 2.45-2.58 (m, 4H) 3.20 (s, 6H) 3.46-3.56 (m, 2H) 3.65-3.83 (m, 6H) 3.69 (s, 6H) 4.51-4.59 (m, 2H) 4.78 (d, J=6.7 Hz, 2H) 5.14 (d, J=6.7 Hz, 2H) 5.39 (d, J=9.3 Hz, 2H) 6.30 (d, J=8.7 Hz, 2H) 7.08 (d, J=8.5 Hz, 4H) 7.16 (d, J=8.8 Hz, 2H) 7.40 (d, J=8.5 Hz, 4H) 8.94 (s, 2H). MS (ESI) m/z 939 $(M+H)^+$.



Example 202

methyl [(1*S*)-2-{(2*S*)-2-[(4-{(2*R*,5*R*)-5-(4-{[(1-{(2*S*)-2-[(methoxycarbonyl)amino]-2-phenylacetyl}pyrrolidin-2-yl)carbonyl]amino}phenyl)-1-[4-(trifluoromethyl)phenyl]pyrrolidin-2-yl}phenyl)carbamoyl]pyrrolidin-1-yl}-2-oxo-1-phenylethyl]carbamate

Example 202A

(S)-2-(methoxycarbonylamino)-2-phenylacetic acid

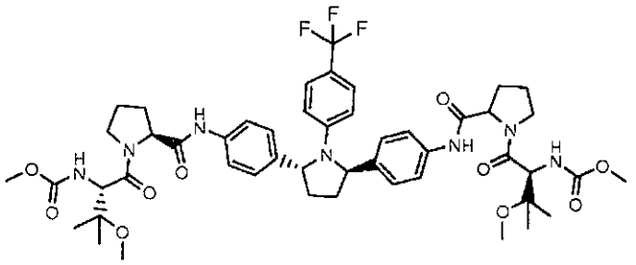
To a solution of (S)-2-amino-2-phenylacetic acid (0.5 g, 3.31 mmol) in dioxane at 0 °C was added NaOH (5.46 g, 10.92 mmol) followed by dropwise addition of methyl chloroformate (0.51 mL, 6.62 mmol) and the solution was warmed to room temperature with stirring over 1 h. Diluted with EtOAc, washed with 1 N HCl, brine, dried (Na_2SO_4), filtered and removed solvent in vacuo to give the title compound (0.35 g, 1.673 mmol, 51%).

Example 202B

methyl [(1*S*)-2-{(2*S*)-2-[(4-{(2*R*,5*R*)-5-(4-{[(1-{(2*S*)-2-[(methoxycarbonyl)amino]-2-phenylacetyl}pyrrolidin-2-yl)carbonyl]amino}phenyl)-1-[4-(trifluoromethyl)phenyl]pyrrolidin-2-yl}phenyl)carbamoyl]pyrrolidin-1-yl}-2-oxo-1-phenylethyl]carbamate

Example 198B (40 mg, 0.068 mmol) and Example 202A (35 mg, 0.169 mmol) were processed in the same manner as Example 199B to give the title compound (7.5 mg, 7.7 μmol, 11%).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.76-2.05 (m, 8H) 2.43-2.58 (m, 4H) 3.18-3.29 (m, 2H) 3.57-3.65 (m, 2H) 3.67 (s, 6H) 4.82-4.86 (m, 2H) 5.18 (d, J=6.9 Hz, 2H) 5.48 (d, J=7.7 Hz, 2H) 5.99 (d, J=7.7 Hz, 2H) 6.35 (d, J=8.8 Hz, 2H) 7.11 (d, J=8.5 Hz, 4H) 7.21 (d, J=8.7 Hz, 2H) 7.27-7.32 (m, 4H) 7.32-7.43 (m, 10H) 8.92 (s, 2H). MS (ESI) m/z 975 $(M+H)^+$.



Example 203

methyl [(2*S*)-3-methoxy-1-{(2*S*)-2-[(4-{(2*R*,5*R*)-5-(4-{[(1-{(2*S*)-3-methoxy-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl)carbonyl]amino}phenyl)-1-[4-(trifluoromethyl)phenyl]pyrrolidin-2-yl}phenyl)carbamoyl]pyrrolidin-1-yl}-3-methyl-1-oxobutan-2-yl]carbamate

Example 203A

(S)-(*tert*-butoxycarbonylamino)-3-hydroxy-3-methylbutanoic acid

A solution of the *(S)*-2-amino-3-hydroxy-3-methylbutanoic acid (252 mg, 1.89 mmol) in saturated sodium bicarbonate solution (6.3 mL) and tetrahydrofuran (6.3 mL) was treated with di-tert-butyl-dicarbonate (764 mg, 3.50 mmol) followed by stirring at RT for 24 h. The mixture was concentrated in vacuo to remove tetrahydrofuran and the mixture was extracted with hexanes. The aqueous phase was cooled to 0 °C and was acidifed to pH 3 by addition of 1 M citric acid solution. The mixture was extracted with ethyl acetate and the combined organic layers were dried (Na_2SO_4). Concentration in vacuo afforded a gummy solid, containing other impurities in addition to the desired product. This material was dissolved in ethyl acetate and the mixture filtered through a millipore filter to remove undissolved material. The filtrate was concentrated in vacuo and after setting at RT for a week, eventually solidified to give the title compound as a white solid. ^{1}H NMR (400 MHz, Methanol-d_4) δ 4.08 (s, 1 H), 1.45 (s, 9 H), 1.29 (s, 3 H), 1.25 (s, 3 H). MS (-ESI) *m/z* (rel abundance) 232 (100, M-H).

Example 203B

(S)-2-(tert-butoxycarbonylamino)-3-methoxy-3-methylbutanoic acid

To a solution of Example 203A (363 mg, 1.56 mmol) in THF (7 mL) at 0 °C was added NaH (373 mg, 9.34 mmol) and stirring was continued for 15 min. Iodomethane (0.78 mL, 12.45 mmol)

was added and the solution was allowed to warm to room temperature and stirred for 18 h. Solution was quenched with H_2O, diluted with EtOAc, washed with H_2O, brine, dried (Na_2SO_4), filtered and solvent removed to give the title compound (165 mg, 0.67 mmol, 43%). MS (ESI) m/z 248 $(M+H)^+$.

Example 203C

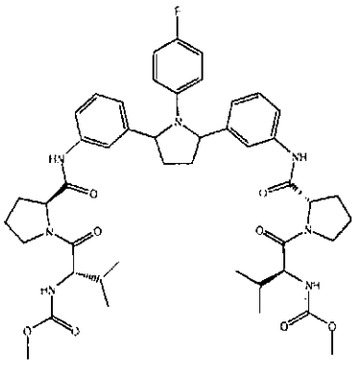
(S)-3-methoxy-2-(methoxycarbonylamino)-3-methylbutanoic acid

To a solution of Example 203B (163 mg, 0.66 mmol) in CH_2Cl_2 (2 mL) was added trifluoroacetic acid (2 mL) and the solution was stirred at room temperature for 1 h. Solvent was removed in vacuo and the residue was suspended in saturated $NaHCO_3$, extracted with EtOAc, the organic extracts combined, washed with brine, dried (Na_2SO_4), filtered and solvent removed in vacuo. The residue was dissolved in dioxane (1 mL) and 1 M NaOH (1.1 mL, 2.175 mmol) was added followed by the dropwise addition of methyl chloroformate (0.102 mL, 1.3 mmol). The solution was stirred at room temperature for 16 h, diluted with EtOAc, washed with 1 N HCl, brine, dried (Na_2SO_4), filtered and solvent removed in vacuo to give the title compound (96 mg, 0.468 mmol, 71%).

Example 203D

methyl [(2*S*)-3-methoxy-1-{(2*S*)-2-[(4-{(2*R*,5*R*)-5-(4-{[(1-{(2*S*)-3-methoxy-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl)carbonyl]amino}phenyl)-1-[4-(trifluoromethyl)phenyl]pyrrolidin-2-yl}phenyl)carbamoyl]pyrrolidin-1-yl}-3-methyl-1-oxobutan-2-yl]carbamate

Example 198B (80.7 mg, 0.136 mmol) and Example 203C (70 mg, 0.341 mmol) were processed in the same manner as Example 199B to give the title compound (62 mg, 0.064 mmol, 47%). ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.25 (s, 3H) 1.33 (s, 3H) 1.39 (s, 2H) 1.74-1.82 (m,2H) 1.89 (s, 2H) 1.93-2.16 (m, 5H) 2.38-2.59 (m, 4H) 3.16-3.27 (m, 2H) 3.24 (s, 3H) 3.43-3.56 (m, 2H) 3.69 (s, 3H) 3.71-3.78 (m, 2H) 3.80 (s, 3H) 3.84-3.94 (m, 1H) 4.61 (s, 1H) 4.70-4.81 (m, 2H) 5.15 (d, J=6.3 Hz, 2H) 5.58 (s, 1H) 6.32 (d, J=8.7 Hz, 2H) 7.05-7.13 (m, 4H) 7.19 (d, J=8.7 Hz, 2H) 7.33-7.50 (m, 4H) 8.71 (s, 1H) 8.92 (s, 1H). MS (ESI) m/z 967 $(M+H)^+$.



Example 204

dimethyl ([(2*S*,5*S*)-1-(4-fluorophenyl)pyrrolidine-2,5-diyl]bis{benzene-3,1-diylcarbamoyl(2*S*)pyrrolidine-2,1-diyl[(2*S*)-3-methyl-1-oxobutane-1,2-diyl]})biscarbamate

and

dimethyl ([(2*R*,5*R*)-1-(4-fluorophenyl)pyrrolidine-2,5-diyl]bis{benzene-3,1-diylcarbamoyl(2*S*)pyrrolidine-2,1-diyl[(2*S*)-3-methyl-1-oxobutane-1,2-diyl]})biscarbamate

Example 204A

(2S,2'S)-tert-butyl 2,2'-(3,3'-((2S,5S)-1-(4-fluorophenyl)pyrrolidine-2,5-diyl)bis(3,1-phenylene))bis(azanediyl)bis(oxomethylene)dipyrrolidine-1-carboxylate

and

(2S,2'S)-tert-butyl 2,2'-(3,3'-((2R,5R)-1-(4-fluorophenyl)pyrrolidine-2,5-diyl)bis(3,1-phenylene))bis(azanediyl)bis(oxomethylene)dipyrrolidine-1-carboxylate

The ether fraction from the work up of Example 55F was concentrated and purified by flash chromatography (silica gel, dichloromethane/EtOAc) to afford the title compound as a mixture of trans diastereomers (0.20 g, 10%). MS (ESI) *m/z* 742 $(M+H)^+$.

Example 204B

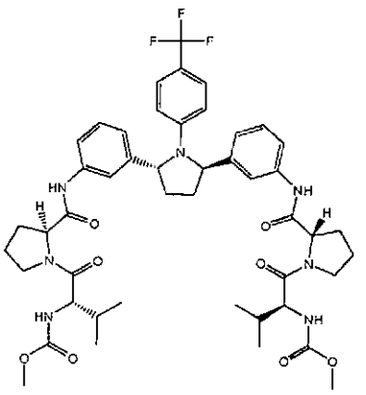
dimethyl ([(2*S*,5*S*)-1-(4-fluorophenyl)pyrrolidine-2,5-diyl]bis{benzene-3,1-diylcarbamoyl(2*S*)pyrrolidine-2,1-diyl[(2*S*)-3-methyl-1-oxobutane-1,2-diyl]})biscarbamate

and

dimethyl ([(2*R*,5*R*)-1-(4-fluorophenyl)pyrrolidine-2,5-diyl]bis{benzene-3,1-diylcarbamoyl(2*S*)pyrrolidine-2,1-diyl[(2*S*)-3-methyl-1-oxobutane-1,2-diyl]})biscarbamate

The product from Example 204A was processed using the method described in Examples 19D and 19E (used (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid) to afford the title compounds (60.5 mg, 22%). ^{1}H NMR (free base) (400 MHz, DMSO-D6) δ 0.99 - 0.81 (m, 12H), 1.67 (dd, J = 3.4, 5.0, 3H), 2.06 - 1.79 (m, 8H), 2.20 - 2.06 (m, 5H), 3.52 (d, J = 2.3, 6H), 3.63 (q, J = 7.1, 1H), 3.88 - 3.75 (m, 1H), 4.08 - 3.96 (m, 2H), 4.41 (dt, J = 12.8, 25.2, 2H), 5.11 (d, J = 28.1, 2H), 6.24 (dd, J =

6.0, 10.9, 2H), 6.80 (td, J = 4.2, 8.9, 2H), 6.88 (dd, J = 5.5, 6.4, 2H), 7.22 (ddd, J = 5.3, 10.4, 20.8, 2H), 7.32 (d, J = 8.3, 2H), 7.43 - 7.34 (m, 2H), 7.57 (d, J = 7.8, 2H), 10.00 (d, J = 7.8, 2H). MS (ESI) *m/z* 856 $(M+H)^+$.



Example 205

dimethyl ({(2R,5R)-1-[4-(trifluoromethyl)phenyl]pyrrolidine-2,5-diyl}bis{benzene-3,1-diylcarbamoyl(2S)pyrrolidine-2,1-diyl[(2S)-3-methyl-1-oxobutane-1,2-diyl]})biscarbamate

Example 205A

(1S,4S)-1,4-bis(3-nitrophenyl)butane-1,4-diol

The product from Example 55A was processed using the method described in Example 33 to afford the title compound (1.74 g, 84%). MS (DCI) *m/z* 350 $(M+NH_4)^+$.

Example 205B

(2R,5R)-2,5-bis(3-nitrophenyl)-1-(4-(trifluoromethyl)phenyl)pyrrolidine

The product from Example 205A and 4-aminobenzotrifluoride were processed using the method described in Examples 55C and 55D to afford the title compound (0.27 g, 19%). MS (ESI) *m/z* 858 $(M+H)^+$.

Example 205C

3,3'-((2R,5R)-1-(4-(trifluoromethyl)phenyl)pyrrolidine-2,5-diyl)dianiline

The product from Example 205B was processed using the method described in Example 55E. The title compound was isolated by flash chromatography (silica gel, methanol/dichloromethane). MS (ESI) *m/z* 398 $(M+H)^+$, 396 $(M-H)^+$.

Example 205D

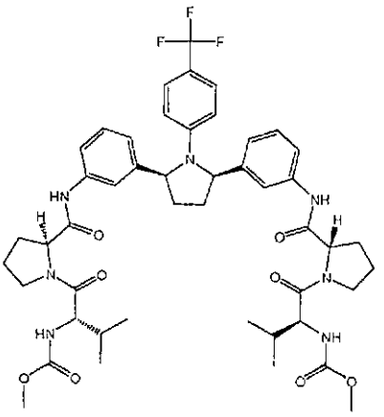
(2S,2'S)-tert-butyl 2,2'-(3,3'-((2R,5R)-1-(4-(trifluoromethyl)phenyl)pyrrolidine-2,5-diyl)bis(3,1-phenylene))bis(azanediyl)bis(oxomethylene)dipyrrolidine-1-carboxylate

The product from Example 205C was processed using the method described in Example 19C replacing DMF with dichloromethane to afford the title compound (0.36 g, 77%). MS (ESI) *m/z* 792 ($M+H^+$).

Example 205E

dimethyl ({(2R,5R)-1-[4-(trifluoromethyl)phenyl]pyrrolidine-2,5-diyl}bis{benzene-3,1-diylcarbamoyl(2S)pyrrolidine-2,1-diyl[(2S)-3-methyl-1-oxobutane-1,2-diyl]})biscarbamate

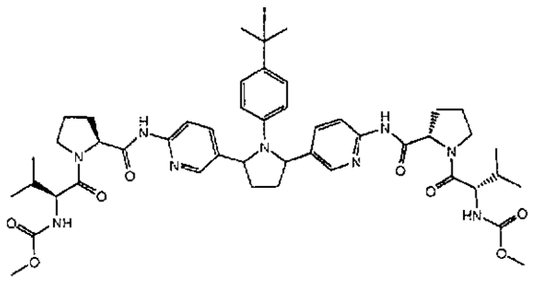
The product from Example 205D was processed using the method described in Examples 19D and 19E (used (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid and replacing HATU with HOBt and EDC) to afford the title compound (13.5 mg, 3%). ^{1}H NMR (TFA salt) (400 MHz, METHANOL-D4) δ 1.08 – 0.89 (m, 12H), 1.88 – 1.73 (m, 2H), 2.32 – 1.93 (m, 10H), 2.62 (t, *J* = 6.9, 2H), 3.64 (s, 6H), 3.77 – 3.67 (m, 2H), 4.00 – 3.90 (m, 2H), 4.20 (d, *J* = 8.0, 2H), 4.56 – 4.45 (m, 2H), 5.26 (d, *J* = 6.5, 2H), 6.42 (d, *J* = 8.8, 2H), 6.98 (d, *J* = 7.6, 2H), 7.17 (d, *J* = 7.4, 2H), 7.27 (t, *J* = 7.8, 2H), 7.52 – 7.37 (m, 4H). MS (ESI) *m/z* 906 $(M+H)^+$, 904 $(M-H)^+$.



Example 206

dimethyl ({(2R,5S)-1-[4-(trifluoromethyl)phenyl]pyrrolidine-2,5-diyl}bis{benzene-3,1-diylcarbamoyl(2S)pyrrolidine-2,1-diyl[(2S)-3-methyl-1-oxobutane-1,2-diyl]})biscarbamate

The product for Example 206 was isolated from the purification of Example 205E (12.5 mg, 3%). ^{1}H NMR (TFA salt) (400 MHz, DMSO-D6) δ 0.90 (dt, *J* = 6.2, 10.3, 12H), 2.23 – 1.73 (m, 12H), 2.47 – 2.39 (m, 6H), 3.52 (d, *J* = 3.3, 4H), 3.89 – 3.73 (m, 2H), 4.03 (t, *J* = 8.4, 2H), 4.44 (dd, *J* = 4.9, 7.8, 2H), 4.83 (t, *J* = 5.5, 2H), 6.50 (d, *J* = 8.7, 2H), 7.36 – 7.15 (m, 6H), 7.39 (d, *J* = 8.7, 2H), 7.73 – 7.57 (m, 4H), 10.04 (d, *J* = 10.0, 2H). MS (ESI) *m/z* 906 $(M+H)^+$, 904 $(M-H)^+$.



Example 207

dimethyl ([(2*S*,5*S*)-1-(4-*tert*-butylphenyl)pyrrolidine-2,5-diyl]bis{pyridine-5,2-diylcarbamoyl(2*S*)pyrrolidine-2,1-diyl[(2*S*)-3-methyl-1-oxobutane-1,2-diyl]})biscarbamate

and

dimethyl ([(2*R*,5*R*)-1-(4-*tert*-butylphenyl)pyrrolidine-2,5-diyl]bis{pyridine-5,2-diylcarbamoyl(2*S*)pyrrolidine-2,1-diyl[(2*S*)-3-methyl-1-oxobutane-1,2-diyl]})biscarbamate

Example 207A

1,4-bis(6-chloropyridin-3-yl)butane-1,4-dione

The zinc chloride (3.04 g, 22.82 mmol), tert-butyl alcohol (1.576 mL, 16.71 mmol) and diethylamine (1.731 mL, 16.71 mmol) were combined in benzene (12 mL). The resulting slurry was stirred at room temperature for 2 hours until all solid dissolved. To this slurry was added 1-(6-chloropyridin-3-yl)ethanone (2.60 g, 16.71 mmol; reference: *Bioorganic & Medicinal Chemistry Letters*, 1998, 8, 3087-3092), followed by 2-bromo-1-(6-chloropyridin-3-yl)ethanone (2.61 g, 11.14 mmol; reference: *Bioorganic & Medicinal Chemistry Letters*, 1998, 8, 3087-3092). The resulting clear yellow solution was stirred at room temperature for 88 hours. The thick reaction mixture was treated with 5% H_2SO_4 (10 mL), stirred for 30 minutes, filtered and dried to give the title compound (2.91g, 85%) as a solid.

Example 207B

1,4-bis(6-chloropyridin-3-yl)butane-1,4-diol

The product from Example 207A (2.90 g, 9.38 mmol) and sodium borohydride (0.745g, 19.70 mmol) were combined in ethanol (94 mL) at 0 °C. The mixture was warmed to room temperature and stirred for 6 hours. The solvent was evaporated and the residue was partitioned between ethyl acetate and 1M HCl. The organic layer was washed with water, brine, dried with sodium sulfate, filtered and evaporated to give the title compound (2.62 g, 89%).

Example 207C

1,4-bis(6-chloropyridin-3-yl)butane-1,4-diyl dimethanesulfonate

The product from Example 207B (2.23 g, 7.12 mmol) and triethylamine (2.98 mL, 21.36 mmol) were combined in dichloromethane (50 mL). The mixture was cooled to -20 °C and methanesulfonyl chloride (1.383 mL, 17.80 mmol) was added. The mixture was stirred at room temperature for 1 hour. The solvent was evaporated to give the title product (approx 3.34 g) which was directly used for the next reaction.

Example 207D

5,5'-(1-(4-tert-butylphenyl)pyrrolidine-2,5-diyl)bis(2-chloropyridine)

The product from Example 207C (3.34 g, 7.12 mmol) and 4-tert-butylaniline (6.38 g, 42.7 mmol) were combined in DMF (20 mL). The mixture was stirred at room temperature for 24 hours. The reaction mixture was partitioned between ethyl acetate and 1M HCl. The organic layer was washed with brine twice, dried with sodium sulfate, filtered and evaporated. The residue was purified by chromatography on silica gel eluting with ethyl acetate/hexane (5% to 30%) to give the title compound (2.95 g, 97%) as a yellow solid as a mixture of stereoisomers.

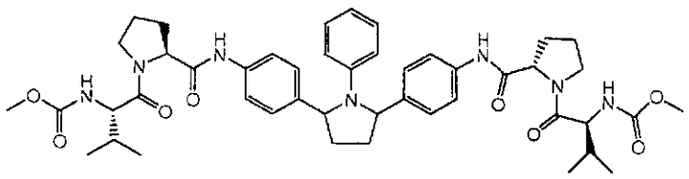
Example 207E

dimethyl ([(2*S*,5*S*)-1-(4-*tert*-butylphenyl)pyrrolidine-2,5-diyl]bis{pyridine-5,2-diylcarbamoyl(2*S*)pyrrolidine-2,1-diyl[(2*S*)-3-methyl-1-oxobutane-1,2-diyl]})biscarbamate

and

dimethyl ([(2*R*,5*R*)-1-(4-*tert*-butylphenyl)pyrrolidine-2,5-diyl]bis{pyridine-5,2-diylcarbamoyl(2*S*)pyrrolidine-2,1-diyl[(2*S*)-3-methyl-1-oxobutane-1,2-diyl]})biscarbamate

The product from Example 207D (0.171 g, 0.40 mmol), the product from Example 116C (0.326 g, 1.200 mmol), cesium carbonate (0.365 g, 1.120 mmol), tris(dibenzylideneacetone)dipalladium(0) (0.022 g, 0.024 mmol) and (9,9-dimethyl-9H-xanthene-4,5-diyl)bis(diphenylphosphine) (0.042 g, 0.072 mmol) were combined in dioxane (4 mL). The mixture was purged with nitrogen for 15 minutes and stirred at 100 °C for 3 hours. The reaction mixture was partitioned between ethyl acetate and saturated sodium bicarbonate. The organic layer was washed with brine, dried with sodium sulfate, filtered and evaporated. The residue was purified by chromatography on silica gel eluting with methanol/dichloromethane (1% to 4%) to give the title compound (5 mg, 1%) as a mixture of trans diastereomers. 1H NMR (500 MHz, DMSO-D6) δ ppm 0.88 (t, J=6.41 Hz, 6 H) 0.92 (t, J=7.32 Hz, 6 H) 1.12 (s, 9 H) 1.68 - 1.75 (m, 2 H) 1.81 - 1.99 (m, 8 H) 2.07 - 2.18 (m, 2 H) 2.50 - 2.53 (m, 2 H) 3.52 (s, 6 H) 3.57 - 3.64 (m, 2 H) 3.78 - 3.86 (m, 2 H) 3.98 - 4.03 (m, 2 H) 4.55 - 4.63 (m, 2 H) 5.27 (d, J=6.26 Hz, 2 H) 6.18 - 6.27 (m, 2 H) 6.99 (dd, J=8.77, 1.60 Hz, 2 H) 7.28 - 7.37 (m, 2 H) 7.59 (dd, J=8.62, 2.06 Hz, 2 H) 7.96 (d, J=8.39 Hz, 2 H) 8.12 - 8.20 (m, 2 H) 10.53 (s, 2 H); MS (ESI+) m/z 896.6 (M+H)+.



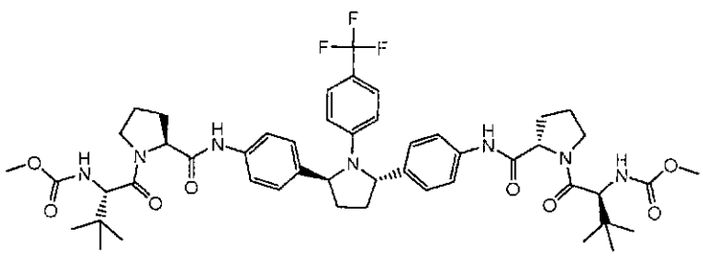
Example 208

dimethyl ([(2S,5S)-1-phenylpyrrolidine-2,5-diyl]bis{benzene-4,1-diylcarbamoyl(2S)pyrrolidine-2,1-diyl[(2S)-3-methyl-1-oxobutane-1,2-diyl]})biscarbamate

and

dimethyl ([(2R,5R)-1-phenylpyrrolidine-2,5-diyl]bis{benzene-4,1-diylcarbamoyl(2S)pyrrolidine-2,1-diyl[(2S)-3-methyl-1-oxobutane-1,2-diyl]})biscarbamate

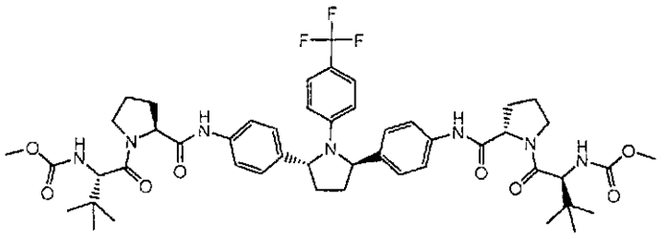
The title compound was isolated from Example 85C as an additional product. 1H NMR (TFA salt) (400 MHz, DMSO-D6) δ ppm 0.83 - 0.88 (m, 6 H), 0.88 - 0.94 (m, 6 H), 1.60 - 1.65 (m, 2 H), 1.79 - 2.02 (m, 8 H), 2.06 - 2.18 (m, 2 H), 3.51 (s, 6 H), 3.55 - 3.64 (m, 2 H), 3.75 - 3.83 (m, 2 H), 4.01 (t, *J*=8.3 Hz, 2 H), 4.38 - 4.43 (m, 2 H), 5.16 (d, *J*=6.4 Hz, 2 H), 6.23 (d, *J*=8.3 Hz, 2 H), 6.39 (t, *J*=7.3 Hz, 1 H), 6.90 (t, *J*=7.9 Hz, 2 H), 7.09 - 7.14 (m, 4 H), 7.25 - 7.31 (m, 2 H), 7.45 - 7.50 (m, 4 H), 9.97 (s, 2 H); MS m/z 838.4 $(M+H)^+$.



Example 209

dimethyl ({(2S,5S)-1-[4-(trifluoromethyl)phenyl]pyrrolidine-2,5-diyl}bis{benzene-4,1-diylcarbamoyl(2S)pyrrolidine-2,1-diyl[(2S)-3,3-dimethyl-1-oxobutane-1,2-diyl]})biscarbamate

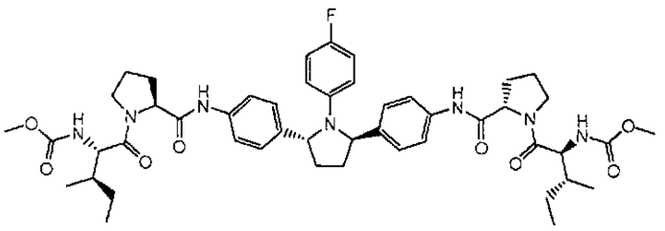
The product from Example 23C was separated by chiral chromatography on a Chiralpak AD-H semi-prep column eluting with 40% 2-PrOH:EtOH (1:1) / 60% hexanes. The title compound was the first of 2 components to elute. 1H NMR (400 MHz, DMSO-D6) δ ppm 0.97 (s, 18 H), 1.61 - 1.73 (m, 2 H), 1.75 - 1.93 (m, 4 H), 1.94 - 2.06 (m, 2 H), 2.08 - 2.21 (m, 2 H), 3.54 (s, 6 H), 3.57 - 3.70 (m, 2 H), 3.70 - 3.83 (m, 2 H), 4.21 (d, *J*=8.89 Hz, 2 H), 4.38 - 4.48 (m, 2 H), 5.27 (d, *J*=6.51 Hz, 2 H), 6.37 (d, *J*=8.78 Hz, 2 H), 7.08 (d, *J*=8.89 Hz, 2 H), 7.15 (d, *J*=8.57 Hz, 4 H), 7.25 (d, *J*=8.89 Hz, 2 H), 7.52 (d, *J*=8.57 Hz, 4 H), 10.02 (s, 2 H); MS (ESI) m/z 951.6 $(M+H)^+$.



Example 210

dimethyl ({(2R,5R)-1-[4-(trifluoromethyl)phenyl]pyrrolidine-2,5-diyl}bis{benzene-4,1-diylcarbamoyl(2S)pyrrolidine-2,1-diyl[(2S)-3,3-dimethyl-1-oxobutane-1,2-diyl]})biscarbamate

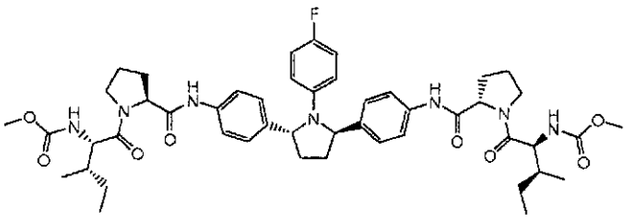
The product from Example 23C was separated by chiral chromatography on a Chiralpak AD-H semi-prep column eluting with 40% 2-PrOH:EtOH (1:1) / 60% hexanes. The title compound was the second of 2 components to elute. 1H NMR (400 MHz, DMSO-D6) δ ppm 0.96 (s, 18 H), 1.64 - 1.75 (m, 2 H), 1.76 - 1.93 (m, 4 H), 1.94 - 2.06 (m, 2 H), 2.07 - 2.21 (m, 2 H), 3.54 (s, 6 H), 3.58 - 3.70 (m, 2 H), 3.70 - 3.86 (m, 2 H), 4.20 (d, *J*=8.89 Hz, 2 H), 4.38 - 4.47 (m, 2 H), 5.28 (d, *J*=6.18 Hz, 2 H), 6.36 (d, *J*=8.89 Hz, 2 H), 7.07 (d, *J*=8.89 Hz, 2 H), 7.14 (d, *J*=8.57 Hz, 4 H), 7.25 (d, *J*=8.78 Hz, 2 H), 7.52 (d, *J*=8.57 Hz, 4 H), 10.03 (s, 2 H); MS (ESI) m/z 951.4 $(M+H)^+$.



Example 211

dimethyl ([(2R,5R)-1-(4-fluorophenyl)pyrrolidine-2,5-diyl]bis{benzene-4,1-diylcarbamoyl(2S)pyrrolidine-2,1-diyl[(2S,3R)-3-methyl-1-oxopentane-1,2-diyl]})biscarbamate

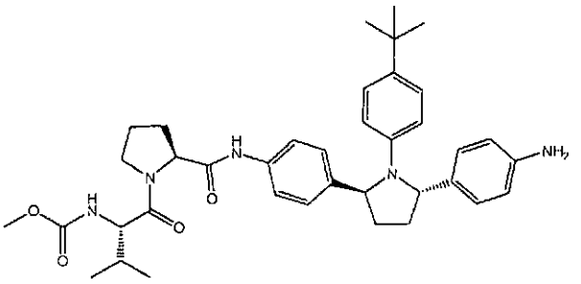
The product from Example 25 was separated by chiral chromatography on a Chiralpak AD-H semi-prep column eluting with 50% 2-PrOH:EtOH (1:1) / 50% hexanes. The title compound was the second of 2 components to elute. 1H NMR (400 MHz, DMSO-D6) δ ppm 0.76 - 0.92 (m, 12 H), 1.05 - 1.19 (m, 2 H), 1.37 - 1.54 (m, 2 H), 1.57 - 1.70 (m, 2 H), 1.69 - 1.96 (m, 6 H), 1.94 - 2.07 (m, 2 H), 2.07 - 2.22 (m, 2 H), 3.53 (s, 6 H), 3.55 - 3.64 (m, 2 H), 3.69 - 3.83 (m, 2 H), 4.17 - 4.28 (m, 2 H), 4.42 (dd, *J*=7.81, 5.20 Hz, 2 H), 5.16 (d, *J*=6.29 Hz, 2 H), 6.20 (dd, *J*=9.22, 4.45 Hz, 2 H), 6.77 (t, *J*=8.95 Hz, 2 H), 7.13 (d, *J*=8.46 Hz, 4 H), 7.49 (d, *J*=8.46 Hz, 2 H), 9.97 (s, 2 H); MS (ESI) m/z 884.4 $(M+H)^+$.



Example 212

dimethyl ([(2R,5R)-1-(4-fluorophenyl)pyrrolidine-2,5-diyl]bis{benzene-4,1-diylcarbamoyl(2S)pyrrolidine-2,1-diyl[(2S,3S)-3-methyl-1-oxopentane-1,2-diyl]})biscarbamate

The product from Example 24 was separated by chiral chromatography on a Chiralpak AD-H semi-prep column eluting with 50% 2-PrOH:EtOH (1:1) / 50% hexanes. The title compound was the second of 2 components to elute. 1H NMR (400 MHz, DMSO-D6) δ ppm 0.80 (t, *J*=7.37 Hz, 6 H), 0.88 (d, *J*=6.72 Hz, 6 H), 1.02 - 1.18 (m, 2 H), 1.41 - 1.59 (m, 2 H), 1.59 - 1.75 (m, 4 H), 1.80 - 1.95 (m, 4 H), 1.95 - 2.06 (m, 2 H), 2.08 - 2.23 (m, 2 H), 3.52 (s, 6 H), 3.56 - 3.67 (m, 2 H), 3.74 - 3.89 (m, 2 H), 4.07 (t, *J*=8.95 Hz, 2 H), 4.39 - 4.47 (m, 2 H), 5.16 (d, *J*=6.18 Hz, 2 H), 6.20 (dd, *J*=9.22, 4.45 Hz, 2 H), 6.78 (t, *J*=8.95 Hz, 2 H), 7.13 (d, *J*=8.46 Hz, 4 H), 7.35 (d, *J*=8.46 Hz, 2 H), 7.50 (d, *J*=8.57 Hz, 4 H), 9.99 (s, 2 H); MS (ESI) m/z 884.4 $(M+H)^+$.

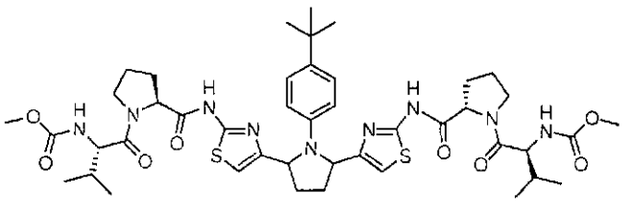


Example 213

N-(methoxycarbonyl)-L-valyl-N-{4-[(2S,5S)-5-(4-aminophenyl)-1-(4-tert-butylphenyl)pyrrolidin-2-yl]phenyl}-L-prolinamide

To a solution of the product from Example 37B (17.7 mg, 0.065 mmol) and the product from Example 37E (50 mg, 0.130 mmol) in anhydrous DMSO (1.3 mL) was added HATU (27.1 mg, 0.071 mmol) and Hunig'sBase (0.015 mL, 0.084 mmol). The resulting mixture was stirred at rt for 30 min, and was then partitioned between H_2O (5 mL) and EtOAc (3 x 5 mL). The combined organic layers were dried over Na_2SO_4. The drying agent was filtered off, and solvent was removed in vacuo. The crude product was purified by column chromatography on silica gel using a solvent gradient of 0-5% MeOH in CH_2Cl_2 to give the title compound (20 mg, 24%). 1H NMR (400 MHz, DMSO-D6) δ ppm 0.88 (d, *J*=6.72 Hz, 3 H), 0.93 (d, *J*=6.72 Hz, 3 H), 1.11 (s, 9 H), 1.52 - 1.66 (m, 2 H), 1.79 - 2.06 (m, 4 H), 2.06 - 2.20 (m, 1 H), 2.34 - 2.47 (m, 2 H), 3.52 (s, 3 H), 3.56 - 3.67 (m, 1 H), 3.74 - 3.87 (m, 1 H), 4.02 (t, *J*=8.51 Hz, 1 H), 4.42 (dd, *J*=8.08, 4.83 Hz, 1 H), 4.83 - 4.94 (m, 2 H), 5.02 (d, *J*=7.16 Hz,

0.5 H), 5.08 (d, *J*=7.59 Hz, 0.5 H), 6.18 (d, *J*=8.78 Hz, 2 H), 6.48 (d, *J*=8.35 Hz, 2 H), 6.84 (d, *J*=8.35 Hz, 2 H), 6.93 (d, *J*=8.89 Hz, 2 H), 7.11 (d, *J*=8.57 Hz, 2 H), 7.31 (d, *J*=8.35 Hz, 1 H), 7.48 (d, *J*=8.57 Hz, 2 H), 9.97 (s, 1 H); MS (ESI) m/z 640.3 $(M+H)^+$.



Example 214

dimethyl (2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-((2R,5R)-1-(4-tert-butylphenyl)pyrrolidine-2,5-diyl)bis(thiazole-4,2-diyl)bis(azanediyl)bis(oxomethylene))bis(pyrrolidine-2,1-diyl))bis(3-methyl-1-oxobutane-2,1-diyl)dicarbamate

and

dimethyl (2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-((2S,5S)-1-(4-tert-butylphenyl)pyrrolidine-2,5-diyl)bis(thiazole-4,2-diyl)bis(azanediyl)bis(oxomethylene))bis(pyrrolidine-2,1-diyl))bis(3-methyl-1-oxobutane-2,1-diyl)dicarbamate

Example 214A

diethyl 1-(4-tert-butylphenyl)pyrrolidine-2,5-dicarboxylate

A solution of diethyl meso-2,5-dibromoadipate (2.0 g, 5.55 mmol) and 4-tert-butylaniline (3.32 g, 22.22 mmol) in dimethoxyethane (12 mL) was stirred at reflux for 10 h. The cooled mixture was partitioned between EtOAc (100 mL) and 1N aq HCl (2x100 mL), and the organic layer was dried over Na_2SO_4. The drying agent was filtered off, and the solvent was removed in vacuo. The crude product was purified by column chromatography on silica gel using a solvent gradient of 0-20% EtOAc in hexanes to give the title compound as an oil (1.95 g, quant.). 1H NMR indicated a 3:2 mixture of cis:trans pyrrolidine isomers.

Example 214B

1-(4-tert-butylphenyl)pyrrolidine-2,5-dicarboxylic acid

To a solution of the product from Example 214A (1.95 g, 5.61 mmol) in MeOH (50 mL) was added a solution of NaOH (0.95 g, 23.8 mmol) in H_2O (10 mL). The resulting mixture was stirred at rt overnight. The mixture was concentrated in vacuo to ca. 10 mL and was poured into 1N HCl (50 mL). The mixture was extracted with CH_2Cl_2 (3 x 50 mL), and the combined organic layers were dried over Na_2SO_4. The drying agent was filtered off, and the solvent was removed in vacuo to give the title compound as a light orange solid (1.42 g, 87%) as a mixture of stereoisomers.

Example 214C

trans-1-(4-tert-butylphenyl)pyrrolidine-2,5-dicarboxylic acid

The product from Example 214B was subjected to column chromatography on C18 silica gel using a solvent gradient of 10-60% acetonitrile in H_2O (0.1% TFA). The title compound was the first of 2 major components to elute.

Example 214D

1,1'-(trans-1-(4-tert-butylphenyl)pyrrolidine-2,5-diyl)bis(2-diazoethanone)

To a solution of the product from Example 214C (0.963 g, 3.31 mmol) in dry CH_2Cl_2 (20 mL) at 0 °C was added oxalyl chloride (1.157 mL, 13.22 mmol), followed by 2-3 drops of DMF, and the resulting mixture was stirred at rt for 30 min until no further bubbling was observed. The cooled mixture was conc by evaporation with dry N_2, and the residue was dissolved in dry CH_2Cl_2 (10 mL). To the 0 °C solution was added a solution of diazomethane in Et_2O (~0.6 M, 20 mL) and the resulting mixture was stirred at 0 °C for 1h. The mixture was concentrated in vacuo, and the crude product was purified by column chromatography on silica gel using a solvent gradient of 0-100% EtOAc in hexanes to give the title compound (0.54 g, 48%).

Example 214E

4,4'-(trans-1-(4-tert-butylphenyl)pyrrolidine-2,5-diyl)dithiazol-2-amine

A solution of the product from Example 214D (0.50 g, 1.47 mmol) in Et_2O (10 mL) was treated dropwise with 48% aq. hydrogen bromide (0.500 mL, 4.42 mmol). The resulting mixture was stirred at rt for 30 min. Water (1 mL) was added, and the mixture was extracted with Et_2O (3 x 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was dissolved in EtOH (15 mL). To the resulting solution was added thiourea (0.45 g, 5.89 mmol), and the resulting mixture was stirred at rt for 1 h and then concentrated to ca. 1 mL. Water (10 mL) was added, and the pH was neutralized using saturated aq. $NaHCO_3$. The resulting solid was collected by filtration and dried in vacuo to give the title compound (0.455 g, 77%).

Example 214F

(2S,2'S)-tert-butyl 2,2'-(4,4'-(trans-1-(4-tert-butylphenyl)pyrrolidine-2,5-diyl)bis(thiazole-4,2-diyl)bis(azanediyl)bis(oxomethylene))dipyrrolidine-1-carboxylate

A mixture of the product from Example 214E (0.2 g, 0.501 mmol), (S)-1-(tert-butoxycarbonyl)pyrrolidine-2-carboxylic acid (0.431 g, 2.002 mmol), and N1-((ethylimino)methylene)-N3,N3-dimethylpropane-1,3-diamine hydrochloride (1.151 g, 6.01 mmol) in DMF (4 mL) and pyridine (4 mL) was stirred at rt overnight. The mixture was partitioned between 1N aq. HCl and EtOAc (3x), and the combined organic layers were dried over Na_2SO_4. The drying

agent was filtered off, and the solvent was removed in vacuo. The crude product was purified by column chromatography on silica gel using a solvent gradient of 0-100% EtOAc in hexanes to give the title compound (0.28 g, 71%) as a mixture of trans diastereomers.

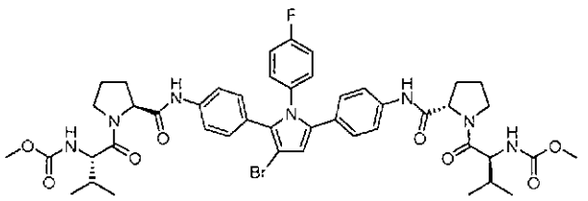
Example 214G

dimethyl (2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-((2R,5R)-1-(4-tert-butylphenyl)pyrrolidine-2,5-diyl)bis(thiazole-4,2-diyl)bis(azanediyl)bis(oxomethylene))bis(pyrrolidine-2,1-diyl))bis(3-methyl-1-oxobutane-2,1-diyl)dicarbamate

and

dimethyl (2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-((2S,5S)-1-(4-tert-butylphenyl)pyrrolidine-2,5-diyl)bis(thiazole-4,2-diyl)bis(azanediyl)bis(oxomethylene))bis(pyrrolidine-2,1-diyl))bis(3-methyl-1-oxobutane-2,1-diyl)dicarbamate

A solution of the product from Example 214F was stirred in 2N HCl in dioxane (0.4 mL) for 1 h and then concentrated in vacuo. The residue was subjected to the procedure described in Example 10 to give the title compound as mixture of trans diastereomers. 1H NMR (free base) (400 MHz, DMSO-D6) δ ppm 0.80 - 0.97 (m, 14 H), 1.12 - 1.16 (m, 9 H), 1.69 - 2.06 (m, 8 H), 2.08 - 2.22 (m, 2 H), 3.51 - 3.57 (m, 6 H), 3.57 - 3.68 (m, 2 H), 3.77 - 3.91 (m, 2 H), 3.95 - 4.06 (m, 2 H), 4.47 - 4.59 (m, *J*=7.16 Hz, 1 H), 5.08 - 5.17 (m, 2 H), 6.31 (t, *J*=8.24 Hz, 2 H), 6.70 (d, *J*=21.04 Hz, 2 H), 7.02 (dd, *J*=8.67, 6.40 Hz, 2 H), 7.35 (d, *J*=8.35 Hz, 2 H), 12.24 (s, 2 H).

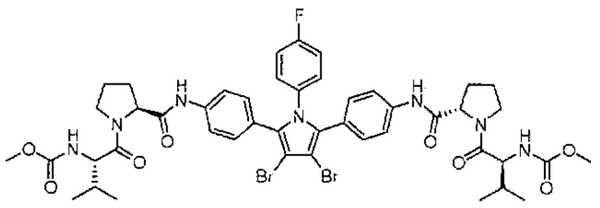


Example 215

dimethyl ([3-bromo-1-(4-fluorophenyl)-1*H*-pyrrole-2,5-diyl]bis{benzene-4,1-diylcarbamoyl(2*S*)pyrrolidine-2,1-diyl[(2*S*)-3-methyl-1-oxobutane-1,2-diyl]})biscarbamate

To a suspension of the product from Example 51 (455 mg, 0.534 mmol) in CH_2Cl_2 (2.7 mL) was added a mixture of 1-bromopyrrolidine-2,5-dione (95 mg, 0.534 mmol) in CH_2Cl_2 (2.7 mL). The mixture was stirred overnight at room temperature then concentrated under reduced pressure and triturated with diethyl ether to provide a mixture of compounds that was subjected to reverse phase HPLC purification eluted with a gradient of 60-100% MeOH in 10mM ammonium acetate to afford the title compound (84 mg, 17% yield). ^{1}H NMR (free base) (400 MHz, DMSO-D6) δ 10.06 (s, 1H), 10.02 (s, 1H), 7.46 (d, *J* = 8.7, 2H), 7.41 (d, *J* = 8.7, 2H), 7.30 (d, *J* = 7.7, 2H), 7.15 – 7.03 (m, 6H), 6.98 (d, *J* = 8.7, 2H), 6.53 (s, 1H), 4.45 – 4.33 (m, 2H), 4.01 (t, *J* = 7.7, 2H), 3.85 – 3.73 (m, 2H), 3.66

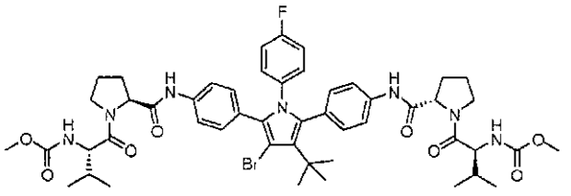
– 3.54 (m, 2H), 3.51 (s, 6H), 2.20 – 2.05 (m, 2H), 2.03 – 1.77 (m, 8H), 0.97 – 0.79 (m, 12H). MS (ESI; M+H) m/z = 933.



Example 216

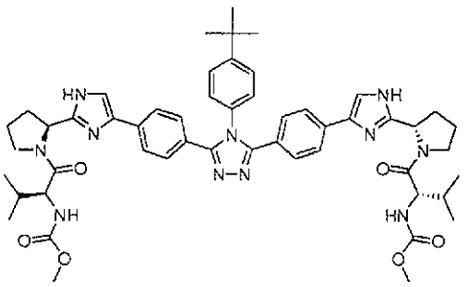
dimethyl ([3,4-dibromo-1-(4-fluorophenyl)-1*H*-pyrrole-2,5-diyl]bis{benzene-4,1-diylcarbamoyl(2*S*)pyrrolidine-2,1-diyl[(2*S*)-3-methyl-1-oxobutane-1,2-diyl]})biscarbamate

The title compound was formed as an additional product in Example 215. The mixture of products was subjected to reverse phase HPLC purification eluted with a gradient of 60-100% MeOH in 10mM ammonium acetate to afford the title compound (125 mg, 23% yield). ^{1}H NMR (free base) (400 MHz, DMSO-D6) δ 10.08 (bs, 2H), 7.47 (d, *J* = 8.7, 4H), 7.33 – 7.27 (m, 2H), 7.13 – 7.01 (m, 8H), 4.43 – 4.35 (m, 2H), 4.01 (t, *J* = 8.4, 2H), 3.84 – 3.74 (m, 2H), 3.65 – 3.55 (m, 2H), 3.51 (s, 6H), 2.21 – 2.05 (m, 2H), 2.05 – 1.78 (m, 8H), 0.91 (d, *J* = 6.7, 6H), 0.86 (d, *J* = 6.6, 6H). MS (ESI; M+H) m/z = 1011.



Example 217

The title compound was formed as a by-product in Example 215. The mixture of products was subjected to reverse phase HPLC purification eluted with a gradient of 60-100% MeOH in 10mM ammonium acetate to afford the title compound (61 mg, 12% yield). ^{1}H NMR (free base) (400 MHz, DMSO-D6) δ 10.00 (s, 2H), 7.41 (d, *J* = 8.7, 2H), 7.38 (d, *J* = 8.9, 2H), 7.29 (d, *J* = 6.6, 2H), 7.14 (d, *J* = 7.3, 1H), 7.11 – 7.05 (m, 3H), 7.01 – 6.93 (m, 2H), 6.89 (t, *J* = 8.7, 2H), 4.37 (dd, *J* = 4.9, 7.4, 2H), 4.00 (t, *J* = 8.4, 2H), 3.84 – 3.74 (m, 2H), 3.64 – 3.55 (m, 2H), 3.51 (s, 6H), 2.19 – 2.05 (m, 2H), 2.03 – 1.78 (m, 8H), 1.23 (s, 9H), 0.91 (dd, *J* = 2.1, 6.6, 6H), 0.86 (d, *J* = 6.4, 6H). MS (ESI; M+H) m/z = 989.



Example 218

methyl {(2*S*)-1-[(2*S*)-2-(4-{4-[4-(4-*tert*-butylphenyl)-5-(4-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1*H*-imidazol-4-yl}phenyl)-4*H*-1,2,4-triazol-3-yl]phenyl}-1*H*-imidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

Example 218A

4-bromo-N'-(4-bromobenzoyl)benzoylhydrazide

Dissolved equimolar amounts of 4-bromobenzohydrazide (1.097 g, 5 mmol) and 4-bromobenzoyl chloride (1.120 g, 5 mmol) in anhydrous pyridine (25 mL) under nitrogen and heated at reflux (oil bath 135 °C) for 6 hr. Cooled reaction to room temperature, poured the mixture into absolute EtOH (100 mL), and cooled in a freezer overnight to give white crystals. Collected solids by vacuum filtration, washed solids with absolute EtOH (2 x 5 mL), and dried *in vacuo* to afford the title compound as a white solid (953 mg, 48%). ^{1}H NMR (400 MHz, DMSO-D6) δ ppm 7.75 (d, *J*=8.57 Hz, 4 H), 7.86 (d, *J*=8.46 Hz, 4 H), 10.63 (s, 2 H); MS (ESI-) m/z 395/397/399 $(M-H)^-$ with two bromines.

Example 218B

3,5-bis(4-bromophenyl)-4-(4-*tert*-butylphenyl)-4*H*-1,2,4-triazole

In an oven-dried 10-mL round bottom flask, equipped with a septum and purged with nitrogen, 4-tert-butylaniline (450 mg, 3.01 mmol) was dissolved in anhydrous 1,2-dichlorobenzene (1.5 mL) and the solution cooled to 0 °C. A solution of phosphorus oxychloride (0.047 mL, 0.502 mmol) in anhydrous 1,2-dichlorobenzene (0.5 mL) was added slowly in dropwise manner from a gas-tight syringe. Upon completion of addition, removed the cooling bath and stirred at room temperature for 1 hr to form the phosphoryl triamide *in situ* (reaction became progressively cloudy). Then added the product of Example 218A (200 mg, 0.502 mmol), replaced septum with a reflux condenser, and heated reaction in an oil bath at 200 °C for 4 hr. Cooled light brown colored solution to room temperature, then placed in a freezer for 3 days and collected an off-white solid (20 mg, 4-bromo-N-(4-tert-butylphenyl)benzamide by-product) by vacuum filtration. The filtrate was treated with hexanes (~50 mL) and the cloudy solution cooled in a freezer for 30 min. Collected an off-white solid (73 mg) by vacuum filtration and concentrated the filtrate by rotary evaporation to a solution of

product in 1,2-dichlorobenzene. The latter was purified by flash chromatography (silica gel, 3.8 cm x 15 cm bed, gradient of CH_2Cl_2 , 20% EtOAc/CH_2Cl_2, and 30% EtOAc/CH_2Cl_2) to afford the title compound as a fluffy white solid (154 mg, 60%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.36 (s, 9 H), 7.06 (d, *J*=8.46 Hz, 2 H), 7.29 (d, *J*=8.57 Hz, 4 H), 7.43 (d, *J*=8.57 Hz, 4 H), 7.46 (d, *J*=8.57 Hz, 2 H); MS (ESI+) m/z 510/512/514 $(M+H)^+$ with two bromines.

Example 218C

4-(4-*tert*-butylphenyl)-3,5-bis((4(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-4*H*-1,2,4-triazole

Charged an oven-dried 25-mL round bottom flask, purged with nitrogen, with the product of Example 218B (144.2 mg, 0.282 mmol), bis(pinacalato)diboron (215 mg, 0.846 mmol), potassium acetate (90 mg, 0.917 mmol), and anhydrous dioxane (1.5 mL). Sparged the mixture with nitrogen for 30 min, added 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex (23.03 mg, 0.028 mmol), re-sparged with nitrogen for 5 min, replaced rubber septum with a glass stopper, and heated in an oil bath (85 °C) for 2 hr. Cooled reaction to room temperature, vacuum filtered through a small bed of Celite 545, washed catalyst thoroughly with CH_2Cl_2, and concentrated the filtrate by rotary evaporation to a dark brown oil. Purified by flash chromatography (silica gel, Alltech Extract-Clean 10g column, 1:1 EtOAc/CH_2Cl_2) to afford a dark beige solid (230 mg). Repurified by flash chromatography (silica gel, Alltech Extract-Clean 10g column, 3% MeOH/CH_2Cl_2) eluting with to afford the title compound as a beige solid (171 mg, 100%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.27 (s, 9 H), 1.33 (s, 24 H), 7.06 (d, *J*=8.46 Hz, 2 H), 7.38 - 7.47 (m, 6 H), 7.71 (d, *J*=7.92 Hz, 4 H); MS (ESI+) m/z 606 $(M+H)^+$, 1211 $(2M+H)^+$.

Example 218D

(2S,2'S)-*tert*-butyl 2,2'-(4,4'-(4,4'-(4-(4-*tert*-butylphenyl)-4*H*-1,2,4-triazole-3,5-diyl)bis(4,1-phenylene))bis(1*H*-imidazole-4,2-diyl))dipyrrolidine-1-carboxylate

Charged a nitrogen-purged microwave tube (size M, 5 mL) with the product of Example 218C (171 mg, 0.282 mmol), the product of Example 26D (223 mg, 0.706 mmol), and a mixture of absolute EtOH (1.5 mL) and toluene (1.5 mL), then added 1M aq sodium carbonate (0.706 mL, 0.706 mmol) and sparged the mixture with nitrogen for 20 min. Added 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex (23.07 mg, 0.028 mmol), sparged again with nitrogen for 5 min, sealed the tube with an aluminum crimp cap, and heated in a microwave reactor (Personal Chemistry Emrys Creator) with stirring at 100 °C for 1 hr. Cooled the reaction to room temperature, diluted reaction in EtOAc (75 mL), washed with H_2O (2 x 25 mL) and brine (25 mL), dried organic phase over anhydrous $MgSO_4$, filtered, and concentrated by rotary evaporation to a yellow solid (330 mg). Purified by flash chromatography (silica gel, 3.8 cm x

15 cm, gradient of 4%, 6%, 8%, and 10% MeOH/CH_2Cl_2) to afford the title compound as a light yellow solid (135 mg, 58%). MS (ESI+) m/z 824 $(M+H)^+$.

Example 218E

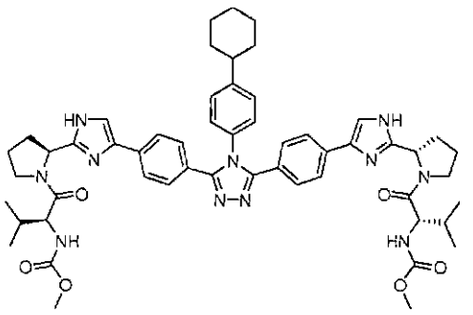
4-(4-*tert*-butylphenyl)-3,5-bis(4-(2-((S)-pyrrolidin-2-yl)-1*H*-imidazol-4-yl)phenyl)-4*H*-1,2,4-triazole

Dissolved the product of Example 218D (131.5 mg, 0.160 mmol) in anhydrous CH_2Cl_2 (2 mL) under nitrogen, added trifluoroacetic acid (1 mL, 12.85 mmol), and stirred at 25 °C for 30 min. Removed the solvent by rotary evaporation, took up the residue in 20% iPrOH/$CHCl_3$ (50 mL), washed with sat'd aq $NaHCO_3$ (10 mL), extracted the aqueous phase with 20% iPrOH/$CHCl_3$ (2 x 25 mL), dried the combined organic extracts over anhydrous $MgSO_4$, filtered, and concentrated by rotary evaporation. Took up residue in 1:5 v/v CH2Cl2/hexanes and concentrated *in* vacuo to afford the title compound as a light tan solid (114 mg). ^{1}H NMR (400 MHz, DMSO-D6) δ ppm 1.30 (s, 9 H), 1.66 - 1.94 (m, 6 H), 1.98 - 2.12 (m, 2 H), 2.80 - 3.07 (m, 4 H), 3.70 - 3.86 (m, 1 H), 4.12 - 4.22 (m, 2 H), 4.34 (d, *J*=4.01 Hz, 1 H), 7.34 (t, *J*=8.08 Hz, 6 H), 7.47 - 7.57 (m, 4 H), 7.68 (d, *J*=8.35 Hz, 4 H), 11.90 (s, 2 H); MS (ESI+) 624 $(M+H)^+$; (ESI-) m/z 622 $(M-H)^-$.

Example 218F

(methyl {(2*S*)-1-[(2*S*)-2-(4-{4-[4-(4-*tert*-butylphenyl)-5-(4-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1*H*-imidazol-4-yl}phenyl)-4*H*-1,2,4-triazol-3-yl]phenyl}-1*H*-imidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

In an oven-dried 5-mL round bottom flask purged with nitrogen, dissolved the product of Example 218E (50 mg, 0.080 mmol) in anhydrous DMF (1 mL), and cooled to 0 °C. Added sequentially (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (29.5 mg, 0.168 mmol), HOBt hydrate (27.6 mg, 0.180 mmol), EDAC (35.3 mg, 0.180 mmol), and N-methylmorpholine (0.035 mL, 0.321 mmol). Stirred the solution at 25 °C for 15 hr. Diluted the reaction in EtOAc (50 mL), washed with sat'd aq $NaHCO_3$ (25 mL), H_2O (3 x 25 mL), and brine (25 mL), dried the organic phase over anhydrous $MgSO_4$, filtered, and concentrated by rotary evaporation to an off-white solid (72 mg). Purified by flash chromatography (silica gel, Alltech Extract-Clean 10g column, gradient of 6% to 8% MeOH/CH_2Cl_2) to afford the title compound as an off-white solid (49 mg, 65%). ^{1}H NMR (400 MHz, DMSO-D6) δ ppm 0.82 (d, *J*=6.72 Hz, 6 H), 0.86 (d, *J*=6.72 Hz, 6 H), 1.29 (s, 9 H), 1.79 - 2.01 (m, 5 H), 2.03 - 2.22 (m, 4 H), 3.53 (s, 6 H), 3.70 - 3.86 (m, 4 H), 4.04 (t, *J*=8.35 Hz, 2 H), 5.04 (dd, *J*=6.67, 3.20 Hz, 2 H), 7.23 - 7.43 (m, 8 H), 7.48 - 7.60 (m, 4 H), 7.61 - 7.73 (m, 4 H), 11.77 - 12.21 (m, 2 H); MS (ESI+) m/z 939 $(M+H)^+$.



Example 219

methyl {(2*S*)-1-[(2*S*)-2-(4-{4-[4-(4-cyclohexylphenyl)-5-(4-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1*H*-imidazol-4-yl}phenyl)-4*H*-1,2,4-triazol-3-yl]phenyl}-1*H*-imidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

Example 219A

3,5-bis(4-bromophenyl)-4-(4-cyclohexylphenyl)-4*H*-1,2,4-triazole

In an oven-dried 10-mL round bottom flask, equipped with a septum and purged with nitrogen, 4-cyclohexylaniline (545 mg, 3.01 mmol) was dissolved in anhydrous 1,2-dichlorobenzene (1.5 mL) and the solution cooled to 0 °C. A solution of phosphorus oxychloride (78 mg, 0.502 mmol) in anhydrous 1,2-dichlorobenzene (0.5 mL) was added slowly in a dropwise manner from a gas-tight syringe. The reaction became an unstirrable solid gel; removed the cooling bath, added additional 1,2-dichlorobenzene (0.5 mL), sonicated the mixture, and stirred the thick suspension at room temperature for 1 hr to form the phosphoryl triamide *in situ*. Added the product of Example 218A (200 mg, 0.502 mmol), replaced the septum with a reflux condenser, and heated the reaction in an oil bath at 200 °C for 4 hr under nitrogen. The reaction quickly became a homogeneous gold colored solution upon refluxing. Cooled the solution to room temperature and purified by flash chromatography (silica gel, 3.8 cm x 15 cm, gradient of CH_2Cl_2 to 20% EtOAc/CH_2Cl_2 to 40% EtOAc/CH_2Cl_2) to afford the title compound as a fluffy white solid (201 mg, 74%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.19 - 1.33 (m, 1 H) 1.35 - 1.50 (m, 4 H) 1.78 (d, *J*=14.42 Hz, 1 H) 1.84 - 1.98 (m, 4 H) 2.51 - 2.65 (m, 1 H) 7.04 (d, *J*=8.35 Hz, 2 H) 7.28 (d, *J*=8.57 Hz, 6 H) 7.43 (d, *J*=8.57 Hz, 4 H); MS (ESI+) m/z 536/538540 $(M+H)^+$, 1072/1074/1076 $(2M+H)^+$ with two bromines.

Example 219B

4-(4-cyclohexylphenyl)-3,5-bis(4(4,4,5,5-tetramethyl-1,3,2-dioxaboralan-2-yl)phenyl)-4*H*-1,2,4-triazole

Charged an oven-dried 10-mL round bottom flask, purged with nitrogen, with the product of Example 219A (100 mg, 0.186 mmol), bis(pinacalato)diboron (142 mg, 0.558 mmol), potassium

acetate (59.4 mg, 0.605 mmol), and anhydrous dioxane (3 mL). Sparged the thick white mixture with nitrogen for 30 min, added 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex (15.20 mg, 0.019 mmol), re-sparged with nitrogen for 5 min, replaced rubber septum with a glass stopper, and heated in an oil bath (85 °C). Reaction became homogeneous upon heating and darkened with time to a reddish-brown color. TLC (SiO2, 50% EtOAc/CH_2Cl_2). After 2 hr, cooled reaction to room temperature, added additional bis(pinacalato)diboron (71 mg, ~1.5 equiv) and potassium acetate (30 mg, ~1.75 equiv), and heated for 1 hr at 85 °C. Cooled the brown colored reaction to room temperature, vacuum filtered through a small bed of Celite 545, washed the collected solids thoroughly with CH_2Cl_2, and concentrated the filtrate by rotary evaporation to a brown foam. Purified by silica gel flash chromatography (Alltech Extract-Clean column, 10g bed) eluting with 30% EtOAc/CH_2Cl_2 to afford the product as a light brown oil (190 mg). Repurified by silica gel flash chromatography (Alltech Extract-Clean column, 10g bed) eluting with 3% MeOH/CH_2Cl_2 to afford the title compound as a light beige foam (122 mg, 100%). MS (ESI+) m/z 632 $(M+H)^+$, 1263 $(2M+H)^+$.

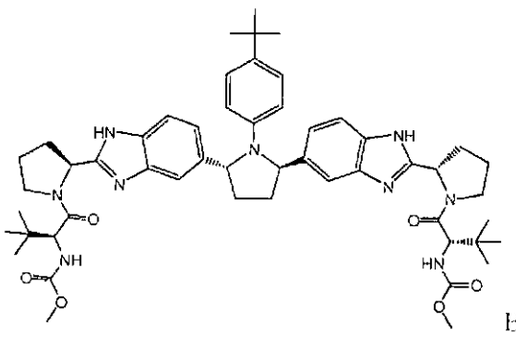
Example 219C

methyl {(2*S*)-1-[(2*S*)-2-(4-{4-[4-(4-cyclohexylphenyl)-5-(4-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1*H*-imidazol-4-yl}phenyl)-4*H*-1,2,4-triazol-3-yl]phenyl}-1*H*-imidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

Charged a nitrogen-purged microwave tube (size M, 5 mL) with the product of Example 219B (118 mg, 0.187 mmol), the product of Example 126G (174 mg, 0.467 mmol), and a mixture of absolute EtOH (1 mL) and toluene (1 mL), then added 1M aq sodium carbonate (0.467 mL, 0.467 mmol) and sparged the mixture with nitrogen for 20 min. Added 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex (15.26 mg, 0.019 mmol), sparged again with nitrogen for 5 min, sealed the tube with an aluminum crimp cap, and heated in a microwave reactor (Personal Chemistry Emrys Creator) with stirring at 100 °C for 1 hr. Cooled reaction to room temperature, diluted reaction in EtOAc (50 mL), washed with H_2O (2 x 25 mL) and brine (25 mL), dried the organic phase over anhydrous $MgSO_4$, filtered, and concentrated by rotary evaporation to a solid. Purified by flash chromatography (silica gel, step gradient 5% to 8% to 10% MeOH/CH_2Cl_2) to afford the product as a tan solid (72 mg) which was ~85% pure (2 main impurities). Dissolved impure product in 1.5 mL 1:1 v/v MeOH/DMSO and purified by RP-C18 HPLC (Waters Prep LC, 40mm Module with Nova Pak HR C_{18} 6µm 40x100mm Prep Pak cartridge) eluting with a 30 min gradient of 95:5 0.1% TFA in H2O/AcCN to 25:75 0.1% TFA in H_2O/AcCN, then 10 min to 100% AcCN at 20 mL/min. Pure fractions were concentrated by rotary evaporation (water bath 35°C) to a small volume, partitioned between 20% iPrOH/$CHCl_3$ (50-mL) and sat'd aq $NaHCO_3$ (15 mL), separated layers, dried the organic extract over anhydrous $MgSO_4$, filtered, and

concentrated by rotary evaporation to afford the title compound as a white solid (34.5 mg, 19%). ^{1}H NMR (400 MHz, DMSO-D6) δ ppm 0.83 (d, *J*=6.72 Hz, 6 H) 0.86 (d, *J*=6.72 Hz, 6 H) 1.29 - 1.47 (m, 5 H) 1.65 - 2.01 (m, 12 H) 2.04 - 2.21 (m, 4 H) 3.53 (s, 6 H) 3.72 - 3.84 (m, 4 H) 4.04 (t, *J*=8.40 Hz, 2 H) 5.04 (dd, *J*=6.89, 3.20 Hz, 2 H) 7.23 - 7.40 (m, 10 H) 7.51 - 7.72 (m, 6 H) 11.84 (s, 2 H); MS (ESI+) m/z 965 $(M+H)^+$.

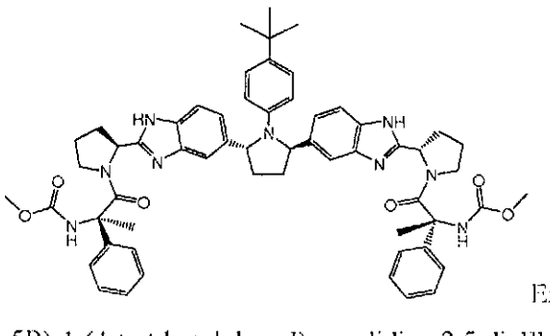
Examples 220-308 were prepared in analogous fashion according to the methods and conditions illustrated in the foregoing schemes and examples.



Example 220

methyl {(2S)-1-[(2S)-2-{5-[(2R,5R)-1-(4-tert-butylphenyl)-5-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3,3-dimethylbutanoyl}pyrrolidin-2-yl]-1H-benzimidazol-5-yl}pyrrolidin-2-yl]-1H-benzimidazol-2-yl}pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl}carbamate

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 0.88 (d, *J*=13.55 Hz, 18 H), 1.07 (s, 9 H), 1.62 - 1.78 (m, 2 H), 1.91 - 2.09 (m, 4 H), 2.10 - 2.26 (m, 4 H), 2.54 - 2.62 (m, 2 H), 3.55 (s, 6 H), 3.74 - 3.90 (m, 4 H), 4.23 (dd, *J*=8.78, 4.55 Hz, 2 H), 5.09 - 5.23 (m, 2 H), 5.31 - 5.43 (m, 2 H), 6.26 (d, *J*=8.89 Hz, 2 H), 6.84 - 6.97 (m, 2 H), 7.06 (dd, *J*=8.29, 2.55 Hz, 2 H), 7.12 (t, *J*=9.43 Hz, 2 H), 7.20 (s, 1 H), 7.30 (s, 1 H), 7.38 (d, *J*=8.24 Hz, 1 H) 7.45 (d, *J*=8.24 Hz, 1 H), 12.02 (s, 2 H); MS (ESI+) m/z 916 $(M+H)^+$.

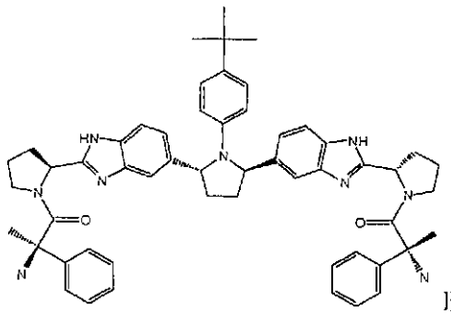


Example 221

dimethyl ([(2R,5R)-1-(4-tert-butylphenyl)pyrrolidine-2,5-diyl]bis{1H-benzimidazole-5,2-diyl(2S)pyrrolidine-2,1-diyl[(2R)-1-oxo-2-phenylpropane-1,2-diyl]})biscarbamate

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 1.03 - 1.10 (m, 9 H), 1.49 - 1.58 (m, 2 H), 1.67 (d, *J*=16.70 Hz, 6 H), 1.70 - 1.95 (m, 4 H), 2.04 (s, 3 H), 2.35 - 2.43 (m, 1 H), 2.97 - 3.11 (m, 2 H), 3.22 - 3.29 (m, 1 H), 3.50 (s, 6 H), 3.61 - 3.91 (m, 1 H), 5.08 - 5.22 (m, 2 H), 5.29 - 5.49 (m, 2 H), 6.21 - 6.39 (m, 2

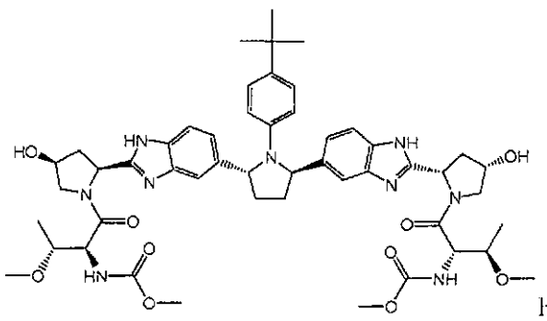
H), 6.84 - 6.99 (m, 2 H), 7.07 - 7.50 (m, 17 H), 7.53 (d, *J*=8.24 Hz, 1 H), 7.61 (s, 2 H), 12.10 (two s, 2 H); MS (ESI+) m/z 984 $(M+H)^+$.



Example 222

(2R,2'R)-1,1'-{[(2R,5R)-1-(4-tert-butylphenyl)pyrrolidine-2,5-diyl]bis[1H-benzimidazole-5,2-diyl(2S)pyrrolidine-2,1-diyl]}bis(2-amino-2-phenylpropan-1-one)

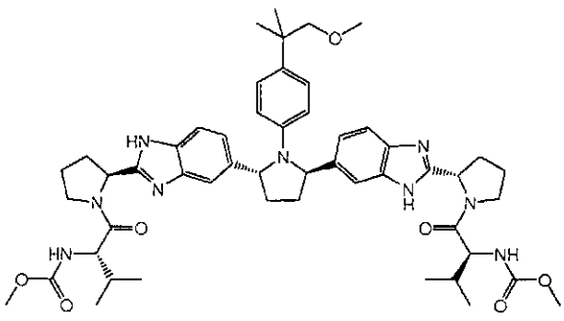
^{1}H NMR (400 MHz, DMSO-d6) δ ppm 1.10 (s, 9 H), 1.55 - 1.66 (m, 3 H), 1.68 - 1.82 (m, 4 H), 1.83 - 2.02 (m, 5 H), 1.93 (s, 6 H), 2.12 - 2.31 (m, 3 H), 2.57 (d, *J*=3.90 Hz, 2 H), 5.26 - 5.36 (m, 2 H), 5.41 - 5.57 (m, 2 H), 6.30 (d, *J*=8.78 Hz, 2 H), 6.93 (d, *J*=8.78 Hz, 2 H), 7.17 - 7.31 (m, 2 H), 7.38 (s, 2 H), 7.47 - 7.66 (m, 13 H), 8.43 (s, 6 H); MS (ESI+) m/z 868 $(M+H)^+$.



Example 223

methyl {(2S,3R)-1-[(2S,4S)-2-{5-[(2R,5R)-1-(4-tert-butylphenyl)-5-(2-{(2S,4S)-4-hydroxy-1-[N-(methoxycarbonyl)-O-methyl-L-threonyl]pyrrolidin-2-yl}-1H-benzimidazol-5-yl)pyrrolidin-2-yl]-1H-benzimidazol-2-yl}-4-hydroxypyrrolidin-1-yl]-3-methoxy-1-oxobutan-2-yl}carbamate

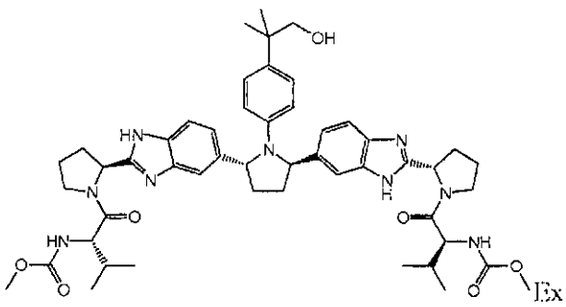
^{1}H NMR (400 MHz, DMSO-d6) δ ppm 0.96 (d, *J*=5.96 Hz, 6 H), 1.09 (s, 9 H), 1.74 (d, *J*=5.64 Hz, 2 H), 2.06 - 2.15 (m, 3 H), 2.96 - 3.03 (m, 1 H), 3.10 (s, 6 H), 3.55 (s, 6 H), 3.72 (dd, *J*=9.65, 2.39 Hz, 3 H), 3.94 (dd, *J*=10.25, 4.72 Hz, 2 H), 4.23 - 4.33 (m, 2 H), 4.38 (t, *J*=7.10 Hz, 1 H), 4.44 - 4.53 (m, 2 H), 5.26 (dd, *J*=8.46, 4.23 Hz, 2 H), 5.49 (d, *J*=5.53 Hz, 2 H), 6.25 (d, *J*=8.78 Hz, 2 H), 6.94 (d, *J*=8.78 Hz, 2 H), 7.22 (d, *J*=8.46 Hz, 2 H), 7.37 (d, *J*=7.59 Hz, 2 H), 7.46 (s, 2 H), 7.69 (d, *J*=7.92 Hz, 2 H); MS (ESI+) m/z 952 $(M+H)^+$.



Example 224

methyl {(2S)-1-[(2S)-2-(6-{(2R,5R)-5-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-benzimidazol-5-yl}-1-[4-(1-methoxy-2-methylpropan-2-yl)phenyl]pyrrolidin-2-yl}-1H-benzimidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

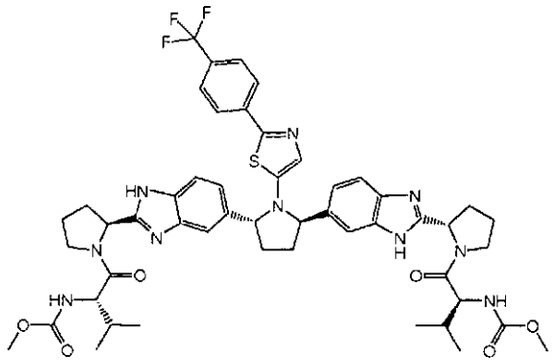
1H NMR (400 MHz, DMSO-D6) δ ppm 0.74 - 0.93 (m, 12 H) 1.04 (s, 6 H) 1.69 (d, J=4.34 Hz, 2 H) 1.85 - 1.94 (m, 2 H) 1.95 - 2.03 (m, 6 H) 2.13 - 2.25 (m, 2 H) 2.53 - 2.63 (m, 4 H) 3.11 (s, 3 H) 3.53 (s, 6 H) 3.81 (s, 4 H) 4.05 - 4.15 (m, 2 H) 5.09 - 5.19 (m, 2 H) 5.32 - 5.41 (m, 2 H) 6.25 (d, J=8.78 Hz, 2 H) 6.87 (ddd, J=8.89, 4.77, 4.55 Hz, 2 H) 7.07 (t, J=7.37 Hz, 2 H) 7.20 (s, 1 H) 7.25 - 7.33 (m, 3 H) 7.38 (d, J=8.24 Hz, 1 H) 7.46 (d, J=8.46 Hz, 1 H) 12.00 - 12.09 (m, 2 H); MS ESI+ 918.



Example 225

methyl {(2S)-1-[(2S)-2-{6-[(2R,5R)-1-[4-(1-hydroxy-2-methylpropan-2-yl)phenyl]-5-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-benzimidazol-5-yl}pyrrolidin-2-yl]-1H-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

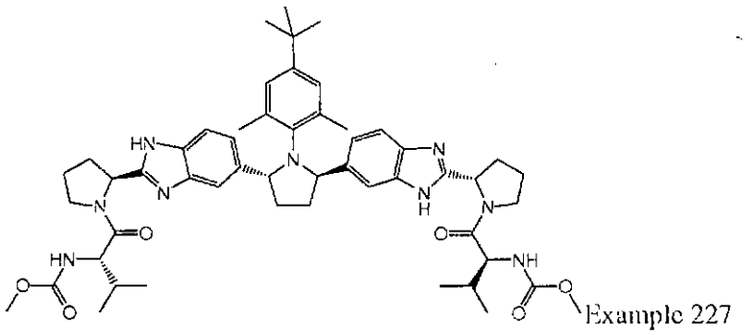
1H NMR (400 MHz, DMSO-D6) d ppm 0.76 - 0.91 (m, 12 H) 1.01 (d, J=2.60 Hz, 6 H) 1.64 - 1.72 (m, 2 H) 1.91 (dd, J=14.42, 6.83 Hz, 2 H) 1.95 - 2.05 (m, 4 H) 2.14 - 2.23 (m, 4 H) 2.54 - 2.60 (m, 2 H) 3.53 (s, 6 H) 3.76 - 3.87 (m, 4 H) 4.11 (q, J=4.77 Hz, 4 H) 4.42 (s, 1 H) 5.09 - 5.17 (m, 2 H) 5.31 - 5.40 (m, 2 H) 6.25 (d, J=8.78 Hz, 2 H) 6.83 - 6.92 (m, 2 H) 7.07 (t, J=7.21 Hz, 2 H) 7.20 (s, 1 H) 7.26 - 7.32 (m, 3 H) 7.38 (d, J=8.13 Hz, 1 H) 7.46 (d, J=8.35 Hz, 1 H) 11.99 - 12.06 (m, 2 H); MS ESI+ m/z 904.5 (M+H)+.



Example 226

methyl {(2S)-1-[(2S)-2-{6-[(2R,5R)-5-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-benzimidazol-5-yl}-1-{2-[4-(trifluoromethyl)phenyl]-1,3-thiazol-5-yl}pyrrolidin-2-yl]-1H-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

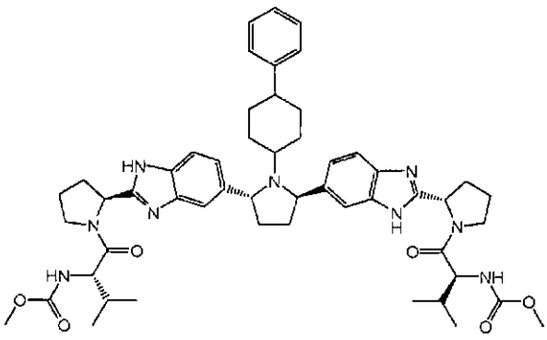
1H NMR (400 MHz, DMSO-D6) d ppm 0.73 - 0.91 (m, 12 H) 1.79 - 1.95 (m, 4 H) 1.96 - 2.06 (m, 4 H) 2.15 - 2.27 (m, 2 H) 2.69 - 2.76 (m, 2 H) 3.43 - 3.50 (m, 2 H) 3.53 (s, 6 H) 3.78 - 3.88 (m, 4 H) 4.01 - 4.10 (m, 2 H) 5.11 - 5.18 (m, 2 H) 5.32 - 5.41 (m, 2 H) 6.43 (s, 1 H) 7.09 - 7.18 (m, 2 H) 7.27 (dd, J=8.24, 2.39 Hz, 2 H) 7.35 (s, 1 H) 7.41 - 7.46 (m, 2 H) 7.51 (d, J=8.35 Hz, 1 H) 7.57 - 7.62 (m, 2 H) 7.64 - 7.70 (m, 2 H) 12.12 (s, 2 H); MS ESI+ m/z 983.4 (M+H)+.



Example 227

methyl {(2S)-1-[(2S)-2-{6-[(2R,5R)-1-(4-tert-butyl-2,6-dimethylphenyl)-5-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-benzimidazol-5-yl}pyrrolidin-2-yl]-1H-benzimidazol-2-yl}pyrrolidin-1-yl}-3-methyl-1-oxobutan-2-yl}carbamate

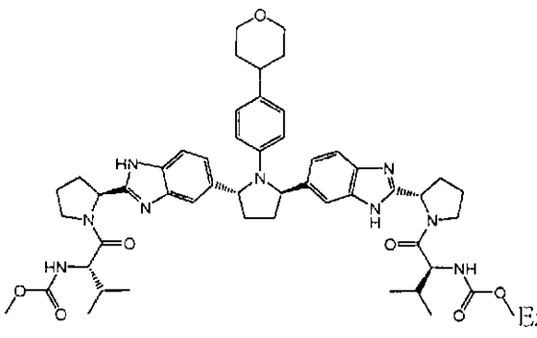
1H NMR (400 MHz, DMSO-D6) d ppm 0.77 - 0.89 (m, 12 H) 1.02 (s, 9 H) 1.84 - 2.05 (m, 10 H) 2.13 - 2.19 (m, 4 H) 2.24 - 2.30 (m, 6 H) 3.53 (s, 6 H) 3.80 (s, 4 H) 4.04 (t, J=8.08 Hz, 2 H) 5.07 - 5.14 (m, 2 H) 5.25 (s, 2 H) 6.61 (dd, J=5.10, 2.71 Hz, 2 H) 7.06 (dd, J=11.87, 8.51 Hz, 2 H) 7.20 - 7.37 (m, 6 H) 11.89 (s, 1 H) 11.99 (s, 1 H); MS ESI+ m/z 916.6 (M+H)+.



Example 228

methyl {(2S)-1-[(2S)-2-{6-[(2R,5R)-5-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-benzimidazol-5-yl}-1-(4-phenylcyclohexyl)pyrrolidin-2-yl]-1H-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

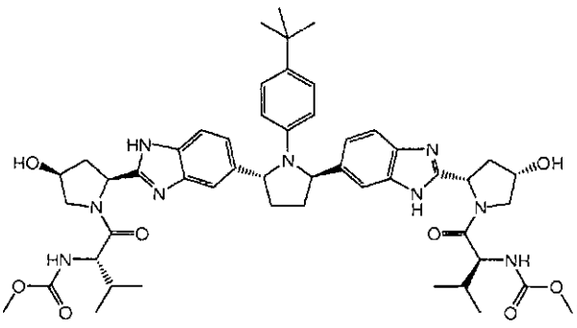
1H NMR (400 MHz, DMSO-D6) d ppm 0.78 - 0.93 (m, 12 H) 1.15 - 1.44 (m, 4 H) 1.46 - 1.59 (m, 2 H) 1.67 - 1.78 (m, 2 H) 1.84 - 1.96 (m, 4 H) 1.98 - 2.10 (m, 4 H) 2.14 - 2.27 (m, 4 H) 2.67 - 2.75 (m, 2 H) 3.07 - 3.21 (m, 1 H) 3.45 - 3.52 (m, 1 H) 3.54 (s, 6 H) 3.78 - 3.91 (m, 4 H) 4.03 - 4.13 (m, 2 H) 4.64 - 4.73 (m, 2 H) 5.17 (d, J=4.88 Hz, 2 H) 7.00 - 7.06 (m, 2 H) 7.09 (t, J=7.32 Hz, 2 H) 7.14 - 7.24 (m, 3 H) 7.30 (d, J=8.46 Hz, 2 H) 7.38 (d, J=8.02 Hz, 1 H) 7.43 - 7.50 (m, 3 H) 12.00 (s, 2 H); MS ESLD+ m/z 914.



Example 229

methyl {(2S)-1-[(2S)-2-(6-{(2R,5R)-5-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-benzimidazol-5-yl}-1-[4-(tetrahydro-2H-pyran-4-yl)phenyl]pyrrolidin-2-yl}-1H-benzimidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

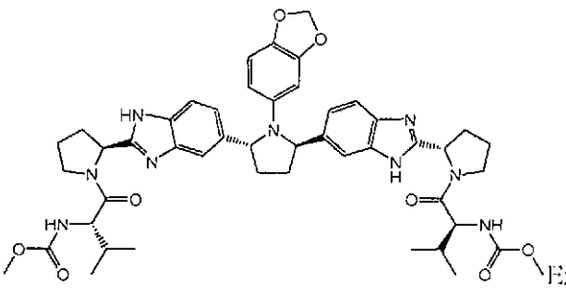
1H NMR (400 MHz, DMSO-D6) d ppm 0.73 - 0.94 (m, 12 H) 1.41 - 1.60 (m, 6 H) 1.65 - 1.75 (m, 2 H) 1.86 - 1.94 (m, 2 H) 1.95 - 2.05 (m, 4 H) 2.14 - 2.24 (m, 4 H) 2.37 - 2.46 (m, 2 H) 3.53 (s, 6 H) 3.77 - 3.86 (m, 7 H) 4.02 - 4.10 (m, 2 H) 5.09 - 5.17 (m, 2 H) 5.32 - 5.39 (m, 2 H) 6.26 (d, J=8.67 Hz, 2 H) 6.72 - 6.81 (m, 2 H) 7.06 (t, J=7.64 Hz, 2 H) 7.20 (s, 1 H) 7.26 - 7.31 (m, 3 H) 7.37 (d, J=8.13 Hz, 1 H) 7.45 (d, J=8.13 Hz, 1 H) 12.00 - 12.05 (m, 2 H); MS ESLD+ m/z 917 (M+H)+.



Example 230

methyl {(2S)-1-[(2S,4S)-2-{6-[(2R,5R)-1-(4-tert-butylphenyl)-5-{2-[(2S,4S)-4-hydroxy-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-benzimidazol-5-yl}pyrrolidin-2-yl]-1H-benzimidazol-2-yl}-4-hydroxypyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

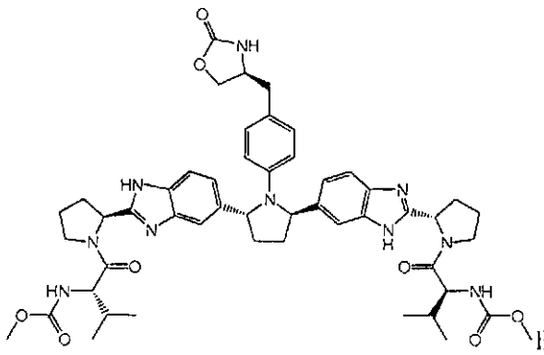
1H NMR (500 MHz, DMSO-D6) d ppm 0.67 - 0.91 (m, 12 H) 1.07 (s, 9 H) 1.69 (d, J=3.97 Hz, 2 H) 1.78 - 1.89 (m, 2 H) 2.01 (d, J=13.12 Hz, 2 H) 2.37 - 2.44 (m, 2 H) 3.53 (s, 6 H) 3.67 (d, J=10.07 Hz, 2 H) 3.95 - 4.07 (m, 4 H) 4.38 (s, 2 H) 5.12 (s, 2 H) 5.37 (s, 2 H) 6.25 (d, J=8.54 Hz, 2 H) 6.34 (s, 2 H) 6.86 - 6.94 (m, 2 H) 7.09 (d, J=7.93 Hz, 2 H) 7.22 - 7.33 (m, 4 H) 7.39 - 7.51 (m, 2 H) 12.27 (d, J=21.05 Hz, 2 H); MS ESLD+ m/z 920.



Example 231

methyl {(2S)-1-[(2S)-2-{6-[(2R,5R)-1-(1,3-benzodioxol-5-yl)-5-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-benzimidazol-5-yl}pyrrolidin-2-yl]-1H-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

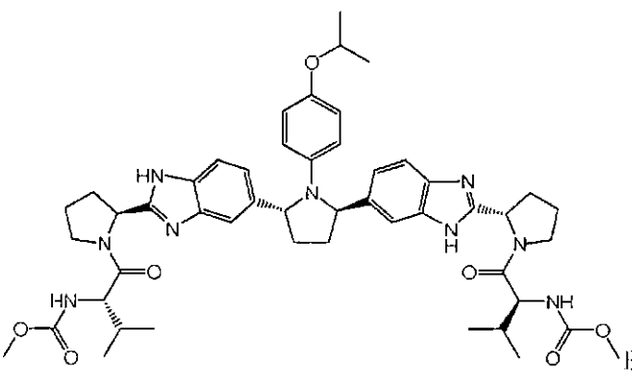
1H NMR (400 MHz, DMSO-D6) d ppm 0.78 - 0.91 (m, 12 H) 1.64 - 1.72 (m, 2 H) 1.86 - 2.04 (m, 6 H) 2.14 - 2.24 (m, 4 H) 3.29 (s, 2 H) 3.54 (s, 6 H) 3.82 (s, 4 H) 4.05 - 4.11 (m, 2 H) 5.10 - 5.18 (m, 2 H) 5.29 - 5.36 (m, 2 H) 5.66 (d, J=2.93 Hz, 1 H) 5.70 - 5.75 (m, 2 H) 5.99 (d, J=2.28 Hz, 1 H) 6.45 - 6.51 (m, 1 H) 7.02 - 7.09 (m, 2 H) 7.21 (s, 1 H) 7.28 (s, 1 H) 7.31 (d, J=6.40 Hz, 2 H) 7.37 (d, J=8.13 Hz, 1 H) 7.45 (d, J=8.24 Hz, 1 H) 12.03 (s, 2 H); MS TFA+ m/z 876.8 (M+H)+.



Example 232

methyl {(2S)-1-[(2S)-2-{6-[(2R,5R)-5-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-benzimidazol-5-yl}-1-(4-{[(4S)-2-oxo-1,3-oxazolidin-4-yl]methyl}phenyl)pyrrolidin-2-yl]-1H-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

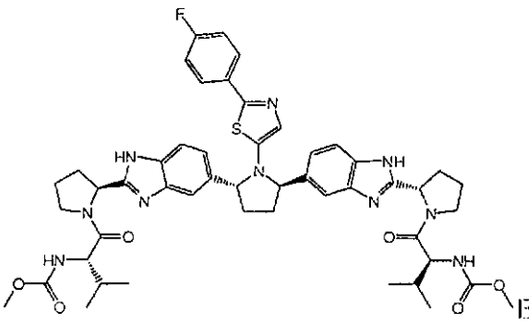
1H NMR (400 MHz, DMSO-D6) d ppm 0.77 - 0.92 (m, 12 H) 1.63 - 1.74 (m, 2 H) 1.86 - 2.04 (m, 6 H) 2.13 - 2.26 (m, 4 H) 2.55 - 2.65 (m, 2 H) 3.25 - 3.33 (m, 2 H) 3.54 (s, 6 H) 3.75 - 3.87 (m, 6 H) 4.05 - 4.17 (m, 3 H) 5.09 - 5.19 (m, 2 H) 5.36 (d, J=5.10 Hz, 2 H) 6.27 (d, J=8.57 Hz, 2 H) 6.71 - 6.79 (m, 2 H) 7.05 (t, J=9.60 Hz, 2 H) 7.20 (s, 1 H) 7.27 - 7.33 (m, 3 H) 7.37 (d, J=8.24 Hz, 1 H) 7.45 (d, J=8.13 Hz, 1 H) 7.63 (s, 1 H) 12.03 (s, 2 H); MS ESI+ m/z 931.5 (M+H)+.



Example 233

methyl {(2S)-1-[(2S)-2-(6-{(2R,5R)-5-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-benzimidazol-5-yl}-1-[4-(propan-2-yloxy)phenyl]pyrrolidin-2-yl}-1H-benzimidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

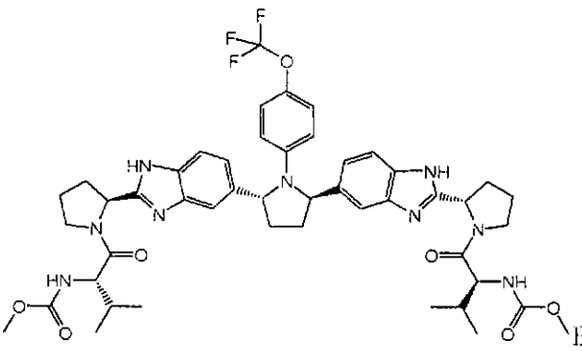
1H NMR (400 MHz, DMSO-D6) d ppm 0.76 - 0.89 (m, 12 H) 1.07 (t, J=5.42 Hz, 6 H) 1.68 (d, J=3.47 Hz, 2 H) 1.85 - 2.05 (m, 6 H) 2.14 - 2.25 (m, 4 H) 2.58 (d, J=4.77 Hz, 2 H) 3.53 (s, 6 H) 3.81 (s, 4 H) 4.05 (t, J=8.40 Hz, 2 H) 4.13 - 4.25 (m, 1 H) 5.08 - 5.20 (m, 2 H) 5.32 (d, J=5.31 Hz, 2 H) 6.23 (d, J=9.00 Hz, 2 H) 6.45 - 6.55 (m, 2 H) 7.05 (t, J=8.19 Hz, 2 H) 7.20 (s, 1 H) 7.26 - 7.33 (m, 3 H) 7.37 (d, J=8.24 Hz, 1 H) 7.44 (d, J=8.35 Hz, 1 H) 12.02 (d, J=4.55 Hz, 2 H); MS ESI+ m/z 890.4 (M+H)+.



Example 234

methyl {(2S)-1-[(2S)-2-{5-[(2R,5R)-1-[2-(4-fluorophenyl)-1,3-thiazol-5-yl]-5-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-benzimidazol-5-yl}pyrrolidin-2-yl}-1H-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

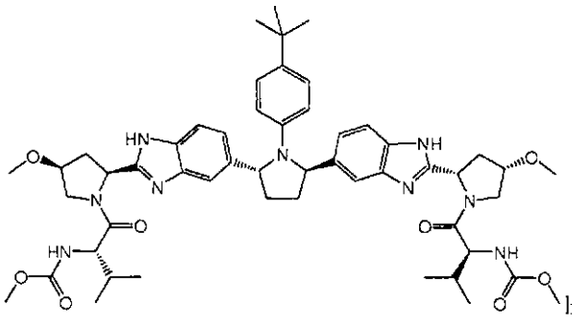
1H NMR (400 MHz, DMSO-D6) d ppm 0.75 - 0.85 (m, 12 H) 1.77 - 1.83 (m, 2 H) 1.87 - 1.93 (m, 2 H) 1.95 - 2.06 (m, 4 H) 2.14 - 2.25 (m, 6 H) 3.53 (s, 6 H) 3.77 - 3.86 (m, 4 H) 4.03 - 4.10 (m, 2 H) 5.12 - 5.18 (m, 2 H) 5.28 - 5.35 (m, 2 H) 7.06 - 7.16 (m, 5 H) 7.28 (dd, J=8.29, 2.01 Hz, 2 H) 7.33 (s, 1 H) 7.40 - 7.45 (m, 2 H) 7.47 - 7.55 (m, 3 H) 12.10 (s, 2 H); MS ESI+ m/z 933.4 (M+H)+.



Example 235

methyl {(2S)-1-[(2S)-2-(5-{(2R,5R)-5-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-benzimidazol-5-yl}-1-[4-(trifluoromethoxy)phenyl]pyrrolidin-2-yl}-1H-benzimidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

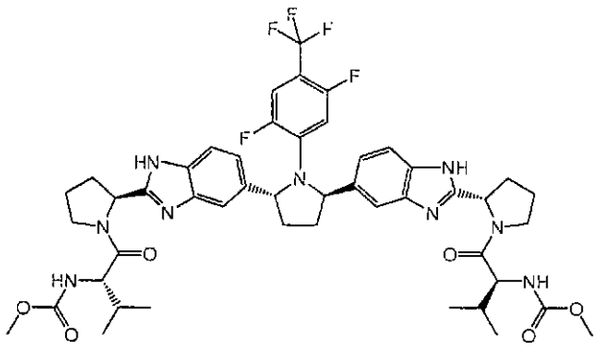
1H NMR (400 MHz, DMSO-D6) d ppm 0.74 - 0.87 (m, 12 H) 1.67 - 1.76 (m, 2 H) 1.86 - 1.92 (m, 2 H) 1.96 - 2.06 (m, 4 H) 2.15 - 2.23 (m, 6 H) 3.53 (s, 6 H) 3.77 - 3.88 (m, 4 H) 4.05 (t, J=8.84 Hz, 2 H) 5.12 (t, J=7.05 Hz, 2 H) 5.37 - 5.46 (m, 2 H) 6.34 (d, J=9.11 Hz, 2 H) 6.89 (q, J=7.30 Hz, 2 H) 7.02 - 7.11 (m, 2 H) 7.21 (s, 1 H) 7.26 - 7.33 (m, 3 H) 7.39 (d, J=8.35 Hz, 1 H) 7.47 (d, J=8.13 Hz, 1 H) 12.06 (d, J=17.02 Hz, 2 H); MS ESI+ m/z 916.4 (M+H)+.



Example 236

methyl {(2S)-1-[(2S,4S)-2-{5-[(2R,5R)-1-(4-tert-butylphenyl)-5-{2-[(2S,4S)-4-methoxy-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-benzimidazol-5-yl}pyrrolidin-2-yl]-1H-benzimidazol-2-yl}-4-methoxypyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

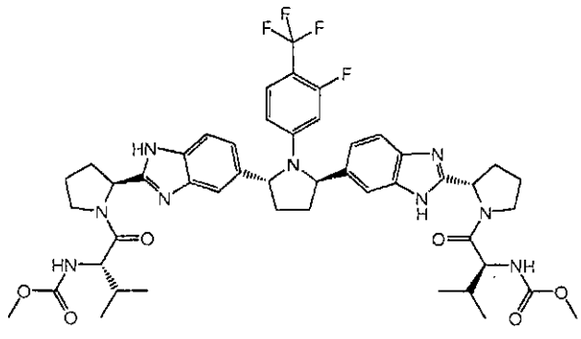
1H NMR (400 MHz, DMSO-D6) d ppm 0.75 - 0.88 (m, 12 H) 1.07 (s, 9 H) 1.67 - 1.76 (m, 2 H) 1.88 - 2.00 (m, 4 H) 2.06 - 2.16 (m, 2 H) 3.12 - 3.21 (m, 2 H) 3.25 (d, J=4.23 Hz, 6 H) 3.54 (s, 6 H) 3.59 - 3.69 (m, 2 H) 4.02 - 4.13 (m, 4 H) 4.16 - 4.28 (m, 2 H) 5.11 (td, J=9.38, 6.51 Hz, 2 H) 5.35 (t, J=5.37 Hz, 2 H) 6.23 - 6.28 (m, 2 H) 6.90 (d, J=8.89 Hz, 2 H) 7.06 (d, J=10.19 Hz, 2 H) 7.22 (d, J=3.25 Hz, 1 H) 7.25 - 7.32 (m, 3 H) 7.38 (d, J=8.35 Hz, 1 H) 7.45 (d, J=8.24 Hz, 1 H) 11.79 (d, J=18.32 Hz, 2 H); MS ESI+ m/z 948.5 (M+H)+.



Example 237

methyl {(2S)-1-[(2S)-2-{5-[(2R,5R)-1-[2,5-difluoro-4-(trifluoromethyl)phenyl]-5-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-benzimidazol-5-yl}pyrrolidin-2-yl]-1H-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

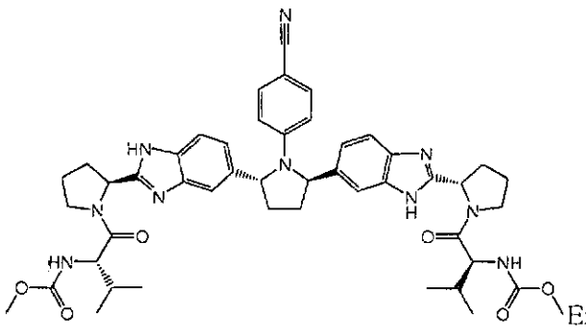
1H NMR (400 MHz, DMSO-D6) d ppm 0.74 - 0.90 (m, 12 H) 1.74 - 1.83 (m, 2 H) 1.86 - 1.93 (m, 2 H) 1.94 - 2.05 (m, 4 H) 2.13 - 2.25 (m, 4 H) 3.44 - 3.48 (m, 2 H) 3.53 (s, 6 H) 3.77 - 3.88 (m, 4 H) 4.06 (t, J=4.23 Hz, 2 H) 5.10 - 5.16 (m, 2 H) 5.63 - 5.74 (m, 2 H) 6.60 - 6.73 (m, 1 H) 7.04 - 7.20 (m, 4 H) 7.24 - 7.31 (m, 3 H) 7.38 (d, J=8.46 Hz, 1 H) 7.46 (d, J=8.13 Hz, 1 H) 12.08 (d, J=27.11 Hz, 2 H); MS ESI+ m/z 936.4 (M+H)+.



Example 238

methyl {(2S)-1-[(2S)-2-{6-[(2R,5R)-1-[3-fluoro-4-(trifluoromethyl)phenyl]-5-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-benzimidazol-5-yl}pyrrolidin-2-yl]-1H-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

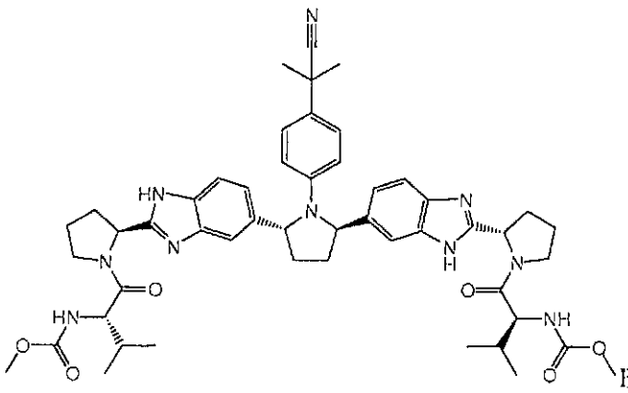
1H NMR (400 MHz, DMSO-D6) d ppm 0.75 - 0.90 (m, 12 H) 1.71 - 1.79 (m, 2 H) 1.87 - 1.95 (m, 2 H) 1.97 - 2.04 (m, 4 H) 2.13 - 2.25 (m, 6 H) 3.53 (s, 6 H) 3.77 - 3.86 (m, 4 H) 4.04 - 4.11 (m, 2 H) 5.11 - 5.18 (m, 2 H) 5.46 - 5.56 (m, 2 H) 6.24 (dd, J=8.24, 2.39 Hz, 2 H) 7.04 - 7.11 (m, 2 H) 7.19 - 7.25 (m, 2 H) 7.28 (dd, J=8.46, 3.69 Hz, 2 H) 7.32 (s, 1 H) 7.41 (d, J=8.13 Hz, 1 H) 7.49 (d, J=8.24 Hz, 1 H) 12.09 (dd, J=15.72, 2.17 Hz, 2 H); MS ESI+ m/z 918.4 (M+H)+.



Example 239

methyl {(2S)-1-[(2S)-2-{6-[(2R,5R)-1-(4-cyanophenyl)-5-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-benzimidazol-5-yl}pyrrolidin-2-yl]-1H-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

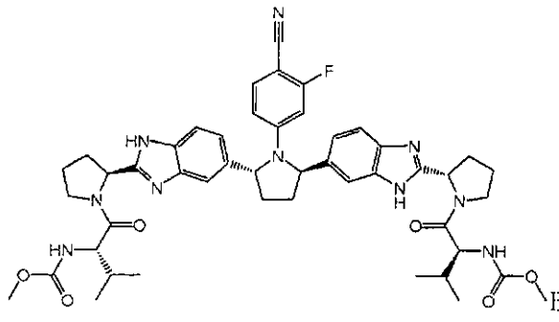
1H NMR (400 MHz, DMSO-D6) d ppm 0.76 - 0.90 (m, 12 H) 1.70 - 1.79 (m, 2 H) 1.90 (dd, J=12.25, 6.40 Hz, 2 H) 1.95 - 2.02 (m, 4 H) 2.15 - 2.24 (m, 6 H) 3.54 (s, 6 H) 3.78 - 3.85 (m, 4 H) 4.06 (t, J=8.29 Hz, 2 H) 5.10 - 5.16 (m, 2 H) 5.46 - 5.55 (m, 2 H) 6.42 (d, J=8.67 Hz, 2 H) 7.05 (dd, J=12.90, 8.57 Hz, 2 H) 7.22 (s, 1 H) 7.25 - 7.34 (m, 5 H) 7.40 (d, J=8.24 Hz, 1 H) 7.47 (d, J=8.24 Hz, 1 H) 12.09 (s, 2 H); MS ESI+ m/z 857.4 (M+H)+.



Example 240

methyl {(2S)-1-[(2S)-2-{6-[(2R,5R)-1-[4-(2-cyanopropan-2-yl)phenyl]-5-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-benzimidazol-5-yl}pyrrolidin-2-yl]-1H-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

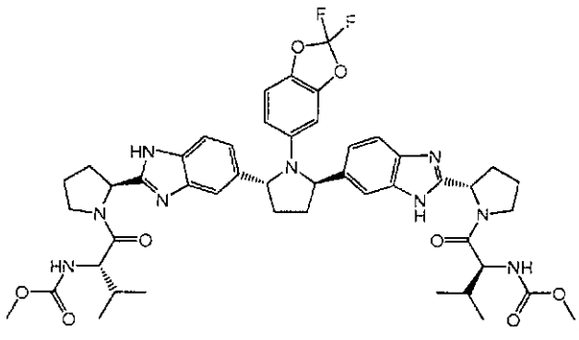
1H NMR (400 MHz, DMSO-D6) d ppm 0.75 - 0.91 (m, 12 H) 1.47 (s, 6 H) 1.67 - 1.76 (m, 2 H) 1.85 - 1.95 (m, 2 H) 1.96 - 2.03 (m, 4 H) 2.15 - 2.24 (m, 6 H) 3.53 (s, 6 H) 3.77 - 3.85 (m, 4 H) 4.05 (t, J=8.46 Hz, 2 H) 5.10 - 5.17 (m, 2 H) 5.37 - 5.45 (m, 2 H) 6.34 (d, J=8.89 Hz, 2 H) 6.97 - 7.04 (m, 2 H) 7.07 (t, J=8.35 Hz, 2 H) 7.21 (s, 1 H) 7.28 (d, J=10.52 Hz, 3 H) 7.39 (d, J=8.13 Hz, 1 H) 7.47 (d, J=8.24 Hz, 1 H) 12.05 (d, J=13.01 Hz, 2 H); MS ESI+ m/z 899.4 (M+H)+.



Example 241

methyl {(2S)-1-[(2S)-2-{6-[(2R,5R)-1-(4-cyano-3-fluorophenyl)-5-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-benzimidazol-5-yl}pyrrolidin-2-yl]-1H-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

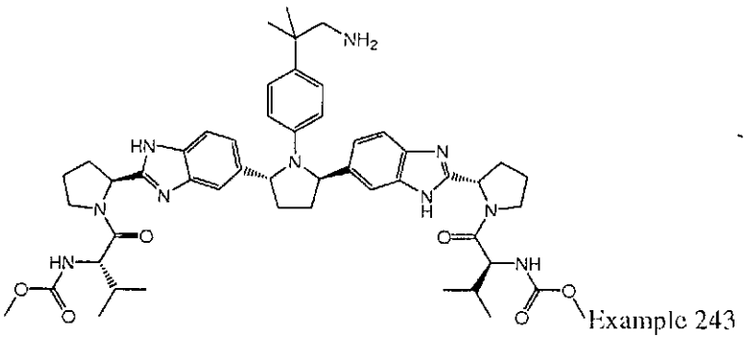
1H NMR (400 MHz, DMSO-D6) d ppm 0.74 - 0.92 (m, 12 H) 1.74 (t, J=9.00 Hz, 2 H) 1.87 - 1.94 (m, 2 H) 1.96 - 2.06 (m, 4 H) 2.15 - 2.25 (m, 4 H) 2.55 - 2.63 (m, 2 H) 3.54 (s, 6 H) 3.82 (s, 4 H) 4.06 (t, J=8.40 Hz, 2 H) 5.14 (d, J=2.28 Hz, 2 H) 5.55 (dd, J=16.26, 6.07 Hz, 2 H) 6.18 - 6.33 (m, 2 H) 7.01 - 7.15 (m, 2 H) 7.23 (s, 1 H) 7.25 - 7.35 (m, 4 H) 7.42 (d, J=7.70 Hz, 1 H) 7.49 (d, J=8.46 Hz, 1 H) 12.10 (s, 2 H); MS ESI+ m/z 875.4 (M+H)+.



Example 242

methyl {(2S)-1-[(2S)-2-{6-[(2R,5R)-1-(2,2-difluoro-1,3-benzodioxol-5-yl)-5-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-benzimidazol-5-yl}pyrrolidin-2-yl]-1H-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

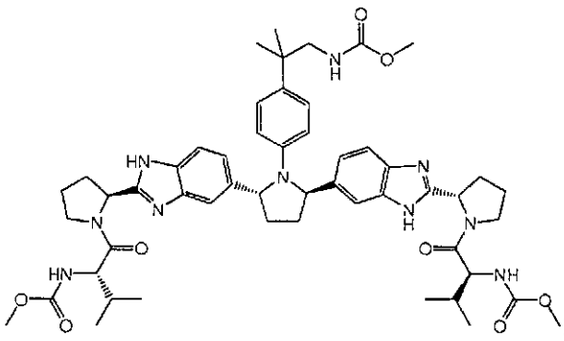
1H NMR (400 MHz, DMSO-D6) d ppm 0.75 - 0.91 (m, 12 H) 1.69 - 1.77 (m, 2 H) 1.91 (dd, J=14.26, 6.67 Hz, 2 H) 1.96 - 2.07 (m, 4 H) 2.14 - 2.24 (m, 4 H) 2.54 - 2.60 (m, 2 H) 3.53 (s, 6 H) 3.78 - 3.86 (m, 4 H) 4.06 (t, J=8.40 Hz, 2 H) 5.10 - 5.17 (m, 2 H) 5.36 - 5.44 (m, 2 H) 6.05 (dd, J=9.11, 2.17 Hz, 1 H) 6.29 (d, J=2.60 Hz, 1 H) 6.89 - 6.95 (m, 1 H) 7.06 (t, J=8.51 Hz, 2 H) 7.22 (s, 1 H) 7.26 - 7.33 (m, 3 H) 7.39 (d, J=8.35 Hz, 1 H) 7.47 (d, J=7.59 Hz, 1 H) 12.03 - 12.09 (m, 2 H); MS ESI+ m/z 912.8 (M+H)+.



Example 243

methyl {(2S)-1-[(2S)-2-{6-[(2R,5R)-1-[4-(1-amino-2-methylpropan-2-yl)phenyl]-5-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-benzimidazol-5-yl}pyrrolidin-2-yl]-1H-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

1H NMR (400 MHz, DMSO-D6) d ppm 0.74 - 0.92 (m, 12 H) 1.01 (d, J=5.20 Hz, 6 H) 1.65 - 1.76 (m, 2 H) 1.86 - 1.93 (m, 2 H) 1.98 (d, J=4.01 Hz, 4 H) 2.13 - 2.25 (m, 4 H) 2.41 (s, 2 H) 2.53 - 2.61 (m, 2 H) 3.53 (s, 6 H) 3.81 (s, 4 H) 4.05 (t, J=8.35 Hz, 2 H) 5.08 - 5.17 (m, 2 H) 5.32 - 5.41 (m, 2 H) 6.27 (d, J=8.89 Hz, 2 H) 6.81 - 6.92 (m, 2 H) 7.07 (t, J=7.97 Hz, 2 H) 7.20 (s, 1 H) 7.25 - 7.32 (m, 3 H) 7.38 (d, J=8.13 Hz, 1 H) 7.46 (d, J=8.13 Hz, 1 H) 12.02 (d, J=19.63 Hz, 2 H); MS ESI+ m/z 903.4 (M+H)+.

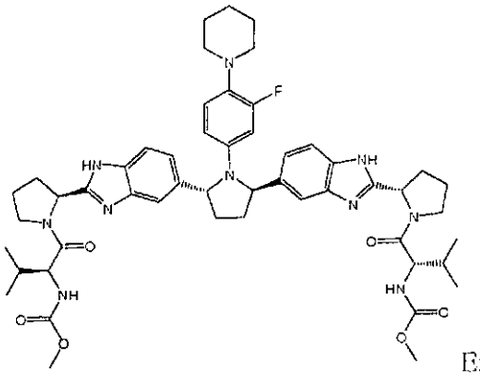


Example 244

methyl (2-{4-[(2R,5R)-2-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-benzimidazol-5-yl}-5-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-benzimidazol-6-yl}pyrrolidin-1-yl]phenyl}-2-methylpropyl)carbamate

1H NMR (400 MHz, DMSO-D6) d ppm 0.75 - 0.91 (m, 12 H) 1.00 (d, J=6.07 Hz, 6 H) 1.64 - 1.75 (m, 2 H) 1.83 - 1.94 (m, 2 H) 1.96 - 2.05 (m, 4 H) 2.14 - 2.23 (m, 4 H) 2.89 - 3.00 (m, 2 H) 3.17 (d, J=5.20 Hz, 2 H) 3.42 (s, 3 H) 3.53 (s, 6 H) 3.77 - 3.87 (m, 4 H) 3.99 - 4.07 (m, 2 H) 5.08 - 5.20 (m, 2 H) 5.32 - 5.42 (m, 2 H) 6.27 (d, J=8.46 Hz, 2 H) 6.72 - 6.80 (m, 1 H) 6.83 - 6.93 (m, 2 H) 7.07 (t, J=8.62 Hz, 2 H) 7.20 (s, 1 H) 7.26 - 7.33 (m, 3 H) 7.38 (d, J=8.13 Hz, 1 H) 7.45 (d, J=8.57 Hz, 1 H) 12.03 (d, J=12.36 Hz, 2 H)

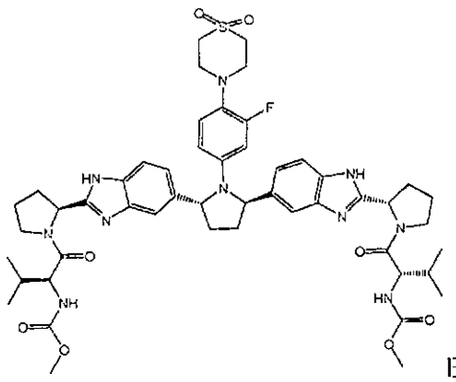
MS ESI+ m/z 961.4 (M+H)+



Example 245

methyl {(2S)-1-[(2S)-2-{5-[(2R,5R)-1-[3-fluoro-4-(piperidin-1-yl)phenyl]-5-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-benzimidazol-5-yl}pyrrolidin-2-yl]-1H-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

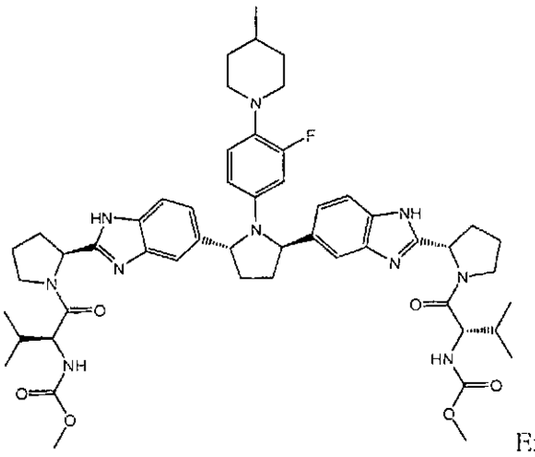
MS (ESI) m/z 934 $(M+H)^+$



Example 246

methyl {(2S)-1-[(2S)-2-{5-[(2R,5R)-1-[4-(1,1-dioxidothiomorpholin-4-yl)-3-fluorophenyl]-5-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-benzimidazol-5-yl}pyrrolidin-2-yl]-1H-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

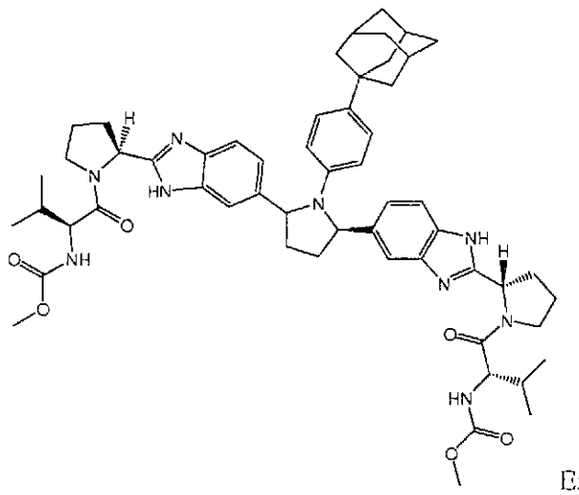
MS (ESI) m/z 984 $(M+H)^+$



Example 247

methyl {(2S)-1-[(2S)-2-{5-[(2R,5R)-1-[3-fluoro-4-(4-methylpiperidin-1-yl)phenyl]-5-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-benzimidazol-5-yl}pyrrolidin-2-yl]-1H-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

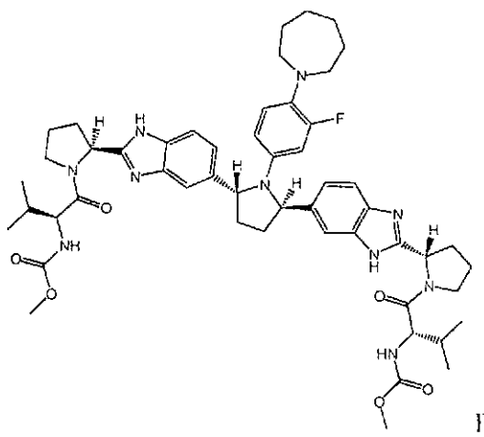
MS (ESI) m/z 948 $(M+H)^+$



Example 248

methyl {(2S)-1-[(2S)-2-(6-{(5R)-5-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-benzimidazol-5-yl}-1-[4-(tricyclo[3.3.1.1~3,7~]dec-1-yl)phenyl]pyrrolidin-2-yl}-1H-benzimidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

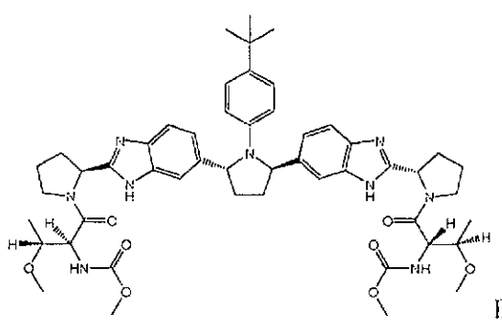
+ESI m/z (rel abundance) 967 (100, M+H)



Example 249

methyl {(2S)-1-[(2S)-2-{6-[(2R,5R)-1-[4-(azepan-1-yl)-3-fluorophenyl]-5-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-benzimidazol-5-yl}pyrrolidin-2-yl]-1H-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

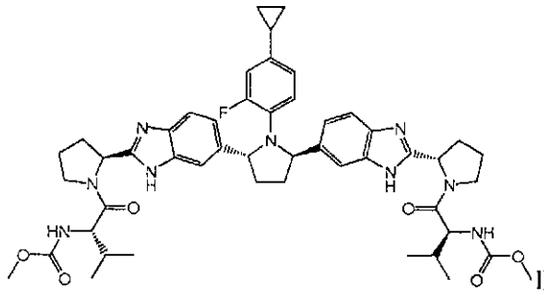
+ESI m/z (rel abundance) 948 (100, M+H)



Example 250

methyl {(2*S*,3*R*)-1-[(2*S*)-2-{6-[(2*R*,5*R*)-1-(4-*tert*-butylphenyl)-5-(2-{(2*S*)-1-[*N*-(methoxycarbonyl)-*O*-methyl-L-threonyl]pyrrolidin-2-yl}-1*H*-benzimidazol-6-yl)pyrrolidin-2-yl]-1*H*-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methoxy-1-oxobutan-2-yl}carbamate

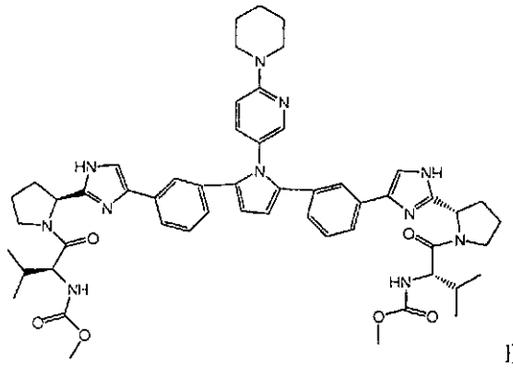
MS (ESI) *m/z* 920 $(M+H)^+$.



Example 251

methyl {(2S)-1-[(2S)-2-{6-[(2R,5R)-1-(4-cyclopropyl-2-fluorophenyl)-5-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-benzimidazol-6-yl}pyrrolidin-2-yl]-1H-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

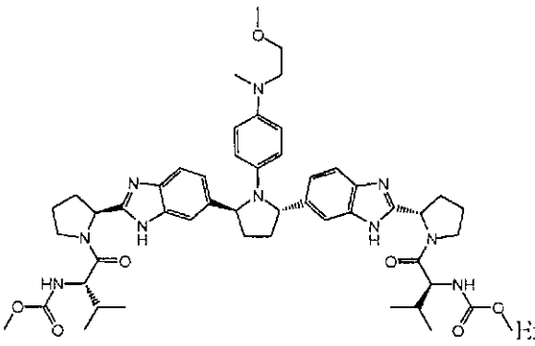
MS (ESI) *m/z* 890 $(M+H)^+$.



Example 252

methyl [(2S)-1-{(2S)-2-[4-(3-{5-(3-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-4-yl}phenyl)-1-[6-(piperidin-1-yl)pyridin-3-yl]-1H-pyrrol-2-yl}phenyl)-1H-imidazol-2-yl]pyrrolidin-1-yl}-3-methyl-1-oxobutan-2-yl]carbamate

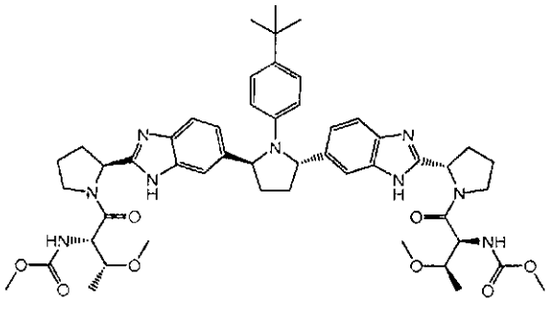
MS (ESI; M+H) m/z = 964.5.



Example 253

methyl {(2S)-1-[(2S)-2-{6-[(2S,5S)-5-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-benzimidazol-6-yl}-1-{4-[(2-methoxyethyl)(methyl)amino]phenyl}pyrrolidin-2-yl]-1H-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

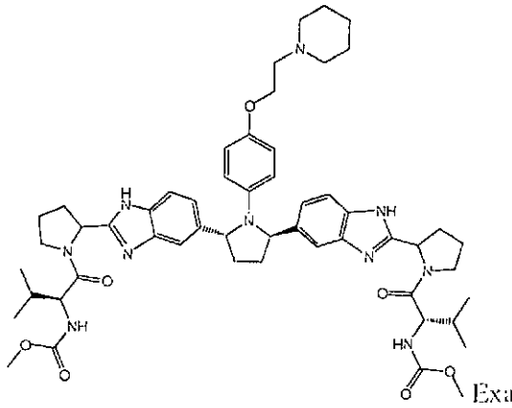
MS (ESI; M+H) m/z = 919.4



Example 254

methyl {(2S,3R)-1-[(2S)-2-{6-[(2S,5S)-1-(4-tert-butylphenyl)-5-(2-{(2S)-1-[N-(methoxycarbonyl)-O-methyl-L-threonyl]pyrrolidin-2-yl}-1H-benzimidazol-6-yl)pyrrolidin-2-yl]-1H-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methoxy-1-oxobutan-2-yl}carbamate

MS (ESI; M+H) m/z = 920.5

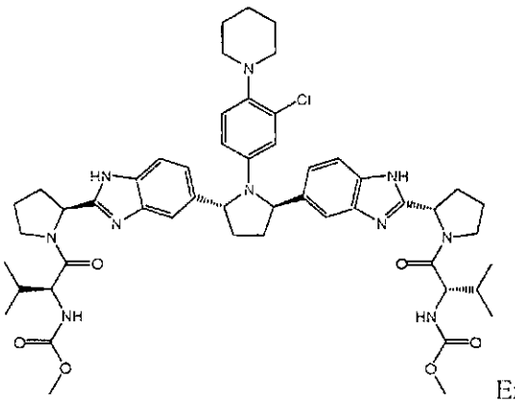


Example 255

methyl [(2*S*)-1-(2-{5-[(2*R*,5*R*)-5-[2-(1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl)-1*H*-benzimidazol-5-yl]-1-{4-[2-(piperidin-1-

yl)ethoxy]phenyl}pyrrolidin-2-yl]-1*H*-benzimidazol-2-yl}pyrrolidin-1-yl)-3-methyl-1-oxobutan-2-yl]carbamate

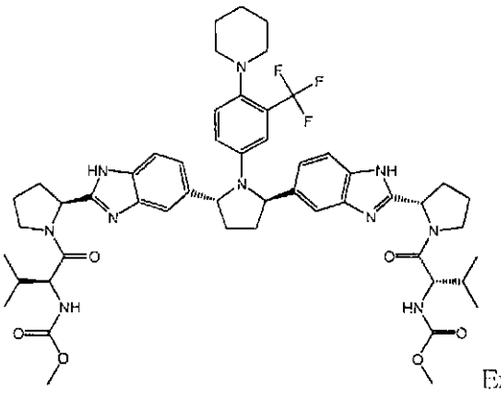
MS (ESI; M+H) m/z = 959.6



Example 256

methyl {(2S)-1-[(2S)-2-{5-[(2R,5R)-1-[3-chloro-4-(piperidin-1-yl)phenyl]-5-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-benzimidazol-5-yl}pyrrolidin-2-yl]-1H-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

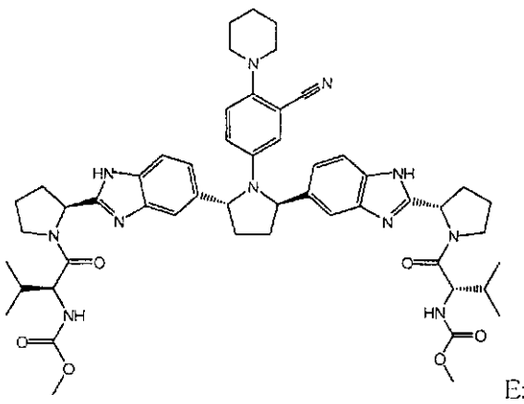
(ESI+) m/z 949.5 (M+H)+



Example 257

methyl {(2S)-1-[(2S)-2-(5-{(2R,5R)-5-[2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-benzimidazol-5-yl}-1-[4-(piperidin-1-yl)-3-(trifluoromethyl)phenyl]pyrrolidin-2-yl}-1H-benzimidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

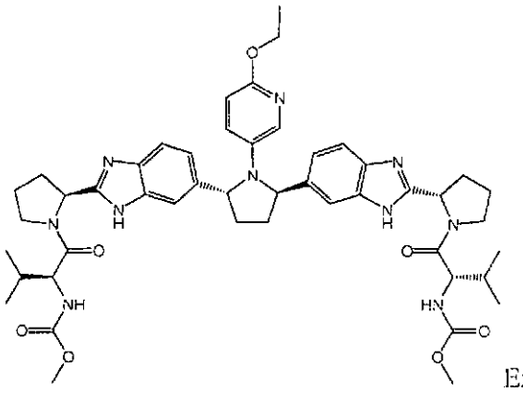
(ESI+) m/z 983.5 (M+H)+



Example 258

methyl {(2S)-1-[(2S)-2-{5-[(2R,5R)-1-{3-cyano-4-(piperidin-1-yl)phenyl}-5-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-benzimidazol-5-yl}pyrrolidin-2-yl]-1H-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

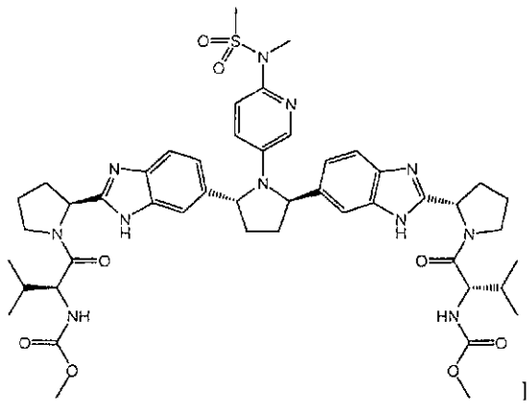
ESI+) m/z 940.4 (M+H)+



Example 259

methyl {(2S)-1-[(2S)-2-{6-[(2R,5R)-1-(6-ethoxypyridin-3-yl)-5-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-benzimidazol-6-yl}pyrrolidin-2-yl]-1H-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

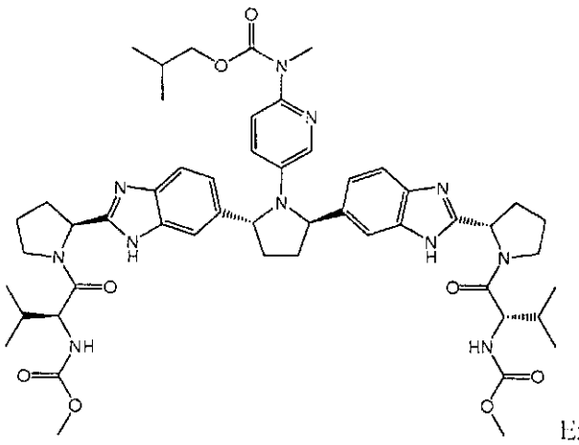
ESI+m/z 878 (M+H)+



Example 260

methyl {(2S)-1-[(2S)-2-{6-[(2R,5R)-5-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-benzimidazol-6-yl}-1-{6-[methyl(methylsulfonyl)amino]pyridin-3-yl}pyrrolidin-2-yl]-1H-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

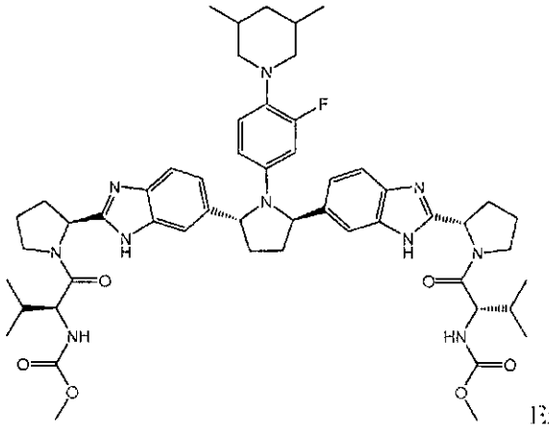
ESI+m/z 940 (M+H)+



Example 261

2-methylpropyl {5-[(2R,5R)-2,5-bis(2-{(2S)-1-[N-(methoxycarbonyl)-L-valyl]pyrrolidin-2-yl}-1H-benzimidazol-6-yl)pyrrolidin-1-yl]pyridin-2-yl}methylcarbamate

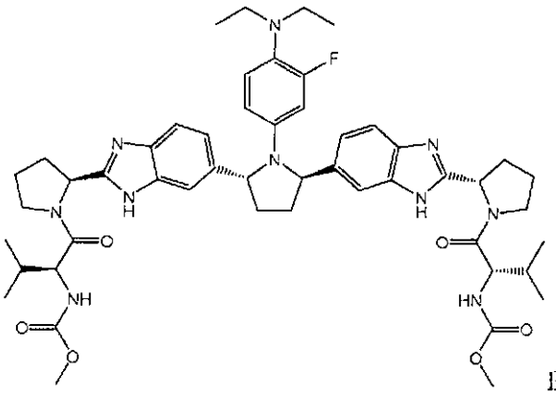
ESI+m/z 963 (M+H)+



Example 262

methyl {(2S)-1-{(2S)-2-{6-[(2R,5R)-1-[4-(3,5-dimethylpiperidin-1-yl)-3-fluorophenyl]-5-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-benzimidazol-6-yl}pyrrolidin-2-yl]-1H-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

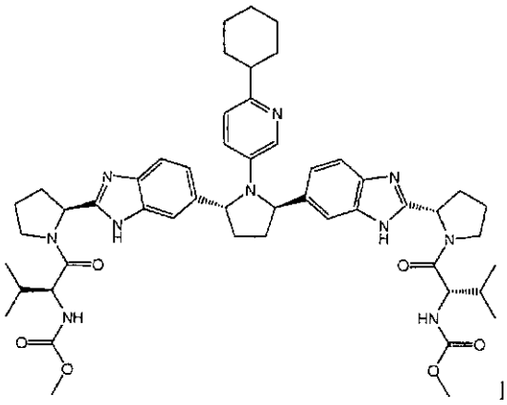
ESI+m/z 962 (M+H)+



Example 263

methyl {(2S)-1-[(2S)-2-{6-[(2R,5R)-1-[4-(diethylamino)-3-fluorophenyl]-5-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-benzimidazol-6-yl}pyrrolidin-2-yl]-1H-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

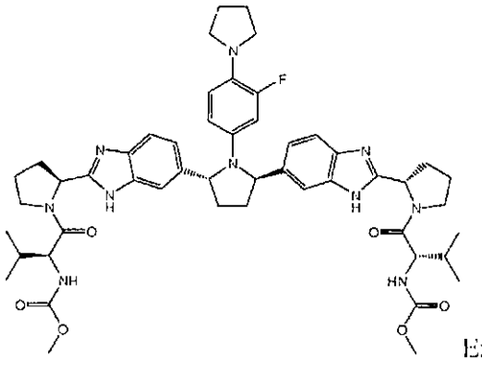
ESI+m/z 922 (M+H)+



Example 264

methyl {(2S)-1-[(2S)-2-{6-[(2R,5R)-1-(6-cyclohexylpyridin-3-yl)-5-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-benzimidazol-6-yl}pyrrolidin-2-yl]-1H-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

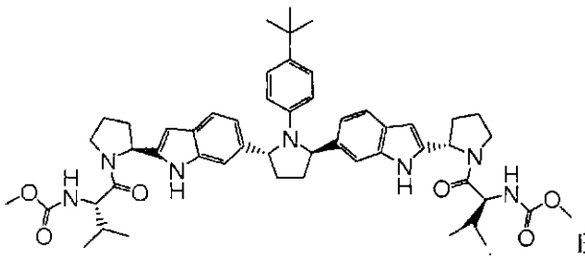
LC/MS : m/z 916.4 TFA method



Example 265

methyl {(2S)-1-[(2S)-2-{6-[(2R,5R)-1-[3-fluoro-4-(pyrrolidin-1-yl)phenyl]-5-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-benzimidazol-6-yl}pyrrolidin-2-yl]-1H-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

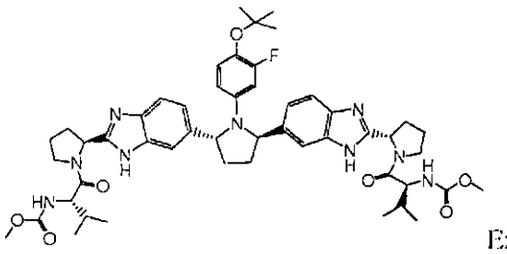
ESI+ (m/z): 919.4 (m+H)



Example 266

methyl {(2*S*)-1-[(2*S*)-2-{6-[(2*R*,5*R*)-1-(4-*tert*-butylphenyl)-5-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1*H*-indol-6-yl}pyrrolidin-2-yl]-1*H*-indol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

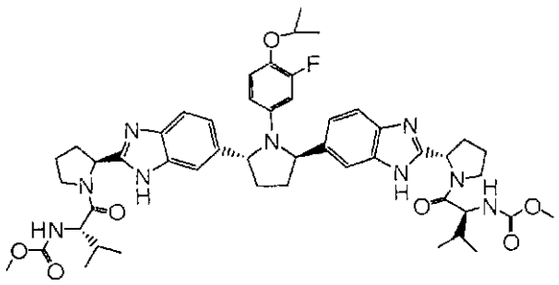
m/z= 886.5 (LC/MS)



Example 267

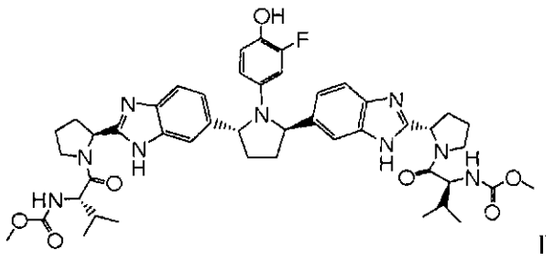
methyl {(2S)-1-[(2S)-2-{6-[(2R,5R)-1-(4-tert-butoxy-3-fluorophenyl)-5-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-benzimidazol-6-yl}pyrrolidin-2-yl]-1H-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

(ESI; M+H) m/z = 922.4



Example 268 methyl {(2S)-1-[(2S)-2-{6-[(2R,5R)-1-[3-fluoro-4-(propan-2-yloxy)phenyl]-5-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-benzimidazol-6-yl}pyrrolidin-2-yl]-1H-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

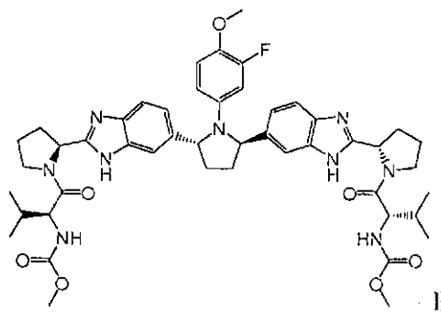
(ESI; M+H) m/z = 908.5



Example 269

methyl {(2S)-1-[(2S)-2-{6-[(2R,5R)-1-(3-fluoro-4-hydroxyphenyl)-5-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-benzimidazol-6-yl}pyrrolidin-2-yl]-1H-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

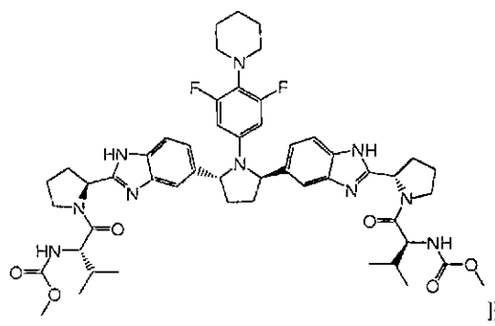
(ESI; M+H) m/z = 866.3



Example 270

methyl {(2S)-1-[(2S)-2-{6-[(2R,5R)-1-(3-fluoro-4-methoxyphenyl)-5-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-benzimidazol-6-yl}pyrrolidin-2-yl]-1H-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

(ESI; M+H) m/z = 880

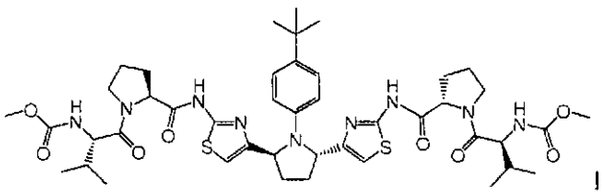


Example 271

methyl {(2S)-1-[(2S)-2-{5-[(2R,5R)-1-[3,5-difluoro-4-(piperidin-1-yl)phenyl]-5-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-benzimidazol-5-yl}pyrrolidin-2-yl]-1H-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

1H NMR (400 MHz, DMSO-D6) δ ppm 0.73 - 0.90 (m, 12 H) 1.32 - 2.28 (m, 20 H) 2.76 (s, 4 H) 3.54 (s, 6 H) 3.82 (s, 4 H) 3.99 - 4.12 (m, 2 H) 5.10 - 5.20 (m, 2 H) 5.36 (d, J=7.59 Hz, 2 H) 5.83 - 5.95 (m,

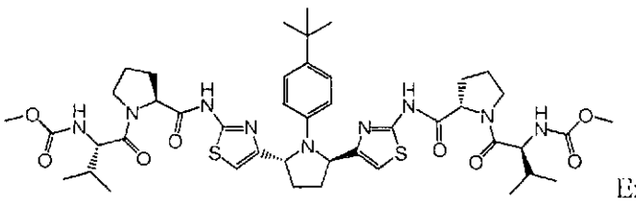
2 H) 7.01 - 7.14 (m, 2 H) 7.20 (s, 1 H) 7.26 - 7.33 (m, 3 H) 7.41 (d, J=8.24 Hz, 1 H) 7.49 (d, J=8.24 Hz, 1 H) 12.01 - 12.31 (m, 2 H); MS (ESI; M+H) m/z = 951.5.



Example 272

dimethyl ([(2S,5S)-1-(4-tert-butylphenyl)pyrrolidine-2,5-diyl]bis{1,3-thiazole-4,2-diylcarbamoyl(2S)pyrrolidine-2,1-diyl[(2S)-3-methyl-1-oxobutane-1,2-diyl]})biscarbamate

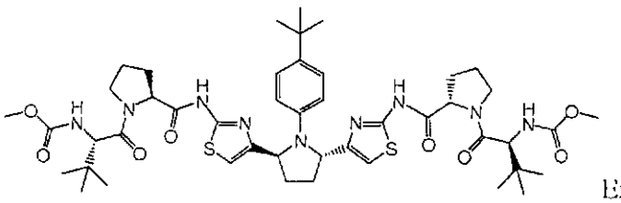
ESI m/z 908.4 (M+H)



Example 273

dimethyl ([(2R,5R)-1-(4-tert-butylphenyl)pyrrolidine-2,5-diyl]bis{1,3-thiazole-4,2-diylcarbamoyl(2S)pyrrolidine-2,1-diyl[(2S)-3-methyl-1-oxobutane-1,2-diyl]})biscarbamate

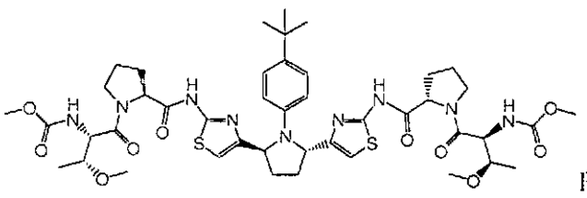
ESI m/z 908.4 (M+H)



Example 274

dimethyl ([(2S,5S)-1-(4-tert-butylphenyl)pyrrolidine-2,5-diyl]bis{1,3-thiazole-4,2-diylcarbamoyl(2S)pyrrolidine-2,1-diyl[(2S)-3,3-dimethyl-1-oxobutane-1,2-diyl]})biscarbamate

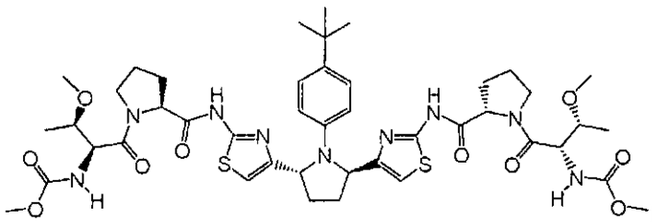
ESI m/z 936.5 (M+H)



Example 275

dimethyl ([(2S,5S)-1-(4-tert-butylphenyl)pyrrolidine-2,5-diyl]bis{1,3-thiazole-4,2-diylcarbamoyl(2S)pyrrolidine-2,1-diyl[(2S,3R)-3-methoxy-1-oxobutane-1,2-diyl]})biscarbamate

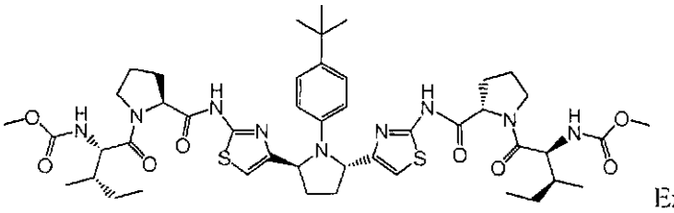
ESI m/z 940.5 (M+H)



Example 276

dimethyl ([(2R,5R)-1-(4-tert-butylphenyl)pyrrolidine-2,5-diyl]bis{1,3-thiazole-4,2-diylcarbamoyl(2S)pyrrolidine-2,1-diyl[(2S,3R)-3-methoxy-1-oxobutane-1,2-diyl]})biscarbamate

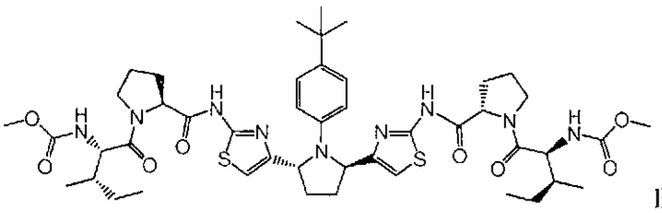
ESI m/z 940.5 (M+H)



Example 277

dimethyl ([(2S,5S)-1-(4-tert-butylphenyl)pyrrolidine-2,5-diyl]bis{1,3-thiazole-4,2-diylcarbamoyl(2S)pyrrolidine-2,1-diyl[(2S,3S)-3-methyl-1-oxopentane-1,2-diyl]})biscarbamate

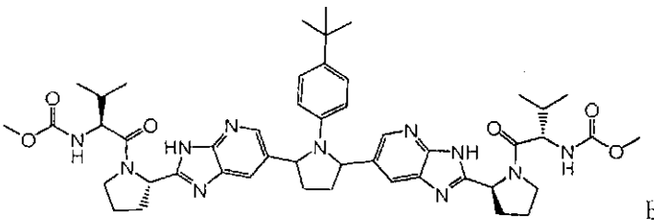
ESI m/z 936.5 (M+H)



Example 278

dimethyl ([(2R,5R)-1-(4-tert-butylphenyl)pyrrolidine-2,5-diyl]bis{1,3-thiazole-4,2-diylcarbamoyl(2S)pyrrolidine-2,1-diyl[(2S,3S)-3-methyl-1-oxopentane-1,2-diyl]})biscarbamate

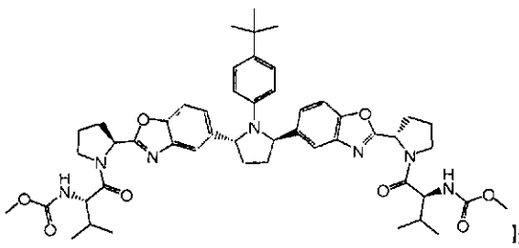
ESI m/z 936.5 (M+H)



Example 279

methyl {(2S)-1-[(2S)-2-{6-[1-(4-tert-butylphenyl)-5-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-3H-imidazo[4,5-b]pyridin-6-yl}pyrrolidin-2-yl]-3H-imidazo[4,5-b]pyridin-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

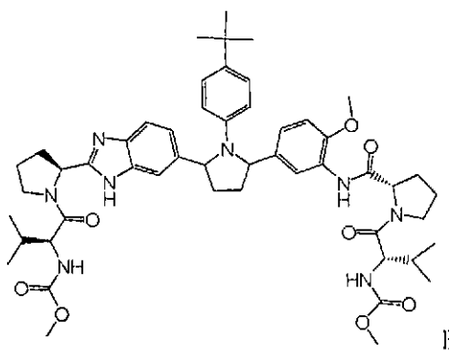
LCMS m/z 890 (M+H)



Example 280

methyl {(2S)-1-[(2S)-2-{6-[(2R,5R)-1-(4-tert-butylphenyl)-5-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1,3-benzoxazol-6-yl}pyrrolidin-2-yl]-1,3-benzoxazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

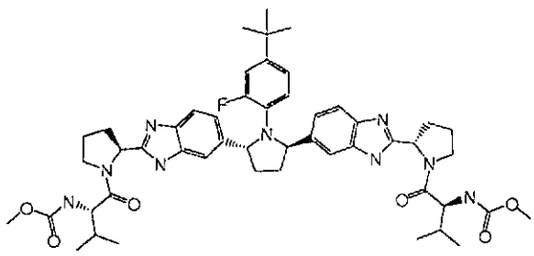
ESI+:(M+H): 890.5



Example 281

N-(methoxycarbonyl)-L-valyl-N-{5-[1-(4-tert-butylphenyl)-5-(2-{(2S)-1-[N-(methoxycarbonyl)-L-valyl]pyrrolidin-2-yl}-1H-benzimidazol-6-yl)pyrrolidin-2-yl]-2-methoxyphenyl}-L-prolinamide

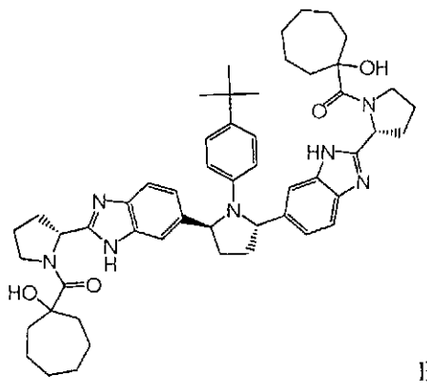
ESI+:(M+H): 921.5



Example 282

methyl {(2S)-1-[(2S)-2-{6-[(2R,5R)-1-(4-tert-butyl-2-fluorophenyl)-5-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-benzimidazol-6-yl}pyrrolidin-2-yl]-1H-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

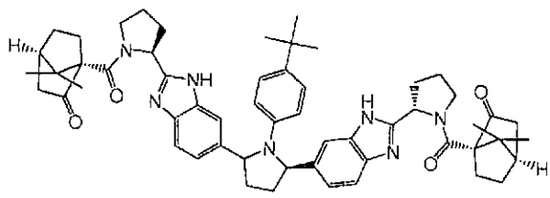
ESI+:(M+H): 906.4



Example 283

{[(2R,5R)-1-(4-tert-butylphenyl)pyrrolidine-2,5-diyl]bis[1H-benzimidazole-6,2-diyl(2S)pyrrolidine-2,1-diyl]}bis[(1-hydroxycycloheptyl)methanone]

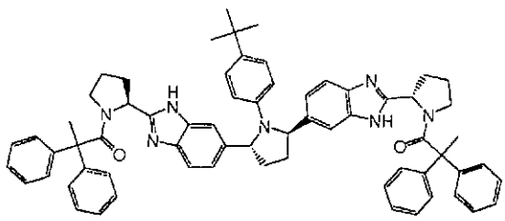
MS (ESI) positive ion 854 $(M+H)^+$.



Example 284

(1S,4R,1'S,4'R)-1,1'-{[(2R)-1-(4-tert-butylphenyl)pyrrolidine-2,5-diyl]bis[1H-benzimidazole-6,2-diyl(2S)pyrrolidine-2,1-diylcarbonyl]}bis(7,7-dimethylbicyclo[2.2.1]heptan-2-one)

MS (ESI) positive ion 902 $(M+H)^+$.

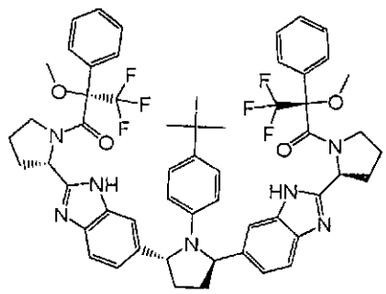


Example 285

1,1'-{[(2R,5R)-1-(4-tert-butylphenyl)pyrrolidine-2,5-diyl]bis[1H-benzimidazole-6,2-diyl(2S)pyrrolidine-2,1-diyl]}bis(2,2-diphenylpropan-1-one)

MS (ESI) positive ion $(M+H)^+$. Is not observed but

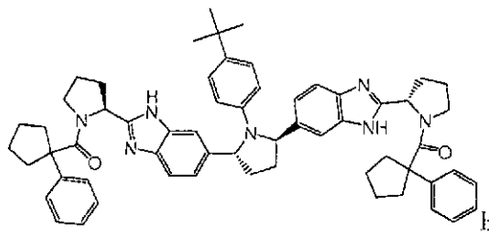
MS (APCI) positive ion 990 $(M+H)^+$ observed



Example 286

(2S,2'S)-1,1'-{[(2R,5R)-1-(4-tert-butylphenyl)pyrrolidine-2,5-diyl]bis[1H-benzimidazole-6,2-diyl(2S)pyrrolidine-2,1-diyl]}bis(3,3,3-trifluoro-2-methoxy-2-phenylpropan-1-one)

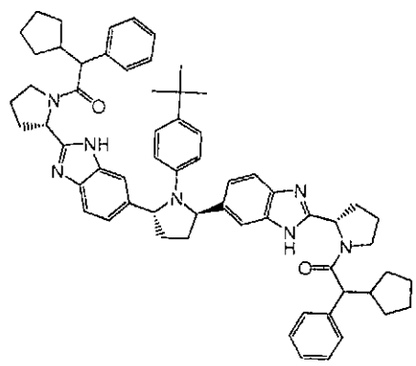
MS (ESI) positive ion 1006 $(M+H)^+$.



Example 287

{[(2R,5R)-1-(4-tert-butylphenyl)pyrrolidine-2,5-diyl]bis[1H-benzimidazole-6,2-diyl(2S)pyrrolidine-2,1-diyl]}bis[(1-phenylcyclopentyl)methanone]

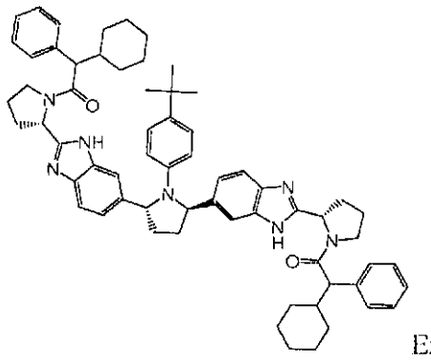
MS (ESI) positive ion 918.6 $(M+H)^+$.



Example 288

1,1'-{[(2R,5R)-1-(4-tert-butylphenyl)pyrrolidine-2,5-diyl]bis[1H-benzimidazole-6,2-diyl(2S)pyrrolidine-2,1-diyl]}bis(2-cyclopentyl-2-phenylethanone)

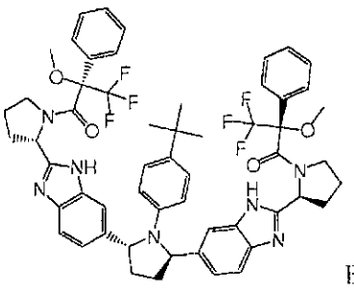
MS (ESI) positive ion 946 $(M+H)^+$.



Example 289

1,1'-{[(2R,5R)-1-(4-tert-butylphenyl)pyrrolidine-2,5-diyl]bis[1H-benzimidazole-6,2-diyl(2S)pyrrolidine-2,1-diyl]}bis(2-cyclohexyl-2-phenylethanone)

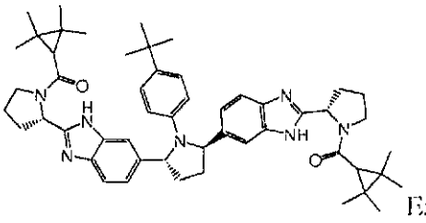
MS (ESI) positive ion 974 $(M+H)^+$.



Example 290

(2R,2'R)-1,1'-{[(2R,5R)-1-(4-tert-butylphenyl)pyrrolidine-2,5-diyl]bis[1H-benzimidazole-6,2-diyl(2S)pyrrolidine-2,1-diyl]}bis(3,3,3-trifluoro-2-methoxy-2-phenylpropan-1-one)

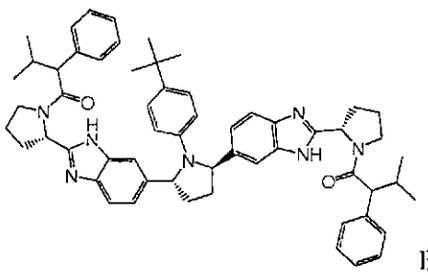
MS (ESI) positive ion 1006 $(M+H)^+$.



Example 291

{[(2R,5R)-1-(4-tert-butylphenyl)pyrrolidine-2,5-diyl]bis[1H-benzimidazole-6,2-diyl(2S)pyrrolidine-2,1-diyl]}bis[(2,2,3,3-tetramethylcyclopropyl)methanone]

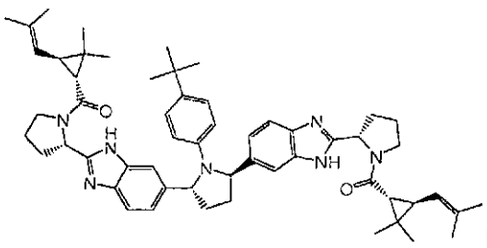
MS (ESI) positive ion 822 $(M+H)^+$.



Example 292

1,1'-{[(2R,5R)-1-(4-tert-butylphenyl)pyrrolidine-2,5-diyl]bis[1H-benzimidazole-6,2-diyl(2S)pyrrolidine-2,1-diyl]}bis(3-methyl-2-phenylbutan-1-one)

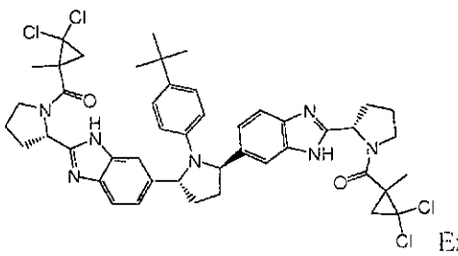
MS (ESI) positive ion 893 $(M+NH_4-H_2O)^+$.



Example 293

{[(2R,5R)-1-(4-tert-butylphenyl)pyrrolidine-2,5-diyl]bis[1H-benzimidazole-6,2-diyl(2S)pyrrolidine-2,1-diyl]}bis{[(1R,3R)-2,2-dimethyl-3-(2-methylprop-1-en-1-yl)cyclopropyl]methanone}

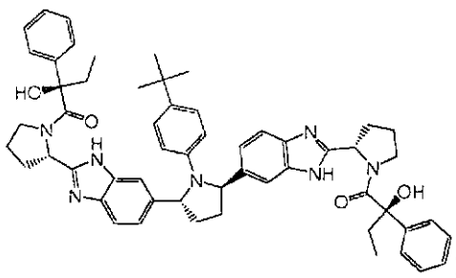
MS (ESI) positive ion 874 $(M+H)^+$.



Example 294

{[(2R,5R)-1-(4-tert-butylphenyl)pyrrolidine-2,5-diyl]bis[1H-benzimidazole-6,2-diyl(2S)pyrrolidine-2,1-diyl]}bis[(2,2-dichloro-1-methylcyclopropyl)methanone]

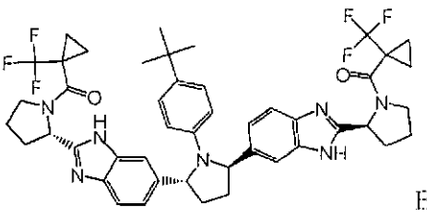
MS (ESI) positive ion 874 $(M+H)^+$.



Example 295

(2R,2'R)-1,1'-{[(2R,5R)-1-(4-tert-butylphenyl)pyrrolidine-2,5-diyl]bis[1H-benzimidazole-6,2-diyl(2S)pyrrolidine-2,1-diyl]}bis(2-hydroxy-2-phenylbutan-1-one)

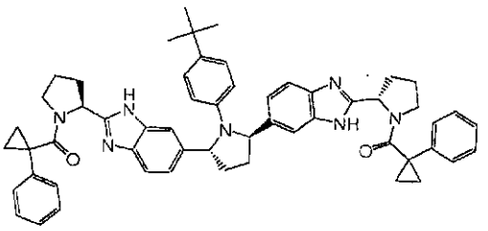
MS (ESI) positive ion $(M+H)^+$.



Example 296

{[(2R,5R)-1-(4-tert-butylphenyl)pyrrolidine-2,5-diyl]bis[1H-benzimidazole-6,2-diyl(2S)pyrrolidine-2,1-diyl]}bis{[1-(trifluoromethyl)cyclopropyl]methanone}

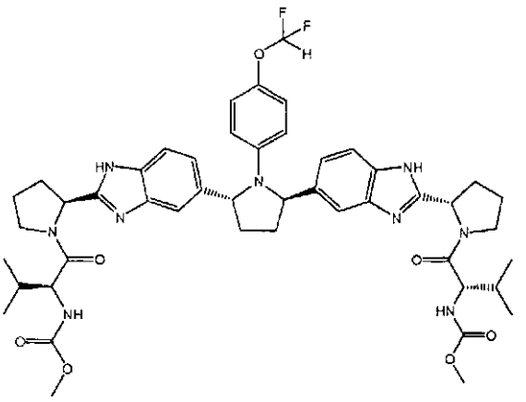
MS (ESI) positive ion 846 $(M+H)^+$.



Example 297

{[(2R,5R)-1-(4-tert-butylphenyl)pyrrolidine-2,5-diyl]bis[1H-benzimidazole-6,2-diyl(2S)pyrrolidine-2,1-diyl]}bis[(1-phenylcyclopropyl)methanone]

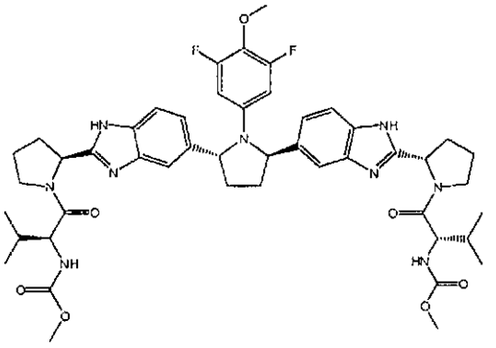
MS (ESI) positive ion 862.5 $(M+H)^+$.



Example 298

methyl {(2S)-1-[(2S)-2-{5-[(2R,5R)-1-{4-(difluoromethoxy)phenyl]-5-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-benzimidazol-5-yl}pyrrolidin-2-yl]-1H-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

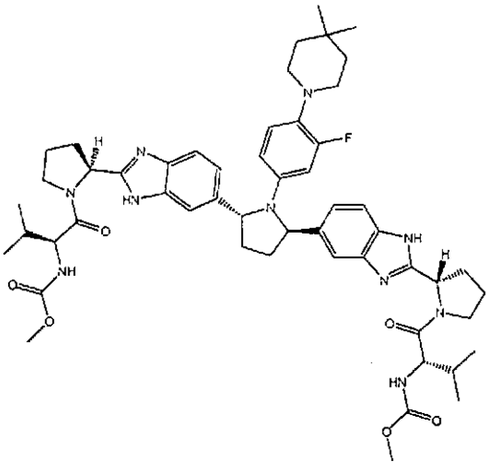
(ESI+) m/z 898.4 (M+H)+



Example 299

methyl {(2S)-1-[(2S)-2-{5-[(2R,5R)-1-(3,5-difluoro-4-methoxyphenyl)-5-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-benzimidazol-5-yl}pyrrolidin-2-yl]-1H-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

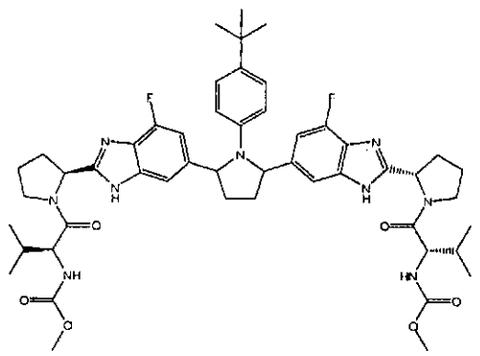
(ESI+) m/z 898.4 (M+H)+



Example 300

methyl {(2S)-1-[(2S)-2-{5-[(2R,5R)-1-[4-(4,4-dimethylpiperidin-1-yl)-3-fluorophenyl]-5-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-benzimidazol-6-yl}pyrrolidin-2-yl]-1H-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

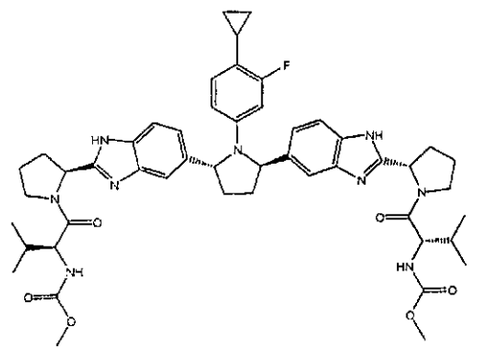
MS +ESI m/z (rel abundance) 962 (100, M+H); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.52 (d, J = 8.2, 1 H), 7.44 (d, J = 8.1, 1 H), 7.35 (d, J = 8.1, 3 H), 7.26 (s, 1 H), 7.14 (m, 2 H), 6.75 (s, 1 H), 6.12 (m, 2 H), 5.40 (s, 2 H), 5.19 (s, 2 H), 4.12 (t, J = 8.4, 2 H), 3.88 (s, 4 H), 3.60 (s, 6 H), 2.70 (m, 5 H), 2.24 (s, 4 H), 1.99 (m, 7 H), 1.75 (s, 2 H), 1.46 (s, 3 H), 1.39 (s, 8 H), 0.89 (m, 20 H).



Example 301

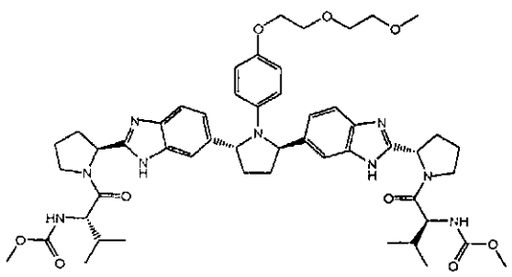
methyl {(2S)-1-[(2S)-2-{6-[1-(4-tert-butylphenyl)-5-{4-fluoro-2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-benzimidazol-6-yl}pyrrolidin-2-yl]-4-fluoro-1H-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

MS (ESI) *m/z* 924 $(M+H)^+$



Example 302 methyl {(2S)-1-[(2S)-2-{5-[(2R,5R)-1-(4-cyclopropyl-3-fluorophenyl)-5-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-benzimidazol-5-yl}pyrrolidin-2-yl]-1H-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

MS (ESI) *m/z* 891 $(M+H)^+$

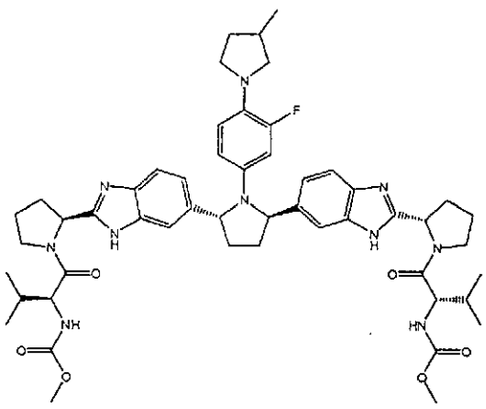


Example 303

methyl {(2S)-1-[(2S)-2-{6-[(2R,5R)-5-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-benzimidazol-6-yl}-1-{4-[2-(2-

methoxyethoxy)ethoxy]phenyl}pyrrolidin-2-yl]-1H-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

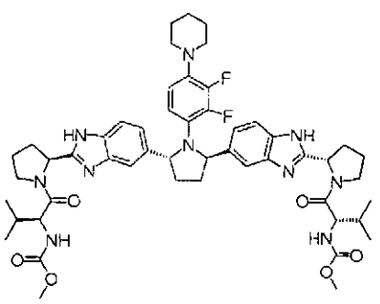
MS (ESI) *m/z* 950 $(M+H)^+$, 948 $(M-H)^+$.



Example 304

methyl {(2S)-1-[(2S)-2-{6-[(2R,5R)-1-[3-fluoro-4-(3-methylpyrrolidin-1-yl)phenyl]-5-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-benzimidazol-6-yl}pyrrolidin-2-yl]-1H-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

1H NMR (400 MHz, DMSO-D6) δ ppm 0.76 - 0.89 (m, 12 H) 0.95 (d, J=6.72 Hz, 3 H) 1.62 - 1.72 (m, 2 H) 1.83 - 2.06 (m, 9 H) 2.09 - 2.24 (m, 6 H) 2.52 - 2.61 (m, 2 H) 2.91 - 3.15 (m, 4 H) 3.52 (s, 6 H) 3.74 - 3.86 (m, 4 H) 4.05 (t, J=8.35 Hz, 2 H) 5.08 - 5.17 (m, 2 H) 5.26 - 5.38 (m, 2 H) 5.97 - 6.10 (m, 2 H) 6.35 - 6.45 (m, 1 H) 7.01 - 7.08 (m, 2 H) 7.19 (s, 1 H) 7.25 - 7.32 (m, 3 H) 7.36 (d, J=8.24 Hz, 1 H) 7.44 (d, J=7.92 Hz, 1 H) 12.01 (s, 2 H).

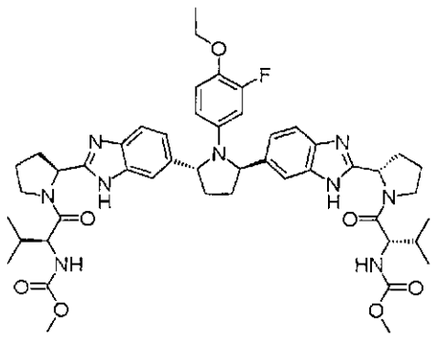


Example 305

methyl {(2*S*)-1-[(2*S*)-2-{5-[(2*R*,5*R*)-1-[2,3-difluoro-4-(piperidin-1-yl)phenyl]-5-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1*H*-benzimidazol-5-yl}pyrrolidin-2-yl]-1*H*-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

ESI+ (m/z): 951.5; 1H NMR (400 MHz, DMSO-D6) δ ppm 0.74 - 0.90 (m, 12 H) 1.35 - 1.41 (m, 2 H) 1.44 - 1.51 (m, 4 H) 1.73 - 1.83 (m, 2 H) 1.86 - 2.02 (m, 6 H) 2.14 - 2.23 (m, 4 H) 2.59 - 2.72 (m, 6 H)

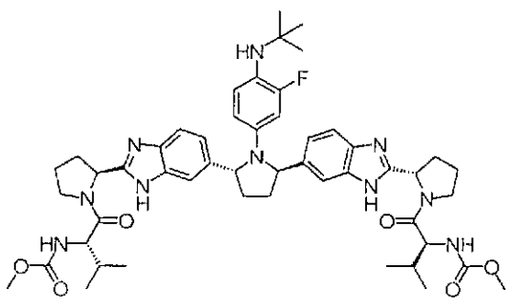
3.53 (s, 6 H) 3.77 - 3.84 (m, 4 H) 3.97 - 4.10 (m, 2 H) 5.06 - 5.18 (m, 2 H) 5.46 - 5.56 (m, 2 H) 6.36 - 6.47 (m, 2 H) 7.03 - 7.11 (m, 2 H) 7.23 - 7.45 (m, 6 H) 11.95 - 12.10 (m, 2 H)



Example 306

methyl {(2*S*)-1-[(2*S*)-2-{6-[(2*R*,5*R*)-1-(4-ethoxy-3-fluorophenyl)-5-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1*H*-benzimidazol-6-yl}pyrrolidin-2-yl]-1*H*-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

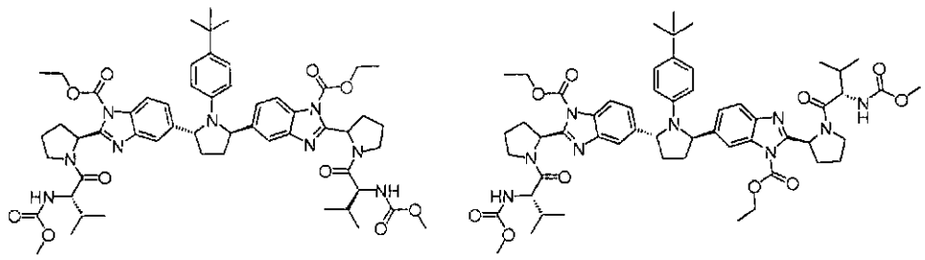
ESI+ (m/z): 894.4



Example 307

methyl {(2*S*)-1-[(2*S*)-2-{6-[(2*R*,5*R*)-1-[4-(*tert*-butylamino)-3-fluorophenyl]-5-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1*H*-benzimidazol-6-yl}pyrrolidin-2-yl]-1*H*-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

ESI+ (m/z): 922; 1H NMR (400 MHz, DMSO-D6) δ ppm 0.75 - 0.90 (m, 12 H) 0.97 (s, 9 H) 1.61 - 1.71 (m, 2 H) 1.83 - 2.04 (m, 6 H) 2.12 - 2.23 (m, 4 H) 3.52 (s, 6 H) 3.76 - 3.86 (m, 4 H) 4.01 - 4.08 (m, 2 H) 5.09 - 5.17 (m, 2 H) 5.27 - 5.37 (m, 2 H) 5.98 - 6.07 (m, 2 H) 6.56 - 6.66 (m, 1 H) 7.06 (t, J=7.92 Hz, 2 H) 7.19 (s, 1 H) 7.27 (d, J=9.00 Hz, 3 H) 7.38 (d, J=8.24 Hz, 1 H) 7.46 (d, J=8.13 Hz, 1 H) 12.00 (s, 1 H) 12.08 (s, 1 H)



Example 308

ethyl 5-{(2*R*,5*R*)-1-(4-*tert*-butylphenyl)-5-[1-(ethoxycarbonyl)-2-{(2*S*)-1-[*N*-(methoxycarbonyl)-L-valyl]pyrrolidin-2-yl}-1*H*-benzimidazol-5-yl]pyrrolidin-2-yl}-2-{1-[*N*-(methoxycarbonyl)-L-valyl]pyrrolidin-2-yl}-1*H*-benzimidazole-1-carboxylate

and

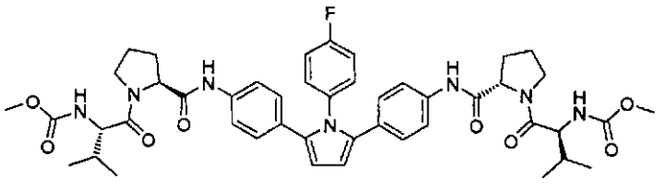
ethyl 5-{(2*R*,5*R*)-1-(4-*tert*-butylphenyl)-5-[1-(ethoxycarbonyl)-2-{(2*S*)-1-[*N*-(methoxycarbonyl)-L-valyl]pyrrolidin-2-yl}-1*H*-benzimidazol-6-yl]pyrrolidin-2-yl}-2-{(2*S*)-1-[*N*-(methoxycarbonyl)-L-valyl]pyrrolidin-2-yl}-1*H*-benzimidazole-1-carboxylate

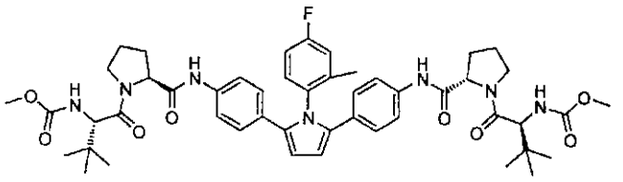
ESI+ (m/z): 1032.5; 1H NMR (400 MHz, DMSO-D6) δ ppm 0.70 - 1.04 (m, 12 H) 1.08 (s, 9 H) 1.33 - 1.46 (m, 6 H) 1.65 - 1.77 (m, 2 H) 1.81 - 2.13 (m, 8 H) 2.20 - 2.28 (m, 2 H) 2.55 - 2.62 (m, 2 H) 3.53 (d, J=4.23 Hz, 6 H) 3.80 - 3.92 (m, 4 H) 4.04 - 4.13 (m, 2 H) 4.41 - 4.59 (m, 4 H) 5.38 - 5.49 (m, 2 H) 5.66 - 5.76 (m, 2 H) 6.17 - 6.33 (m, 2 H) 6.82 - 7.00 (m, 3 H) 7.18 - 7.56 (m, 5 H) 7.75 - 7.91 (m, 2 H)

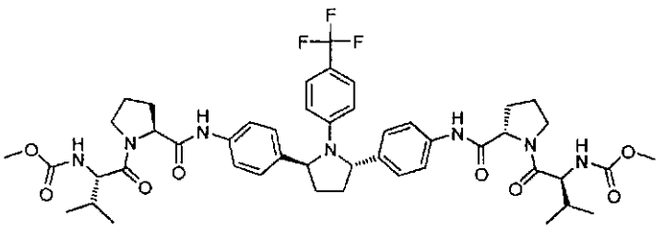
The title compounds of Examples 52, 53, 54, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 74, 75, 76, 77, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 93, 94, 95, 96, 97, 99, 101, 102, 103, 109, 110, 111, 112, 113, 117, 121, 122, 123, 125, 126, 127, 128, 129, 130, 131, 132, 135, 136, 137, 138, 139, 140, 141, 144, 145, 146, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 159, 160, 161, 162, 163, 166, 167, 168, 169, 170, 171, 173, 176, 178, 179, 180, 181, 183, 184, 185, 186, 188, 189, 191, 192, 194, 195, 197, 198, 199, 200, 201, 202, 203, 205, 207, 208, 209, 210, 211, 212, 214, 215, 216, 217, 218, 219, 220, 221, 224, 226, 227, 228, 229, 230, 231, 233, 234, 235, 236, 237, 238, 240, 241, 242, 245, 247, 248, 250, 251, 252, 254, 256, 257, 258, 262, 263, 264, 266, 267, 268, 270, 271, 272, 273, 274, 275, 276, 277, 278, 282, 294, 295, 296, 297, 298, 299, 300, 301, 302, 305, and 306 showed an EC_{50} value of less than about 0.1 nM in HCV 1b-Con1 replicon assays in the presence of 5% FBS. The title compounds of Examples 51, 55, 56, 57, 70, 71, 72, 73, 78, 98, 100, 108, 114, 115, 116, 119, 120, 133, 134, 142, 143, 147, 164, 172, 174, 182, 196, 204, 206, 222, 223, 225, 239, 244, 249, 253, 259, 261, 265, 281, 287, 288, 292, 303, 304, 307, and 308 showed an EC_{50} value of from about 0.1 to about 1 nM in HCV 1b-Con1 replicon assays in the presence of 5% FBS. The title compounds of Examples 92, 105, 106, 107, 118, 124, 158, 165, 175, 177, 187, 190, 193, 213, 232, 243, 246, 255, 260, 269, 279, 280, 283, 284, 285, 286, 289, 290, 291, and 293 showed an EC_{50} value of from about 1 to about 100 nM in HCV 1b-Con1 replicon assays in the presence of 5% FBS.

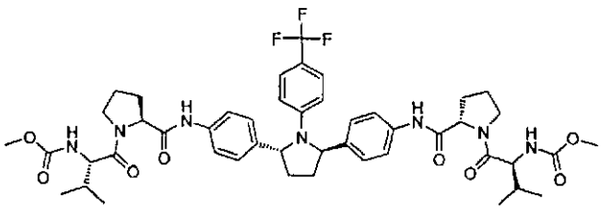
The present invention also contemplates pharmaceutically acceptable salts of each compound in Examples 1-308, as well as pharmaceutically acceptable salts of each compound described hereinbelow.

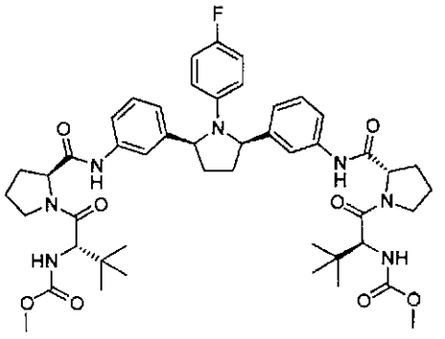
The following compounds were similarly prepared according to the procedures described above:

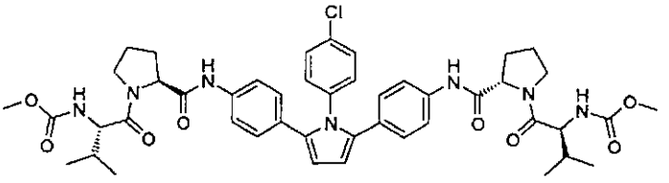


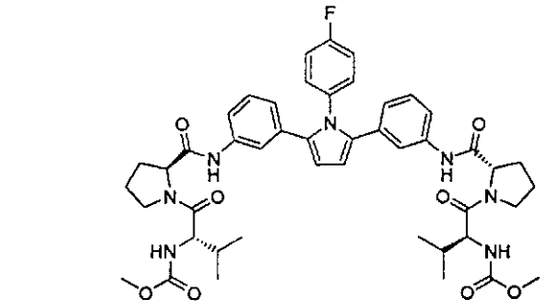


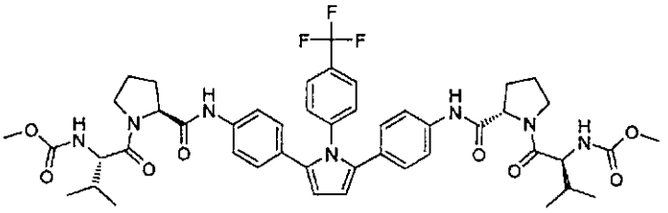


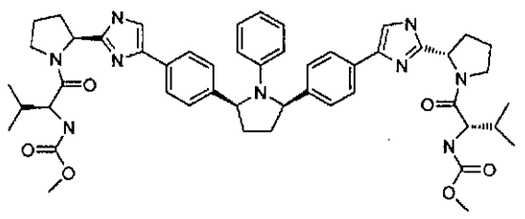


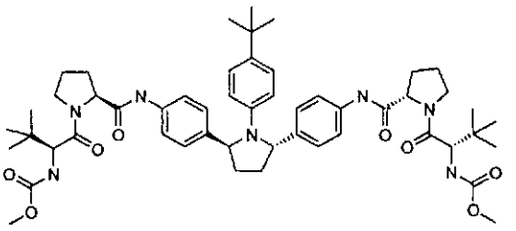


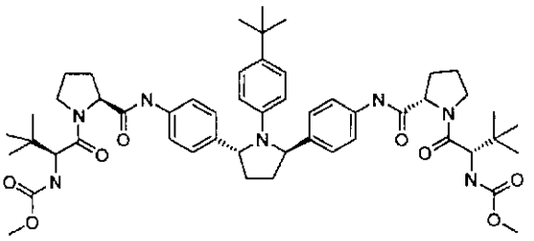


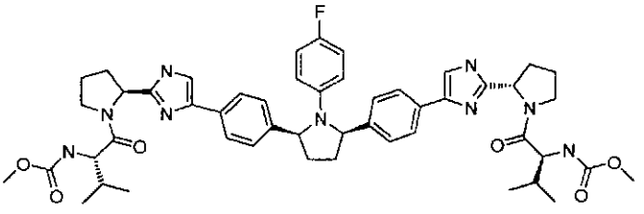


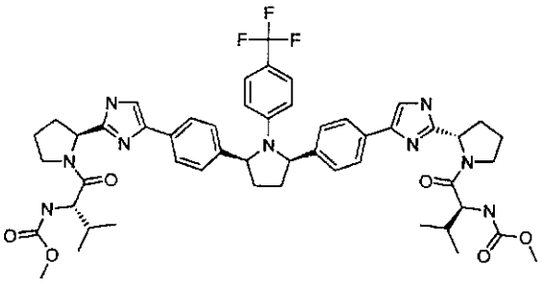


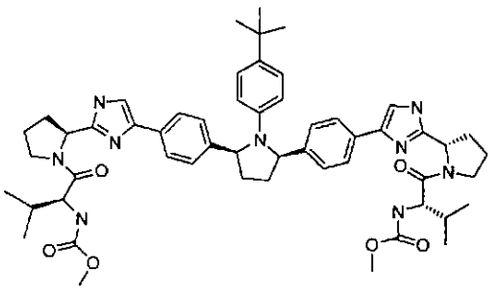


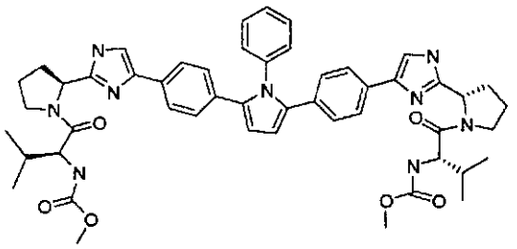


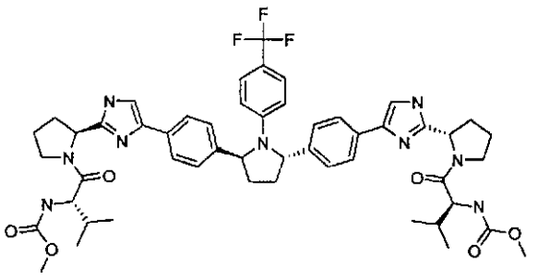


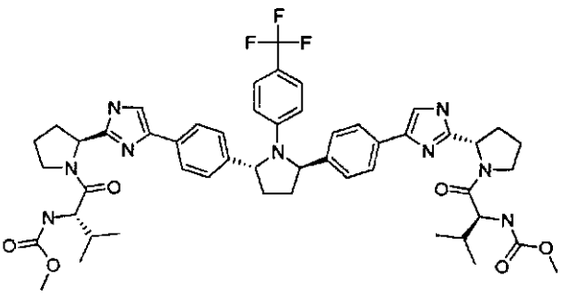


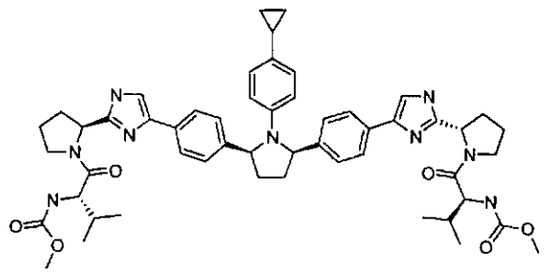


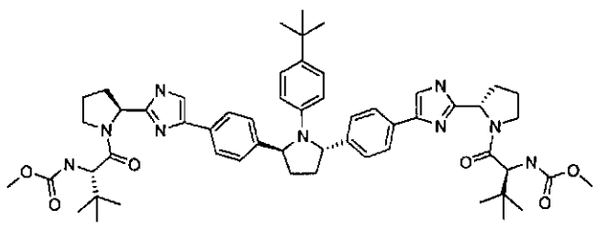


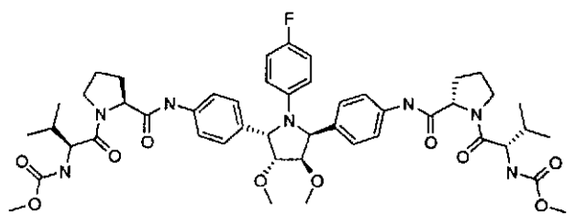


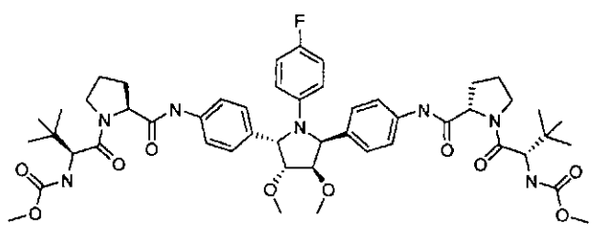


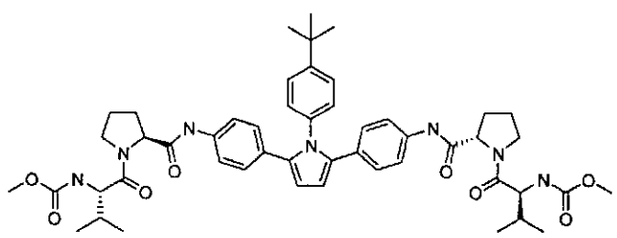


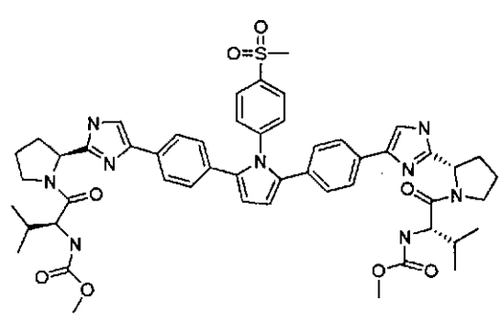


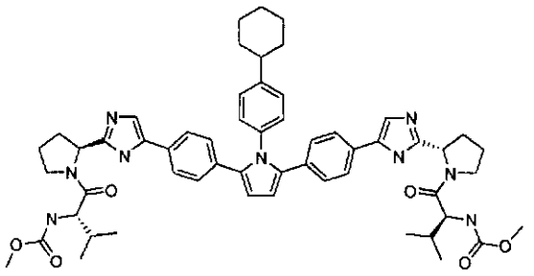


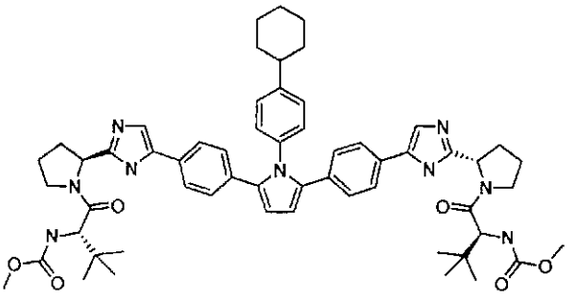


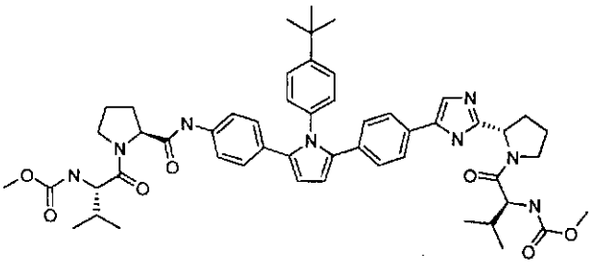


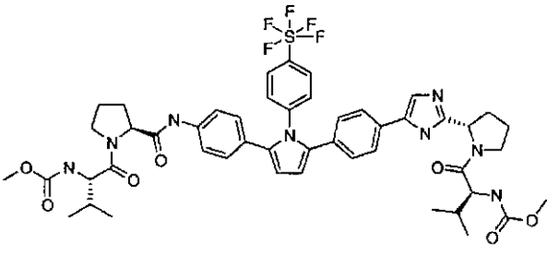


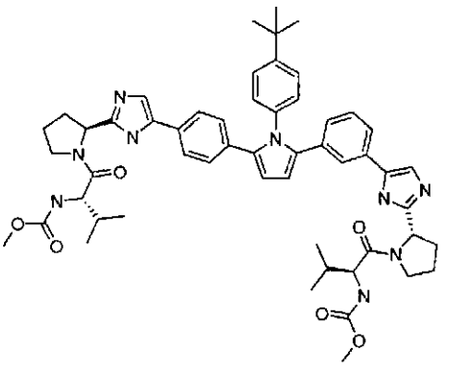


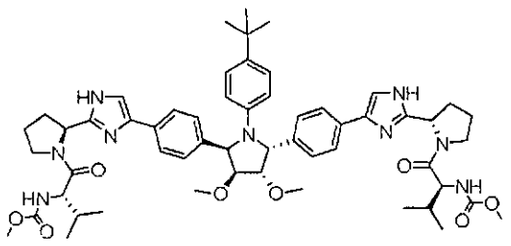


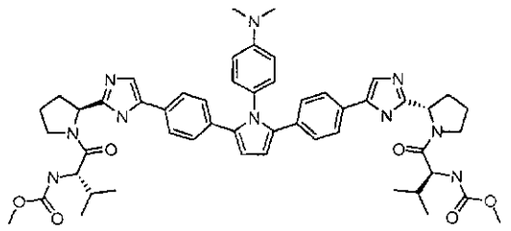






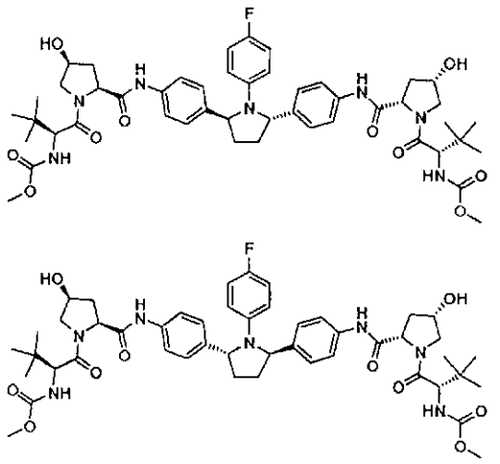




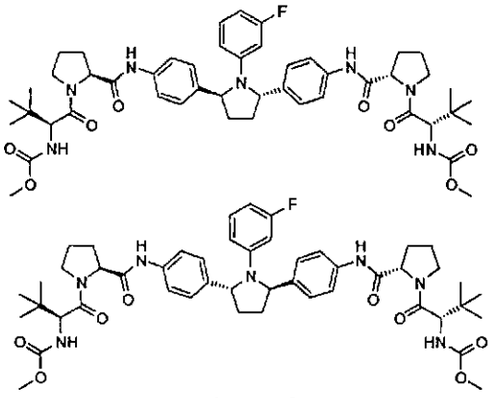


When tested using HCV 1b-Con1 replicon assays in the presence of 5% FBS, each of the above compounds showed an EC_{50} value of less than 1 nM.

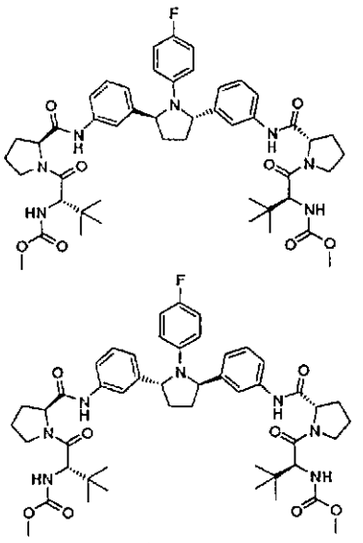
In addition, the following mixtures of stereoisomers were prepared according to procedures similar to those described above, where each compound in each stereoisomer mixture can be readily isolated using chiral chromatography or other suitable methods as appreciated by those skilled in the art and, therefore, the present invention also features each compound in these stereoisomer mixtures:



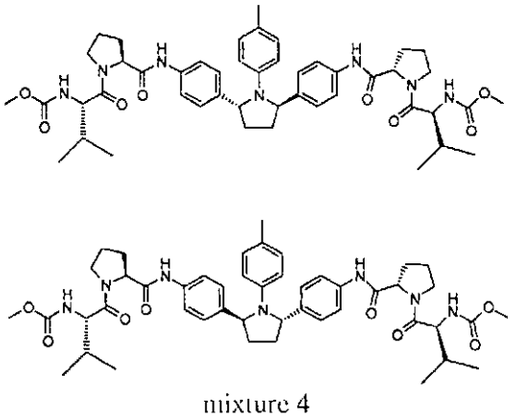
mixture 1



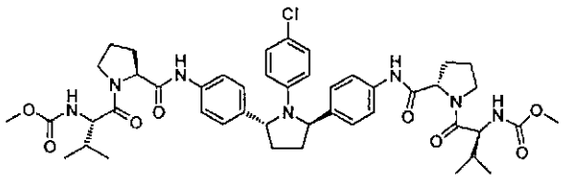
mixture 2

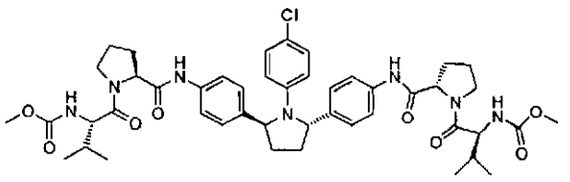


mixture 3

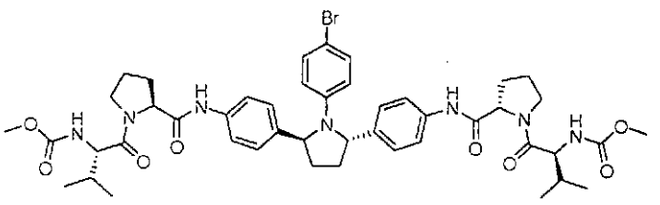


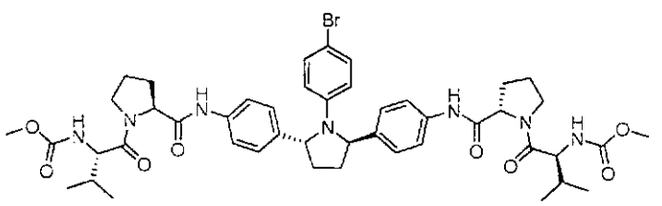
mixture 4



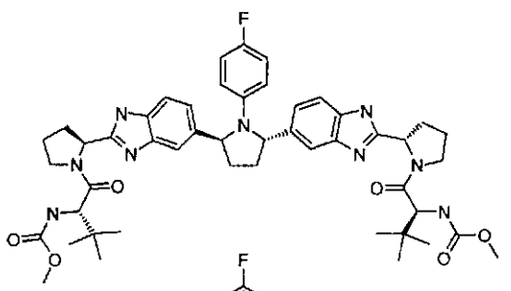


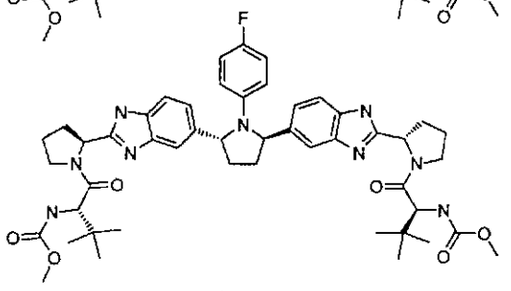
mixture 5



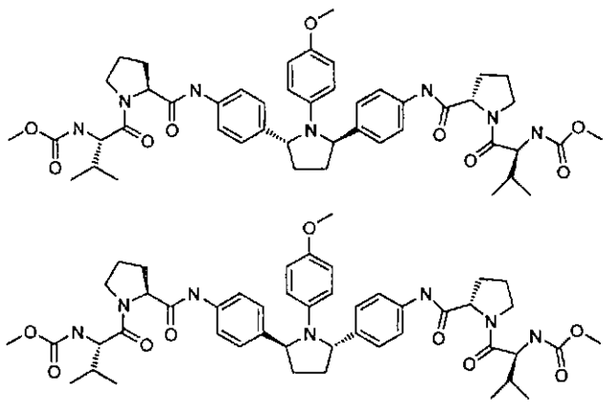


mixture 6

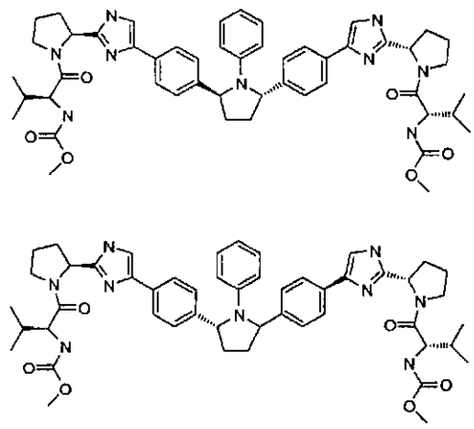




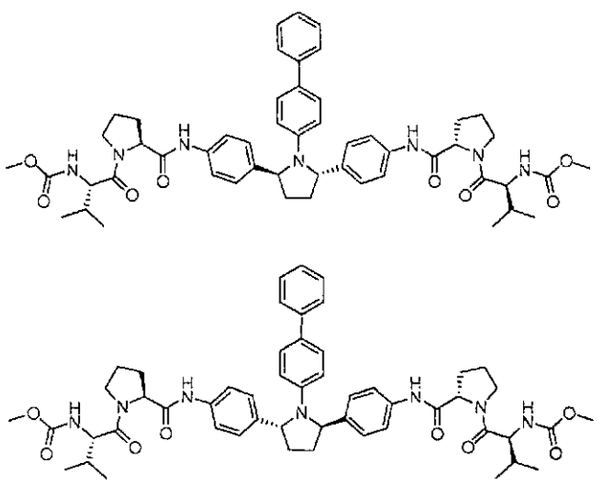
mixture 7



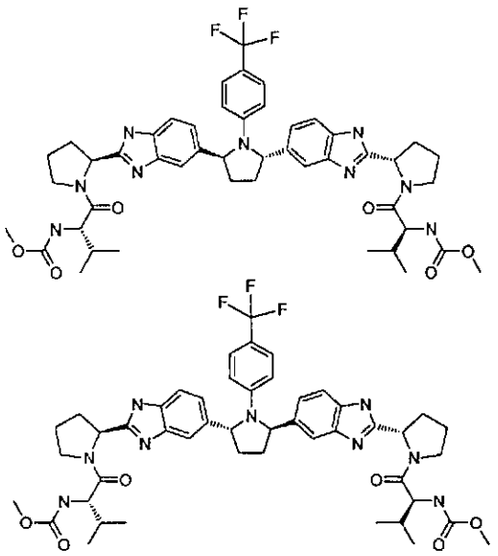
mixture 8



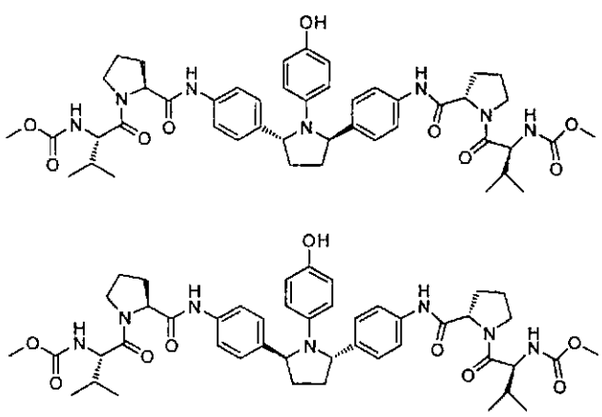
mixture 9



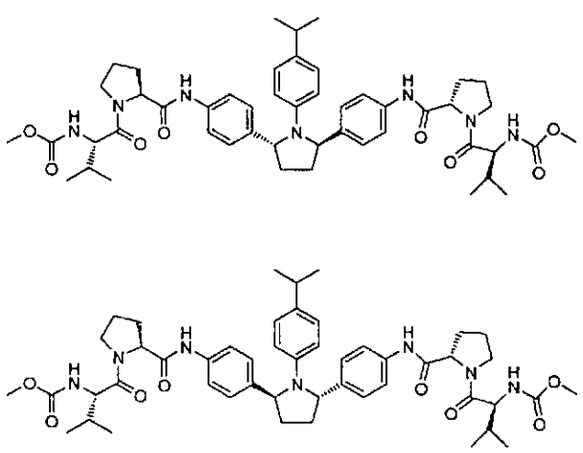
mixture 10



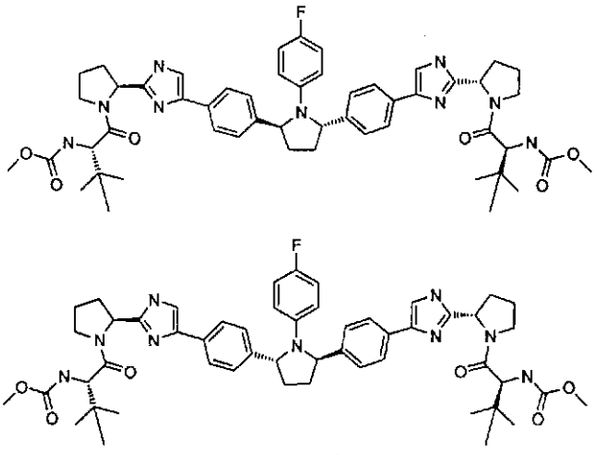
mixture 11



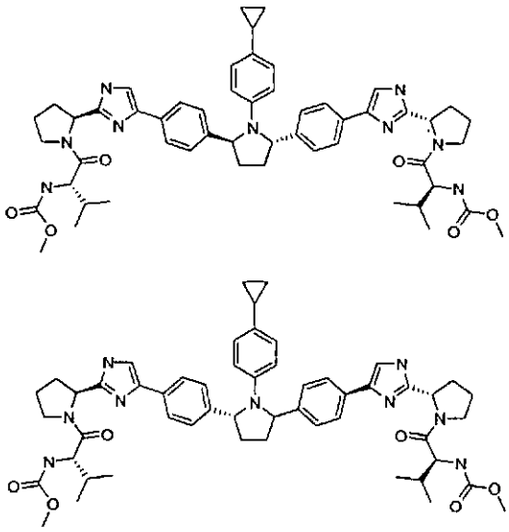
mixture 12



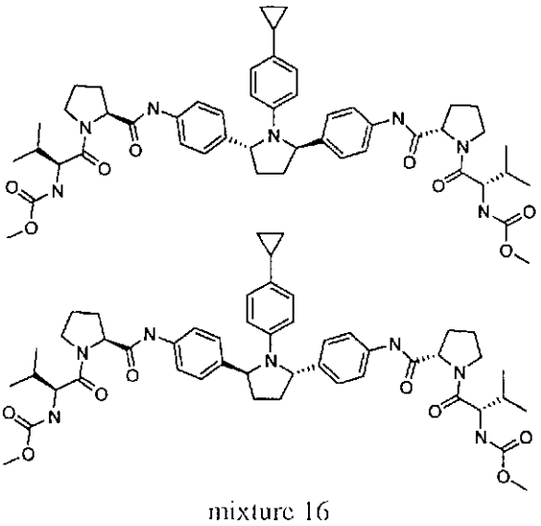
mixture 13



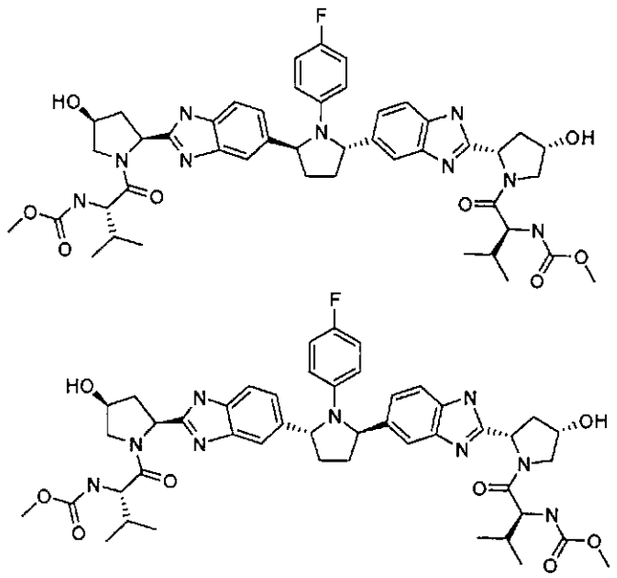
mixture 14



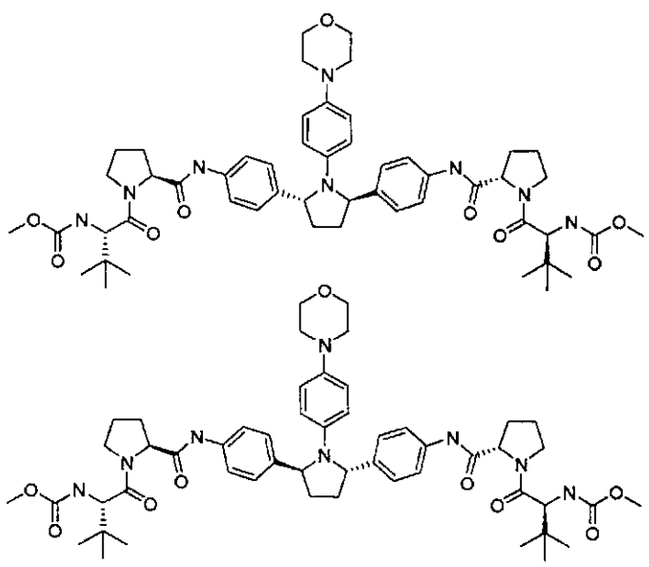
mixture 15



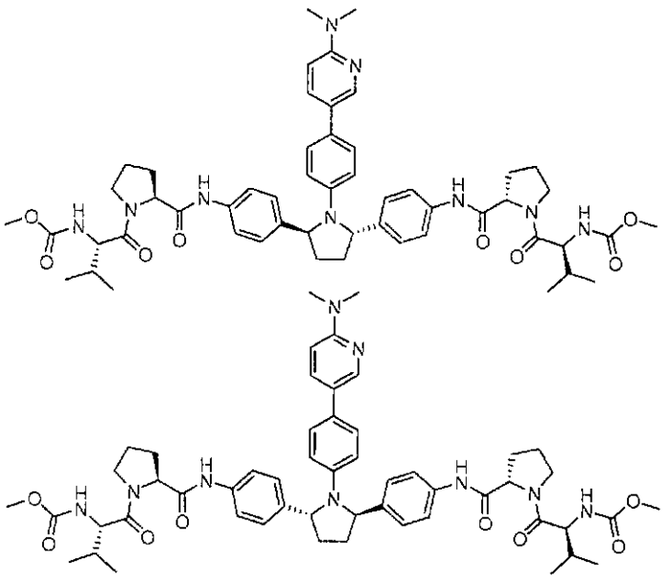
mixture 16



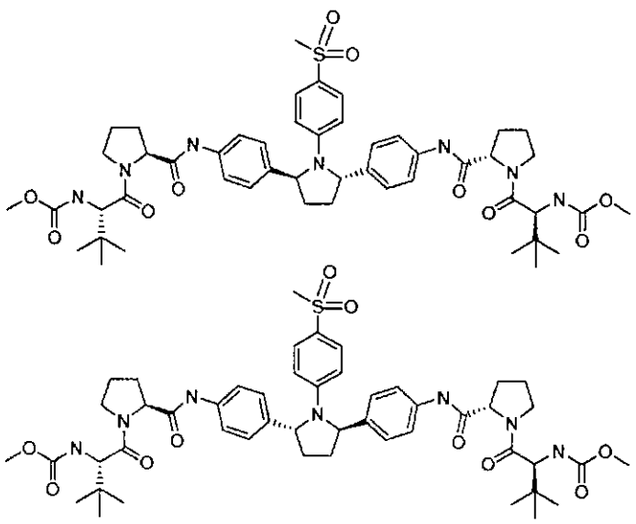
mixture 17



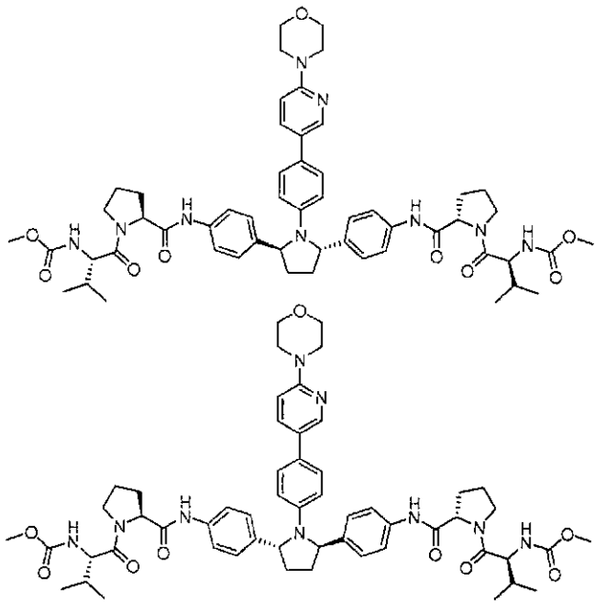
mixture 18



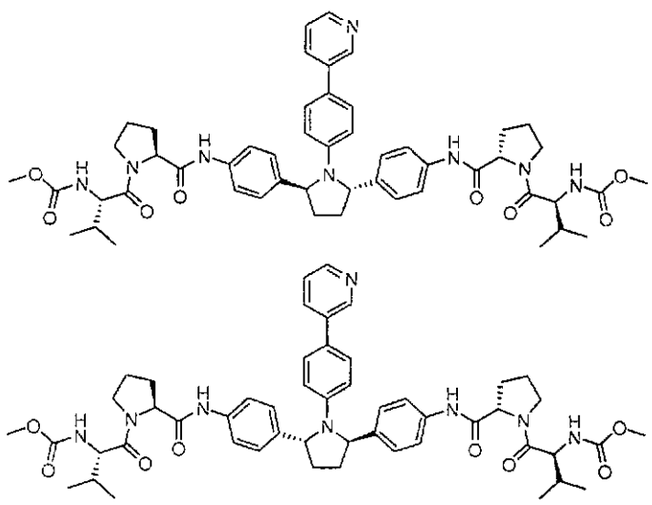
mixture 19



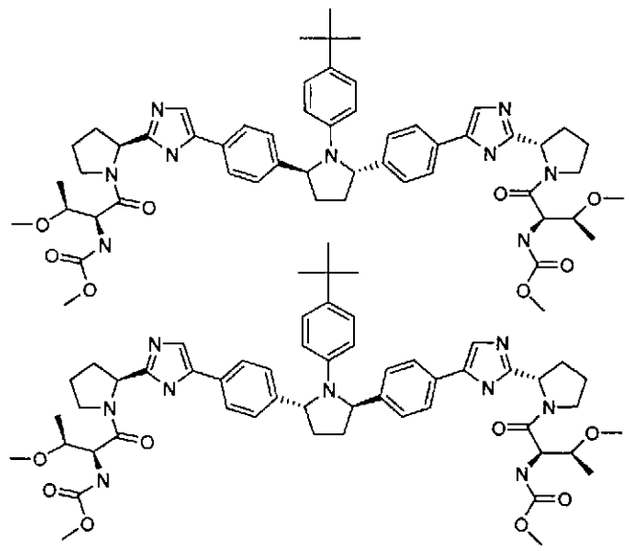
mixture 20



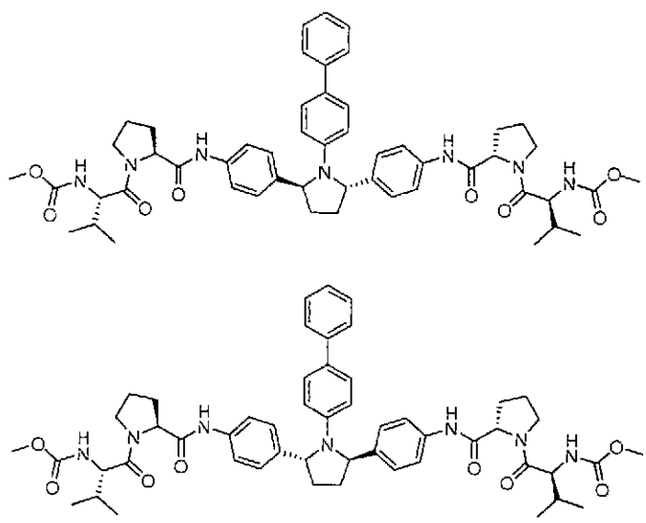
mixture 21



mixture 22



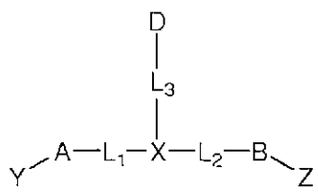
mixture 23



mixture 24

When tested using HCV 1b-Con1 replicon assays in the presence of 5% FBS, each of the above mixtures (except mixture 12) showed an EC_{50} value of less than 1 nM. Mixture 12 showed an EC_{50} value of from about 1 to 10 nM in HCV 1b-Con1 replicon assays in the presence of 5% FBS.

Likewise, the following compounds of Formula I or pharmaceutically acceptable salts thereof can be similarly prepared according to the schemes and procedures described above,



I

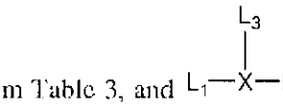
wherein A is selected from Table 1a, B is selected from Table 1b, D is selected from Table 2, Y and Z are each independently selected from Table 3, and  is selected from Table 4, and A, B, D and X are each independently optionally substituted with one or more R_A, and wherein L_1, L_2, L_3 and R_A are as described above. Preferably, L_1, L_2 and L_3 are bond.

Table 1a. A

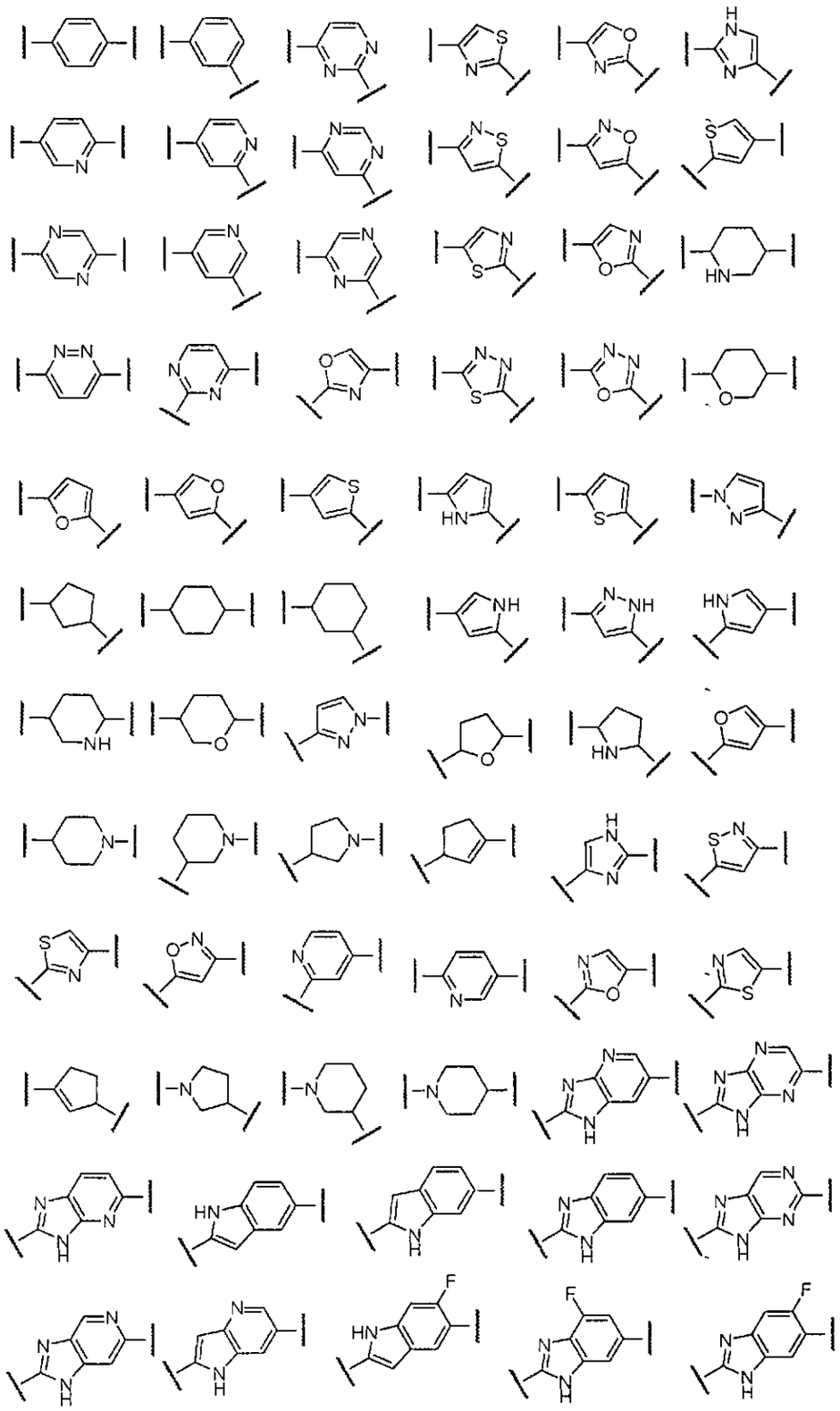


Table 1b. B

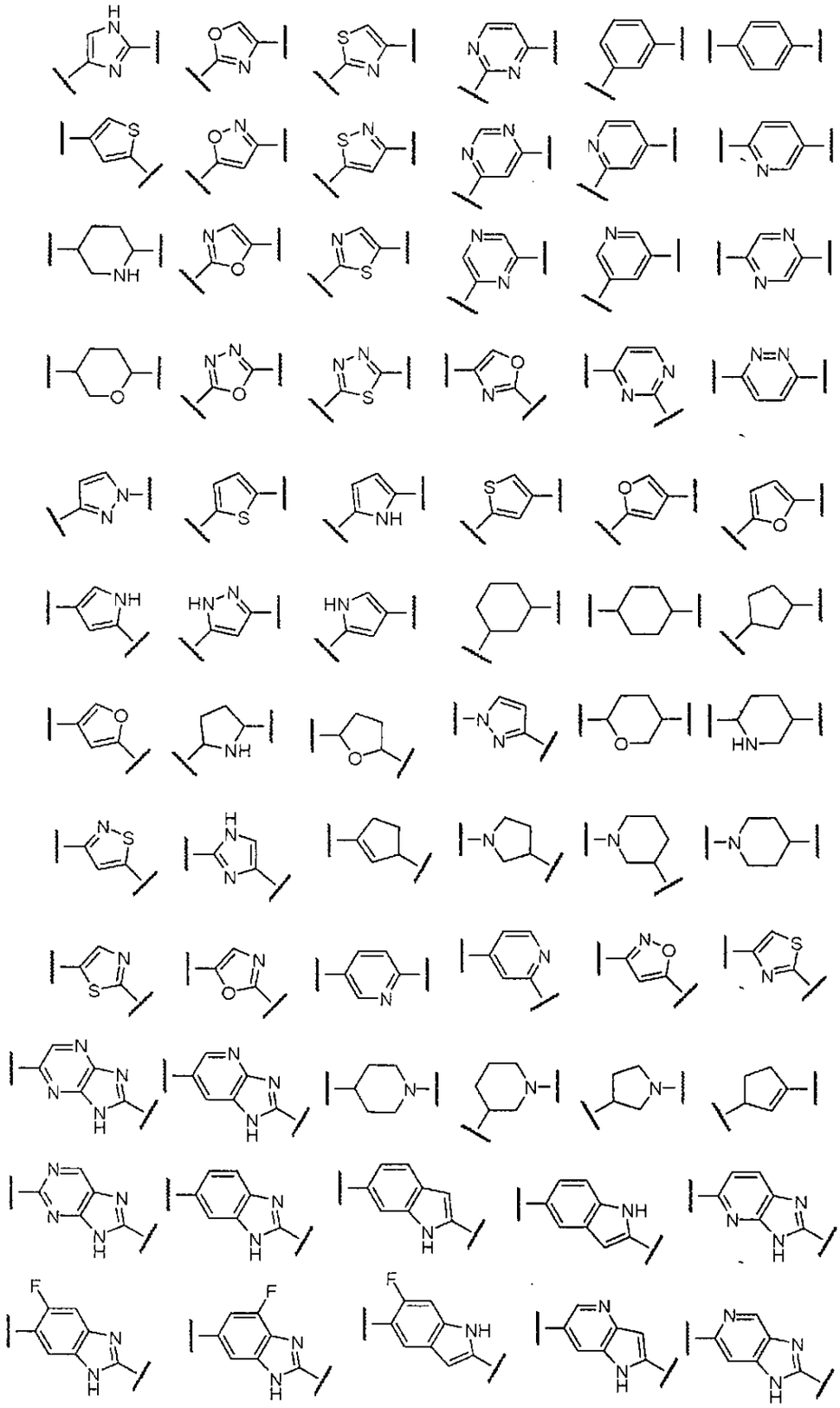


Table 2. D

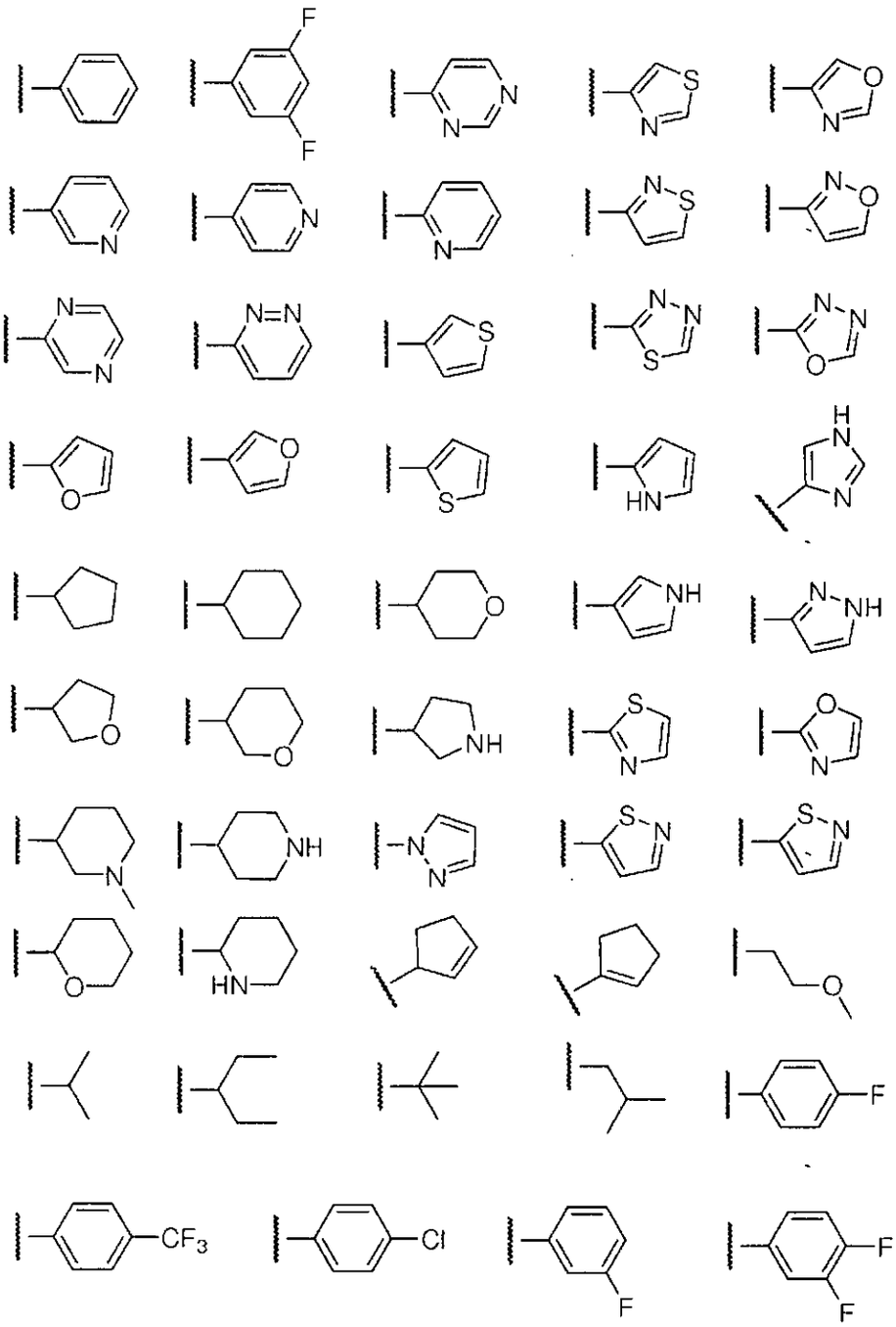

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Table 3. Y and Z

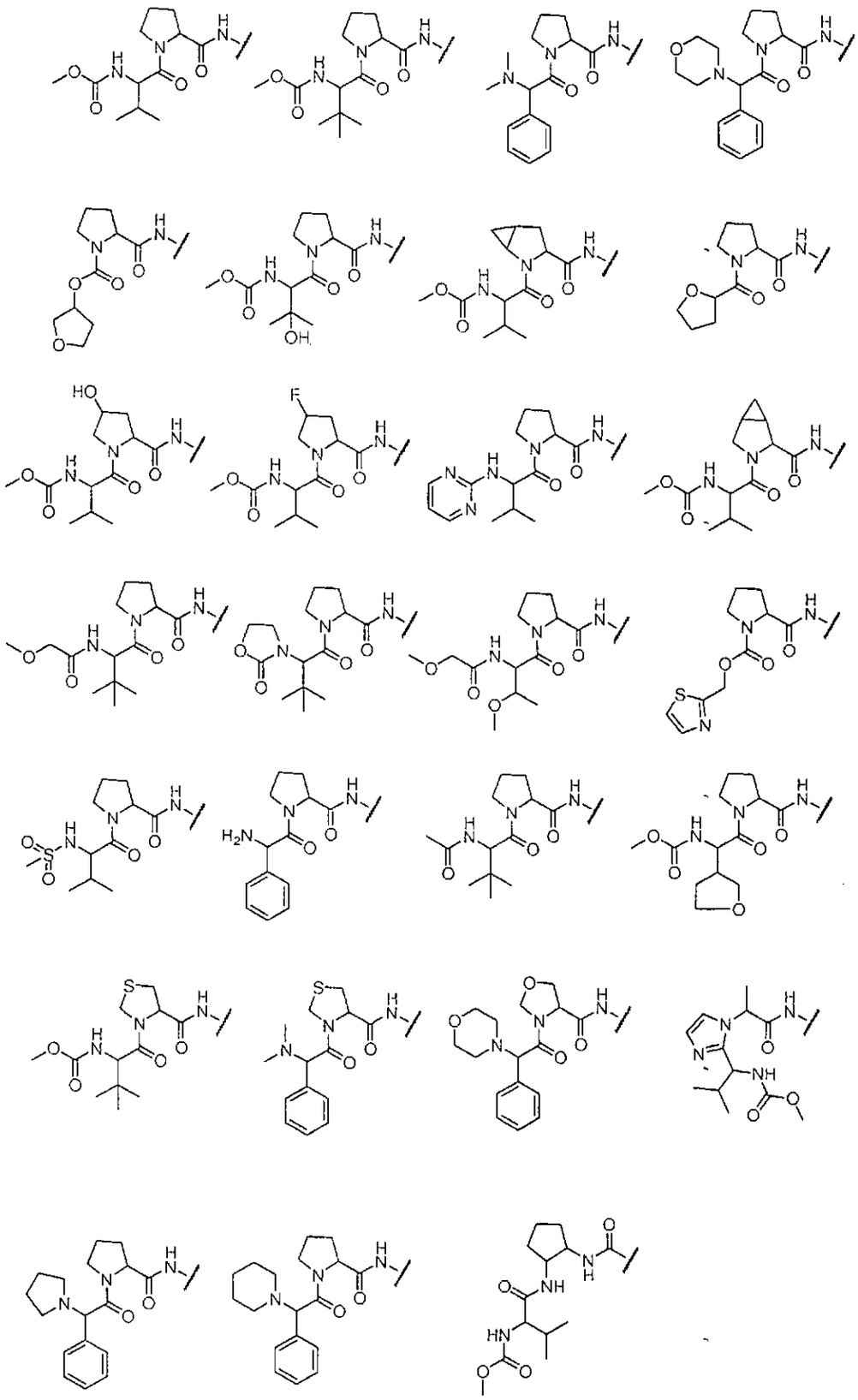


Table 3. Y and Z (continued)

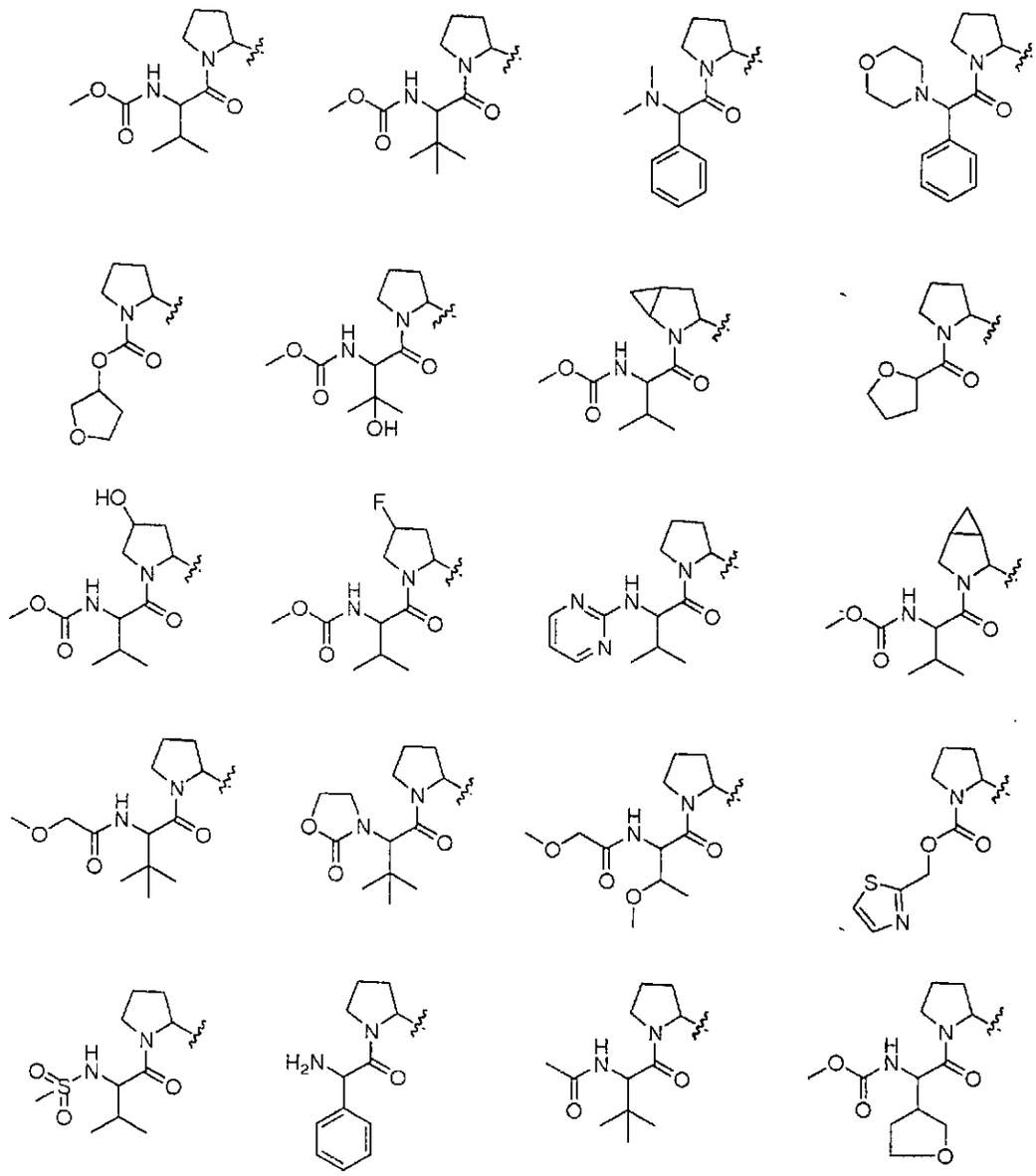


Table 3. Y and Z (continued)

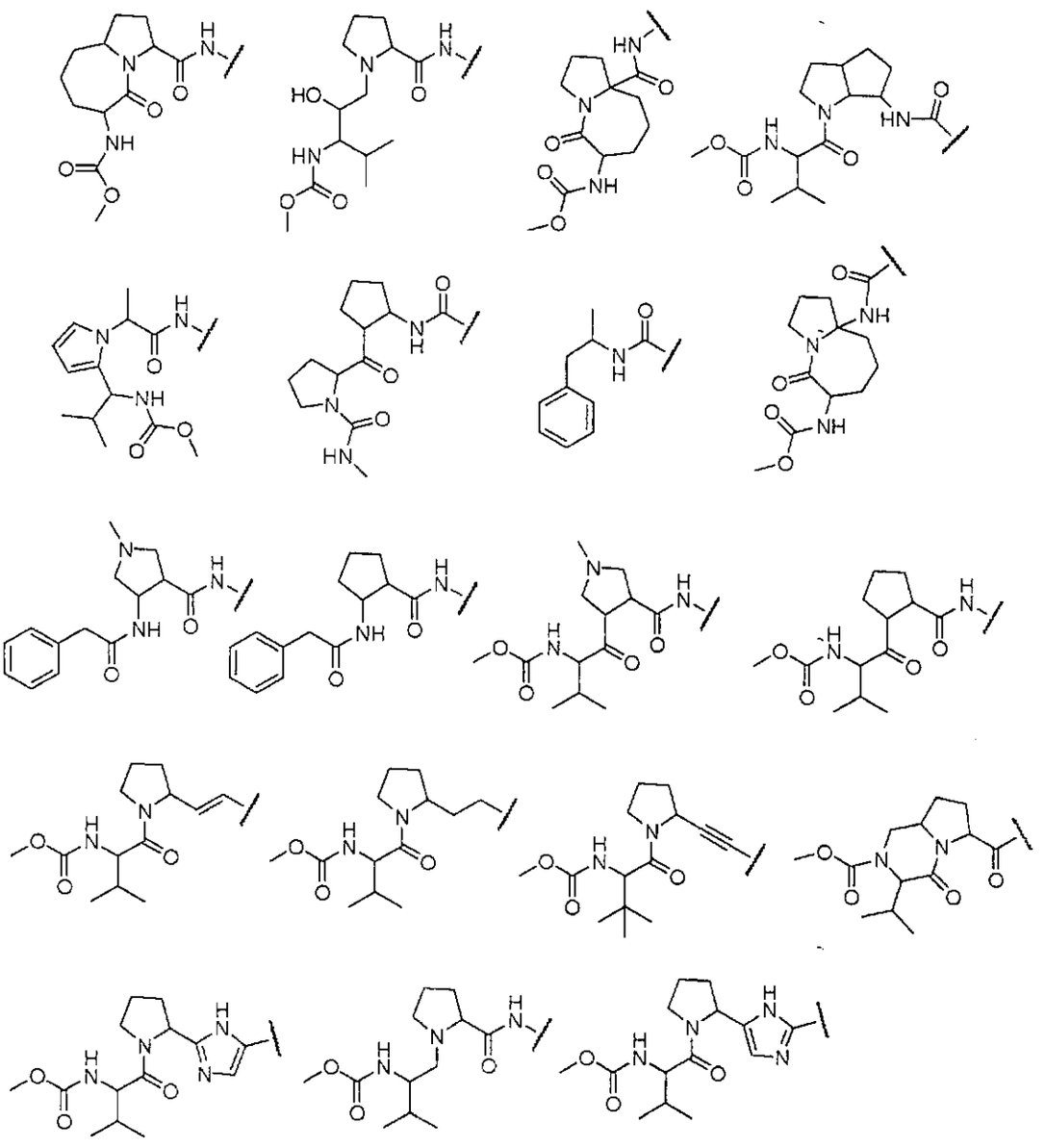
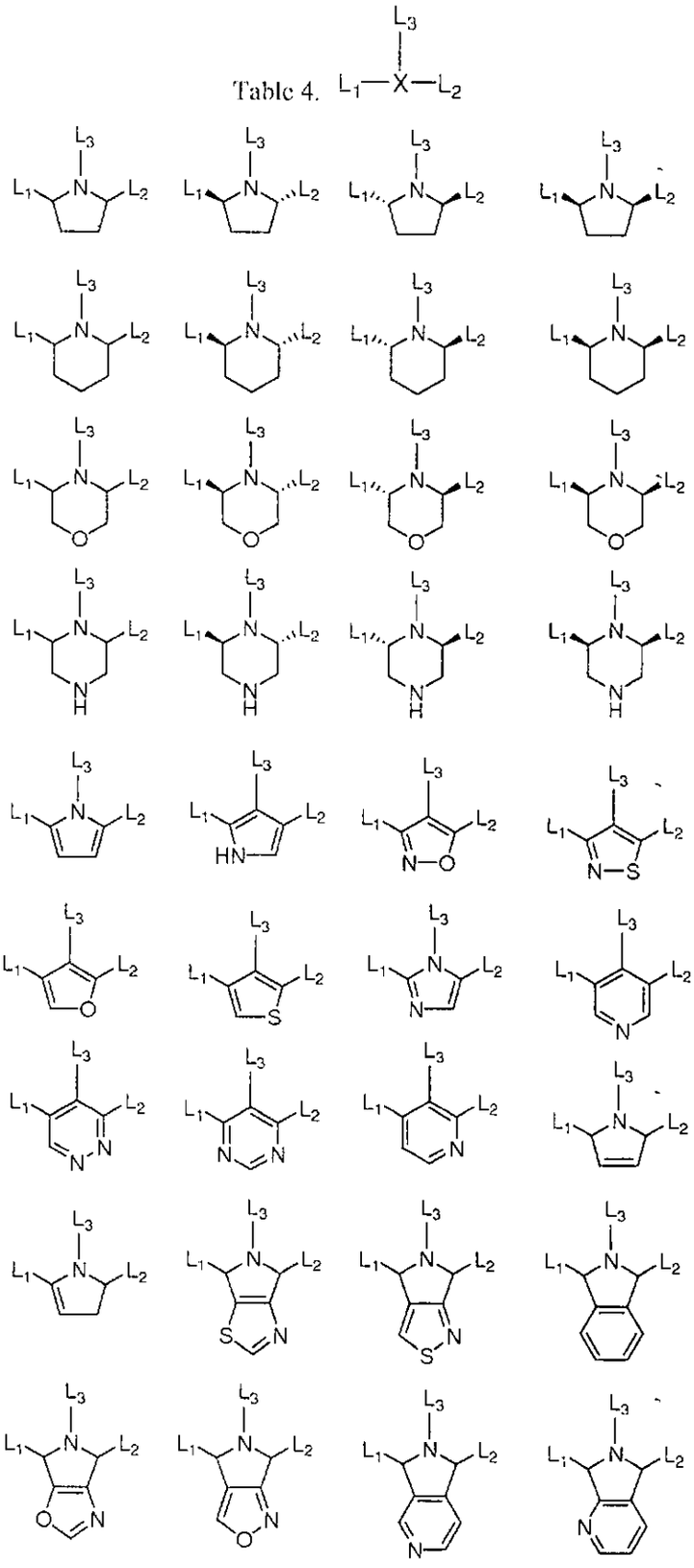
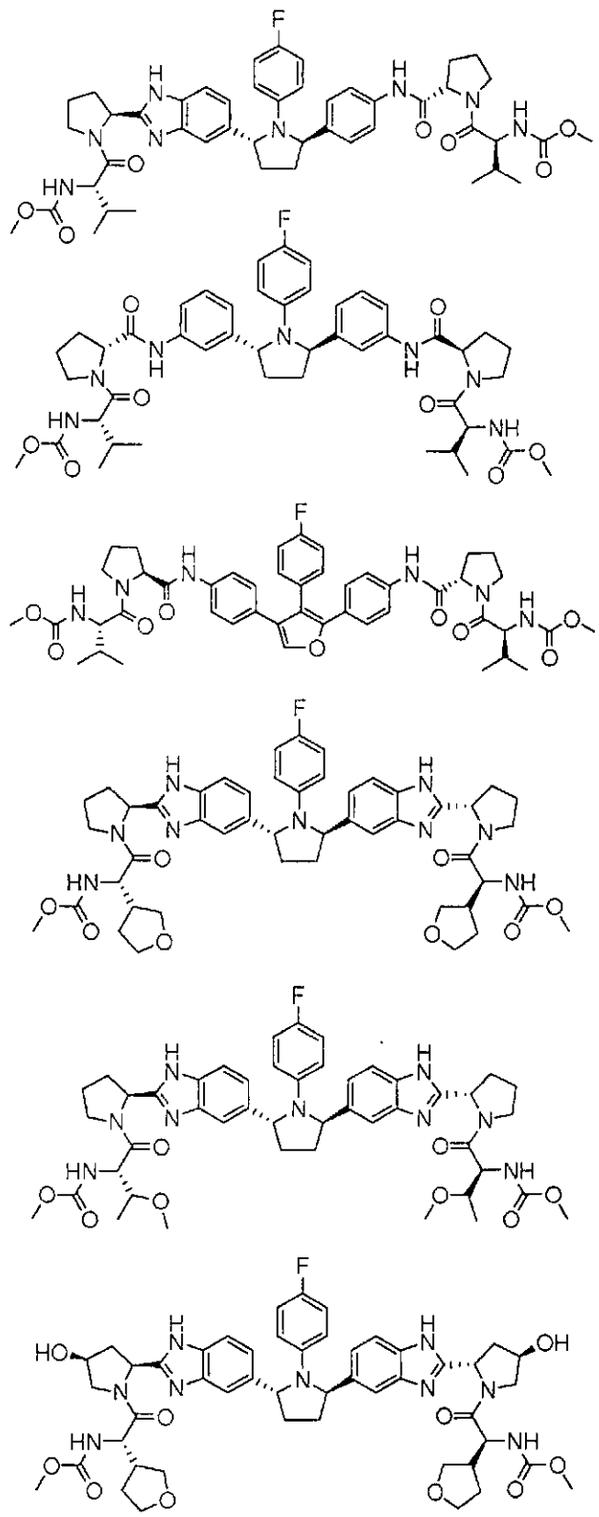


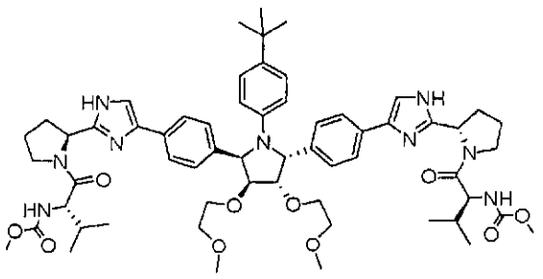
Table 4.

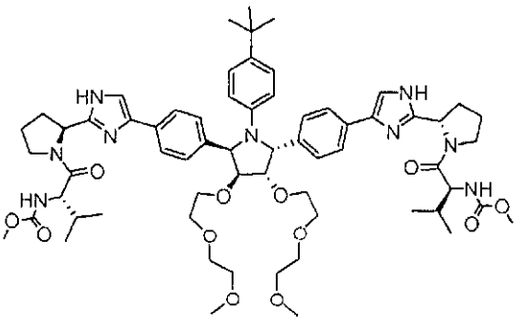


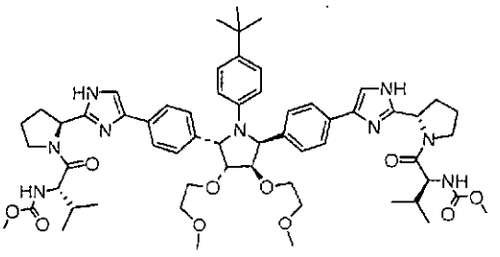
Other examples of the compounds of Formula I are provided in Table 5.

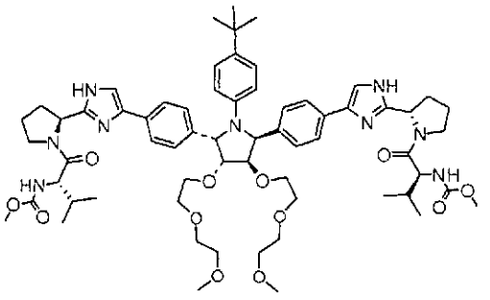
Table 5

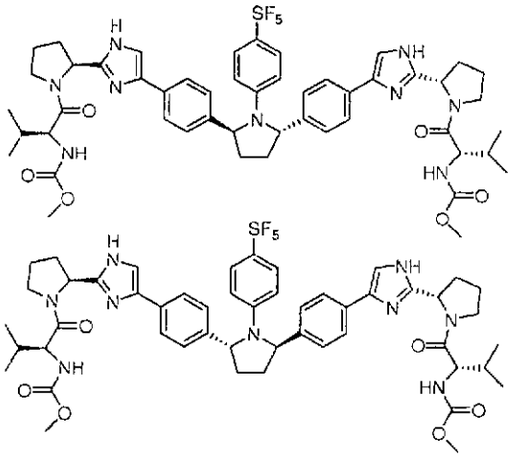


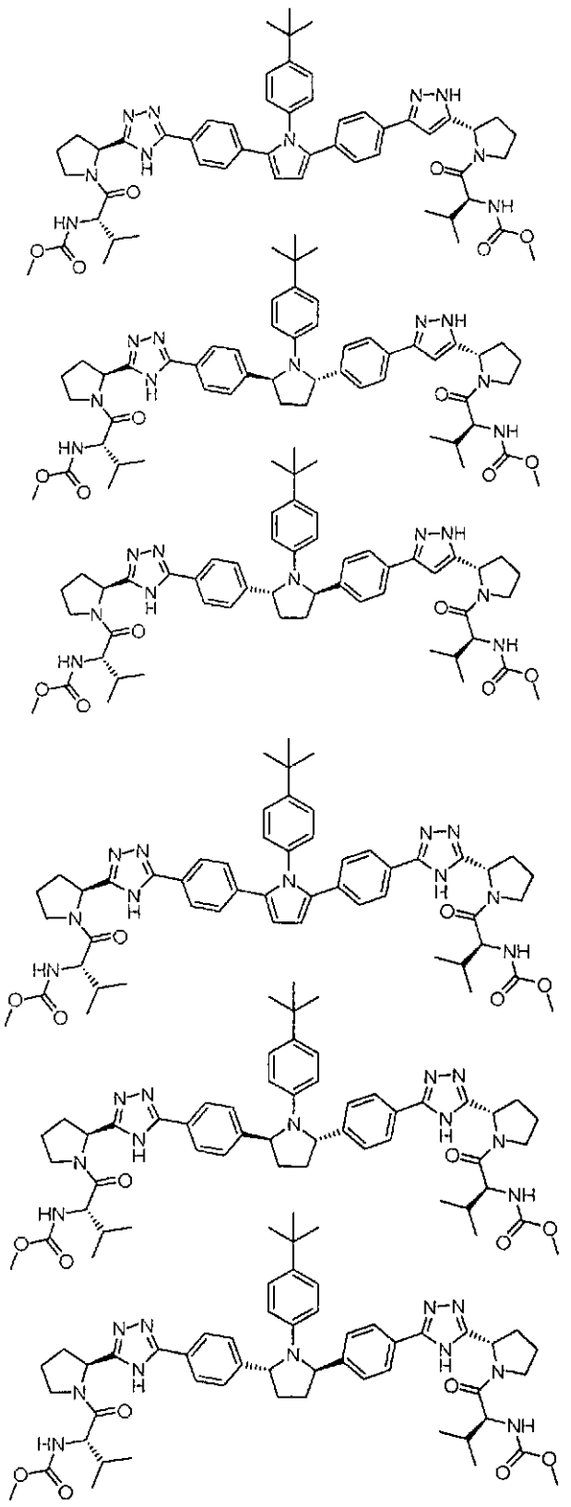


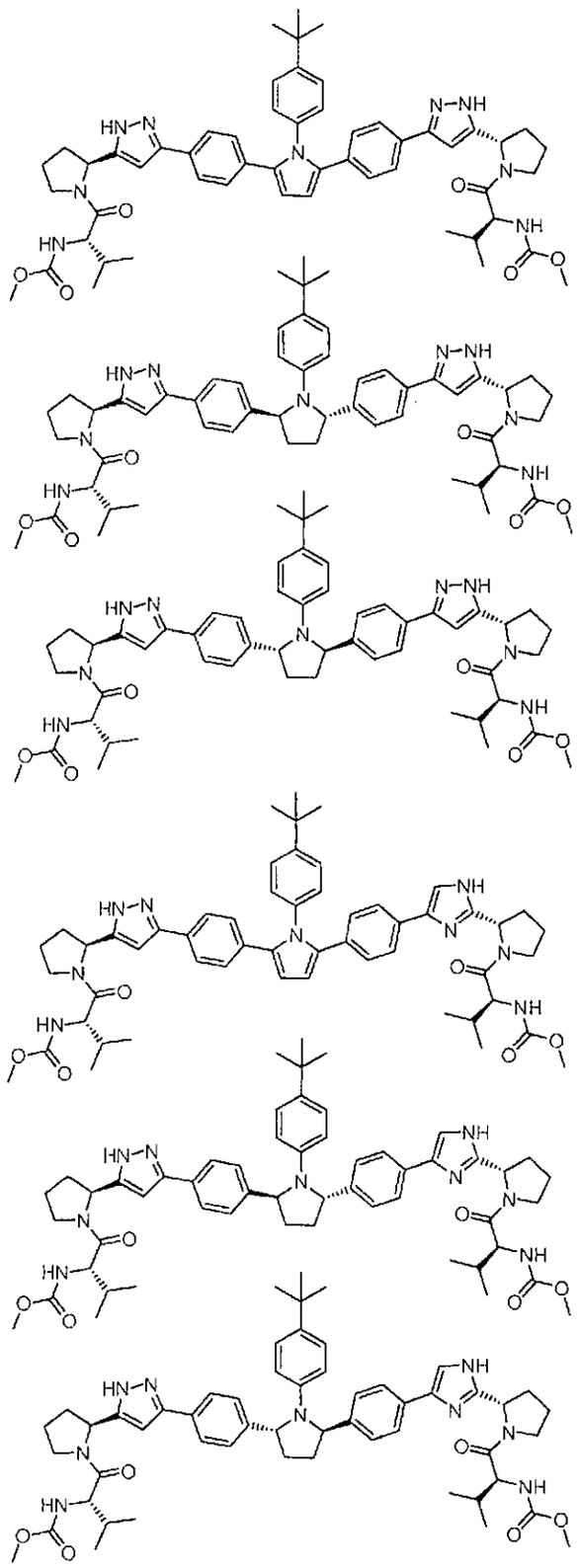


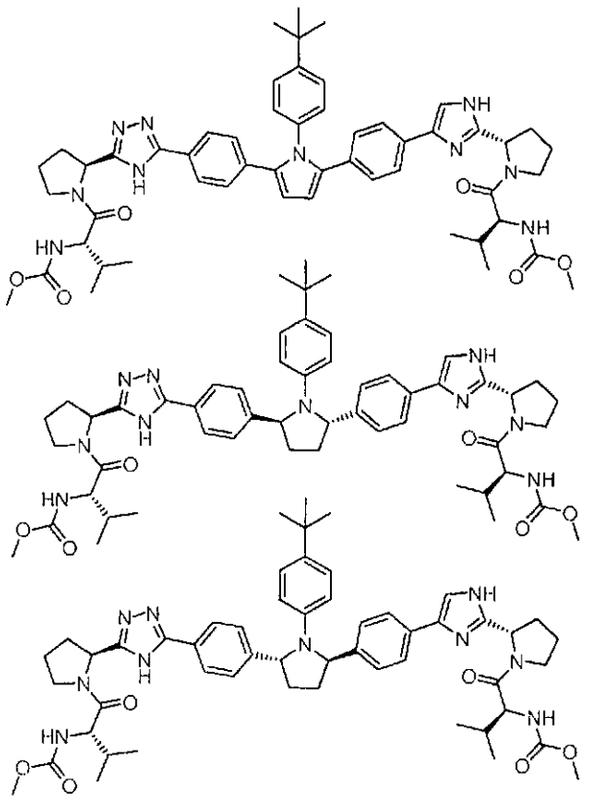












Each compound's anti-HCV activity can be determined by measuring the activity of the luciferase reporter gene in the replicon in the presence of 5% FBS. The luciferase reporter gene is placed under the translational control of the poliovirus IRES instead of the HCV IRES, and Huh-7 cells are used to support the replication of the replicon.

The inhibitory activities of the compounds of the present invention can be evaluated using a variety of assays known in the art. For instance, two stable subgenomic replicon cell lines can be used for compound characterization in cell culture: one derived from genotype 1a-H77 and the other derived from genotype 1b-Con1, obtained from University of Texas Medical Branch, Galveston, TX or Apath, LLC, St. Louis, MO, respectively. The replicon constructs can be bicistronic subgenomic replicons. The genotype 1a replicon construct contains NS3-NS5B coding region derived from the H77 strain of HCV (1a-H77). The replicon also has a firefly luciferase reporter and a neomycin phosphotransferase (Neo) selectable marker. These two coding regions, separated by the EMDV 2a protease, comprise the first cistron of the bicistronic replicon construct, with the second cistron containing the NS3-NS5B coding region with addition of adaptive mutations E1202G, K1691R, K2040R and S2204I. The 1b-Con1 replicon construct is identical to the 1a-H77 replicon, except that the HCV 5' UTR, 3' UTR, and NS3-NS5B coding region are derived from the 1b-Con1 strain, and the adaptive mutations are K1609E, K1846T and Y3005C. In addition, the 1b-Con1 replicon construct contains a poliovirus IRES between the HCV IRES and the luciferase gene. Replicon cell lines can be maintained in Dulbecco's modified Eagles medium (DMEM) containing 10% (v/v) fetal

bovine serum (FBS), 100 IU/ml penicillin, 100 mg/ml streptomycin (Invitrogen), and 200 mg/ml G418 (Invitrogen).

The inhibitory effects of the compounds of the invention on HCV replication can be determined by measuring activity of the luciferase reporter gene. For example, replicon-containing cells can be seeded into 96 well plates at a density of 5000 cells per well in 100 μl DMEM containing 5% FBS. The following day compounds can be diluted in dimethyl sulfoxide (DMSO) to generate a 200x stock in a series of eight half-log dilutions. The dilution series can then be further diluted 100-fold in the medium containing 5% FBS. Medium with the inhibitor is added to the overnight cell culture plates already containing 100 μl of DMEM with 5% FBS. In assays measuring inhibitory activity in the presence of human plasma, the medium from the overnight cell culture plates can be replaced with DMEM containing 40% human plasma and 5% FBS. The cells can be incubated for three days in the tissue culture incubators after which time 30 μl of Passive Lysis buffer (Promega) can be added to each well, and then the plates are incubated for 15 minutes with rocking to lyse the cells. Luciferin solution (100 μl, Promega) can be added to each well, and luciferase activity can be measured with a Victor II luminometer (Perkin-Elmer). The percent inhibition of HCV RNA replication can be calculated for each compound concentration and the EC_{50} value can be calculated using nonlinear regression curve fitting to the 4-parameter logistic equation and GraphPad Prism 4 software. Using the above-described assays or similar cell-based replicon assays, representative compounds of the present invention showed significantly inhibitory activities against HCV replication.

The present invention also features pharmaceutical compositions comprising the compounds of the invention. A pharmaceutical composition of the present invention can comprise one or more compounds of the invention, each of which has Formula I (or I_A, I_B, I_C or I_D).

In addition, the present invention features pharmaceutical compositions comprising pharmaceutically acceptable salts, solvates, or prodrugs of the compounds of the invention. Without limitation, pharmaceutically acceptable salts can be zwitterions or derived from pharmaceutically acceptable inorganic or organic acids or bases. Preferably, a pharmaceutically acceptable salt retains the biological effectiveness of the free acid or base of the compound without undue toxicity, irritation, or allergic response, has a reasonable benefit/risk ratio, is effective for the intended use, and is not biologically or otherwise undesirable.

The present invention further features pharmaceutical compositions comprising a compound of the invention (or a salt, solvate or prodrug thereof) and another therapeutic agent. By way of illustration not limitation, these other therapeutic agents can be selected from antiviral agents (e.g., anti-HIV agents, anti-HBV agents, or other anti-HCV agents such as HCV protease inhibitors, HCV polymerase inhibitors, HCV helicase inhibitors, IRES inhibitors or NS5A inhibitors), anti-bacterial agents, anti-fungal agents, immunomodulators, anti-cancer or chemotherapeutic agents, anti-

inflammation agents, antisense RNA, siRNA, antibodies, or agents for treating cirrhosis or inflammation of the liver. Specific examples of these other therapeutic agents include, but are not limited to, ribavirin, α-interferon, β-interferon, pegylated interferon-α, pegylated interferon-lambda, ribavirin, viramidine, R-5158, nitazoxanide, amantadine, Debio-025, NIM-811, R7128, R1626, R4048, T-1106, PSI-7851 (Pharmasset) (nucleoside polymerase inhibitor), PSI-938 (Pharmasset) (nucleoside polymerase inhibitor), PF-00868554, ANA-598, IDX184 (nucleoside polymerase inhibitor), IDX102, IDX375 (non-nucleoside polymerase inhibitor), GS-9190 (non-nucleoside polymerase inhibitor), VCH-759, VCH-916, MK-3281, BCX-4678, MK-3281, VBY708, ANA598, GL59728, GL60667, BMS-790052 (NS5A inhibitor), BMS-791325 (protease Inhibitor), BMS-650032, BMS-824393, GS-9132, ACH-1095 (protease inhibitor), AP-H005, A-831 (Arrow Therapeutics) (NS5A inhibitor), A-689 (Arrow Therapeutics) (NS5A inhibitor), INX08189 (Inhibitex) (polymerase inhibitor), AZD2836, telaprevir (protease Inhibitor), boceprevir (protease Inhibitor), ITMN-191 (Intermune/Roche), BI-201335 (protease Inhibitor), VBY-376, VX-500 (Vertex) (protease Inhibitor), PHX-B, ACH-1625, IDX136, IDX316, VX-813 (Vertex) (protease Inhibitor), SCH 900518 (Schering-Plough), TMC-435 (Tibotec) (protease Inhibitor), ITMN-191 (Intermune, Roche) (protease Inhibitor), MK-7009 (Merck) (protease Inhibitor), IDX-PI (Novartis), BI-201335 (Boehringer Ingelheim), R7128 (Roche) (nucleoside polymerase inhibitor), MK-3281 (Merck), MK-0608 (Merck) (nucleoside polymerase inhibitor), PF-868554 (Pfizer) (non-nucleoside polymerase inhibitor), PF-4878691 (Pfizer), IDX-184 (Novartis), IDX-375 (Pharmasset), PPI-461 (Presidio) (NS5A inhibitor), BILB-1941 (Boehringer Ingelheim), GS-9190 (Gilead), BMS-790052 (BMS), Albuferon (Novartis), ABT-450 (Abbott/Enanta) (protease Inhibitor), ABT-333 (Abbott) (non-nucleoside polymerase inhibitor), ABT-072 (Abbott) (non-nucleoside polymerase inhibitor), ritonavir, another cytochrome P450 monooxygenase inhibitor, or any combination thereof.

In one embodiment, a pharmaceutical composition of the present invention comprises one or more compounds of the present invention (or salts, solvates or prodrugs thereof), and one or more other antiviral agents.

In another embodiment, a pharmaceutical composition of the present invention comprises one or more compounds of the present invention (or salts, solvates or prodrugs thereof), and one or more other anti-HCV agents. For example, a pharmaceutical composition of the present invention can comprise a compound(s) of the present invention having Formula I, I_A, I_B, I_C, or I_D (or a salt, solvate or prodrug thereof), and an agent selected from HCV polymerase inhibitors (including nucleoside or non-nucleoside type of polymerase inhibitors), HCV protease inhibitors, HCV helicase inhibitors, CD81 inhibitors, cyclophilin inhibitors, IRES inhibitors, or NS5A inhibitors.

In yet another embodiment, a pharmaceutical composition of the present invention comprises one or more compounds of the present invention (or salts, solvates or prodrugs thereof), and one or more other antiviral agents, such as anti-HBV, anti-HIV agents, or anti-hepatitis A, anti-hepatitis D,

anti-hepatitis E or anti-hepatitis G agents. Non-limiting examples of anti-HBV agents include adefovir, lamivudine, and tenofovir. Non-limiting examples of anti-HIV drugs include ritonavir, lopinavir, indinavir, nelfinavir, saquinavir, amprenavir, atazanavir, tipranavir, TMC-114, fosamprenavir, zidovudine, lamivudine, didanosine, stavudine, tenofovir, zalcitabine, abacavir, efavirenz, nevirapine, delavirdine, TMC-125, L-870812, S-1360, enfuvirtide, T-1249, or other HIV protease, reverse transcriptase, integrase or fusion inhibitors. Any other desirable antiviral agents can also be included in a pharmaceutical composition of the present invention, as appreciated by those skilled in the art.

In a preferred embodiment, a pharmaceutical composition of the invention comprises a compound of the invention (e.g., a compound of Formula I, I_A, I_B, I_C, or I_D, or preferably a compound selected from Examples 1-308, or a salt, solvate or prodrug thereof), and a HCV protease inhibitor. In another preferred embodiment, a pharmaceutical composition of the invention comprises a compound of the invention (e.g., a compound of Formula I, I_A, I_B, I_C, or I_D, or preferably a compound selected from Examples 1-308, or a salt, solvate or prodrug thereof), and a HCV polymerase inhibitor (e.g., a non-nucleoside polymerase inhibitor, or preferably a nucleoside polymerase inhibitor). In yet another preferred embodiment, a pharmaceutical composition of the present invention comprises (1) a compound of the invention (e.g., a compound of Formula I, I_A, I_B, I_C, or I_D, or preferably a compound selected from Examples 1-308, or a salt, solvate or prodrug thereof), (2) a HCV protease inhibitor, and (3) a HCV polymerase inhibitor (e.g., a non-nucleoside polymerase inhibitor, or preferably a nucleoside polymerase inhibitor). Non-limiting examples of protease and polymerase inhibitors are described above.

A pharmaceutical composition of the present invention typically includes a pharmaceutically acceptable carrier or excipient. Non-limiting examples of suitable pharmaceutically acceptable carriers/excipients include sugars (e.g., lactose, glucose or sucrose), starches (e.g., corn starch or potato starch), cellulose or its derivatives (e.g., sodium carboxymethyl cellulose, ethyl cellulose or cellulose acetate), oils (e.g., peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil or soybean oil), glycols (e.g., propylene glycol), buffering agents (e.g., magnesium hydroxide or aluminum hydroxide), agar, alginic acid, powdered tragacanth, malt, gelatin, talc, cocoa butter, pyrogen-free water, isotonic saline, Ringer's solution, ethanol, or phosphate buffer solutions. Lubricants, coloring agents, releasing agents, coating agents, sweetening, flavoring or perfuming agents, preservatives, or antioxidants can also be included in a pharmaceutical composition of the present invention.

The pharmaceutical compositions of the present invention can be formulated based on their routes of administration using methods well known in the art. For example, a sterile injectable preparation can be prepared as a sterile injectable aqueous or oleagenous suspension using suitable dispersing or wetting agents and suspending agents. Suppositories for rectal administration can be

prepared by mixing drugs with a suitable nonirritating excipient such as cocoa butter or polyethylene glycols which are solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum and release the drugs. Solid dosage forms for oral administration can be capsules, tablets, pills, powders or granules. In such solid dosage forms, the active compounds can be admixed with at least one inert diluent such as sucrose lactose or starch. Solid dosage forms may also comprise other substances in addition to inert diluents, such as lubricating agents. In the case of capsules, tablets and pills, the dosage forms may also comprise buffering agents. Tablets and pills can additionally be prepared with enteric coatings. Liquid dosage forms for oral administration can include pharmaceutically acceptable emulsions, solutions, suspensions, syrups or elixirs containing inert diluents commonly used in the art. Liquid dosage forms may also comprise wetting, emulsifying, suspending, sweetening, flavoring, or perfuming agents. The pharmaceutical compositions of the present invention can also be administered in the form of liposomes, as described in U.S. Patent No. 6,703,403. Formulation of drugs that are applicable to the present invention is generally discussed in, for example, Hoover, John E., REMINGTON'S PHARMACEUTICAL SCIENCES (Mack Publishing Co., Easton, PA: 1975), and Lachman, L., eds., PHARMACEUTICAL DOSAGE FORMS (Marcel Decker, New York, N.Y., 1980).

Any compound described herein, or a pharmaceutically acceptable salt thereof, can be used to prepared pharmaceutical compositions of the present invention.

In a preferred embodiment, a compound of the invention (e.g., a compound of Formula I, I_A, I_B, I_C, or I_D, or preferably a compound selected from Examples 1-308, or a salt, solvate or prodrug thereof) is formulated in a solid dispersion, where the compound of the invention can be molecularly dispersed in an amorphous matrix which comprises a pharmaceutically acceptable, hydrophilic polymer. The matrix may also contain a pharmaceutically acceptable surfactant. Suitable solid dispersion technology for formulating a compound of the invention includes, but is not limited to, melt-extrusion, spray-drying, co-precipitation, freeze drying, or other solvent evaporation techniques, with melt-extrusion and spray-drying being preferred. In one example, a compound of the invention is formulated in a solid dispersion comprising copovidone and vitamin E TPGS. In another example, a compound of the invention is formulated in a solid dispersion comprising copovidone and Span 20.

A solid dispersion described herein may contain at least 30% by weight of a pharmaceutically acceptable hydrophilic polymer or a combination of such hydrophilic polymers. Preferably, the solid dispersion contains at least 40% by weight of a pharmaceutically acceptable hydrophilic polymer or a combination of such hydrophilic polymers. More preferably, the solid dispersion contains at least 50% (including, e.g., at least 60%, 70%, 80% or 90%) by weight of a pharmaceutically acceptable hydrophilic polymer or a combination of such polymers. A solid dispersion described herein may also contain at least 1% by weight of a pharmaceutically acceptable surfactant or a combination of such surfactants. Preferably, the solid dispersion contains at least 2% by weight of a pharmaceutically

acceptable surfactant or a combination of such surfactants. More preferably, the solid dispersion contains from 4% to 20% by weight of the surfactant(s), such as from 5% to 10% by weight of the surfactant(s). In addition, a solid dispersion described herein may contain at least 1% by weight of a compound of the invention, preferably at least 5%, including, e.g., at least 10%. In one example, the solid dispersion comprises 5% of a compound of the invention (e.g., a compound of Formula I, I_A, I_B, I_C, or I_D, or preferably a compound selected from Examples 1-308, or a salt, solvate or prodrug thereof), which is molecularly dispersed in a an amorphous matrix comprising 7% Vitamin E-TPGS and 88% copovidone; the solid dispersion can also be mixed with other excipients such as mannitol/aerosil (99:1), and the weight ratio of the solid dispersion over the other excipients can range from 5:1 to 1:5 with 1:1 being preferred. In another example, the solid dispersion comprises 5% of a compound of the invention (e.g., a compound of Formula I, I_A, I_B, I_C, or I_D, or preferably a compound selected from Examples 1-308, or a salt, solvate or prodrug thereof), which is molecularly dispersed in a an amorphous matrix comprising 5% Span 20 and 90% copovidone; the solid dispersion can also be mixed with other excipients such as mannitol/aerosil (99:1), the solid dispersion can also be mixed with other excipients such as mannitol/aerosil (99:1), and the weight ratio of the solid dispersion over the other excipients can range from 5:1 to 1:5 with 1:1 being preferred.

Various additives can also be included in or mixed with the solid dispersion. For instance, at least one additive selected from flow regulators, binders, lubricants, fillers, disintegrants, plasticizers, colorants, or stabilizers may be used in compressing the solid dispersion to tablets. These additives can be mixed with ground or milled solid dispersion before compacting. Disintegrants promote a rapid disintegration of the compact in the stomach and keeps the liberated granules separate from one another. Non-limiting examples of suitable disintegrants are cross-linked polymers such as cross-linked polyvinyl pyrrolidone, cross-linked sodium carboxymethylcellulose or sodium croscarmellose. Non-limiting examples of suitable fillers (also referred to as bulking agents) are lactose monohydrate, calcium hydrogenphosphate, microcrystalline cellulose (e.g., Avicell), silicates, in particular silicium dioxide, magnesium oxide, talc, potato or corn starch, isomalt, or polyvinyl alcohol. Non-limiting examples of suitable flow regulators include highly dispersed silica (e.g., colloidal silica such as Aerosil), and animal or vegetable fats or waxes. Non-limiting examples of suitable lubricants include polyethylene glycol (e.g., having a molecular weight of from 1000 to 6000), magnesium and calcium stearates, sodium stearyl fumarate, and the like. Non-limiting examples of stabilizers include antioxidants, light stabilizers, radical scavengers, or stabilizers against microbial attack.

The present invention further features methods of using the compounds of the present invention (or salts, solvates or prodrugs thereof) to inhibit HCV replication. The methods comprise contacting cells infected with HCV virus with an effective amount of a compound of the present invention (or a salt, solvate or prodrug thereof), thereby inhibiting the replication of HCV virus in the cells. As used herein, "inhibiting" means significantly reducing, or abolishing, the activity being

inhibited (e.g., viral replication). In many cases, representative compounds of the present invention can reduce the replication of HCV virus (e.g., in an HCV replicon assay as described above) by at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95% or more.

The compounds of the present invention may inhibit one or more HCV subtypes. Examples of HCV subtypes that are amenable to the present invention include, but are not be limited to, HCV genotypes 1, 2, 3, 4, 5 and 6, including HCV genotypes 1a, 1b, 2a, 2b, 2c, 3a or 4a. In one embodiment, a compound or compounds of the present invention (or salts, solvates or prodrugs thereof) are used to inhibit the replication of HCV genotype 1a. In another embodiment, a compound or compounds of the present invention (or salts, solvates or prodrugs thereof) are used to inhibit the replication of HCV genotype 1b. In still another embodiment, a compound or compounds of the present invention (or salts, solvates or prodrugs thereof) are used to inhibit the replication of both HCV genotypes 1a and 1b.

The present invention also features methods of using the compounds of the present invention (or salts, solvates or prodrugs thereof) to treat HCV infection. The methods typically comprise administering a therapeutic effective amount of a compound of the present invention (or a salt, solvate or prodrug thereof), or a pharmaceutical composition comprising the same, to an HCV patient, thereby reducing the HCV viral level in the blood or liver of the patient. As used herein, the term "treating" refers to reversing, alleviating, inhibiting the progress of, or preventing the disorder or condition, or one or more symptoms of such disorder or condition to which such term applies. The term "treatment" refers to the act of treating. In one embodiment, the methods comprise administering a therapeutic effective amount of two or more compounds of the present invention (or salts, solvates or prodrugs thereof), or a pharmaceutical composition comprising the same, to an HCV patient, thereby reducing the HCV viral level in the blood or liver of the patient.

A compound of the present invention (or a salt, solvate or prodrug thereof) can be administered as the sole active pharmaceutical agent, or in combination with another desired drug, such as other anti-HCV agents, anti-HIV agents, anti-HBV agents, anti-hepatitis A agents, anti-hepatitis D agents, anti-hepatitis E agents, anti-hepatitis G agents, or other antiviral drugs. Any compound described herein, or a pharmaceutically acceptable salt thereof, can be employed in the methods of the present invention. In one embodiment, the present invention features methods of treating HCV infection, wherein said methods comprise administering a compound of the invention (e.g., a compound of Formula I, I_A, I_B, I_C, or I_D, or preferably a compound selected from Examples 1-308, or a salt, solvate or prodrug thereof), interferon and ribavirin to an HCV patient. The interferon preferably is α-interferon, and more preferably, pegylated interferon-α such as PEGASYS (peginterferon alfa-2a).

A compound of the present invention (or a salt, solvent or prodrug thereof) can be administered to a patient in a single dose or divided doses. A typical daily dosage can range, without

limitation, from 0.1 to 200 mg/kg body weight, such as from 0.25 to 100 mg/kg body weight. Single dose compositions can contain these amounts or submultiples thereof to make up the daily dose. Preferably, each dosage contains a sufficient amount of a compound of the present invention that is effective in reducing the HCV viral load in the blood or liver of the patient. The amount of the active ingredient, or the active ingredients that are combined, to produce a single dosage form may vary depending upon the host treated and the particular mode of administration. It will be understood that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination, and the severity of the particular disease undergoing therapy.

The present invention further features methods of using the pharmaceutical compositions of the present invention to treat HCV infection. The methods typically comprise administering a pharmaceutical composition of the present invention to an HCV patient, thereby reducing the HCV viral level in the blood or liver of the patient. Any pharmaceutical composition described herein can be used in the methods of the present invention.

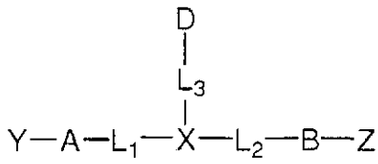
In addition, the present invention features use of the compounds or salts of the present invention for the manufacture of medicaments for the treatment of HCV infection. Any compound described herein, or a pharmaceutically acceptable salt thereof, can be used to make medicaments of the present invention.

The compounds of the present invention can also be isotopically substituted. Preferred isotopic substitution include substitutions with stable or nonradioactive isotopes such as deuterium, ^{13}C, ^{15}N or ^{18}O. Incorporation of a heavy atom, such as substitution of deuterium for hydrogen, can give rise to an isotope effect that could alter the pharmacokinetics of the drug. In one example, at least 5 mol % (e.g., at least 10 mol %) of hydrogen in a compound of the present invention is substituted with deuterium. In another example, at least 25 mole % of hydrogen in a compound of the present invention is substituted with deuterium. In a further example, at least 50, 60,70, 80 or 90 mole % of hydrogen in a compound of the present invention is substituted with deuterium. The natural abundance of deuterium is about 0.015%. Deuterium substitution or enrichment can be achieved, without limitation, by either exchanging protons with deuterium or by synthesizing the molecule with enriched or substituted starting materials. Other methods known in the art can also be used for isotopic substitutions.

The foregoing description of the present invention provides illustration and description, but is not intended to be exhaustive or to limit the invention to the precise one disclosed. Modifications and variations are possible in light of the above teachings or may be acquired from practice of the invention. Thus, it is noted that the scope of the invention is defined by the claims and their equivalents.

What is claimed is:

1. A compound of Formula I, or a pharmaceutically acceptable salt thereof,



I

wherein:

X is C_3-C_{12}carbocycle or 3- to 12-membered heterocycle, and is optionally substituted with one or more R_A;

L_1 and L_2 are each independently selected from bond; or C_1-C_6alkylene, C_2-C_6alkenylene or C_2-C_6alkynylene, each of which is independently optionally substituted at each occurrence with one or more R_L;

L_3 is bond or $-L_S-K-L_S'-$, wherein K is selected from bond, $-O-$, $-S-$, $-N(R_B)-$, $-C(O)-$, $-S(O)_2-$, $-S(O)-$, $-OS(O)-$, $-OS(O)_2-$, $-S(O)_2O-$, $-S(O)O-$, $-C(O)O-$, $-OC(O)-$, $-OC(O)O-$, $-C(O)N(R_B)-$, $-N(R_B)C(O)-$, $-N(R_B)C(O)O-$, $-OC(O)N(R_B)-$, $-N(R_B)S(O)-$, $-N(R_B)S(O)_2-$, $-S(O)N(R_B)-$, $-S(O)_2N(R_B)-$, $-C(O)N(R_B)C(O)-$, $-N(R_B)C(O)N(R_B')-$, $-N(R_B)SO_2N(R_B')-$, or $-N(R_B)S(O)N(R_B')-$;

A and B are each independently C_3-C_{12}carbocycle or 3- to 12-membered heterocycle, and are each independently optionally substituted with one or more R_A;

D is C_3-C_{12}carbocycle or 3- to 12-membered heterocycle, and is optionally substituted with one or more R_A; or D is hydrogen or R_A;

Y is selected from $-T'-C(R_1R_2)N(R_5)-T-R_D$, $-T'-C(R_3R_4)C(R_6R_7)-T-R_D$, $-L_K-T-R_D$, or $-L_K-L_E$;

R_1 and R_2 are each independently R_C, and R_5 is R_B; or R_1 is R_C, and R_2 and R_5, taken together with the atoms to which they are attached, form a 3- to 12-membered heterocycle which is optionally substituted with one or more R_A;

R_3, R_4, R_6, and R_7 are each independently R_C; or R_3 and R_6 are each independently R_C, and R_4 and R_7, taken together with the atoms to which they are attached, form a 3- to 12-membered carbocycle or heterocycle which is optionally substituted with one or more R_A;

Z is selected from $-T'-C(R_8R_9)N(R_{12})-T-R_D$, $-T'-C(R_{10}R_{11})C(R_{13}R_{14})-T-R_D$, $-L_K-T-R_D$, or $-L_K-L_E$;

R_8 and R_9 are each independently R_C, and R_{12} is R_B; or R_8 is R_C, and R_9 and R_{12}, taken together with the atoms to which they are attached, form a 3- to 12-membered heterocycle which is optionally substituted with one or more R_A;

R_{10}, R_{11}, R_{13}, and R_{14} are each independently R_C; or R_{10} and R_{13} are each independently R_C, and R_{11} and R_{14}, taken together with the atoms to which they are attached, form a 3- to 12-membered carbocycle or heterocycle which is optionally substituted with one or more R_A;

T and T" are each independently selected at each occurrence from bond, $-L_S-$, $-L_S-M-L_S'-$, or $-L_S-M-L_S'-M'-L_S''-$, wherein M and M' are each independently selected at each occurrence from bond, $-O-$, $-S-$, $-N(R_B)-$, $-C(O)-$, $-S(O)_2-$, $-S(O)-$, $-OS(O)-$, $-OS(O)_2-$, $-S(O)_2O-$, $-S(O)O-$, $-C(O)O-$, $-OC(O)-$, $-OC(O)O-$, $-C(O)N(R_B)-$, $-N(R_B)C(O)-$, $-N(R_B)C(O)O-$, $-OC(O)N(R_B)-$, $-N(R_B)S(O)-$, $-N(R_B)S(O)_2-$, $-S(O)N(R_B)-$, $-S(O)_2N(R_B)-$, $-C(O)N(R_B)C(O)-$, $-N(R_B)C(O)N(R_B')-$, $-N(R_B)SO_2N(R_B')-$, $-N(R_B)S(O)N(R_B')-$, C_3-C_{12}carbocycle or 3- to 12-membered heterocycle, and wherein said C_3-C_{12}carbocycle and 3- to 12-membered heterocycle are each independently optionally substituted at each occurrence with one or more R_A;

L_K is independently selected at each occurrence from bond, $-L_S-N(R_B)C(O)-L_S'-$ or $-L_S-C(O)N(R_B)-L_S'-$; or C_1-C_6alkylene, C_2-C_6alkenylene or C_2-C_6alkynylene, each of which is independently optionally substituted at each occurrence with one or more R_L; or C_3-C_{12}carbocycle or 3- to 12-membered heterocycle, each of which is independently optionally substituted at each occurrence with one or more R_A;

E is independently selected at each occurrence from C_3-C_{12}carbocycle or 3- to 12-membered heterocycle, and is independently optionally substituted at each occurrence with one or more R_A;

R_D is each independently selected at each occurrence from hydrogen or R_A;

R_A is independently selected at each occurrence from halogen, nitro, oxo, phosphonoxy, phosphono, thioxo, cyano, or $-L_S-R_E$, wherein two adjacent R_A, taken together with the atoms to which they are attached and any atoms between the atoms to which they are attached, can optionally form carbocycle or heterocycle;

R_B and R_B' are each independently selected at each occurrence from hydrogen; or C_1-C_6alkyl, C_2-C_6alkenyl or C_2-C_6alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano or 3- to 6-membered carbocycle or heterocycle; or 3- to 6-membered carbocycle or heterocycle; wherein each 3- to 6-membered carbocycle or heterocycle in R_B or R_B' is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6haloalkyl, C_2-C_6haloalkenyl or C_2-C_6haloalkynyl;

R_C is independently selected at each occurrence from hydrogen, halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl or cyano; or C_1-C_6alkyl, C_2-C_6alkenyl or C_2-C_6alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano or 3- to 6-membered carbocycle or heterocycle; or 3- to 6-membered carbocycle or heterocycle; wherein each 3- to 6-membered carbocycle or heterocycle in R_C is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6haloalkyl, C_2-C_6haloalkenyl or C_2-C_6haloalkynyl;

R_E is independently selected at each occurrence from $-O-R_S$, $-S-R_S$, $-C(O)R_S$, $-OC(O)R_S$, $-C(O)OR_S$, $-N(R_SR_S')$, $-S(O)R_S$, $-SO_2R_S$, $-C(O)N(R_SR_S')$, $-N(R_S)C(O)R_S'$, $-N(R_S)C(O)N(R_S'R_S'')$, $-N(R_S)SO_2R_S'$, $-SO_2N(R_SR_S')$, $-N(R_S)SO_2N(R_S'R_S'')$, $-N(R_S)S(O)N(R_S'R_S'')$, $-OS(O)-R_S$, $-OS(O)_2-R_S$, $-S(O)_2OR_S$, $-S(O)OR_S$, $-OC(O)OR_S$, $-N(R_S)C(O)OR_S'$, $-OC(O)N(R_SR_S')$, $-N(R_S)S(O)-R_S'$, $-S(O)N(R_SR_S')$ or $-C(O)N(R_S)C(O)-R_S'$; or C_1-C_6alkyl, C_2-C_6alkenyl or C_2-C_6alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl or cyano; or C_3-C_6carbocycle or 3- to 6-membered heterocycle, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6haloalkyl, C_2-C_6haloalkenyl or C_2-C_6haloalkynyl;

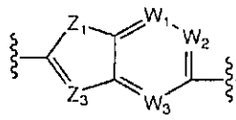
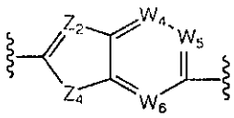
R_L is independently selected at each occurrence from halogen, nitro, oxo, phosphonoxy, phosphono, thioxo, cyano, $-O-R_S$, $-S-R_S$, $-C(O)R_S$, $-OC(O)R_S$, $-C(O)OR_S$, $-N(R_SR_S')$, $-S(O)R_S$, $-SO_2R_S$, $-C(O)N(R_SR_S')$ or $-N(R_S)C(O)R_S'$; or C_3-C_6carbocycle 3- to 6-membered heterocycle, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6haloalkyl, C_2-C_6haloalkenyl or C_2-C_6haloalkynyl;

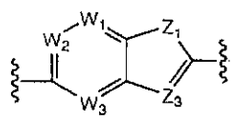
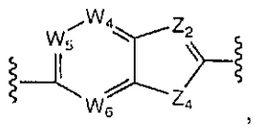
L_S, L_S' and L_S'' are each independently selected at each occurrence from bond; or C_1-C_6alkylene, C_2-C_6alkenylene or C_2-C_6alkynylene, each of which is independently optionally substituted at each occurrence with one or more R_L; and

R_S, R_S' and R_S'' are each independently selected at each occurrence from hydrogen; C_1-C_6alkyl, C_2-C_6alkenyl or C_2-C_6alkynyl, each of which is independently optionally

substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano or 3- to 6-membered carbocycle or heterocycle; or 3- to 6-membered carbocycle or heterocycle; wherein each 3- to 6-membered carbocycle or heterocycle in R_S, R_S' or R_S'' is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6haloalkyl, C_2-C_6haloalkenyl or C_2-C_6haloalkynyl.

2. The compound or salt of claim 1, wherein:

A is selected from C_5-C_6carbocycle, 5- to 6-membered heterocycle,  or  , and is optionally substituted with one or more R_A;

B is selected from C_5-C_6carbocycle, 5- to 6-membered heterocycle,  or  , and is optionally substituted with one or more R_A;

D is selected from C_5-C_6carbocycle or 5- to 6-membered heterocycle, and is optionally substituted with one or more R_A; or D is hydrogen or R_A;

Z_1 is independently selected at each occurrence from O, S, NH or CH_2;

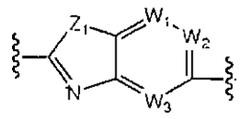
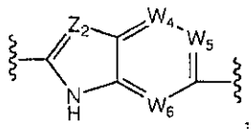
Z_2 is independently selected at each occurrence from N or CH;

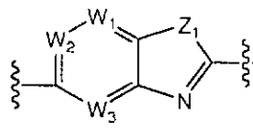
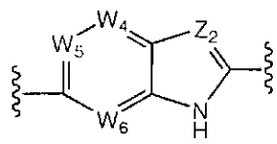
Z_3 is independently selected at each occurrence from N or CH;

Z_4 is independently selected at each occurrence from O, S, NH or CH_2; and

W_1, W_2, W_3, W_4, W_5 and W_6 are each independently selected at each occurrence from CH or N..

3. The compound or salt of claim 1, wherein:

A is selected from C_5-C_6carbocycle, 5- to 6-membered heterocycle,  or  , and is optionally substituted with one or more R_A;

B is selected from C_5-C_6carbocycle, 5- to 6-membered heterocycle,  or  , and is optionally substituted with one or more R_A;

D is selected from C_5-C_6carbocycle or 5- to 6-membered heterocycle, and is optionally substituted with one or more R_A; or D is hydrogen or R_A;

Z_1 is independently selected at each occurrence from O, S, NH or CH_2;

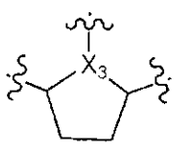
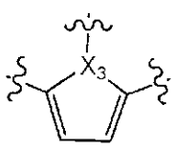
Z_2 is independently selected at each occurrence from N or CH; and

W_1, W_2, W_3, W_4, W_5 and W_6 are each independently selected at each occurrence from CH or N.

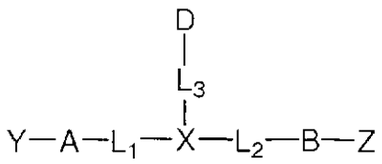
4. The compound or salt of claim 1, wherein:

A and B are each independently C_5-C_6carbocycle or 5- to 6-membered heterocycle, and are each independently optionally substituted with one or more R_A;

D is selected from C_5-C_6carbocycle or 5- to 6-membered heterocycle, and is optionally substituted with one or more R_A; and

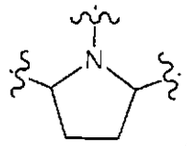
X is  or  , wherein X_3 is N and is directly linked to $-L_3-D$, and X is optionally substituted with one or more R_A, and two adjacent R_A on X, taken together with the ring atoms to which they are attached, optionally form a 5- to 6-membered carbocycle or heterocycle.

5. A compound of Formula I, or a pharmaceutically acceptable salt thereof,

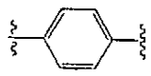


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wherein:

X is  , wherein the nitrogen ring atom is directly linked to $-L_3-D$, and wherein X is optionally substituted with one or more R_A;

L_1, L_2 and L_3 are bond;

A and B are each independently  , and are each independently optionally substituted with one or more R_A;

D is C_3-C_{12}carbocycle or 3- to 12-membered heterocycle, and is optionally substituted with one or more R_A;

Y is $-G-C(R_1R_2)N(R_5)-T-R_D$, $-G-C(R_3R_4)C(R_6R_7)-T-R_D$, $-N(R_B)C(O)C(R_1R_2)N(R_5)-T-R_D$, or $-N(R_B)C(O)C(R_3R_4)C(R_6R_7)-T-R_D$;

Z is $-G-C(R_8R_9)N(R_{12})-T-R_D$, $-G-C(R_{10}R_{11})C(R_{13}R_{14})-T-R_D$, $-N(R_B)C(O)C(R_8R_9)N(R_{12})-T-R_D$, or $-N(R_B)C(O)C(R_{10}R_{11})C(R_{13}R_{14})-T-R_D$;

R_1 is R_C, and R_2 and R_5, taken together with the atoms to which they are attached, form a 3- to 12-membered heterocycle which is optionally substituted with one or more R_A;

R_3 and R_6 are each independently R_C, and R_4 and R_7, taken together with the atoms to which they are attached, form a 3- to 12-membered carbocycle or heterocycle which is optionally substituted with one or more R_A;

R_8 is R_C, and R_9 and R_{12}, taken together with the atoms to which they are attached, form a 3- to 12-membered heterocycle which is optionally substituted with one or more R_A;

R_{10} and R_{13} are each independently R_C, and R_{11} and R_{14}, taken together with the atoms to which they are attached, form a 3- to 12-membered carbocycle or heterocycle which is optionally substituted with one or more R_A;

G is each independently C_5-C_6carbocycle or 5- to 6-membered heterocycle, and is each independently optionally substituted with one or more R_A;

T is each independently selected at each occurrence from bond, $-L_S-$, $-L_S-M-L_S'-$, or $-L_S-M-L_S'-M'-L_S''-$, wherein M and M' are each independently selected at each occurrence from bond, $-O-$, $-S-$, $-N(R_B)-$, $-C(O)-$, $-S(O)_2-$, $-S(O)-$, $-OS(O)-$, $-OS(O)_2-$, $-S(O)_2O-$, $-S(O)O-$, $-C(O)O-$, $-OC(O)-$, $-OC(O)O-$, $-C(O)N(R_B)-$, $-N(R_B)C(O)-$, $-N(R_B)C(O)O-$, $-OC(O)N(R_B)-$, $-N(R_B)S(O)-$, $-N(R_B)S(O)_2-$, $-S(O)N(R_B)-$, $-S(O)_2N(R_B)-$, $-C(O)N(R_B)C(O)-$, $-N(R_B)C(O)N(R_B')-$, $-N(R_B)SO_2N(R_B')-$, $-N(R_B)S(O)N(R_B')-$, C_3-C_{12}carbocycle or 3- to 12-membered heterocycle, and wherein

said C_3-C_{12}carbocycle and 3- to 12-membered heterocycle are each independently optionally substituted at each occurrence with one or more R_A;

R_D is each independently selected at each occurrence from hydrogen or R_A;

R_A is independently selected at each occurrence from halogen, nitro, oxo, phosphonoxy, phosphono, thioxo, cyano, or $-L_S-R_E$;

R_B and R_B' are each independently selected at each occurrence from hydrogen; or C_1-C_6alkyl, C_2-C_6alkenyl or C_2-C_6alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano or 3- to 6-membered carbocycle or heterocycle; or 3- to 6-membered carbocycle or heterocycle; wherein each 3- to 6-membered carbocycle or heterocycle in R_B or R_B' is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6haloalkyl, C_2-C_6haloalkenyl or C_2-C_6haloalkynyl;

R_C is independently selected at each occurrence from hydrogen, halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl or cyano; or C_1-C_6alkyl, C_2-C_6alkenyl or C_2-C_6alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano or 3- to 6-membered carbocycle or heterocycle; or 3- to 6-membered carbocycle or heterocycle; wherein each 3- to 6-membered carbocycle or heterocycle in R_C is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6haloalkyl, C_2-C_6haloalkenyl or C_2-C_6haloalkynyl;

R_E is independently selected at each occurrence from $-O-R_S$, $-S-R_S$, $-C(O)R_S$, $-OC(O)R_S$, $-C(O)OR_S$, $-N(R_SR_S')$, $-S(O)R_S$, $-SO_2R_S$, $-C(O)N(R_SR_S')$, $-N(R_S)C(O)R_S'$, $-N(R_S)C(O)N(R_S'R_S'')$, $-N(R_S)SO_2R_S'$, $-SO_2N(R_SR_S')$, $-N(R_S)SO_2N(R_S'R_S'')$, $-N(R_S)S(O)N(R_S'R_S'')$, $-OS(O)-R_S$, $-OS(O)_2-R_S$, $-S(O)_2OR_S$, $-S(O)OR_S$, $-OC(O)OR_S$, $-N(R_S)C(O)OR_S'$, $-OC(O)N(R_SR_S')$, $-N(R_S)S(O)-R_S'$, $-S(O)N(R_SR_S')$ or $-C(O)N(R_S)C(O)-R_S'$; or C_1-C_6alkyl, C_2-C_6alkenyl or C_2-C_6alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl or cyano; or C_3-C_6carbocycle or 3- to 6-membered heterocycle, each of which is independently optionally substituted at each occurrence

with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6haloalkyl, C_2-C_6haloalkenyl or C_2-C_6haloalkynyl;

R_L is independently selected at each occurrence from halogen, nitro, oxo, phosphonoxy, phosphono, thioxo, cyano, –O–R_S, –S–R_S, –C(O)R_S, –OC(O)R_S, –C(O)OR_S, –N($R_S$$R_S$'), –S(O)$R_S$, –$SO_2$$R_S$, –C(O)N($R_S$$R_S$') or –N($R_S$)C(O)$R_S$'; or C_3-C_6carbocycle 3- to 6-membered heterocycle, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6haloalkyl, C_2-C_6haloalkenyl or C_2-C_6haloalkynyl;

L_S, L_S' and L_S'' are each independently selected at each occurrence from bond; or C_1-C_6alkylene, C_2-C_6alkenylene or C_2-C_6alkynylene, each of which is independently optionally substituted at each occurrence with one or more R_L; and

R_S, R_S' and R_S'' are each independently selected at each occurrence from hydrogen; C_1-C_6alkyl, C_2-C_6alkenyl or C_2-C_6alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano or 3- to 6-membered carbocycle or heterocycle; or 3- to 6-membered carbocycle or heterocycle; wherein each 3- to 6-membered carbocycle or heterocycle in R_S , R_S' or R_S' is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6haloalkyl, C_2-C_6haloalkenyl or C_2-C_6haloalkynyl.

6. The compound or salt of claim 5, wherein:

T is independently selected at each occurrence from –C(O)–L_S'–M'–L_S''– or –N(R_B)C(O)–L_S'–M'–L_S''–; and

L_S' is each independently C_1-C_6alkylene, and is independently optionally substituted at each occurrence with one or more R_L.

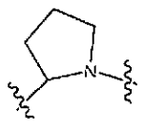
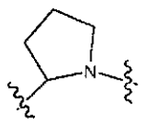
7. The compound or salt of claim 5, wherein:

Y is –N(R_B)C(O)C($R_1$$R_2$)N($R_5$)–T–$R_D$;

Z is –N(R_B)C(O)C($R_8$$R_9$)N($R_{12}$)–T–$R_D$;

T is independently selected at each occurrence from –C(O)–L_S'–M'–L_S''–; and

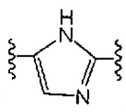
D is C_5-C_6carbocycle, 5- to 6-membered heterocycle, or 6- to 10-membered bicycles, and is substituted with one or more R_A.

8. The compound or salt of claim 7, wherein T is independently selected at each occurrence from –C(O)–L_S'–N(R_B)C(O)–L_S''– or –C(O)–L_S'–N(R_B)C(O)O–L_S''–; and R_2 and R_5, taken together with the atoms to which they are attached, form  which is optionally substituted with one or more R_A; and R_9 and R_{12}, taken together with the atoms to which they are attached, form  which is optionally substituted with one or more R_A.

9. The compound or salt of claim 5, wherein:

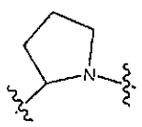
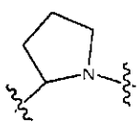
Y is –G–C(R_1R_2)N(R_5)–T–R_D;

Z is –G–C(R_8R_9)N(R_{12})–T–R_D;

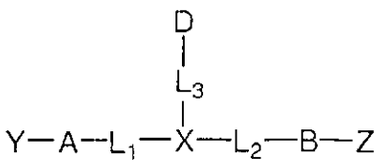
G is each independently  , and is each independently optionally substituted with one or more R_A;

T is independently selected at each occurrence from –C(O)–L_S'–M'–L_S''–; and

D is C_5-C_6carbocycle, 5- to 6-membered heterocycle, or 6- to 10-membered bicycles, and is substituted with one or more R_A.

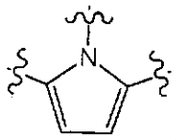
10. The compound or salt of claim 9, wherein T is independently selected at each occurrence from –C(O)–L_S'–N(R_B)C(O)–L_S''– or –C(O)–L_S'–N(R_B)C(O)O–L_S''–; and R_2 and R_5, taken together with the atoms to which they are attached, form  which is optionally substituted with one or more R_A; and R_9 and R_{12}, taken together with the atoms to which they are attached, form  which is optionally substituted with one or more R_A.

11. A compound of Formula I, or a pharmaceutically acceptable salt thereof,

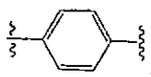


I

wherein:

X is  , wherein the nitrogen ring atom is directly linked to $-L_3-D$, and wherein X is optionally substituted with one or more R_A;

L_1, L_2 and L_3 are bond;

A and B are each independently  , and are each independently optionally substituted with one or more R_A;

D is C_3-C_{12}carbocycle or 3- to 12-membered heterocycle, and is optionally substituted with one or more R_A;

Y is $-G-C(R_1R_2)N(R_5)-T-R_D$, $-G-C(R_3R_4)C(R_6R_7)-T-R_D$, $-N(R_B)C(O)C(R_1R_2)N(R_5)-T-R_D$, or $-N(R_B)C(O)C(R_3R_4)C(R_6R_7)-T-R_D$;

Z is $-G-C(R_8R_9)N(R_{12})-T-R_D$, $-G-C(R_{10}R_{11})C(R_{13}R_{14})-T-R_D$, $-N(R_B)C(O)C(R_8R_9)N(R_{12})-T-R_D$, or $-N(R_B)C(O)C(R_{10}R_{11})C(R_{13}R_{14})-T-R_D$;

R_1 is R_C, and R_2 and R_5, taken together with the atoms to which they are attached, form a 3- to 12-membered heterocycle which is optionally substituted with one or more R_A;

R_3 and R_6 are each independently R_C, and R_4 and R_7, taken together with the atoms to which they are attached, form a 3- to 12-membered carbocycle or heterocycle which is optionally substituted with one or more R_A;

R_8 is R_C, and R_9 and R_{12}, taken together with the atoms to which they are attached, form a 3- to 12-membered heterocycle which is optionally substituted with one or more R_A;

R_{10} and R_{13} are each independently R_C, and R_{11} and R_{14}, taken together with the atoms to which they are attached, form a 3- to 12-membered carbocycle or heterocycle which is optionally substituted with one or more R_A;

G is each independently C_5-C_6carbocycle or 5- to 6-membered heterocycle, and is each independently optionally substituted with one or more R_A;

T is each independently selected at each occurrence from bond, $-L_S-$, $-L_S-M-L_S'-$, or $-L_S-M-L_S'-M'-L_S''-$, wherein M and M' are each independently selected at each occurrence from bond, $-O-$, $-S-$, $-N(R_B)-$, $-C(O)-$, $-S(O)_2-$, $-S(O)-$, $-OS(O)-$, $-OS(O)_2-$, $-S(O)_2O-$, $-S(O)O-$, $-C(O)O-$, $-OC(O)-$, $-OC(O)O-$, $-C(O)N(R_B)-$, $-N(R_B)C(O)-$, $-N(R_B)C(O)O-$, $-OC(O)N(R_B)-$, $-N(R_B)S(O)-$, $-N(R_B)S(O)_2-$, $-S(O)N(R_B)-$, $-S(O)_2N(R_B)-$, $-C(O)N(R_B)C(O)-$, $-N(R_B)C(O)N(R_B')-$, $-N(R_B)SO_2N(R_B')-$, $-N(R_B)S(O)N(R_B')-$, C_3-C_{12}carbocycle or 3- to 12-membered heterocycle, and wherein

said C_3-C_{12}carbocycle and 3- to 12-membered heterocycle are each independently optionally substituted at each occurrence with one or more R_A;

R_D is each independently selected at each occurrence from hydrogen or R_A;

R_A is independently selected at each occurrence from halogen, nitro, oxo, phosphonoxy, phosphono, thioxo, cyano, or $-L_S-R_E$;

R_B and R_B' are each independently selected at each occurrence from hydrogen; or C_1-C_6alkyl, C_2-C_6alkenyl or C_2-C_6alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano or 3- to 6-membered carbocycle or heterocycle; or 3- to 6-membered carbocycle or heterocycle; wherein each 3- to 6-membered carbocycle or heterocycle in R_B or R_B' is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6haloalkyl, C_2-C_6haloalkenyl or C_2-C_6haloalkynyl;

R_C is independently selected at each occurrence from hydrogen, halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl or cyano; or C_1-C_6alkyl, C_2-C_6alkenyl or C_2-C_6alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano or 3- to 6-membered carbocycle or heterocycle; or 3- to 6-membered carbocycle or heterocycle; wherein each 3- to 6-membered carbocycle or heterocycle in R_C is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6haloalkyl, C_2-C_6haloalkenyl or C_2-C_6haloalkynyl;

R_E is independently selected at each occurrence from $-O-R_S$, $-S-R_S$, $-C(O)R_S$, $-OC(O)R_S$, $-C(O)OR_S$, $-N(R_SR_S')$, $-S(O)R_S$, $-SO_2R_S$, $-C(O)N(R_SR_S')$, $-N(R_S)C(O)R_S'$, $-N(R_S)C(O)N(R_S'R_S'')$, $-N(R_S)SO_2R_S'$, $-SO_2N(R_SR_S')$, $-N(R_S)SO_2N(R_S'R_S'')$, $-N(R_S)S(O)N(R_S'R_S'')$, $-OS(O)-R_S$, $-OS(O)_2-R_S$, $-S(O)_2OR_S$, $-S(O)OR_S$, $-OC(O)OR_S$, $-N(R_S)C(O)OR_S'$, $-OC(O)N(R_SR_S')$, $-N(R_S)S(O)-R_S'$, $-S(O)N(R_SR_S')$ or $-C(O)N(R_S)C(O)-R_S'$; or C_1-C_6alkyl, C_2-C_6alkenyl or C_2-C_6alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl or cyano; or C_3-C_6carbocycle or 3- to 6-membered heterocycle, each of which is independently optionally substituted at each occurrence

with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6haloalkyl, C_2-C_6haloalkenyl or C_2-C_6haloalkynyl;

R_L is independently selected at each occurrence from halogen, nitro, oxo, phosphonoxy, phosphono, thioxo, cyano, –O–R_S, –S–R_S, –C(O)R_S, –OC(O)R_S, –C(O)OR_S, –N($R_S$$R_S$'), –S(O)$R_S$, –$SO_2$$R_S$, –C(O)N($R_S$$R_S$') or –N($R_S$)C(O)$R_S$'; or C_3-C_6carbocycle 3- to 6-membered heterocycle, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6haloalkyl, C_2-C_6haloalkenyl or C_2-C_6haloalkynyl;

L_S, L_S' and L_S'' are each independently selected at each occurrence from bond; or C_1-C_6alkylene, C_2-C_6alkenylene or C_2-C_6alkynylene, each of which is independently optionally substituted at each occurrence with one or more R_L; and

R_S, R_S' and R_S'' are each independently selected at each occurrence from hydrogen; C_1-C_6alkyl, C_2-C_6alkenyl or C_2-C_6alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano or 3- to 6-membered carbocycle or heterocycle; or 3- to 6-membered carbocycle or heterocycle; wherein each 3- to 6-membered carbocycle or heterocycle in R_S , R_S' or R_S' is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6haloalkyl, C_2-C_6haloalkenyl or C_2-C_6haloalkynyl.

12. The compound or salt of claim 11, wherein:

T is independently selected at each occurrence from –C(O)–L_S'–M'–L_S''– or –N(R_B)C(O)–L_S'–M'–L_S''–; and

L_S' is each independently C_1-C_6alkylene, and is independently optionally substituted at each occurrence with one or more R_L.

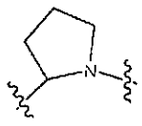
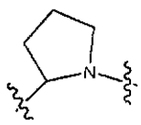
13. The compound or salt of claim 11, wherein:

Y is –N(R_B)C(O)C($R_1$$R_2$)N($R_5$)–T–$R_D$;

Z is –N(R_B)C(O)C($R_8$$R_9$)N($R_{12}$)–T–$R_D$;

T is independently selected at each occurrence from –C(O)–L_S'–M'–L_S''–; and

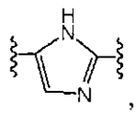
D is C_5-C_6carbocycle, 5- to 6-membered heterocycle, or 6- to 10-membered bicycles, and is substituted with one or more R_A.

14. The compound or salt of claim 13, wherein T is independently selected at each occurrence from $-C(O)-L_S'-N(R_B)C(O)-L_S''-$ or $-C(O)-L_S'-N(R_B)C(O)O-L_S''-$; and R_2 and R_5, taken together with the atoms to which they are attached, form  which is optionally substituted with one or more R_A; and R_9 and R_{12}, taken together with the atoms to which they are attached, form  which is optionally substituted with one or more R_A.

15. The compound or salt of claim 11, wherein:

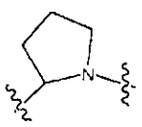
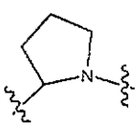
Y is $-G-C(R_1R_2)N(R_5)-T-R_D$;

Z is $-G-C(R_8R_9)N(R_{12})-T-R_D$;

G is each independently selected at each occurrence  , and is each independently optionally substituted with one or more R_A;

T is independently selected at each occurrence from $-C(O)-L_S'-M'-L_S''-$; and

D is C_5-C_6carbocycle, 5- to 6-membered heterocycle, or 6- to 10-membered bicycles, and is substituted with one or more R_A.

16. The compound or salt of claim 15, wherein T is independently selected at each occurrence from $-C(O)-L_S'-N(R_B)C(O)-L_S''-$ or $-C(O)-L_S'-N(R_B)C(O)O-L_S''-$; and R_2 and R_5, taken together with the atoms to which they are attached, form  which is optionally substituted with one or more R_A; and R_9 and R_{12}, taken together with the atoms to which they are attached, form  which is optionally substituted with one or more R_A.

17. A pharmaceutical composition comprising a compound or salt according to claim 1.

18. A pharmaceutical composition comprising a compound or salt according to claim 1 and another anti-HCV agent.

19. A method of treating HCV infection, comprising administering to an HCV patient a compound or salt according to claim 1.

20. A process of making a compound according to claim 1, comprising a step described in one of the schemes or examples described hereinabove.

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Act. 411 PRESENTACION Folios: 872
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SOLICITUD DE

PATENTE DE INVENCION
PCT ENTRADA EN FASE NACIONAL

(II PARTE)

21. EXPEDIENTE No. 11-38996

54. TITULO: **COMPUESTOS ANTIVIRALES**

52. CLASIFICACION INTERNACIONAL: **C07D 403/14**

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COMPUESTOS ANTIVIRALES

La presente solicitud invoca el beneficio e incorpora a modo de referencia el contenido completo de la Solicitud Provisional de Patente de los EE.UU. N° Acta: 61/186.291, presentada el 11 de junio, 2009, Solicitud Provisional de Patente de los EE.UU. N° Acta: 61/242.836, presentada el 16 de septiembre, 2009, y la Solicitud Provisional de Patente de los EE.UU. N° Acta: 61/243.596, presentada el 18 de septiembre, 2009.

CAMPO

La presente invención se relaciona con compuestos eficaces para inhibir la replicación del virus de la hepatitis C ("HCV"). La presente invención también se relaciona con composiciones que comprenden estos compuestos y con métodos de uso de estos compuestos para tratar una infección por HCV.

ANTECEDENTES

El HCV es un virus a ARN que pertenece al género Hepacivirus en la familia Flaviviridae. El virión del HCV con envoltura contiene un genoma de ARN de cadena positiva que codifica todas las proteínas específicas de virus conocidas en un solo marco de lectura abierto, no interrumpido. El marco de lectura abierto comprende aproximadamente 9500 nucleótidos y codifica una sola gran poliproteína de 3000 aminoácidos aproximadamente. La poliproteína comprende una proteína nuclear, las proteínas de la envoltura E1 y E2, una proteína p7 unida a membrana y las proteínas no estructurales NS2, NS3, NS4A, NS4B, NS5A y NS5B.

La infección por HCV está asociada con una patología hepática progresiva, incluyendo cirrosis y carcinoma hepatocelular. La hepatitis C crónica puede ser tratada con PEG-interferón-alfa en combinación con ribavirina. Las limitaciones sustanciales de eficacia y tolerabilidad persisten ya que muchos usuarios sufren de efectos secundarios, y la eliminación viral del cuerpo es muy a menudo inadecuada. Por ello, persiste la necesidad de nuevas drogas para tratar una infección por HCV.

RESUMEN

La presente invención está dirigida a compuestos de las fórmulas I, I_A, I_B, I_C y I_D y sales farmacéuticamente aceptables de los mismos. Estos compuestos y las sales pueden inhibir la replicación del HCV y por ello son de utilidad para el tratamiento de una infección por HCV.

La presente invención también está dirigida a composiciones que comprenden los compuestos o las sales de la presente invención. Las composiciones también pueden incluir agentes terapéuticos adicionales, tales como inhibidores de helicasa del HCV, inhibidores de polimerasa del HCV, inhibidores de proteasa del HCV, inhibidores de NS5A

del HCV, inhibidores de CD81, inhibidores de ciclofilina o inhibidores del sitio interno de entrada a ribosomas (IRES).

La presente invención está dirigida además a métodos de uso de los compuestos o las sales de la presente invención para inhibir la replicación del HCV. Los métodos comprenden el contacto de células infectadas con el virus del HCV con un compuesto o una sal de la presente invención, inhibiendo de esa manera la replicación del virus del HCV en las células.

Además, la presente invención está dirigida a métodos de uso de los compuestos o sales de la presente invención, o de composiciones que comprenden a los mismos, para tratar una infección por HCV. Los métodos comprenden administrar un compuesto o una sal de la presente invención, o una composición farmacéutica que comprende al mismo, a un paciente que lo necesita, reduciendo de esa manera el nivel en sangre o tejidos del virus del HCV en el paciente.

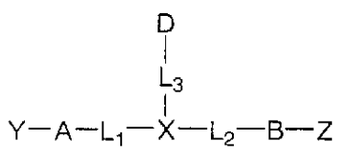
La presente invención también está dirigida al uso de los compuestos o sales de la presente invención en la elaboración de medicamentos para el tratamiento de una infección por HCV.

Además, la presente invención está dirigida a procesos de elaboración de los compuestos o las sales de la invención.

Otras características, objetos y ventajas de la presente invención resultarán evidentes a partir de la siguiente descripción detallada. Sin embargo, se debe tener en cuenta que la descripción detallada, si bien indica las realizaciones preferidas de la invención, solamente se ofrece a modo ilustrativo, no en un sentido limitativo. Los diversos cambios y modificaciones que se pueden efectuar dentro del alcance de la invención resultarán evidentes para los especialistas en la técnica a partir de la descripción detallada.

DESCRIPCIÓN DETALLADA

La presente invención se refiere a compuestos de fórmula I, y sus sales farmacéuticamente aceptables,



I

donde:

X es carbociclo de C_3-C_{12} o heterociclo de 3 a 12 miembros, y está opcionalmente sustituido con uno o más R_A;

L_1 y L_2 se seleccionan en forma independiente entre sí entre una unión; o alquileno de C_1-C_6, alquenileno de C_2-C_6 o alquinileno de C_2-C_6, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más R_L;

L_3 es una unión o $-L_S-K-L_S'-$, donde K se selecciona entre una unión, $-O-$, $-S-$, $-N(R_B)-$, $-C(O)-$, $-S(O)_2-$, $-S(O)-$, $-OS(O)-$, $-OS(O)_2-$, $-S(O)_2O-$, $-S(O)O-$, $-C(O)O-$, $-OC(O)-$, $-OC(O)O-$, $-C(O)N(R_B)-$, $-N(R_B)C(O)-$, $-N(R_B)C(O)O-$, $-OC(O)N(R_B)-$, $-N(R_B)S(O)-$, $-N(R_B)S(O)_2-$, $-S(O)N(R_B)-$, $-S(O)_2N(R_B)-$, $-C(O)N(R_B)C(O)-$, $-N(R_B)C(O)N(R_B')-$, $-N(R_B)SO_2N(R_B')-$, o $-N(R_B)S(O)N(R_B')-$;

A y B son en forma independiente entre sí carbociclo de C_3-C_{12} o heterociclo de 3 a 12 miembros, y están sustituidos en forma independiente entre sí con uno o más R_A;

D es carbociclo de C_3-C_{12} o heterociclo de 3 a 12 miembros, y está opcionalmente sustituido con uno o más R_A; o D es hidrógeno o R_A;

Y se selecciona entre $-T'-C(R_1R_2)N(R_5)-T-R_D$, $-T'-C(R_3R_4)C(R_6R_7)-T-R_D$, $-L_K-T-R_D$, o $-L_K-E$;

R_1 y R_2 son en forma independiente entre sí R_C, y R_5 es R_B; o R_1 es R_C, y R_2 y R_5, tomados junto con los átomos a los cuales están unidos, forman un heterociclo de 3 a 12 miembros que está opcionalmente sustituido con uno o más R_A;

R_3, R_4, R_6, y R_7 son en forma independiente entre sí R_C; o R_3 y R_6 son en forma independiente entre sí R_C, y R_4 y R_7, tomados junto con los átomos a los cuales están unidos, forman un carbociclo o heterociclo de 3 a 12 miembros que está opcionalmente sustituido con uno o más R_A;

Z se selecciona entre $-T'-C(R_8R_9)N(R_{12})-T-R_D$, $-T'-C(R_{10}R_{11})C(R_{13}R_{14})-T-R_D$, $-L_K-T-R_D$, o $-L_K-E$;

R_8 y R_9 son en forma independiente entre sí R_C, y R_{12} es R_B; o R_8 es R_C, y R_9 y R_{12}, tomados junto con los átomos a los cuales están unidos, forman un heterociclo de 3 a 12 miembros que está opcionalmente sustituido con uno o más R_A;

R_{10}, R_{11}, R_{13}, y R_{14} son en forma independiente entre sí R_C; o R_{10} y R_{13} son en forma independiente entre sí R_C, y R_{11} y R_{14}, tomados junto con los átomos a los cuales están unidos, forman un carbociclo o heterociclo de 3 a 12 miembros que está opcionalmente sustituido con uno o más R_A;

T y T' se seleccionan en forma independiente entre sí entre una unión, $-L_S-$, $-L_S-M-L_S'-$, o $-L_S-M-L_S'-M'-L_S''-$, donde M y M' se seleccionan en forma independiente entre sí entre una unión, $-O-$, $-S-$, $-N(R_B)-$, $-C(O)-$, $-S(O)_2-$, $-S(O)-$, $-OS(O)-$, $-OS(O)_2-$, $-S(O)_2O-$, $-S(O)O-$, $-C(O)O-$, $-OC(O)-$, $-OC(O)O-$, $-C(O)N(R_B)-$, $-N(R_B)C(O)-$, $-N(R_B)C(O)O-$, $-OC(O)N(R_B)-$, $-N(R_B)S(O)-$, $-N(R_B)S(O)_2-$, $-S(O)N(R_B)-$, $-S(O)_2N(R_B)-$, $-C(O)N(R_B)C(O)-$, $-N(R_B)C(O)N(R_B')-$, $-N(R_B)SO_2N(R_B')-$, $-N(R_B)S(O)N(R_B')-$, carbociclo

de C_3-C_{12} o heterociclo de 3 a 12 miembros, y donde dicho carbociclo de C_3-C_{12} y heterociclo de 3 a 12 miembros están opcionalmente sustituidos en forma independiente entre sí en cada caso con uno o más R_A;

L_K se seleccionan en forma independiente en cada caso entre una unión , $-L_S-N(R_B)C(O)-L_S'-$ o $-L_S-C(O)N(R_B)-L_S'-$; o alquileno de C_1-C_6, alquenileno de C_2-C_6 o alquinileno de C_2-C_6, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más R_L; o carbociclo de C_3-C_{12} o heterociclo de 3 a 12 miembros, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más R_A;

E se selecciona en forma independiente en cada caso en cada caso entre carbociclo de C_3-C_{12} o heterociclo de 3 a 12 miembros, y está opcionalmente sustituido en forma independiente en cada caso con uno o más R_A;

R_D se selecciona cada uno en forma independiente en cada caso entre hidrógeno o R_A;

R_A se selecciona en forma independiente en cada caso en cada caso entre halógeno, nitro, oxo, fosfonoxi, fosfono, tioxo, ciano, o $-L_S-R_E$, donde dos R_A adyacentes, tomados junto con los átomos a los cuales están unidos y cualesquier átomos entre los átomos a los cuales están unidos, pueden formar opcionalmente carbociclo o heterociclo;

R_B y R_B' se seleccionan en forma independiente entre sí en cada caso entre hidrógeno; o alquilo de C_1-C_6, alquenilo de C_2-C_6 o alquinilo de C_2-C_6, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano o carbociclo o heterociclo de 3 a 6 miembros; o carbociclo o heterociclo de 3 a 6 miembros; donde cada carbociclo o heterociclo de 3 a 6 miembros en R_B o R_B' está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, alquilo de C_1-C_6, alquenilo de C_2-C_6, alquinilo de C_2-C_6, haloalquilo de C_1-C_6, haloalquenilo de C_2-C_6 o haloalquinilo de C_2-C_6;

R_C se selecciona en forma independiente en cada caso en cada caso entre hidrógeno, halógeno, hidroxilo, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo o ciano; o alquilo de C_1-C_6, alquenilo de C_2-C_6 o alquinilo de C_2-C_6, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano o carbociclo o heterociclo de 3 a 6 miembros; o carbociclo o heterociclo de 3 a 6 miembros; donde cada carbociclo o heterociclo de 3 a 6 miembros en R_C está opcionalmente sustituido en forma independiente en cada caso

con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, alquilo de C_1-C_6, alquenilo de C_2-C_6, alquinilo de C_2-C_6, haloalquilo de C_1-C_6, haloalquenilo de C_2-C_6 o haloalquinilo de C_2-C_6;

R_E se selecciona en forma independiente en cada caso entre $-O-R_S$, $-S-R_S$, $-C(O)R_S$, $-OC(O)R_S$, $-C(O)OR_S$, $-N(R_SR_S')$, $-S(O)R_S$, $-SO_2R_S$, $-C(O)N(R_SR_S')$, $-N(R_S)C(O)R_S'$, $-N(R_S)C(O)N(R_S'R_S'')$, $-N(R_S)SO_2R_S'$, $-SO_2N(R_SR_S')$, $-N(R_S)SO_2N(R_S'R_S'')$, $-N(R_S)S(O)N(R_S'R_S'')$, $-OS(O)-R_S$, $-OS(O)_2-R_S$, $-S(O)_2OR_S$, $-S(O)OR_S$, $-OC(O)OR_S$, $-N(R_S)C(O)OR_S'$, $-OC(O)N(R_SR_S')$, $-N(R_S)S(O)-R_S'$, $-S(O)N(R_SR_S')$ o $-C(O)N(R_S)C(O)-R_S'$; o alquilo de C_1-C_6, alquenilo de C_2-C_6 o alquinilo de C_2-C_6, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo o ciano; o carbociclo de C_3-C_6 o heterociclo de 3 a 6 miembros, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, alquilo de C_1-C_6, alquenilo de C_2-C_6, alquinilo de C_2-C_6, haloalquilo de C_1-C_6, haloalquenilo de C_2-C_6 o haloalquinilo de C_2-C_6;

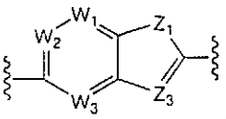
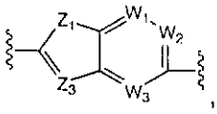
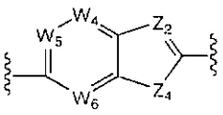
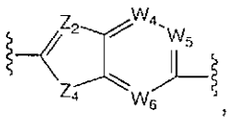
R_L se selecciona en forma independiente en cada caso en cada caso entre halógeno, nitro, oxo, fosfonoxi, fosfono, tioxo, ciano, $-O-R_S$, $-S-R_S$, $-C(O)R_S$, $-OC(O)R_S$, $-C(O)OR_S$, $-N(R_SR_S')$, $-S(O)R_S$, $-SO_2R_S$, $-C(O)N(R_SR_S')$ o $-N(R_S)C(O)R_S'$; o carbociclo de C_3-C_6 heterociclo de 3 a 6 miembros, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, alquilo de C_1-C_6, alquenilo de C_2-C_6, alquinilo de C_2-C_6, haloalquilo de C_1-C_6, haloalquenilo de C_2-C_6 o haloalquinilo de C_2-C_6; donde dos R_L adyacentes, tomados junto con los átomos a los cuales están unidos y cualesquier átomos entre los átomos a los cuales están unidos, pueden formar opcionalmente carbociclo o heterociclo;

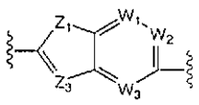
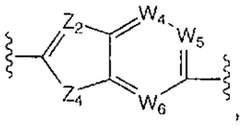
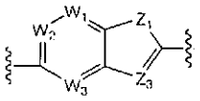
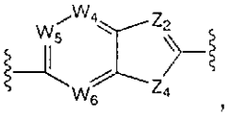
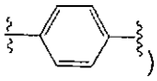
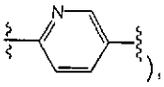
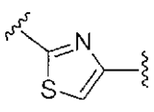
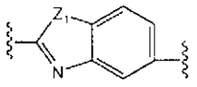
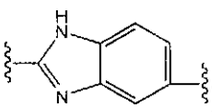
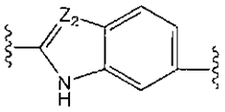
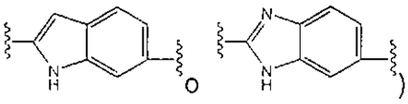
L_S, L_S' y L_S'' se seleccionan en forma independiente entre sí entre una unión; o alquileno de C_1-C_6, alquenileno de C_2-C_6 o alquinileno de C_2-C_6, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más R_L; y

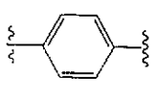
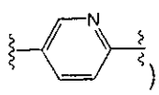
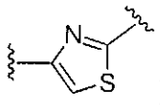
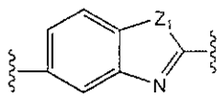
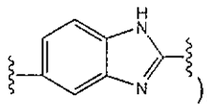
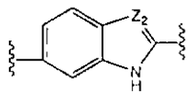
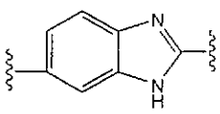
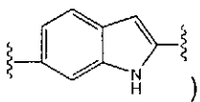
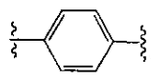
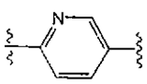
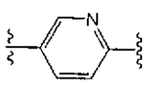
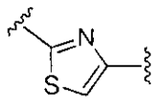
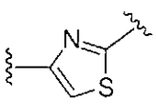
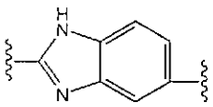
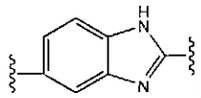
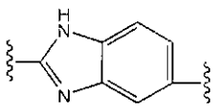
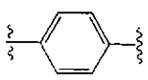
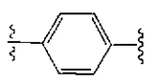
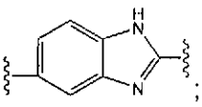
R_S, R_S' y R_S'' se seleccionan en forma independiente entre sí en cada caso entre hidrógeno; alquilo de C_1-C_6, alquenilo de C_2-C_6 o alquinilo de C_2-C_6, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, mercapto, amino, carboxi,

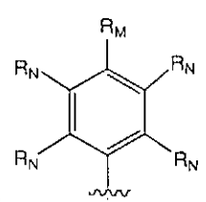
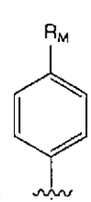
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nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano o carbociclo o heterociclo de 3 a 6 miembros; o carbociclo o heterociclo de 3 a 6 miembros; donde cada carbociclo o heterociclo de 3 a 6 miembros en R_S , R_S' o R_S' está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, alquilo de C_1-C_6, alquenilo de C_2-C_6, alquinilo de C_2-C_6, haloalquilo de C_1-C_6, haloalquenilo de C_2-C_6 o haloalquinilo de C_2-C_6.

A y B preferentemente se seleccionan en forma independiente entre carbociclo de C_5-C_6 (por ejemplo, fenilo), heterociclo de 5 a 6 miembros (por ejemplo, piridinilo o tiazolilo), o biciclos de 8 a 12 miembros tal como  ,  ,  o  , donde Z_1 se selecciona en forma independiente en cada caso entre O, S, NH o CH_2, Z_2 se selecciona en forma independiente en cada caso entre N o CH, Z_3 se selecciona en forma independiente en cada caso entre N o CH, Z_4 se selecciona en forma independiente en cada caso entre O, S, NH o CH_2, y W_1, W_2, W_3, W_4, W_5 y W_6 se seleccionan en forma independiente entre sí en cada caso entre CH o N. A y B están sustituidos en forma independiente entre sí con uno o más R_A.

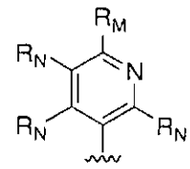
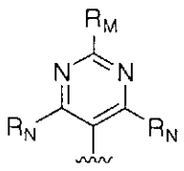
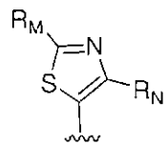
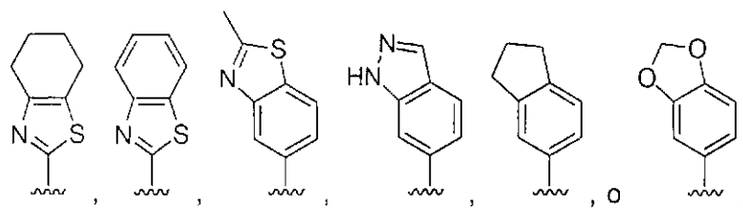
Más preferentemente, A se selecciona entre C_5-C_6carbociclo, heterociclo de 5 a 6 miembros,  o  , y está opcionalmente sustituido con uno o más R_A; B se selecciona entre C_5-C_6carbociclo, heterociclo de 5 a 6 miembros,  o  , y está opcionalmente sustituido con uno o más R_A; donde Z_1, Z_2, Z_3, Z_4, W_1, W_2, W_3, W_4, W_5, W_6 tienen los valores que se definen precedentemente. Preferentemente, Z_3 es N y Z_4 es NH. Por ejemplo, A se puede seleccionar entre fenilo (por ejemplo, ), piridinilo (por ejemplo, ), tiazolilo (por ejemplo, ),  (por ejemplo, ), o  (por ejemplo, ), y está opcionalmente

sustituido con uno o más R_A; y B se puede seleccionar entre fenilo (por ejemplo, ), piridinilo (por ejemplo, ), tiazolilo (por ejemplo, ),  (por ejemplo, ), o  (por ejemplo,  o ), y está opcionalmente sustituido con uno o más R_A. Con gran preferencia, ambos A y B son fenilo (por ejemplo, ambos A y B son ). También con gran preferencia, A es  y B es  ; o A es  y B es  ; o A es  y B es  ; o A es  y B es  ; o A es  y B es  ; donde cada A y B es en forma independiente opcionalmente sustituido con uno o más R_A.

D preferentemente se selecciona entre C_5-C_6carbociclo, heterociclo de 5 a 6 miembros, o biciclos de 6 a 12 miembros, y está opcionalmente sustituido con uno o más R_A. D también se puede seleccionar preferentemente entre alquilo de C_1-C_6, alquenilo de C_2-C_6 o alquinilo de C_2-C_6, y está opcionalmente sustituido con uno o más sustituyentes seleccionados entre R_L. Más preferentemente, D es carbociclo de C_5-C_6 (por ejemplo, fenilo), heterociclo de 5 a 6 miembros (por ejemplo, piridinilo, pirimidinilo, tiazolilo), biciclos de 6 a 12 miembros (por ejemplo, indanilo, 4,5,6,7-tetrahidrobenzo[d]tiazolilo, benzo[d]tiazolilo, indazolilo, benzo[d][1,3]dioxol-5-ilo), y se sustituye con uno o más R_M, donde R_M es halógeno, nitro, oxo, fosfonoxi, fosfono, tioxo, ciano, o $-L_S-R_E$. También preferentemente, D es fenilo, y está opcionalmente sustituido con uno o más R_A. Más preferentemente, D es fenilo, y se sustituye con uno o más R_M, donde R_M tiene los valores que se definen precedentemente. Con gran preferencia, D es  o  , donde R_M tiene los valores que se definen precedentemente, y cada R_N se selecciona en

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forma independiente entre R_D y preferentemente es hidrógeno.

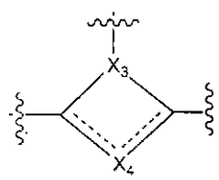
D es también preferentemente piridinilo, pirimidinilo, o tiazolilo, opcionalmente sustituido con uno o más R_A. Más preferentemente D es piridinilo, pirimidinilo, o tiazolilo, y se sustituye con uno o más R_M. Con gran preferencia, D es  ,  , o  , donde R_M tiene los valores que se definen precedentemente, y cada R_N se selecciona en forma independiente entre R_D y preferentemente es hidrógeno. D es también preferentemente indanilo, 4,5,6,7-tetrahidrobenzo[d]tiazolilo, benzo[d]tiazolilo, o indazolilo, y está opcionalmente sustituido con uno o más R_A. Más preferentemente D es indanilo, 4,5,6,7-tetrahidrobenzo[d]tiazolilo, benzo[d]tiazolilo, indazolilo, o benzo[d][1,3]dioxol-5-ilo, y se sustituye con uno o más R_M. Con gran preferencia, D es  , y está opcionalmente sustituido con uno o más R_M.

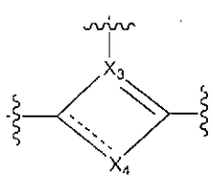
Preferentemente, R_M es halógeno, hidroxilo, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, ciano; o alquilo de C_1-C_6, alquenilo de C_2-C_6 o alquinilo de C_2-C_6, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo o ciano; o carbociclo de C_3-C_6 o heterociclo de 3 a 6 miembros, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, alquilo de C_1-C_6, alquenilo de C_2-C_6, alquinilo de C_2-C_6, haloalquilo de C_1-C_6, haloalquenilo de C_2-C_6 o haloalquinilo de C_2-C_6. Más preferentemente, R_M es halógeno, hidroxilo, mercapto, amino, carboxi; o alquilo de C_1-C_6, alquenilo de C_2-C_6 o alquinilo de C_2-C_6, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, mercapto, amino o carboxi. Con gran preferencia, R_M es alquilo de C_1-C_6 el cual está

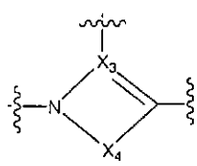
opcionalmente sustituido con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, mercapto, amino o carboxi.

También preferentemente, R_M es halógeno, hidroxilo, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, o ciano; o R_M es $-L_S-R_E$, donde L_S es una unión o alquileno de C_1-C_6, y R_E es $-N(R_SR_S')$, $-O-R_S$, $-C(O)R_S$, $-C(O)OR_S$, $-C(O)N(R_SR_S')$, $-N(R_S)C(O)R_S'$, $-N(R_S)C(O)OR_S'$, $-N(R_S)SO_2R_S'$, $-SO_2R_S$, $-SR_S$, o $-P(O)(OR_S)_2$, donde R_S y R_S' pueden seleccionarse en forma independiente en cada caso, por ejemplo, entre (1) hidrógeno o (2) alquilo de C_1-C_6 opcionalmente sustituido en cada caso con uno o más halógeno, hidroxilo, –O–alquilo de C_1-C_6 o heterociclo de 3 a 6 miembros; o R_M es alquilo de C_1-C_6, alquenilo de C_2-C_6 o alquinilo de C_2-C_6, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo o ciano; o R_M es carbociclo de C_3-C_6 o heterociclo de 3 a 6 miembros, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, alquilo de C_1-C_6, alquenilo de C_2-C_6, alquinilo de C_2-C_6, haloalquilo de C_1-C_6, haloalquenilo de C_2-C_6, haloalquinilo de C_2-C_6, $-C(O)OR_S$, o $-N(R_SR_S')$. Más preferentemente, R_M es halógeno (por ejemplo, fluoro, cloro, bromo, yodo), hidroxilo, mercapto, amino, carboxi, o alquilo de C_1-C_6 (por ejemplo, metilo, isopropilo, tert-butilo), alquenilo de C_2-C_6 o alquinilo de C_2-C_6, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, mercapto, amino, ciano, o carboxi. Por ejemplo R_M es CF_3, $-C(CF_3)_2-OH$, $-C(CH_3)_2-CN$, $-C(CH_3)_2-CH_2OH$, o $-C(CH_3)_2-CH_2NH_2$. También preferentemente R_M es $-L_S-R_E$ donde L_S es una unión y R_E es $-N(R_SR_S')$, $-O-R_S$, $-N(R_S)C(O)OR_S'$, $-N(R_S)SO_2R_S'$, $-SO_2R_S$, o $-SR_S$. Por ejemplo donde L_S es una unión, R_E es $-N(C_1$-C_6alquil$)_2$ (por ejemplo, $-NMe_2$); $-N(C_1$-C_6alquilen–O–C_1-C_6alquil$)_2$ (por ejemplo $-N(CH_2CH_2OMe)_2$); $-N(C_1$-C_6alquil$)(C_1$-C_6alquilen–O–alquilo de C_1-C_6) (por ejemplo $-N(CH_3)(CH_2CH_2OMe)$);—O–alquilo de C_1-C_6 (por ejemplo, –O–Me, –O–Et, –O–isopropilo, –O–tert-butilo, –O–n-hexilo); –O–haloalquilo de C_1-C_6 (por ejemplo, – OCF_3, $-OCH_2CF_3$); –O–C_1-C_6alquilen–piperidina (por ejemplo, –O–CH_2CH_2–1-piperidil); $-N(C_1$-C_6alquil$)C(O)O$alquilo de C_1-C_6 (por ejemplo, $-N(CH_3)C(O)O-CH_2CH(CH_3)_2$), $-N(C_1$-C_6alquil$)SO_2$alquilo de C_1-C_6 (por ejemplo, $-N(CH_3)SO_2CH_3$); $-SO_2$alquilo de C_1-C_6 (por ejemplo, $-SO_2Me$); $-SO_2$haloalquilo de C_1-C_6 (por ejemplo, $-SO_2CF_3$); o –S–haloalquilo de C_1-C_6 (por ejemplo, SCF_3). También preferentemente R_M es $-L_S-R_E$ donde L_S es alquileno de C_1-C_6 (por ejemplo, $-CH_2-$, $-C(CH_3)_2-$, $-C(CH_3)_2-CH_2-$) y R_E es $-O-R_S$, $-C(O)OR_S$, $-N(R_S)C(O)OR_S'$, o $-P(O)(OR_S)_2$.

Por ejemplo R_M es $-C_1$-C_6alquilen–O–R_S (por ejemplo, $-C(CH_3)_2-CH_2-OMe$); $-C_1$-C_6alquilen–C(O)OR_S (por ejemplo, $-C(CH_3)_2-C(O)OMe$); $-C_1$-C_6alquilen–N(R_S)C(O)OR_S' (por ejemplo, $-C(CH_3)_2-CH_2-NHC(O)OCH_3$); o $-C_1$-C_6alquilen–P(O)(OR_S)$_2$ (por ejemplo, $-CH_2-P(O)(OEt)_2$). También más preferentemente R_M es carbociclo de C_3-C_6 o heterociclo de 3 a 6 miembros, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, alquilo de C_1-C_6, alquenilo de C_2-C_6, alquinilo de C_2-C_6, haloalquilo de C_1-C_6, haloalquenilo de C_2-C_6, haloalquinilo de C_2-C_6, $-C(O)OR_S$, o $-N(R_SR_S')$. Por ejemplo R_M es cicloalquilo (por ejemplo, ciclopropilo, 2,2-dicloro-1-metilcicloprop-1-ilo, ciclohexilo), fenilo, heterociclilo (por ejemplo, morfolin-4-ilo, 1,1-dioxidotiomorfolin-4-ilo, 4-metilpiperazin-1-ilo, 4-metoxicarbonilpiperazin-1-ilo, pirrolidin-1-ilo, piperidin-1-ilo, 4-metilpiperidin-1-ilo, 3,5-dimetilpiperidin-1-ilo, 4,4-difluoropiperidin-1-ilo, tetrahidropiran-4-ilo, piridinilo, piridin-3-ilo, 6-(dimetilamino)piridin-3-ilo). Con gran preferencia, R_M es alquilo de C_1-C_6 el cual está opcionalmente sustituido con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, mercapto, amino o carboxi (por ejemplo, tert-butilo, CF_3).

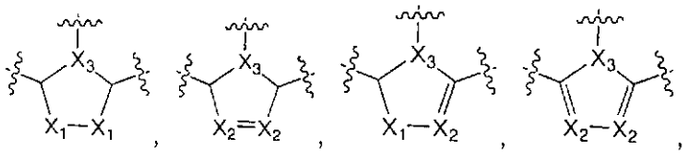
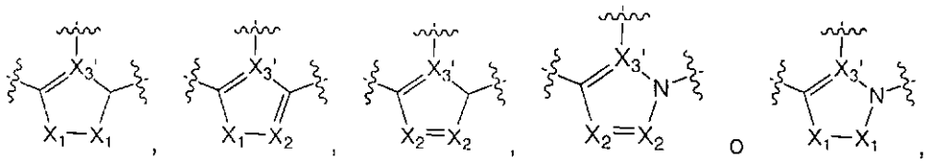
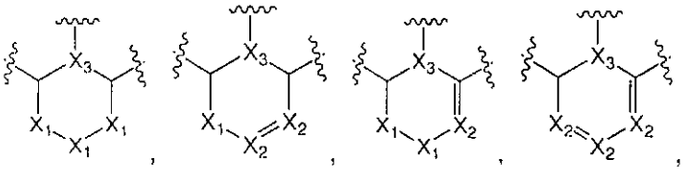
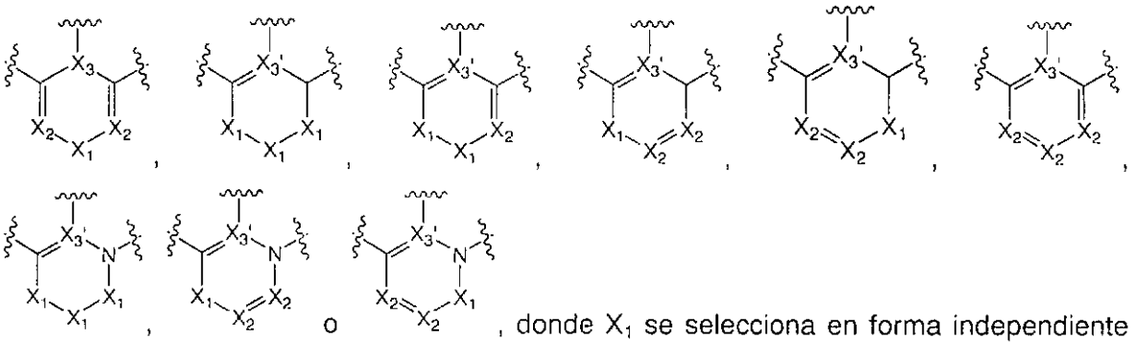
X preferentemente es C_5-C_6carbociclo, heterociclo de 5 a 6 miembros, o biciclos de 6 a 12 miembros, y está opcionalmente sustituido con uno o más R_A. X también puede ser Carbociclo de C_5-C_6 o heterociclo de 5 a 6 miembros que está opcionalmente sustituido con uno o más R_A, donde dos R_A adyacentes sobre X, tomados junto con los átomos del anillo a los cuales están unidos, forman opcionalmente un carbocilo o heterociclo de 5 a 6 miembros. También preferentemente, X es 

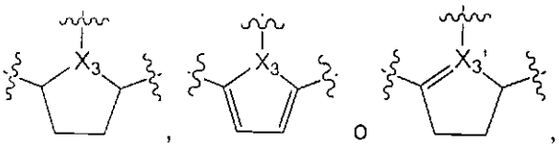
, donde X_3 es C(H) o preferentemente N y está vinculado directamente a $-L_3-D$; X_4 es C_2-C_4alquileno, C_2-C_4alquenileno o C_2-C_4alquinileno, cada uno de los cuales opcionalmente contiene uno o dos heteroátomos seleccionados entre O, S o N; y X está opcionalmente sustituido con uno o más R_A, y dos R_A adyacentes sobre X, tomados junto con los átomos del anillo a los cuales están unidos, pueden formar opcionalmente un carbocilo o heterociclo de 5 a 6 miembros. Además, X puede ser 

o 

, donde X_3 es C y está ligado directamente a $-L_3-D$, X_4 es C_2-C_4alquileno, C_2-C_4alquenileno o C_2-C_4alquinileno cada uno de los cuales opcionalmente contiene uno o dos heteroátomos

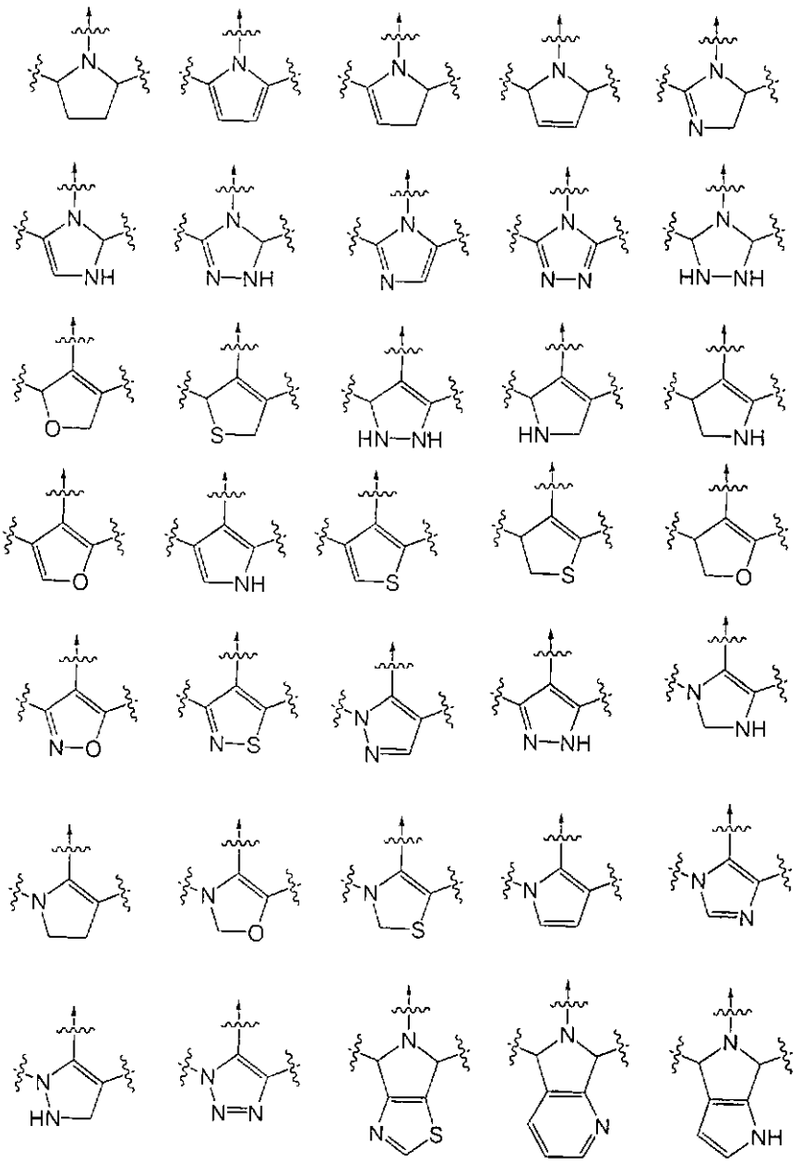
seleccionados entre O, S o N, y X está opcionalmente sustituido con uno o más R_A, y dos R_A adyacentes sobre X, tomados junto con los átomos del anillo a los cuales están unidos, forman opcionalmente un carbocilo o heterociclo de 5 a 6 miembros.

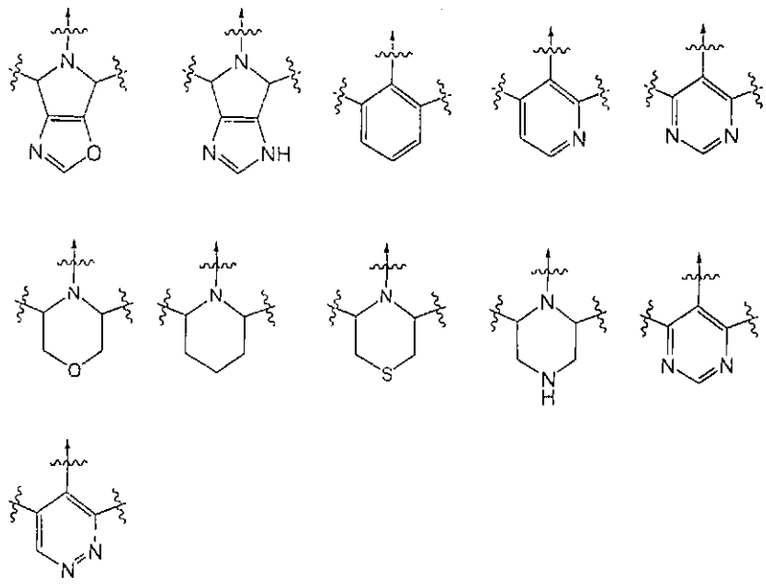
Por ejemplo, X puede ser  ,  , donde X_1 se selecciona en forma independiente en cada caso entre CH_2, O, S o NH, X_2 se selecciona en forma independiente en cada caso entre CH o N, X_3 es N y está ligado directamente a $-L_3-D$, y X_3' es C y está ligado directamente a $-L_3-D$; y X está opcionalmente sustituido con uno o más R_A, y dos R_A adyacentes sobre X, tomados junto con los átomos del anillo a los cuales están unidos, forman opcionalmente un carbocilo o heterociclo de 5 a 6 miembros. En otro ejemplo, X es  ,  , donde X_1 se selecciona en forma independiente en cada caso entre CH_2, O, S o NH, X_2 se selecciona en forma independiente en cada caso entre CH o N, X_3 es N y está ligado directamente a $-L_3-D$, y X_3' es C y está ligado directamente a $-L_3-D$; y donde X está opcionalmente sustituido con uno o más R_A, y dos R_A adyacentes sobre X, tomados junto con los átomos del anillo a los cuales están unidos, forman opcionalmente un carbocilo o heterociclo de 5 a 6 miembros.

Con gran preferencia, X es  , donde X_3 es C(H) o N y está ligado directamente a $-L_3-D$, X_3' es C y está ligado directamente a $-L_3-D$, y donde X está opcionalmente sustituido con uno o más R_A, y dos R_A adyacentes

sobre X, tomados junto con los átomos del anillo a los cuales están unidos, forman opcionalmente un carbocilo o heterociclo de 5 a 6 miembros. Más preferentemente, X_3 es N.

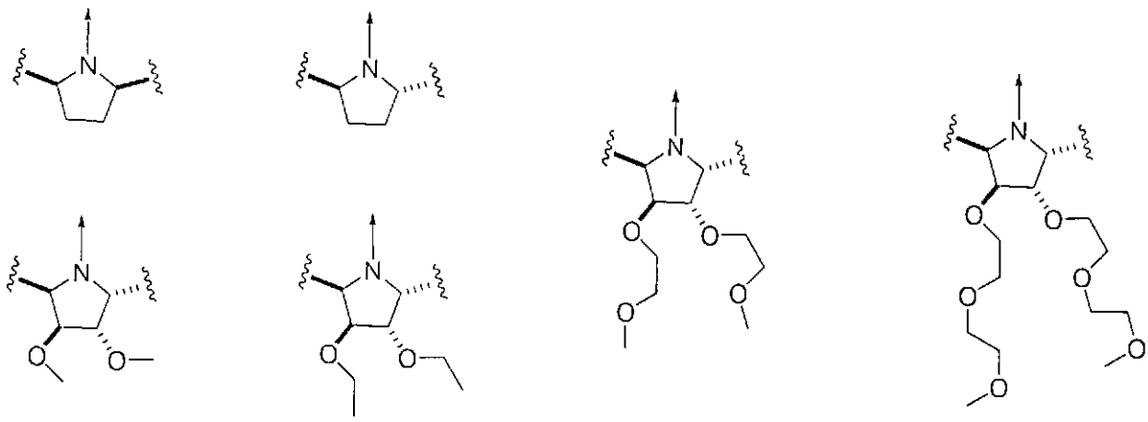
Entre los ejemplos no limitativos de X se incluyen:





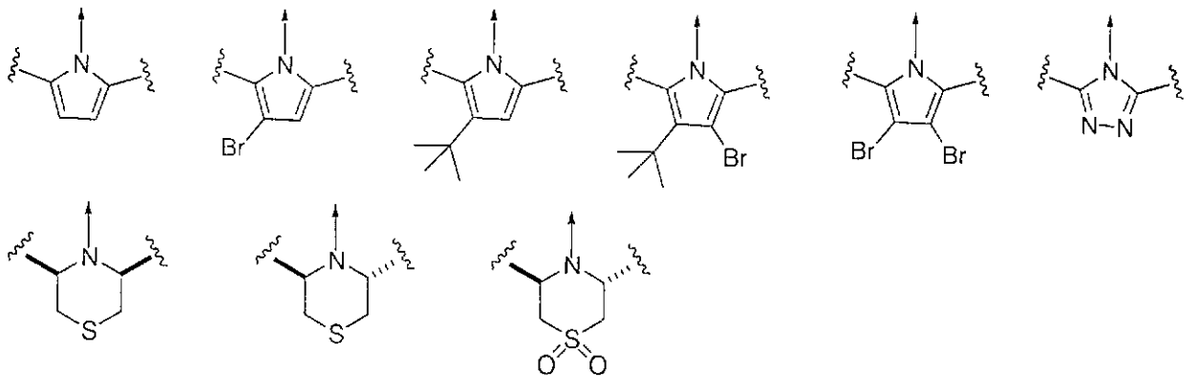
donde "→" indica la unión covalente a $-L_3-D$. Cada X puede estar opcionalmente sustituido con uno o más R_A, y dos R_A adyacentes sobre X, tomados junto con los átomos del anillo a los cuales están unidos, forman opcionalmente un carbocilo o heterociclo de 5 a 6 miembros.

Entre los ejemplos no limitativos de X preferidos se incluyen los siguientes anillos pirrolidina, cada uno de los cuales está opcionalmente sustituido con uno o más R_A:



Como se muestra, la estereoquímica relativa en las posiciones 2 y 5 del anillo pirrolidina precedente puede ser cis o trans. las estereoquímicas de los sustituyentes optativos R_A en las posiciones 3 ó 4 de la pirrolidina pueden variar en relación con cualquier sustituyente en cualquier otra posición en anillo pirrolidina. según los sustituyentes específicos unidos a la pirrolidina, la estereoquímica en cualquier carbono puede ser (R) o (S).

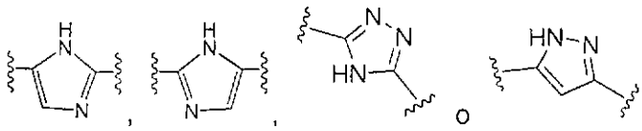
Entre los ejemplos no limitativos de X preferido también se incluyen los siguientes anillos pirrol, triazol o tiomorfolina, cada uno de los cuales está opcionalmente sustituido con uno o más R_A:



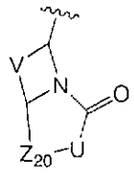
Como se puede observar, la estereoquímica relativa en las posiciones 3 a 5 del anillo tiomorfolina puede ser cis o trans. según los sustituyentes específicos unidos a la tiomorfolina, la estereoquímica en cualquier carbono puede ser (R) o (S).

L_1 y L_2 son preferentemente en forma independiente una unión o alquileno de C_1-C_6, L_3 se selecciona preferentemente entre una unión, alquileno de C_1-C_6 o –C(O)–, y L_1, L_2, y L_3 están sustituidos en forma independiente entre sí con uno o más R_L. Más preferentemente, L_1, L_2 y L_3 son en forma independiente entre sí una unión o alquileno de C_1-C_6 (por ejemplo, $–CH_2–$ o $–CH_2CH_2–$), y están sustituidos en forma independiente entre sí con uno o más R_L. Con gran preferencia, L_1, L_2 y L_3 son una unión.

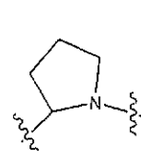
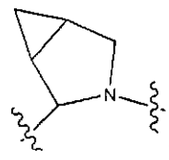
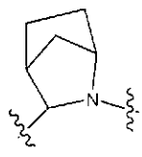
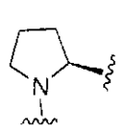
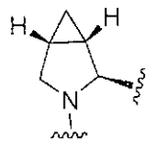
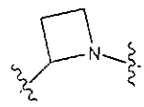
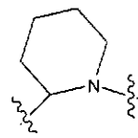
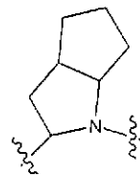
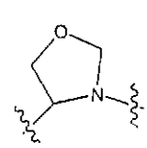
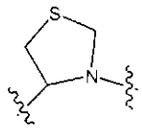
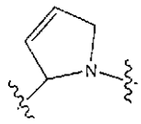
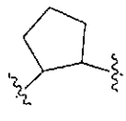
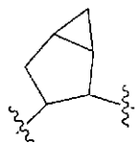
Y se selecciona preferentemente entre $–L_S–C(R_1R_2)N(R_5)–T–R_D$, $–L_S–C(R_3R_4)C(R_6R_7)–T–R_D$, $–G–C(R_1R_2)N(R_5)–T–R_D$, $–G–C(R_3R_4)C(R_6R_7)–T–R_D$, $–N(R_B)C(O)C(R_1R_2)N(R_5)–T–R_D$, $–N(R_B)C(O)C(R_3R_4)C(R_6R_7)–T–R_D$, $–C(O)N(R_B)C(R_1R_2)N(R_5)–T–R_D$, $–C(O)N(R_B)C(R_3R_4)C(R_6R_7)–T–R_D$, $–N(R_B)C(O)–L_S–E$, o $–C(O)N(R_B)–L_S–E$. G es carbociclo de C_5-C_6 o heterociclo de 5 a 6 miembros, tal como

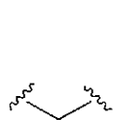
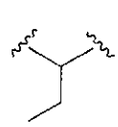
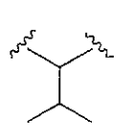
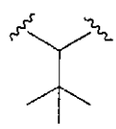
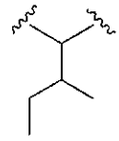


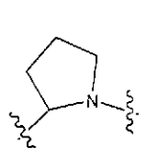
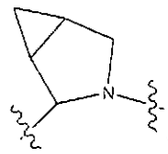
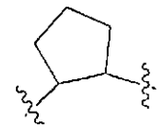
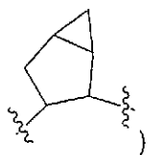
, y está opcionalmente sustituido con uno o más R_A (por ejemplo, uno o más cloro o bromo). E preferentemente es un biciclo de 7 a 12 miembros (tal como

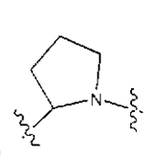
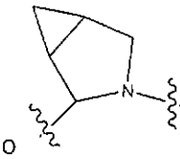


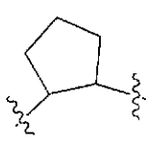
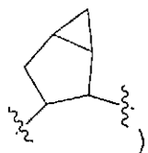
, donde U se selecciona en forma independiente en cada caso entre -(CH_2)- o -(NH)-; V y Z_{20} se seleccionan en forma independiente entre sí entre C_1-C_4alquileno, C_2-C_4alquenileno o C_2-C_4alquinileno, en donde al menos un átomo de carbono opcionalmente se puede reemplazar en forma independiente con O, S o N), y está opcionalmente sustituido con uno o más R_A. Más preferentemente, R_1 es R_C, y R_2 y R_5, tomados junto con los átomos a los cuales están unidos, forman un heterociclo de 5 a

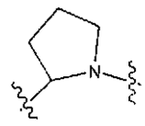
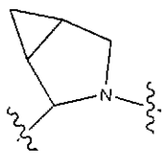
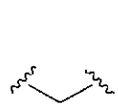
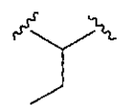
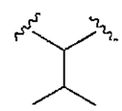
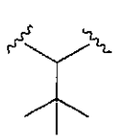
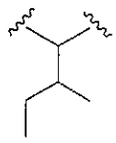
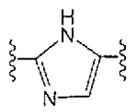
6 miembros o biciclo de 6 a 12 miembros (por ejemplo,  o  ; o  ,  ,  ; o  ,  ,  ,  ,  , o ) que está opcionalmente sustituido con uno o más R_A (tal como, pero no taxativamente un hidroxilo, halo (por ejemplo, fluoro), alquilo de C_1-C_6 (por ejemplo, metilo), o alquenilo de C_2-C_6 (por ejemplo, alilo)); y R_3 y R_6 son en forma independiente entre sí R_C, y R_4 y R_7, tomados junto con los átomos a los cuales están unidos, forman un carbociclo de 5 a 6 miembros/heterociclo o biciclo de 6 a 12 miembros (por ejemplo,  o ) que está opcionalmente sustituido con uno o más R_A (tal como, pero no taxativamente un hidroxilo, halo (por ejemplo, fluoro), alquilo de C_1-C_6 (por ejemplo, metilo), o alquenilo de C_2-C_6 (por ejemplo, alilo)).

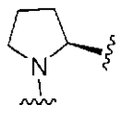
Y también puede seleccionarse entre $-M-C(R_1R_2)N(R_5)-C(O)-L_Y'-M'-R_D$, $-M-C(R_1R_2)N(R_5)-L_Y'-M'-R_D$, $-L_S-C(R_1R_2)N(R_5)-C(O)-L_Y'-M'-R_D$, $-L_S-C(R_1R_2)N(R_5)-L_Y'-M'-R_D$, $-M-C(R_3R_4)C(R_6R_7)-C(O)-L_Y'-M'-R_D$, $-M-C(R_3R_4)C(R_6R_7)-L_Y'-M'-R_D$, $-L_S-C(R_3R_4)C(R_6R_7)-C(O)-L_Y'-M'-R_D$, o $-L_S-C(R_3R_4)C(R_6R_7)-L_Y'-M'-R_D$, donde M preferentemente es una unión, $-C(O)N(R_B)-$ o $-N(R_B)C(O)-$, M' preferentemente es una unión, $-C(O)N(R_B)-$, $-N(R_B)C(O)-$, $-N(R_B)C(O)O-$, $N(R_B)C(O)N(R_B')-$, $-N(R_B)S(O)-$ o $-N(R_B)S(O)_2-$, y L_Y' preferentemente es alquileno de C_1-C_6 que está opcionalmente sustituido con uno o más R_L. L_Y', por ejemplo, es un alquileno de C_1-C_6 tal como, pero no taxativamente, un  ,  ,  ,  , o  ; y el R_L optativo es un sustituyente tal como, pero no taxativamente, un fenilo, –SMe, o metoxi. Cualquier estereoquímica en un carbono dentro del grupo L_Y' puede ser (R) o (S). Más preferentemente, R_1 es R_C, y R_2 y R_5, tomados junto con los átomos a los cuales están unidos, forman un heterociclo de 5 a 6 miembros o biciclo de 6 a 12 miembros (por

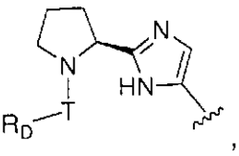
ejemplo,  o ) que está opcionalmente sustituido con uno o más R_A (por ejemplo, uno o más hidroxi); y R_3 y R_6 son en forma independiente entre sí R_C, y R_4 y R_7, tomados junto con los átomos a los cuales están unidos, forman un carbociclo de 5 a 6 miembros/heterociclo o biciclo de 6 a 12 miembros (por ejemplo,  o ) que está opcionalmente sustituido con uno o más R_A.

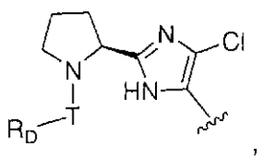
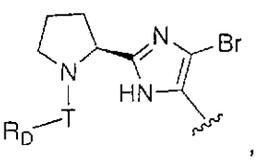
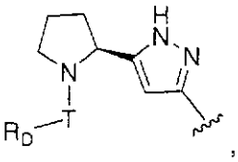
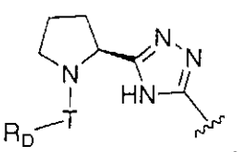
También preferentemente, Y se selecciona entre $-N(R_B)CO-C(R_1R_2)N(R_5)-C(O)-L_Y'-N(R_B)C(O)O-R_D$, $-N(R_B)CO-C(R_1R_2)N(R_5)-C(O)-L_Y'-N(R_B)C(O)-R_D$, $-N(R_B)CO-C(R_1R_2)N(R_5)-C(O)-L_Y'-N(R_B)S(O)_2-R_D$, $-N(R_B)CO-C(R_1R_2)N(R_5)-C(O)-L_Y'-N(R_BR_B')-R_D$, $-N(R_B)CO-C(R_1R_2)N(R_5)-C(O)-L_Y'-O-R_D$, $-N(R_B)CO-C(R_1R_2)N(R_5)-C(O)-L_Y'-R_D$, $-N(R_B)CO-C(R_1R_2)N(R_5)-R_D$, $-L_S-C(R_1R_2)N(R_5)-C(O)-L_Y'-N(R_B)C(O)O-R_D$, $-L_S-C(R_1R_2)N(R_5)-C(O)-L_Y'-N(R_B)C(O)-R_D$, $-L_S-C(R_1R_2)N(R_5)-C(O)-L_Y'-N(R_B)S(O)_2-R_D$, $-L_S-C(R_1R_2)N(R_5)-C(O)-L_Y'-N(R_BR_B')-R_D$, $-L_S-C(R_1R_2)N(R_5)-C(O)-L_Y'-O-R_D$, $-L_S-C(R_1R_2)N(R_5)-C(O)-L_Y'-R_D$, $-L_S-C(R_1R_2)N(R_5)-R_D$, $-N(R_B)CO-C(R_3R_4)C(R_6R_7)-C(O)-L_Y'-N(R_B)C(O)O-R_D$, $-N(R_B)CO-C(R_3R_4)C(R_6R_7)-C(O)-L_Y'-N(R_B)C(O)-R_D$, $-N(R_B)CO-C(R_3R_4)C(R_6R_7)-C(O)-L_Y'-N(R_B)S(O)_2-R_D$, $-N(R_B)CO-C(R_3R_4)C(R_6R_7)-C(O)-L_Y'-N(R_BR_B')-R_D$, $-N(R_B)CO-C(R_3R_4)C(R_6R_7)-C(O)-L_Y'-O-R_D$, $-N(R_B)CO-C(R_3R_4)C(R_6R_7)-C(O)-L_Y'-R_D$, $-N(R_B)CO-C(R_3R_4)C(R_6R_7)-R_D$, $-L_S-C(R_3R_4)C(R_6R_7)-C(O)-L_Y'-N(R_B)C(O)O-R_D$, $-L_S-C(R_3R_4)C(R_6R_7)-C(O)-L_Y'-N(R_B)C(O)-R_D$, $-L_S-C(R_3R_4)C(R_6R_7)-C(O)-L_Y'-N(R_B)S(O)_2-R_D$, $-L_S-C(R_3R_4)C(R_6R_7)-C(O)-L_Y'-N(R_BR_B')-R_D$, $-L_S-C(R_3R_4)C(R_6R_7)-C(O)-L_Y'-O-R_D$, $-L_S-C(R_3R_4)C(R_6R_7)-C(O)-L_Y'-R_D$, o $-L_S-C(R_3R_4)C(R_6R_7)-R_D$, donde L_Y' preferentemente es alquileno de C_1-C_6 que está opcionalmente sustituido con uno o más R_L. R_1 puede ser R_C, y R_2 y R_5, tomados junto con los átomos a los cuales están unidos, pueden formar un heterociclo de 5 a 6 miembros o biciclo de 6 a 12 miembros (por ejemplo,  o ) que está opcionalmente sustituido con uno o más R_A; y R_3 y R_6 pueden ser cada uno en forma independiente R_C, y R_4 y R_7, tomados junto con los átomos a los cuales están unidos,

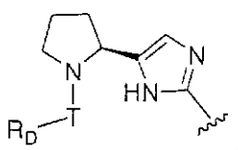
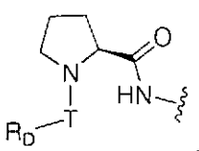
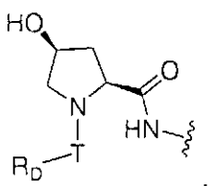
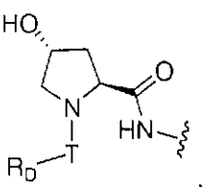
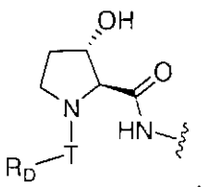
pueden formar un carbociclo de 5 a 6 miembros/heterociclo o biciclo de 6 a 12 miembros (por ejemplo,  o ) que está opcionalmente sustituido con uno o más R_A.

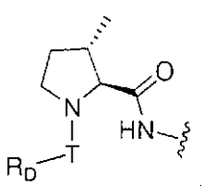
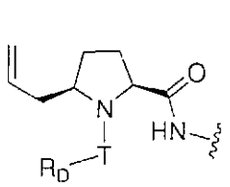
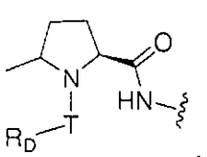
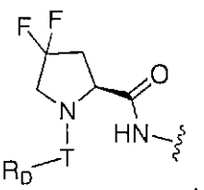
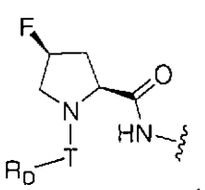
Con gran preferencia, Y se selecciona entre $-N(R_B'')CO-C(R_1R_2)N(R_5)-C(O)-L_Y-N(R_B'')C(O)-L_S-R_E$ o $-C(R_1R_2)N(R_5)-C(O)-L_Y-N(R_B'')C(O)-L_S-R_E$, o Y es $-G-C(R_1R_2)N(R_5)-C(O)-L_Y-N(R_B'')C(O)-L_S-R_E$, donde L_Y es alquileno de C_1-C_6 opcionalmente sustituido con uno o más R_L, y R_B'' es cada uno en forma independiente R_B. R_B'' y R_1 son cada uno preferentemente hidrógeno o alquilo de C_1-C_6, y R_2 y R_5, tomados junto con los átomos a los cuales están unidos, preferentemente forman un heterociclo de 5 a 6 miembros o biciclo de 6 a 12 miembros (por ejemplo,  o ) que está opcionalmente sustituido con uno o más R_A (tal como, pero no taxativamente un hidroxilo, halo (por ejemplo, fluoro), alquilo de C_1-C_6 (por ejemplo, metilo), o alquenilo de C_2-C_6 (por ejemplo, alilo)). Preferentemente, L_Y es alquileno de C_1-C_6 sustituido con uno o más R_L tal como un carbociclo de C_3-C_6 heterociclo de 3 a 6 miembros que está opcionalmente sustituido con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, alquilo de C_1-C_6, alquenilo de C_2-C_6, alquinilo de C_2-C_6, haloalquilo de C_1-C_6, haloalquenilo de C_2-C_6 o haloalquinilo de C_2-C_6. Con gran preferencia, L_Y es un alquileno de C_1-C_6 tal como, pero no taxativamente, un  ,  ,  ,  , o  (la estereoquímica en un carbono dentro del grupo L_Y puede ser (R) o (S)), L_Y está opcionalmente sustituido con uno o más R_L (por ejemplo, uno o más fenilo o metoxi), G preferentemente es  , R_B'' es hidrógeno; $-C(R_1R_2)N(R_5)-$ es

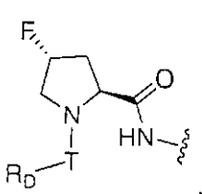
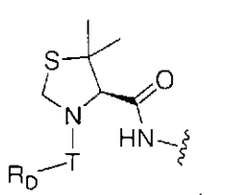
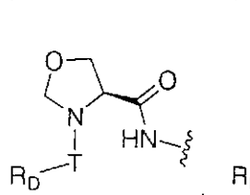
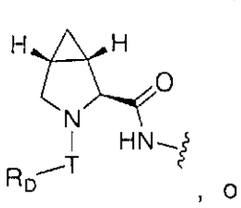

; L_S es una unión; y R_E es metoxi.

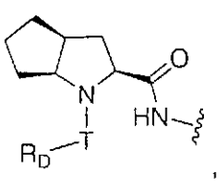
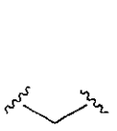
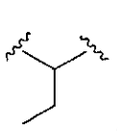
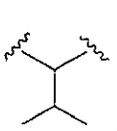
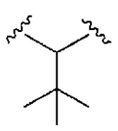
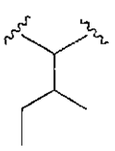
Entre los ejemplos no limitativos de Y preferido se incluyen:  ,

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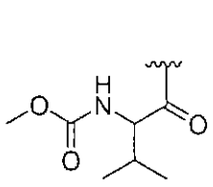
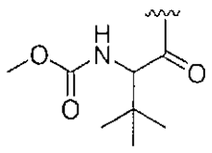
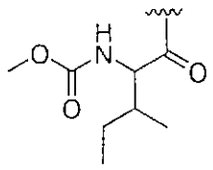
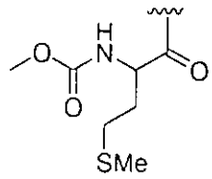
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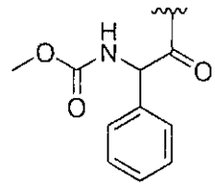
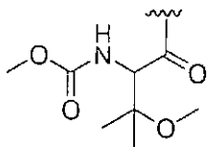
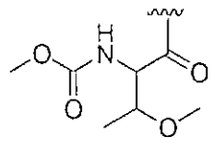
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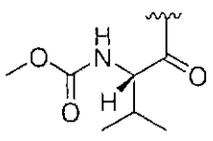
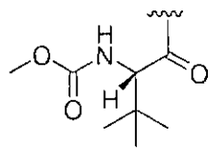
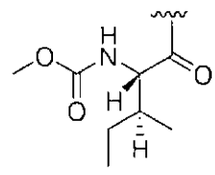
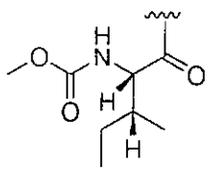
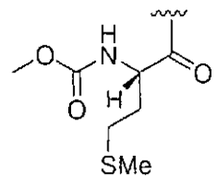
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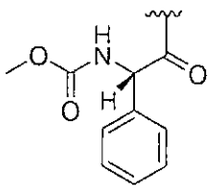
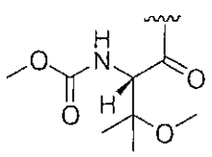
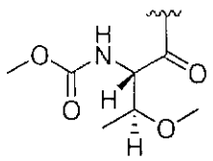
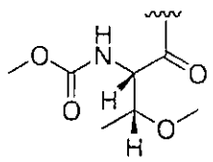
 , donde T y R_D tienen los valores que se han definido. T, por ejemplo, puede ser $-L_S-M-L_S'-M'-L_S''-$ donde L_S es una unión; M es C(O); L_S' es alquileno de C_1-C_6 tal como, pero no taxativamente, un  ,  ,  ,  , o  , donde L_S' está opcionalmente sustituido con uno o más R_L; R_L es un sustituyente tal como, pero no taxativamente, un fenilo o metoxi; M' es $-NHC(O)-$ o $-NMeC(O)-$; y L_S'' es una unión. Cualquier estereoquímica en un carbono dentro del grupo

L_S' puede ser (R) o (S). R_D, por ejemplo es metoxi. T-R_D incluye, pero no taxativamente:

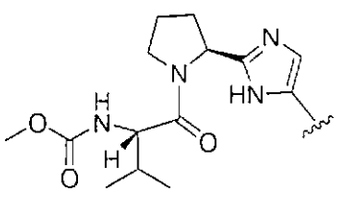
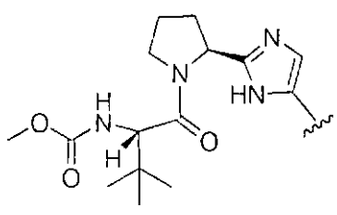
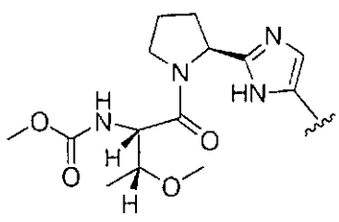
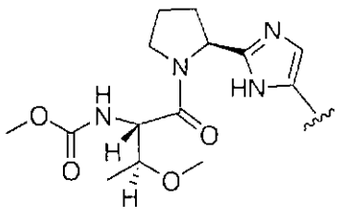
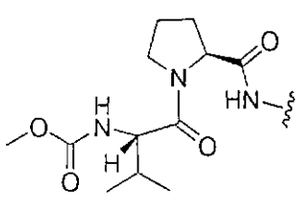
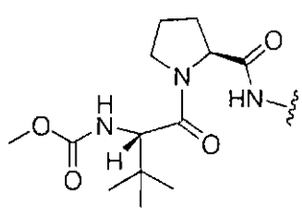
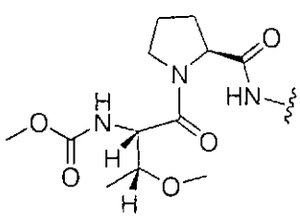
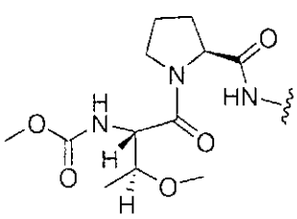
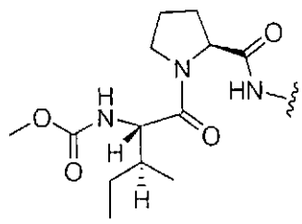





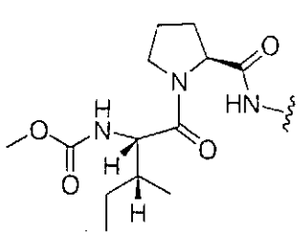
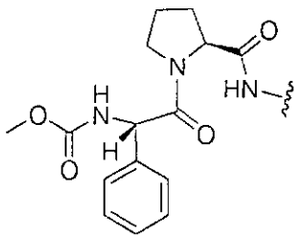
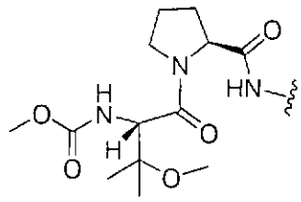


, o

. T-R_D pueden también incluir algunas configuraciones esteroquímicas; por lo tanto T-R_D incluye, pero no taxativamente:

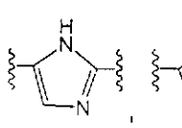
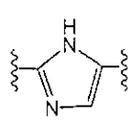
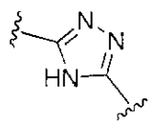
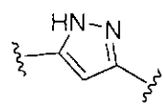
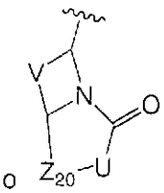
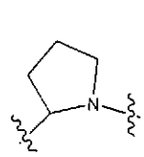
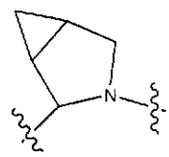
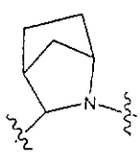
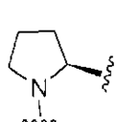
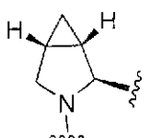
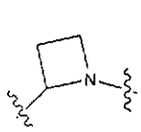
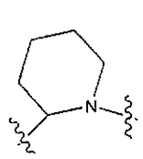
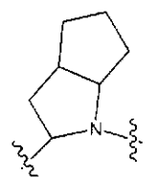
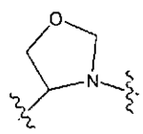
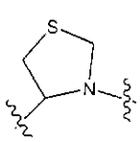
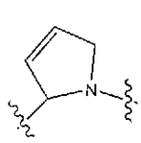



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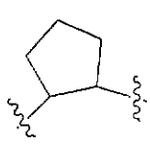
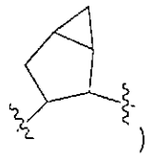
Entre los ejemplos no limitativos de Y preferido también se incluyen:

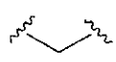
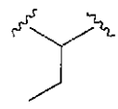
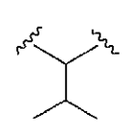
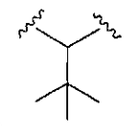
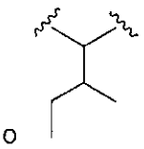
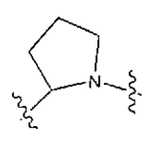
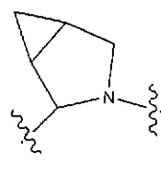
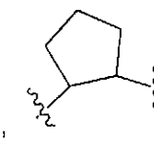
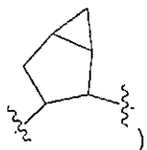



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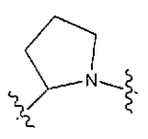
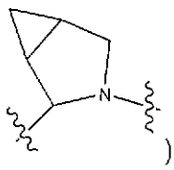
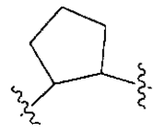
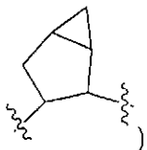


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Z se selecciona preferentemente entre $-L_S-C(R_8R_9)N(R_{12})-T-R_D$, $-L_S-C(R_{10}R_{11})C(R_{13}R_{14})-T-R_D$, $-G-C(R_8R_9)N(R_{12})-T-R_D$, $-G-C(R_{10}R_{11})C(R_{13}R_{14})-T-R_D$, $-N(R_B)C(O)C(R_8R_9)N(R_{12})-T-R_D$, $-N(R_B)C(O)C(R_{10}R_{11})C(R_{13}R_{14})-T-R_D$, $-C(O)N(R_B)C(R_8R_9)N(R_{12})-T-R_D$, $-C(O)N(R_B)C(R_{10}R_{11})C(R_{13}R_{14})-T-R_D$, $-N(R_B)C(O)-L_S-E$, o $-C(O)N(R_B)-L_S-E$. G es carbociclo de C_5-C_6 o heterociclo de 5 a 6 miembros, tal como

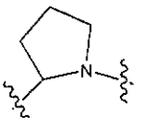
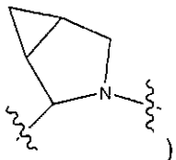
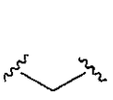
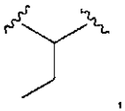
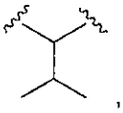
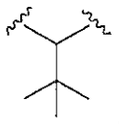
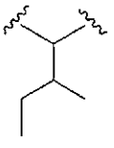
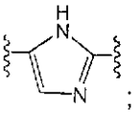
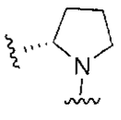

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, y está opcionalmente sustituido con uno o más R_A (por ejemplo, uno o más cloro o bromo). E preferentemente es un biciclo de 8 a 12 miembros (tal como

, donde U se selecciona en forma independiente en cada caso entre -(CH_2)- o -(NH)-; y V y Z_{20} se seleccionan en forma independiente entre sí entre C_1-C_4alquileno, C_2-C_4alquenileno o C_2-C_4alquinileno, en donde al menos un átomo de carbono en forma independiente se reemplaza optativamente con O, S o N), y está opcionalmente sustituido con uno o más R_A. Más preferentemente, R_8 es R_C, y R_9 y R_{12}, tomados junto con los átomos a los cuales están unidos, forman un heterociclo de 5 a 6 miembros o biciclo de 6 a 12 miembros (por ejemplo,

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)) que está opcionalmente sustituido con uno o más R_A (tal como, pero no taxativamente un hidroxilo, halo (por ejemplo, fluoro), alquilo de C_1-C_6 (por

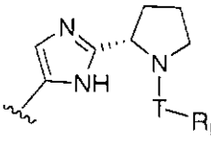
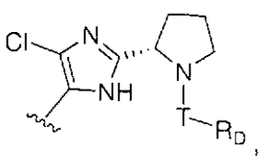
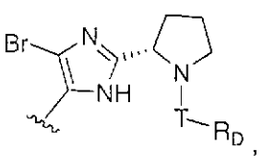
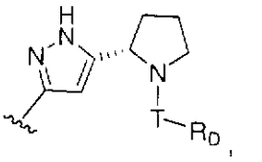
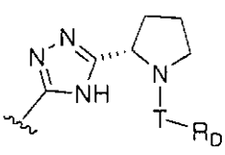
ejemplo, metilo), o alquenilo de C_2-C_6 (por ejemplo, alilo)); y R_{10} y R_{13} son en forma independiente entre sí R_C, y R_{11} y R_{14}, tomados junto con los átomos a los cuales están unidos, forman un carbociclo de 5 a 6 miembros/heterociclo o biciclo de 6 a 12 miembros (por ejemplo,  o ) que está opcionalmente sustituido con uno o más R_A (tal como, pero no taxativamente un hidroxilo, halo (por ejemplo, fluoro), alquilo de C_1-C_6 (por ejemplo, metilo), o alquenilo de C_2-C_6 (por ejemplo, alilo)).

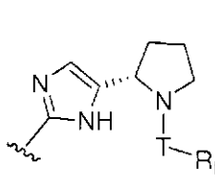
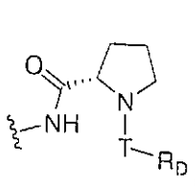
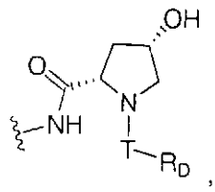
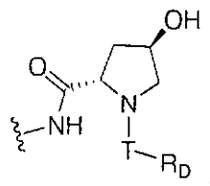
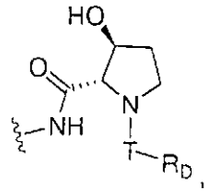
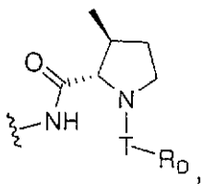
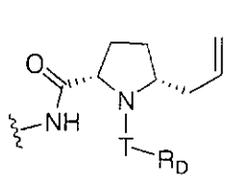
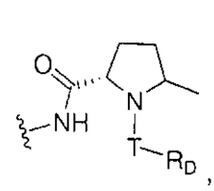
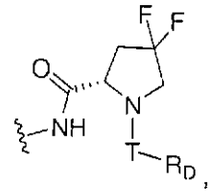
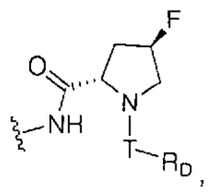
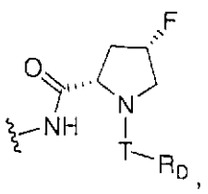
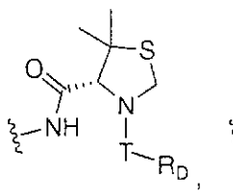
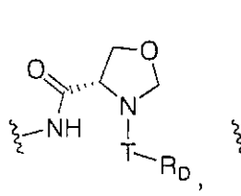
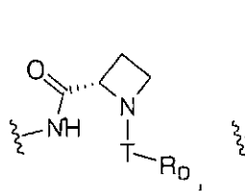
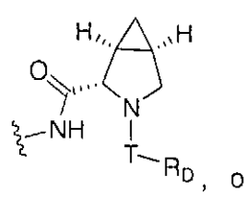
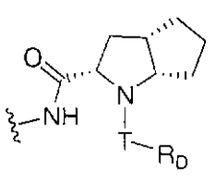
Z también puede seleccionarse entre $-M-C(R_8R_9)N(R_{12})-C(O)-L_Y'-M'-R_D$, $-M-C(R_8R_9)N(R_{12})-L_Y'-M'-R_D$, $-L_S-C(R_8R_9)N(R_{12})-C(O)-L_Y'-M'-R_D$, $-L_S-C(R_8R_9)N(R_{12})-L_Y'-M'-R_D$, $-M-C(R_{10}R_{11})C(R_{13}R_{14})-C(O)-L_Y'-M'-R_D$, $-M-C(R_{10}R_{11})C(R_{13}R_{14})-L_Y'-M'-R_D$, $-L_S-C(R_{10}R_{11})C(R_{13}R_{14})-C(O)-L_Y'-M'-R_D$, o $-L_S-C(R_{10}R_{11})C(R_{13}R_{14})-L_Y'-M'-R_D$, donde M preferentemente es una unión, $-C(O)N(R_B)-$ o $-N(R_B)C(O)-$, M' preferentemente es una unión, $-C(O)N(R_B)-$, $-N(R_B)C(O)-$, $-N(R_B)C(O)O-$, $N(R_B)C(O)N(R_B')-$, $-N(R_B)S(O)-$ o $-N(R_B)S(O)_2-$, y L_Y' preferentemente es alquileno de C_1-C_6 que está opcionalmente sustituido con uno o más R_L. L_Y', por ejemplo, es un alquileno de C_1-C_6 tal como, pero no taxativamente, un  ,  ,  ,  , o  ; y el R_L optativo es un sustituyente tal como, pero no taxativamente, un fenilo, –SMe, o metoxi. Cualquier estereoquímica en un carbono dentro del grupo L_Y' puede ser (R) o (S). Más preferentemente, R_8 es R_C, y R_9 y R_{12}, tomados junto con los átomos a los cuales están unidos, forman un heterociclo de 5 a 6 miembros o biciclo de 6 a 12 miembros (por ejemplo,  o ) que está opcionalmente sustituido con uno o más R_A (por ejemplo, uno o más hidroxi); y R_{10} y R_{13} son en forma independiente entre sí R_C, y R_{11} y R_{14}, tomados junto con los átomos a los cuales están unidos, forman un carbociclo de 5 a 6 miembros/heterociclo o biciclo de 6 a 12 miembros (por ejemplo,  o ) que está opcionalmente sustituido con uno o más R_A.

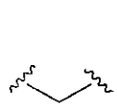
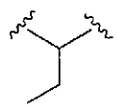
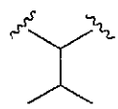
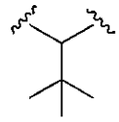
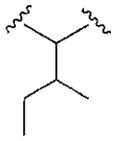
También preferentemente, Z se selecciona entre $-N(R_B)CO-C(R_8R_9)N(R_{12})-C(O)-L_Y'-N(R_B)C(O)O-R_D$, $-N(R_B)CO-C(R_8R_9)N(R_{12})-C(O)-L_Y'-N(R_B)C(O)-R_D$, $-N(R_B)CO-C(R_8R_9)N(R_{12})-C(O)-L_Y'-N(R_B)S(O)_2-R_D$, $-N(R_B)CO-C(R_8R_9)N(R_{12})-C(O)-L_Y'-N(R_BR_B')-R_D$, $-N(R_B)CO-C(R_8R_9)N(R_{12})-C(O)-L_Y'-O-R_D$, $-N(R_B)CO-C(R_8R_9)N(R_{12})-C(O)-L_Y'-R_D$, $-N(R_B)CO-C(R_8R_9)N(R_{12})-R_D$, $-L_S-C(R_8R_9)N(R_{12})-C(O)-L_Y'-N(R_B)C(O)O-R_D$, $-L_S-C(R_8R_9)N(R_{12})-C(O)-L_Y'-N(R_B)C(O)-R_D$, $-L_S-C(R_8R_9)N(R_{12})-C(O)-L_Y'-N(R_B)S(O)_2-R_D$, $-L_S-C(R_8R_9)N(R_{12})-C(O)-L_Y'-N(R_BR_B')-R_D$, $-L_S-C(R_8R_9)N(R_{12})-C(O)-L_Y'-O-R_D$, $-L_S-C(R_8R_9)N(R_{12})-C(O)-L_Y'-R_D$, $-L_S-C(R_8R_9)N(R_{12})-R_D$, $-N(R_B)CO-C(R_{10}R_{11})C(R_{13}R_{14})-C(O)-L_Y'-N(R_B)C(O)O-R_D$, $-N(R_B)CO-C(R_{10}R_{11})C(R_{13}R_{14})-C(O)-L_Y'-N(R_B)C(O)-R_D$, $-N(R_B)CO-C(R_{10}R_{11})C(R_{13}R_{14})-C(O)-L_Y'-N(R_B)S(O)_2-R_D$, $-N(R_B)CO-C(R_{10}R_{11})C(R_{13}R_{14})-C(O)-L_Y'-N(R_BR_B')-R_D$, $-N(R_B)CO-C(R_{10}R_{11})C(R_{13}R_{14})-C(O)-L_Y'-O-R_D$, $-N(R_B)CO-C(R_{10}R_{11})C(R_{13}R_{14})-C(O)-L_Y'-R_D$, $-N(R_B)CO-C(R_{10}R_{11})C(R_{13}R_{14})-R_D$, $-L_S-C(R_{10}R_{11})C(R_{13}R_{14})-C(O)-L_Y'-N(R_B)C(O)O-R_D$, $-L_S-C(R_{10}R_{11})C(R_{13}R_{14})-C(O)-L_Y'-N(R_B)C(O)-R_D$, $-L_S-C(R_{10}R_{11})C(R_{13}R_{14})-C(O)-L_Y'-N(R_B)S(O)_2-R_D$, $-L_S-C(R_{10}R_{11})C(R_{13}R_{14})-C(O)-L_Y'-N(R_BR_B')-R_D$, $-L_S-C(R_{10}R_{11})C(R_{13}R_{14})-C(O)-L_Y'-O-R_D$, $-L_S-C(R_{10}R_{11})C(R_{13}R_{14})-C(O)-L_Y'-R_D$, o $-L_S-C(R_{10}R_{11})C(R_{13}R_{14})-R_D$, donde L_Y' preferentemente es alquileno de C_1-C_6 que está opcionalmente sustituido con uno o más R_L. R_8 puede ser R_C, y R_9 y R_{12}, tomados junto con los átomos a los cuales están unidos, pueden formar un heterociclo de 5 a 6 miembros o biciclo de 6 a 12 miembros (por ejemplo,  o ) que está opcionalmente sustituido con uno o más R_A; y R_{10} y R_{13} pueden ser cada uno en forma independiente R_C, y R_{11} y R_{14}, tomados junto con los átomos a los cuales están unidos, pueden formar un carbociclo de 5 a 6 miembros/heterociclo o biciclo de 6 a 12 miembros (por ejemplo,  o ) que está opcionalmente sustituido con uno o más R_A.

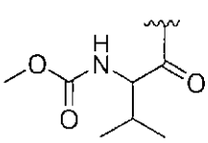
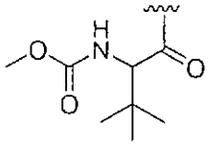
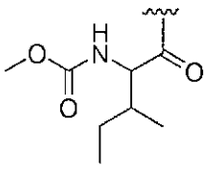
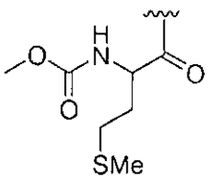
Con gran preferencia, Z se selecciona entre $-N(R_B'')CO-C(R_8R_9)N(R_{12})-C(O)-L_Y-N(R_B'')C(O)-L_S-R_E$ o $-C(R_8R_9)N(R_{12})-C(O)-L_Y-N(R_B'')C(O)-L_S-R_E$, o Z es $-G-C(R_8R_9)N(R_{12})-C(O)-L_Y-N(R_B'')C(O)-L_S-R_E$, donde L_Y es alquileno de C_1-C_6 opcionalmente sustituido con uno o más R_L, y R_B'' es cada uno en forma independiente R_B. R_B'' y R_8 son cada uno preferentemente hidrógeno o alquilo de C_1-C_6, y R_9 y R_{12},

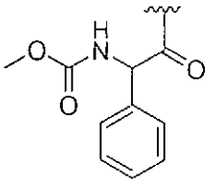
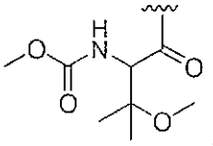
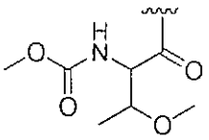
tomados junto con los átomos a los cuales están unidos, preferentemente forman un heterociclo de 5 a 6 miembros o biciclo de 6 a 12 miembros (por ejemplo,  o ) que está opcionalmente sustituido con uno o más R_A (tal como, pero no taxativamente un hidroxilo, halo (por ejemplo, fluoro), alquilo de C_1-C_6 (por ejemplo, metilo), o alquenilo de C_2-C_6 (por ejemplo, alilo)). Preferentemente, L_Y es alquileno de C_1-C_6 sustituido con uno o más R_L tal como un carbociclo de C_3-C_6 heterociclo de 3 a 6 miembros que está opcionalmente sustituido con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, alquilo de C_1-C_6, alquenilo de C_2-C_6, alquinilo de C_2-C_6, haloalquilo de C_1-C_6, haloalquenilo de C_2-C_6 o haloalquinilo de C_2-C_6. Con gran preferencia, L_Y es un alquileno de C_1-C_6 tal como, pero no taxativamente, un  ,  ,  ,  ,  , o (la estereoquímica en un carbono dentro del grupo L_Y puede ser (R) o (S)); L_Y está opcionalmente sustituido con uno o más R_L (por ejemplo, uno o más fenilo o metoxi); G preferentemente es  ; R_B'' es hidrógeno; $-C(R_8R_9)N(R_{12})-$ es  ; L_S es una unión; y R_E es metoxi.

Entre los ejemplos no limitativos de Z preferido se incluyen:  ,  ,  ,  ,  ,

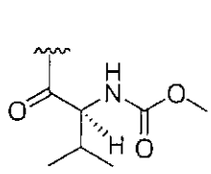
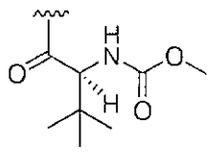
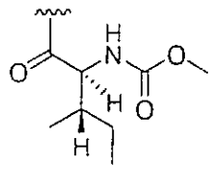
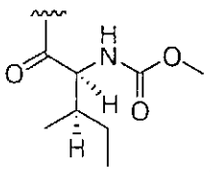
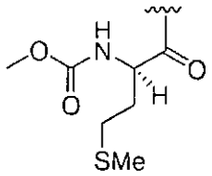

















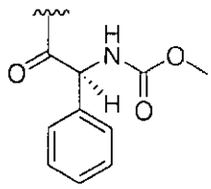
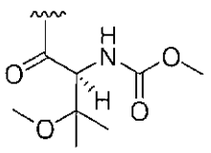
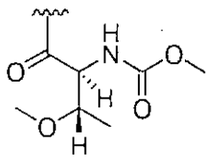
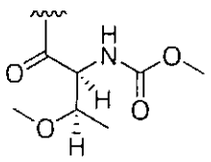
, donde T y R_D tienen los valores que se han definido. T, por ejemplo, puede ser $-L_S-M-L_S'-M'-L_S''-$ donde L_S es una unión; M es C(O); L_S' es alquileno de C_1-C_6 tal como, pero no taxativamente, un  ,  ,  ,  , o  , donde L_S' está opcionalmente sustituido con uno o más R_L; el R_L optativo es un sustituyente tal como, pero no taxativamente, un fenilo o metoxi; M' es –NHC(O)– o –NMeC(O)–; y L_S'' es una unión. Cualquier estereoquímica en un carbono dentro del grupo L_S' puede ser (R) o (S). R_D, por ejemplo es metoxi. T-R_D incluye, pero no taxativamente:

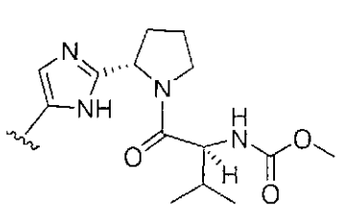
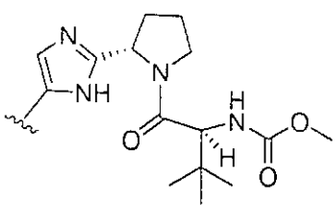
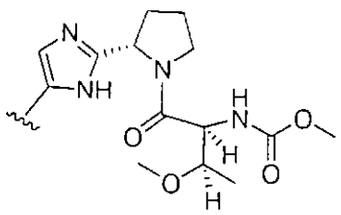
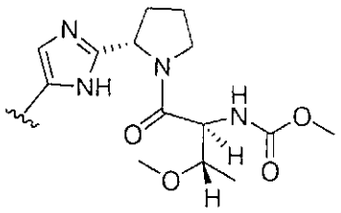
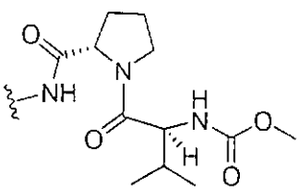
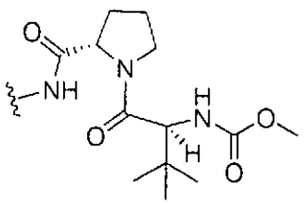
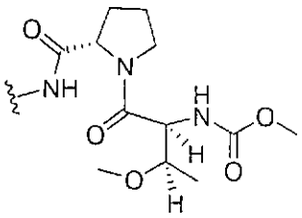
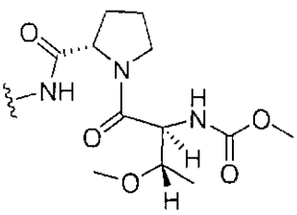
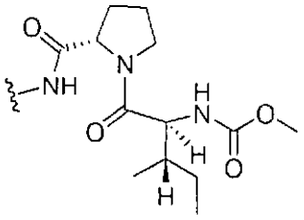
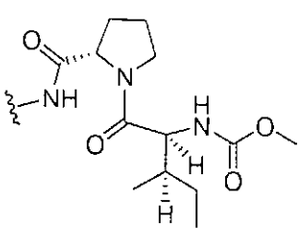
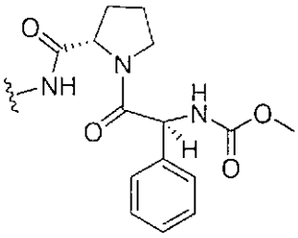
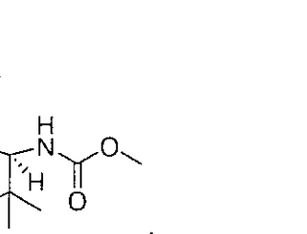
. T-R_D pueden también incluir algunas configuraciones esteroquímicas; por lo tanto T-R_D incluye, pero no taxativamente:

, y .

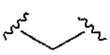
Entre los ejemplos no limitativos de Z preferido también se incluyen:

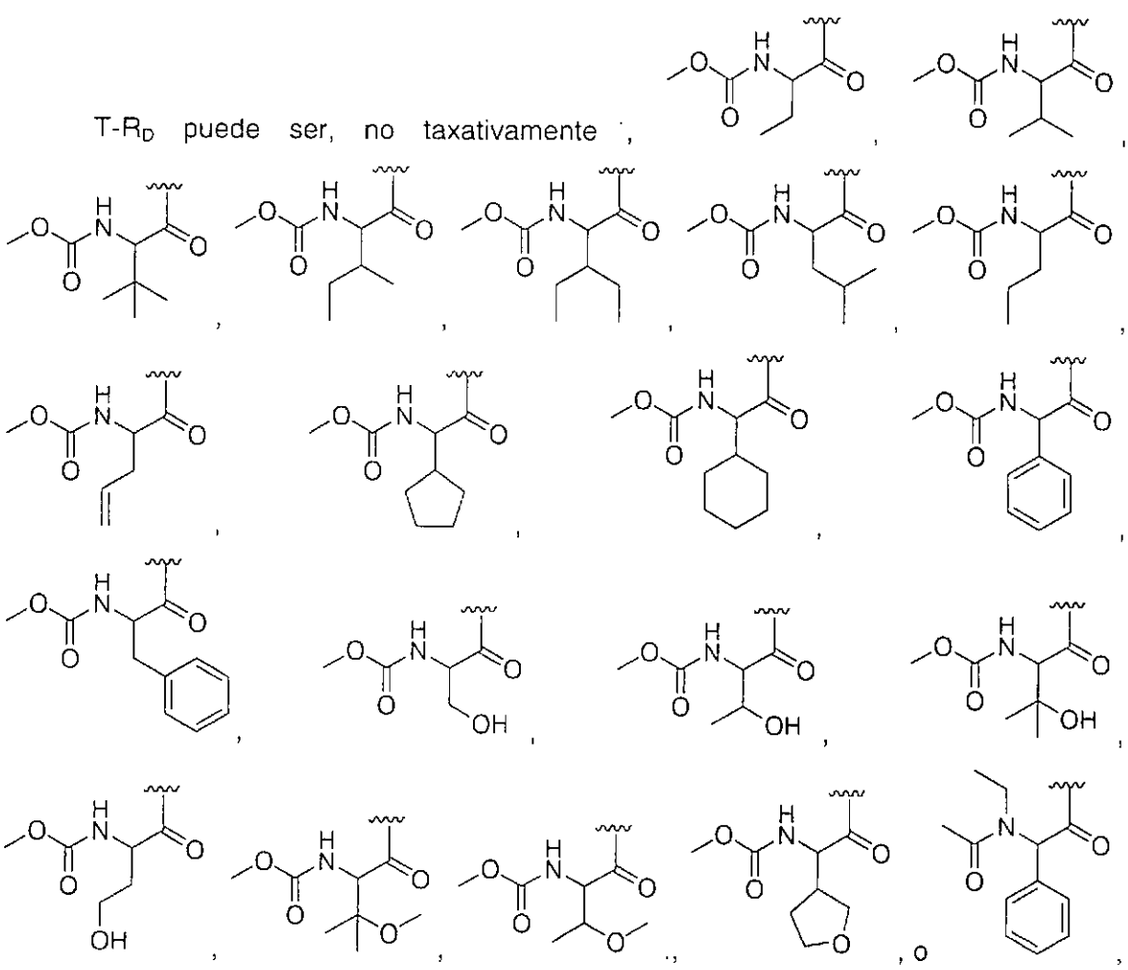













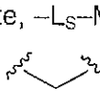
, o .

T se puede seleccionar en forma independiente en cada caso, pero no taxativamente, entre $-C(O)-L_S'-$, $-C(O)O-L_S'-$, $-C(O)-L_S'-N(R_B)C(O)-L_S''-$, $-C(O)-L_S'-N(R_B)C(O)O-L_S''-$, $-N(R_B)C(O)-L_S'-N(R_B)C(O)-L_S''-$, $-N(R_B)C(O)-L_S'—N(R_B)C(O)O-L_S''-$, o $-N(R_B)C(O)-L_S'—N(R_B)-L_S''-$. Preferentemente, T se selecciona en forma independiente en cada caso entre $-C(O)-L_S'-M'-L_S''-$ o $-N(R_B)C(O)-L_S'-M'-L_S''-$. Más preferentemente, T se selecciona en forma independiente en cada caso entre $-C(O)-L_S'-$

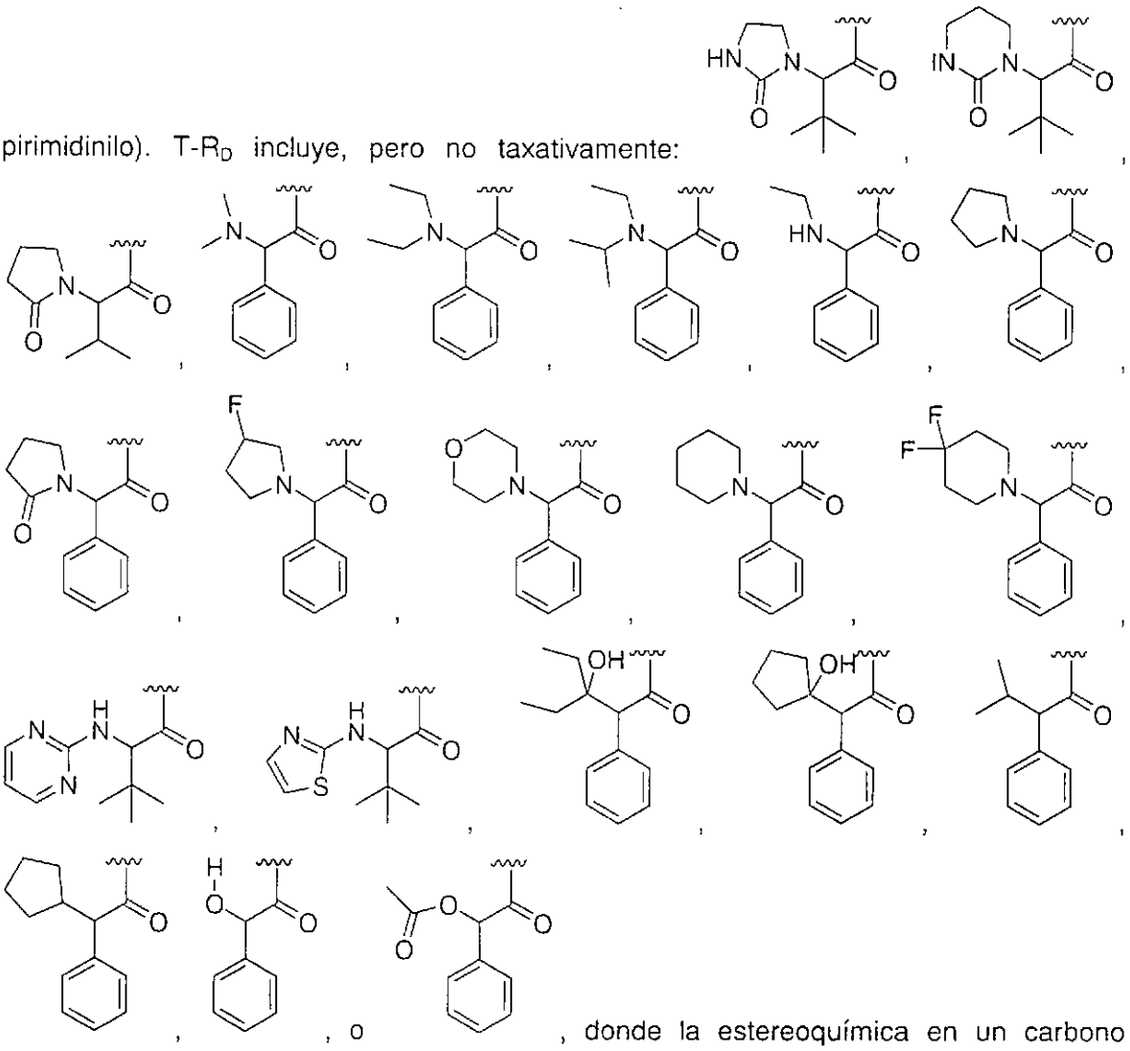
$N(R_B)C(O)–L_S''–$ o $–C(O)–L_S'–N(R_B)C(O)O–L_S''–$.

T también pueden ser, por ejemplo, $–L_S–M–L_S'–M'–L_S''–$ donde L_S es una unión; M es C(O); L_S' es alquileno de C_1-C_6 (por ejemplo, ), donde L_S' está opcionalmente sustituido con R_T; el R_T opcional es un sustituyente seleccionado entre –alquilo de C_1-C_6, –alquenilo de C_2-C_6, $–C_1$-C_6alquil–OH, $–C_1$-C_6alquil–O–alquilo de C_1-C_6, heterociclo de 3 a 6 miembros (por ejemplo, tetrahidrofuranilo), o carbociclilo de C_3-C_6 (por ejemplo, fenilo, ciclohexilo); M' es –NHC(O)–, –N(Et)C(O)– o –N(Me)C(O)–; y L_S'' es una unión. R_D preferentemente es hidrógeno, –alquilo de C_1-C_6 (por ejemplo, metilo), –O–alquilo de C_1-C_6 (por ejemplo, metoxi, tert-butoxi), metoximetilo, o $–N(C_1$-C_6alquil$)_2$ (por ejemplo, $–NMe_2$).

T-R_D puede ser, no taxativamente  , donde la estereoquímica en un carbono dentro del grupo T-R_D puede ser (R) o (S).

T can también puede ser, no taxativamente, $–L_S–M–L_S'–$ donde L_S es una unión; M es C(O); L_S' es alquileno de C_1-C_6 (por ejemplo, ) donde L_S' está opcionalmente sustituido con R_T; el R_T opcional es un sustituyente seleccionado entre –alquilo de C_1-C_6, $–C_1$-C_6alquil–OH, $–C_1$-C_6alquil–O–alquilo de C_1-C_6, o un carbociclilo de C_3-C_6 (por

ejemplo, fenilo, ciclohexilo). R_D, por ejemplo es –OH; –OC(O)Me; –NH(alquilo de C_1-C_6) (por ejemplo, –NHMe, –NHEt); –N(C_1-C_6alquil)$_2$ (por ejemplo, –NMe_2, –NEt_2); un heterociclilo de 3 a 10 miembros (por ejemplo, pirrolidinilo, imidazolidinilo, hexahidropirimidinilo, morfolinilo, piperidinilo) opcionalmente sustituido con uno o más halógeno, oxo; C_3-C_{10}carbociclo (por ejemplo, ciclopentilo) opcionalmente sustituido con –OH; –alquilo de C_1-C_6 (por ejemplo, isopropilo, 3-pentilo) opcionalmente sustituido con –OH; o NHR_T donde R_T es un heterociclilo de 3 a 6 miembros (por ejemplo, tiazolilo, pirimidinilo). T-R_D incluye, pero no taxativamente:



, donde la estereoquímica en un carbono dentro del grupo T-R_D puede ser (R) o (S).

Para cada compuesto de Fórmula I, L_K también se puede seleccionar en forma independiente en cada caso entre una unión; –L_S'–N(R_B)C(O)–L_S–; –L_S'–C(O)N(R_B)–L_S–; o alquileno de C_1-C_6, alquenileno de C_2-C_6, alquinileno de C_2-C_6, carbocilo de C_3-C_{10} o heterociclo de 3 a 10 miembros, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, R_T, –O–R_S, –S–R_S, –N($R_S$$R_S$'), –OC(O)$R_S$, –C(O)O$R_S$, nitro, oxo, fosfonoxi,

fosfono, tioxo, formilo o ciano, donde L_S y L_S' tienen los valores que se definen precedentemente.

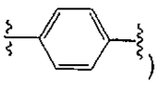
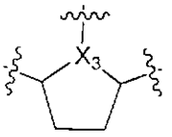
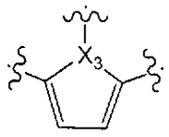
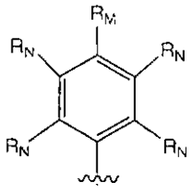
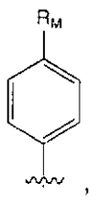
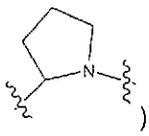
Para la Fórmula I así como también las Fórmulas I_A, I_B, I_C y I_D que se describen más adelante, que incluyen todas y cada una de las formas de realización que se describen en la presente, R_A preferentemente es halógeno, hidroxilo, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, ciano; o alquilo de C_1-C_6, alquenilo de C_2-C_6 o alquinilo de C_2-C_6, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo o ciano; o carbociclo de C_3-C_6 o heterociclo de 3 a 6 miembros, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, alquilo de C_1-C_6, alquenilo de C_2-C_6, alquinilo de C_2-C_6, haloalquilo de C_1-C_6, haloalquenilo de C_2-C_6 o haloalquinilo de C_2-C_6; o $-L_A-O-R_S$, $-L_A-S-R_S$, $-L_A-C(O)R_S$, $-L_A-OC(O)R_S$, $-L_A-C(O)OR_S$, $-L_A-N(R_SR_S')$, $-L_A-S(O)R_S$, $-L_A-SO_2R_S$, $-L_A-C(O)N(R_SR_S')$, $-L_A-N(R_S)C(O)R_S'$, $-L_A-N(R_S)C(O)N(R_S'R_S'')$, $-L_A-N(R_S)SO_2R_S'$, $-L_A-SO_2N(R_SR_S')$, $-L_A-N(R_S)SO_2N(R_S'R_S'')$, $-L_A-N(R_S)S(O)N(R_S'R_S'')$, $-L_A-OS(O)-R_S$, $-L_A-OS(O)_2-R_S$, $-L_A-S(O)_2OR_S$, $-L_A-S(O)OR_S$, $-L_A-OC(O)OR_S$, $-L_A-N(R_S)C(O)OR_S'$, $-L_A-OC(O)N(R_SR_S')$, $-L_A-N(R_S)S(O)-R_S'$, $-L_A-S(O)N(R_SR_S')$ o $-L_A-C(O)N(R_S)C(O)-R_S'$, donde L_A es una unión, alquileno de C_1-C_6, alquenileno de C_2-C_6 o alquinileno de C_2-C_6.

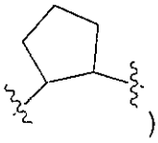
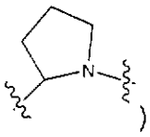
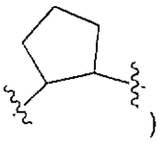
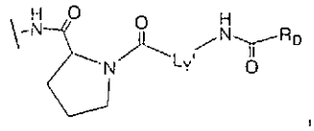
Más preferentemente, R_A es halógeno, hidroxilo, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, ciano; o alquilo de C_1-C_6, alquenilo de C_2-C_6 o alquinilo de C_2-C_6, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo o ciano; o carbociclo de C_3-C_6 o heterociclo de 3 a 6 miembros, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, alquilo de C_1-C_6, alquenilo de C_2-C_6, alquinilo de C_2-C_6, haloalquilo de C_1-C_6, haloalquenilo de C_2-C_6 o haloalquinilo de C_2-C_6.

Con gran preferencia, R_A es halógeno, hidroxilo, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, ciano; o alquilo de C_1-C_6, alquenilo de C_2-C_6 o alquinilo de C_2-C_6, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo o ciano.

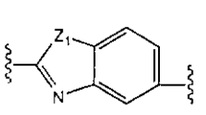
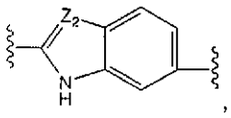
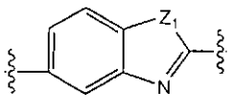
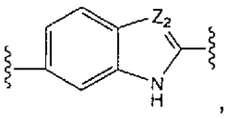
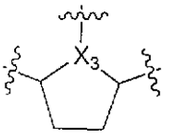
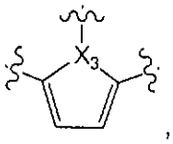
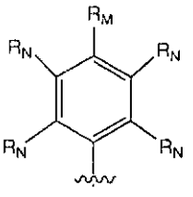
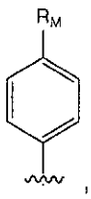
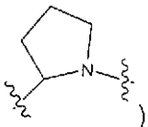
L_S, L_S' y L_S" preferentemente se seleccionan en forma independiente entre sí entre una unión; o alquileno de C_1-C_6, alquenileno de C_2-C_6 o alquinileno de C_2-C_6.

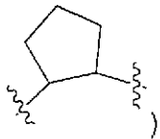
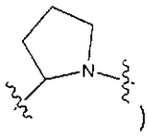
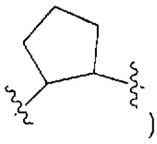
A y B pueden ser iguales o diferentes. En forma similar, L_1 y L_2, o Y y Z, o Y–A– y Z–B–, o –A–L_1– y –B–L_2–, pueden ser iguales o diferentes. En algunos casos, Y–A–L_1– es idéntico a Z–B–L_2–. En algunos otros casos, Y–A–L_1– es diferente de Z–B–L_2–.

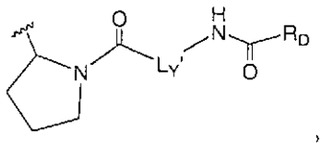
En una realización, A y B son en forma independiente entre sí carbociclo o heterociclo de 5 o 6 miembros (por ejemplo, fenilo tal como ), y están sustituidos en forma independiente entre sí con uno o más R_A. X es carbociclo o heterociclo de 5 o 6 miembros o biciclo de 6 a 12 miembros (por ejemplo,  o  , donde X_3 es N y está ligado directamente a –L_3–D) y está opcionalmente sustituido con uno o más R_A. Algunos ejemplos específicos de X son los descritos precedentemente. D es carbociclo de C_5-C_6 o heterociclo de 5 a 6 miembros (por ejemplo, fenilo), y está opcionalmente sustituido con uno o más R_A. Preferentemente, D es  o  , donde R_M y R_N tienen los valores que se definen precedentemente. L_1 y L_2 son en forma independiente entre sí una unión o alquileno de C_1-C_6, y L_3 es una unión, alquileno de C_1-C_6 o -C(O)-, y L_1, L_2, y L_3 están sustituidos en forma independiente entre sí con uno o más R_L. Preferentemente, L_1, L_2, y L_3 son una unión. Y es –N(R_B)C(O)C(R_1R_2)N(R_5)–T–R_D, o –N(R_B)C(O)C(R_3R_4)C(R_6R_7)–T–R_D, y Z es –N(R_B)C(O)C(R_8R_9)N(R_{12})–T–R_D, o –N(R_B)C(O)C($R_{10}R_{11}$)C($R_{13}R_{14}$)–T–R_D. R_1 es R_C, y R_2 y R_5, tomados junto con los átomos a los cuales están unidos, forman un anillo heterocíclico de 5 a 6 miembros (por ejemplo, ) que está opcionalmente sustituido con uno o más R_A; R_3 y R_6 son en forma independiente entre sí R_C, y R_4 y R_7, tomados junto con los átomos a los cuales están unidos, forman un anillo carbocíclico o heterocíclico de 5 a 6

miembros (por ejemplo, ) que está opcionalmente sustituido con uno o más R_A. R_8 es R_C, y R_9 y R_{12}, tomados junto con los átomos a los cuales están unidos, forman un anillo heterocíclico de 5 a 6 miembros (por ejemplo, ) que está opcionalmente sustituido con uno o más R_A; y R_{10} y R_{13} son en forma independiente entre sí R_C, y R_{11} y R_{14}, tomados junto con los átomos a los cuales están unidos, forman un anillo carbocíclico o heterocíclico de 5 a 6 miembros (por ejemplo, ) que está opcionalmente sustituido con uno o más R_A. T preferentemente se selecciona en forma independiente en cada caso entre $-C(O)-L_Y'-N(R_B)C(O)-L_S''-$ o $-C(O)-L_Y'-N(R_B)C(O)O-L_S''-$. L_Y' es cada uno en forma independiente L_S' y, preferentemente, es cada uno en forma independiente alquileno de C_1-C_6 (por ejemplo, $-CH_2-$) y opcionalmente sustituido con uno o más sustituyentes seleccionados entre R_L. T también se puede seleccionar, no taxativamente, entre $-C(O)-L_Y'-L_S''-$, $-C(O)-L_Y'-O-L_S''-$, $-C(O)-L_Y'-N(R_B)-L_S''-$, o $-C(O)-L_Y'-N(R_B)S(O)_2-L_S''-$. En algunos casos, al menos uno de Y y Z es, o ambos Y y Z son independientemente,  , donde entre los ejemplos no limitativos de R_D se incluyen (1) –O–alquilo de C_1-C_6, –O–alquenilo de C_2-C_6, –O–alquinilo de C_2-C_6, alquilo de C_1-C_6, alquenilo de C_2-C_6 o alquinilo de C_2-C_6, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, carbociclo de C_3-C_6 o heterociclo de 3 a 6 miembros; o (2) carbociclo de C_3-C_6 o heterociclo de 3 a 6 miembros cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, alquilo de C_1-C_6, alquenilo de C_2-C_6, alquinilo de C_2-C_6, haloalquilo de C_1-C_6, haloalquenilo de C_2-C_6 o haloalquinilo de C_2-C_6; y entre los ejemplos no limitativos de L_Y' se incluyen alquileno de C_1-C_6 opcionalmente sustituido con halógeno, hidroxilo, mercapto, amino, carboxi, fosfonoxi, –O–alquilo de C_1-C_6, –O–alquenilo de C_2-C_6, –O–alquinilo de C_2-C_6, o carbociclo o heterociclo de 3 a 6 miembros, estando dicho carbociclo o heterociclo de 3 a 6 miembros opcionalmente

sustituido con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, alquilo de C_1-C_6, alquenilo de C_2-C_6, alquinilo de C_2-C_6, haloalquilo de C_1-C_6, haloalquenilo de C_2-C_6 o haloalquinilo de C_2-C_6.

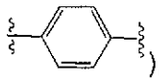
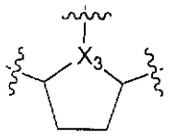
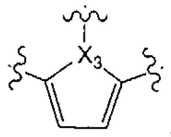
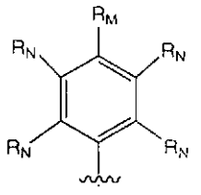
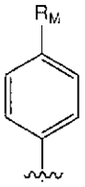
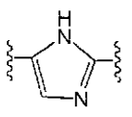
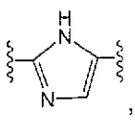
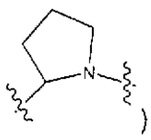
En otra realización, A es  o  , y está opcionalmente sustituido con uno o más R_A; B es  o  , y está opcionalmente sustituido con uno o más R_A. Z_1 se selecciona en forma independiente en cada caso entre O, S, NH o CH_2; y Z_2 se selecciona en forma independiente en cada caso entre N o CH. X es carbociclo o heterociclo de 5 o 6 miembros o biciclo de 6 a 12 miembros (por ejemplo,  o  , donde X_3 es N y está ligado directamente a $-L_3-D$) y está opcionalmente sustituido con uno o más R_A. Algunos ejemplos específicos de X se describen precedentemente. D es carbociclo de C_5-C_6 o heterociclo de 5 a 6 miembros (por ejemplo, fenilo), y está opcionalmente sustituido con uno o más R_A. Preferentemente, D es  o  , donde R_M y R_N tienen los valores que se definen precedentemente. L_1 y L_2 son en forma independiente entre sí una unión o alquileno de C_1-C_6, y L_3 es una unión, alquileno de C_1-C_6 o -C(O)-, y L_1, L_2, y L_3 están sustituidos en forma independiente entre sí con uno o más R_L. Preferentemente, L_1, L_2, y L_3 son una unión. Y es $-L_S-C(R_1R_2)N(R_5)-T-R_D$ o $-L_S-C(R_3R_4)C(R_6R_7)-T-R_D$, y Z es $-L_S-C(R_8R_9)N(R_{12})-T-R_D$ o $-L_S-C(R_{10}R_{11})C(R_{13}R_{14})-T-R_D$. R_1 es R_C, y R_2 y R_5, tomados junto con los átomos a los cuales están unidos, forman un anillo heterocíclico de 5 a 6 miembros (por ejemplo, ) que está opcionalmente sustituido con uno o más R_A; R_3 y R_6 son en forma independiente entre sí R_C, y R_4 y R_7, tomados junto con los átomos a los cuales están unidos, forman un anillo carbocíclico o heterocíclico de 5 a 6 miembros

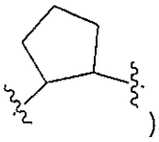
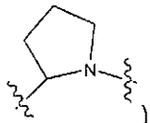
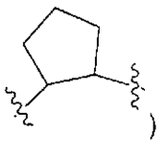
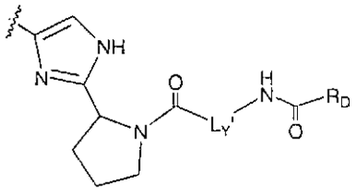
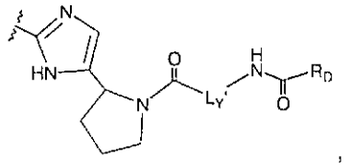
(por ejemplo, ) que está opcionalmente sustituido con uno o más R_A. R_8 es R_C, y R_9 y R_{12}, tomados junto con los átomos a los cuales están unidos, forman un anillo heterocíclico de 5 a 6 miembros (por ejemplo, ) que está opcionalmente sustituido con uno o más R_A; y R_{10} y R_{13} son en forma independiente entre sí R_C, y R_{11} y R_{14}, tomados junto con los átomos a los cuales están unidos, forman un anillo carbocíclico o heterocíclico de 5 a 6 miembros (por ejemplo, ) que está opcionalmente sustituido con uno o más R_A. T preferentemente se selecciona en forma independiente en cada caso entre $-C(O)-L_Y'-N(R_B)C(O)-L_S''-$ o $-C(O)-L_Y'-N(R_B)C(O)O-L_S''-$. L_Y' es cada uno en forma independiente L_S' y, preferentemente, es en forma independiente alquileno de C_1-C_6 (por ejemplo, $-CH_2-$) y opcionalmente sustituido con uno o más sustituyentes seleccionados entre R_L. T también se puede seleccionar, no taxativamente, entre $-C(O)-L_Y'-L_S''-$, $-C(O)-L_Y'-O-L_S''-$, $-C(O)-L_Y'-N(R_B)-L_S''-$, o $-C(O)-L_Y'-N(R_B)S(O)_2-L_S''-$. En algunos casos, al menos uno de Y y Z es, o ambos Y y Z son independientemente,



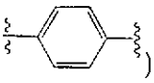
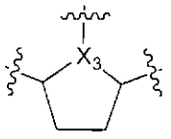
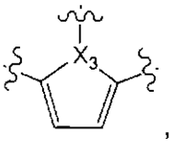
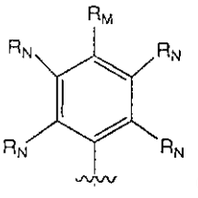
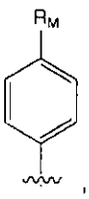
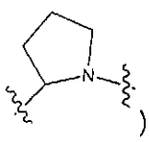
, donde entre los ejemplos no limitativos de R_D se incluyen (1) –O–alquilo de C_1-C_6, –O–alquenilo de C_2-C_6, –O–alquinilo de C_2-C_6, alquilo de C_1-C_6, alquenilo de C_2-C_6 o alquinilo de C_2-C_6, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, carbociclo de C_3-C_6 o heterociclo de 3 a 6 miembros; o (2) carbociclo de C_3-C_6 o heterociclo de 3 a 6 miembros cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, alquilo de C_1-C_6, alquenilo de C_2-C_6, alquinilo de C_2-C_6, haloalquilo de C_1-C_6, haloalquenilo de C_2-C_6 o haloalquinilo de C_2-C_6; y entre los ejemplos no limitativos de L_Y' se incluyen alquileno de C_1-C_6 opcionalmente sustituido con halógeno, hidroxilo, mercapto, amino, carboxi, fosfonoxi, –O–alquilo de C_1-C_6, –O–alquenilo de C_2-C_6, –O–alquinilo de C_2-C_6, o carbociclo o heterociclo de 3 a 6 miembros,

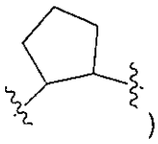
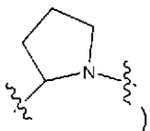
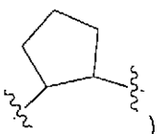
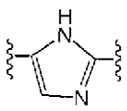
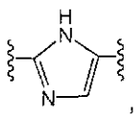
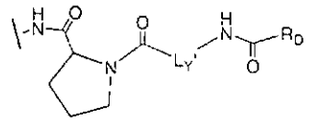
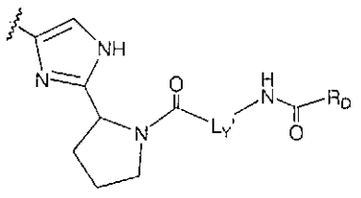
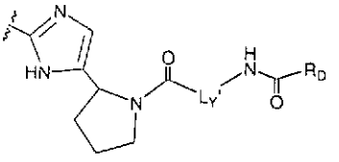
estando dicho carbociclo o heterociclo de 3 a 6 miembros opcionalmente sustituido con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, alquilo de C_1-C_6, alquenilo de C_2-C_6, alquinilo de C_2-C_6, haloalquilo de C_1-C_6, haloalquenilo de C_2-C_6 o haloalquinilo de C_2-C_6.

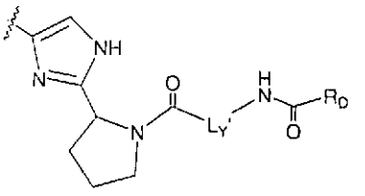
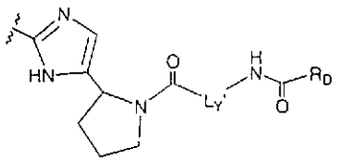
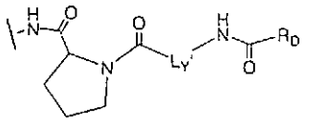
En aún otra forma de realización, A y B son en forma independiente entre sí carbociclo o heterociclo de 5 o 6 miembros (por ejemplo, A y B son en forma independiente entre sí fenilo, tal como ), y están sustituidos en forma independiente entre sí con uno o más R_A. X es carbociclo o heterociclo de 5 o 6 miembros o biciclo de 6 a 12 miembros (por ejemplo,  o  , donde X_3 es N y está ligado directamente a $-L_3-D$) y está opcionalmente sustituido con uno o más R_A. Algunos ejemplos específicos de X se describen precedentemente. D puede ser, por ejemplo, carbociclo de C_5-C_6 o heterociclo de 5 a 6 miembros (por ejemplo, fenilo), y está opcionalmente sustituido con uno o más R_A. Preferentemente, D es  o  , donde R_M y R_N tienen los valores que se definen precedentemente. L_1 y L_2 son en forma independiente entre sí una unión o alquileno de C_1-C_6, y L_3 es una unión, alquileno de C_1-C_6 o -C(O)-, y L_1, L_2, y L_3 están sustituidos en forma independiente entre sí con uno o más R_L. Preferentemente, L_1, L_2, y L_3 son una unión. Y es $-G-C(R_1R_2)N(R_5)-T-R_D$ o $-G-C(R_3R_4)C(R_6R_7)-T-R_D$, y Z es $-G-C(R_8R_9)N(R_{12})-T-R_D$ o $-G-C(R_{10}R_{11})C(R_{13}R_{14})-T-R_D$. G es en forma independiente carbociclo de C_5-C_6 o heterociclo de 5 a 6 miembros, tal como  o  , y en forma independiente está opcionalmente sustituido con uno o más R_A. R_1 es R_C, y R_2 y R_5, tomados junto con los átomos a los cuales están unidos, forman un anillo heterocíclico de 5 a 6 miembros (por ejemplo, ) que

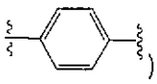
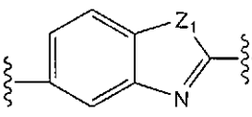
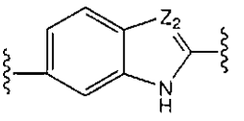
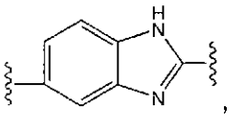
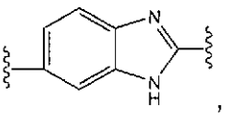
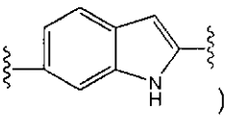
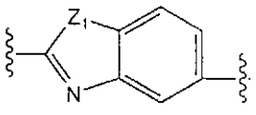
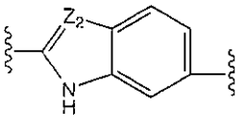
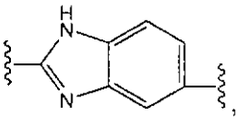
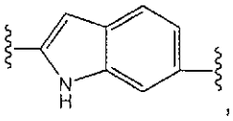
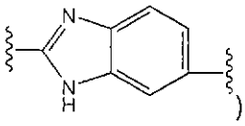
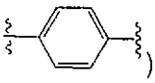
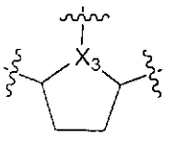
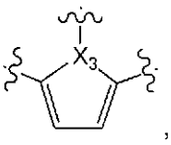
está opcionalmente sustituido con uno o más R_A; R_3 y R_6 son en forma independiente entre sí R_C, y R_4 y R_7, tomados junto con los átomos a los cuales están unidos, forman un anillo carbocíclico o heterocíclico de 5 a 6 miembros (por ejemplo, ) que está opcionalmente sustituido con uno o más R_A. R_8 es R_C, y R_9 y R_{12}, tomados junto con los átomos a los cuales están unidos, forman un anillo heterocíclico de 5 a 6 miembros (por ejemplo, ) que está opcionalmente sustituido con uno o más R_A; y R_{10} y R_{13} son en forma independiente entre sí R_C, y R_{11} y R_{14}, tomados junto con los átomos a los cuales están unidos, forman un anillo carbocíclico o heterocíclico de 5 a 6 miembros (por ejemplo, ) que está opcionalmente sustituido con uno o más R_A. T preferentemente se selecciona en forma independiente en cada caso entre $-C(O)-L_Y'-N(R_B)C(O)-L_S''-$ o $-C(O)-L_Y'-N(R_B)C(O)O-L_S''-$. L_Y' es cada uno en forma independiente L_S' y, preferentemente, es cada uno en forma independiente alquileno de C_1-C_6 (por ejemplo, $-CH_2-$) y opcionalmente sustituido con uno o más sustituyentes seleccionados entre R_L. T también se puede seleccionar, no taxativamente, entre $-C(O)-L_Y'-L_S''-$, $-C(O)-L_Y'-O-L_S''-$, $-C(O)-L_Y'-N(R_B)-L_S''-$, o $-C(O)-L_Y'-N(R_B)S(O)_2-L_S''-$. En algunos casos, al menos uno de Y y Z es, o ambos Y y Z son independientemente,  o  , donde entre los ejemplos no limitativos de R_D se incluyen (1) –O–alquilo de C_1-C_6, –O–alquenilo de C_2-C_6, –O–alquinilo de C_2-C_6, alquilo de C_1-C_6, alquenilo de C_2-C_6 o alquinilo de C_2-C_6, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, carbociclo de C_3-C_6 o heterociclo de 3 a 6 miembros; o (2) carbociclo de C_3-C_6 o heterociclo de 3 a 6 miembros cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, alquilo de C_1-C_6, alquenilo de C_2-C_6,

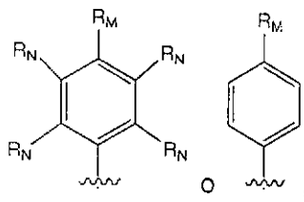
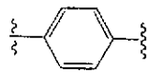
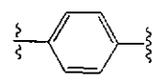
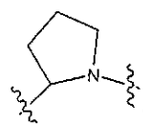
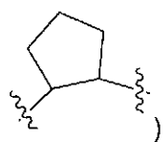
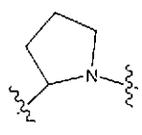
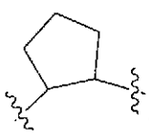
alquinilo de C_2-C_6, haloalquilo de C_1-C_6, haloalquenilo de C_2-C_6 o haloalquinilo de C_2-C_6; y entre los ejemplos no limitativos de L_Y' se incluyen alquileno de C_1-C_6 opcionalmente sustituido con halógeno, hidroxilo, mercapto, amino, carboxi, fosfonoxi, –O–alquilo de C_1-C_6, –O–alquenilo de C_2-C_6, –O–alquinilo de C_2-C_6, o carbociclo o heterociclo de 3 a 6 miembros, estando dicho carbociclo o heterociclo de 3 a 6 miembros opcionalmente sustituido con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, alquilo de C_1-C_6, alquenilo de C_2-C_6, alquinilo de C_2-C_6, haloalquilo de C_1-C_6, haloalquenilo de C_2-C_6 o haloalquinilo de C_2-C_6.

En aún otra realización, A y B son en forma independiente entre sí carbociclo o heterociclo de 5 o 6 miembros (por ejemplo, A y B son en forma independiente entre sí fenilo, tal como ), y están sustituidos en forma independiente entre sí con uno o más R_A. X es carbociclo o heterociclo de 5 o 6 miembros o biciclo de 6 a 12 miembros (por ejemplo,  o  , donde X_3 es N y está ligado directamente a –L_3–D) y está opcionalmente sustituido con uno o más R_A. Algunos ejemplos específicos de X se describen precedentemente. D puede ser, por ejemplo, Carbociclo de C_5-C_6 o heterociclo de 5 a 6 miembros (por ejemplo, fenilo), y está opcionalmente sustituido con uno o más R_A. Preferentemente, D es  o  , donde R_M y R_N tienen los valores que se definen precedentemente. L_1 y L_2 son en forma independiente entre sí una unión o alquileno de C_1-C_6, y L_3 es una unión, alquileno de C_1-C_6 o -C(O)-, y L_1, L_2, y L_3 están sustituidos en forma independiente entre sí con uno o más R_L. Preferentemente, L_1, L_2, y L_3 son una unión. Y es –N(R_B)C(O)C(R_1R_2)N(R_5)–T–R_D o –N(R_B)C(O)C(R_3R_4)C(R_6R_7)–T–R_D, y Z es –G–C(R_8R_9)N(R_{12})–T–R_D o –G–C($R_{10}R_{11}$)C($R_{13}R_{14}$)–T–R_D; o Y es –G–C(R_1R_2)N(R_5)–T–R_D o –G–C(R_3R_4)C(R_6R_7)–T–R_D, y Z es –N(R_B)C(O)C(R_8R_9)N(R_{12})–T–R_D o –N(R_B)C(O)C($R_{10}R_{11}$)C($R_{13}R_{14}$)–T–R_D. R_1 es R_C, y R_2 y R_5, tomados junto con los átomos a los cuales están unidos, forman un anillo heterocíclico de 5 a 6 miembros (por ejemplo, ) que está opcionalmente

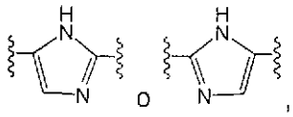
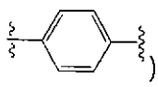
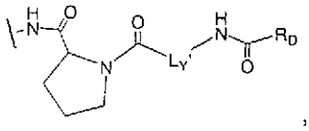
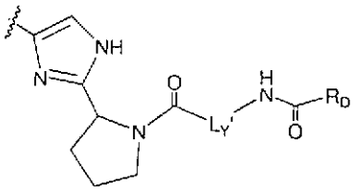
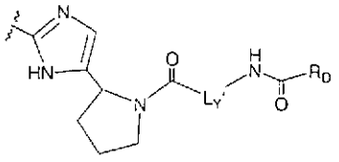
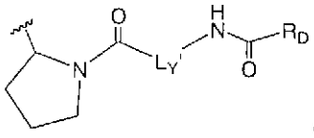
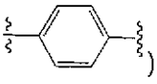
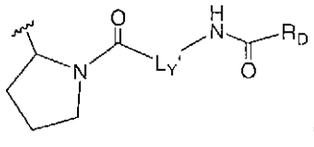
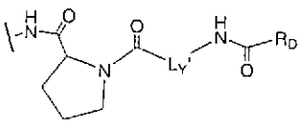
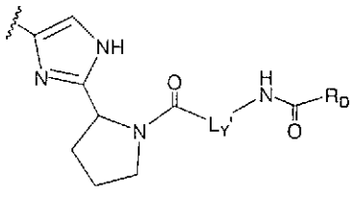
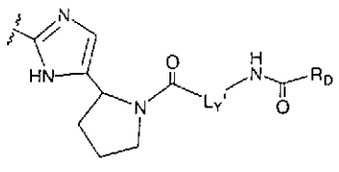
sustituido con uno o más R_A; R_3 y R_6 son en forma independiente entre sí R_C, y R_4 y R_7, tomados junto con los átomos a los cuales están unidos, forman un anillo carbocíclico o heterocíclico de 5 a 6 miembros (por ejemplo, ) que está opcionalmente sustituido con uno o más R_A. R_8 es R_C, y R_9 y R_{12}, tomados junto con los átomos a los cuales están unidos, forman un anillo heterocíclico de 5 a 6 miembros (por ejemplo, ) que está opcionalmente sustituido con uno o más R_A; y R_{10} y R_{13} son en forma independiente entre sí R_C, y R_{11} y R_{14}, tomados junto con los átomos a los cuales están unidos, forman un anillo carbocíclico o heterocíclico de 5 a 6 miembros (por ejemplo, ) que está opcionalmente sustituido con uno o más R_A. G es en forma independiente carbociclo de C_5-C_6 o heterociclo de 5 a 6 miembros, tal como  o  , y en forma independiente está opcionalmente sustituido con uno o más R_A. T preferentemente se selecciona en forma independiente en cada caso entre –C(O)–L_Y'–N(R_B)C(O)–L_S"– o –C(O)–L_Y'–N(R_B)C(O)O–L_S"–. L_Y' es cada uno en forma independiente L_S' y, preferentemente, es cada uno en forma independiente alquileno de C_1-C_6 (por ejemplo, -CH_2-) y opcionalmente sustituido con uno o más sustituyentes seleccionados entre R_L. T también se puede seleccionar, no taxativamente, entre –C(O)–L_Y'–L_S"–, –C(O)–L_Y'–O–L_S"–, –C(O)–L_Y'–N(R_B)–L_S"–, o –C(O)–L_Y'–N(R_B)S(O)$_2$–L_S"–. En algunos casos, Y es  como se describe precedentemente, y Z es  o  como se describe

precedentemente. En algunos otros casos, Y es  o  como se describe precedentemente , y Z es  como se describe precedentemente.

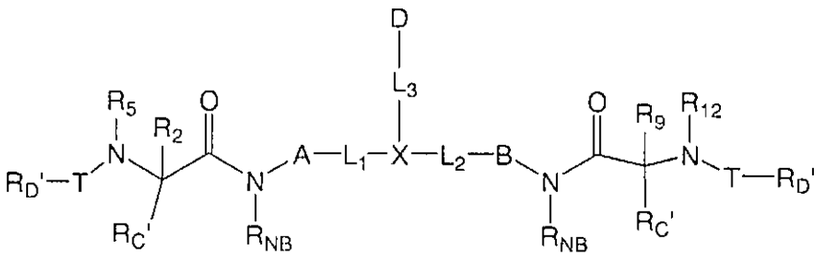
En aún otra realización, A es carbociclo o heterociclo de 5 o 6 miembros (por ejemplo, fenilo tal como ), y B es  o  (por ejemplo,  ,  , o ); o A es  o  (por ejemplo,  ,  , o ), y B es carbociclo o heterociclo de 5 o 6 miembros (por ejemplo, fenilo tal como ). A y B están sustituidos en forma independiente entre sí con uno o más R_A. Z_1 se selecciona en forma independiente en cada caso entre O, S, NH o CH_2; y Z_2 se selecciona en forma independiente en cada caso entre N o CH. X es carbociclo o heterociclo de 5 o 6 miembros o biciclo de 6 a 12 miembros (por ejemplo,  o  , donde X_3 es N y está ligado directamente a $-L_3-D$) y está opcionalmente sustituido con uno o más R_A. Algunos ejemplos específicos de X se describen precedentemente. D es carbociclo de C_5-C_6 o heterociclo de 5 a 6 miembros (por ejemplo, fenilo), y está opcionalmente sustituido con

uno o más R_A. Preferentemente, D es  o , donde R_M y R_N tienen los valores que se definen precedentemente. L_1 y L_2 son en forma independiente entre sí una unión o alquileno de C_1-C_6, y L_3 es una unión, alquileno de C_1-C_6 o -C(O)-, y L_1, L_2, y L_3 están sustituidos en forma independiente entre sí con uno o más R_L. Preferentemente, L_1, L_2, y L_3 son una unión. Cuando A es carbociclo o heterociclo de 5 o 6 miembros (por ejemplo, fenilo tal como ), Y es $-N(R_B)C(O)C(R_1R_2)N(R_5)-T-R_D$, $-N(R_B)C(O)C(R_3R_4)C(R_6R_7)-T-R_D$, $-G-C(R_1R_2)N(R_5)-T-R_D$ o $-G-C(R_3R_4)C(R_6R_7)-T-R_D$, y Z es $-L_S-C(R_8R_9)N(R_{12})-T-R_D$ o $-L_S-C(R_{10}R_{11})C(R_{13}R_{14})-T-R_D$. Cuando B es carbociclo o heterociclo de 5 o 6 miembros (por ejemplo, fenilo tal como ), Y es $-L_S-C(R_1R_2)N(R_5)-T-R_D$ o $-L_S-C(R_3R_4)C(R_6R_7)-T-R_D$, y Z es $-N(R_B)C(O)C(R_8R_9)N(R_{12})-T-R_D$, $-N(R_B)C(O)C(R_{10}R_{11})C(R_{13}R_{14})-T-R_D$, $-G-C(R_8R_9)N(R_{12})-T-R_D$ o $-G-C(R_{10}R_{11})C(R_{13}R_{14})-T-R_D$. R_1 es R_C, y R_2 y R_5, tomados junto con los átomos a los cuales están unidos, forman un anillo heterocíclico de 5 a 6 miembros (por ejemplo, ) que está opcionalmente sustituido con uno o más R_A; R_3 y R_6 son en forma independiente entre sí R_C, y R_4 y R_7, tomados junto con los átomos a los cuales están unidos, forman un anillo carbocíclico o heterocíclico de 5 a 6 miembros (por ejemplo, ) que está opcionalmente sustituido con uno o más R_A. R_8 es R_C, y R_9 y R_{12}, tomados junto con los átomos a los cuales están unidos, forman un anillo heterocíclico de 5 a 6 miembros (por ejemplo, ) que está opcionalmente sustituido con uno o más R_A; y R_{10} y R_{13} son en forma independiente entre sí R_C, y R_{11} y R_{14}, tomados junto con los átomos a los cuales están unidos, forman un anillo carbocíclico o heterocíclico de 5 a 6 miembros (por ejemplo, ) que está opcionalmente sustituido con uno o más R_A. G es en forma independiente carbociclo de C_5-C_6 o heterociclo de 5 a 6 miembros, tal como

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, y en forma independiente está opcionalmente sustituido con uno o más R_A. T preferentemente se selecciona en forma independiente en cada caso entre –C(O)–L_Y'–N(R_B)C(O)–L_S"– o –C(O)–L_Y'–N(R_B)C(O)O–L_S"–. L_Y' es cada uno en forma independiente L_S' y, preferentemente, es cada uno en forma independiente alquileno de C_1-C_6 (por ejemplo, -CH_2-) y opcionalmente sustituido con uno o más sustituyentes seleccionados entre R_L. T también se puede seleccionar, no taxativamente, entre –C(O)–L_Y'–L_S"–, –C(O)–L_Y'–O–L_S"–, –C(O)–L_Y'–N(R_B)–L_S"–, o –C(O)–L_Y'–N(R_B)S(O)$_2$–L_S"–. En algunos casos cuando A es carbociclo o heterociclo de 5 o 6 miembros (por ejemplo, fenilo tal como ), Y es  ,  o  como se describe precedentemente, y Z es  como se describe precedentemente. En algunos otros casos cuando B es carbociclo o heterociclo de 5 o 6 miembros (por ejemplo, fenilo tal como ), Y es  como se describe precedentemente, y Z es  ,  o  como se describe precedentemente.

En otro aspecto, la presente invención presenta compuestos de fórmula I_A y sus sales farmacéuticamente aceptables.



I_A

donde:

R_{NB} se selecciona cada uno en forma independiente entre R_B;

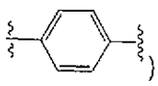
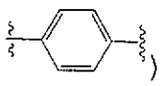
R_C' se selecciona cada uno en forma independiente entre R_C;

R_D' se selecciona cada uno en forma independiente entre R_D;

R_2 y R_5, tomados junto con los átomos a los cuales están unidos, forman un heterociclo de 3 a 12 miembros que está opcionalmente sustituido con uno o más R_A;

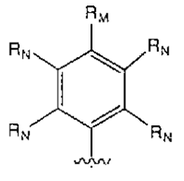
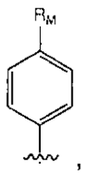
R_9 y R_{12}, tomados junto con los átomos a los cuales están unidos, forman un heterociclo de 3 a 12 miembros que está opcionalmente sustituido con uno o más R_A;

A, B, D, X, L_1, L_2, L_3, T, R_A, R_B, R_C, y R_D tienen los valores que se describen precedentemente en la Fórmula I.

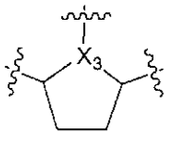
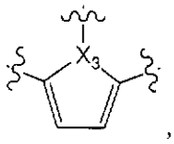
En este aspecto, A y B preferentemente se seleccionan en forma independiente entre carbociclo de C_5-C_6 o heterociclo de 5 a 6 miembros, y están sustituidos en forma independiente entre sí con uno o más R_A. Más preferentemente, al menos uno de A y B es fenilo (por ejemplo, ), y está opcionalmente sustituido con uno o más R_A. Con gran preferencia, ambos A y B son en forma independiente entre sí fenilo (por ejemplo, ), y están sustituidos en forma independiente entre sí con uno o más R_A.

D preferentemente se selecciona entre C_5-C_6carbociclo, heterociclo de 5 a 6 miembros, o biciclos de 8 a 12 miembros, y está opcionalmente sustituido con uno o más R_A. D también se puede seleccionar preferentemente entre alquilo de C_1-C_6, alquenilo de C_2-C_6 o alquinilo de C_2-C_6, y está opcionalmente sustituido con uno o más R_L. Más preferentemente, D es C_5-C_6carbociclo, heterociclo de 5 a 6 miembros, o biciclos de 6 a 12 miembros, y se sustituye con uno o más R_M, donde R_M es halógeno, nitro, oxo, fosfonoxi, fosfono, tioxo, ciano, o $-L_S-R_E$. También preferentemente, D es fenilo, y está opcionalmente sustituido con uno o más R_A. Más preferentemente, D es fenilo, y se sustituye con uno o más R_M, donde R_M tiene los valores que se definen precedentemente.

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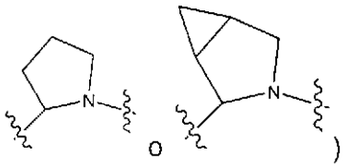
Con gran preferencia, D es  o  , donde R_M tiene los valores que se definen precedentemente, y cada R_N se selecciona en forma independiente entre R_D y preferentemente es hidrógeno.

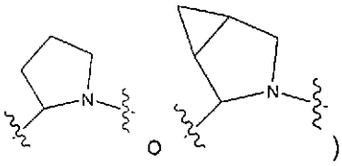
Preferentemente, R_M es halógeno, hidroxilo, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, ciano; o alquilo de C_1-C_6, alquenilo de C_2-C_6 o alquinilo de C_2-C_6, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo o ciano; o carbociclo de C_3-C_6 o heterociclo de 3 a 6 miembros, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, alquilo de C_1-C_6, alquenilo de C_2-C_6, alquinilo de C_2-C_6, haloalquilo de C_1-C_6, haloalquenilo de C_2-C_6 o haloalquinilo de C_2-C_6. Más preferentemente, R_M es halógeno, hidroxilo, mercapto, amino, carboxi; o alquilo de C_1-C_6, alquenilo de C_2-C_6 o alquinilo de C_2-C_6, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, mercapto, amino o carboxi. Con gran preferencia, R_M es alquilo de C_1-C_6 el cual está opcionalmente sustituido con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, mercapto, amino o carboxi.

X preferentemente es C_5-C_6carbociclo, heterociclo de 5 a 6 miembros, biciclos de 6 a 12 miembros (por ejemplo,  o  , donde X_3 es N y está ligado directamente a $-L_3-D$), y está opcionalmente sustituido con uno o más R_A. Algunos ejemplos de X son los descritos precedentemente sin carácter taxativo.

L_1 y L_2 son preferentemente en forma independiente una unión o alquileno de C_1-C_6, L_3 se selecciona preferentemente entre una unión, alquileno de C_1-C_6 o $-C(O)-$, y L_1, L_2, y L_3 están sustituidos en forma independiente entre sí con uno o más R_L. Más preferentemente, L_1, L_2 y L_3 son en forma independiente entre sí una unión o alquileno de C_1-C_6 (por ejemplo, $-CH_2-$ o $-CH_2CH_2-$), y están sustituidos en forma independiente entre sí con uno o más R_L. Con gran preferencia, L_1, L_2 y L_3 son una unión.

R_2 y R_5, tomados junto con los átomos a los cuales están unidos, preferentemente forman un heterociclo de 5 a 6 miembros o biciclo de 6 a 12 miembros (por ejemplo,

), que está opcionalmente sustituido con uno o más R_A.

R_9 y R_{12}, tomados junto con los átomos a los cuales están unidos, preferentemente forman un heterociclo de 5 a 6 miembros o biciclo de 6 a 12 miembros (por ejemplo, ), que está opcionalmente sustituido con uno o más R_A.

-T-R_D' se puede seleccionar en forma independiente en cada caso, pero no taxativamente, entre –C(O)–L_Y'–, –C(O)O–L_Y'–R_D', –C(O)–L_Y'–N(R_B)C(O)–L_S''–R_D', –C(O)–L_Y'–N(R_B)C(O)O–L_S''–R_D', –N(R_B)C(O)–L_Y'–N(R_B)C(O)–L_S''–R_D', –N(R_B)C(O)–L_Y'—N(R_B)C(O)O–L_S''–R_D', o –N(R_B)C(O)–L_Y'—N(R_B)–L_S''–R_D', donde L_Y' es cada uno en forma independiente L_S' y, preferentemente, es cada uno en forma independiente alquileno de C_1-C_6 (por ejemplo, -CH_2-) y opcionalmente sustituido con uno o más sustituyentes seleccionados entre R_L. Preferentemente, -T-R_D' se selecciona en forma independiente en cada caso entre –C(O)–L_Y'–M'–L_S''–R_D' o –N(R_B)C(O)–L_Y'–M'–L_S''–R_D'. Más preferentemente, -T-R_D' se selecciona en forma independiente en cada caso entre –C(O)–L_Y'–N(R_B)C(O)–L_S''–R_D' o –C(O)–L_Y'–N(R_B)C(O)O–L_S''–R_D'. Con gran preferencia, -T-R_D' se selecciona en forma independiente en cada caso entre –C(O)–L_Y'–N(R_B)C(O)–R_D' o –C(O)–L_Y'–N(R_B)C(O)O–R_D', donde L_Y' preferentemente es cada uno en forma independiente alquileno de C_1-C_6 (por ejemplo, -CH_2-) y opcionalmente sustituido con uno o más sustituyentes seleccionados entre R_L.

R_{NB} y R_C' son preferentemente hidrógeno, y R_D' preferentemente se selecciona en forma independiente en cada caso entre R_E. Más preferentemente, R_D' se selecciona en forma independiente en cada caso entre alquilo de C_1-C_6, alquenilo de C_2-C_6 o alquinilo de C_2-C_6, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, carbociclo de C_3-C_6 o heterociclo de 3 a 6 miembros; o carbociclo de C_3-C_6 o heterociclo de 3 a 6 miembros, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, alquilo de C_1-C_6, alquenilo de C_2-C_6, alquinilo de C_2-C_6, haloalquilo de C_1-C_6, haloalquenilo de C_2-C_6 o haloalquinilo de C_2-C_6.

R_A preferentemente es halógeno, hidroxilo, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, ciano; o alquilo de C_1-C_6, alquenilo de C_2-C_6 o alquinilo de C_2-C_6, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo o ciano; o carbociclo de C_3-C_6 o heterociclo de 3 a 6 miembros, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, alquilo de C_1-C_6, alquenilo de C_2-C_6, alquinilo de C_2-C_6, haloalquilo de C_1-C_6, haloalquenilo de C_2-C_6 o haloalquinilo de C_2-C_6; o $-L_A-O-R_S$, $-L_A-S-R_S$, $-L_A-C(O)R_S$, $-L_A-OC(O)R_S$, $-L_A-C(O)OR_S$, $-L_A-N(R_SR_S')$, $-L_A-S(O)R_S$, $-L_A-SO_2R_S$, $-L_A-C(O)N(R_SR_S')$, $-L_A-N(R_S)C(O)R_S'$, $-L_A-N(R_S)C(O)N(R_S'R_S'')$, $-L_A-N(R_S)SO_2R_S'$, $-L_A-SO_2N(R_SR_S')$, $-L_A-N(R_S)SO_2N(R_S'R_S'')$, $-L_A-N(R_S)S(O)N(R_S'R_S'')$, $-L_A-OS(O)-R_S$, $-L_A-OS(O)_2-R_S$, $-L_A-S(O)_2OR_S$, $-L_A-S(O)OR_S$, $-L_A-OC(O)OR_S$, $-L_A-N(R_S)C(O)OR_S'$, $-L_A-OC(O)N(R_SR_S')$, $-L_A-N(R_S)S(O)-R_S'$, $-L_A-S(O)N(R_SR_S')$ o $-L_A-C(O)N(R_S)C(O)-R_S'$, donde L_A es una unión, alquileno de C_1-C_6, alquenileno de C_2-C_6 o alquinileno de C_2-C_6.

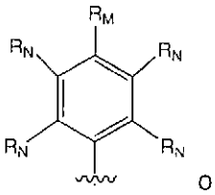
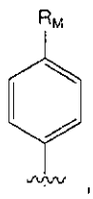
Más preferentemente, R_A es halógeno, hidroxilo, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, ciano; o alquilo de C_1-C_6, alquenilo de C_2-C_6 o alquinilo de C_2-C_6, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo o ciano; o carbociclo de C_3-C_6 o heterociclo de 3 a 6 miembros, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, alquilo de C_1-C_6, alquenilo de C_2-C_6, alquinilo de C_2-C_6, haloalquilo de C_1-C_6, haloalquenilo de C_2-C_6 o haloalquinilo de C_2-C_6.

Con gran preferencia, R_A es halógeno, hidroxilo, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, ciano; o alquilo de C_1-C_6, alquenilo de C_2-C_6 o alquinilo de C_2-C_6, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo o ciano.

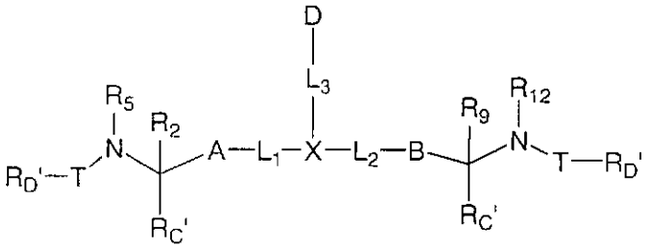
L_S, L_S' y L_S'' preferentemente se seleccionan en forma independiente entre sí entre una unión; o alquileno de C_1-C_6, alquenileno de C_2-C_6 o alquinileno de C_2-C_6.

A y B pueden ser iguales o diferentes. En forma similar, L_1 y L_2 pueden ser iguales o diferentes.

En una realización de este aspecto, A, B, y D son en forma independiente entre sí

fenilo, y están sustituidos en forma independiente entre sí con uno o más R_A. Preferentemente, D es  o  , donde R_M y R_N tienen los valores que se definen precedentemente. L_1 y L_2 son en forma independiente entre sí una unión o alquileno de C_1-C_6, y L_3 es una unión, alquileno de C_1-C_6 o -C(O)-, y L_1, L_2, y L_3 están sustituidos en forma independiente entre sí con uno o más R_L. Preferentemente, L_1, L_2, y L_3 son una unión. -T-R_D' se selecciona en forma independiente en cada caso entre –C(O)–L_Y'–N(R_B)C(O)–L_S"–R_D' o –C(O)–L_Y'–N(R_B)C(O)O–L_S"–R_D', donde L_Y' es alquileno de C_1-C_6 (por ejemplo, -CH_2-) y opcionalmente sustituido con uno o más sustituyentes seleccionados entre R_L, y L_S" preferentemente es una unión. –T-R_D' también se puede seleccionar, no taxativamente, entre –C(O)–L_Y'–L_S"–R_D', –C(O)–L_Y'–O–L_S"–R_D', –C(O)–L_Y'–N(R_B)–L_S"–R_D', o –C(O)–L_Y'–N(R_B)S(O)$_2$–L_S"–R_D'.

En aún otro aspecto, la presente invención presenta compuestos de fórmula I_B y sus sales farmacéuticamente aceptables:



I_B

donde:

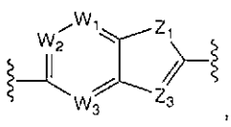
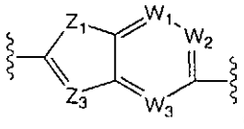
R_C' se selecciona cada uno en forma independiente entre R_C;

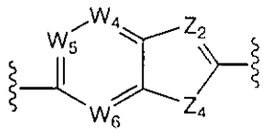
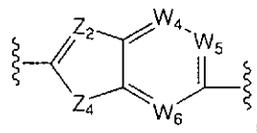
R_D' se selecciona cada uno en forma independiente entre R_D;

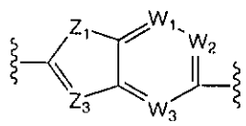
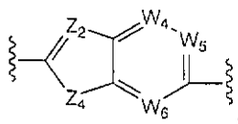
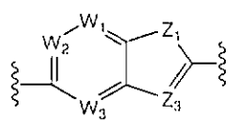
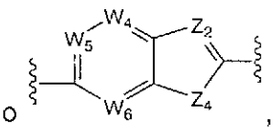
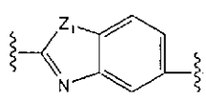
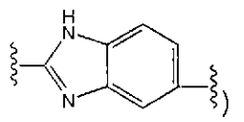
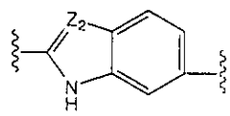
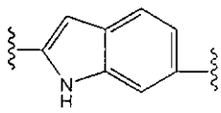
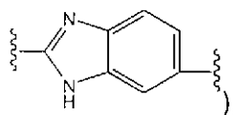
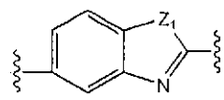
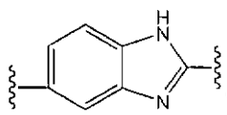
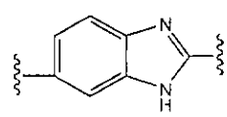
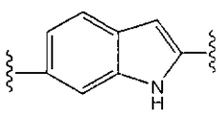
R_2 y R_5, tomados junto con los átomos a los cuales están unidos, forman un heterociclo de 3 a 12 miembros que está opcionalmente sustituido con uno o más R_A;

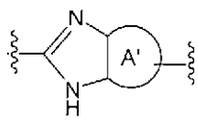
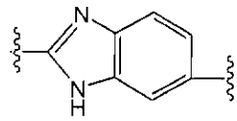
R_9 y R_{12}, tomados junto con los átomos a los cuales están unidos, forman un heterociclo de 3 a 12 miembros que está opcionalmente sustituido con uno o más R_A;

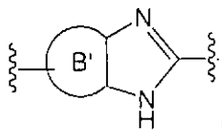
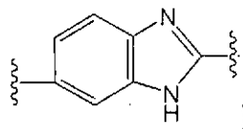
A, B, D, X, L_1, L_2, L_3, T, R_A, R_C, y R_D tienen los valores que se describen precedentemente en la Fórmula I.

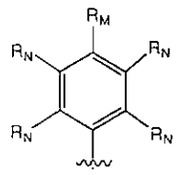
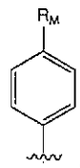
En este aspecto, A y B preferentemente se seleccionan en forma independiente entre biciclos de 8 a 12 miembros tal como  ,  ,

 o  , donde Z_1 se selecciona en forma independiente en cada caso entre O, S, NH o CH_2, Z_2 se selecciona en forma independiente en cada caso entre N o CH, Z_3 se selecciona en forma independiente en cada caso entre N o CH, Z_4 se selecciona en forma independiente en cada caso entre O, S, NH o CH_2, y W_1, W_2, W_3, W_4, W_5 y W_6 se seleccionan en forma independiente entre sí en cada caso entre CH o N. A y B están sustituidos en forma independiente entre sí con uno o más R_A.

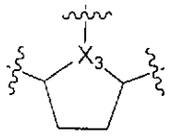
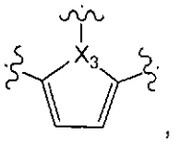
Más preferentemente, A se selecciona entre  o  , y está opcionalmente sustituido con uno o más R_A; B se selecciona entre  o  , y está opcionalmente sustituido con uno o más R_A, donde Z_1, Z_2, Z_3, Z_4, W_1, W_2, W_3, W_4, W_5, W_6 tienen los valores que se definen precedentemente. Preferentemente, Z_3 es N y Z_4 es NH. Por ejemplo, A se puede seleccionar entre  (por ejemplo, ) o  (por ejemplo,  o ), y está opcionalmente sustituido con uno o más R_A; y B se puede seleccionar entre  (por ejemplo, ) o  (por ejemplo,  o ), y está opcionalmente sustituido con uno o más R_A.

También preferentemente, A es  (por ejemplo, ),

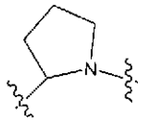
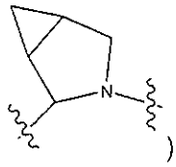
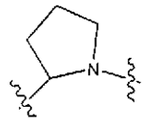
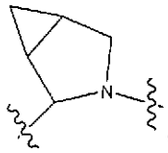
y B es  (por ejemplo, ), donde A' y B' se seleccionan en forma independiente entre carbociclo de C_5-C_6 o heterociclo de 5 a 6 miembros, y A y B son en forma independiente opcionalmente sustituido con uno o más R_A.

D preferentemente se selecciona entre C_5-C_6carbociclo, heterociclo de 5 a 6 miembros, o biciclos de 6 a 12 miembros, y está opcionalmente sustituido con uno o más R_A. D también se puede seleccionar preferentemente entre alquilo de C_1-C_6, alquenilo de C_2-C_6 o alquinilo de C_2-C_6, y está opcionalmente sustituido con uno o más sustituyentes seleccionados entre R_L. Más preferentemente, D es C_5-C_6carbociclo, heterociclo de 5 a 6 miembros, o biciclos de 6 a 12 miembros, y se sustituye con uno o más R_M, donde R_M es halógeno, nitro, oxo, fosfonoxi, fosfono, tioxo, ciano, o $-L_S-R_E$. También preferentemente, D es fenilo, y está opcionalmente sustituido con uno o más R_A. Más preferentemente, D es fenilo, y se sustituye con uno o más R_M, donde R_M tiene los valores que se definen precedentemente. Con gran preferencia, D es  o  , donde R_M tiene los valores que se definen precedentemente, y cada R_N se selecciona en forma independiente entre R_D y preferentemente es hidrógeno.

Preferentemente, R_M es halógeno, hidroxilo, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, ciano; o alquilo de C_1-C_6, alquenilo de C_2-C_6 o alquinilo de C_2-C_6, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo o ciano; o carbociclo de C_3-C_6 o heterociclo de 3 a 6 miembros, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, alquilo de C_1-C_6, alquenilo de C_2-C_6, alquinilo de C_2-C_6, haloalquilo de C_1-C_6, haloalquenilo de C_2-C_6 o haloalquinilo de C_2-C_6. Más preferentemente, R_M es halógeno, hidroxilo, mercapto, amino, carboxi; o alquilo de C_1-C_6, alquenilo de C_2-C_6 o alquinilo de C_2-C_6, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, mercapto, amino o carboxi. Con gran preferencia, R_M es alquilo de C_1-C_6 el cual está opcionalmente sustituido con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, mercapto, amino o carboxi.

X preferentemente es C_5-C_6carbociclo, heterociclo de 5 a 6 miembros, biciclos de 6 a 12 miembros (por ejemplo,  o  , donde X_3 es N y está ligado directamente a $-L_3-D$), y está opcionalmente sustituido con uno o más R_A. Algunos ejemplos de X son los descritos precedentemente sin carácter taxativo.

L_1 y L_2 son preferentemente en forma independiente una unión o alquileno de C_1-C_6, L_3 se selecciona preferentemente entre una unión, alquileno de C_1-C_6 o $-C(O)-$, y L_1, L_2, y L_3 están sustituidos en forma independiente entre sí con uno o más R_L. Más preferentemente, L_1, L_2 y L_3 son en forma independiente entre sí una unión o alquileno de C_1-C_6 (por ejemplo, $-CH_2-$ o $-CH_2CH_2-$), y están sustituidos en forma independiente entre sí con uno o más R_L. Con gran preferencia, L_1, L_2 y L_3 son una unión.

R_2 y R_5, tomados junto con los átomos a los cuales están unidos, preferentemente forman un heterociclo de 5 a 6 miembros o biciclo de 6 a 12 miembros (por ejemplo,  o ) que está opcionalmente sustituido con uno o más R_A. R_9 y R_{12}, tomados junto con los átomos a los cuales están unidos, preferentemente forman un heterociclo de 5 a 6 miembros o biciclo de 6 a 12 miembros (por ejemplo,  o ) que está opcionalmente sustituido con uno o más R_A.

-T-R_D' se puede seleccionar en forma independiente en cada caso, pero no taxativamente, entre $-C(O)-L_Y'-R_D'$, $-C(O)O-L_Y'-R_D'$, $-C(O)-L_Y'-N(R_B)C(O)-L_S''-R_D'$, $-C(O)-L_Y'-N(R_B)C(O)O-L_S''-R_D'$, $-N(R_B)C(O)-L_Y'-N(R_B)C(O)-L_S''-R_D'$, $-N(R_B)C(O)-L_Y'-N(R_B)C(O)O-L_S''-R_D'$, o $-N(R_B)C(O)-L_Y'-N(R_B)-L_S''-R_D'$, donde L_Y' es cada uno en forma independiente L_S' y, preferentemente, es cada uno en forma independiente alquileno de C_1-C_6 (por ejemplo, -CH_2-) y opcionalmente sustituido con uno o más sustituyentes seleccionados entre R_L. Preferentemente, -T-R_D' se selecciona en forma independiente en cada caso entre $-C(O)-L_Y'-M'-L_S''-R_D'$ o $-N(R_B)C(O)-L_Y'-M'-L_S''-R_D'$. Más preferentemente, -T-R_D' se selecciona en forma independiente en cada caso entre $-C(O)-L_Y'-N(R_B)C(O)-L_S''-R_D'$ o $-C(O)-L_Y'-N(R_B)C(O)O-L_S''-R_D'$. Con gran preferencia, -T-R_D'

se selecciona en forma independiente en cada caso entre $-C(O)-L_Y'-N(R_B)C(O)-R_D'$ o $-C(O)-L_Y'-N(R_B)C(O)O-R_D'$, donde L_Y' preferentemente es cada uno en forma independiente alquileno de C_1-C_6 (por ejemplo, $-CH_2-$) y opcionalmente sustituido con uno o más sustituyentes seleccionados entre R_L.

R_C' es preferentemente hidrógeno, y R_D' preferentemente se selecciona en forma independiente en cada caso entre R_E. Más preferentemente, R_D' se selecciona en forma independiente en cada caso entre alquilo de C_1-C_6, alquenilo de C_2-C_6 o alquinilo de C_2-C_6, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, carbociclo de C_3-C_6 o heterociclo de 3 a 6 miembros; o carbociclo de C_3-C_6 o heterociclo de 3 a 6 miembros, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, alquilo de C_1-C_6, alquenilo de C_2-C_6, alquinilo de C_2-C_6, haloalquilo de C_1-C_6, haloalquenilo de C_2-C_6 o haloalquinilo de C_2-C_6.

R_A preferentemente es halógeno, hidroxilo, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, ciano; o alquilo de C_1-C_6, alquenilo de C_2-C_6 o alquinilo de C_2-C_6, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo o ciano; o carbociclo de C_3-C_6 o heterociclo de 3 a 6 miembros, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, alquilo de C_1-C_6, alquenilo de C_2-C_6, alquinilo de C_2-C_6, haloalquilo de C_1-C_6, haloalquenilo de C_2-C_6 o haloalquinilo de C_2-C_6; o $-L_A-O-R_S$, $-L_A-S-R_S$, $-L_A-C(O)R_S$, $-L_A-OC(O)R_S$, $-L_A-C(O)OR_S$, $-L_A-N(R_SR_S')$, $-L_A-S(O)R_S$, $-L_A-SO_2R_S$, $-L_A-C(O)N(R_SR_S')$, $-L_A-N(R_S)C(O)R_S'$, $-L_A-N(R_S)C(O)N(R_S'R_S'')$, $-L_A-N(R_S)SO_2R_S'$, $-L_A-SO_2N(R_SR_S')$, $-L_A-N(R_S)SO_2N(R_S'R_S'')$, $-L_A-N(R_S)S(O)N(R_S'R_S'')$, $-L_A-OS(O)-R_S$, $-L_A-OS(O)_2-R_S$, $-L_A-S(O)_2OR_S$, $-L_A-S(O)OR_S$, $-L_A-OC(O)OR_S$, $-L_A-N(R_S)C(O)OR_S'$, $-L_A-OC(O)N(R_SR_S')$, $-L_A-N(R_S)S(O)-R_S'$, $-L_A-S(O)N(R_SR_S')$ o $-L_A-C(O)N(R_S)C(O)-R_S'$, donde L_A es una unión, alquileno de C_1-C_6, alquenileno de C_2-C_6 o alquinileno de C_2-C_6.

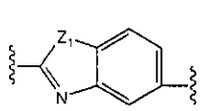
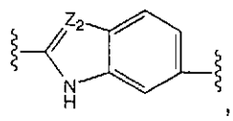
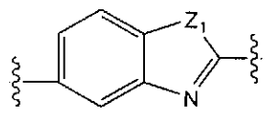
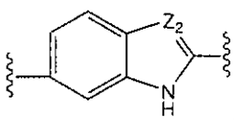
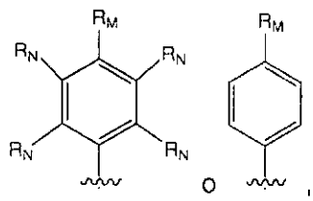
Más preferentemente, R_A es halógeno, hidroxilo, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, ciano; o alquilo de C_1-C_6, alquenilo de C_2-C_6 o alquinilo de C_2-C_6, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxilo,

mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo o ciano; o carbociclo de C_3-C_6 o heterociclo de 3 a 6 miembros, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, alquilo de C_1-C_6, alquenilo de C_2-C_6, alquinilo de C_2-C_6, haloalquilo de C_1-C_6, haloalquenilo de C_2-C_6 o haloalquinilo de C_2-C_6.

Con gran preferencia, R_A es halógeno, hidroxilo, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, ciano; o alquilo de C_1-C_6, alquenilo de C_2-C_6 o alquinilo de C_2-C_6, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo o ciano.

L_S, L_S' y L_S'' preferentemente se seleccionan en forma independiente entre sí entre una unión; o alquileno de C_1-C_6, alquenileno de C_2-C_6 o alquinileno de C_2-C_6.

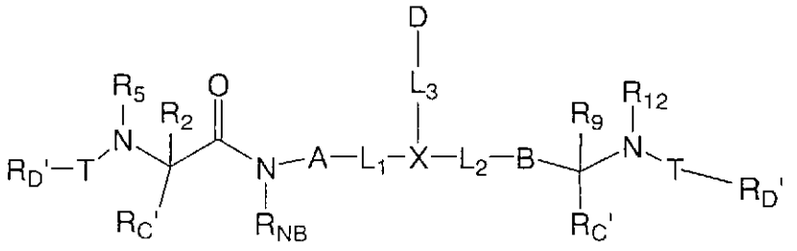
A y B pueden ser iguales o diferentes. En forma similar, L_1 y L_2 pueden ser iguales o diferentes.

En una realización de este aspecto, A es  o  , y está opcionalmente sustituido con uno o más R_A; B es  o  , y está opcionalmente sustituido con uno o más R_A; y D es carbociclo de C_5-C_6 o heterociclo de 5 a 6 miembros (por ejemplo, fenilo), y está opcionalmente sustituido con uno o más R_A. Preferentemente, D es  o , donde R_M y R_N tienen los valores que se definen precedentemente. Z_1 se selecciona en forma independiente en cada caso entre O, S, NH o CH_2; y Z_2 se selecciona en forma independiente en cada caso entre N o CH. L_1 y L_2 son en forma independiente entre sí una unión o alquileno de C_1-C_6, y L_3 es una unión, alquileno de C_1-C_6 o -C(O)-, y L_1, L_2, y L_3 están sustituidos en forma independiente entre sí con uno o más R_L. Preferentemente, L_1, L_2, y L_3 son una unión. –T-R_D' se selecciona en forma independiente en cada caso entre –C(O)–L_Y'–N(R_B)C(O)–L_S''–R_D' o –C(O)–L_Y'–N(R_B)C(O)O–L_S''–R_D', donde L_Y' es alquileno de C_1-C_6 (por ejemplo, -CH_2-) y opcionalmente sustituido con uno o más

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sustituyentes seleccionados entre R_L, y L_S" preferentemente es una unión. –T-R_D' también se puede seleccionar, no taxativamente, entre –C(O)–L_Y'–L_S"–R_D', –C(O)–L_Y'–O–L_S"–R_D', –C(O)–L_Y'–N(R_B)–L_S"–R_D', o –C(O)–L_Y'–N(R_B)S(O)$_2$–L_S"–R_D'.

En aún otro aspecto, la presente invención presenta además compuestos de fórmula I_C y sus sales farmacéuticamente aceptables.



I_C

donde:

R_{NB} es R_B;

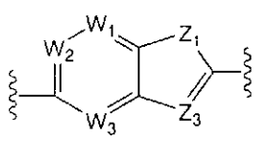
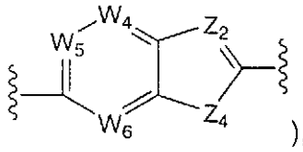
R_C' se selecciona cada uno en forma independiente entre R_C;

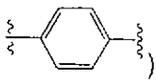
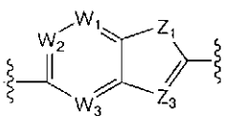
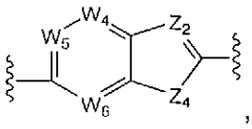
R_D' se selecciona cada uno en forma independiente entre R_D;

R_2 y R_5, tomados junto con los átomos a los cuales están unidos, forman un heterociclo de 3 a 12 miembros que está opcionalmente sustituido con uno o más R_A;

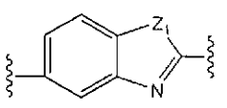
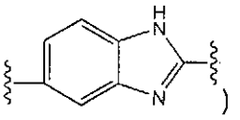
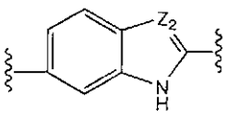
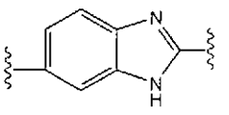
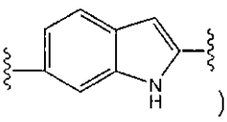
R_9 y R_{12}, tomados junto con los átomos a los cuales están unidos, forman un heterociclo de 3 a 12 miembros que está opcionalmente sustituido con uno o más R_A;

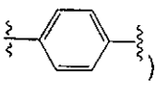
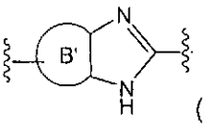
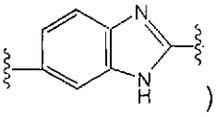
A, B, D, X, L_1, L_2, L_3, T, R_A, R_B, R_C, y R_D tienen los valores que se describen precedentemente en la Fórmula I.

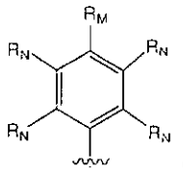
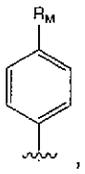
En este aspecto, A preferentemente es carbociclo de C_5-C_6 o heterociclo de 5 a 6 miembros, y está opcionalmente sustituido con uno o más R_A; y B preferentemente es biciclo de 8 a 12 miembros (tal como  o ), y está opcionalmente sustituido con uno o más R_A. Z_1 es O, S, NH o CH_2; Z_2 es N o CH; Z_3 es N o CH; Z_4 es O, S, NH o CH_2; y W_1, W_2, W_3, W_4, W_5 y W_6 se seleccionan en forma independiente entre sí entre CH o N.

Más preferentemente, A es fenilo (por ejemplo, ), y está opcionalmente sustituido con uno o más R_A; y B es  o  , y está opcionalmente sustituido con uno o más R_A, donde Z_1, Z_2, Z_3, Z_4, W_1, W_2, W_3, W_4, W_5, W_6

tienen los valores que se definen precedentemente. Preferentemente, Z_3 es N y Z_4 es NH.

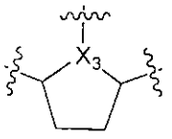
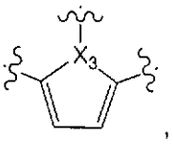
Por ejemplo, B puede ser  (por ejemplo, ) o  (por ejemplo,  o ), y está opcionalmente sustituido con uno o más R_A.

También preferentemente, A es carbociclo de C_5-C_6 (por ejemplo, fenilo tal como ) o heterociclo de 5 a 6 miembros; y B es  (por ejemplo, ), donde B' se selecciona entre carbociclo de C_5-C_6 o heterociclo de 5 a 6 miembros. A y B son en forma independiente opcionalmente sustituido con uno o más R_A.

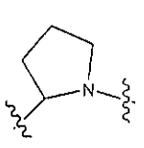
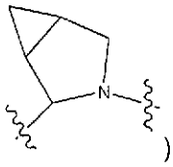
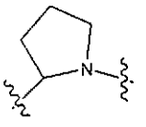
D preferentemente se selecciona entre C_5-C_6carbociclo, heterociclo de 5 a 6 miembros, o biciclos de 6 a 12 miembros, y está opcionalmente sustituido con uno o más R_A. D también se puede seleccionar preferentemente entre alquilo de C_1-C_6, alquenilo de C_2-C_6 o alquinilo de C_2-C_6, y está opcionalmente sustituido con uno o más sustituyentes seleccionados entre R_L. Más preferentemente, D es C_5-C_6carbociclo, heterociclo de 5 a 6 miembros, o biciclos de 6 a 12 miembros, y se sustituye con uno o más R_M, donde R_M es halógeno, nitro, oxo, fosfonoxi, fosfono, tioxo, ciano, o $-L_S-R_E$. También preferentemente, D es fenilo, y está opcionalmente sustituido con uno o más R_A. Más preferentemente, D es fenilo, y se sustituye con uno o más R_M, donde R_M tiene los valores que se definen precedentemente. Con gran preferencia, D es  o  , donde R_M tiene los valores que se definen precedentemente, y cada R_N se selecciona en forma independiente entre R_D y preferentemente es hidrógeno.

Preferentemente, R_M es halógeno, hidroxilo, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, ciano; o alquilo de C_1-C_6, alquenilo de C_2-C_6 o alquinilo de C_2-C_6, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo o ciano; o carbociclo de C_3-C_6 o heterociclo de 3 a 6 miembros, cada uno de los cuales está opcionalmente sustituido en

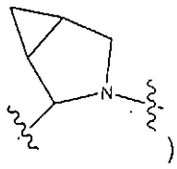
forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, alquilo de C_1-C_6, alquenilo de C_2-C_6, alquinilo de C_2-C_6, haloalquilo de C_1-C_6, haloalquenilo de C_2-C_6 o haloalquinilo de C_2-C_6. Más preferentemente, R_M es halógeno, hidroxilo, mercapto, amino, carboxi; o alquilo de C_1-C_6, alquenilo de C_2-C_6 o alquinilo de C_2-C_6, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, mercapto, amino o carboxi. Con gran preferencia, R_M es alquilo de C_1-C_6 el cual está opcionalmente sustituido con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, mercapto, amino o carboxi.

X preferentemente es C_5-C_6carbociclo, heterociclo de 5 a 6 miembros, biciclos de 6 a 12 miembros (por ejemplo,  o  , donde X_3 es N y está ligado directamente a $-L_3-D$), y está opcionalmente sustituido con uno o más R_A. Algunos ejemplos de X son los descritos precedentemente sin carácter taxativo.

L_1 y L_2 son preferentemente en forma independiente una unión o alquileno de C_1-C_6, L_3 se selecciona preferentemente entre una unión, alquileno de C_1-C_6 o $-C(O)-$, y L_1, L_2, y L_3 están sustituidos en forma independiente entre sí con uno o más R_L. Más preferentemente, L_1, L_2 y L_3 son en forma independiente entre sí una unión o alquileno de C_1-C_6 (por ejemplo, $-CH_2-$ o $-CH_2CH_2-$), y están sustituidos en forma independiente entre sí con uno o más R_L. Con gran preferencia, L_1, L_2 y L_3 son una unión. L_1 y L_2 pueden ser iguales o diferentes.

R_2 y R_5, tomados junto con los átomos a los cuales están unidos, preferentemente forman un heterociclo de 5 a 6 miembros o biciclo de 6 a 12 miembros (por ejemplo,  o ) que está opcionalmente sustituido con uno o más R_A. R_9 y R_{12}, tomados junto con los átomos a los cuales están unidos, preferentemente forman un heterociclo de 5 a 6 miembros o biciclo de 6 a 12 miembros (por ejemplo,  o

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) que está opcionalmente sustituido con uno o más R_A.

-T-R_D' se puede seleccionar en forma independiente en cada caso, pero no taxativamente, entre –C(O)–L_Y'–R_D', –C(O)O–L_Y'–R_D', –C(O)–L_Y'–N(R_B)C(O)–L_S''–R_D', –C(O)–L_Y'–N(R_B)C(O)O–L_S''–R_D', –N(R_B)C(O)–L_Y'–N(R_B)C(O)–L_S''–R_D', –N(R_B)C(O)–L_Y'—N(R_B)C(O)O–L_S''–R_D', o –N(R_B)C(O)–L_Y'—N(R_B)–L_S''–R_D', donde L_Y' es cada uno en forma independiente L_S' y, preferentemente, es cada uno en forma independiente alquileno de C_1-C_6 (por ejemplo, -CH_2-) y opcionalmente sustituido con uno o más sustituyentes seleccionados entre R_L. Preferentemente, -T-R_D' se selecciona en forma independiente en cada caso entre –C(O)–L_Y'–M'–L_S''–R_D' o –N(R_B)C(O)–L_Y'–M'–L_S''–R_D'. Más preferentemente, -T-R_D' se selecciona en forma independiente en cada caso entre –C(O)–L_Y'–N(R_B)C(O)–L_S''–R_D' o –C(O)–L_Y'–N(R_B)C(O)O–L_S''–R_D'. Con gran preferencia, -T-R_D' se selecciona en forma independiente en cada caso entre –C(O)–L_Y'–N(R_B)C(O)–R_D' o –C(O)–L_Y'–N(R_B)C(O)O–R_D', donde L_Y' preferentemente es cada uno en forma independiente alquileno de C_1-C_6 (por ejemplo, -CH_2-) y opcionalmente sustituido con uno o más sustituyentes seleccionados entre R_L.

R_{NB} y R_C' son preferentemente hidrógeno, y R_D' preferentemente se selecciona en forma independiente en cada caso entre R_E. Más preferentemente, R_D' se selecciona en forma independiente en cada caso entre alquilo de C_1-C_6, alquenilo de C_2-C_6 o alquinilo de C_2-C_6, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, carbociclo de C_3-C_6 o heterociclo de 3 a 6 miembros; o carbociclo de C_3-C_6 o heterociclo de 3 a 6 miembros, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, alquilo de C_1-C_6, alquenilo de C_2-C_6, alquinilo de C_2-C_6, haloalquilo de C_1-C_6, haloalquenilo de C_2-C_6 o haloalquinilo de C_2-C_6.

R_A preferentemente es halógeno, hidroxilo, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, ciano; o alquilo de C_1-C_6, alquenilo de C_2-C_6 o alquinilo de C_2-C_6, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo o ciano; o carbociclo de C_3-C_6 o heterociclo de 3 a 6 miembros, cada uno de los cuales está opcionalmente sustituido en

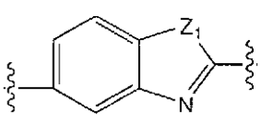
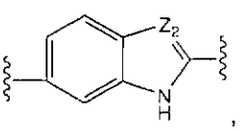
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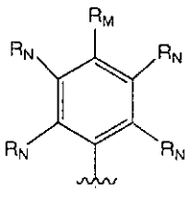
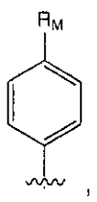
forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, alquilo de C_1-C_6, alquenilo de C_2-C_6, alquinilo de C_2-C_6, haloalquilo de C_1-C_6, haloalquenilo de C_2-C_6 o haloalquinilo de C_2-C_6; o $-L_A-O-R_S$, $-L_A-S-R_S$, $-L_A-C(O)R_S$, $-L_A-OC(O)R_S$, $-L_A-C(O)OR_S$, $-L_A-N(R_SR_S')$, $-L_A-S(O)R_S$, $-L_A-SO_2R_S$, $-L_A-C(O)N(R_SR_S')$, $-L_A-N(R_S)C(O)R_S'$, $-L_A-N(R_S)C(O)N(R_S'R_S'')$, $-L_A-N(R_S)SO_2R_S'$, $-L_A-SO_2N(R_SR_S')$, $-L_A-N(R_S)SO_2N(R_S'R_S'')$, $-L_A-N(R_S)S(O)N(R_S'R_S'')$, $-L_A-OS(O)-R_S$, $-L_A-OS(O)_2-R_S$, $-L_A-S(O)_2OR_S$, $-L_A-S(O)OR_S$, $-L_A-OC(O)OR_S$, $-L_A-N(R_S)C(O)OR_S'$, $-L_A-OC(O)N(R_SR_S')$, $-L_A-N(R_S)S(O)-R_S'$, $-L_A-S(O)N(R_SR_S')$ o $-L_A-C(O)N(R_S)C(O)-R_S'$, donde L_A es una unión, alquileno de C_1-C_6, alquenileno de C_2-C_6 o alquinileno de C_2-C_6.

Más preferentemente, R_A es halógeno, hidroxilo, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, ciano; o alquilo de C_1-C_6, alquenilo de C_2-C_6 o alquinilo de C_2-C_6, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo o ciano; o carbociclo de C_3-C_6 o heterociclo de 3 a 6 miembros, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, alquilo de C_1-C_6, alquenilo de C_2-C_6, alquinilo de C_2-C_6, haloalquilo de C_1-C_6, haloalquenilo de C_2-C_6 o haloalquinilo de C_2-C_6.

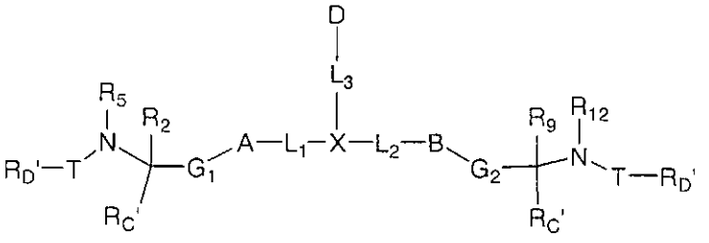
Con gran preferencia, R_A es halógeno, hidroxilo, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, ciano; o alquilo de C_1-C_6, alquenilo de C_2-C_6 o alquinilo de C_2-C_6, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo o ciano.

L_S, L_S' y L_S'' preferentemente se seleccionan en forma independiente entre sí entre una unión; o alquileno de C_1-C_6, alquenileno de C_2-C_6 o alquinileno de C_2-C_6.

En una realización de este aspecto, A es fenilo, y está opcionalmente sustituido con uno o más R_A; y B es  o  , y está opcionalmente sustituido con uno o más R_A, donde Z_1 es O, S, NH o CH_2; y Z_2 es N o CH. D es carbociclo de C_5-C_6 o heterociclo de 5 a 6 miembros (por ejemplo, fenilo), y está opcionalmente

sustituido con uno o más R_A. Preferentemente, D es  o  , donde R_M y R_N tienen los valores que se definen precedentemente. L_1 y L_2 son en forma independiente entre sí una unión o alquileno de C_1-C_6, y L_3 es una unión, alquileno de C_1-C_6 o -C(O)-, y L_1, L_2, y L_3 están sustituidos en forma independiente entre sí con uno o más R_L. Preferentemente, L_1, L_2, y L_3 son una unión. $-T-R_D'$ se selecciona en forma independiente en cada caso entre $-C(O)-L_Y'-N(R_B)C(O)-L_S''-R_D'$ o $-C(O)-L_Y'-N(R_B)C(O)O-L_S''-R_D'$, donde L_Y' es alquileno de C_1-C_6 (por ejemplo, $-CH_2-$) y opcionalmente sustituido con uno o más sustituyentes seleccionados entre R_L, y L_S'' preferentemente es una unión. $-T-R_D'$ también se puede seleccionar, no taxativamente, entre $-C(O)-L_Y'-L_S''-R_D'$, $-C(O)-L_Y'-O-L_S''-R_D'$, $-C(O)-L_Y'-N(R_B)-L_S''-R_D'$, o $-C(O)-L_Y'-N(R_B)S(O)_2-L_S''-R_D'$.

En aún otro aspecto, la presente invención presenta compuestos de fórmula I_D y sus sales farmacéuticamente aceptables.



I_D

donde:

G_1 y G_2 se seleccionan en forma independiente entre sí entre carbociclo de C_5-C_6 o heterociclo de 5 a 6 miembros, y están sustituidos en forma independiente entre sí con uno o más R_A;

R_C' se selecciona cada uno en forma independiente entre R_C;

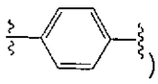
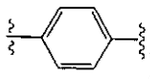
R_D' se selecciona cada uno en forma independiente entre R_D;

R_2 y R_5, tomados junto con los átomos a los cuales están unidos, forman un heterociclo de 3 a 12 miembros que está opcionalmente sustituido con uno o más R_A;

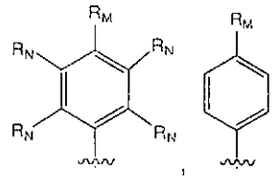
R_9 y R_{12}, tomados junto con los átomos a los cuales están unidos, forman un heterociclo de 3 a 12 miembros que está opcionalmente sustituido con uno o más R_A;

A, B, D, X, L_1, L_2, L_3, T, R_A, R_C, y R_D tienen los valores que se describen precedentemente en la Fórmula I.

En este aspecto, A y B preferentemente se seleccionan en forma independiente

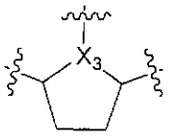
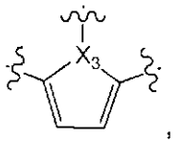
entre carbociclo de C_5-C_6 o heterociclo de 5 a 6 miembros, y están sustituidos en forma independiente entre sí con uno o más R_A. Más preferentemente, al menos uno de A y B es fenilo (por ejemplo, ), y está opcionalmente sustituido con uno o más R_A. Con gran preferencia, ambos A y B son en forma independiente entre sí fenilo (por ejemplo, ), y están sustituidos en forma independiente entre sí con uno o más R_A.

D preferentemente se selecciona entre C_5-C_6carbociclo, heterociclo de 5 a 6 miembros, o biciclos de 8 a 12 miembros, y está opcionalmente sustituido con uno o más R_A. D también se puede seleccionar preferentemente entre alquilo de C_1-C_6, alquenilo de C_2-C_6 o alquinilo de C_2-C_6, y está opcionalmente sustituido con uno o más R_L. Más preferentemente, D es C_5-C_6carbociclo, heterociclo de 5 a 6 miembros, o biciclos de 6 a 12 miembros, y se sustituye con uno o más R_M, donde R_M es halógeno, nitro, oxo, fosfonoxi, fosfono, tioxo, ciano, o $-L_S-R_E$. También preferentemente, D es fenilo, y está opcionalmente sustituido con uno o más R_A. Más preferentemente, D es fenilo, y se sustituye con uno o más R_M, donde R_M tiene los valores que se definen precedentemente.

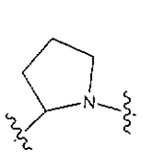
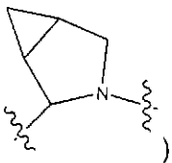
Con gran preferencia, D es  , donde R_M tiene los valores que se definen precedentemente, y cada R_N se selecciona en forma independiente entre R_D y preferentemente es hidrógeno.

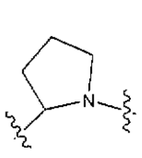
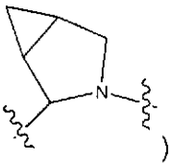
Preferentemente, R_M es halógeno, hidroxilo, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, ciano; o alquilo de C_1-C_6, alquenilo de C_2-C_6 o alquinilo de C_2-C_6, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo o ciano; o carbociclo de C_3-C_6 o heterociclo de 3 a 6 miembros, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, alquilo de C_1-C_6, alquenilo de C_2-C_6, alquinilo de C_2-C_6, haloalquilo de C_1-C_6, haloalquenilo de C_2-C_6 o haloalquinilo de C_2-C_6. Más preferentemente, R_M es halógeno, hidroxilo, mercapto, amino, carboxi; o alquilo de C_1-C_6, alquenilo de C_2-C_6 o alquinilo de C_2-C_6, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, mercapto, amino o carboxi. Con gran preferencia, R_M es alquilo de C_1-C_6 el cual está

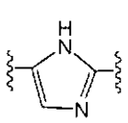
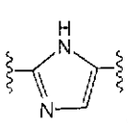
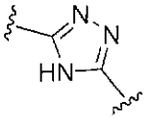
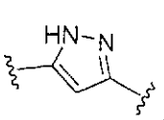
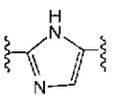
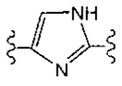
opcionalmente sustituido con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, mercapto, amino o carboxi.

X preferentemente es C_5-C_6carbociclo, heterociclo de 5 a 6 miembros, biciclos de 6 a 12 miembros (por ejemplo,  o  , donde X_3 es N y está ligado directamente a $-L_3-D$), y está opcionalmente sustituido con uno o más R_A. Algunos ejemplos de X son los descritos precedentemente sin carácter taxativo.

L_1 y L_2 son preferentemente en forma independiente una unión o alquileno de C_1-C_6, L_3 se selecciona preferentemente entre una unión, alquileno de C_1-C_6 o $-C(O)-$, y L_1, L_2, y L_3 están sustituidos en forma independiente entre sí con uno o más R_L. Más preferentemente, L_1, L_2 y L_3 son en forma independiente entre sí una unión o alquileno de C_1-C_6 (por ejemplo, $-CH_2-$ o $-CH_2CH_2-$), y están sustituidos en forma independiente entre sí con uno o más R_L. Con gran preferencia, L_1, L_2 y L_3 son una unión.

R_2 y R_5, tomados junto con los átomos a los cuales están unidos, preferentemente forman un heterociclo de 5 a 6 miembros o biciclo de 6 a 12 miembros (por ejemplo,  o ), que está opcionalmente sustituido con uno o más R_A.

R_9 y R_{12}, tomados junto con los átomos a los cuales están unidos, preferentemente forman un heterociclo de 5 a 6 miembros o biciclo de 6 a 12 miembros (por ejemplo,  o ), que está opcionalmente sustituido con uno o más R_A.

G_1 y G_2 preferentemente se seleccionan en forma independiente entre sí entre  ,  ,  o  , y están sustituidos en forma independiente entre sí con uno o más R_A (por ejemplo, uno o más cloro o bromo). Más preferentemente, G_1 es  (incluyendo cualquiera de sus tautómeros), y G_2 es  (incluyendo cualquiera de sus tautómeros), y cada G_1 y G_2 es en forma independiente opcionalmente sustituido con uno o más R_A (por ejemplo, uno o más cloro o

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bromo).

-T-R_D' se puede seleccionar en forma independiente en cada caso, pero no taxativamente, entre –C(O)–L_Y'–, –C(O)O–L_Y'–R_D', –C(O)–L_Y'–N(R_B)C(O)–L_S''–R_D', –C(O)–L_Y'–N(R_B)C(O)O–L_S''–R_D', –N(R_B)C(O)–L_Y'–N(R_B)C(O)–L_S''–R_D', –N(R_B)C(O)–L_Y'—N(R_B)C(O)O–L_S''–R_D', o –N(R_B)C(O)–L_Y'—N(R_B)–L_S''–R_D', donde L_Y' es cada uno en forma independiente L_S' y, preferentemente, es cada uno en forma independiente alquileno de C_1-C_6 (por ejemplo, -CH_2-) y opcionalmente sustituido con uno o más sustituyentes seleccionados entre R_L. Preferentemente, -T-R_D' se selecciona en forma independiente en cada caso entre –C(O)–L_Y'–M'–L_S''–R_D' o –N(R_B)C(O)–L_Y'–M'–L_S''–R_D'. Más preferentemente, -T-R_D' se selecciona en forma independiente en cada caso entre –C(O)–L_Y'–N(R_B)C(O)–L_S''–R_D' o –C(O)–L_Y'–N(R_B)C(O)O–L_S''–R_D'. Con gran preferencia, -T-R_D' se selecciona en forma independiente en cada caso entre –C(O)–L_Y'–N(R_B)C(O)–R_D' o –C(O)–L_Y'–N(R_B)C(O)O–R_D', donde L_Y' preferentemente es cada uno en forma independiente alquileno de C_1-C_6 (por ejemplo, -CH_2-) y opcionalmente sustituido con uno o más sustituyentes seleccionados entre R_L.

R_C' es preferentemente hidrógeno, y R_D' preferentemente se selecciona en forma independiente en cada caso entre R_E. Más preferentemente, R_D' se selecciona en forma independiente en cada caso entre alquilo de C_1-C_6, alquenilo de C_2-C_6 o alquinilo de C_2-C_6, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, carbociclo de C_3-C_6 o heterociclo de 3 a 6 miembros; o carbociclo de C_3-C_6 o heterociclo de 3 a 6 miembros, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, alquilo de C_1-C_6, alquenilo de C_2-C_6, alquinilo de C_2-C_6, haloalquilo de C_1-C_6, haloalquenilo de C_2-C_6 o haloalquinilo de C_2-C_6.

R_A preferentemente es halógeno, hidroxilo, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, ciano; o alquilo de C_1-C_6, alquenilo de C_2-C_6 o alquinilo de C_2-C_6, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo o ciano; o carbociclo de C_3-C_6 o heterociclo de 3 a 6 miembros, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, alquilo de C_1-C_6, alquenilo de C_2-C_6, alquinilo de C_2-C_6, haloalquilo de C_1-C_6,

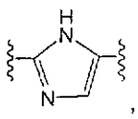
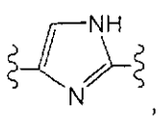
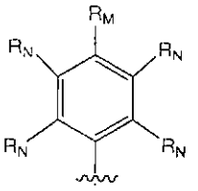
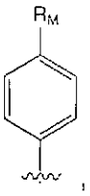
haloalquenilo de C_2-C_6 o haloalquinilo de C_2-C_6; o $-L_A-O-R_S$, $-L_A-S-R_S$, $-L_A-C(O)R_S$, $-L_A-OC(O)R_S$, $-L_A-C(O)OR_S$, $-L_A-N(R_SR_S')$, $-L_A-S(O)R_S$, $-L_A-SO_2R_S$, $-L_A-C(O)N(R_SR_S')$, $-L_A-N(R_S)C(O)R_S'$, $-L_A-N(R_S)C(O)N(R_S'R_S'')$, $-L_A-N(R_S)SO_2R_S'$, $-L_A-SO_2N(R_SR_S')$, $-L_A-N(R_S)SO_2N(R_S'R_S'')$, $-L_A-N(R_S)S(O)N(R_S'R_S'')$, $-L_A-OS(O)-R_S$, $-L_A-OS(O)_2-R_S$, $-L_A-S(O)_2OR_S$, $-L_A-S(O)OR_S$, $-L_A-OC(O)OR_S$, $-L_A-N(R_S)C(O)OR_S'$, $-L_A-OC(O)N(R_SR_S')$, $-L_A-N(R_S)S(O)-R_S'$, $-L_A-S(O)N(R_SR_S')$ o $-L_A-C(O)N(R_S)C(O)-R_S'$, donde L_A es una unión, alquileno de C_1-C_6, alquenileno de C_2-C_6 o alquinileno de C_2-C_6.

Más preferentemente, R_A es halógeno, hidroxilo, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, ciano; o alquilo de C_1-C_6, alquenilo de C_2-C_6 o alquinilo de C_2-C_6, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo o ciano; o carbociclo de C_3-C_6 o heterociclo de 3 a 6 miembros, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, alquilo de C_1-C_6, alquenilo de C_2-C_6, alquinilo de C_2-C_6, haloalquilo de C_1-C_6, haloalquenilo de C_2-C_6 o haloalquinilo de C_2-C_6.

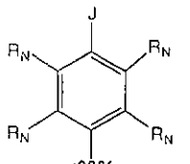
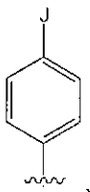
Con gran preferencia, R_A es halógeno, hidroxilo, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, ciano; o alquilo de C_1-C_6, alquenilo de C_2-C_6 o alquinilo de C_2-C_6, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo o ciano.

L_S, L_S' y L_S'' preferentemente se seleccionan en forma independiente entre sí entre una unión; o alquileno de C_1-C_6, alquenileno de C_2-C_6 o alquinileno de C_2-C_6.

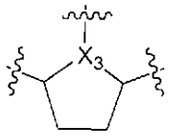
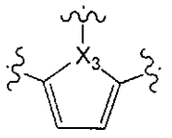
A y B pueden ser iguales o diferentes. En forma similar, L_1 y L_2 pueden ser iguales o diferentes.

En una realización de este aspecto, A, B, y D son en forma independiente entre sí fenilo, y están sustituidos en forma independiente entre sí con uno o más R_A; y G_1 es  , G_2 es  , y cada G_1 y G_2 es en forma independiente opcionalmente sustituido con uno o más R_A (por ejemplo, uno o más cloro o bromo). Preferentemente, D es  o  , donde R_M y R_N tienen los valores que se definen

precedentemente. L_1 y L_2 son en forma independiente entre sí una unión o alquileno de C_1-C_6, y L_3 es una unión, alquileno de C_1-C_6 o -C(O)-, y L_1, L_2, y L_3 están sustituidos en forma independiente entre sí con uno o más R_L. Preferentemente, L_1, L_2, y L_3 son una unión. -T-R_D' se selecciona en forma independiente en cada caso entre –C(O)–L_Y'–$N(R_B)C(O)$–L_S"–R_D' o –C(O)–L_Y'–$N(R_B)C(O)O$–L_S"–R_D', donde L_Y' es alquileno de C_1-C_6 (por ejemplo, -CH_2-) y opcionalmente sustituido con uno o más sustituyentes seleccionados entre R_L, y L_S" preferentemente es una unión. –T-R_D' también se puede seleccionar, no taxativamente, entre –C(O)–L_Y'–L_S"–R_D', –C(O)–L_Y'–O–L_S"–R_D', –C(O)–L_Y'–$N(R_B)$–L_S"–R_D', o –C(O)–L_Y'–$N(R_B)S(O)_2$–L_S"–R_D'.

La presente invención también presenta compuestos de las Fórmulas I, I_A, I_B, I_C y I_D como se describe aquí (incluyendo cada una de las formas de realización que se han descrito) o sus sales, excepto que D es carbociclo de C_3-C_{12} o heterociclo de 3 a 12 miembros que está sustituido con J y opcionalmente sustituido con uno o más R_A, donde J es carbociclo de C_3-C_{12} o heterociclo de 3 a 12 miembros y está opcionalmente sustituido con uno o más R_A, o J es –SF_5. Preferentemente, D es C_5-C_6carbociclo, heterociclo de 5 a 6 miembros o biciclo de 6 a 12 miembros y está opcionalmente sustituido con uno o más R_A, y J es carbociclo de C_3-C_6 o heterociclo de 3 a 6 miembros y está opcionalmente sustituido con uno o más R_A. Más preferentemente, D es carbociclo de C_5-C_6 o heterociclo de 5 a 6 miembros y está opcionalmente sustituido con uno o más R_A, y J es carbociclo de C_3-C_6 o heterociclo de 3 a 6 miembros y está opcionalmente sustituido con uno o más R_A. Con gran preferencia, D es fenilo sustituido con J y opcionalmente sustituido con uno o más R_A, donde J es carbociclo de C_3-C_6 o heterociclo de 3 a 6 miembros y está opcionalmente sustituido con uno o más R_A. Los R_As preferidos tienen los valores que se describen precedentemente. En una realización, D es  , donde cada R_N se selecciona en forma independiente entre R_D y preferentemente es hidrógeno, y J tiene los valores que se definen precedentemente y preferentemente es carbociclo de C_3-C_6 o heterociclo de 3 a 6 miembros opcionalmente sustituido con uno o más R_A. En otra realización, D es  , y J es carbociclo de C_3-C_6 o heterociclo de 3 a 6 miembros y está opcionalmente sustituido con uno o más R_A.

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Además, la presente invención presenta compuestos de las Fórmulas I, I_A, I_B, I_C y I_D como se describe aquí (incluyendo cada una de las formas de realización que se han descrito, así como también donde D es carbociclo de C_3-C_{12} o heterociclo de 3 a 12 miembros sustituido con J y opcionalmente sustituido con uno o más R_A como se describe precedentemente) o sus sales, excepto que X está opcionalmente sustituido con uno o más R_A'. Los ejemplos específicos de X tienen los valores que se describen precedentemente, tal como  o  donde X_3 es N y está ligado directamente a $-L_3-D$. Cada R_A' es en forma independiente R_A; o C_1-C_{10}alquilo, C_2-C_{10}alquenilo o C_2-C_{10}alquinilo, cada uno de los cuales contiene 0, 1, 2, 3, 4 o 5 heteroátomos seleccionados entre O, S o N y está opcionalmente sustituido con uno o más R_L. R_A tiene los valores que se definen precedentemente. En una realización, cada R_A' es en forma independiente R_A; o C_1-C_{10}alquilo, C_2-C_{10}alquenilo o C_2-C_{10}alquinilo, cada uno de los cuales contiene 0, 1, 2, 3, 4 o 5 heteroátomos seleccionados entre O, S o N y está opcionalmente sustituido con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo o ciano. En otra realización, cada R_A' se selecciona en forma independiente entre R_A; o C_1-C_{10}alquilo, C_2-C_{10}alquenilo o C_2-C_{10}alquinilo, cada uno de los cuales contiene 0, 1, 2, 3, 4 o 5 O y está opcionalmente sustituido con uno o más R_L. En una realización adicional, cada R_A' se selecciona en forma independiente entre C_1-C_{10}alquilo, C_2-C_{10}alquenilo o C_2-C_{10}alquinilo, cada uno de los cuales contiene 0, 1, 2 o 3 O y está opcionalmente sustituido con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo o ciano.

En otro aspecto de la invención, cada R_A' es en forma independiente R_A o $-(R_X-R_Y)_N-(R_X-R_Y')$, donde N es 0, 1, 2, 3, 4; cada R_X es en forma independiente O, S o $N(R_B)$; cada R_Y es en forma independiente alquileno de C_1-C_6, alquenileno de C_2-C_6 o alquinileno de C_2-C_6 cada uno de los cuales está opcionalmente sustituido con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo o ciano; y R_Y' es en forma independiente alquilo de C_1-C_6, alquenilo de C_2-C_6 o alquinilo de C_2-C_6 cada uno de los cuales está opcionalmente sustituido con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo o ciano. R_A y R_B tienen los valores que se definen precedentemente. En una realización, cada R_X es O. Por ejemplo, cada R_A' se selecciona entre $-(O-C_1$-C_6alquilene$)_N-(O-$alquilo de C_1-$C_6)$, donde N preferentemente es 0, 1, 2 o 3.

Además, la presente invención presenta compuestos de las Fórmulas I, I_A, I_B, I_C y I_D como se describe aquí (incluyendo cada una de las formas de realización que se han descrito, así como también donde D es carbociclo de C_3-C_{12} o heterociclo de 3 a 12 miembros sustituido con J y opcionalmente sustituido con uno o más R_A como se describe precedentemente, o donde X está opcionalmente sustituido con uno o más R_A' como se describe precedentemente), donde:

R_E se selecciona en forma independiente en cada caso entre –O–R_S, –S–R_S, –C(O)R_S, –OC(O)R_S, –C(O)OR_S, –N($R_S$$R_S$'), –S(O)$R_S$, –$SO_2R_S$, –C(O)N($R_S$$R_S$'), –N($R_S$)C(O)$R_S$', –N($R_S$)C(O)N($R_S$'$R_S$''), –N($R_S$)$SO_2R_S$', –$SO_2$N($R_S$$R_S$'), –N($R_S$)$SO_2$N($R_S$'$R_S$''), –N($R_S$)S(O)N($R_S$'$R_S$''), –OS(O)–$R_S$, –OS(O)$_2$–$R_S$, –S(O)$_2OR_S$, –S(O)O$R_S$, –OC(O)O$R_S$, –N($R_S$)C(O)O$R_S$', –OC(O)N($R_S$$R_S$'), –N($R_S$)S(O)–$R_S$', –S(O)N($R_S$$R_S$'), –P(O)(O$R_S$)$_2$, o –C(O)N($R_S$)C(O)–$R_S$'; o alquilo de C_1-C_6, alquenilo de C_2-C_6 o alquinilo de C_2-C_6, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo o ciano; o carbociclo de C_3-C_6 o heterociclo de 3 a 6 miembros, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, alquilo de C_1-C_6, alquenilo de C_2-C_6, alquinilo de C_2-C_6, haloalquilo de C_1-C_6, haloalquenilo de C_2-C_6, haloalquinilo de C_2-C_6, C(O)OR_S, o –N($R_S$$R_S$'); y

R_S, R_S' y R_S'' se seleccionan en forma independiente entre sí en cada caso entre hidrógeno; alquilo de C_1-C_6, alquenilo de C_2-C_6 o alquinilo de C_2-C_6, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, –O–alquilo de C_1-C_6, –O–C_1-C_6alquilen–O–alquilo de C_1-C_6, o carbociclo o heterociclo de 3 a 6 miembros; o carbociclo o heterociclo de 3 a 6 miembros; donde cada carbociclo o heterociclo de 3 a 6 miembros en R_S , R_S' o R_S' está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, alquilo de C_1-C_6, alquenilo de C_2-C_6, alquinilo de C_2-C_6, haloalquilo de C_1-C_6, haloalquenilo de C_2-C_6 o haloalquinilo de C_2-C_6.

Los compuestos de la presente invención se pueden usar en la forma de sales. Según el compuesto particular, una sal de un compuesto puede ser ventajosa debido a una o más de las propiedades físicas de la sal, tal como una mayor estabilidad farmacéutica bajo determinadas condiciones o la solubilidad deseada en agua o aceite. En algunos casos, una sal de un compuesto puede ser de utilidad para el aislamiento o la purificación del

compuesto.

Cuando la sal será administrada a un paciente, la sal preferentemente es una sal farmacéuticamente aceptable. Las sales farmacéuticamente aceptables incluyen, pero en un sentido no limitativo, sales de adición ácida, sales de adición básica y sales de metales alcalinos.

Las sales de adición ácida farmacéuticamente aceptables se pueden preparar a partir de ácidos inorgánicos u orgánicos. Los ejemplos de ácidos inorgánicos adecuados incluyen, pero en un sentido no limitativo, ácido clorhídrico, bromhídrico, iodhídrico, nítrico, carbónico, sulfúrico y fosfórico. Los ejemplos de ácidos orgánicos adecuados incluyen, pero en un sentido no limitativo, las clases de ácidos orgánicos alifáticos, cicloalifáticos, aromáticos, aralifáticos, heterociclilo, carboxílicos y sulfónicos. Los ejemplos específicos de los ácidos orgánicos adecuados incluyen acetato, trifluoroacetato, formiato, propionato, succinato, glicolato, gluconato, digluconato, lactato, malato, ácido tartárico, citrato, ascorbato, glucuronato, maleato, fumarato, piruvato, aspartato, glutamato, benzoato, ácido antranílico, mesilato, estearato, salicilato, p-hidroxibenzoato, fenilacetato, mandelato, embonato (pamoato), metansulfonato, etansulfonato, bencensulfonato, pantotenato, toluensulfonato, 2-hidroxietansulfonato, sulfanilato, ciclohexilaminosulfonato, ácido algínico, ácido beta-hidroxibutírico, galactarato, galacturonato, adipato, alginato, bisulfato, butirato, alcanforato, alcanforsulfonato, ciclopentanpropionato, dodecilsulfato, glicoheptanoato, glicerofosfato, hemisulfato, heptanoato, hexanoato, nicotinato, 2-naftalensulfonato, oxalato, palmoato, pectinato, persulfato, 3-fenilpropionato, picrato, pivalato, tiocianato, tosilato y undecanoato.

Las sales de adición básica farmacéuticamente aceptable incluyen, pero en un sentido no limitativo, sales metálicas y sales orgánicas. Los ejemplos no limitativos de sales metálicas adecuadas incluyen sales de metales alcalinos (grupo Ia), sales de metales alcalino-térreos (grupo IIa) y otras sales de metales farmacéuticamente aceptables. Dichas sales pueden ser, en un sentido no limitativo, de aluminio, calcio, litio, magnesio, potasio, sodio y zinc. Los ejemplos no limitativos de sales orgánicas adecuadas se pueden elaborar a partir de aminas terciarias y aminas cuaternarias, tales como trometamina, dietilamina, N,N'-dibenciletilendiamina, cloroprocaína, colina, dietanolamina, etilendiamina, meglumina (N-metilglucamina) y procaína. Los grupos que contienen nitrógeno básico se pueden cuaternizar con agentes tales como haluros de alquilo (por ejemplo, metilo, etilo, propilo, butilo, decilo, laurilo, miristilo y cloruros/bromuros/ioduros de estearilo), sulfatos de dialquilo (por ejemplo, sulfatos de dimetilo, dietilo, dibutilo y diamilo), haluros de aralquilo (por ejemplo, bromuros de bencilo y fenetilo) y otros.

Los compuestos o las sales de la presente invención pueden existir en la forma de

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solvatos, tal como con agua (es decir, hidratos), o con solventes orgánicos (por ejemplo, con metanol, etanol o acetonitrilo para formar, respectivamente, metanolato, etanolato o acetonitrilato).

Los compuestos o sales de la presente invención también se pueden usar en la forma de prodrogas. Algunas prodrogas son ésteres alifáticos o aromáticos derivados de grupos ácidos sobre los compuestos de la invención. Otras son ésteres alifáticos o aromáticos de grupos hidroxilo o amino sobre los compuestos de la invención. Las prodrogas de fosfato de grupos hidroxilo son las prodrogas preferidas.

Los compuestos de la invención pueden comprender átomos de carbono sustituidos de manera asimétrica conocidos como centros quirales. Estos compuestos pueden existir, en un sentido no limitativo, como estereoisómeros individuales (por ejemplo, enantiómeros individuales o diastereómeros individuales), mezclas de estereoisómeros (por ejemplo, una mezcla de enantiómeros o diastereómeros) o mezclas racémicas. Los compuestos identificados en la presente como estereoisómeros individuales describen compuestos que están presentes en una forma que está sustancialmente libres de otros estereoisómeros (por ejemplo, sustancialmente libres de otros enantiómeros o diastereómeros). El término "sustancialmente libre", significar que al menos un 80% del compuesto en una composición es el estereoisómero descrito; preferentemente, al menos un 90% del compuesto en una composición es el estereoisómero descrito; y más preferentemente, al menos un 95%, 96%, 97%, 98% o 99% del compuesto en una composición es el estereoisómero descrito. Cuando no se especifica la estereoquímica de un carbono quiral en la estructura química de un compuesto, dicha estructura química pretende abarcar compuestos que contienen cualquier estereoisómero del centro quiral.

Los estereoisómeros individuales de los compuestos de esta invención se pueden preparar usando una variedad de métodos conocidos en el arte. Estos métodos incluyen, pero en un sentido no limitativo, síntesis estereoespecífica, separación cromatográfica de diastereómeros, resolución cromatográfica de enantiómeros, conversión de enantiómeros en una mezcla enantiomérica en diastereómeros seguido por separación cromatográfica de los diastereómeros y regeneración de los enantiómeros individuales y resolución enzimática.

La síntesis estereoespecífica comprende típicamente el uso de materiales ópticamente puros (enantioméricamente puros) o sustancialmente ópticamente puros apropiados y reacciones de síntesis que no causan racemización o inversión de la estereoquímica en los centros quirales. Las mezclas de estereoisómeros de compuestos, incluyendo mezclas racémicas, resultantes de una reacción de síntesis se pueden separar, por ejemplo, mediante técnicas cromatográficas, como podrán apreciar los especialistas en el arte. La

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resolución cromatográfica de enantiómeros se puede efectuar usando resinas de cromatografía quiral, muchos de los cuales se encuentran disponibles comercialmente. En un ejemplo no limitativo, el racemato se pone en solución y se carga sobre la columna que contiene una fase estacionaria quiral. Los enantiómeros se pueden separar luego por HPLC.

La resolución de enantiómeros también se puede efectuar por conversión de los enantiómeros en una mezcla en diastereómeros por reacción con auxiliares quirales. Los diastereómeros resultantes se pueden separar luego por cromatografía en columna o por cristalización/recristalización. Esta técnica es de utilidad cuando los compuestos a separar contienen un grupo carboxilo, amino o hidroxilo que formará una sal o un enlace covalente con el auxiliar quiral. Los ejemplos no limitativos de auxiliares quirales adecuado incluyen aminoácidos, ácidos carboxílicos orgánicos o ácidos organosulfónicos quiralmente puros. Una vez que los diastereómeros fueron separados por cromatografía, se pueden regenerar los enantiómeros individuales. Con frecuencia se pueden recuperar y volver a usar los auxiliares quirales.

Hay enzimas, tales como estearasas, fosfatasas o lipasas, que pueden ser de utilidad para la resolución de derivados de enantiómeros en una mezcla enantiomérica. Por ejemplo, se puede tratar un éster derivado de un grupo carboxilo en los compuestos a separar con una enzima que sólo hidroliza selectivamente uno de los enantiómeros en la mezcla. El ácido enantioméricamente puro resultante se puede separar luego del éster no hidrolizado.

Como alternativa, se pueden preparar sales de enantiómeros en una mezcla usando cualquier método adecuado conocido en el arte, incluyendo tratamiento del ácido carboxílico con una base ópticamente pura adecuada, tales como alcaloides o fenetilamina, seguido por precipitación o cristalización/re-cristalización de las sales enantioméricamente puras. Los métodos adecuados para la resolución/separación de una mezcla de estereoisómeros, incluyendo mezclas racémicas, se pueden consultar en ENANTIOMERS, RACEMATES, AND RESOLUTIONS (Jacques *et al.*, 1981, John Wiley and Sons, Nueva York, NY).

Un compuesto de esta invención puede tener uno o más enlaces dobles carbono-carbono insaturados. Todos los isómeros de enlaces dobles, tales como los isómeros cis (Z) y trans (E), y mezclas de los mismos, se consideran dentro del alcance de un compuesto indicado a menos que se especifique de otra manera. Además, cuando un compuesto existe en distintas formas tautoméricas, el compuesto no se limita a ningún tautómero específico, sino que se pretende que abarque todas las formas tautoméricas.

Determinados compuestos de la invención pueden existir en diferentes formas de

conformación estables que se pueden separar. La asimetría de torsión debida a rotaciones restringidas alrededor de una unión simple asimétrica, por ejemplo debido al impedimento estérico o tensión en el anillo, puede permitir la separación de los diferentes confórmeros. La invención abarca cada isómero de conformación de estos compuestos y mezclas de los mismos.

Determinados compuestos de la invención también pueden existir en una forma zwiteriónica y la invención abarca cada forma zwiteriónica de estos compuestos y mezclas de los mismos.

Los compuestos de la presente invención generalmente se describen en la presente usando la nomenclatura estándar. En el caso de un compuesto indicado con uno o más centros asimétricos, se debe tener en cuenta que todos los estereoisómeros del compuesto y mezclas de los mismos están comprendidos en la presente invención a menos que se especifique de otra manera. Los ejemplos no limitativos de estereoisómeros incluyen enantiómeros, diastereómeros y cis-trans-isómeros. Cuando un compuesto indicado existe en distintas formas tautoméricas, se considera que el compuesto abarca todas dichas formas tautoméricas. En la presente, determinados compuestos se describen usando fórmulas generales que incluyen variables (por ejemplo, A, B, D, X, L_1, L_2, L_3, Y, Z, T, R_A o R_B,). A menos que se especifique de otra manera, cada variable dentro de dicha fórmula se define de forma independiente de cualquier otra variable, y cualquier variable que aparece más de una vez en una fórmula se define de manera independiente en cada aparición. Si los grupos se describen como seleccionados "de manera independiente" de un grupo, cada grupo se selecciona de manera independiente de los demás. Por ello es que cada grupo puede ser idéntico o diferente de los demás grupos.

La cantidad de átomos de carbono en un grupo hidrocarbilo se puede indicar con el prefijo "C_x-C_y", donde x es la cantidad mínima e y es la cantidad máxima de átomos de carbono en el grupo. Así, por ejemplo, "C_1-C_6-alquilo" significa un sustituyente alquilo que contiene entre 1 y 6 átomos de carbono. A modo de ilustración adicional, un C_3-C_6-cicloalquilo significa un anillo hidrocarbilo saturado que contiene entre 3 y 6 átomos de carbono en el anillo. Un prefijo unido a un sustituyente de múltiples componentes solamente se aplica al primer componente que le sigue inmediatamente al prefijo. A efectos ilustrativos, el término "carbociclilalquilo" contiene dos componentes: carbociclilo y alquilo. Así, por ejemplo, C_3-C_6carbociclilC_1-C_6alquilo se refiere a un C_3-C_6carbociclilo unido a la porción molecular parental a través de un grupo C_1-C_6alquilo.

A menos que se especifique de otra manera, cuando un elemento de unión une otros dos elementos en una estructura química indicada, el componente descrito que se encuentra

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más hacia la izquierda del elemento conector está unido al elemento de la izquierda en la estructura indicada, y el componente descrito que se encuentra más hacia la derecha del elemento conector está unido al elemento de la derecha en la estructura indicada. A efectos ilustrativos, si la estructura química es $-L_S-M-L_S'-$ y M es $-N(R_B)S(O)-$, entonces la estructura química es $-L_S-N(R_B)S(O)-L_S'-$.

Si un elemento conector en una estructura indicada es un enlace, entonces el elemento de la izquierda con respecto al elemento conector está unido directamente al elemento de la derecha con respecto al elemento conector a través de un enlace covalente. Por ejemplo, si la estructura química se representa como $-L_S-M-L_S'-$ y M se selecciona como un enlace, entonces la estructura química será $-L_S-L_S'-$. Si dos o más elementos conectores adyacentes en una estructura indicada son enlaces, entonces el elemento de la izquierda con respecto a estos elementos conectores está unido directamente al elemento de la derecha con respecto a estos elementos conectores por medio de un enlace covalente. Por ejemplo, si la estructura química se representa como $-L_S-M-L_S'-M'-L_S''-$, y M y L_S' se seleccionan como enlaces, entonces la estructura química será $-L_S-M'-L_S''-$. Asimismo, si una estructura química se representa como $-L_S-M-L_S'-M'-L_S''-$, y M, L_S' y M' son enlaces, entonces la estructura química será $-L_S-L_S''-$.

Cuando se usa una fórmula química para describir un grupo, el o los guiones indican la porción del grupo que tiene una o más valencias libres.

Si un grupo se describe como "sustituido opcionalmente", el grupo puede estar sustituido o no sustituido. Si un grupo se describe como sustituido opcionalmente con un número particular máximo de radicales distintos de hidrógeno, dicho grupo puede no estar sustituido o puede estar sustituido por un número que comprende hasta dicho número particular de radicales distintos de hidrógeno o por un número que comprende hasta el número máximo de posiciones sustituibles sobre el grupo, cualquiera de ellos sea el menor. Así, por ejemplo, si un grupo se describe como un heterociclo sustituido opcionalmente con hasta tres radicales distintos de hidrógeno, entonces cualquier heterociclo con menos que tres posiciones sustituibles estará sustituido opcionalmente con hasta tantos radicales distintos de hidrógeno como posiciones sustituibles haya en el heterociclo. A fines ilustrativos, un tetrazolilo (que solamente tiene una posición sustituible) estaría sustituido opcionalmente con hasta un radical distinto de hidrógeno. A efectos ilustrativos adicionales, si se describe un nitrógeno de amino como sustituido opcionalmente con hasta dos radicales distintos de hidrógeno, entonces un nitrógeno de un amino primario estará sustituido opcionalmente con hasta dos radicales distintos de hidrógeno, en tanto un nitrógeno de un amino secundario estará sustituido opcionalmente con tan solo un radical distinto de hidrógeno como máximo.

El término "alquenilo" se refiere a una cadena hidrocarbilo lineal o ramificada que contiene uno o más enlaces dobles. Cada enlace doble carbono-carbono puede tener una geometría cis o trans dentro del grupo alquenilo, con relación a los grupos sustituidos sobre los carbonos del enlace doble. Los ejemplos no limitativos de grupos alquenilo incluyen etenilo (vinilo), 2-propenilo, 3-propenilo, 1,4-pentadienilo, 1,4-butadienilo, 1-butenilo, 2-butenilo y 3-butenilo.

El término "alquenileno" se refiere a una cadena de hidrocarbilo insaturada divalente que puede ser lineal o ramificada y que tiene al menos un enlace doble carbono-carbono. Los ejemplos no limitativos de grupos de alquenileno incluyen —C(H)=C(H)—, —C(H)=C(H)—CH_2—, —C(H)=C(H)—CH_2—CH_2—, —CH_2—C(H)=C(H)—CH_2—, —C(H)=C(H)—CH(CH_3)— y —CH_2—C(H)=C(H)—CH(CH_2CH_3)—.

El término "alquilo" hace referencia a una cadena de hidrocarbilo saturada lineal o ramificada. Los ejemplos no limitativos de dichos sustituyentes incluyen metilo, etilo, n-propilo, isopropilo, n-butilo, isobutilo, sec-butilo, ter-butilo, pentilo, iso-amilo y hexilo.

El término "alquileno" indica un grupo hidrocarbilo divalente saturado que puede ser lineal o ramificado. Los ejemplos representativos de alquileno incluyen, pero en un sentido no limitativo, -CH_2-, -CH_2CH_2-, -$CH_2CH_2CH_2$-, -$CH_2CH_2CH_2CH_2$- y -$CH_2CH(CH_3)CH_2$-.

El término "alquinilo" se refiere a una cadena de hidrocarbilo lineal o ramificada que contiene uno o más enlaces triples. Los ejemplos no limitativos de alquinilo incluyen etinilo, 1-propinilo, 2-propinilo, 3-propinilo, decinilo, 1-butinilo, 2-butinilo y 3-butinilo.

El término "alquinileno" se refiere a un grupo hidrocarbonado divalente insaturado que puede ser lineal o ramificado y que tiene al menos un enlace triple carbono-carbono. Los grupos alquinileno representativos incluyen, a modo de ejemplo, —C≡C—, —C≡C—CH_2—, —C≡C—CH_2—CH_2—, —CH_2—C≡C—CH_2—, —C≡C—CH(CH_3)— y —CH_2—C≡C—CH(CH_2CH_3)—.

El término "carbociclo" o "carbocíclico" o "carbociclilo" se refiere a un sistema de anillos saturado (por ejemplo, "cicloalquilo"), parcialmente saturado (por ejemplo, "cicloalquenilo" o "cicloalquinilo") o completamente insaturado (por ejemplo, "arilo") que contiene cero heteroátomos entre los átomos del anillo. Los "átomos del anillo" o "miembros del anillo" son los átomos unidos entre sí para formar el o los anillos. Un carbociclilo puede ser, en un sentido no limitativo, un solo anillo, dos anillos fusionados o anillos con puente o espiro. Un carbociclilo sustituido puede tener una geometría cis o trans. Los ejemplos representativos de grupos carbociclilo incluyen, pero en un sentido no limitativo, ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, cicloheptilo, ciclooctilo, ciclopentenilo, ciclopentadienilo, ciclohexadienilo, adamantilo, decahidro-naftalenilo, octahidro-indenilo, ciclohexenilo, fenilo, naftilo, indanilo, 1,2,3,4-tetrahidro-naftilo, indenilo, isoindenilo, decalinilo y norpinanilo. Se puede unir un grupo carbociclo a la porción molecular parental

por medio de cualquier átomo del anillo de carbono sustituible. Cuando un grupo carbociclo es un grupo divalente que une otros dos elementos en una estructura química indicada (tal como A en la fórmula I), dicho grupo carbociclo se puede unir a los otros dos elementos a través de cualesquiera dos átomos del anillo sustituibles. Asimismo, cuando un grupo carbociclo es un grupo trivalente que une otros tres elementos en una estructura química indicada (tal como X en la fórmula I), dicho grupo carbociclo se puede unir a los otros tres elementos por medio de cualesquiera tres átomos del anillo sustituibles, respectivamente.

El término "carbociclilalquilo" se refiere a un grupo carbociclilo unido a la porción molecular parental por medio de un grupo alquileno. Por ejemplo, C_3-C_6carbociclilC_1-C_6alquilo se refiere a un grupo C_3-C_6carbociclilo unido a la porción molecular parental a través de un C_1-C_6alquileno.

El término "cicloalquenilo" se refiere a un grupo carbociclilo no aromático, parcialmente insaturado que tiene cero miembros del anillo de heteroátomos. Los ejemplos representativos de cicloalquenilo grupos incluyen, pero en un sentido no limitativo, ciclobutenilo, ciclopentenilo, ciclohexenilo y octahidronaftalenilo.

El término "cicloalquilo" se refiere a un grupo carbociclilo saturado que contiene cero miembros del anillo de heteroátomos. Los ejemplos no limitativos de cicloalquilos incluyen ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, cicloheptilo, ciclooctilo, decalinilo y norpinanilo.

El prefijo "halo" indica que el sustituyente al cual se refiere dicho prefijo está sustituido con uno o varios radicales halógenos seleccionados de forma independiente entre sí. Por ejemplo, "C_1-C_6haloalquilo" se refiere a un sustituyente C_1-C_6alquilo en donde uno o más átomos de hidrógeno son reemplazados de manera independiente con radicales de halógeno seleccionados. Los ejemplos no limitativos de C_1-C_6haloalquilo incluyen clorometilo, 1-bromoetilo, fluorometilo, difluorometilo, trifluorometilo y 1,1,1-trifluoroetilo. Se debe tener en cuenta que si un sustituyente está sustituido por más de un radical halógeno, dichos radicales halógeno pueden ser idénticos o diferentes (a menos que se indique lo contrario).

Los términos "heterociclo" o "heterocíclico" o "heterociclilo" se refieren a un sistema de anillos saturado (por ejemplo, "heterocicloalquilo"), parcialmente insaturado (por ejemplo, "heterocicloalquenilo" o "heterocicloalquinilo") o completamente insaturado (por ejemplo, "heteroarilo"), donde al menos uno de los átomos del anillo es un heteroátomo (es decir, nitrógeno, oxígeno o azufre), donde el resto de los átomos del anillo se seleccionan de manera independiente del grupo que consiste de carbono, nitrógeno, oxígeno y azufre. Un heterociclo puede ser, en un sentido no limitativo, un solo anillo, dos anillos fusionados o

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anillos con puente o espiro. Un grupo heterocíclico se puede unir a la porción molecular parental a través de cualquier átomo de carbono o nitrógeno sustituible en el grupo. Cuando un grupo heterociclo es un grupo divalente que une otros dos elementos en una estructura química indicada (tal como A en la fórmula I), dicho grupo heterociclo se puede unir a los otros dos elementos a través de cualesquiera dos átomos del anillo sustituibles. Asimismo, cuando un grupo heterociclo es un grupo trivalente que une otros tres elementos en una estructura química indicada (tal como X en la fórmula I), dicho grupo heterociclo se puede unir a los otros tres elementos por medio de cualesquiera tres átomos del anillo sustituibles, respectivamente.

Un heterociclilo puede ser, en un sentido no limitativo, un monociclo que contiene un solo anillo. Los ejemplos no limitativos de monociclos incluyen furanilo, dihidrofuranilo, tetrahidrofuranilo, pirrolilo, isopirrolilo, pirrolinilo, pirrolidinilo, imidazolilo, isoimidazolilo, imidazolinilo, imidazolidinilo, pirazolilo, pirazolinilo, pirazolidinilo, triazolilo, tetrazolilo, ditiolilo, oxatiolilo, oxazolilo, isoxazolilo, tiazolilo, isotiazolilo, tiazolinilo, isotiazolinilo, tiazolidinilo, isotiazolidinilo, tiodiazolilo, oxatiazolilo, oxadiazolilo (incluyendo 1,2,3-oxadiazolilo, 1,2,4-oxadiazolilo (también conocido como "azoximilo"), 1,2,5-oxadiazolilo (también conocido como "furazanilo") y 1,3,4-oxadiazolilo), oxatriazolilo (incluyendo 1,2,3,4-oxatriazolilo y 1,2,3,5-oxatriazolilo), dioxazolilo (incluyendo 1,2,3-dioxazolilo, 1,2,4-dioxazolilo, 1,3,2-dioxazolilo y 1,3,4-dioxazolilo), oxatiolanilo, piranilo (incluyendo 1,2-piranilo y 1,4-piranilo), dihidropiranilo, piridinilo, piperidinilo, diazinilo (incluyendo piridazinilo (también conocido como "1,2-diazinilo"), pirimidinilo (también conocido como "1,3-diazinilo") y pirazinilo (también conocido como "1,4-diazinilo")), piperazinilo, triazinilo (incluyendo s-triazinilo (también conocido como "1,3,5-triazinilo"), as-triazinilo (también conocido como 1,2,4-triazinilo) y v-triazinilo (también conocido como "1,2,3-triazinilo), oxazinilo (incluyendo 1,2,3-oxazinilo, 1,3,2-oxazinilo, 1,3,6-oxazinilo (también conocido como "pentoxazolilo"), 1,2,6-oxazinilo y 1,4-oxazinilo), isoxazinilo (incluyendo o-isoxazinilo y p-isoxazinilo), oxazolidinilo, isoxazolidinilo, oxatiazinilo (incluyendo 1,2,5-oxatiazinilo o 1,2,6-oxatiazinilo), oxadiazinilo (incluyendo 1,4,2-oxadiazinilo y 1,3,5,2-oxadiazinilo), morfolinilo, azepinilo, oxepinilo, tiepinilo, tiomorfolinilo y diazepinilo.

Un heterociclilo también puede ser, en un sentido no limitativo, un biciclo que contiene dos anillos fusionados, tal como, por ejemplo, naftiridinilo (incluyendo [1,8] naftiridinilo y [1,6] naftiridinilo), tiazolpirimidinilo, tienopirimidinilo, pirimidopirimidinilo, piridopirimidinilo, pirazolpirimidinilo, indolizinilo, pirindinilo, piranopirrolilo, 4H-quinolizinilo, purinilo, piridopiridinilo (incluyendo pirido[3,4-b]-piridinilo, pirido[3,2-b]-piridinilo y pirido[4,3-b]-piridinilo), piridopirimidina y pteridinilo. Otros ejemplos no limitativos de heterociclos de anillos fusionados incluyen heterociclilos benzo-fusionados, tales como indolilo, isoindolilo,

indoleninilo (también conocido como "pseudoindolilo"), isoindazolilo (también conocido como "benzpirazolilo" o indazolilo), benzazinilo (incluyendo quinolinilo (también conocido como "1-benzazinilo") e isoquinolinilo (también conocido como "2-benzazinilo")), benzimidazolilo, ftalazinilo, quinoxalinilo, benzodiazinilo (incluyendo cinolinilo (también conocido como "1,2-benzodiazinilo") y quinazolinilo (también conocido como "1,3-benzodiazinilo")), benzopiranilo (incluyendo "cromenilo" e "isocromenilo"), benzotiopiranilo (también conocido como "tiocromenilo"), benzoxazolilo, indoxazinilo (también conocido como "benzisoxazolilo"), antranililo, benzodioxolilo, benzodioxanilo, benzoxadiazolilo, benzofuranilo (también conocido como "coumaronilo"), isobenzofuranilo, benzotienilo (también conocido como "benzotiofenilo", "tionaftenilo" y "benzotiofuranilo"), isobenzotienilo (también conocido como "isobenzotiofenilo", "isotionaftenilo" e "isobenzotiofuranilo"), benzotiazolilo, 4,5,6,7-tetrahidrobenzo[d]tiazolilo, benzotiadiazolilo, benzimidazolilo, benzotriazolilo, benzoxazinilo (incluyendo 1,3,2-benzoxazinilo, 1,4,2-benzoxazinilo, 2,3,1-benzoxazinilo y 3,1,4-benzoxazinilo), benzisoxazinilo (incluyendo 1,2-benzisoxazinilo y 1,4-benzisoxazinilo) y tetrahidroisoquinolinilo.

Un heterociclilo también puede ser, en un sentido no limitativo, un sistema de anillos espiro, tal como, por ejemplo, 1,4-dioxa-8-azaspiro[4.5]decanilo.

Un heterociclilo puede comprender uno o más átomos de azufre como miembros del anillo; y en algunos casos, el o los átomos de azufre se oxidan en SO o SO_2. El o los heteroátomos de nitrógeno en un heterociclilo se pueden cuaternizar, o no, y se pueden oxidar, o no, en un N-óxido. Además, el o los heteroátomos de nitrógeno pueden estar N-protegidos, o no.

⁻⁻⁻⁻⁻ en una fórmula química se refiere un enlace simple o doble.

El término "farmacéuticamente aceptable" se usa como un adjetivo para indicar que el sustantivo modificado es apropiado para su uso como un producto farmacéutico o como parte de un producto farmacéutico.

El término "cantidad terapéuticamente eficaz" se refiere a la cantidad total de cada sustancia activa que es suficiente para ofrecer un beneficio significativo para el paciente, por ejemplo, una reducción en la carga viral.

El término "prodroga" se refiere a derivados de los compuestos de la invención que contienen grupos químicamente o metabólicamente clivables y que se convierten, por solvólisis o bajo condiciones fisiológicas, en los compuestos de la invención que son farmacéuticamente activos *in vivo*. Una prodroga de un compuesto se puede formar de una manera convencional por reacción de un grupo funcional del compuesto (tal como un grupo amino, hidroxilo o carboxilo). Las prodrogas a menudo ofrecen ventajas de solubilidad, compatibilidad tisular o liberación demorada en mamíferos (véase, Bundgard,

H., DESIGN OF PRODRUGS, páginas 7-9, 21-24, Elsevier, Amsterdam 1985). Las prodrogas incluyen derivados ácidos bien conocidos por los especialistas del arte, tal como, por ejemplo, ésteres preparados por reacción del compuesto ácido parental con un alcohol adecuado, o amidas preparadas por reacción del compuesto ácido parental con una amina adecuada. Los ejemplos de prodrogas incluyen, pero en un sentido no limitativo, derivados de acetato, formato, benzoato u otros derivados acilados de grupos funcionales de alcohol y amina en los compuestos de la invención.

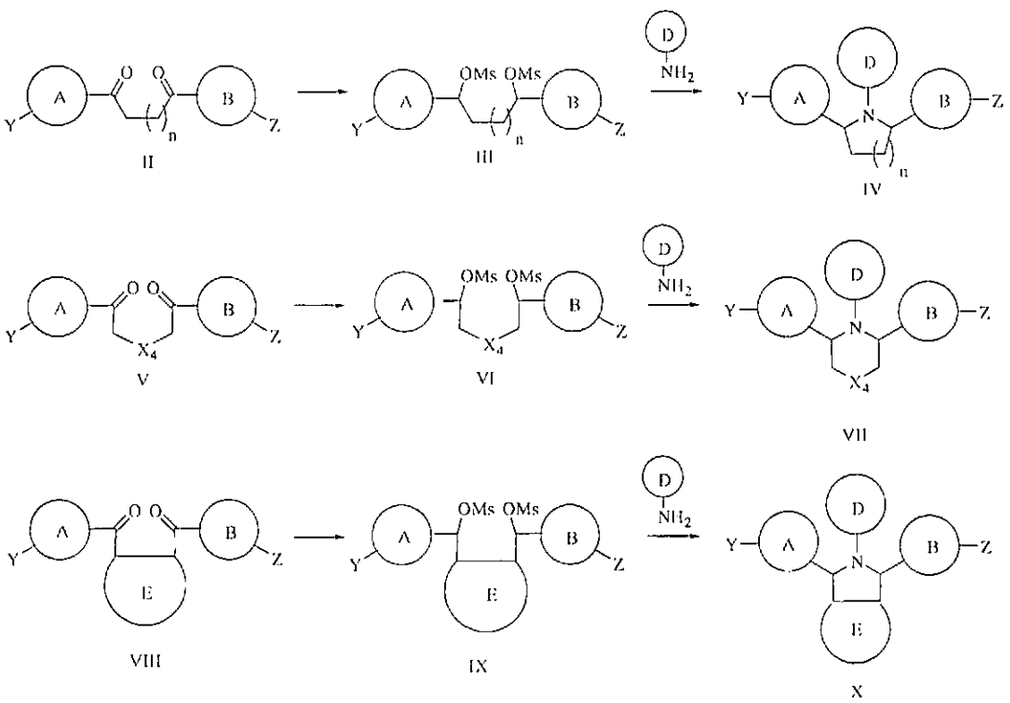
El término "solvato" se refiere a la asociación física de un compuesto de esta invención con una o más moléculas de solvente, ya sea orgánica o inorgánica. Esta asociación física a menudo incluye enlaces de hidrógeno. En determinados casos, el solvato permite el aislamiento, por ejemplo, cuando se incorpora una o más moléculas de solvente en la red cristalina del sólido cristalino. Un "solvato" abarca ambos solvatos en fase de solución y aislables. Los ejemplos de solvatos incluyen, pero en un sentido no limitativo, hidratos, etanolatos y metanolatos.

El término "grupo N-protector" o "N-protegido" se refiere a aquellos grupos capaces de proteger un grupo amino contra reacciones indeseables. Los grupos N-protectores usados comúnmente se describen en Greene y Wuts, PROTECTING GROUPS IN CHEMICAL SYNTHESIS (3ª ed., John Wiley & Sons, NY (1999). Los ejemplos no limitativos de grupos N-protectores incluyen grupos acilo tales como formilo, acetilo, propionilo, pivaloilo, t-butilacetilo, 2-cloroacetilo, 2-bromoacetilo, trifluoroacetilo, tricloroacetilo, ftalilo o-nitrofenoxiacetilo, benzoílo, 4-clorobenzoílo, 4-bromobenzoílo o 4-nitrobenzoílo; grupos sulfonilo tales como bencensulfonilo o p-toluensulfonilo; grupos sulfenilo tales como fenilsulfenilo (fenil-S-) o trifenilmetilsulfenilo (tritil-S-); grupos sulfinilo tales como p-metilfenilsulfinilo (p-metilfenil-S(O)-) o t-butilsulfinilo (t-Bu-S(O)-); grupos formadores de carbamato tales como benciloxicarbonilo, p-clorobenciloxicarbonilo, p-metoxibenciloxicarbonilo, p-nitrobenciloxicarbonilo, 2-nitrobenciloxicarbonilo, p-bromobenciloxicarbonilo, 3,4-dimetoxibenciloxicarbonilo, 3,5-dimetoxibenciloxicarbonilo, 2,4-dimetoxibenciloxicarbonilo, 4-metoxibenciloxicarbonilo, 2-nitro-4,5-dimetoxibenciloxicarbonilo, 3,4,5-trimetoxibenciloxicarbonilo, 1-(p-bifenililo)-1-metiletoxicarbonilo, dimetil-3,5-dimetoxibenciloxicarbonilo, benzhidriloxicarbonilo, t-butiloxicarbonilo, diisopropilmetoxicarbonilo, isopropiloxicarbonilo, etoxicarbonilo, metoxicarbonilo, aliloxicarbonilo, 2,2,2-tricloro-etoxi-carbonilo, fenoxicarbonilo, 4-nitro-fenoxicarbonilo, ciclopentiloxicarbonilo, adamantiloxicarbonilo, ciclohexiloxicarbonilo o feniltiocarbonilo; grupos alquilo tales como bencilo, p-metoxibencilo, trifenilmetilo o benciloximetilo; p-metoxifenilo; y grupos sililo tal como trimetilsililo. Los grupos N-protectores preferidos incluyen, formilo, acetilo, benzoílo, pivaloílo, t-butilacetilo,

fenilsulfonilo, bencilo, t-butiloxicarbonilo (BOC) y benciloxicarbonilo (Cbz).

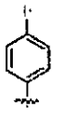
Los compuestos de la presente invención se pueden preparar usando una variedad de métodos. A modo de ejemplos no limitativo, los compuestos de la presente invención se pueden preparar de acuerdo con el Esquema I a partir de compuestos de la fórmula II (por ejemplo, n = 0 a 8), de la fórmula V (X_4 puede ser, por ejemplo, O o NR_A, donde R_A es como se describió precedentemente y es preferentemente H o R_E como se definió previamente tal como C1-C6alquilo, carbociclo o heterociclo de 3 a 12 miembros, $-C(O)R_S$, $-C(O)OR_S$, $-C(O)N(R_SR_S')$, $-SO_2N(R_SR_S')$, $-S(O)_2OR_S$, $-S(O)OR_S$, $-S(O)N(R_SR_S')$, o un grupo protector adecuado tal como Boc o Fmoc) o de la fórmula VIII (E puede ser, por ejemplo, carbociclo o heterociclo de 3 a 7 miembros y está sustituido opcionalmente con uno o más R_A), en donde A, B, D, Y, Z y R_A son como se describieron previamente. Las 1,4-dicetonas II, V y VIII se pueden reducir a los 1,4-dioles usando los métodos descritos más adelante, y los 1,4-dioles racémicos, enantioméricamente enriquecidos o meso resultantes se pueden convertir en los dimesilatos III, VI o IX o, como alternativa, en ditriflatos, ditosilatos o dihaluros mediante los métodos descritos más adelante. Los dimesilatos III, VI y IX, ditriflatos, ditosilatos o dihaluros se pueden hacer reaccionar con una amina, incluyendo pero en un sentido no taxativo, anilina, 3,5-difluoroanilina, 3,4-difluoroanilina, 4-fluoroanilina, 3-fluoroanilina, 4-trifluorometilanilina, 4-cloroanilina, heteroarilaminas, alquilaminas, cicloalquilaminas, bencilaminas sustituidas o alilamina, bajo las condiciones descritas más adelante para dar los compuestos de la invención. L_1 y L_2 se pueden introducir fácilmente en las fórmulas II, V y VIII, como podrán apreciar los especialistas en el arte a la luz de la presente invención. Asimismo, se puede usar $D\text{-}L_3\text{-}NH_2$ en lugar de $D\text{-}NH_2$, como podrán apreciar los especialistas en el arte.

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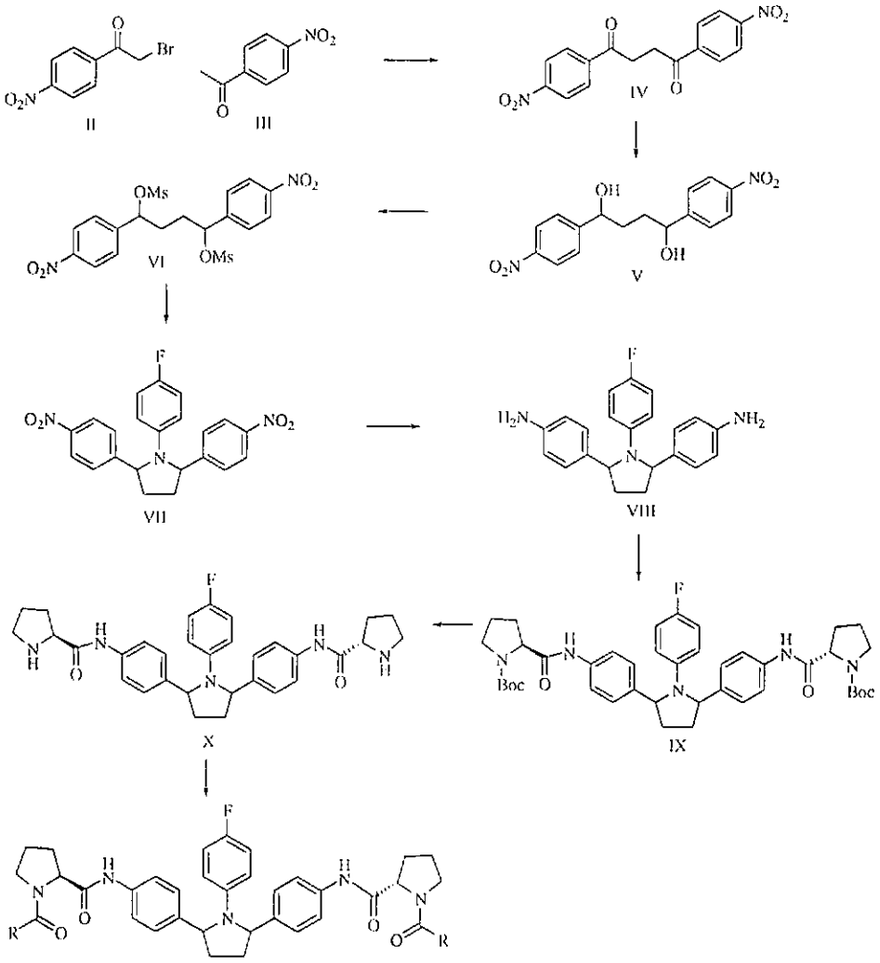


Esquema I

A modo de otro ejemplo no limitativo, los compuestos de la presente invención se pueden preparar comenzando a partir de los compuestos de la fórmula II y de la fórmula III como se muestra en el esquema II. Las 1,4-dicetonas, tal como de la fórmula IV, se pueden preparar usando métodos conocidos (véase Nevar, et al., *Synthesis*:1259-1262 (2000), tal como la reacción de α-bromocetonas, tal como de la fórmula II, con metilcetonas, tal como de la fórmula III, en la presencia de un ácido de Lewis adecuado, tal como $ZnCl_2$ o $Ti(0iPr)_4$. Las 1,4-dicetonas IV se pueden reducir en los 1,4-dioles, tal como V, por la acción de $NaBH_4$, $LiAlH_4$ o DIBAL. Como alternativa, la reducción enantioselectiva de 1,4-dicetonas, tal como de la fórmula IV, se puede efectuar por analogía con los métodos informados (véase Chong, et al., *Tetrahedron: Asymmetry* 6: 409-418 (1995), Li, et al., *Tetrahedron* 63: 8046-8053 (2007), Aldous, et al., *Tetrahedron: Asymmetry* 11: 2455-2462 (2000), Masui, et al., *Synlett*: 273-274 (1997), Jing, et al., *Adv. Synth. Catal.* 347: 1193-1197 (2005), Sato, et al., *Synthesis*: 1434-1438 (2004)), tal como reducción con (-) o (+)-diisopinocamdeilcloroborano (cloruro-DIP), con borano y un catalizador de oxazaborolidina, o con hidrogenación asimétrica en la presencia de un catalizador de rutenio (II) adecuado, tal como [RuCl2{(R)-BINAP}{(R,R)-DPEN}] (BINAP=2,2'-bis(diarilfosfino)-1,1'-binaftilo; DPEN = 1,2-difeniletilendiamina). Los 1,4-dioles racémicos, enantioméricamente enriquecidos o meso V resultantes se pueden hacer reaccionar con cloruro de metansulfonilo para proveer el dimesilato de la fórmula VI. Como alternativa, la fórmula V se puede convertir en un ditriflato o ditosilato por la acción de cloruro de p-

toluensulfonilo o anhídrido tríflico, o en un dihaluro, tal como un dibromuro o dicloruro, por la acción de PPh_3 en la presencia de CCl_4 o CBr_4, o por la acción de $SOCl_2$, $POCl_3$ o PBr_3. El dimesilato, ditriflato, ditosilato o dihaluro se puede hacer reaccionar con una amina, tal como 4-fluoroanilina (como se muestra a efectos ilustrativos en el esquema II), con o sin un co-solvente, tal como DMF, a temperatura ambiente hasta 100 °C, para dar pirrolidinas tal como de la fórmula VII. Además de la 4-fluoroanilina, se pueden hacer reaccionar aminas alternativas con el dimesilato de la fórmula VI, incluyendo pero en un sentido no taxativo anilina, 3,5-difluoroanilina, 3,4-difluoroanilina, 3-fluoroanilina, 4-trifluorometilanilina, 4-cloroanilina, heteroarilaminas, alquilaminas, cicloalquilaminas, bencilaminas sustituidas o alilamina. El dinitro de la fórmula VII se puede reducir en la diamino de la fórmula VIII usando Fe en la presencia de NH_4Cl, HCl o ácido acético, o por tratamiento con un agente reductor de hidruro, tal como borohidruro de sodio (con o sin la adición de una sal de un metal de transición, tal como $BiCl_3$, $SbCl_3$, $NiCl_2$, Cu_2Cl_2 o $CoCl_2$) en un solvente, tal como etanol o THF. Como alternativa, la fórmula VII se puede reducir en el producto de la fórmula VIII por hidrogenación en la presencia de un catalizador adecuado, tal como un catalizador de paladio o platino o níquel Raney. La diamina de la fórmula VIII se puede hacer reaccionar con una prolina ácida adecuadamente protegida (se indica Boc, aunque puede sustituirse por Cbz, Troc o Fmoc) en la presencia de un reactivo de acoplamiento peptídico, tal como EDAC/HOBT, PyBOP, HATU o DEBPT, en un solvente tal como THF, DMF, diclorometano o DMSO, con o sin la adición de una base de amina, tal como la base de Hunig, piridina, 2,6-lutidina o trietilamina, para dar directamente compuestos de la presente invención (fórmula IX).  en cada Fórmula dentro del Esquema II se puede reemplazar por  , donde D se define anteriormente y dichos compuestos se pueden preparar de acuerdo con el proceso descripto en el Esquema II (incluida la prodeucción del compuesto XI directmanete a partir del compuesto VIII).

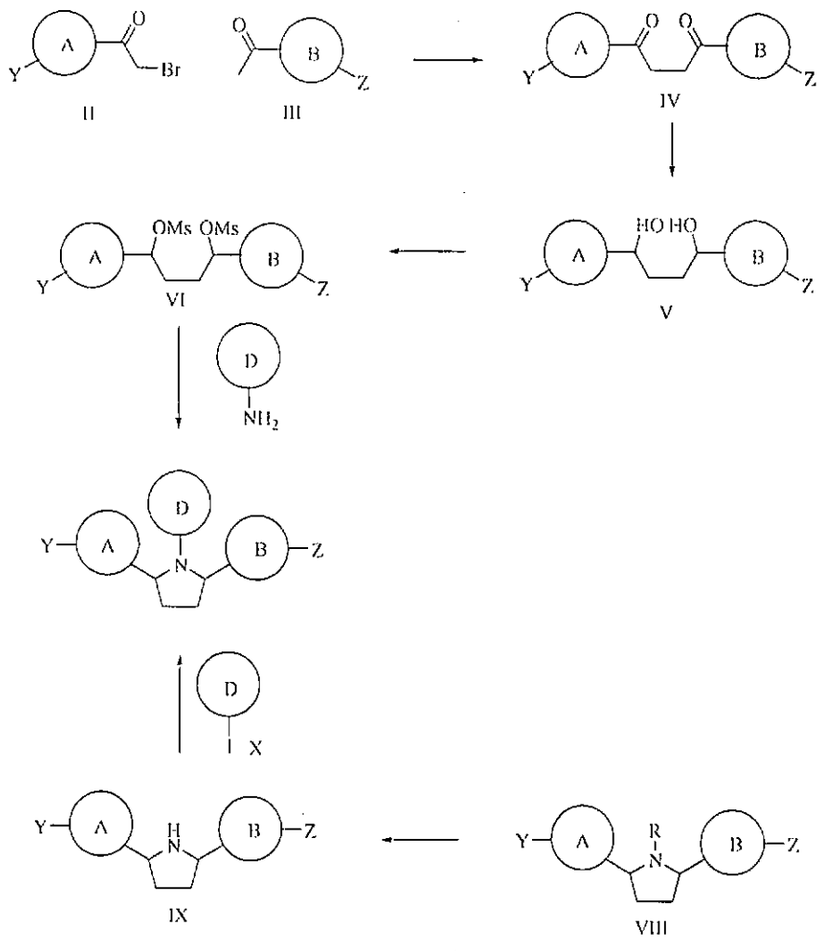
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Esquema II

Como aún otro ejemplo no limitativo, los compuestos de la presente invención se pueden preparar comenzando a partir de los compuestos de la fórmula II y de la fórmula III como se muestra en el esquema III, donde A, B, D, Y y Z son como se describieron previamente, usando condiciones similares a las descritas previamente para la preparación de IV en el esquema II. De manera similar, la 1,4-dicetona IV resultante se puede reducir en los 1,4-dioles V usando los métodos que se describieron previamente para el esquema II. Los 1,4-dioles racémicos, enantioméricamente enriquecidos o meso V resultantes se pueden convertir en el dimesilato VI o, como alternativa, en un ditriflato, ditosilato o dihaluro mediante los métodos que se describieron previamente. El dimesilato VI, ditriflato, ditosilato o dihaluro se puede hacer reaccionar con una amina, incluyendo pero en un sentido no taxativo, anilina, 3,5-difluoroanilina, 3,4-difluoroanilina, 4-fluoroanilina, 3-fluoroanilina, 4-trifluorometilanilina, 4-cloroanilina, heteroarilaminas, alquilaminas, cicloalquilaminas, bencilaminas sustituidas o alilamina, bajo las condiciones descritas previamente para dar los compuestos de la invención. Como alternativa, los

compuestos tales como VIII, donde R es un grupo tal como alilo, 4-metoxibencilo o 2,4-dimetoxibencilo, se pueden tratar con reactivos de utilidad para la eliminación del grupo R (catalizador de rodio tal como $Rh(Ph_3P)_3Cl$ para R = alilo, tratamiento con un ácido tal como TFA o HCl para R = 4-metoxibencilo o 2,4-dimetoxibencilo, hidrogenólisis con un catalizador de Pd para R = bencilo sustituido) para generar compuestos tales como IX. La amina IX se puede hacer reaccionar con un haluro o triflato de arilo, tal como X (se muestra ioduro a efectos ilustrativos), empleando la reacción de Buchwald-Hartwig en la presencia de un catalizador de paladio (tal como $Pd(OAc)_2$ o $Pd_2(dba)_3$) y un ligando de fosfina (tal como trifenilfosfina o XantPhos) y una base (tal como bis(trimetilsilil)amida de sodio, ter-butóxido de potasio o K_3PO_4) para dar los compuestos de la presente invención. Como alternativa, los compuestos de la presente invención se pueden obtener por reacción de IX con un aldehído o una cetona por aminación reductora en la presencia de un agente reductor de hidruro, tal como borohidruro de sodio o cianoborohidruro de sodio (con o sin la adición de un ácido, tal como ácido acético) en un solvente, tal como etanol, tolueno, THF o diclorometano. Como alternativa, la aminación reductora se puede conducir mediante el uso de hidrogenación en la presencia de un catalizador adecuado, tal como un catalizador de paladio o platino o níquel Raney. Como alternativa, la amina IX puede reaccionar con reactivos electrofílicos, tales como haluros de alquilo, o con electrófilos de arilo (convenientemente haluros y triflatos de arilo y heteroarilo deficientes en electrones) a través de reacciones de sustitución nucleofílica aromática para dar los compuestos de la presente invención.

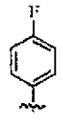


R = alilo o bencilo sustituido

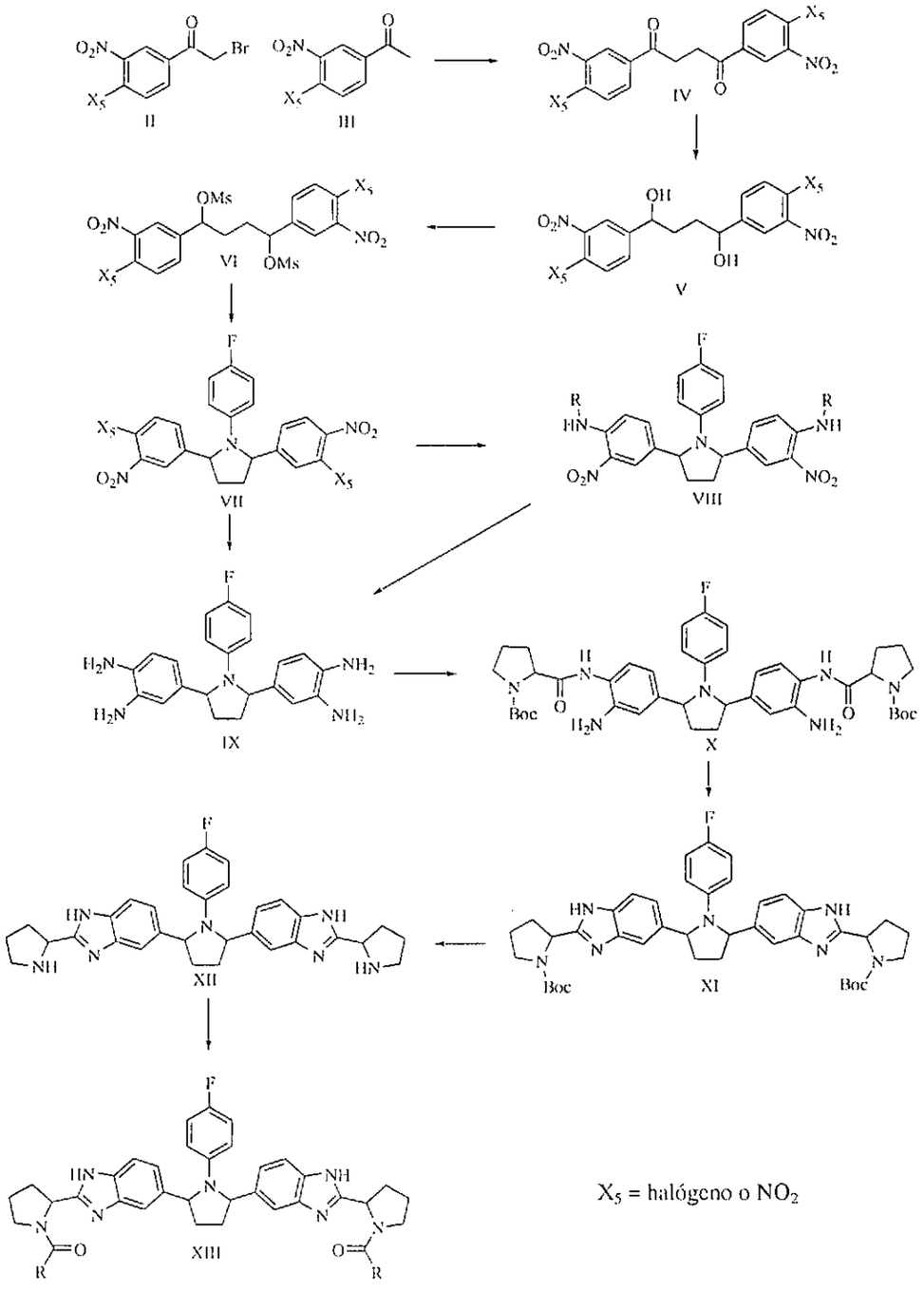
Esquema III

A modo de ejemplo no limitativo adicional, los compuestos de la presente invención se pueden preparar comenzando a partir de los compuestos de la fórmula II y de la fórmula III como se muestra en el esquema IV, donde X_5 en la fórmula II y la fórmula III representa un halógeno (por ejemplo, Cl, Br o F) o un grupo nitro. Las 1,4-dicetonas, tal como IV, se pueden preparar usando los métodos conocidos descritos previamente para la preparación de IV en el Esquema II. Las 1,4-dicetonas IV se pueden reducir en los 1,4-dioles, tal como V, por la acción de $NaBH_4$, $LiAlH_4$ o DIBAL. Como alternativa, se puede conducir una reducción enantioselectiva de 1,4-dicetona, tal como IV, mediante los métodos que se describieron previamente para la preparación de V en el esquema II. Los 1,4-dioles racémicos, enantioméricamente enriquecidos o meso V resultantes se pueden hacer reaccionar con cloruro de metansulfonilo para proveer el dimesilato VI. Como alternativa V se puede convertir en un ditriflato o ditosilato mediante los métodos que se describieron previamente para el esquema II. El dimesilato, ditriflato, ditosilato o dihaluro

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se puede hacer reaccionar con una amina, incluyendo pero en un sentido no taxativo, anilina, 3,5-difluoroanilina, 3,4-difluoroanilina, 4-fluoroanilina, 3-fluoroanilina, 4-trifluorometilanilina, 4-cloroanilina, heteroarilaminas, alquilaminas, cicloalquilaminas, bencilaminas sustituidas o alilamina para dar VII. Cuando X_5 en la fórmula VII es nitro, los grupos nitro se pueden reducir en el producto de tetraamina IX usando Fe en la presencia de NH_4Cl, HCl o ácido acético o con un agente reductor de hidruro, tal como borohidruro de sodio (con o sin la adición de una sal de un metal de transición, tal como $BiCl_3$, $SbCl_3$, $NiCl_2$, Cu_2Cl_2 o $CoCl_2$) en un solvente, tal como etanol o THF. Como alternativa, VII (X_5 = nitro) se puede reducir en el producto de la fórmula IX por hidrogenación en la presencia de un catalizador adecuado, tal como un catalizador de paladio o platino o níquel Raney. Como alternativa, los compuestos VII, donde X_5 = halógeno, se pueden hacer reaccionar con amoníaco (R = H) o una amina que lleva un grupo protector adecuado (R = bencilo sustituido, tal como 4-metoxibencilo o 2,4 dimetoxibencilo o R = alilo). Los productos resultantes VIII se pueden tratar con un reactivo de utilidad para la eliminación del grupo protector R (catalizador de rodio tal como $Rh(Ph_3P)_3Cl$ para R = alilo, tratamiento con un ácido tal como TFA o HCl para R = 4-metoxibencilo o 2,4-dimetoxibencilo, hidrogenólisis con un catalizador de Pd para R = bencilo sustituido) para dar el producto IX. La fórmula IX se puede hacer reaccionar con una prolina ácida adecuadamente protegida (se indica Boc, aunque puede sustituirse por Cbz, Troc o Fmoc) en la presencia de un reactivo de acoplamiento peptídico, tal como EDAC/HOBT, PyBOP, HATU o DEBPT, en un solvente tal como THF, DMF, diclorometano o DMSO, con o sin la adición de una base de amina, tal como la base de Hunig, piridina, 2,6-lutidina o trietilamina, para dar la fórmula X como una mezcla de los productos de amida. La conversión en el compuesto benzimidazol XI se puede efectuar por calentamiento de X en ácido acético (50-100 °C). Como alternativa, XI se puede preparar por reacción de IX con un aldehído, seguido por tratamiento con un oxidante, tal como $Cu(OAc)_2$ o MnO_2 (véase Penning, et al., *Bioorg. Med. Chem.* 16: 6965-6975 (2008). Después de la eliminación de los grupos protectores Boc de XI (efectuado por tratamiento con un ácido, tal como TFA, HCl o ácido fórmico), los compuestos de la presente invención se pueden preparar por acoplamiento de la diamina XII resultante con un ácido de elección usando los reactivos y las condiciones de acoplamiento de péptidos estándar que se describieron previamente para el esquema II.  en cada Fórmula

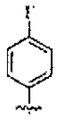
dentro del Esquema IV se puede reeemplazar con  , donde D se definió anteriormente, y tales compuestos se pueden preparar de acuerdo con el proceso descripto en el Esquema IV.

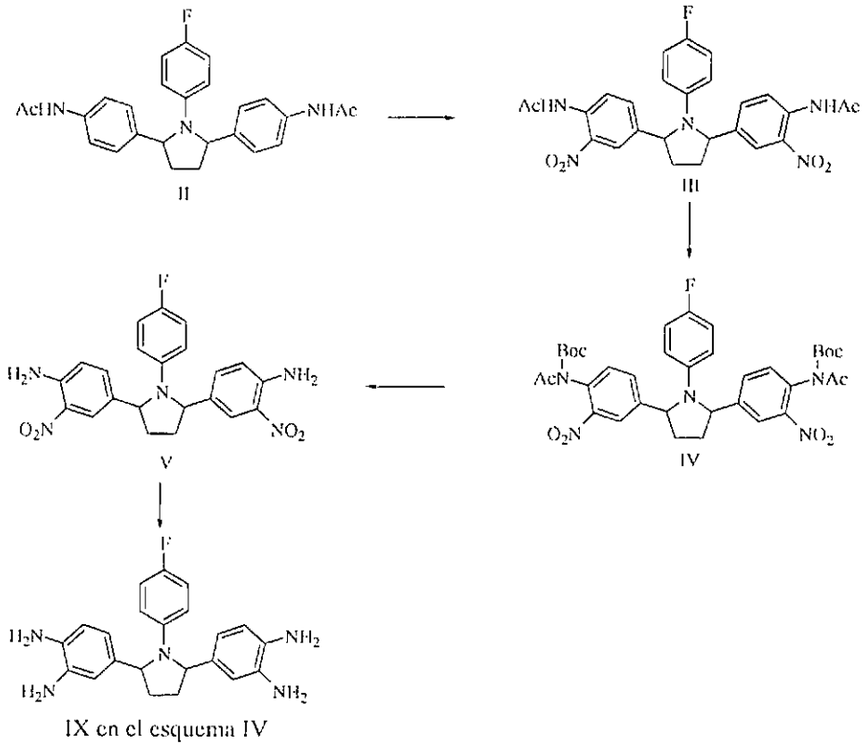


Esquema IV

Como alternativa IX, en el esquema IV, se puede preparar a partir de un compuesto de la

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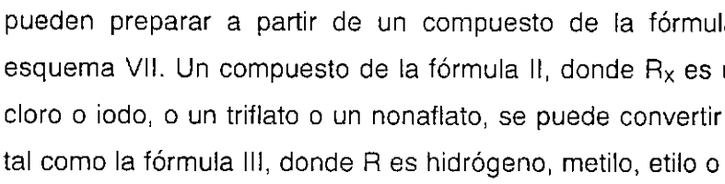
fórmula II como se muestra en el esquema V. El compuesto VIII del esquema II se puede tratar con un agente acilante, tal como cloruro de acetilo o anhídrido acético, para dar el compuesto II (Esquema V). La nitración del compuesto II para proveer III se puede conducir usando métodos conocidos, tal como el tratamiento con ácido nítrico o nitrato de potasio en la presencia de un ácido tal como ácido sulfúrico o tratamiento con NO_2BF_4. La eliminación del grupo protector de acetamida se puede efectuar por tratamiento con anhídrido de Boc en la presencia de DMAP para dar IV, seguido por tratamiento sucesivo de IV con hidróxido (tal como NaOH, KOH o LiOH) para remover el grupo acetilo y un ácido fuerte, tal como TFA o HCl, para remover el grupo protector Boc. Los grupos nitro en V se pueden reducir en grupos amino usando los métodos que se describieron previamente para el esquema IV.  en cada Fórmula dentro del Esquema V se puede reemplazar con  , donde D se definió anteriormente, y tales compuestos se pueden preparar de acuerdo con el proceso descripto en el Esquema V.



Esquema V

Como aún otro ejemplo no limitativo adicional, los compuestos de la presente invención se

pueden preparar comenzando a partir de los compuestos de la fórmula II como se muestra en el esquema VI, donde A, B, D, Y y Z son como se describieron previamente. Se puede hacer reaccionar un compuesto 1,4-dicetona de la fórmula II (preparada como se describió en el esquema III) con una amina incluyendo, pero en un sentido no taxativo, anilina, 3,5-difluoroanilina, 3,4-difluoroanilina, 4-fluoroanilina, 3-fluoroanilina, 4-trifluorometilanilina, 4-cloroanilina, heteroarilaminas, alquilaminas cicloalquilaminas, bencilaminas sustituidas o alilamina, bajo condiciones catalizadas con ácido, tal como ácido acético, TFA, ácido fórmico o HCl, para dar los compuestos de la invención.



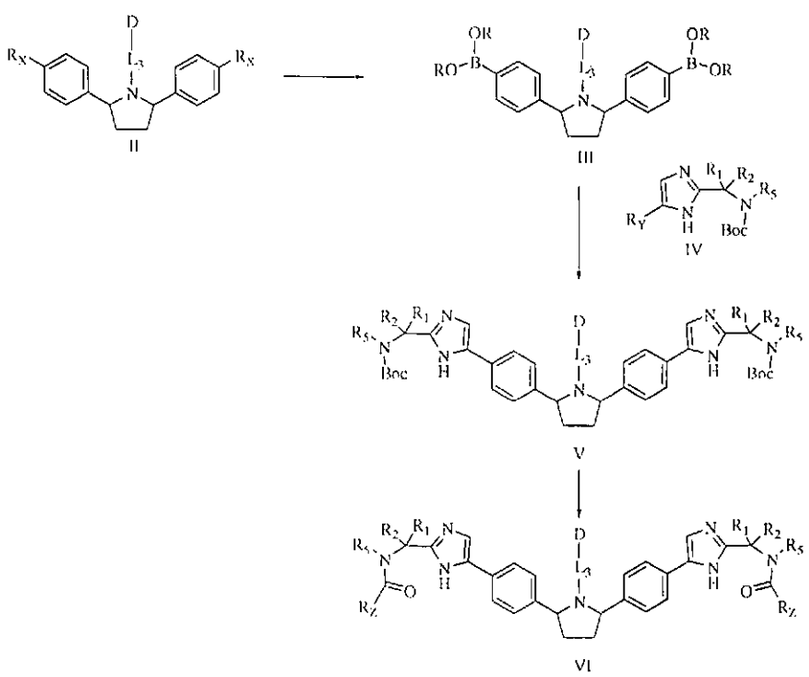
Esquema VI

A modo de ejemplo no limitativo adicional, los compuestos de la presente invención se pueden preparar a partir de un compuesto de la fórmula II como se muestra en el esquema VII. Un compuesto de la fórmula II, donde R_X es un halógeno, tal como bromo, cloro o iodo, o un triflato o un nonaflato, se puede convertir en un ácido o éster borónico, tal como la fórmula III, donde R es hidrógeno, metilo, etilo o un éster de pinacolato cíclico. Por ejemplo, un compuesto de la fórmula II se puede transformar en un compuesto de III mediante tratamiento con pinacol-borano en la presencia de un catalizador tal como, por ejemplo, tris(dibencilidinacetona)paladio (0), y un ligando tal como, por ejemplo, tri-t-butilfosfina, en solventes tales como, por ejemplo, tetrahidrofurano, dioxano o tolueno a temperaturas que varían en un rango entre ambiente y 130°C aproximadamente. Como alternativa, el compuesto II se puede hacer reaccionar con bis(pinacolato)diboro en presencia de un catalizador tal como, por ejemplo, Combiphos-Pd6 (CombiPhos Catalysts, Inc. (NJ, EE.UU.), aducto de diclorometano y dicloro[1,1'-bis(difenilfosfino)ferroceno]paladio (II) o acetato de paladio en presencia de un ligando tal como, por ejemplo, 2-diciclohexilfosfino-2',4',6'-triisopropilbifenilo (XPhos) y una base tal como, por ejemplo, acetato de potasio en solventes tales como, por ejemplo, tolueno, dioxano, tetrahidrofurano, dimetilformamida o dimetilsulfóxido a temperaturas entre aproximadamente 60 y aproximadamente 130 °C para obtener el compuesto III. Como alternativa, se puede hacer reaccionar un compuesto de la fórmula II con un reactivo de organolitio, tal como n-BuLi, sec-BuLi o t-BuLi, seguido por reacción con borato de trimetilo o borato de trietilo, para dar un compuesto de la fórmula III.

Un compuesto de la fórmula III en el esquema VII se puede acoplar a un compuesto de la fórmula IV, donde R_Y es un halógeno, tal como bromo, cloro o iodo, bajo condiciones de reacción de Suzuki para proveer un compuesto de la fórmula V. Dichas condiciones

incluyen, por ejemplo, el uso de un catalizador de paladio tal como, por ejemplo, tris(dibencilidinacetona)paladio (0), acetato de paladio, cloruro de bis(trifenilfosfina)paladio (II), tetrakis(trifenilfosfina)paladio o aducto de diclorometano y dicloro[1,1'-bis(difenilfosfino)ferroceno] paladio (II); una base tal como, por ejemplo, carbonato de potasio, fosfato de potasio, t-butóxido de potasio, carbonato de sodio, carbonato de cesio o fluoruro de cesio; y un solvente tal como, por ejemplo, tolueno, etanol, agua o tetrahidrofurano, o mezclas de los mismos, calentados en un rango de temperaturas entre aproximadamente 40 y aproximadamente 130 °C.

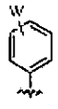
La eliminación de los grupos protectores Boc de V se puede efectuar por tratamiento con un ácido, tal como TFA, HCl o ácido fórmico. Los compuestos de la presente invención, tal como VI, se pueden preparar por acoplamiento de los compuestos de amino resultantes con un ácido de elección usando los reactivos de acoplamiento de péptidos estándar, tal como EDAC/HOBT, PyBOP, HATU o DEBPT, en un solvente tal como THF, DMF, diclorometano o DMSO, con o sin la adición de una base de amina tal como una base de Hunig, piridina, 2,6-lutidina o trietilamina. Cada R_Z es, de manera independiente, $-L_Y'-M'-R_D$ (por ejemplo, $-L_Y-N(R_B'')C(O)-L_S-R_E$), y D, L_3, R_1, R_2, R_5, L_Y, R_B'', L_S, R_E, L_Y', M' y R_D son como se definieron previamente.



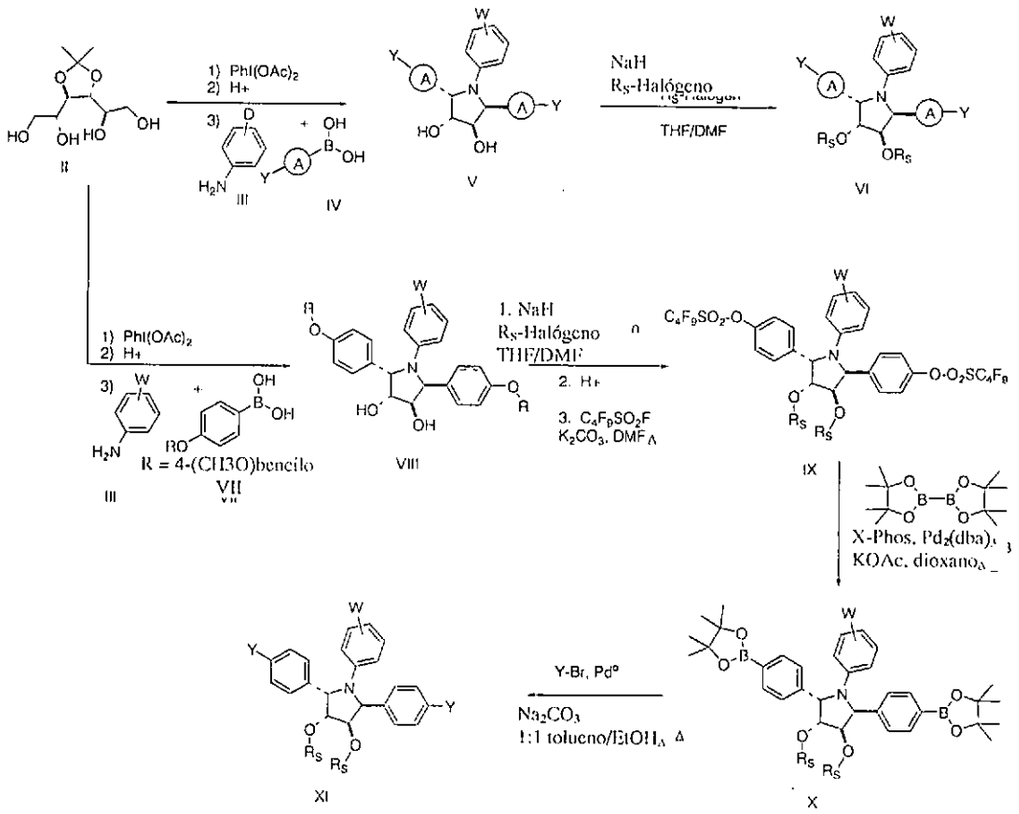
Esquema VII

A modo de otro ejemplo no limitativo, los compuestos de la presente invención se pueden preparar de acuerdo con el esquema VIII comenzando a partir del compuesto de la fórmula II, clivando inicialmente el diol a modo oxidativo seguido por una subsiguiente

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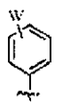
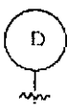
hidrólisis ácida de la acetonida. Este intermediario dialdehído es tratado luego con un boronato de arilo o ácido arilborónico (compuesto IV, donde A e Y son como se describieron previamente, o el compuesto VII) y anilina III (donde W es R_M o J, y R_M y J son como se definieron previamente) dando como resultado la formación de la fórmula V o de la fórmula VIII, respectivamente. La fórmula V se puede derivatizar por desprotonación de los grupos hidroxilo con una base fuerte, tal como hidruro de sodio, butillitio o hidruro de potasio, seguido por alquilación con R_S-halógeno. Como alternativa, la fórmula VIII se puede desprotonar con una base fuerte (por ejemplo, hidruro de sodio) y alquilar con R_S-halógeno, seguido por hidrólisis ácida de los grupos protectores de fenol. La sulfonilación de los fenoles con fluoruro de nonafluorobutilsulfonilo en la presencia de un agente neutralizante, tal como carbonato de potasio, en un solvente aprótico polar, tal como DMF, seguido por calentamiento, provee un compuesto de la fórmula IX. El boronato de la fórmula X es producido por calentamiento de la fórmula IX con bis(pinacolato)diboro en la presencia de X-phos y un catalizador de paladio, tal como Pd2(dba)3, y una base tal como acetato de potasio en un solvente orgánico, tal como dioxano. La fórmula X se derivativa además en un producto final por calentamiento de un heteroarilhaluro convenientemente sustituido en la presencia de un catalizador de paladio, tal como PdCl2(dppf), en la presencia de una base, tal como carbonato de sodio en una mezcla de tolueno y etanol. R_S es como se definió previamente.  en cada Fórmula dentro del Esquema VIII se puede reemplazar con  , donde D se definió anteriormente, y tales compuestos se pueden preparar de acuerdo con el proceso descripto en el Esquema VIII.

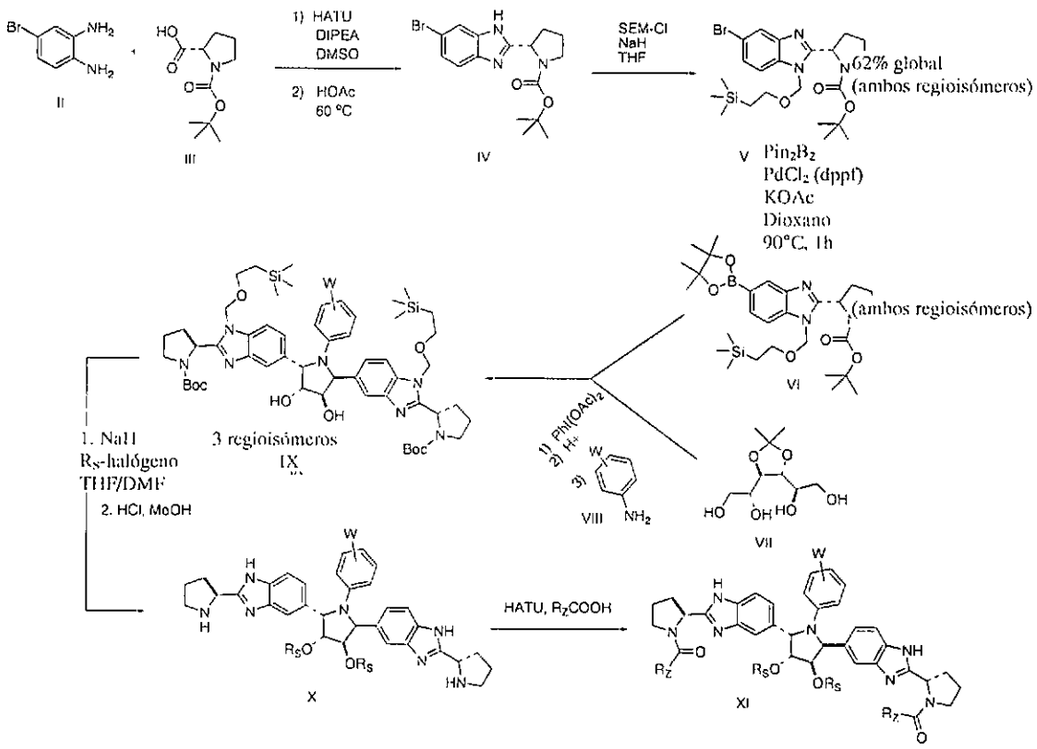
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Esquema VIII

Como aún otro ejemplo no limitativo, los compuestos de la presente invención se pueden preparar de acuerdo con el esquema IX comenzando a partir de los compuestos de la fórmula II y de la fórmula III. El ácido carboxílico de la fórmula III es activado para el acoplamiento usando reactivos tales como isobutilcloroformato, DCC, EDAC o HATU en la presencia de una base orgánica, tal como diisopropiletilamina. Con la activación, se agrega la dianilina de la fórmula II a la reacción, con el aislamiento de un intermediario amida, que se calienta en ácido acético, preferentemente a 60 °C, para dar el compuesto de la fórmula IV. El benzimidazol de la fórmula IV es tratado con SEM-Cl en la presencia de una base en un solvente aprótico, tal como THF, dando como resultado dos regioisómeros de benzimidazol protegidos V. Los ésteres boronato VI se producen por calentamiento de la fórmula V con bis(pinacolato)diboro en la presencia de un catalizador de paladio, tal como PdCl2(dppf), X-Phos, y una base tal como acetato de potasio en un solvente orgánico, tal como dioxano. El calentamiento permite obtener ambos regioisómeros del benzimidazol VI. El diol VII es clivado de manera oxidativa seguido por una subsiguiente hidrólisis ácida de la acetonida. Este intermediario de dialdehído es tratado luego con un boronato de arilo VI y la anilina VIII (donde W es R_M o J, y R_M y J son como se definieron previamente) dando como resultado la formación de los regioisómeros

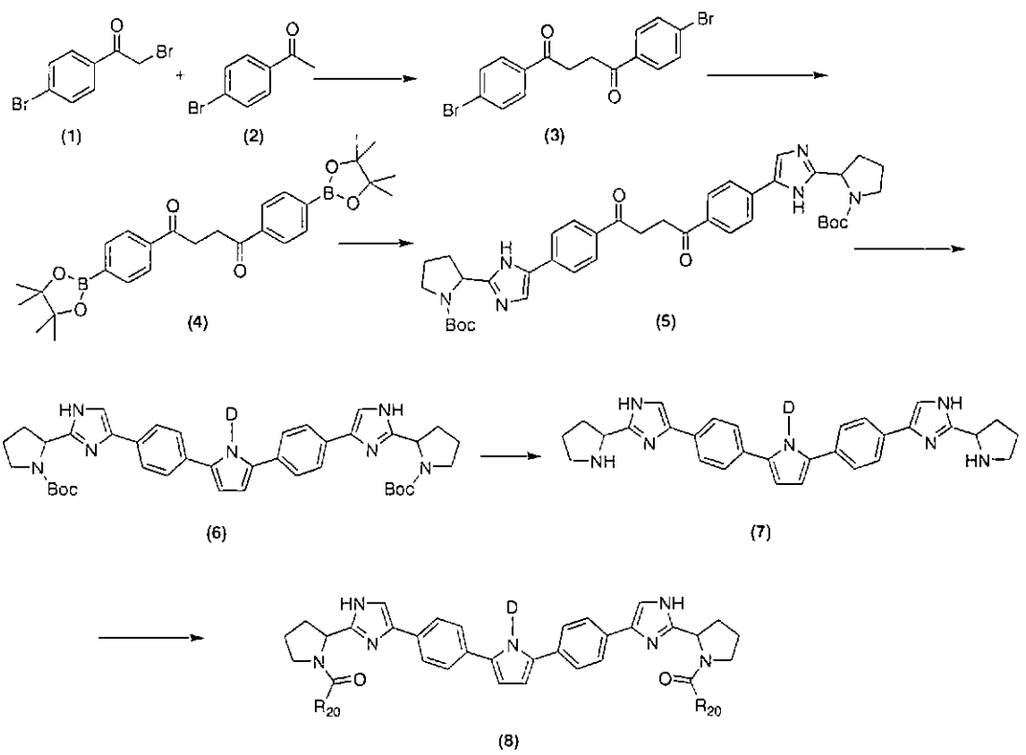
3-benzimidazol de la fórmula IX. La fórmula X se produce por desprotonación de los grupos hidroxilo con una base fuerte, tal como hidruro de sodio, butillitio o hidruro de potasio, seguido por alquilación con R_S-halógeno, seguido por hidrólisis ácida de la pirrolidina y grupos protectores de benzimidazol, preferentemente mediante tratamiento con un ácido mineral, tal como ácido clorhídrico en un solvente de alcohol, tal como metanol. El ácido carboxílico R_Z-COOH es activado para el acoplamiento usando reactivos tales como isobutilcloroformiato, DCC, EDAC o HATU en la presencia de una base orgánica, tal como diisopropiletilamina. Con la activación, se agrega la fórmula X a la reacción, con el aislamiento de la fórmula XI.  en cada Fórmula dentro del Esquema IX se puede reemplazar por  , donde D se definió anteriormente, y tales compuestos se pueden preparar de acuerdo con el proceso descripto en el Esquema IX.



Esquema IX

Los compuestos de la invención de la fórmula general (8), donde R_{20} es $-L_S'-M'-L_S''-R_D$ y D es como se describió previamente, se pueden preparar de acuerdo con los métodos del esquema X. La bromoalquilcetona (1) se puede hacer reaccionar con una arilalquilcetona (2) usando las condiciones mediadas por un ácido de Lewis, descritas previamente en el

esquema II, para dar la diarildicetona (3). La dicetona (3) se puede convertir en el bisboronato (4) por reacción con bis(pinacolato)diborano en la presencia de una base, tal como acetato de potasio, un catalizador, tal como $PdCl_2(dppf)$-CH_2Cl_2, en un solvente, tal como DMSO, dimetoxietano o dioxanos, con calentamiento a una temperatura de 60-100 °C. El bisboronato (4) se puede convertir en el intermediario (5) por reacción de Suzuki usando, de manera análoga, las condiciones de Suzuki que se describieron en el esquema VII. El intermediario (5) se puede convertir en (6) por reacción con una amina D–NH_2 bajo condiciones análogas a las descritas en el esquema VI. Por ejemplo, la reacción de (5) con D–NH_2 en la presencia de un ácido tal como, pero en un sentido no taxativo, TFA, en un solvente tal como, pero en un sentido no taxativo, tolueno y con calentamiento hasta 110 °C puede proporcionar los intermediarios de la estructura general (6). Los compuestos (6) se pueden convertir en los compuestos de las fórmulas generales (7) y luego (8) usando, de manera análoga, los métodos que se describen en el esquema VII.

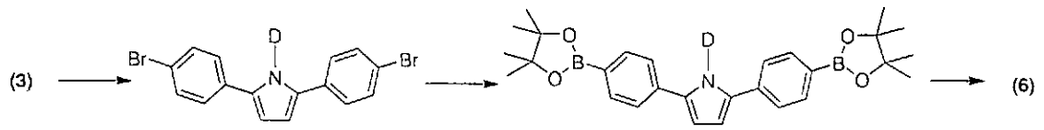


Esquema X

Los intermediarios (6) también se pueden preparar usando la ruta representada en el esquema XI. El intermediario (3) se puede hacer reaccionar con una amina D–NH_2 usando, de manera análoga, las condiciones que se describen en los esquemas VI y X para proveer los intermediarios (9), que se pueden convertir en (10) usando, de manera

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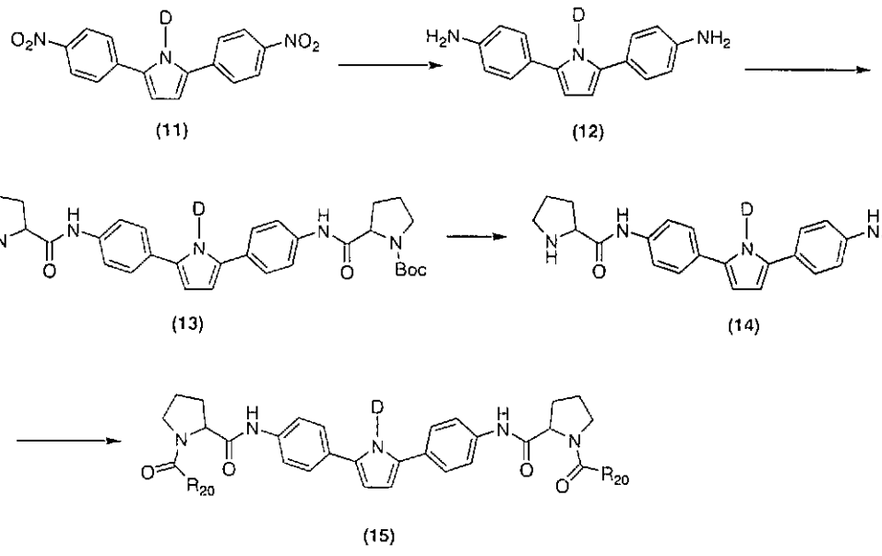
análoga, las condiciones que se describieron previamente en el esquema X; y, a su vez, (10) se puede convertir en los compuestos (6) usando las condiciones de la reacción de Suzuki que se describen en el esquema VII.



(9) (10)

Esquema XI

Los compuestos de la invención de la fórmula general (15), donde R_{20} es $-L_S'-M'-L_S''-R_D$ y D es como se describió previamente, se pueden preparar de acuerdo con los métodos del esquema XII. Los compuestos (11) se pueden preparar de acuerdo con los procedimientos para convertir (3) en (9), usando las condiciones generales que se describen en el esquema VI, tal como por reacción de una nitrofenildicetona apropiada con una amina $D-NH_2$ con calentamiento en ácido acético a una temperatura de aproximadamente 70 °C. Los compuestos (11) se pueden convertir en (12) usando las condiciones de reducción que se describen en el esquema II. Los compuestos (12) se pueden convertir sucesivamente en los compuestos de las fórmulas generales (13), (14) y (15) usando, de manera análoga, los métodos que se describen en el esquema II.

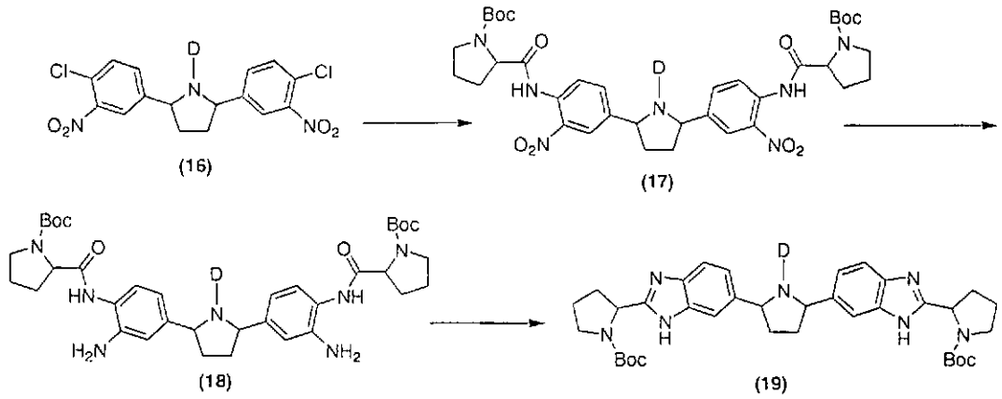


(11) (12) (13) (14) (15)

Esquema XII

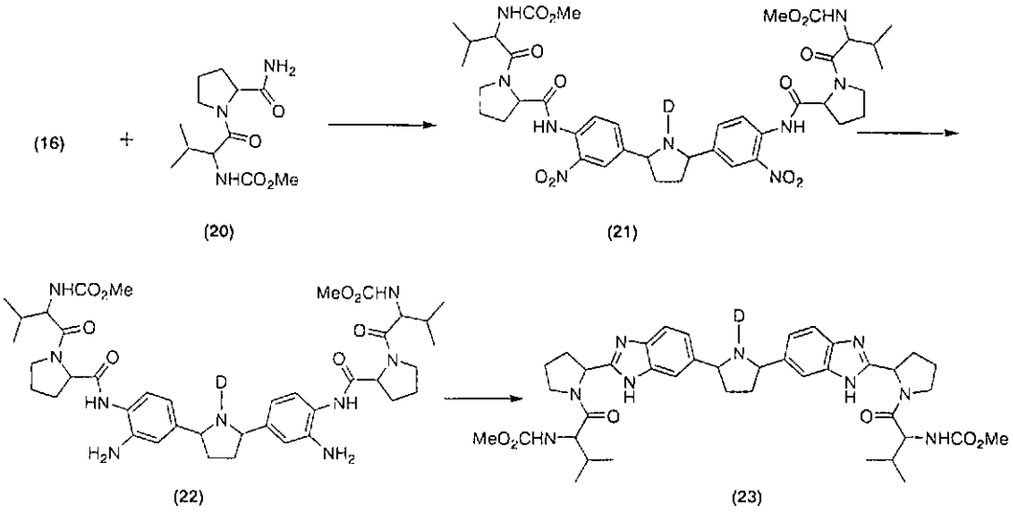
Los compuestos de la fórmula general (19), donde D es como se describió previamente, se pueden preparar de acuerdo con los métodos del esquema XIII. Los compuestos de la fórmula general (16) se pueden convertir en los compuestos de la fórmula general (17) usando una reacción de Buchwald con 2-carbamoilpirrolidina-1-carboxilato de ter-butilo.

Esta reacción de Buchwald se puede conducir en la presencia de una base (por ejemplo, carbonato de cesio), un catalizador de paladio (por ejemplo, tris(dibencilidenacetona)dipaladio(0)), un ligando de fosfina (por ejemplo, 4,5-bis(difenilfosfino)-9,9-dimetilxanteno) en un solvente tal como dioxano con calentamiento hasta 80-120 °C aproximadamente. El intermediario (17) se puede reducir en (18) y ciclar en (19) usando, de manera análoga, las condiciones que se describe en general en el esquema IV. Los compuestos (19) se pueden hacer reaccionar además como se ilustra en el esquema IV para proveer los compuestos de la invención.



Esquema XIII

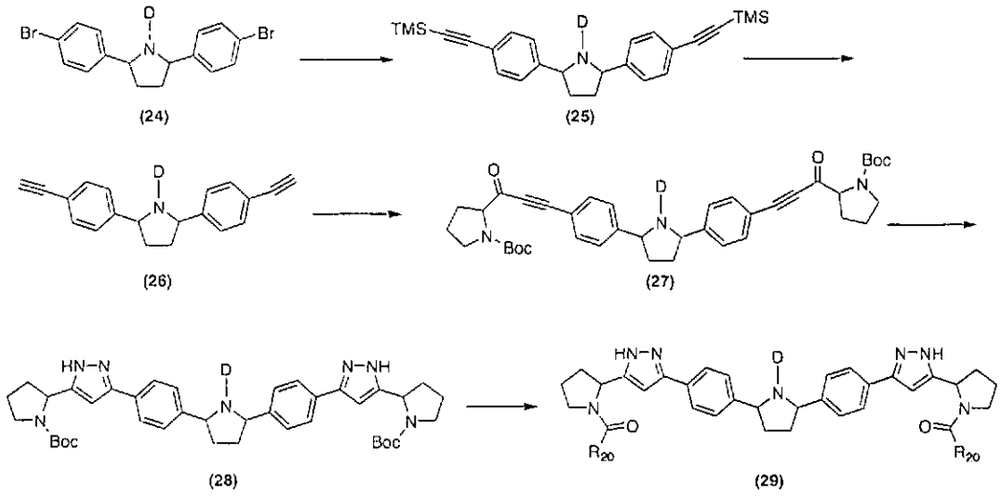
Los compuestos de la invención de la fórmula general (23), donde D es como se describió previamente, se pueden preparar de acuerdo con los métodos del esquema XIV. Los compuestos (16) se pueden hacer reaccionar con los compuesto (20) usando una reacción de Buchwald como se describe en general en el esquema XIII para proveer los compuestos (21). Los compuestos (21) se pueden reducir en los compuestos (22) y ciclar en (23) usando, de manera análoga, las condiciones que se describen en general en los esquemas precedentes.



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Esquema XIV

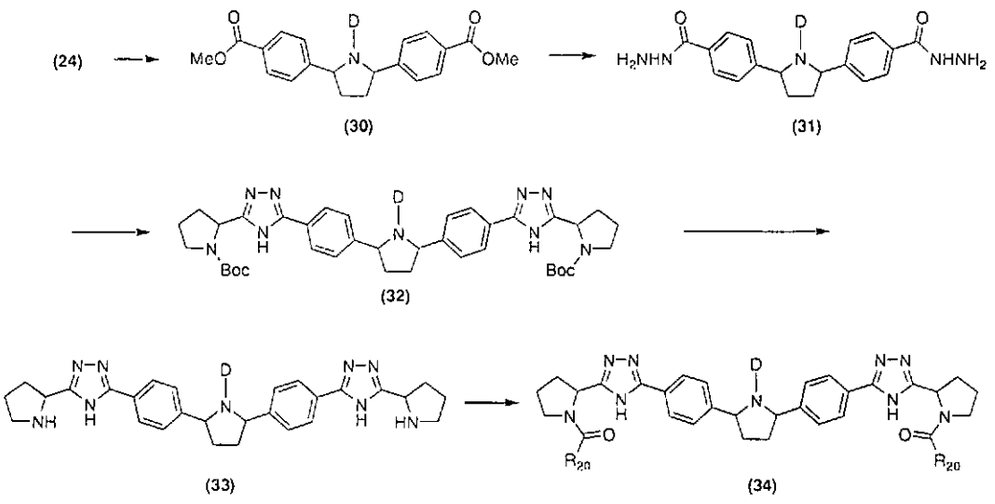
Los compuestos de la invención de la fórmula general (29), donde R_{20} es $-L_S'-M'-L_S''-R_D$ y D es como se describió previamente, se pueden preparar de acuerdo con los métodos del esquema XV. Los compuestos de la fórmula (24) se pueden convertir en los compuestos de la fórmula (25) (reacción de Sonogashira) por reacción con trimetilsililacetileno, un catalizador de paladio (por ejemplo, cloruro de bis(trifenilfosfina)paladio(II)), un catalizador de cobre (por ejemplo, ioduro de cobre(I)) y una base (por ejemplo, trietilamina), en donde también se puede usar una base de amina como solvente. Los compuestos (25) se pueden desililar en los compuestos (26) por reacción con una fuente de fluoruro (por ejemplo, fluoruro de tetrabutilamonio) en un solvente tal como THF. Los compuestos (26) se pueden convertir en los compuestos (27) por formación del dianión de (26) con n-butillitio y subsiguiente reacción con una amida de Weinreb (por ejemplo, N-(ter-butoxicarbonil)-L-prolin-N'-metoxi-N'-metilamida). Esta reacción se puede conducir en un solvente apropiado tal como THF o dimetoxietano. Los compuestos (27) se pueden convertir en los compuestos (28) por reacción con hidrazina en un solvente tal como etanol. Los compuestos (28) se pueden convertir en los compuestos (29) usando los métodos que se describieron en general en los esquemas precedentes.



Esquema XV

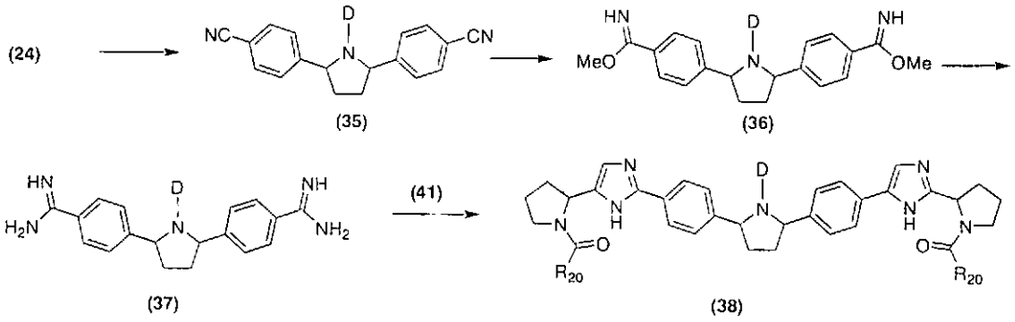
Los compuestos de la invención de la fórmula general (34), donde R_{20} es $-L_S'-M'-L_S''-R_D$ y D es como se describió previamente, se pueden preparar de acuerdo con los métodos del esquema XVI. Los compuestos (24) se pueden convertir en los compuestos (30) por reacción de (24) con CO(g) bajo presión (60 psi aproximadamente) en la presencia de un catalizador de paladio (por ejemplo, $PdCl_2(dppf)$) en metanol como solvente y con calentamiento hasta alrededor de 100 °C. Los compuestos (30) se pueden convertir en los

compuestos (31) por reacción con hidrazina en un solvente, tal como metanol, con calentamiento hasta aproximadamente 60-80 °C. Los compuestos (31) se pueden convertir en los compuestos (32) por reacción con N-Boc-2-ciano-pirrolidina en la presencia de una base (por ejemplo, carbonato de potasio) en un solvente, tal como butanol, y con calentamiento hasta alrededor de 150 °C con irradiación en un reactor de microondas. Los compuestos (32) se pueden desproteger en los compuestos (33) y acilar en (34) usando, de manera análoga, las condiciones que se describen en general en los esquemas precedentes.



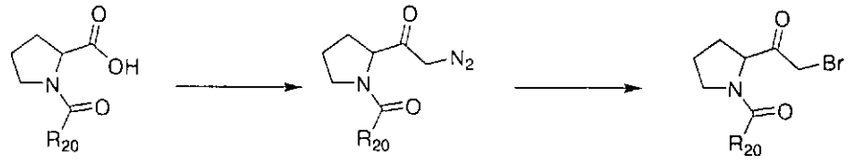
Esquema XVI

Los compuestos de la invención de la fórmula general (38), donde R_{20} es $-L_S'-M'-L_S''-R_D$ y D es como se describió previamente, se pueden preparar de acuerdo con los métodos del esquema XVII. Los compuestos de la fórmula (24) se pueden convertir en los compuestos (35) por reacción con CuCN en un solvente, tal como DMF, y con calentamiento hasta aproximadamente 160 °C con irradiación de microondas. Los compuestos (35) se pueden convertir en los compuestos (36) por reacción con HCl(g) en metanol anhidro a 0 °C con calentamiento hasta temperatura ambiente. Los compuestos (36) se pueden convertir en los compuestos (37) por reacción con NH_3(g) en metanol anhidro a 0 °C con calentamiento hasta temperatura ambiente. Los compuestos (37) se pueden convertir en los compuestos (38) por reacción con (41) en THF en la presencia de una base (por ejemplo, carbonato de potasio).



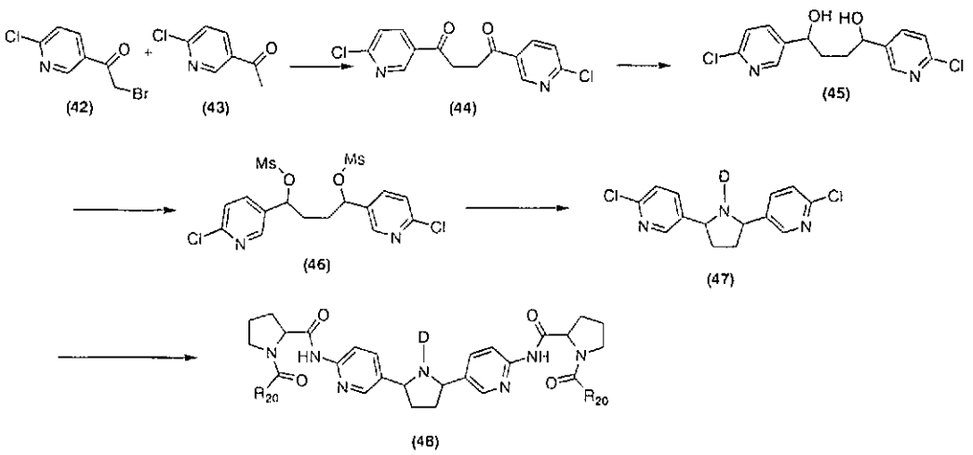
Esquema XVII

Los compuestos de la fórmula (41), donde R_{20} es $-L_S'-M'-L_S''-R_D$, se pueden preparar usando los métodos del esquema XVIII. Los compuestos (39) se pueden convertir en los compuestos (40) por reacción sucesiva de (39) con isobutilcloroformiato en THF a 0 °C seguido por diazometano. Los compuestos (40) se pueden convertir en los compuestos (41) por reacción con HBr en ácido acético.



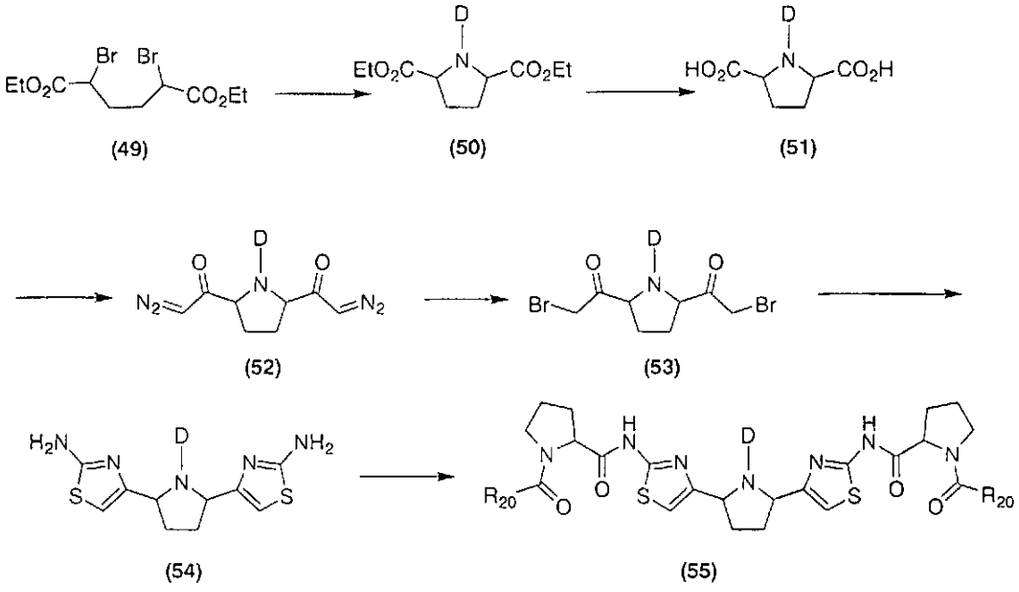
Esquema XVIII

Los compuestos de la invención de la fórmula general (48), donde R_{20} es $-L_S'-M'-L_S''-R_D$ y D es como se describió previamente, se pueden preparar de acuerdo con los métodos del esquema XIX. El compuesto (42) se puede hacer reaccionar con el compuesto (43) usando, de manera análoga, las condiciones mediadas por ácido de Lewis que se describieron previamente en el esquema II para proveer el compuesto (44). El compuesto (44) se puede convertir sucesivamente en el diol (45), el mesilato (46) y el intermediario cíclico (47) usando, de manera análoga, las condiciones del esquema II. Los compuestos (47) se pueden convertir en los compuestos (48) por reacción con (20) bajo condiciones de Buchwald, tales como las indicadas en el esquema XIV y que se describen en el esquema XIII.



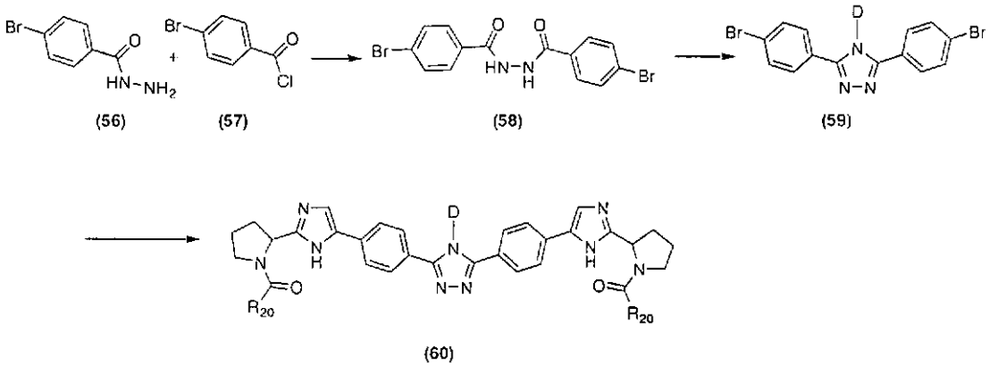
Esquema XIX

Los compuestos de la invención de la fórmula general (55), donde R_{20} es $-L_S'-M'-L_S''-R_D$ y D es como se describió previamente, se pueden preparar de acuerdo con los métodos del esquema XX. Se puede hacer reaccionar meso-2,5-dibromoadipato de dietilo (49) con una amina $D-NH_2$ en un solvente, tal como THF, dioxano o dimetoxietano, con calentamiento a una temperatura de 50-100 °C para dar los compuestos (50). Los compuestos (50) se pueden convertir en (51) por hidrólisis alcalina con una base (por ejemplo, NaOH, KOH) en un alcohol (por ejemplo, metanol, etanol) y una mezcla agua como solvente. Los compuestos (51) se pueden convertir en (52) por reacción primero con cloruro de oxalilo y tratamiento del intermediario de cloruro ácido con diazometano a 0 °C. Los compuestos (52) se pueden convertir en (53) por reacción con HBr acuoso. Los compuestos (53) se pueden convertir en los compuestos (54) por reacción con tiourea en etanol o un solvente similar. Los compuestos (54) se pueden convertir en los compuestos (55) usando, de manera análoga, las condiciones que se describieron previamente en el esquema II.



Esquema XX

Los compuestos de la invención de la fórmula general (60), donde R_{20} es $-L_S'-M'-L_S''-R_D$ y D es como se describió previamente, se pueden preparar de acuerdo con los métodos del esquema XXI. El compuesto (56) se puede hacer reaccionar con el compuesto (57) en piridina con calentamiento hasta aproximadamente 135 °C para formar el compuesto (58). El compuesto (58) se pueden convertir en los compuestos (59) por reacción de una amina $D\text{-}NH_2$ con $POCl_3$ seguido por adición de (58) y calentamiento a aproximadamente 200 °C en 1,2-diclorobenceno. Los compuestos (59) se pueden convertir en los compuestos (60) usando, de manera análoga, las condiciones que se describieron previamente en el esquema VII.

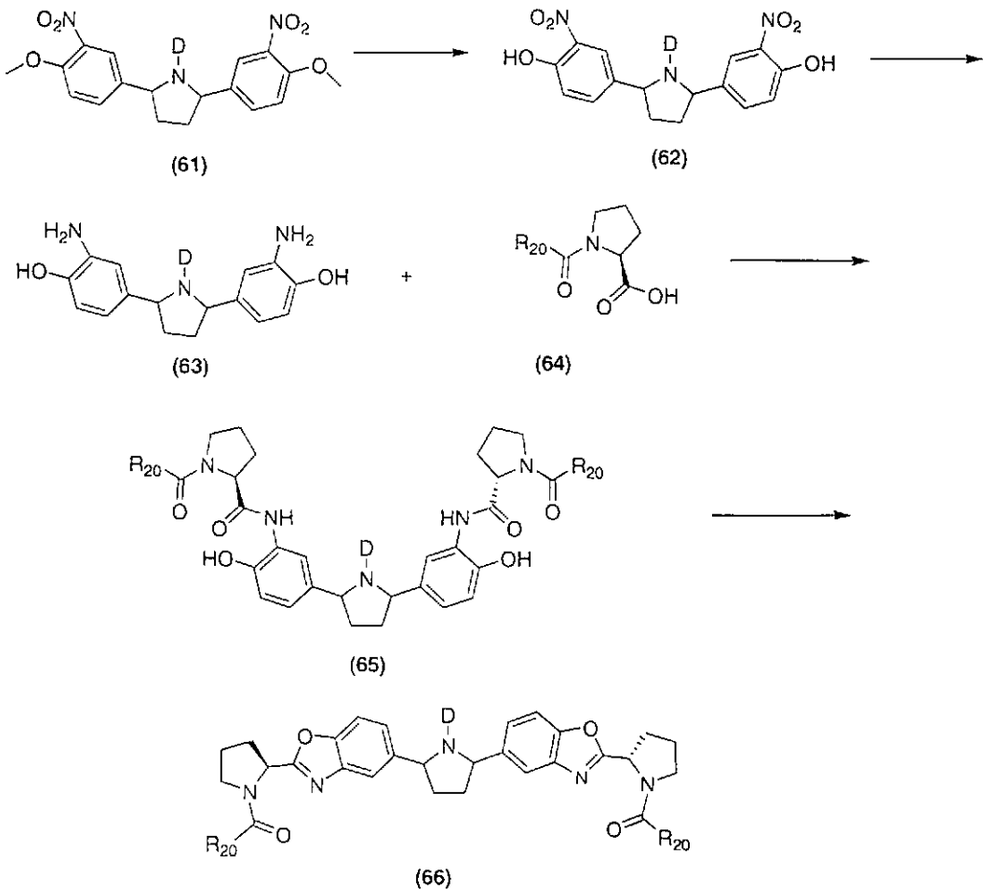


Esquema XXI

Los compuestos de la invención de la fórmula general (66), donde R_{20} es $-L_S'-M'-L_S''-R_D$ y D son como se describieron previamente, se pueden preparar de acuerdo con los métodos del esquema XXII. Los compuestos de la fórmula general (61) se pueden hacer reaccionar con tribromuro de boro en diclorometano a 0 °C para dar los compuestos (62),

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que pueden someterse luego a condiciones de hidrogenólisis usando óxido de platino(II) para dar los compuestos (63). El acoplamiento entre los compuestos (63) y los derivados prolina (64) se puede llevar a cabo usando las condiciones de acoplamiento estándar que se describieron previamente para dar los compuestos (65), que se pueden convertir en (66) por la acción de dietilazodicarboxilato y trifenilfosfina en THF.

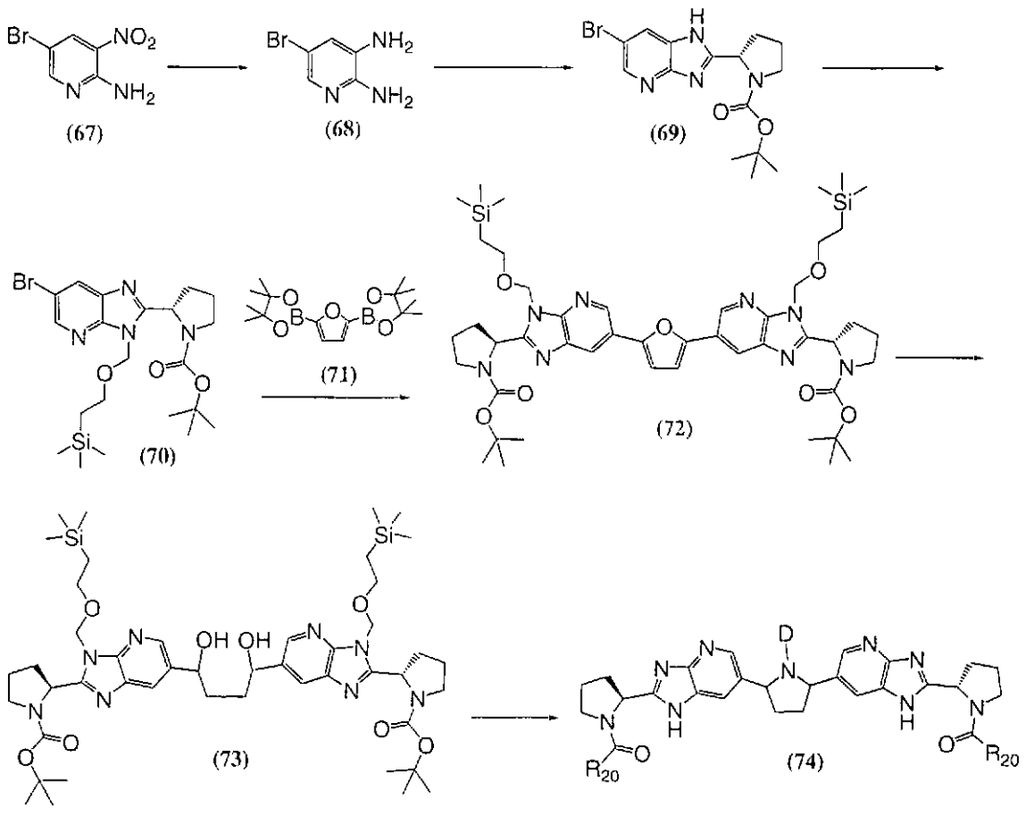


Esquema XXII

Los compuestos de la invención de la fórmula general (74), donde R_{20} es $-L_S'-M'-L_S''-R_D$ y D es como se describió previamente, se pueden preparar de acuerdo con los métodos del esquema XXIII. El compuesto (67) se puede convertir en (68) por reducción del grupo nitro usando cloruro de estaño(II) en etanol. El compuesto (69) se puede obtener a partir de (68) por acoplamiento de péptidos con Boc-prolina, seguido por calentamiento de la amida resultante en ácido acético a 80 °C. El compuesto (69) se puede hacer reaccionar con SEM-Cl y diisopropiletilamina en diclorometano para dar (70), que se puede acoplar con (71) usando un catalizador de paladio, tal como PXPd, usando una base, tal como fluoruro de cesio, en un solvente, tal como N,N-dimetilformamida, a 100 °C para dar (72). El compuesto (72) se puede convertir en (73) por reacción con Selectfluor® en una mezcla de THF y agua, seguido por hidrogenación usando Pt sobre carbón 3% en acetato

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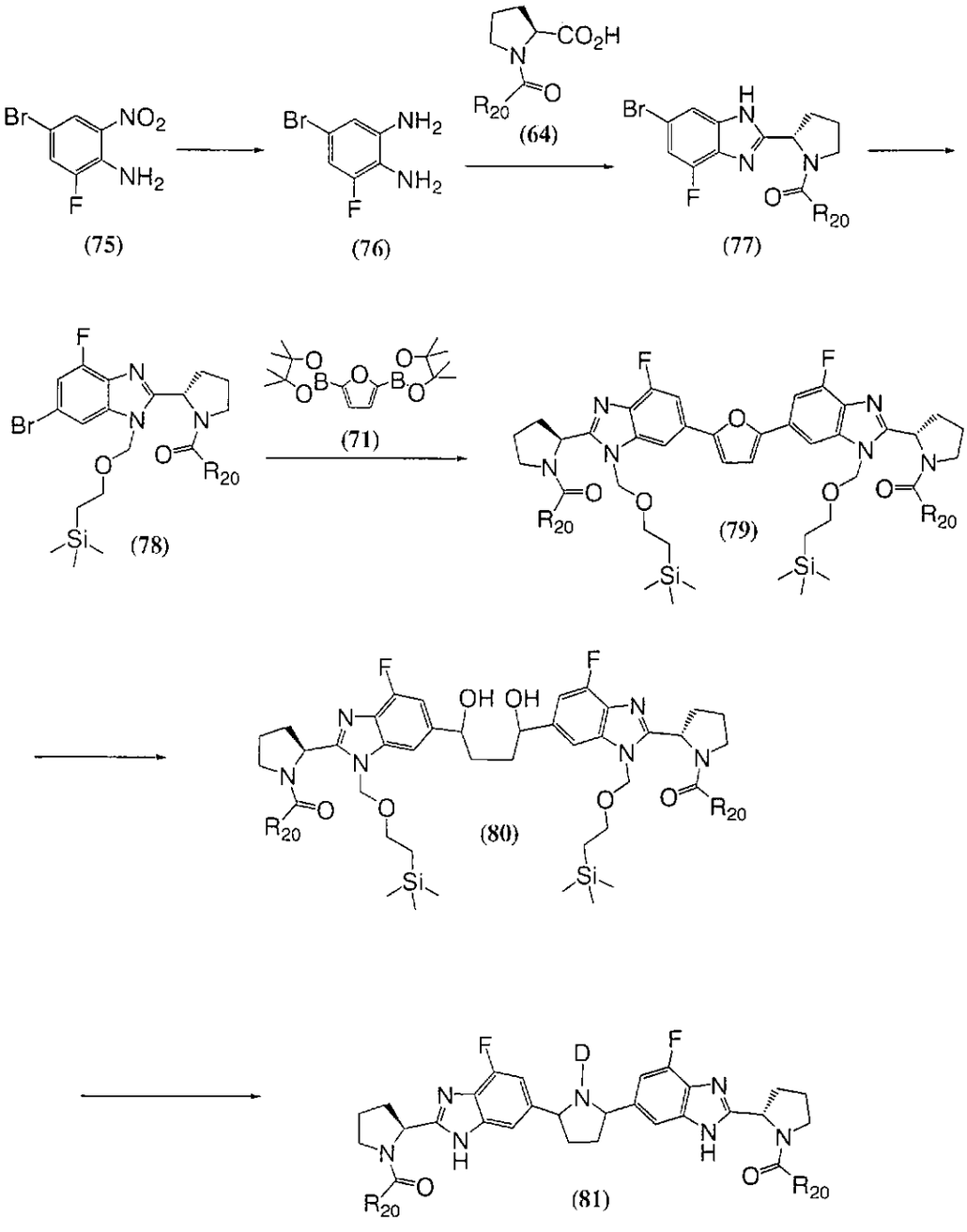
de etilo y luego reducción usando borohidruro de sodio en metanol. El compuesto (73) se puede hacer reaccionar con cloruro de metansulfonilo y trietilamina en diclorometano a -10 °C, seguido por adición de una amina (H_2N-D) para dar un intermediario que se puede convertir en (74) por desprotección usando HCl 4 N en 1,4-dioxano y luego acoplamiento con $R_{20}CO_2H$ usando los procedimientos de acoplamiento de péptidos que se describieron previamente.



Esquema XXIII

Los compuestos de la invención de la fórmula general (81), donde R_{20} es $-L_S'-M'-L_S''-R_D$ y D es como se describió previamente, se pueden preparar de acuerdo con los métodos del esquema XXIV. El compuesto (75) se puede convertir en (76) usando $SnCl_2$ en etanol. El acoplamiento de (76) con (64) usando los procedimientos de acoplamiento de péptidos que se describieron previamente para dar una amida que se puede calentar en ácido acético a 100 °C para dar (77). El compuesto (77) se puede hacer reaccionar con SEM-Cl y diisopropiletilamina en diclorometano para dar (78), que se puede hacer reaccionar con (71) como se describió previamente para dar (79). El compuesto (79) se puede convertir en (80) usando Selectfluor® en una mezcla de THF y agua, seguido por hidrogenación con Pt sobre carbón en acetato de etilo y reducción con borohidruro de sodio en metanol. El compuesto (80) se puede convertir en los compuestos (81) por mesilación con cloruro

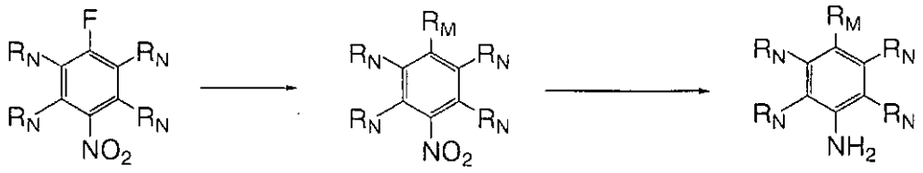
de metansulfonilo y trietilamina a temperaturas menores que 0 °C, seguido por reacción con una amina primaria H_2N-D y desprotección usando HCl 4 N en 1,4-dioxano.



Esquema XXIV

Determinadas aminas, D–NH_2, están representadas en los esquemas precedentes por la fórmula (84), y se pueden preparar de acuerdo con el método general que se muestra en el esquema XXV, en donde R_N es como se definió previamente (por ejemplo, halógeno, alquilo, haloalquilo) y R_M es –N($R_SR_{S'}$) (por ejemplo, –NEt_2), heterociclilo (por ejemplo, pirrolidin-1-ilo, piperidin-1-ilo, etc.) o –OR_S (por ejemplo, –O–t-butilo, –O–isopropilo, etc.).

Los fluoronitrobencenos (82) se pueden hacer reaccionar con una amina apropiada en la presencia de fosfato de potasio dibásico en un solvente, tal como DMSO, opcionalmente con calentamiento para dar los intermediarios (83), en donde R_M es $-N(R_SR_S)$ (por ejemplo, $-NEt_2$) o heterociclilo (por ejemplo, pirrolidin-1-ilo, piperidin-1-ilo, etc.). Los fluoronitrobencenos (82) también se pueden hacer reaccionar con alcóxidos de metales alcalinos (por ejemplo, ter-butóxido de potasio) para dar los intermediarios (83), en donde R_M es $-OR_S$ (por ejemplo, –O–t-butil, –O–isopropilo, etc.). Los intermediarios (83) se pueden convertir en (84) usando condiciones bien conocidas de reducción de grupos nitro. Por ejemplo, (83) se puede convertir en (84) por hidrogenación catalítica usando paladio sobre carbón. Como alternativa, (83) se puede convertir en (84) por reacción con hierro/cloruro de amonio en THF/metanol/agua como solvente. Otras condiciones para conducir la reducción de nitro incluyen las que se describieron en los esquemas precedentes y los que son conocidos en general por el especialista en el arte.



(82) (83) (84)

Esquema XXV

En los esquemas precedentes, se muestran compuestos en donde un anillo aromático (por ejemplo, fenilo) está sustituido con grupos con una regioquímica particular (por ejemplo, para). En los esquemas precedentes, un material de partida o un intermediario con una sustitución en *para* provee un producto final con una sustitución en *para*. El especialista en el arte comprenderá que, en los esquemas precedentes, una substitución de un material de partida o de un intermediario con una regioquímica diferente (por ejemplo, meta) proporcionaría un producto final con una regioquímica diferente. Por ejemplo, el reemplazo de un material de partida o de un intermediario sustituido en *para* en los esquemas precedentes con un material de partida o un intermediario sustituido en *meta* proporcionaría a un producto sustituido en meta.

Si un grupo descrito en la presente (por ejemplo, $-NH_2$ o –OH) no es compatible con los métodos de síntesis, dicho grupo puede ser protegido con un grupo protector adecuado que sea estable para las condiciones de reacción usadas en los métodos. El grupo protector se puede remover en un momento adecuado durante la secuencia de reacción para proveer un compuesto intermediario o blanco deseado. Los grupos protectores y los métodos adecuados para proteger o desproteger grupos son bien conocidos en el arte, y se pueden consultar ejemplos de los mismos en Greene y Wuts, *supra*. Las condiciones

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de reacción y los tiempos de reacción óptimos para cada paso individual pueden variar dependiendo de los reactivos que se empleen en particular y de los sustituyentes presentes en los reactivos que se utilicen. Un especialista en el arte puede seleccionar fácilmente los solventes, las temperaturas y otras condiciones de reacción en base a la presente invención.

Otros compuestos de la invención se pueden preparar de manera similar según los esquemas descritos precedentemente, así como usando los procedimientos que se describirán en los siguientes ejemplos, como podrán apreciar los especialistas en el arte. Se comprenderá que las formas de realización y los esquemas descritos precedentemente y los siguientes ejemplos solamente se ofrecen a efectos ilustrativos, no en un sentido limitativo. Los diversos cambios y modificaciones que se pueden efectuar dentro del alcance de la presente invención resultarán evidentes para los especialistas en la técnica a partir de la presente descripción.

Los compuestos de los siguientes ejemplos se nombraron usando el programa ChemDraw versión 9.0 o bien, el programa ACD versión 12 (ACD v12). Los compuestos finales de los ejemplos 1-50 se nombraron usando ChemDraw a menos que se indique lo contrario, es decir, que se nombraron usando ACD v12. Los compuestos finales después del ejemplo 50 se nombraron usando ACD v12. Los intermediarios se nombraron usando ChemDraw, a menos que se indique de otra manera, es decir, que se nombraron usando ACD v12.

Determinados compuestos en los siguientes ejemplos se purificaron usando HPLC de fase reversa. La purificación se condujo usando una columna de fase reversa C18 o C8. Los compuestos se eluyeron usando un gradiente de 10-100% aproximadamente de acetonitrilo en TFA acuoso 0,1%; aproximadamente 60-100% de metanol en acetato de amonio acuoso 10 mM; o aproximadamente 10-95% de metanol en acetato de amonio acuoso 10 mM. Para las purificaciones realizadas con TFA, el producto así obtenido se puede encontrar en la forma de una sal de TFA. Los compuestos se pueden caracterizar como la sal de TFA o como la base libre después de la neutralización, la extracción y el aislamiento.

Determinados compuestos en los siguientes ejemplos se purificaron usando cromatografía sobre gel de sílice en fase normal incluyendo la tradicional cromatografía flash o un sistema de purificación automático (por ejemplo, Isco Combi-Flash, Analogix Intelliflash) usando columnas de gel de sílice pre-empaquetadas (columnas de gel de sílice de 55 ó 35 µm, Isco gold)

Los solventes típicos para la cromatografía sobre gel de sílice incluyen: acetato de etilo en hexanos, dietiléter en hexanos, THF en hexanos, acetato de etilo en cloruro de metileno,

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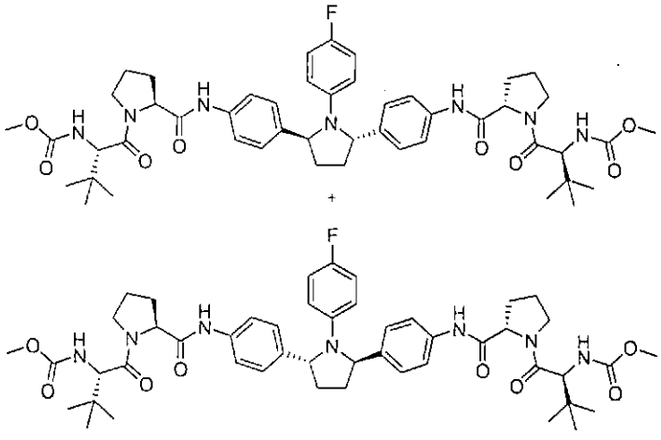
metanol en cloruro de metileno, metanol en cloruro de metileno con NH_4OH, acetona en hexanos y cloruro de metileno en hexanos.

Ejemplo 1

(2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-((2S,5S)-1-(4-fluorofenil)pirrolidin-2,5-diil)bis(4,1-fenilen))bis(azandiil)bis(oxometilen)bis(pirrolidin-2,1-diil))bis(3,3-dimetil-1-oxobutan-2,1-diil)dicarbamato de dimetilo

y

(2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-((2R,5R)-1-(4-fluorofenil)pirrolidin-2,5-diil)bis(4,1-fenilen))bis(azandiil)bis(oxometilen)bis(pirrolidin-2,1-diil))bis(3,3-dimetil-1-oxobutan-2,1-diil)dicarbamato de dimetilo



Ejemplo 1A

1,4-Bis(4-nitrofenil)butan-1,4-diona

Se agitó cloruro de cinc(II) anhidro (2,73 g, 20,00 mmol) en benceno seco (15 ml) mientras se agregaba dietilamina (1,558 ml, 15,00 mmol) y t-butanol (1,435 ml, 15,00 mmol), y la mezcla resultante se agitó a temperatura ambiente por 90 min para dar una solución turbia. A esta mezcla se agregó 2-bromo-1-(4-nitrofenil)etanona (2,44 g, 10,00 mmol) y 1-(4-nitrofenil)etanona (2,477 g, 15,00 mmol), y la mezcla resultante se agitó a temperatura ambiente durante la noche. La mezcla se vertió en agua (50 ml) y se extrajo con acetato de etilo (3 x 50 ml). Las capas orgánicas combinadas se secaron sobre Na_2SO_4, se filtró y se concentró. El residuo resultante se trituró con diclorometano para dar un sólido anaranjado que se recogió mediante filtración y se secó para dar el compuesto del título (2,0 gm, 61% de rendimiento).

Ejemplo 1B

1,4-Bis(4-nitrofenil)butan-1,4-diol

A una solución del producto del Ejemplo 1A (1,0 g, 3,05 mmol) en THF anhidro (30 ml) a 0°C se agregó borhidruro de sodio (0,357 g, 9,44 mmol). La mezcla resultante se

agitó a 50°C durante la noche. La mezcla fría se vertió en agua, se extrajo con acetato de etilo, se secó sobre Na_2SO_4, se filtró y se concentró al vacío. El sólido resultante se trituró con diclorometano para dar un sólido color tostado que se recogió mediante filtración y se secó para dar el compuesto del título (0,82 gm, 81% de rendimiento).

Ejemplo 1C

dimetansulfonato de 1,4-Bis(4-nitrofenil)butan-1,4-diilo

A una solución del producto del Ejemplo 1B (0,80 g, 2,407 mmol) en CH_2Cl_2 seco (25 ml) a 0°C se agregó trietilamina (1,007 ml, 7,22 mmol), seguido por la adición por goteo de cloruro de metansulfonilo (0,469 ml, 6,02 mmol). La mezcla resultante se agitó a 0°C por 30 min, durante los cuales el material de partida entró lentamente en solución. Luego de agitar 1 h adicional a 0°C, comenzó a formarse un precipitado. Se agregó NH_4Cl acuoso saturado (4 ml), y la agitación se continuó a temperatura ambiente por 20 min. La mezcla se lavó con agua (2 x 10 ml), y la capa orgánica se trató con hexanos (10 ml) para dar un sólido anaranjado que se recogió mediante filtración para dar el compuesto del título (0,75 gm, 64% de rendimiento).

Ejemplo 1D

1-(4-Fluorofenil)-2,5-bis(4-nitrofenil)pirrolidina

Se combinó el producto del Ejemplo 1C (0,6 gm, 1,228 mmol) y 4-fluoroanilina (2,0 ml, 20,82 mmol) y se agitó a 50°C durante la noche. La mezcla resultante se particionó entre HCl 0,2 N (50 ml) y acetato de etilo (3 x 50 ml), y las capas orgánicas combinadas se secaron sobre Na_2SO_4, se filtró y se concentró al vacío. El producto crudo se purificó mediante cromatografía sobre gel de sílice usando un gradiente de solvente de acetato de etilo al 0-40% en hexano para dar el compuesto del título como una mezcla de isómeros cis y trans (0,5 gm, 100% de rendimiento).

Ejemplo 1E

4,4'-(1-(4-Fluorofenil)pirrolidin-2,5-diil)dianilina

A una solución del producto del Ejemplo 1D (0,501 g, 1,23 mmol) en etanol (5 ml) y THF (5,00 ml) se agregó polvo de hierro (0,412 g, 7,38 mmol) y una solución de cloruro de amonio (0,197 g, 3,69 mmol) en agua (1,0 ml). La mezcla resultante se agitó a 80°C por 45 min. La mezcla se enfrió, se filtró a través de celite, se lavó con etanol, y se concentró al vacío. El producto crudo se purificó mediante cromatografía sobre gel de sílice usando un gradiente de solvente de 0-100% acetato de etilo en hexanos para dar el compuesto del título como una mezcla de isómeros cis y trans (0,135 gm, 32%).

Ejemplo 1F

(2S,2'S)-2,2'-(4,4'-(1-(4-fluorofenil)pirrolidin-2,5-diil)bis(4,1-fenilen))bis(azandiil)bis(oxometilen)dipirrolidin-1-carboxilato de tert-butilo

A una mezcla del producto del Ejemplo 1E (0,13 gm, 0,374 mmol), ácido (S)-1-(tert-butoxicarbonil)pirrolidin-2-carboxílico (0,201 gm, 0,935 mmol) y HATU (0,356 gm, 0,935 mmol) en DMSO (3 ml) se agregó base de Hunig (0,196 ml, 1,123 mmol), y la mezcla de reacción se agitó a temperatura ambiente por 90 min. La mezcla se vertió en agua y se extrajo con acetato de etilo. El extracto orgánico se secó sobre Na_2SO_4, se filtró y se concentró al vacío para dar un producto crudo que se purificó mediante cromatografía de columna sobre gel de sílice, eluyendo con un gradiente de solvente de 5-100% acetato de etilo en hexano para dar compuesto del título (0,28 gm, 100%).

Ejemplo 1G

(2S,2'S)-N,N'-(4,4'-(1-(4-Fluorofenil)pirrolidin-2,5-diil)bis(4,1-fenilen))dipirrolidin-2-carboxamida

Al producto del Ejemplo 1F (0,28 gm, 0,377 mmol) en CH_2Cl_2 (2,0 ml) se agregó TFA (2,0 ml). La mezcla de la reacción se agitó a temperatura ambiente por 45 min y se concentró al vacío. El residuo se particionó entre 3:1 CH_2Cl_2:2-PrOH y $NaHCO_3$ acuoso saturado. La capa orgánica se secó sobre Na_2SO_4, se filtró y se concentró para dar el compuesto del título (0,195 gm, 95% de rendimiento).

Ejemplo 1H

(2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-((2S,5S)-1-(4-fluorofenil)pirrolidin-2,5-diil)bis(4,1-fenilen))bis(azandiil)bis(oxometilen)bis(pirrolidin-2,1-diil))bis(3,3-dimetil-1-oxobutan-2,1-diil)dicarbamato de dimetilo

y

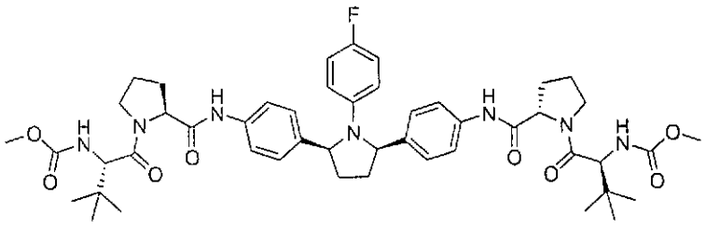
(2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-((2R,5R)-1-(4-fluorofenil)pirrolidin-2,5-diil)bis(4,1-fenilen))bis(azandiil)bis(oxometilen)bis(pirrolidin-2,1-diil))bis(3,3-dimetil-1-oxobutan-2,1-diil)dicarbamato de dimetilo

A una mezcla del producto del Ejemplo 1G (0,03 gm, 0,055 mmol), ácido (S)-2-(metoxicarbonilamino)-3,3-dimetilbutanoico (0,0262 gm, 0,138 mmol) y HATU (0,0526 gm, 0,138 mmol) en DMSO (0,5 ml) se agregó base de Hunig (0,029 ml, 0,166 mmol), y la mezcla resultante se agitó a temperatura ambiente por 90 min. La mezcla se vertió en agua (2 ml) y se extrajo con acetato de etilo (2 x 2 ml), y las capas orgánicas combinadas se concentraron y se sometió a purificación HPLC en una columna de fase inversa C18 semipreparativa usando un gradiente de 10-100% acetonitrilo en TFA acuoso al 0,1%. El isómero pirrolidina trans-sustituido fue el primero de 2 estereoisómeros en eluir, para dar el compuesto del título como una mezcla 1:1 de diastereómeros (0,014 gm, 29% de rendimiento): 1H RMN (Sal TFA) (400 MHz, DMSO-D6) δ ppm 0,93 – 1,01 (m, *J*=4,99 Hz, 18 H) 1,62 – 1,68 (m, 2 H) 1,81 – 1,93 (m, 6 H) 1,94 – 2,04 (m, 2 H) 2,09 – 2,20 (m, 2 H) 3,54 (s, 6 H) 3,59 – 3,69 (m, 2 H) 3,73 – 3,81 (m, 2 H) 4,18 – 4,24 (m, 2 H) 4,43 (dd,

J=7,81, 5,42 Hz, 2 H) 5,16 (d, 2 H) 6,20 (dd, *J*=9,05, 4,39 Hz, 2 H) 6,78 (t, *J*=8,89 Hz, 2 H) 7,09 (d, *J*=8,89 Hz, 2 H) 7,12 (d, 4 H) 7,50 (d, *J*=8,02 Hz, 4 H) 9,99 (s, 2 H). El compuesto del título mostró un valor de EC_{50} inferior a aproximadamente 0,1 nM en Ensayos de replicones del VHC 1b-Con1 en presencia de FBS al 5%. El ensayo de replicones 1b-Con1 se describe más adelante.

Ejemplo 2

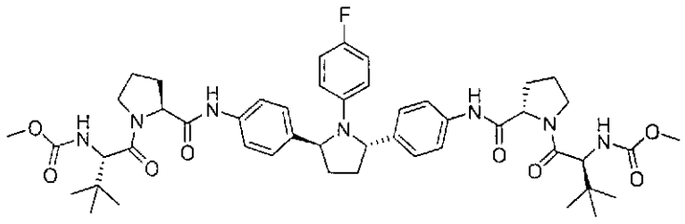
(2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-((2S,5R)-1-(4-fluorofenil)pirrolidin-2,5-diil)bis(4,1-fenilen))bis(azandiil)bis(oxometilen)bis(pirrolidin-2,1-diil))bis(3,3-dimetil-1-oxobutan-2,1-diil)dicarbamato de dimetilo



A una mezcla del producto del Ejemplo 1G (0,03 gm, 0,055 mmol), ácido (S)-2-(metoxicarbonilamino)-3,3-dimetilbutanoico (0,0262 gm, 0,138 mmol) y HATU (0,0526 gm, 0,138 mmol) en DMSO (0,5 ml) se agregó base de Hunig (0,029 ml, 0,166 mmol), y la mezcla resultante se agitó a temperatura ambiente por 90 min. La mezcla se vertió en agua (2 ml) y se extrajo con acetato de etilo (2 x 2 ml), y las capas orgánicas combinadas se concentraron y se sometió a purificación HPLC en una columna de fase inversa C18 semipreparativa usando un gradiente de 10-100% acetonitrilo en TFA acuoso al 0,1%. El isómero pirrolidina cis-sustituido fue el segundo de 2 estereoisómeros en eluir, para dar el compuesto del título (0,018 gm, 37% de rendimiento): 1H RMN (Sal TFA) (400 MHz, DMSO-D6) δ ppm 0,93 – 1,01 (m, *J*=3,04 Hz, 18 H) 1,75 – 1,94 (m, 6 H) 1,94 – 2,05 (m, 2 H) 2,11 – 2,22 (m, 2 H) 2,31 – 2,35 (m, 1 H) 3,54 (s, 6 H) 3,61 – 3,70 (m, 2 H) 3,74 – 3,83 (m, 2 H) 4,22 (d, *J*=8,78 Hz, 2 H) 4,46 (dd, *J*=8,02, 5,42 Hz, 2 H) 4,65 (t, 2 H) 6,34 (dd, 2 H) 6,86 (t, *J*=8,89 Hz, 2 H) 7,08 (d, 2 H) 7,43 (d, *J*=7,81 Hz, 4 H) 7,60 (d, *J*=8,57 Hz, 4 H) 10,05 (s, 2 H). El compuesto del título mostró un valor de EC_{50} inferior a aproximadamente 0,1 nM en ensayos de replicones del VHC 1b-Con1 en presencia de FBS al 5%.

Ejemplo 3

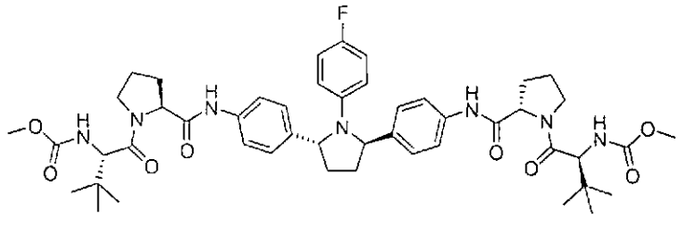
(2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-((2S,5S)-1-(4-fluorofenil)pirrolidin-2,5-diil)bis(4,1-fenilen))bis(azandiil)bis(oxometilen)bis(pirrolidin-2,1-diil))bis(3,3-dimetil-1-oxobutan-2,1-diil)dicarbamato de dimetilo



El producto del Ejemplo 1H se purificó mediante cromatografía quiral en una columna semipreparativa Chiralpak AD-H eluyendo con una mezcla 1:1 de hexanos:(2:1 IPA:EtOH). El compuesto del título fue el primero de 2 estereoisómeros en eluir. 1H RMN (400 MHz, DMSO-D6) δ ppm 0,97 (s, 18 H) 1,61 – 1,67 (m, *J*=5,64 Hz, 2 H) 1,79 – 1,92 (m, 6 H) 1,93 – 2,04 (m, *J*=5,86 Hz, 2 H) 2,07 – 2,20 (m, *J*=6,51 Hz, 2 H) 3,54 (s, 6 H) 3,59 – 3,69 (m, 2 H) 3,71 – 3,83 (m, 2 H) 4,21 (d, *J*=8,89 Hz, 2 H) 4,43 (dd, *J*=7,97, 5,37 Hz, 2 H) 5,15 (d, *J*=6,51 Hz, 2 H) 6,20 (dd, 2 H) 6,78 (t, *J*=8,95 Hz, 2 H) 7,13 (d, *J*=8,57 Hz, 4 H) 7,50 (d, *J*=8,57 Hz, 4 H) 9,99 (s, 2 H). El compuesto del título mostró un valor de EC_{50} inferior a aproximadamente 0,1 nM en ensayos de replicones del VHC 1b-Con1 en presencia de FBS al 5%.

Ejemplo 4

(2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-((2R,5R)-1-(4-fluorofenil)pirrolidin-2,5-diil)bis(4,1-fenilen))bis(azandiil)bis(oxometilen)bis(pirrolidin-2,1-diil))bis(3,3-dimetil-1-oxobutan-2,1-diil)dicarbamato de dimetilo



El producto del Ejemplo 1H se separó mediante cromatografía quiral en una columna semipreparativa Chiralpak AD-H eluyendo con una mezcla 1:1 de hexanos:(2:1 IPA:EtOH). El compuesto del título fue el segundo de 2 estereoisómeros en eluir. 1H RMN (400 MHz, DMSO-D6) δ ppm 0,96 (s, 18 H) 1,64 (d, *J*=5,53 Hz, 2 H) 1,78 – 1,93 (m, 6 H) 1,94 – 2,06 (m, 2 H) 2,09 – 2,21 (m, 2 H) 3,54 (s, 6 H) 3,59 – 3,69 (m, 2 H) 3,72 – 3,83 (m, 2 H) 4,20 (d, *J*=8,89 Hz, 2 H) 4,43 (dd, *J*=7,92, 5,42 Hz, 2 H) 5,16 (d, *J*=6,29 Hz, 2 H) 6,20 (dd, *J*=9,16, 4,39 Hz, 2 H) 6,77 (t, *J*=8,95 Hz, 2 H) 7,12 (d, *J*=8,57 Hz, 4 H) 7,50 (d, *J*=8,57 Hz, 4 H) 9,99 (s, 2 H). El compuesto del título mostró un valor de EC_{50} inferior a aproximadamente 0,1 nM en ensayos de replicones del VHC 1b-Con1 en presencia de FBS al 5%.

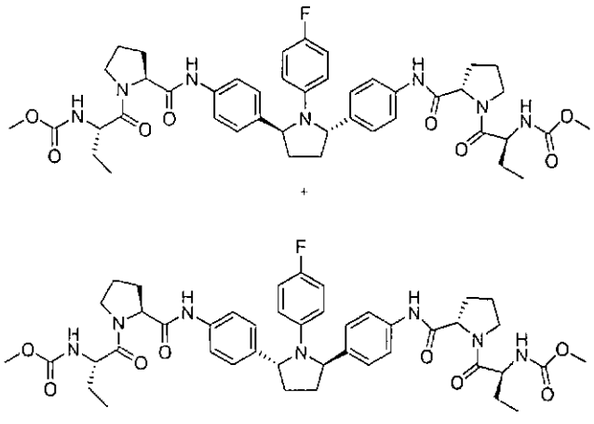
Ejemplo 5

(2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-((2S,5S)-1-(4-fluorofenil)pirrolidin-2,5-diil)bis(4,1-

fenilen))bis(azandiil)bis(oxometilen)bis(pirrolidin-2,1-diil))bis(1-oxobutan-2,1-diil)dicarbamato de dimetilo

y

(2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-((2R,5R)-1-(4-fluorofenil)pirrolidin-2,5-diil)bis(4,1-fenilen))bis(azandiil)bis(oxometilen)bis(pirrolidin-2,1-diil))bis(1-oxobutan-2,1-diil)dicarbamato de dimetilo



Ejemplo 5A

4,4'-((2S,5S)-1-(4-Fluorofenil)pirrolidin-2,5-diil)dianilina y 4,4'-((2R,5R)-1-(4-Fluorofenil)pirrolidin-2,5-diil)dianilina

El producto del Ejemplo 1E se purificó mediante cromatografía de columna sobre gel de sílice, eluyendo con un gradiente de solvente de 0-100% acetato de etilo en hexanos. El compuesto del título eluyó como el primero de 2 estereoisómeros y se obtuvo como una mezcla racémica de trans diastereómeros. 1H RMN (400 MHz, DMSO-D6) δ ppm 1,57 (d, *J*=5,64 Hz, 2 H) 2,36 - 2,42 (m, 2 H) 4,86 - 4,91 (m, 4 H) 4,96 (d, *J*=6,61 Hz, 2 H) 6,17 - 6,25 (m, 2 H) 6,47 (d, *J*=8,35 Hz, 4 H) 6,74 (t, 2 H) 6,82 (d, *J*=8,35 Hz, 4 H).

Ejemplo 5B

(2S,2'S)-2,2'-(4,4'-((2S,5S)-1-(4-fluorofenil)pirrolidin-2,5-diil)bis(4,1-fenilen))bis(azandiil)bis(oxometilen)dipirrolidin-1-carboxilato de tert-butilo y (2S,2'S)-2,2'-(4,4'-((2R,5R)-1-(4-fluorofenil)pirrolidin-2,5-diil)bis(4,1-fenilen))bis(azandiil)bis(oxometilen)dipirrolidin-1-carboxilato de tert-butilo

El producto del Ejemplo 5A (50 mg, 0,144 mmol) se sometió a las condiciones descritas en Ejemplo 1F para dar el compuesto del título como una mezcla 1:1 de diastereómeros (105 mg, 98%): 1H RMN (400 MHz, DMSO-D6) δ ppm 1,34 (d, 18 H) 1,66 (d, *J*=5,10 Hz, 2 H) 1,74 - 1,89 (m, 6 H) 2,07 - 2,23 (m, 2 H) 4,15 - 4,25 (m, 2 H) 5,18 (d, *J*=3,47 Hz, 2 H) 6,18 - 6,25 (m, 2 H) 6,78 (t, *J*=8,95 Hz, 2 H) 7,14 (d, *J*=8,24 Hz, 4 H) 7,51 (t, *J*=8,29 Hz, 4 H) 9,92 (d, 2 H).

Ejemplo 5C

(2S,2'S)-N,N'-(4,4'-((2S,5S)-1-(4-Fluorofenil)pirrolidin-2,5-diil)bis(4,1-fenilen))dipirrolidin-2-carboxamida y (2S,2'S)-N,N'-(4,4'-((2R,5R)-1-(4-Fluorofenil)pirrolidin-2,5-diil)bis(4,1-fenilen))dipirrolidin-2-carboxamida

El producto del Ejemplo 5B se sometió a las condiciones descritas en Ejemplo 1G para dar el compuesto del título como una mezcla 1:1 de diastereómeros.

Ejemplo 5D

(2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-((2S,5S)-1-(4-fluorofenil)pirrolidin-2,5-diil)bis(4,1-fenilen))bis(azandiil)bis(oxometilen)bis(pirrolidin-2,1-diil))bis(1-oxobutan-2,1-diil)dicarbamato de dimetilo y (2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-((2R,5R)-1-(4-fluorofenil)pirrolidin-2,5-diil)bis(4,1-fenilen))bis(azandiil)bis(oxometilen)bis(pirrolidin-2,1-diil))bis(1-oxobutan-2,1-diil)dicarbamato de dimetilo

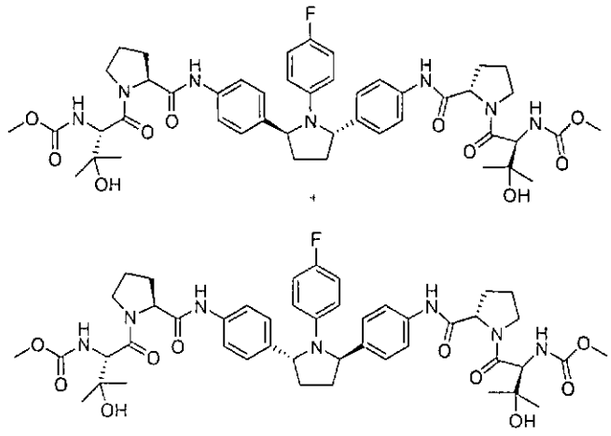
A una mezcla del producto del Ejemplo 5C (0,102 g, 0,188 mmol), ácido (S)-2-(metoxicarbonilamino)butanoico (0,064 g, 0,395 mmol) y HATU (0,150 g, 0,395 mmol) en DMSO (2 ml) se agregó base de Hunig (0,099 ml, 0,565 mmol), y la reacción se agitó a temperatura ambiente por 45 min. La mezcla de la reacción se particionó entre agua y acetato de etilo, y la capa orgánica se secó sobre Na_2SO_4, se filtró y se concentró al vacío. El producto crudo se purificó mediante cromatografía de columna sobre gel de sílice usando un gradiente de solvente de MeOH al 0-4% en diclorometano para dar el compuesto del título como una mezcla 1:1 de estereoisómeros (0,158 gm, 94% de rendimiento): 1H RMN (400 MHz, DMSO-D6) δ ppm 0,86 - 0,96 (m, 6 H) 1,53 (d, *J*=4,34 Hz, 2 H) 1,59 - 1,73 (m, 2 H) 1,80 - 1,96 (m, *J*=6,29 Hz, 4 H) 1,96 - 2,06 (m, 2 H) 2,08 - 2,20 (m, 2 H) 3,52 (s, 6 H) 3,67 - 3,79 (m, 2 H) 4,12 - 4,23 (m, 2 H) 4,42 (dd, *J*=8,13, 4,66 Hz, 2 H) 5,16 (d, *J*=6,40 Hz, 2 H) 6,20 (dd, *J*=9,22, 4,45 Hz, 2 H) 6,77 (t, *J*=8,89 Hz, 2 H) 7,12 (d, *J*=7,59 Hz, 4 H) 7,30 (dd, *J*=7,59, 3,25 Hz, 2 H) 7,50 (d, *J*=8,24 Hz, 4 H) 8,16 (s, 2 H) 9,95 (s, 2 H). El compuesto del título mostró un valor de EC_{50} de entre aproximadamente 0,1 y aproximadamente 1 nM en ensayos de replicones del VHC 1b-Con1 en presencia de FBS al 5%.

Ejemplo 6

(2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-((2S,5S)-1-(4-fluorofenil)pirrolidin-2,5-diil)bis(4,1-fenilen))bis(azandiil)bis(oxometilen)bis(pirrolidin-2,1-diil))bis(3-hidroxi-3-metil-1-oxobutan-2,1-diil)dicarbamato de dimetilo

y

(2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-((2R,5R)-1-(4-fluorofenil)pirrolidin-2,5-diil)bis(4,1-fenilen))bis(azandiil)bis(oxometilen)bis(pirrolidin-2,1-diil))bis(3-hidroxi-3-metil-1-oxobutan-2,1-diil)dicarbamato de dimetilo



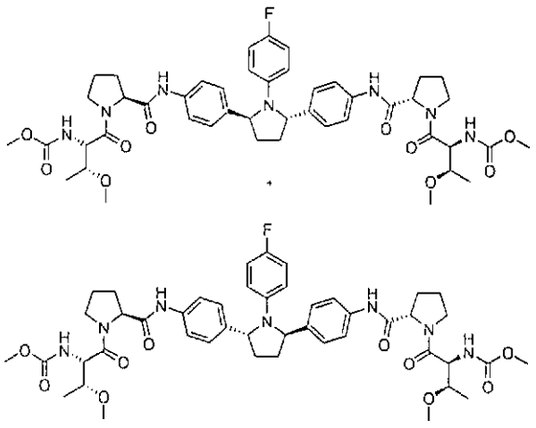
A una mezcla del producto del Ejemplo 5C (0,1 g, 0,185 mmol), ácido (S)-3-hidroxi-2-(metoxicarbonilamino)-3-metilbutanoico (0,074 g, 0,388 mmol) y HATU (0,147 g, 0,388 mmol) en DMSO (2 ml) se agregó base de Hunig (0,097 ml, 0,554 mmol), y la mezcla de la reacción se agitó a temperatura ambiente por 45 min. La mezcla de la reacción se particionó entre agua y acetato de etilo, y la capa orgánica se secó sobre Na_2SO_4, se filtró y se concentró al vacío. El producto crudo se purificó mediante cromatografía de columna sobre gel de sílice usando un gradiente de solvente de MeOH al 0-4% en diclorometano para dar el compuesto del título como una mezcla 1:1 de estereoisómeros (0,162 gm, 97% de rendimiento): 1H RMN (400 MHz, DMSO-D6) δ ppm 1,15 (d, *J*=10,19 Hz, 12 H) 1,64 (d, *J*=5,64 Hz, 2 H) 1,87 - 1,98 (m, 6 H) 2,09 – 2,22 (m, 2 H) 3,55 (s, 6 H) 3,58 – 3,66 (m, 2 H) 3,66 – 3,74 (m, 2 H) 3,83 – 3,92 (m, 2 H) 4,37 (s, 2 H) 4,44 – 4,50 (m, 2 H) 5,07 (s, 2 H) 5,11 (s, 2 H) 5,17 (d, *J*=6,18 Hz, 2 H) 6,15 – 6,28 (m, 2 H) 6,78 (t, *J*=8,89 Hz, 2 H) 7,13 (d, *J*=8,13 Hz, 4 H) 7,51 (d, *J*=7,81 Hz, 4 H) 8,11 – 8,23 (m, 2 H) 9,67 (d, *J*=9,11 Hz, 2 H). El compuesto del título mostró un valor de EC_{50} inferior a aproximadamente 0,1 nM en ensayos de replicones del VHC 1b-Con1 en presencia de FBS al 5%.

Ejemplo 7

(2S,2'S,3R,3'R)-1,1'-((2S,2'S)-2,2'-(4,4'-((2S,5S)-1-(4-fluorofenil)pirrolidin-2,5-diil)bis(4,1-fenilen))bis(azandiil)bis(oxometilen)bis(pirrolidin-2,1-diil))bis(3-metoxi-1-oxobutan-2,1-diil)dicarbamato de dimetilo

y

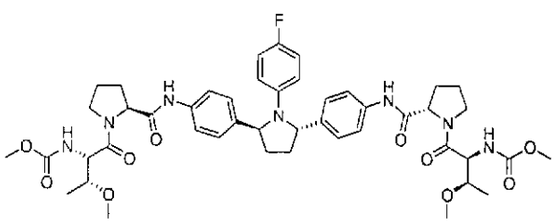
(2S,2'S,3R,3'R)-1,1'-((2S,2'S)-2,2'-(4,4'-((2R,5R)-1-(4-fluorofenil)pirrolidin-2,5-diil)bis(4,1-fenilen))bis(azandiil)bis(oxometilen)bis(pirrolidin-2,1-diil))bis(3-metoxi-1-oxobutan-2,1-diil)dicarbamato de dimetilo



A una mezcla del producto del Ejemplo 5C (0,025 gm, 0,046 mmol), ácido (2S,3R)-3-metoxi-2-(metoxicarbonilamino)butanoico (0,01941 gm, 0,102 mmol) y HATU (0,0439 gm, 0,115 mmol) en DMSO (0,2 ml) se agregó base de Hunig (0,024 ml, 0,138 mmol). La mezcla se agitó a temperatura ambiente por 2 hr, y luego se vertió en agua y se extrajo con acetato de etilo. La fase orgánica se secó sobre Na_2SO_4, se filtró y se concentró al vacío, y el producto crudo se purificó mediante cromatografía sobre gel de sílice usando un gradiente de solvente de 0-5%MeOH en CH_2Cl_2 para dar el compuesto del título (0,040 gm, 93% de rendimiento): 1H RMN (400 MHz, DMSO-D6) δ ppm 1,09 - 1,31 (m, 6 H) 1,64 (d, *J*=5,10 Hz, 2 H) 1,83 - 1,93 (m, *J*=12,42, 12,42 Hz, 4 H) 1,93 - 2,03 (m, 2 H) 2,11 - 2,19 (m, 2 H) 3,10 - 3,18 (m, *J*=6,94 Hz, 2 H) 3,24 (d, *J*=4,99 Hz, 6 H) 3,42 - 3,49 (m, *J*=10,84, 6,72 Hz, 2 H) 3,53 (s, 6 H) 3,58 - 3,70 (m, 2 H) 3,79 - 3,89 (m, 2 H) 4,26 (t, *J*=7,10 Hz, 2 H) 4,41 (dd, *J*=7,97, 4,93 Hz, 2 H) 5,16 (d, *J*=6,29 Hz, 2 H) 6,20 (dd, *J*=9,11, 4,34 Hz, 2 H) 6,78 (t, *J*=8,95 Hz, 2 H) 7,12 (d, 4 H) 7,33 (dd, *J*=7,70, 3,47 Hz, 2 H) 7,50 (d, *J*=8,13 Hz, 4 H) 9,95 (s, 2 H). El compuesto del título mostró un valor de EC_{50} de entre aproximadamente 0,1 y aproximadamente 1 nM en ensayos de replicones del VHC 1b-Con1 en presencia de FBS al 5%.

Ejemplo 8

(2S,2'S,3R,3'R)-1,1'-((2S,2'S)-2,2'-(4,4'-((2S,5S)-1-(4-fluorofenil)pirrolidin-2,5-diil)bis(4,1-fenilen))bis(azandiil)bis(oxometilen)bis(pirrolidin-2,1-diil))bis(3-metoxi-1-oxobutan-2,1-diil)dicarbamato de dimetilo

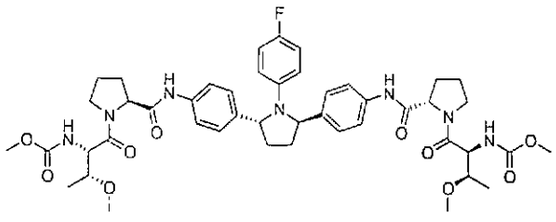


El producto del Ejemplo 7 se purificó mediante cromatografía quiral en una columna semipreparativa Chiralpak AD-H eluyendo con una mezcla 1:3 de hexanos:(1:1

IPA:EtOH). El compuesto del título fue el primero de 2 estereoisómeros en eluir. 1H RMN (400 MHz, DMSO-D6) δ ppm 1,13 (d, *J*=6,18 Hz, 6 H) 1,64 (d, *J*=5,64 Hz, 2 H) 1,82 - 1,93 (m, 4 H) 1,95 - 2,04 (m, 2 H) 2,10 - 2,19 (m, 2 H) 3,25 (s, 6 H) 3,44 - 3,48 (m, 2 H) 3,53 (s, 6 H) 3,62 - 3,71 (m, 2 H) 3,79 - 3,87 (m, 2 H) 4,26 (t, *J*=7,75 Hz, 2 H) 4,41 (dd, *J*=7,92, 4,99 Hz, 2 H) 5,16 (d, *J*=6,51 Hz, 2 H) 6,20 (dd, *J*=9,16, 4,39 Hz, 2 H) 6,78 (t, *J*=8,89 Hz, 2 H) 7,13 (d, *J*=8,57 Hz, 4 H) 7,34 (d, *J*=7,92 Hz, 2 H) 7,50 (d, *J*=8,57 Hz, 4 H) 9,95 (s, 2 H). El compuesto del título mostró un valor de EC_{50} inferior a aproximadamente 0,1 nM en ensayos de replicones del VHC 1b-Con1 en presencia de FBS al 5%.

Ejemplo 9

(2S,2'S,3R,3'R)-1,1'-((2S,2'S)-2,2'-(4,4'-((2R,5R)-1-(4-fluorofenil)pirrolidin-2,5-diil)bis(4,1-fenilen))bis(azandiil)bis(oxometilen)bis(pirrolidin-2,1-diil))bis(3-metoxi-1-oxobutan-2,1-diil)dicarbamato de dimetilo



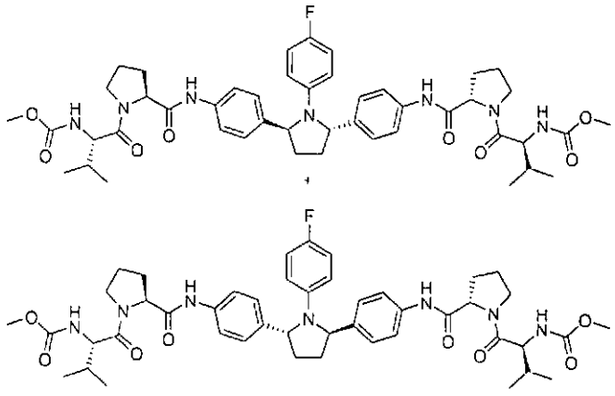
El producto del Ejemplo 7 se purificó mediante cromatografía quiral en una columna semipreparativa Chiralpak AD-H eluyendo con una mezcla 1:3 de hexanos:(1:1 IPA:EtOH). El compuesto del título fue el segundo de 2 estereoisómeros en eluir. 1H RMN (400 MHz, DMSO-D6) δ ppm 1,12 (d, *J*=6,18 Hz, 6 H) 1,64 (d, *J*=5,64 Hz, 2 H) 1,82 - 1,93 (m, 4 H) 1,95 - 2,06 (m, 2 H) 2,10 - 2,21 (m, 2 H) 3,24 (s, 6 H) 3,42 - 3,48 (m, 2 H) 3,53 (s, 6 H) 3,61 - 3,73 (m, 2 H) 3,78 - 3,88 (m, 2 H) 4,26 (t, *J*=7,75 Hz, 2 H) 4,41 (dd, *J*=7,92, 4,99 Hz, 2 H) 5,16 (d, *J*=6,18 Hz, 2 H) 6,20 (dd, 2 H) 6,78 (t, *J*=8,89 Hz, 2 H) 7,13 (d, *J*=8,46 Hz, 4 H) 7,33 (d, *J*=7,81 Hz, 2 H) 7,49 (d, *J*=8,46 Hz, 4 H) 9,95 (s, 2 H). El compuesto del título mostró un valor de EC_{50} de entre aproximadamente 0,1 y aproximadamente 1 nM en ensayos de replicones del VHC 1b-Con1 en presencia de FBS al 5%.

Ejemplo 10

(2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-((2S,5S)-1-(4-fluorofenil)pirrolidin-2,5-diil)bis(4,1-fenilen))bis(azandiil)bis(oxometilen)bis(pirrolidin-2,1-diil))bis(3-metil-1-oxobutan-2,1-diil)dicarbamato de dimetilo

y

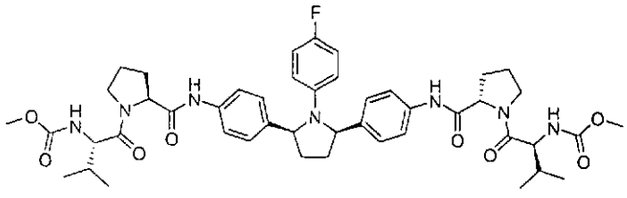
(2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-((2R,5R)-1-(4-fluorofenil)pirrolidin-2,5-diil)bis(4,1-fenilen))bis(azandiil)bis(oxometilen)bis(pirrolidin-2,1-diil))bis(3-metil-1-oxobutan-2,1-diil)dicarbamato de dimetilo



A una mezcla del producto del Ejemplo 1G (0,030 g, 0,055 mmol), ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico (0,024 g, 0,14 mmol) y HATU (0,052 g, 0,14 mmol) en DMSO (0,3 ml) se agregó base de Hunig (0,024 ml, 0,166 mmol), y la mezcla resultante se agitó a temperatura ambiente por 90 min. La mezcla se particionó entre agua y acetato de etilo, y la capa orgánica se concentró y se sometió a purificación HPLC en una columna de fase inversa C18 semipreparativa usando un gradiente de 10-100% acetonitrilo en TFA acuoso al 0,1%. El isómero pirrolidina trans-sustituido fue el primero de 2 estereoisómeros en eluir, para dar el compuesto del título como una mezcla 1:1 de diastereómeros (9 mg, 16%): 1H RMN (Sal TFA) (400 MHz, DMSO-D6) δ ppm 0,85 - 0,96 (m, 12 H) 1,64 (d, *J*=5,75 Hz, 2 H) 1,82 - 1,92 (m, 6 H) 1,95 - 2,06 (m, 2 H) 2,08 - 2,20 (m, 2 H) 3,52 (s, 6 H) 3,57 - 3,68 (m, 2 H) 3,74 - 3,86 (m, *J*=5,86 Hz, 2 H) 4,02 (t, *J*=8,35 Hz, 2 H) 4,42 (dd, *J*=7,92, 4,88 Hz, 2 H) 5,16 (d, *J*=6,18 Hz, 2 H) 6,20 (dd, *J*=9,16, 4,39 Hz, 2 H) 6,77 (t, *J*=8,89 Hz, 2 H) 7,12 (dd, *J*=8,51, 1,68 Hz, 4 H) 7,31 (dd, *J*=8,24, 3,36 Hz, 2 H) 7,50 (d, *J*=7,26 Hz, 4 H) 9,99 (s, 2 H). El compuesto del título mostró un valor de EC_{50} inferior a aproximadamente 0,1 nM en ensayos de replicones del VHC 1b-Con1 en presencia de FBS al 5%.

Ejemplo 11

(2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-((2S,5R)-1-(4-fluorofenil)pirrolidin-2,5-diil)bis(4,1-fenilen))bis(azandiil)bis(oxometilen)bis(pirrolidin-2,1-diil))bis(3-metil-1-oxobutan-2,1-diil)dicarbamato de dimetilo

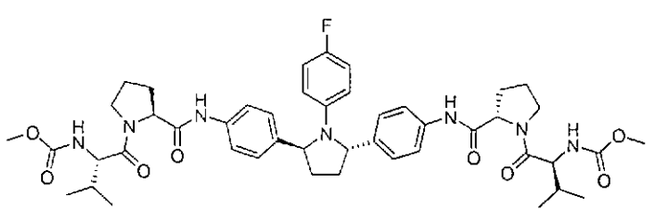


A una mezcla del producto del Ejemplo 1G (0,030 g, 0,055 mmol), ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico (0,024 g, 0,14 mmol) y HATU (0,052 g, 0,14 mmol) en DMSO (0,3 ml) se agregó base de Hunig (0,024 ml, 0,166 mmol), y la mezcla

resultante se agitó a temperatura ambiente por 90 min. La mezcla se particionó entre agua y acetato de etilo, y la capa orgánica se concentró y se sometió a purificación HPLC en una columna de fase inversa C18 semipreparativa usando un gradiente de 10-100% acetonitrilo en TFA acuoso al 0,1%. El isómero pirrolidina cis-sustituido fue el segundo de 2 estereoisómeros en eluir, para dar el compuesto del título (11 mg, 20%): 1H RMN (Sal TFA) (400 MHz, DMSO-D6) δ ppm 9,35 (s, 2 H) 8,26 (s, 2 H) 7,77 - 7,83 (m, 4 H) 7,68 - 7,73 (m, 4 H) 7,01 (t, *J*=8,95 Hz, 2 H) 6,61 - 6,71 (m, 2 H) 6,23 (d, *J*=8,35 Hz, 2 H) 4,87 - 4,97 (m, 2 H) 4,67 - 4,78 (m, 2 H) 4,42 - 4,52 (m, 2 H) 3,99 - 4,09 (m, 2 H) 3,87 - 3,97 (m, 2 H) 3,84 (s, 6 H) 1,22 (dd, *J*=6,78, 2,11 Hz, 6 H) 1,15 (dd, *J*=6,72, 2,06 Hz, 6 H). El compuesto del título mostró un valor de EC_{50} inferior a aproximadamente 0,1 nM en ensayos de replicones del VHC 1b-Con1 en presencia de FBS al 5%.

Ejemplo 12

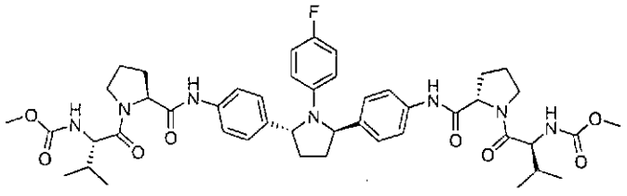
(2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-((2S,5S)-1-(4-fluorofenil)pirrolidin-2,5-diil)bis(4,1-fenilen))bis(azandiil)bis(oxometilen)bis(pirrolidin-2,1-diil))bis(3-metil-1-oxobutan-2,1-diil)dicarbamato de dimetilo



El producto del Ejemplo 10 se separó mediante cromatografía quiral en una columna semipreparativa Chiralpak AD-H eluyendo con una mezcla 1:1 de hexanos:(2:1 2-PrOH:EtOH). El compuesto del título eluyó como el primero de 2 estereoisómeros. 1H RMN (400 MHz, DMSO-D6) δ ppm 0,84 – 0,97 (m, 12 H) 1,64 (d, *J*=5,64 Hz, 2 H) 1,88 (s, 6 H) 1,95 – 2,05 (m, 2 H) 2,08 – 2,19 (m, 2 H) 3,52 (s, 6 H) 3,58 – 3,66 (m, 2 H) 3,76 – 3,85 (m, 2 H) 4,02 (t, *J*=8,51 Hz, 2 H) 4,42 (dd, *J*=8,02, 4,88 Hz, 2 H) 5,15 (d, *J*=6,51 Hz, 2 H) 6,20 (dd, *J*=9,16, 4,39 Hz, 2 H) 6,78 (t, *J*=8,89 Hz, 2 H) 7,13 (d, *J*=8,46 Hz, 4 H) 7,31 (d, *J*=8,35 Hz, 2 H) 7,50 (d, *J*=8,46 Hz, 4 H) 9,99 (s, 2 H). El compuesto del título mostró un valor de EC_{50} inferior a aproximadamente 0,1 nM en ensayos de replicones del VHC 1b-Con1 en presencia de FBS al 5%.

Ejemplo 13

(2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-((2R,5R)-1-(4-fluorofenil)pirrolidin-2,5-diil)bis(4,1-fenilen))bis(azandiil)bis(oxometilen)bis(pirrolidin-2,1-diil))bis(3-metil-1-oxobutan-2,1-diil)dicarbamato de dimetilo



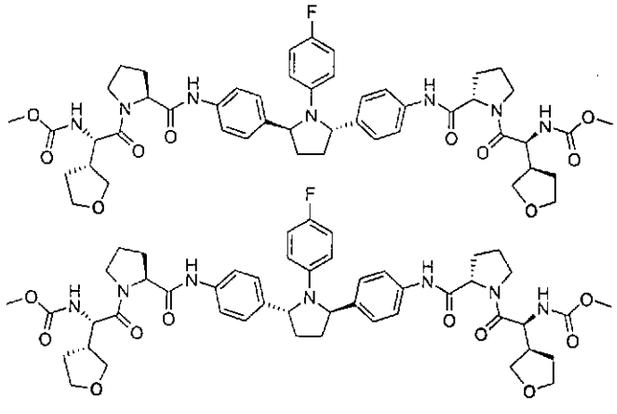
El producto del Ejemplo 10 se separó mediante cromatografía quiral en una columna semipreparativa Chiralpak AD-H eluyendo con una mezcla 1:1 de hexanos:(2:1 2-PrOH:EtOH). El compuesto del título eluyó como el segundo de 2 estereoisómeros. 1H RMN (400 MHz, DMSO-D6) δ ppm 0,82 – 0,97 (m, 12 H) 1,65 (d, 2 H) 1,80 – 2,05 (m, 8 H) 2,08 – 2,20 (m, 2 H) 3,52 (s, 6 H) 3,57 – 3,68 (m, 2 H) 3,76 – 3,87 (m, 2 H) 4,01 (t, 2 H) 4,42 (dd, 2 H) 5,16 (d, *J*=6,40 Hz, 2 H) 6,20 (dd, *J*=9,22, 4,45 Hz, 2 H) 6,77 (t, *J*=8,95 Hz, 2 H) 7,12 (d, *J*=8,57 Hz, 4 H) 7,30 (d, *J*=8,35 Hz, 2 H) 7,50 (d, *J*=8,46 Hz, 4 H) 9,98 (s, 2 H). El compuesto del título mostró un valor de EC_{50} inferior a aproximadamente 0,1 nM en ensayos de replicones del VHC 1b-Con1 en presencia de FBS al 5%.

Ejemplo 14

(1S,1'S)-2,2'-((2S,2'S)-2,2'-(4,4'-((2S,5S)-1-(4-fluorofenil)pirrolidin-2,5-diil)bis(4,1-fenilen))bis(azandiil)bis(oxometilen)bis(pirrolidin-2,1-diil))bis(2-oxo-1-((R)-tetrahidrofurano-3-il)etan-2,1-diil)dicarbamato de dimetilo

y

(1S,1'S)-2,2'-((2S,2'S)-2,2'-(4,4'-((2R,5R)-1-(4-fluorofenil)pirrolidin-2,5-diil)bis(4,1-fenilen))bis(azandiil)bis(oxometilen)bis(pirrolidin-2,1-diil))bis(2-oxo-1-((R)-tetrahidrofurano-3-il)etan-2,1-diil)dicarbamato de dimetilo

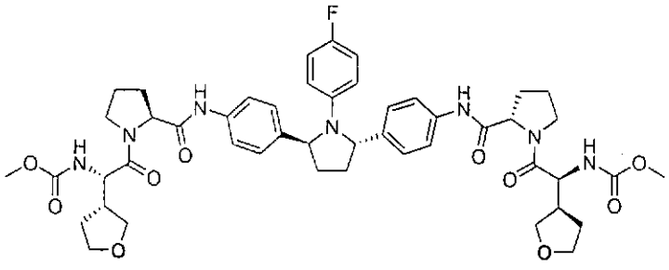


A una mezcla del producto del Ejemplo 5C (0,013 g, 0,024 mmol), HATU (0,02275 gm, 0,060 mmol), y ácido (S)-2-(metoxicarbonilamino)-2-((R)-tetrahidrofurano-3-il)acético (0,0107 gm, 0,053 mmol) en DMSO (0,200 ml) se agregó Base de Hunig (0,013 ml, 0,072 mmol). La reacción se agitó a temperatura ambiente por 2 hr, se vertió en agua, y se extrajo con acetato de etilo. El extracto orgánico se secó sobre Na_2SO_4, se filtró y se concentró al vacío, y el material crudo se purificó en una columna de fase inversa C18

semipreparativa usando un gradiente de 10-100% acetonitrilo en TFA acuoso al 0,1% para dar el compuesto del título (6,9 mg, 28% de rendimiento): 1H RMN (Sal TFA) (400 MHz, DMSO-D6) δ ppm 1,61 - 1,77 (m, 4 H) 1,80 - 1,94 (m, 6 H) 1,93 - 2,06 (m, 2 H) 2,08 - 2,21 (m, 2 H) 3,44 (dd, *J*=8,46, 6,29 Hz, 2 H) 3,53 (s, 6 H) 3,56 - 3,68 (m, 8 H) 3,68 - 3,77 (m, 2 H) 3,80 - 3,90 (m, 2 H) 4,23 (t, *J*=8,84 Hz, 2 H) 4,43 (dd, *J*=8,02, 4,77 Hz, 2 H) 5,16 (d, *J*=6,29 Hz, 2 H) 6,20 (dd, *J*=9,11, 4,45 Hz, 2 H) 6,77 (t, *J*=8,95 Hz, 2 H) 7,13 (d, *J*=8,57 Hz, 4 H) 7,50 (d, *J*=8,57 Hz, 4 H) 7,60 (d, *J*=7,92 Hz, 2 H) 9,98 (s, 2 H). El compuesto del título mostró un valor de EC_{50} de entre aproximadamente 0,1 y aproximadamente 1 nM en ensayos de replicones del VHC 1b-Con1 en presencia de FBS al 5%.

Ejemplo 15

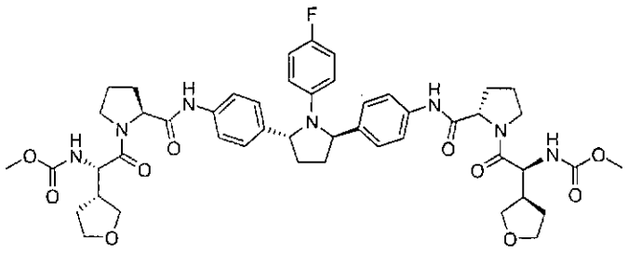
(1S,1'S)-2,2'-((2S,2'S)-2,2'-(4,4'-((2S,5S)-1-(4-fluorofenil)pirrolidin-2,5-diil)bis(4,1-fenilen))bis(azandiil)bis(oxometilen)bis(pirrolidin-2,1-diil))bis(2-oxo-1-((R)-tetrahidrofurano-3-il)etan-2,1-diil)dicarbamato de dimetilo



El producto del Ejemplo 14 se separó mediante cromatografía quiral en una columna semipreparativa Chiralpak AD-H eluyendo con una mezcla 2:3 de hexanos:(1:1 2-PrOH:EtOH). El compuesto del título eluyó como el primero de 2 estereoisómeros. 1H RMN (400 MHz, DMSO-D6) δ ppm 1,59 - 1,78 (m, 4 H) 1,79 - 1,94 (m, 6 H) 1,94 - 2,05 (m, 2 H) 2,09 - 2,23 (m, *J*=5,10 Hz, 2 H) 3,44 (dd, *J*=8,35, 6,40 Hz, 2 H) 3,53 (s, 6 H) 3,57 - 3,73 (m, 8 H) 3,71 - 3,80 (m, 2 H) 3,81 - 3,89 (m, 2 H) 4,23 (t, *J*=8,78 Hz, 2 H) 4,43 (dd, *J*=7,97, 4,83 Hz, 2 H) 5,16 (d, *J*=6,07 Hz, 2 H) 6,16 - 6,24 (m, 2 H) 6,78 (t, *J*=8,89 Hz, 2 H) 7,13 (d, *J*=8,57 Hz, 4 H) 7,50 (d, *J*=8,46 Hz, 4 H) 7,60 (d, *J*=8,02 Hz, 2 H) 9,98 (s, 2 H). El compuesto del título mostró un valor de EC_{50} inferior a aproximadamente 0,1 nM en ensayos de replicones del VHC 1b-Con1 en presencia de FBS al 5%.

Ejemplo 16

(1S,1'S)-2,2'-((2S,2'S)-2,2'-(4,4'-((2R,5R)-1-(4-fluorofenil)pirrolidin-2,5-diil)bis(4,1-fenilen))bis(azandiil)bis(oxometilen)bis(pirrolidin-2,1-diil))bis(2-oxo-1-((R)-tetrahidrofurano-3-il)etan-2,1-diil)dicarbamato de dimetilo

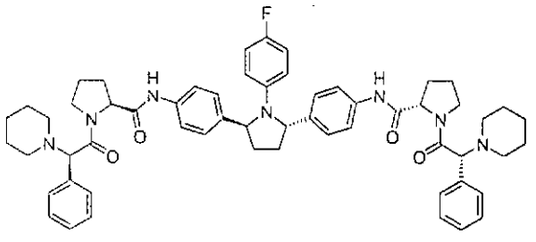


El producto del Ejemplo 14 se separó mediante cromatografía quiral en una columna semipreparativa Chiralpak AD-H eluyendo con una mezcla 2:3 de hexanos:(1:1 2-PrOH:EtOH). El compuesto del título eluyó como el segundo de 2 estereoisómeros. 1H RMN (400 MHz, DMSO-D6) δ ppm 1,61 - 1,77 (m, 4 H) 1,80 - 1,94 (m, 6 H) 1,93 - 2,06 (m, 2 H) 2,08 - 2,21 (m, 2 H) 3,44 (dd, *J*=8,46, 6,29 Hz, 2 H) 3,53 (s, 6 H) 3,56 - 3,68 (m, 8 H) 3,68 - 3,77 (m, 2 H) 3,80 - 3,90 (m, 2 H) 4,23 (t, *J*=8,84 Hz, 2 H) 4,43 (dd, *J*=8,02, 4,77 Hz, 2 H) 5,16 (d, *J*=6,29 Hz, 2 H) 6,20 (dd, *J*=9,11, 4,45 Hz, 2 H) 6,77 (t, *J*=8,95 Hz, 2 H) 7,13 (d, *J*=8,57 Hz, 4 H) 7,50 (d, *J*=8,57 Hz, 4 H) 7,60 (d, *J*=7,92 Hz, 2 H) 9,98 (s, 2 H). El compuesto del título mostró un valor de EC_{50} de entre aproximadamente 0,1 y aproximadamente 1 nM en ensayos de replicones del VHC 1b-Con1 en presencia de FBS al 5%.

Ejemplo 17

(R,2S,2'S)-N,N'-(4,4'-((2S,5S)-1-(4-Fluorofenil)pirrolidin-2,5-diil)bis(4,1-fenilen))bis(1-((R)-2-fenil-2-(piperidin-1-il)acetil)pirrolidin-2-carboxamida) y

(R,2S,2'S)-N,N'-(4,4'-((2R,5R)-1-(4-Fluorofenil)pirrolidin-2,5-diil)bis(4,1-fenilen))bis(1-((R)-2-fenil-2-(piperidin-1-il)acetil)pirrolidin-2-carboxamida)

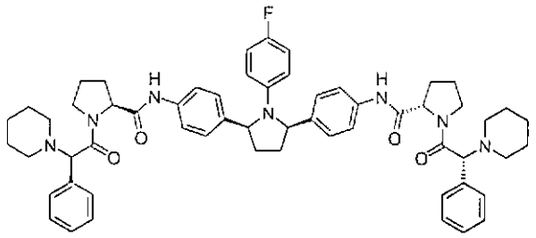


A una mezcla de sal TFA de ácido (R)-2-fenil-2-(piperidin-1-il)acético (0,0455 mg, 0,137 mmol), el producto del Ejemplo 1G (0,030 gm, 0,055 mmol), y HATU (0,0526 gm, 0,138 mmol) en DMSO (0,300 ml) se agregó base de Hunig (0,029,0 ml, 0,166 mmol), y la mezcla resultante se agitó a temperatura ambiente por 2 hr. La mezcla se particionó entre agua y acetato de etilo, la capa orgánica se secó sobre Na_2SO_4, se filtró y se concentró al vacío. El producto crudo se sometió a purificación HPLC en una columna de fase inversa C18 semipreparativa usando un gradiente de 10-100% acetonitrilo en TFA acuoso al 0,1% (8,3 mg, 11%): 1H RMN (Sal TFA) (400 MHz, DMSO-D6) δ ppm 1,20 - 1,42 (m, 4 H) 1,61 - 2,02 (m, 16 H) 2,62 - 2,81 (m, 4 H) 3,01 - 3,23 (m, *J*=9,32 Hz, 4 H) 3,87 - 3,98 (m, 2 H)

4,40 - 4,47 (m, *J*=8,24 Hz, 2 H) 5,14 - 5,24 (m, 2 H) 5,50 (d, *J*=8,78 Hz, 2 H) 6,23 (dd, *J*=8,89, 4,34 Hz, 2 H) 6,75 - 6,84 (m, 2 H) 7,16 (d, *J*=7,81 Hz, 4 H) 7,48 - 7,59 (m, 12 H) 7,62 (d, *J*=3,69 Hz, 4 H) 9,89 (s, 2 H) 10,17 (s, 2 H). El compuesto del título mostró un valor de EC_{50} de entre aproximadamente 0,1 y aproximadamente 1 nM en ensayos de replicones del VHC 1b-Con1 en presencia de FBS al 5%.

Ejemplo 18

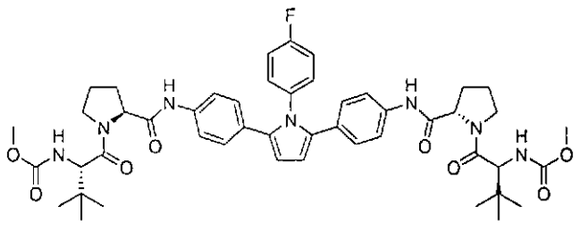
(R,2S,2'S)-N,N'-(4,4'-((2S,5R)-1-(4-fluorofenil)pirrolidin-2,5-diil)bis(4,1-fenilen))bis(1-((R)-2-fenil-2-(piperidin-1-il)acetil)pirrolidin-2-carboxamida)



A una mezcla de sal TFA de ácido (R)-2-fenil-2-(piperidin-1-il)acético (0,0455 mg, 0,137 mmol), el producto del Ejemplo 1G (0,030 gm, 0,055 mmol), y HATU (0,0526 gm, 0,138 mmol) en DMSO (0,300 ml) se agregó base de Hunig (0,029,0 ml, 0,166 mmol), y la mezcla resultante se agitó a temperatura ambiente por 2 hr. La mezcla se particionó entre agua y acetato de etilo, la capa orgánica se secó sobre Na_2SO_4, se filtró y se concentró al vacío. El producto crudo se sometió a purificación HPLC en una columna de fase inversa C18 semipreparativa usando un gradiente de 10-100% acetonitrilo en TFA acuoso al 0,1% (8,7 mg, 12%): 1H RMN (Sal TFA) (400 MHz, DMSO-D6) δ ppm 1,22 - 1,43 (m, 4 H) 1,62 - 2,03 (m, *J*=80,02 Hz, 16 H) 2,08 - 2,18 (m, 2 H) 2,62 - 2,85 (m, 4 H) 3,04 - 3,24 (m, 4 H) 3,88 - 3,99 (m, 2 H) 4,41 - 4,52 (m, 2 H) 4,64 - 4,72 (m, 2 H) 5,52 (d, *J*=8,24 Hz, 2 H) 6,36 (dd, *J*=9,05, 4,50 Hz, 2 H) 6,88 (t, *J*=8,89 Hz, 2 H) 7,41 - 7,68 (m, 18 H) 9,89 (s, 2 H) 10,23 (s, 2 H). El compuesto del título mostró un valor de EC_{50} inferior a aproximadamente 0,1 nM en ensayos de replicones del VHC 1b-Con1 en presencia de FBS al 5%.

Ejemplo 19

(2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-(1-(4-fluorofenil)-1H-pirrol-2,5-diil)bis(4,1-fenilen))bis(azandiil)bis(oxometilen)bis(pirrolidin-2,1-diil))bis(3,3-dimetil-1-oxobutan-2,1-diil)dicarbamato de dimetilo



Ejemplo 19A

1-(4-Fluorofenil)-2,5-bis(4-nitrofenil)-1H-pirrol

A una lechada del producto del Ejemplo 1A (1,5 g, 4,57 mmol) en ácido acético (22,85 ml) se agregó 4-fluoroanilina (4,33 ml, 45,7 mmol). La mezcla se calentó a 70 °C por 24 h. Luego de enfriar a temperatura ambiente la mezcla se diluyó con agua y éter y se agitó enérgicamente, se filtró y se secó para dar 1,67 g (91%) del compuesto del título.

Ejemplo 19B

4,4'-(1-(4-Fluorofenil)-1H-pirrol-2,5-diil)dianilina

A una solución de ejemplo 19A (1,017 g, 2,496 mmol) en etanol (15 ml) y THF (15 ml) se agregó polvo de hierro (0,836 g, 14,98 mmol) seguido por cloruro de amonio (0,401 g, 7,49 mmol) y agua (3,75 ml). La mezcla de reacción se sometió a reflujo por 45 minutos. La lechada se filtró a través de celite, se lavó con etanol, el material filtrado combinado se concentró y el residuo se purificó mediante cromatografía de columna (gradiente de elución entre 30% y 50% EtOAc:hexanos) para dar 1,09 g (77%) del compuesto del título.

Ejemplo 19C

(2S,2'S)-2,2'-(4,4'-(1-(4-fluorofenil)-1H-pirrol-2,5-diil)bis(4,1-fenilen))bis(azandiil)bis(oxometilen)dipirrolidin-1-carboxilato de tert-butilo

A una solución de Ejemplo 19B (1,09 g, 3,17 mmol) en DMF (15,87 ml) a temperatura ambiente se agregó HATU (2,66 g, 6,98 mmol), ácido (S)-1-(tert-butoxicarbonil)pirrolidin-2-carboxílico (1,503 g, 6,98 mmol), y base de Hunig (2,218 ml, 12,70 mmol). La agitación se continuó durante la noche. La mezcla se particionó entre agua y se agregó EtOAc. La fase orgánica se lavó con salmuera, se secó (Na_2SO_4) y se concentró. El residuo se purificó mediante cromatografía de columna (gradiente de elución entre 20% y 50% EtOAc/ hexanos). MS (ESI; M+H) m/z = 738.

Ejemplo 19D

(2S,2'S)-N,N'-(4,4'-(1-(4-Fluorofenil)-1H-pirrol-2,5-diil)bis(4,1-fenilen))dipirrolidin-2-carboxamida

Al producto del Ejemplo 19C (100 mg, 0,136 mmol) en CH_2Cl_2 (2,0 ml) se agregó TFA (1,0 ml) y la reacción se agitó 1 h. La mezcla se concentró, el residuo se particionó entre agua y 25% IPA-$CHCl_3$ y se neutralizó con $NaHCO_3$. La capa orgánica se secó sobre Na_2SO_4, se filtró y se concentró para dar el compuesto del título como un sólido blanco que se usó sin purificación adicional. MS (DCI; M+H) m/z = 538.

Ejemplo 19E

(2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-(1-(4-fluorofenil)-1H-pirrol-2,5-diil)bis(4,1-fenilen))bis(azandiil)bis(oxometilen)bis(pirrolidin-2,1-diil))bis(3,3-dimetil-1-oxobutan-2,1-diil)dicarbamato de dimetilo

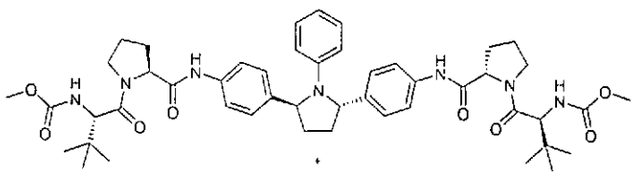
A una mezcla del producto del Ejemplo 19D (0,073 g, 0,136 mmol) en CH_2Cl_2 (10 ml) a temperatura ambiente se agregó base de Hunig (0,070 ml, 0,407 mmol). A esto luego se agregó ácido (S)-2-metoxicarbonilamino-3,3-dimetil-butírico (0,054 g, 0,285 mmol) seguido por HATU (0,114 g, 0,299 mmol). La mezcla se agitó por 2 hrs luego se lavó con $NaHCO_3$ saturado y la fase orgánica se concentró y el residuo se purificó mediante cromatografía de columna (1% gradiente de elución entre 0% y 3% MeOH-CH_2Cl_2) para dar el compuesto deseado como un sólido color tostado claro. MS (ESI; M+H) m/z = 881; 1H RMN (400 MHz, DMSO-D6) δ ppm 0,96 (s, 18 H), 1,81-1,89 (m, 4 H), 1,95-2,00 (m, 2 H), 2,11-2,16 (m, 2 H), 3,53 (s, 6 H), 3,61-3,65 (m, 2 H), 3,75-3,79 (m, 2 H), 4,20 (d, J=8,85 Hz, 2 H), 4,39-4,42 (m, 2 H), 6,39 (s, 2 H), 6,96 (d, J=8,69 Hz, 4 H), 7,07-7,10 (m, 4 H), 7,17 (dd, J=8,70, 8,70 Hz, 2 H), 7,41 (d, J=8,70 Hz, 4 H), 10,01 (br s, 2 H). El compuesto del título mostró un valor de EC_{50} inferior a aproximadamente 0,1 nM en ensayos de replicones del VHC 1b-Con1 en presencia de FBS al 5%.

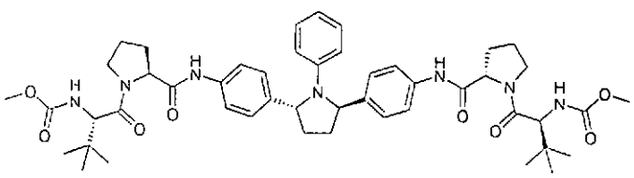
Ejemplo 20

(2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-((2S,5S)-1-fenilpirrolidin-2,5-diil)bis(4,1-fenilen))bis(azandiil)bis(oxometilen)bis(pirrolidin-2,1-diil))bis(3,3-dimetil-1-oxobutan-2,1-diil)dicarbamato de dimetilo

y

(2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-((2R,5R)-1-fenilpirrolidin-2,5-diil)bis(4,1-fenilen))bis(azandiil)bis(oxometilen)bis(pirrolidin-2,1-diil))bis(3,3-dimetil-1-oxobutan-2,1-diil)dicarbamato de dimetilo





Ejemplo 20A

2,5-Bis(4-nitrofenil)-1-fenilpirrolidina

Una mezcla del producto del Ejemplo 1C (50 mg, 0,102 mmol) y anilina (0,2 ml, 2,19 mmol) se agitaron a temperatura ambiente por 48h. La mezcla se particionó entre HCl 1N acuoso y acetato de etilo, y la capa orgánica se secó sobre Na_2SO_4, se filtró y se concentró al vacío. El producto crudo se purificó mediante cromatografía de columna sobre gel de sílice usando un gradiente de solvente de acetato de etilo al 0-50% en

hexanos. El compuesto del título se obtuvo como un sólido amarillo (19 mg, 48%).

Ejemplo 20B

(2S,2'S)-2,2'-(4,4'-(1-fenilpirrolidin-2,5-diil)bis(4,1-fenilen))bis(azandiil)bis(oxometilen)dipirrolidin-1-carboxilato de tert-butilo

El producto del Ejemplo 20A (19 mg, 0,049 mmol) se sometió a las condiciones descritas en Ejemplo 1E. El producto crudo se sometió a las condiciones descritas en Ejemplo 1F para dar el compuesto del título (33 mg, 93%).

Ejemplo 20C

(2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-((2S,5S)-1-fenilpirrolidin-2,5-diil)bis(4,1-fenilen))bis(azandiil)bis(oxometilen)bis(pirrolidin-2,1-diil))bis(3,3-dimetil-1-oxobutan-2,1-diil)dicarbamato de dimetilo

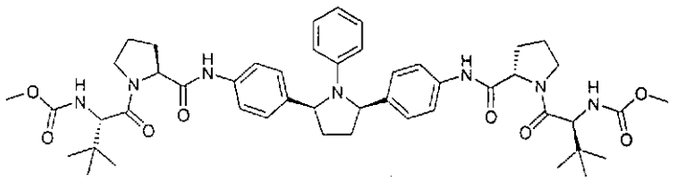
y

(2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-((2R,5R)-1-fenilpirrolidin-2,5-diil)bis(4,1-fenilen))bis(azandiil)bis(oxometilen)bis(pirrolidin-2,1-diil))bis(3,3-dimetil-1-oxobutan-2,1-diil)dicarbamato de dimetilo

El producto del Ejemplo 20B (30 mg, 0,041 mmol) se sometió a las condiciones descritas en Ejemplo 1G, y el producto crudo se sometió a las condiciones descritas en Ejemplo 1H. El producto crudo se sometió a purificación HPLC en una columna de fase inversa C18 semipreparativa usando un gradiente de 10-100% acetonitrilo en TFA acuoso al 0,1%. El isómero pirrolidina trans-sustituido fue el primero de 2 estereoisómeros en eluir, para dar el compuesto del título como una mezcla 1:1 de diastereómeros (7 mg, 19%): 1H RMN (Sal TFA) (400 MHz, DMSO-D6) δ ppm 0,95 (d, *J*=5,31 Hz, 18 H) 1,59 - 1,67 (m, 2 H) 1,79 - 1,91 (m, 4 H) 1,91 - 2,02 (m, 2 H) 2,08 - 2,17 (m, 2 H) 3,52 (s, 6 H) 3,58 - 3,68 (m, 2 H) 3,71 - 3,82 (m, 2 H) 4,19 (d, *J*=9,00 Hz, 2 H) 4,42 (dd, 2 H) 5,17 (d, *J*=5,64 Hz, 2 H) 6,24 (d, *J*=8,35 Hz, 2 H) 6,39 (t, *J*=7,37 Hz, 2 H) 6,90 (t, *J*=7,92 Hz, 2 H) 7,07 (d, 2 H) 7,11 (d, 4 H) 7,48 (d, *J*=8,24 Hz, 4 H) 9,98 (s, 2 H). El compuesto del título mostró un valor de EC_{50} inferior a aproximadamente 0,1 nM en ensayos de replicones del VHC 1b-Con1 en presencia de FBS al 5%.

Ejemplo 21

(2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-((2S,5R)-1-fenilpirrolidin-2,5-diil)bis(4,1-fenilen))bis(azandiil)bis(oxometilen)bis(pirrolidin-2,1-diil))bis(3,3-dimetil-1-oxobutan-2,1-diil)dicarbamato de dimetilo



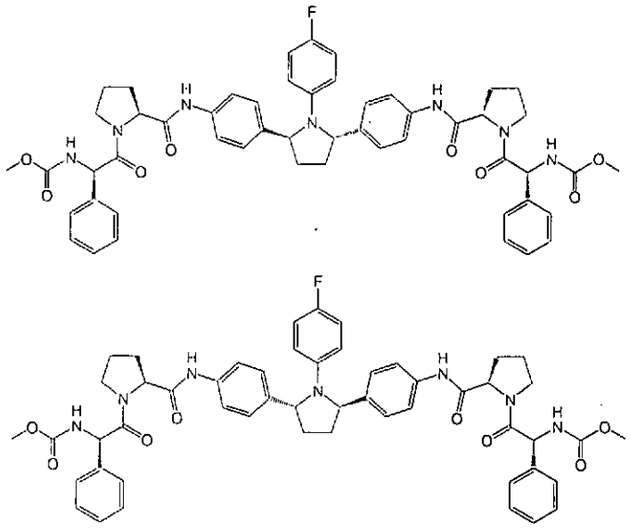
El producto del Ejemplo 20B (30 mg, 0,041 mmol) se sometió a las condiciones descritas en Ejemplo 1G, y el producto crudo se sometió a las condiciones descritas en Ejemplo 1H. El producto crudo se sometió a purificación HPLC en una columna de fase inversa C18 semipreparativa usando un gradiente de 10-100% acetonitrilo en TFA acuoso al 0,1%. El isómero pirrolidina cis-sustituido fue el segundo de 2 estereoisómeros en eluir, para dar el compuesto del título (8,5 mg, 24%): 1H RMN (Sal TFA) (400 MHz, DMSO-D6) δ ppm 0,96 (d, *J*=3,25 Hz, 18 H) 1,74 - 1,91 (m, 6 H) 1,93 - 2,03 (m, 2 H) 2,10 - 2,20 (m, 2 H) 3,53 (s, 6 H) 3,58 - 3,69 (m, 2 H) 3,72 - 3,83 (m, 2 H) 4,20 (d, *J*=8,89 Hz, 2 H) 4,45 (dd, *J*=7,97, 5,37 Hz, 2 H) 4,68 (t, *J*=5,20 Hz, 2 H) 6,37 (d, *J*=8,24 Hz, 2 H) 6,56 (t, *J*=7,26 Hz, 2 H) 6,98 (t, *J*=7,92 Hz, 2 H) 7,07 (d, 2 H) 7,42 (d, *J*=8,02 Hz, 4 H) 7,58 (d, *J*=8,57 Hz, 4 H) 10,03 (s, 2 H). El compuesto del título mostró un valor de EC_{50} inferior a aproximadamente 0,1 nM en ensayos de replicones del VHC 1b-Con1 en presencia de FBS al 5%.

Ejemplo 22

(1R,1'R)-2,2'-((2S,2'S)-2,2'-(4,4'-((2S,5S)-1-(4-fluorofenil)pirrolidin-2,5-diil)bis(4,1-fenilen))bis(azandiil)bis(oxometilen)bis(pirrolidin-2,1-diil))bis(2-oxo-1-feniletan-2,1-diil)dicarbamato de dimetilo

y

(1R,1'R)-2,2'-((2S,2'S)-2,2'-(4,4'-((2R,5R)-1-(4-fluorofenil)pirrolidin-2,5-diil)bis(4,1-fenilen))bis(azandiil)bis(oxometilen)bis(pirrolidin-2,1-diil))bis(2-oxo-1-feniletan-2,1-diil)dicarbamato de dimetilo



El producto del Ejemplo 5C (25 mg, 0,046 mmol) se sometió a las condiciones descritas en Ejemplo 5D, utilizando ácido (R)-2-(metoxicarbonilamino)-2-fenilacético en lugar de ácido (S)-2-(metoxicarbonilamino)butanoico, para dar el compuesto del título

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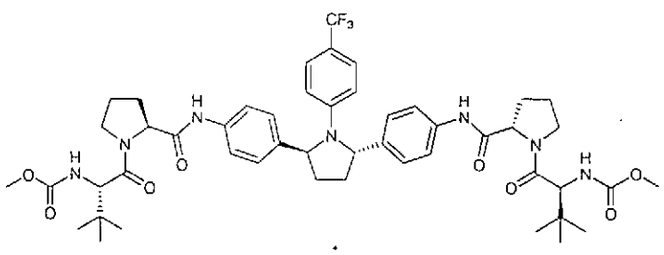
como una mezcla 1:1 de diastereómeros (42 mg, 48%): 1H RMN (400 MHz, DMSO-D6) δ ppm 9,83 (s, 2 H) 7,67 (d, *J*=7,81 Hz, 2 H) 7,51 - 7,57 (m, 4 H) 7,29 - 7,44 (m, 8 H) 7,15 (d, *J*=8,46 Hz, 4 H) 6,74 - 6,83 (m, 2 H) 6,17 - 6,28 (m, *J*=9,00, 4,34 Hz, 2 H) 5,48 (d, *J*=7,81 Hz, 2 H) 5,12 - 5,24 (m, 1 H) 4,33 - 4,43 (m, *J*=8,13 Hz, 2 H) 3,75 - 3,87 (m, 2 H) 3,54 (s, 6 H) 1,73 - 2,05 (m, 8 H) 1,62 - 1,70 (m, 2 H). El compuesto del título mostró un valor de EC_{50} inferior a aproximadamente 0,1 nM en ensayos de replicones del VHC 1b-Con1 en presencia de FBS al 5%.

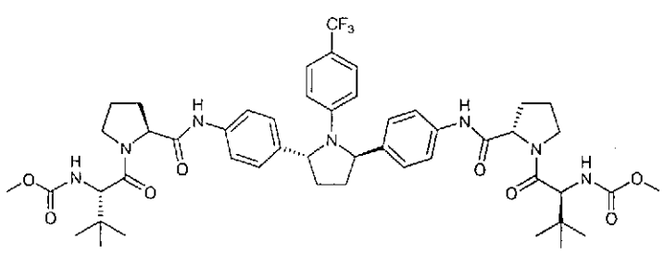
Ejemplo 23

(2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-((2S,5S)-1-(4-(trifluorometil)fenil)pirrolidin-2,5-diil)bis(4,1-fenilen))bis(azandiil)bis(oxometilen)bis(pirrolidin-2,1-diil))bis(3,3-dimetil-1-oxobutan-2,1-diil)dicarbamato de dimetilo

y

(2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-((2R,5R)-1-(4-(trifluorometil)fenil)pirrolidin-2,5-diil)bis(4,1-fenilen))bis(azandiil)bis(oxometilen)bis(pirrolidin-2,1-diil))bis(3,3-dimetil-1-oxobutan-2,1-diil)dicarbamato de dimetilo





Ejemplo 23A

4,4'-((2S,5S)-1-(4-(Trifluorometil)fenil)pirrolidin-2,5-diil)dianilina y 4,4'-((2R,5R)-1-(4-(Trifluorometil)fenil)pirrolidin-2,5-diil)dianilina

El producto del Ejemplo 1C (0,74 g, 1,5 mmol) se sometió a las condiciones descritas en Ejemplo 1D, utilizando 4-(trifluorometil)anilina en lugar de 4-fluoroanilina. El producto así obtenido se sometió a las condiciones descritas en Ejemplo 1E para dar el compuesto del título como una mezcla racémica de estereoisómeros pirrolidina trans-sustituidos (0,10 g, 17%).

Ejemplo 23B

(2S,2'S)-N,N'-(4,4'-((2S,5S)-1-(4-(Trifluorometil)fenil)pirrolidin-2,5-diil)bis(4,1-fenilen))dipirrolidin-2-carboxamida y (2S,2'S)-N,N'-(4,4'-((2R,5R)-1-(4-(Trifluorometil)fenil)pirrolidin-2,5-diil)bis(4,1-fenilen))dipirrolidin-2-carboxamida

El producto del Ejemplo 23A (0,95 g, 0,24 mmol) se sometió a las condiciones descritas en Ejemplo 1F para dar un sólido (0,166 g, 88%), el cual se disolvió en HCl 4M en 1,4-dioxano (2 ml), y la mezcla resultante se agitó a temperatura ambiente por 30 min. La mezcla resultante se concentró y se secó al vacío para dar una sal de HCl del compuesto del título como una mezcla 1:1 de estereoisómeros.

Ejemplo 23C

(2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-((2S,5S)-1-(4-(trifluorometil)fenil)pirrolidin-2,5-diil)bis(4,1-fenilen))bis(azandiil)bis(oxometilen)bis(pirrolidin-2,1-diil))bis(3,3-dimetil-1-oxobutan-2,1-diil)dicarbamato de dimetilo

y

(2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-((2R,5R)-1-(4-(trifluorometil)fenil)pirrolidin-2,5-diil)bis(4,1-fenilen))bis(azandiil)bis(oxometilen)bis(pirrolidin-2,1-diil))bis(3,3-dimetil-1-oxobutan-2,1-diil)dicarbamato de dimetilo

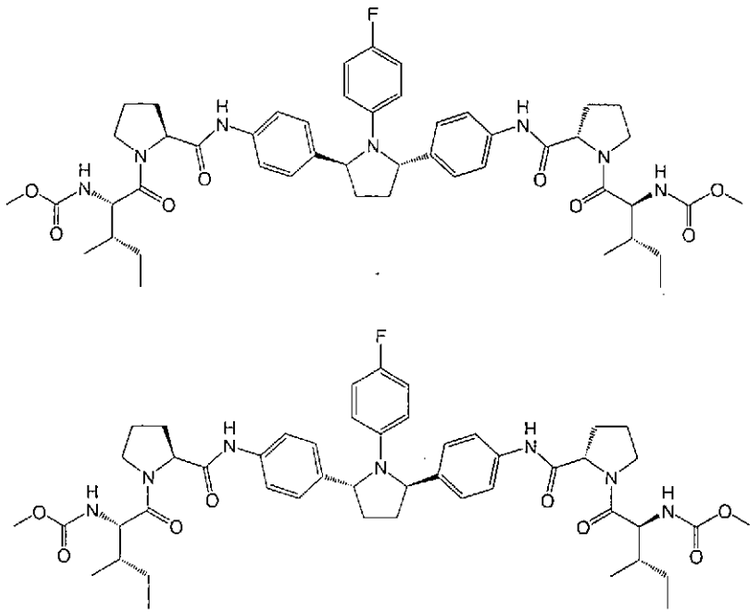
El producto del Ejemplo 23B (58 mg, 0,083 mmol) se sometió a las condiciones descritas en Ejemplo 1H para dar el compuesto del título como un sólido incoloro (30 mg, 39%): 1H RMN (free base) (400 MHz, DMSO-D6) δ ppm 10,03 (s, 2 H) 7,52 (d, *J*=8,46 Hz, 4 H) 7,25 (d, *J*=8,89 Hz, 2 H) 7,14 (d, *J*=7,48 Hz, 4 H) 7,06 - 7,11 (m, 2 H) 6,36 (d, *J*=8,35 Hz, 2 H) 5,23 - 5,33 (m, 2 H) 4,39 - 4,48 (m, 2 H) 4,21 (d, *J*=8,46 Hz, 2 H) 3,71 - 3,82 (m, 2 H) 3,58 - 3,69 (m, 2 H) 3,54 (s, 6 H) 2,08 - 2,21 (m, 2 H) 1,93 - 2,06 (m, 2 H) 1,76 - 1,94 (m, 4 H) 1,61 - 1,73 (m, 2 H) 0,96 (m, 18 H). El compuesto del título mostró un valor de EC_{50} inferior a aproximadamente 0,1 nM en ensayos de replicones del VHC 1b-Con1 en presencia de FBS al 5%.

Ejemplo 24

(2S,2'S,3S,3'S)-1,1'-((2S,2'S)-2,2'-(4,4'-((2S,5S)-1-(4-fluorofenil)pirrolidin-2,5-diil)bis(4,1-fenilen))bis(azandiil)bis(oxometilen)bis(pirrolidin-2,1-diil))bis(3-metil-1-oxopentan-2,1-diil)dicarbamato de dimetilo

y

(2S,2'S,3S,3'S)-1,1'-((2S,2'S)-2,2'-(4,4'-((2R,5R)-1-(4-fluorofenil)pirrolidin-2,5-diil)bis(4,1-fenilen))bis(azandiil)bis(oxometilen)bis(pirrolidin-2,1-diil))bis(3-metil-1-oxopentan-2,1-diil)dicarbamato de dimetilo



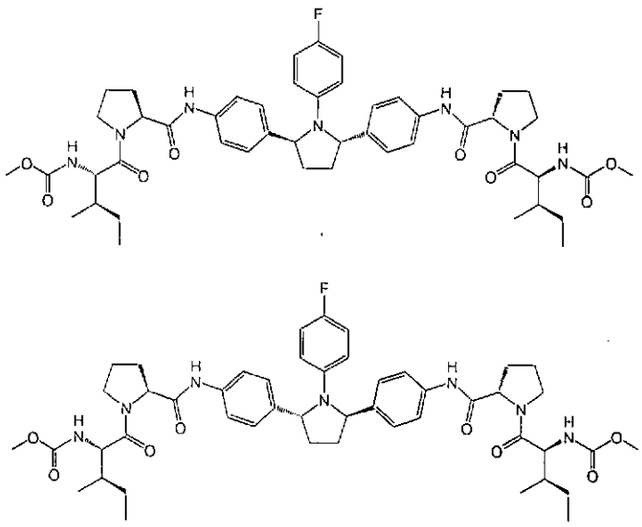
El producto del Ejemplo 1G (20 mg, 0,037 mmol) se sometió a las condiciones descritas en Ejemplo 1H, utilizando ácido (2S,3S)-2-(metoxicarbonilamino)-3-metilpentanoico (15,4 mg, 0,081 mmol) en lugar de ácido (S)-2-(metoxicarbonilamino)-3,3-dimetilbutanoico. El compuesto del título se obtuvo como una mezcla 1:1 de diastereómeros (13,5 mg, 41%) luego de la cromatografía sobre gel de sílice (0-5% MeOH/CH_2Cl_2): 1H RMN (base libre) (400 MHz, DMSO-D6) δ ppm 9,99 (s, 2 H) 7,50 (dd, *J*=8,46, 1,52 Hz, 4 H) 7,36 (dd, *J*=8,35, 3,04 Hz, 2 H) 7,13 (dd, *J*=8,62, 1,79 Hz, 4 H) 6,78 (t, *J*=8,89 Hz, 2 H) 6,20 (dd, *J*=9,16, 4,39 Hz, 2 H) 5,16 (d, *J*=6,29 Hz, 2 H) 4,43 (dd, *J*=7,92, 4,77 Hz, 2 H) 4,02 - 4,13 (m, 2 H) 3,77 - 3,89 (m, 2 H) 3,57 - 3,67 (m, 2 H) 3,52 (s, 6 H) 2,08 - 2,21 (m, *J*=14,96 Hz, 2 H) 1,94 - 2,05 (m, 2 H) 1,81 - 1,93 (m, *J*=5,42 Hz, 4 H) 1,60 - 1,79 (m, 4 H) 1,42 - 1,57 (m, 2 H) 1,04 - 1,18 (m, 2 H) 0,89 (t, *J*=6,51 Hz, 6 H) 0,76 - 0,85 (m, 6 H). El compuesto del título mostró un valor de EC_{50} inferior a aproximadamente 0,1 nM en ensayos de replicones del VHC 1b-Con1 en presencia de FBS al 5%.

Ejemplo 25

(2S,2'S,3R,3'R)-1,1'-((2S,2'S)-2,2'-(4,4'-((2S,5S)-1-(4-fluorofenil)pirrolidin-2,5-diil)bis(4,1-fenilen))bis(azandiil)bis(oxometilen)bis(pirrolidin-2,1-diil))bis(3-metil-1-oxopentan-2,1-diil)dicarbamato de dimetilo

y

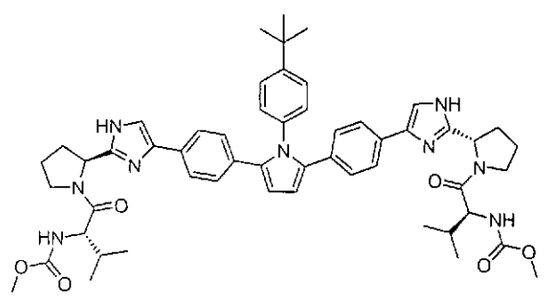
(2S,2'S,3R,3'R)-1,1'-((2S,2'S)-2,2'-(4,4'-((2R,5R)-1-(4-fluorofenil)pirrolidin-2,5-diil)bis(4,1-fenilen))bis(azandiil)bis(oxometilen)bis(pirrolidin-2,1-diil))bis(3-metil-1-oxopentan-2,1-diil)dicarbamato de dimetilo



El producto del Ejemplo 1G (25 mg, 0,046 mmol) se sometió a las condiciones descritas en Ejemplo 1H, utilizando ácido (2S,3R)-2-(metoxicarbonilamino)-3-metilpentanoico (19,2 mg, 0,102 mmol) en lugar de ácido (S)-2-(metoxicarbonilamino)-3,3-dimetilbutanoico. El compuesto del título se obtuvo como una mezcla 1:1 de diastereómeros (20,5 mg, 50%) luego de la cromatografía sobre gel de sílice (0-5% MeOH/CH_2Cl_2): 1H RMN (base libre) (400 MHz, DMSO-D6) δ ppm 9,96 (s, 2 H) 7,49 (d, *J*=8,35 Hz, 4 H) 7,14 (t, *J*=7,43 Hz, 4 H) 6,77 (t, *J*=8,89 Hz, 2 H) 6,20 (dd, *J*=9,11, 4,45 Hz, 2 H) 5,16 (d, *J*=6,40 Hz, 2 H) 4,38 - 4,48 (m, 2 H) 4,18 - 4,28 (m, 2 H) 3,69 - 3,82 (m, 2 H) 3,55 - 3,64 (m, 2 H) 3,52 (s, 6 H) 2,09 - 2,20 (m, 2 H) 1,95 - 2,05 (m, 2 H) 1,72 - 1,95 (m, 6 H) 1,58 - 1,70 (m, *J*=5,64 Hz, 2 H) 1,40 - 1,55 (m, 2 H) 1,06 - 1,18 (m, 2 H) 0,79 - 0,91 (m, 12 H). El compuesto del título mostró un valor de EC_{50} inferior a aproximadamente 0,1 nM en ensayos de replicones del VHC 1b-Con1 en presencia de FBS al 5%.

Ejemplo 26

(2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-(4,4'-(1-(4-tert-butilfenil)-1H-pirrol-2,5-diil)bis(4,1-fenilen))bis(1H-imidazol-4,2-diil))bis(pirrolidin-2,1-diil))bis(3-metil-1-oxobutan-2,1-diil)dicarbamato de dimetilo



Ejemplo 26A

(S)-2-formilpirrolidin-1-carboxilato de tert-butilo

A un recipiente de 3 cuellos de 500 ml secado en horno purgado con nitrógeno se agregó cloruro de oxalilo (5,32 ml, 60,8 mmol) y diclorometano anhidro (125 ml), y la solución se enfrió a -78 °C. Una solución de DMSO anhidro (7,30 ml, 103 mmol) en diclorometano anhidro (25 ml) se agregó por goteo desde un embudo de adición a presión constante durante un periodo de 20 min. Una solución de (S)-2-(hidroximetil)pirrolidin-1-carboxilato de tert-butilo (9,41 g, 46,8 mmol) en diclorometano anhidro (50 ml) se agregó por goteo desde un embudo de adición a presión constante a lo largo de un periodo de 20 min, luego se agitó la mezcla de reacción a -78 °C por 30 min. Se agregó trietilamina (32,6 ml, 234 mmol) por goteo mediante una jeringa a lo largo de un periodo de 5 min y se agitó la mezcla blanca espesa en un baño de agua-hielo por 30 min. La reacción se detuvo con ácido clorhídrico acuoso al 10% (p/v) (30 ml), se vertió la reacción en un embudo de separación con Et_2O (550 ml) y ácido cítrico acuoso al 10% (p/v), las capas se separaron, y se lavó la fase orgánica con agua y salmuera. Se secó la fase orgánica sobre Na_2SO_4 anhidro, se filtró, y se concentró para dar un aceite amarillo (9,4 g), el cual se usó directamente en la siguiente reacción.

Ejemplo 26B

(S)-2-(1H-imidazol-2-il)pirrolidin-1-carboxilato de tert-butilo

El producto del Ejemplo 26A (20 g, 100 mmol) se disolvió en metanol (50,2 ml) y se agregó hidróxido de amonio (50,2 ml). A esta solución se agregó glioxal (40% en agua; 24,08 ml, 211 mmol), por goteo, a lo largo de 10 min. La reacción se agitó a temperatura ambiente durante la noche. La reacción se concentró bajo presión reducida, se diluyó con 50 ml de agua, y luego se extrajo con acetato de etilo. Se lavó la capa orgánica con salmuera, se secó (Na_2SO_4) y se concentró para dar un sólido color tostado. El sólido se trató con éter y se concentró. El sólido luego se trituró con 2:1 éter dietílico:hexanos (150 ml) para dar 17 g de un sólido, el cual se usó directamente en la siguiente reacción.

Ejemplo 26C

(S)-2-(4,5-dibromo-1H-imidazol-2-il)pirrolidin-1-carboxilato de tert-butilo

Se agregó N-bromosuccinimida (108 mmol) a una solución fría (0 °C) del producto del Ejemplo 26B (12,05 g, 50,8 mmol) en diclorometano (200 ml). Se dejó agitar en baño de hielo por 2 h y luego se concentró, se disolvió en acetato de etilo (250 ml), se lavó con agua (3 x 150 ml), salmuera (1 x 100 ml), se secó ($MgSO_4$) y se concentró para dar un residuo muy oscuro, se procesó con diclorometano/hexanos (1:1) para dar un sólido marrón (~19 g). El sólido se trituró con éter (~100 ml), se filtró para aislar un sólido color tostado (13,23 g, 65% de rendimiento).

Ejemplo 26D

(S)-2-(5-bromo-1H-imidazol-2-il)pirrolidin-1-carboxilato de tert-butilo o (S)-2-(4-bromo-1H-

imidazol-2-il)pirrolidin-1-carboxilato de tert-butilo

Se disolvió el producto del Ejemplo 26C (6,25 g, 15,82 mmol) en dioxano (200 ml) y agua (200 ml) en un balón de 1 L equipado con un condensador y tapón de vidrio, se agregó una solución de sulfito de sodio (22,38 g, 174 mmol) en agua (200 ml), y se calentó a reflujo con manto calefactor por 16 h. La reacción fue una solución homogénea rojiza-ámbar. Se enfrió la reacción a temperatura ambiente, se eliminó dioxano y algo de agua por evaporación por rotación, se extrajo con diclorometano, se lavó los extractos orgánicos combinados con salmuera (50 ml), se secó sobre Na_2SO_4 anhidro, se filtró, y se concentró por evaporación por rotación, co-evaporando con 2:1 hexanos/diclorometano (100 ml) para dar una espuma beige (4,38 g). Se disolvió la espuma en diclorometano (2 ml), se agregó hexanos (2 ml), se aplicó la solución a una columna, y se purificó mediante cromatografía flash en gel de sílice eluyendo con acetato de etilo entre 30% y 80%/hexanos para dar el compuesto del título como un sólido blanco (3,48 g).

Ejemplo 26E

1,4-bis(4-bromofenil)butan-1,4-diona

A una solución de cloruro de cinc(II) (19,62 g, 144 mmol) en benceno (108 ml) se agregaron dietilamina (11,16 ml, 108 mmol) y 2-metilpropan-2-ol (10,32 ml, 108 mmol) y la mezcla se agitó a temperatura ambiente por 2 h. Se agregó 2-bromo-1-(4-bromofenil)etanona (20,0 g, (72 mmol) y 1-(4-bromofenil)etanona (21,48 g, 108 mmol) en una porción, y la mezcla se agitó durante la noche (18 h). Se detuvo con H_2SO_4 al 5% (500 ml) y se agitó enérgicamente para inducir la precipitación del producto, el cual se recogió mediante filtración al vacío y se lavó con benceno, agua, metanol, luego diclorometano, en forma sucesiva. El producto se secó bajo vacío para dar el compuesto del título como un sólido blanco (11,15 g, 39,1% de rendimiento).

Ejemplo 26F

2,5-bis(4-bromofenil)-1-(4-tert-butilfenil)-1H-pirrol

A una solución del producto del Ejemplo 26E (4,00 g, 10,10 mmol) en tolueno (40 ml) se agregó 4-tert-butilanilina (1,81 g, 12,12 mmol) seguido por TFA (2,30 g, 20,20 mmol). La mezcla se calentó a 110 °C por 2 h. La mezcla se enfrió a temperatura ambiente y se agregó agua y éter dietílico. Se agitó por 15 min, se filtró, se lavó con agua y éter dietílico y se secó para dar el compuesto del título como un sólido blanco (4,61 g; 90% de rendimiento).

Ejemplo 26G

1-(4-tert-butilfenil)-2,5-bis(4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)-1H-pirrol

A una solución del producto del Ejemplo 26F (2,32 g, 4,56 mmol) en DMSO (26 ml) a temperatura ambiente se agregaron bis(pinacolato)diborano (2,54 g, 10,02 mmol),

acetato de potasio (5,00 g, 36,4 mmol) y $PdCl_2$(dppf) (744 mg, 0,91 mmol). La mezcla se desgasificó y se calentó a 85 °C. Luego de 4 h, la mezcla se enfrió a temperatura ambiente, se diluyó con diclorometano y se lavó con agua seguido por salmuera. La fase orgánica se secó (Na_2SO_4) y se concentró. El residuo se colocó en 20% acetato de etilo:hexanos y se filtró a través de un tapón corto de gel de sílice (elución con 20% acetato de etilo:hexanos) y se concentró para dar el compuesto del título como un sólido amarillo claro (1,62 g; 59% de rendimiento).

Ejemplo 26H

(2S,2'S)-2,2'-(4,4'-(4,4'-(1-(4-tert-butilfenil)-1H-pirrol-2,5-diil)bis(4,1-fenilen))bis(1H-imidazol-4,2-diil))dipirrolidin-1-carboxilato de tert-butilo

Una mezcla del producto del Ejemplo 26D (664 mg, 2,10 mmol), el producto del Ejemplo 26G (1,48 g, 2,45 mmol), carbonato de sodio 2 M (1400 µL, 2,80 mmol), y Pd(dppf)Cl2 (51,2 mg, 0,070 mmol) en DME (2800 µL) se sometió a irradiación de microondas a 140 °C por 20 min. La mezcla se diluyó con acetato de etilo, luego se lavó con agua y salmuera, y se secó sobre Na_2SO_4. El producto se purificó sobre gel de sílice eluyendo con acetato de etilo entre 30% y 70%:hexanos para dar el compuesto del título (140 mg; 24% de rendimiento).

Ejemplo 26I

(2S,2'S)-4,4'-(4,4'-(1-(4-tert-butilfenil)-1H-pirrol-2,5-diil)bis(4,1-fenilen))bis(2-(pirrolidin-2-il)-1H-imidazol)

A una solución del producto del Ejemplo 26H (135 mg, 0,164 mmol) en diclorometano (2 ml) a temperatura ambiente se agregó TFA (0,60 ml). Luego de 3 h, el solvente se eliminó y el residuo se particionó entre agua y 25% alcohol isopropílico:$CHCl_3$; se neutralizó con $NaHCO_3$. La fase orgánica se secó (Na_2SO_4), se filtró y se concentró. El residuo se usó directamente en la siguiente reacción (98 mg; 96% de rendimiento).

Ejemplo 26J

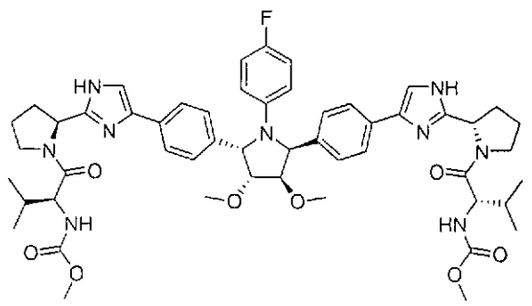
(2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-(4,4'-(1-(4-tert-butilfenil)-1H-pirrol-2,5-diil)bis(4,1-fenilen))bis(1H-imidazol-4,2-diil))bis(pirrolidin-2,1-diil))bis(3-metil-1-oxobutan-2,1-diil)dicarbamato de dimetilo

A una solución del producto del Ejemplo 26I (98 mg, 0,158 mmol) en DMF (2 ml) a temperatura ambiente se agregó ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico (61 mg, 0,347 mmol), EDAC (66 mg, 0,347 mmol) y hidrato de 1-hidroxibenzotriazol (53 mg, 0,347 mmol). Luego de 3 h, la mezcla se transfirió a un embudo de separación con acetato de etilo y agua. La fase orgánica se concentró y el residuo se purificó mediante cromatografía (1% gradiente de elución entre 0% y 4% metanol:diclorometano) para dar el material deseado como un sólido amarillo claro (70 mg; 30% de rendimiento). ^{1}HNMR

(MeOH-d4; 400 MHz): δ 7,55-7,30 (m, 6H), 7,25-6,96 (m, 8H), 6,45 (s, 2H), 5,12 (dd, J=5,43, 5,43 Hz, 2H), 4,20 (d, J=7,26 Hz, 2H), 4,02-3,90 (m, 2H), 3,85-3,80 (m, 2H), 3,64 (s, 6H), 2,36-1,93 (m, 10H), 1,31 (s, 9H), 0,97-0,86 (m, 12H). El compuesto del título mostró un valor de EC_{50} inferior a aproximadamente 0,1 nM en ensayos de replicones del VHC 1b-Con1 en presencia de FBS al 5%.

Ejemplo 27

(2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-(4,4'-((2S,3R,4R,5S)-1-(4-fluorofenil)-3,4-dimetoxipirrolidin-2,5-diil)bis(4,1-fenilen))bis(1H-imidazol-4,2-diil))bis(pirrolidin-2,1-diil))bis(3-metil-1-oxobutan-2,1-diil)dicarbamato de dimetilo



Ejemplo 27A

(2S,3R,4R,5S)-2,5-bis(4-bromofenil)-1-(4-fluorofenil)pirrolidin-3,4-diol

Una solución de 3,4-O-isopropiliden-D-mannitol (2,24 g, 10,08 mmol) en 2:1 metanol-diclorometano (45 ml) se trató con diacetato de yodobenceno (7,95 g, 24,19 mmol) seguido por agitación a temperatura ambiente por 5 h. La mezcla se concentró por evaporación por rotación y el residuo se disolvió en solución acuosa de ácido sulfúrico 0,1 M (20,6 ml) seguido por agitación a temperatura ambiente por 18 h. La mezcla se ajustó a pH 6 mediante la adición de bicarbonato de sodio sólido. La mezcla luego se trató en forma consecutiva con 4-fluoroanilina (1,96 ml, 20,16 mmol), ácido 4-bromofenilborónico (3,64 g, 18,14 mmol), y etanol absoluto (40 ml). La mezcla luego se calentó en un baño de aceite (110 °C) a reflujo por 20 h. La mezcla marrón oscuro se enfrió a temperatura ambiente y se concentró al vacío. El residuo se colocó en acetato de etilo (100 ml), se lavó con agua (50 ml), solución tribásica de fosfato de potasio 0,33M (2 x 50 ml), y salmuera (50 ml). La fase orgánica se secó sobre sulfato de sodio anhidro, se filtró, y el material filtrado se concentró mediante evaporación por rotación a un aceite rojizo-marrón oscuro. El aceite disuelto en diclorometano-hexanos, se concentró al vacío, y se secó al vacío para dar un espuma marrón oscuro. La purificación mediante cromatografía flash en gel de sílice eluyendo con un gradiente escalonado de acetato de etilo entre 10% y 15%/diclorometano dio producto puro como un sólido amarillo (1,216 g, 24%).

Ejemplo 27B

(2S,3R,4R,5S)-2,5-bis(4-bromofenil)-1-(4-fluorofenil)-3,4-dimetoxipirrolidina

Se disolvió el producto de Ejemplo 27A (237 mg, 0,467 mmol) en una mezcla de THF (3 ml) y DMF (1 ml) bajo una atmósfera de nitrógeno y se enfrió a 0 °C. Se agregó dispersión de hidruro de sodio al 60% en aceite mineral (56,1 mg, 1,402 mmol) en porciones y se agitó la mezcla a 0 °C por 15 min. Luego se agregó yodometano límpido (65 µL, 1,028 mmol), se eliminó el baño de frío, y se agitó la reacción a temperatura ambiente por 14,5 h. Se diluyó la reacción en acetato de etilo (50 ml), se lavó con solución acuosa saturada de cloruro de amonio (25 ml), agua (2 x 25 ml), y salmuera (25 ml). Se secó la fase orgánica sobre sulfato de sodio anhidro, se filtró, y se concentró el material filtrado por evaporación por rotación. El residuo amarillo se purificó mediante cromatografía flash en gel de sílice eluyendo con 30% hexanos/diclorometano para dar el compuesto del título como una espuma blanca (206 mg, 82%).

Ejemplo 27C

(2S,3R,4R,5S)-1-(4-fluorofenil)-3,4-dimetoxi-2,5-bis(4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)pirrolidina

Se cargó un recipiente purgado con nitrógeno con el producto de Ejemplo 27B (204 mg, 0,381 mmol), bis(pinacalato)diboro (242 mg, 0,953 mmol), acetato de potasio (112 mg, 1,143 mmol), y dioxano anhidro (2 ml). Se roció la mezcla con nitrógeno por 30 min, se agregó complejo dicloruro de 1,1'-bis(difenilfosfino)ferrocen-paladio (II) diclorometano (31,1 mg, 0,038 mmol), se roció la mezcla nuevamente con nitrógeno por 5 min, y se calentó en un baño de aceite a 85 °C por 6 h. La reacción se filtró al vacío a través de una cama pequeña de celite 545, los sólidos recogidos se lavaron a fondo con metanol al 5%/diclorometano, y el material filtrado se concentró al vacío, procesando el residuo con diclorometano/hexanos para dar un sólido color tostado. La purificación mediante cromatografía flash en gel de sílice eluyendo con 5% acetato de etilo/diclorometano dio el compuesto del título como un sólido color salmón (238 mg, 99%).

Ejemplo 27D

(2S,2'S)-2,2'-(4,4'-(4,4'-((2S,3R,4R,5S)-1-(4-fluorofenil)-3,4-dimetoxipirrolidin-2,5-diil)bis(4,1-fenilen))bis(1H-imidazol-4,2-diil))dipirrolidin-1-carboxilato de tert-butilo

Un tubo de microondas de 5 ml purgado con nitrógeno se cargó con el producto de Ejemplo 27C (237 mg, 0,377 mmol), el producto del Ejemplo 26D (298 mg, 0,941 mmol), y una mezcla de etanol absoluto (1,5 ml) y tolueno (1,5 ml). Se sonicó para obtener una mezcla turbia anaranjada, se agregó carbonato de sodio acuoso 1M (0,941 ml, 0,941 mmol), y se roció con nitrógeno por 20 min. Se agregó complejo dicloruro de 1,1'-bis(difenilfosfino)ferrocen-paladio (II) diclorometano (30,8 mg, 0,038 mmol), se roció la

mezcla nuevamente con nitrógeno por 5 min, se selló el tubo de reacción con un tapón alabeado de aluminio, y se calentó en un reactor de microondas con agitación a 100 °C por 1 h. Se enfrió la reacción a temperatura ambiente, se diluyó en acetato de etilo (75 ml), se lavó con agua (2 x 25 ml) y salmuera (25 ml), se secó la fase orgánica sobre sulfato de magnesio anhidro, se filtró, y se concentró el material filtrado mediante evaporación por rotación para dar un sólido amarillo oscuro. La purificación mediante cromatografía flash en gel de sílice eluyendo con 4% metanol/diclorometano dio el compuesto del título como un sólido amarillo (221 mg, 69%).

Ejemplo 27E

(S)-4,4'-(4,4'-((2S,3R,4R,5S)-1-(4-fluorofenil)-3,4-dimetoxipirrolidin-2,5-diil)bis(4,1-fenilen))bis(2-((S)-pirrolidin-2-il)-1H-imidazol)

Una solución del producto de Ejemplo 27D (147,5 mg, 0,174 mmol) en diclorometano anhidro (2 ml) bajo nitrógeno se trató con TFA (1 ml) y se agitó a temperatura ambiente por 30 min. El solvente se eliminó al vacío y se trató con 1:10 diclorometano-hexanos (3 x 50 ml) para dar un sólido amarillo pálido (193 mg). La sal de TFA sólida se disolvió en metanol anhidro (15 ml), se trató con resina Amberlite IRA-400(OH) seca (1,66 g, 10 g de resina húmeda (Supelco) lavada previamente con agua desionizada (3 x 25 ml) y metanol (3 x 25 ml), luego secada al vacío), y se agitó por 2 h a temperatura ambiente. La mezcla luego se filtró al vacío, la resina recogida se lavó a fondo con metanol, el material filtrado se concentró por evaporación por rotación, y el residuo se trató con 1:10 diclorometano-hexanos para dar el compuesto del título como un sólido amarillo claro (94 mg, 0,145 mmol, 83%).

Ejemplo 27F

(2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-(4,4'-((2S,3R,4R,5S)-1-(4-fluorofenil)-3,4-dimetoxipirrolidin-2,5-diil)bis(4,1-fenilen))bis(1H-imidazol-4,2-diil))bis(pirrolidin-2,1-diil))bis(3-metil-1-oxobutan-2,1-diil)dicarbamato de dimetilo

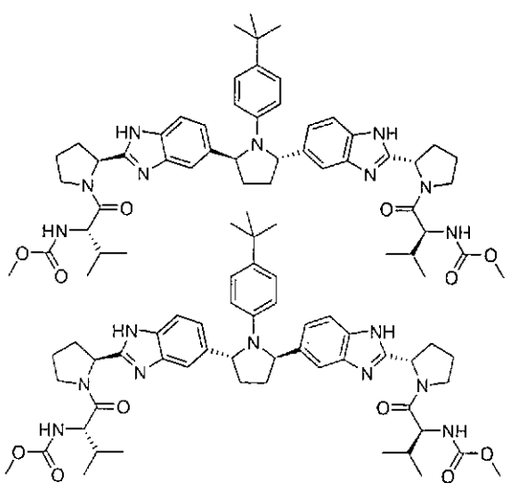
En un balón secado en horno, se disolvió el producto de Ejemplo 27E (92 mg, 0,142 mmol) en una mezcla de DMF (1 ml) y DMSO (1 ml) bajo nitrógeno y se enfrió la solución a 0 °C. Se agregó en forma consecutiva ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico (53,5 mg, 0,305 mmol), EDAC (61,1 mg, 0,312 mmol), hidrato de 1-hidroxibenzotriazol (47,8 mg, 0,312 mmol), y N-metilmorfolina (47 µL, 0,426 mmol). Se eliminó el baño de frío y se agitó a temperatura ambiente por 15 h. Se diluyó la reacción con acetato de etilo (50 ml), se lavó con solución saturada acuosa de bicarbonato de sodio (25 ml), agua (2 x 25 ml), y salmuera (25 ml). La fase orgánica se secó sobre sulfato de magnesio anhidro, se filtró, y el material filtrado se concentró por evaporación por rotación. La purificación mediante cromatografía flash en gel de sílice eluyendo con

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metanol al 5%/diclorometano dio el compuesto del título como un sólido amarillo pálido (78 mg, 56%). ^{1}H RMN (400 MHz, DMSO-d6) δ ppm 0,86 (dd, J=17,67, 6,72 Hz, 12 H), 0,97 - 1,37 (m, 3 H), 1,41 - 2,29 (m, 11 H), 3,53 (s, 6 H), 3,69 - 3,86 (m, 4 H), 4,04 (q, J=8,02 Hz, 2 H), 4,12 - 4,23 (m, 2 H), 5,07 (d, J=3,80 Hz, 2 H), 5,35 - 5,48 (m, 2 H), 6,31 (dd, J=9,16, 4,39 Hz, 2 H), 6,74 (t, J=8,89 Hz, 2 H), 7,12 - 7,71 (m, 12 H), 11,53 - 12,31 (m, 2 H); MS (ESI+) m/z 963 (M+H)+. El compuesto del título mostró un valor de EC_{50} inferior a aproximadamente 0,1 nM en ensayos de replicones del VHC 1b-Con1 en presencia de FBS al 5%.

Ejemplo 28

(2S,2'S)-1,1'-((2S,2'S)-2,2'-(5,5'-((2R,5R)-1-(4-tert-butilfenil)pirrolidin-2,5-diil)bis(1H-benzo[d]imidazol-5,2-diil))bis(pirrolidin-2,1-diil))bis(3-metil-1-oxobutan-2,1-diil)dicarbamato de dimetilo y (2S,2'S)-1,1'-((2S,2'S)-2,2'-(5,5'-((2S,5S)-1-(4-tert-butilfenil)pirrolidin-2,5-diil)bis(1H-benzo[d]imidazol-5,2-diil))bis(pirrolidin-2,1-diil))bis(3-metil-1-oxobutan-2,1-diil)dicarbamato de dimetilo



Ejemplo 28A

1,4-bis(4-cloro-3-nitrofenil)butan-1,4-diona

Se combinó cloruro de cinc (27,4g, 201 mmol), dietilamina (15,6 ml, 151 mmol) y t-butanol (14,4 ml, 151 mmol) en benceno (151 ml) a temperatura ambiente bajo una atmósfera de nitrógeno y se agitó por 2 h. Se agregó 1-(4-cloro-3-nitrofenil)etanona (30,1 g, 151 mmol) y 2-bromo-1-(4-cloro-3-nitrofenil)etanona (28 g, 101 mmol). La mezcla se agitó enérgicamente por 20 h, y el sólido producto se recogió mediante filtración y se enjuagó con benceno, agua, metanol, y diclorometano. El sólido se secó en un horno de vacío.

Ejemplo 28B

1,4-bis(4-cloro-3-nitrofenil)butan-1,4-diol

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El producto de Ejemplo 28A (5,75 g, 14,48 mmol) se disolvió en etanol (150 ml) a temperatura ambiente y se trató con borhidruro de sodio (1,21 g, 31,9 mmol) por porciones a lo largo de 5 minutos. La solución se calentó a 70 °C por 1 h y luego se enfrió a temperatura ambiente, se detuvo con agua, se extrajo con acetato de etilo, se secó sobre sulfato de sodio, y se concentró hasta secar para dar 4,81g (83%) de un sólido blanco opaco.

Ejemplo 28C

dimetansulfonato de 1,4-bis(4-cloro-3-nitrofenil)butan-1,4-diilo

El producto de Ejemplo 28B (4,81 g, 11,99 mmol) y trietilamina (5,85 ml, 42,0 mmol) se disolvieron en diclorometano (80 ml) a temperatura ambiente y se trató con cloruro de metansulfonilo (2,34 ml, 30,0 mmol) por goteo a lo largo de 10 minutos. La solución resultante se agitó por 2 h luego se concentró hasta secar y se usó directamente en el siguiente paso.

Ejemplo 28D

1-(4-tert-butilfenil)-2,5-bis(4-cloro-3-nitrofenil)pirrolidina

Se formó una lechada con producto del Ejemplo 28C (6,6 g, 11,84 mmol) en DMF (30 ml) y se agregó 4-t-butilanilina (18,7 ml, 118 mmol) y la solución se calentó a 55 °C por 2 h luego se enfrió y se vertió en agua y se extrajo con diclorometano. Los orgánicos se concentraron y el residuo se purificó mediante cromatografía sobre columna de 120 g de gel de sílice, eluyendo con 0-5%acetato de etilo/hexanos para dar 4,41g (72%) de un aceite espeso.

Ejemplo 28E

4,4'-(1-(4-tert-butilfenil)pirrolidin-2,5-diil)bis(N-(4-metoxibencil)-2-nitroanilina)

El producto del Ejemplo 28D (4,41 g, 8,57 mmol) se combinó, puro, con p-metoxi bencilamina (8,93 ml, 68,6 mmol) y se calentó a 145 °C por 1 h. La mezcla se diluyó con diclorometano y se filtró. El material filtrado se lavó con HCl 0,5 M, luego solución de $NaHCO_3$, luego salmuera, se concentró y se purificó mediante cromatografía sobre gel de sílice con una columna de 80g, eluyendo con acetato de etilo al 0-50%/hexanos para dar 4,13g (67%) de un sólido espumoso anaranjado.

Ejemplo 28F

4,4'-(1-(4-tert-butilfenil)pirrolidin-2,5-diil)bis(N1-(4-metoxibencil)bencen-1,2-diamina)

El producto del Ejemplo 28E (2 g, 2,79 mmol) se disolvió en una mezcla de THF (15 ml), etanol (15 ml), y acetato de etilo (5 ml) luego se agregó óxido de platino (0,254 g, 1,12 mmol) se agregó mediante una lechada en THF. El recipiente se evacuó y se purgó con nitrógeno dos veces, luego se evacuó y se abrió a un globo de hidrógeno. La mezcla se agitó a temperatura ambiente por 20 h, luego se filtró a través de celite, se concentró, y

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se purificó mediante cromatografía sobre gel de sílice con una columna de 80g, eluyendo con acetato de etilo al 0-40%/diclorometano para dar el primer pico del producto trans 0,508 g (28%).

Ejemplo 28G

(2S,2'S)-2,2'-(5,5'-(1-(4-tert-butilfenil)pirrolidin-2,5-diil)bis(2-(4-metoxibencilamino)-5,1-fenilen)bis(azandiil)bis(oxometilen))dipirrolidin-1-carboxilato de tert-butilo

El producto del Ejemplo 28F (0,422 g, 0,643 mmol) y diisopropiletilamina (0,674 ml, 3,86 mmol) se disolvieron en DMSO (6 ml) a temperatura ambiente y se trató con S-Boc-prolina (0,319 g, 1,48 mmol) seguido por HATU (0,514 g, 1,35 mmol). La solución se agitó por 1 h a temperatura ambiente luego se diluyó con agua y el producto sólido se retiró por filtración y se purificó mediante cromatografía sobre gel de sílice con una columna de 40g, eluyendo con acetato de etilo al 0-50% en diclorometano para dar 0,565 g (84%) de un sólido amarillo.

Ejemplo 28H

(2S,2'S)-2,2'-(5,5'-(1-(4-tert-butilfenil)pirrolidin-2,5-diil)bis(2-amino-5,1-fenilen)bis(azandiil)bis(oxometilen))dipirrolidin-1-carboxilato de tert-butilo

El producto del Ejemplo 28G (0,565 g, 0,538 mmol) se disolvió en diclorometano (5 ml) y agua (0,25 ml) a temperatura ambiente y se trató con DDQ (0,244 g, 1,076 mmol) por porciones a lo largo de 2 minutos. La mezcla se diluyó con solución de bicarbonato de sodio, se extrajo con diclorometano, se concentró y se purificó mediante cromatografía sobre gel de sílice con una columna de 40g, eluyendo con metanol al 0-15%/diclorometano para dar 0,355 g (81%) de un sólido amarillo.

Ejemplo 28I

(2S,2'S)-2,2'-(5,5'-(1-(4-tert-butilfenil)pirrolidin-2,5-diil)bis(1H-benzo[d]imidazol-5,2-diil))dipirrolidin-1-carboxilato de tert-butilo

El producto del Ejemplo 28H se disolvió en ácido acético puro (3 ml) y se calentó a 72 °C por 2 h. La solución se concentró y luego se vertió en agua y se ajustó en pH a ~7-8 con bicarbonato de sodio. El producto se extrajo con diclorometano, se concentró y se purificó mediante cromatografía sobre gel de sílice con una columna de 40g, eluyendo con 0-5%metanol/diclorometano para dar 0,185 g (55%) de un sólido amarillo claro.

Ejemplo 28J

(S)-5,5'-(1-(4-tert-butilfenil)pirrolidin-2,5-diil)bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol)

El producto del Ejemplo 28I (0,204 g, 0,264 mmol) se disolvió en THF (2 ml) a temperatura ambiente y se trató con ácido clorhídrico 4 M en dioxano (2 ml). La mezcla se concentró hasta secar y se usó directamente en el siguiente paso.

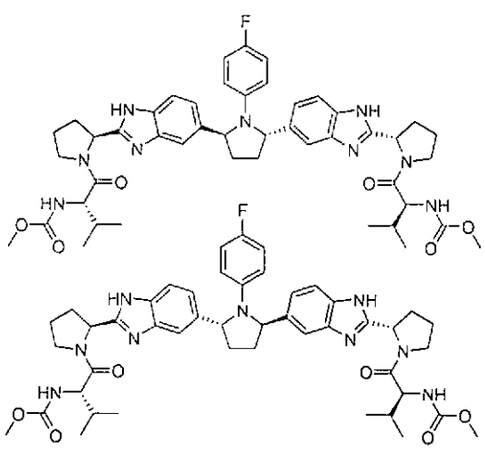
Ejemplo 28K

(2S,2'S)-1,1'-((2S,2'S)-2,2'-(5,5'-((2R,5R)-1-(4-tert-butilfenil)pirrolidin-2,5-diil)bis(1H-benzo[d]imidazol-5,2-diil))bis(pirrolidin-2,1-diil))bis(3-metil-1-oxobutan-2,1-diil)dicarbamato de dimetilo y (2S,2'S)-1,1'-((2S,2'S)-2,2'-(5,5'-((2S,5S)-1-(4-tert-butilfenil)pirrolidin-2,5-diil)bis(1H-benzo[d]imidazol-5,2-diil))bis(pirrolidin-2,1-diil))bis(3-metil-1-oxobutan-2,1-diil)dicarbamato de dimetilo

El producto del Ejemplo 28J (0,150 g, 0,261 mmol) y diisopropiletilamina (0,365 ml, 2,09 mmol) se disolvieron en DMSO (3 ml) a temperatura ambiente y se trató con ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico (0,105 g, 0,601 mmol) seguido por HATU (0,204 g, 0,536 mmol). La solución se agitó por 1 h a temperatura ambiente luego se diluyó con agua y el producto sólido se retiró por filtración y se purificó mediante cromatografía sobre gel de sílice con una columna de 12g, eluyendo con 0-8% metanol en diclorometano para dar 0,143 g (60%) de un sólido amarillo. ^{1}H RMN (400 MHz, DMSO-D6) δ ppm 0,75 - 0,92 (m, 12 H) 1,07 (s, 9 H) 1,64 - 1,76 (m, 2 H) 1,85 - 2,04 (m, 6 H) 2,12 - 2,26 (m, 4 H) 2,43 (dd, J=7,75, 4,07 Hz, 2 H) 3,53 (s, 6 H) 3,76 - 3,87 (m, 4 H) 4,04 (dd, J=11,49, 6,51 Hz, 2 H) 5,12 (t, J=7,59 Hz, 2 H) 5,35 (d, J=3,25 Hz, 2 H) 6,25 (d, J=8,46 Hz, 2 H) 6,85 - 6,96 (m, 2 H) 7,07 (t, J=7,97 Hz, 2 H) 7,19 (s, 1 H) 7,28 (d, J=8,35 Hz, 3 H) 7,38 (dd, J=8,19, 1,90 Hz, 1 H) 7,46 (d, J=8,13 Hz, 1 H) 11,97 - 12,09 (m, 2 H). El compuesto del título mostró un valor de EC_{50} inferior a aproximadamente 0,1 nM en ensayos de replicones del VHC 1b-Con1 en presencia de FBS al 5%.

Ejemplo 29

(2S,2'S)-1,1'-((2S,2'S)-2,2'-(5,5'-((2R,5R)-1-(4-fluorofenil)pirrolidin-2,5-diil)bis(1H-benzo[d]imidazol-5,2-diil))bis(pirrolidin-2,1-diil))bis(3-metil-1-oxobutan-2,1-diil)dicarbamato de dimetilo y (2S,2'S)-1,1'-((2S,2'S)-2,2'-(5,5'-((2S,5S)-1-(4-fluorofenil)pirrolidin-2,5-diil)bis(1H-benzo[d]imidazol-5,2-diil))bis(pirrolidin-2,1-diil))bis(3-metil-1-oxobutan-2,1-diil)dicarbamato de dimetilo



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Ejemplo 29A

2,5-bis(4-cloro-3-nitrofenil)-1-(4-fluorofenil)pirrolidina

El producto del Ejemplo 28C (2,9 g, 5,2 mmol) y 4-fluoroanilina (5,0 ml, 52,0 mmol) se combinaron, puros, y se calentó a 45 °C por 20 h luego se enfrió y se vertió en agua y se extrajo con diclorometano. Los orgánicos se concentraron, el residuo se purificó mediante cromatografía sobre gel de sílice con una columna de 120g, eluyendo con 0-5% acetato de etilo/hexanos para dar 0,59g (24%) de un aceite espeso.

Ejemplo 29B

4,4'-(1-(4-fluorofenil)pirrolidin-2,5-diil)bis(N-(4-metoxibencil)-2-nitroanilina)

El producto del Ejemplo 29A (0,88 g, 1,86 mmol) se combinó con 4-metoxi bencilamina (3,64 ml, 28,0 mmol) y se calentó a 145 °C por 1 h en un reactor de microondas. La mezcla se diluyó con diclorometano y se filtró. El material filtrado se concentró y se purificó mediante cromatografía sobre gel de sílice con una columna de 330g, eluyendo con acetato de etilo al 0-60%/hexanos para dar 0,79g (62%) de un sólido espumoso anaranjado.

Ejemplo 29C

4,4'-(1-(4-fluorofenil)pirrolidin-2,5-diil)bis(2-nitroanilina)

El producto del Ejemplo 29B (0,78 g, 1,15 mmol) se disolvió en diclorometano (10 ml) a temperatura ambiente y se trató con TFA (1,8 ml, 23,0 mmol) por 3 h. El residuo se concentró y se particionó entre diclorometano y solución de bicarbonato de sodio. Los orgánicos se concentraron y se purificó mediante cromatografía sobre gel de sílice con una columna de 40g, eluyendo con diclorometano para dar 0,218 g (43%) de el isómero trans.

Ejemplo 29D

4,4'-(1-(4-fluorofenil)pirrolidin-2,5-diil)dibencen-1,2-diamina

El producto del Ejemplo 29C (0,218 g, 0,50 mmol) se disolvió en DMF (5 ml) luego se agregó óxido de platino (0,226 g, 0,99 mmol) mediante una lechada en THF. El recipiente se evacuó y se purgó con nitrógeno dos veces, luego se evacuó y se abrió a un globo de hidrógeno. La mezcla se agitó a temperatura ambiente por 20 h. La solución se colocó en el siguiente paso sin purificación.

Ejemplo 29E

(2S,2'S)-2,2'-(5,5'-(1-(4-fluorofenil)pirrolidin-2,5-diil)bis(2-amino-5,1-fenilen))bis(azandiil)bis(oxometilen)dipirrolidin-1-carboxilato de tert-butilo

La solución cruda del producto del Ejemplo 29D en DMF se trató con diisopropiletilamina (0,296 ml, 1,70 mmol) y S-Boc-prolina (0,192 g, 0,89 mmol) seguido por HATU (0,322 g, 0,85 mmol). La solución se agitó por 1,5 h a temperatura ambiente luego se diluyó con

agua y el producto sólido se retiró por filtración y se purificó mediante cromatografía sobre gel de sílice con una columna de 12g, eluyendo con 0-3% metanol en diclorometano para dar 0,235 g (72%) de un sólido amarillo.

Ejemplo 29F

(2S,2'S)-2,2'-(5,5'-(1-(4-fluorofenil)pirrolidin-2,5-diil)bis(1H-benzo[d]imidazol-5,2-diil))dipirrolidin-1-carboxilato de tert-butilo

El producto del Ejemplo 29E se disolvió en ácido acético puro (2 ml) y se calentó a 60 °C por 1 h. La solución se concentró luego se vertió en agua y se ajustó en pH a ~7-8 con bicarbonato de sodio. El producto se extrajo con diclorometano, se concentró y se purificó mediante cromatografía sobre gel de sílice con una columna de 12g, eluyendo con 0-20% acetato de etilo en diclorometano para dar 0,124 g (55%) de un sólido amarillo claro.

Ejemplo 29G

(S)-5,5'-(1-(4-fluorofenil)pirrolidin-2,5-diil)bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol)

El producto del Ejemplo 29F (0,120 g, 0,163 mmol) se disolvió en diclorometano (2 ml) a temperatura ambiente y se trató con TFA (1 ml). La mezcla se concentró hasta secar, se disolvió en alcohol isopropilico al 25%/diclorometano y se lavó con solución de bicarbonato de sodio. Los sólidos resultantes se retiraron por filtración y se secó y los orgánicos se concentraron y se secó para dar el compuesto del título (0,062 g 72% de rendimiento) de un sólido blanco opaco.

Ejemplo 29H

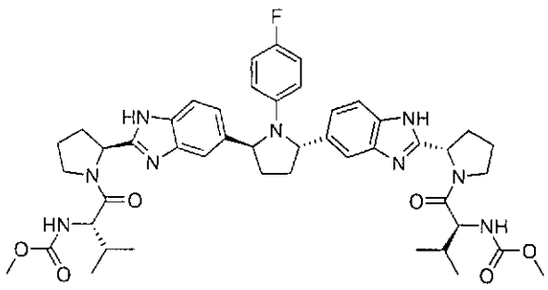
(2S,2'S)-1,1'-((2S,2'S)-2,2'-(5,5'-((2R,5R)-1-(4-fluorofenil)pirrolidin-2,5-diil)bis(1H-benzo[d]imidazol-5,2-diil))bis(pirrolidin-2,1-diil))bis(3-metil-1-oxobutan-2,1-diil)dicarbamato de dimetilo y (2S,2'S)-1,1'-((2S,2'S)-2,2'-(5,5'-((2S,5S)-1-(4-fluorofenil)pirrolidin-2,5-diil)bis(1H-benzo[d]imidazol-5,2-diil))bis(pirrolidin-2,1-diil))bis(3-metil-1-oxobutan-2,1-diil)dicarbamato de dimetilo

El producto del Ejemplo 29G (0,062 g, 0,116 mmol) y diisopropiletilamina (0,101 ml, 0,58 mmol) se disolvieron en DMSO (2 ml) a temperatura ambiente y se trató con ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico (0,051 g, 0,289 mmol) seguido por HATU (0,092 g, 0,243 mmol). La solución se agitó por 1 h a temperatura ambiente luego se diluyó con agua y el producto sólido se retiró por filtración y se purificó mediante cromatografía sobre gel de sílice con una columna de 12g, eluyendo con 0-7% metanol en diclorometano para dar 0,021 g (21%) de un sólido amarillo. ^{1}H RMN (400 MHz, DMSO-D6) δ ppm 0,78 - 0,90 (m, 12 H) 1,70 (s, 2 H) 1,87 - 2,03 (m, 6 H) 2,13 - 2,26 (m, 4 H) 2,54 - 2,62 (m, 2 H) 3,54 (s, 6 H) 3,82 (s, 4 H) 4,03 - 4,11 (m, 2 H) 5,09 - 5,18 (m, 2 H) 5,32 - 5,42 (m, 2 H) 6,28 (dd, J=8,89, 4,34 Hz, 2 H) 6,70 - 6,80 (m, 2 H) 7,01 - 7,10 (m, 2 H) 7,20 (d, J=9,32 Hz, 1 H) 7,27 - 7,34 (m, 3 H) 7,38 (dd, J=8,13, 2,71 Hz, 1 H) 7,45 (d, J=8,02 Hz, 1 H) 12,03 (s, 2

H). El compuesto del título mostró un valor de EC_{50} inferior a aproximadamente 0,1 nM en ensayos de replicones del VHC 1b-Con1 en presencia de FBS al 5%.

Ejemplo 30

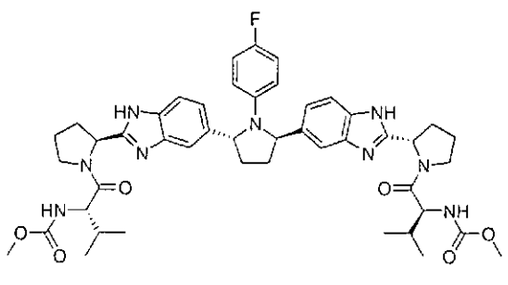
(2S,2'S)-1,1'-((2S,2'S)-2,2'-(5,5'-((2S,5S)-1-(4-fluorofenil)pirrolidin-2,5-diil)bis(1H-benzo[d]imidazol-5,2-diil))bis(pirrolidin-2,1-diil))bis(3-metil-1-oxobutan-2,1-diil)dicarbamato de dimetilo



El producto del Ejemplo 29H se purificó mediante cromatografía quiral en una columna Chiralpak IA eluyendo con una mezcla de hexano/EtOH/MeOH/1,2 Dicloroetano/dietilamina (25/25/25/25/0,1). ^{1}H RMN (400 MHz, DMSO-D6) δ ppm 0,75 - 0,89 (m, 12 H) 1,64 - 1,73 (m, 2 H) 1,85 - 2,03 (m, 6 H) 2,12 - 2,24 (m, 4 H) 2,81 - 2,90 (m, 2 H) 3,52 (s, 6 H) 3,76 - 3,87 (m, 4 H) 4,01 - 4,09 (m, 2 H) 5,08 - 5,16 (m, 2 H) 5,34 (q, J=6,65 Hz, 2 H) 6,26 (dd, J=9,05, 4,50 Hz, 2 H) 6,67 - 6,78 (m, 2 H) 7,03 (t, J=8,02 Hz, 2 H) 7,20 (s, 1 H) 7,24 - 7,32 (m, 3 H) 7,36 (d, J=8,13 Hz, 1 H) 7,44 (d, J=7,92 Hz, 1 H) 12,01 - 12,07 (m, 2 H). El compuesto del título mostró un valor de EC_{50} inferior a aproximadamente 0,1 nM en ensayos de replicones del VHC 1b-Con1 en presencia de FBS al 5%.

Ejemplo 31

(2S,2'S)-1,1'-((2S,2'S)-2,2'-(5,5'-((2R,5R)-1-(4-fluorofenil)pirrolidin-2,5-diil)bis(1H-benzo[d]imidazol-5,2-diil))bis(pirrolidin-2,1-diil))bis(3-metil-1-oxobutan-2,1-diil)dicarbamato de dimetilo

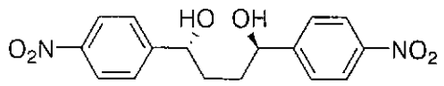


El producto del Ejemplo 29H se purificó mediante cromatografía quiral en una columna Chiralpak IA eluyendo con una mezcla de hexano/EtOH/MeOH/1,2 Dicloroetano/dietilamina (25/25/25/25/0,1). ^{1}H RMN (400 MHz, DMSO-D6) δ ppm 0,74 -

0,93 (m, 12 H) 1,69 (t, J=9,65 Hz, 2 H) 1,82 - 2,06 (m, 6 H) 2,09 - 2,26 (m, 4 H) 3,04 - 3,23 (m, 2 H) 3,52 (s, 6 H) 3,73 - 3,90 (m, 4 H) 4,06 (t, J=8,46 Hz, 2 H) 5,05 - 5,21 (m, 2 H) 5,29 - 5,44 (m, 2 H) 6,21 - 6,32 (m, 2 H) 6,67 - 6,86 (m, 2 H) 7,05 (t, J=8,78 Hz, 2 H) 7,18 (s, 1 H) 7,23 - 7,33 (m, 3 H) 7,37 (d, J=8,13 Hz, 1 H) 7,45 (d, J=8,02 Hz, 1 H) 12,04 (d, J=14,96 Hz, 2 H). El compuesto del título mostró un valor de EC_{50} inferior a aproximadamente 0,1 nM en ensayos de replicones del VHC 1b-Con1 en presencia de FBS al 5%.

Ejemplo 32

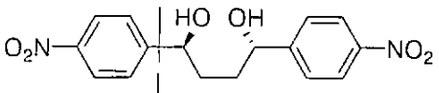
(1R,4R)-1,4-bis(4-nitrofenil)butan-1,4-diol



A (S)-(-)-α,α-difenil-2-pirrolidinmetanol (2,71 g, 10,70 mmol) se agregó THF (80 ml) a 23 °C. La suspensión muy fina se trató con borato de trimetilo (1,44 g, 13,86 mmol) durante 30 segundos, y la solución resultante se mezcló a 23 °C por 1 h. La solución se enfrió a 16-19 °C, y se agregó N,N-dietilanilina-borano (21,45 g, 132 mmol) por goteo mediante una jeringa a lo largo de 3-5 min (precaución: evolución enérgica de H_2), manteniendo la temperatura interna a 16-19 °C. Luego de 15 min, la evolución de H_2 se detuvo. A un recipiente separado se agregó el producto del Ejemplo 1A (22,04 g, 95 p%, 63,8 mmol), seguido por THF (80 ml), para formar una lechada anaranjada. Luego de enfriar la lechada a 11 °C, la solución de borano se transfirió mediante cánulos a la lechada de diona a lo largo de 3-5 min. Durante este periodo, la temperatura interna de la lechada se elevó a 16 °C. Luego de completarse la adición, la reacción se mantuvo a 20-27 °C por 2,5 h adicionales. Luego de completarse la reacción, la mezcla se enfrió a 5 °C y se agregó metanol (16,7 g, 521 mmol) por goteo a lo largo de 5-10 min, manteniendo una temperatura interna <20 °C (nota: evolución enérgica de H_2). Luego de detenerse la reacción exotérmica (aproximadamente 10 min), la temperatura se ajustó a 23 °C, y la reacción se mezcló hasta que los sólidos se disolvieron completamente. Se agregó acetato de etilo (300 ml) y HCl 1 M (120 ml), y las fases se particionaron. La fase orgánica luego se lavó en forma sucesiva con HCl 1 M (2 x 120 ml), H_2O (65 ml), y NaCl acuoso al 10% (65 ml). Los orgánicos se secaron sobre $MgSO_4$, se filtró, y se concentró al vacío. La cristalización del producto ocurrió durante la concentración. La lechada se calentó a 50 °C, y se agregó heptano (250 ml) durante 15 min. La lechada luego se dejó mezclar a 23 °C por 30 min y se filtró. La torta húmeda se lavó con 3:1 heptano:acetato de etilo (75 ml), y los sólidos cristalinos anaranjados a 45 °C por 24 h para dar el compuesto del título (15,35 g, 99,3% ee, 61% de rendimiento), el cual estaba contaminado con 11% del meso isómero (vs. dl isómero).

Ejemplo 33

(1S,4S)-1,4-bis(4-nitrofenil)butan-1,4-diol



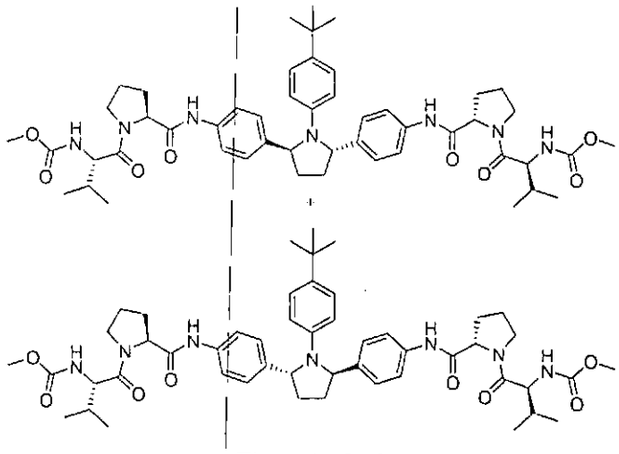
El producto del Ejemplo 1A (30 g, 95 p%, 91,4 mmol) se sometió a las condiciones descritas en Ejemplo 32, utilizando (R)-(-)-[illegible]-difenil-2-pirrolidinmetanol en lugar de (S)-(-)-[illegible]-difenil-2-pirrolidinmetanol, para dar el compuesto del título (20,14 g, >99,55 ee, 61% de rendimiento) el cual estaba contaminado con 9,7% del meso isómero (vs. dl isómero).

Ejemplo 34

(2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-((2S,5S)-1-(4-tert-butilfenil)pirrolidin-2,5-diil)bis(4,1-fenilen))bis(azandiil)bis(oxometilen)bis(pirrolidin-2,1-diil))bis(3-metil-1-oxobutan-2,1-diil)dicarbamato de dimetilo

y

(2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-((2R,5R)-1-(4-tert-butilfenil)pirrolidin-2,5-diil)bis(4,1-fenilen))bis(azandiil)bis(oxometilen)bis(pirrolidin-2,1-diil))bis(3-metil-1-oxobutan-2,1-diil)dicarbamato de dimetilo



Ejemplo 34A

1-(4-*tert*-butilfenil)-2,5-bis(4-nitrofenil)pirrolidina

El producto del Ejemplo 1C (3,67 g, 7,51 mmol) y 4-*tert*-butilanilina (11,86 ml, 75 mmol) en DMF (40 ml) se agitó bajo nitrógeno a 50 °C por 4 h. La mezcla resultante se diluyó en acetato de etilo, se trató con HCl 1M, se agitó por 10 minutos y se filtró para eliminar los sólidos. El material filtrado de la capa orgánica se lavó dos veces con salmuera, se secó con sulfato de sodio, se filtró y se evaporó. El residuo se purificó mediante cromatografía sobre gel de sílice eluyendo con acetato de etilo en hexano (5% a 30%) para dar un sólido. El sólido se trituró en un volumen mínimo de 1:9 acetato de etilo/hexano para dar un sólido amarillo claro como una mezcla de isómeros cis y trans

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(1,21 g, 36%).

Ejemplo 34B

4,4'-((2S,5S)-1-(4-*tert*-butilfenil)pirrolidin-2,5-diil)dianilina y 4,4'-((2R,5R)-1-(4-*tert*-butilfenil)pirrolidin-2,5-diil)dianilina

A una solución del producto del Ejemplo 34A (1,1 g, 2,47 mmol) en etanol (20 ml) y THF (20 ml) se agregó PtO_2 (0,22 g, 0,97 mmol) en una botella de presión de 50 ml y se agitó bajo 30 psi de hidrógeno a temperatura ambiente por 1 h. La mezcla se filtró a través de una membrana de nylon y se evaporó. El residuo se purificó mediante cromatografía sobre gel de sílice eluyendo con acetato de etilo en hexano (20% a 60%). El compuesto del título eluyó como el primero de 2 estereoisómeros (isómero trans, 0,51 g, 54%).

Ejemplo 34C

(2S,2'S)-2,2'-(4,4'-((2S,5S)-1-(4-*tert*-butilfenil)pirrolidin-2,5-diil)bis(4,1-fenilen))bis(azandiil)bis(oxometilen)dipirrolidin-1-carboxilato de tert-butilo y (2S,2'S)-2,2'-(4,4'-((2R,5R)-1-(4-*tert*-butilfenil)pirrolidin-2,5-diil)bis(4,1-fenilen))bis(azandiil)bis(oxometilen)dipirrolidin-1-carboxilato de tert-Butilo

A una mezcla del producto del Ejemplo 34B (250 mg, 0,648 mmol), ácido (S)-1-(tert-butoxicarbonil)pirrolidin-2-carboxílico (307 mg, 1,427 mmol) y HATU (542 mg, 1,427 mmol) en DMSO (10 ml) se agregó base de Hunig (0,453 ml, 2,59 mmol). La mezcla de la reacción se agitó a temperatura ambiente por 1 h. La mezcla se particionó con acetato de etilo y agua. La capa orgánica se lavó con salmuera, se secó con sulfato de sodio, se filtró y se evaporó. El residuo se purificó mediante cromatografía sobre gel de sílice eluyendo con acetato de etilo en hexano (10% a 50%) para dar el compuesto del título (500 mg, 99%).

Ejemplo 34D

(2S,2'S)-N,N'-(4,4'-((2S,5S)-1-(4-*tert*-butilfenil)pirrolidin-2,5-diil)bis(4,1-fenilen))dipirrolidin-2-carboxamida y (2S,2'S)-N,N'-(4,4'-((2R,5R)-1-(4-*tert*-butilfenil)pirrolidin-2,5-diil)bis(4,1-fenilen))dipirrolidin-2-carboxamida

Al producto del Ejemplo 34C (498 mg, 0,638 mmol) en diclorometano (4 ml) se agregó TFA (6 ml). La mezcla de la reacción se agitó a temperatura ambiente por 1 h y se concentró al vacío. El residuo se particionó entre 3:1 $CHCl_3$:alcohol isopropílico y $NaHCO_3$ acuoso saturado. La capa acuosa se extrajo con 3:1 $CHCl_3$:alcohol isopropílico nuevamente. Las capas orgánicas combinadas se secaron sobre Na_2SO_4, se filtró y se concentró para dar el compuesto del título (345 mg, 93%).

Ejemplo 34E

(2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-((2S,5S)-1-(4-tert-butilfenil)pirrolidin-2,5-diil)bis(4,1-fenilen))bis(azandiil)bis(oxometilen)bis(pirrolidin-2,1-diil))bis(3-metil-1-oxobutan-2,1-

diil)dicarbamato de dimetilo

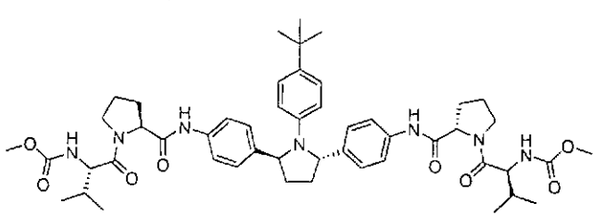
y

(2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-((2R,5R)-1-(4-tert-butilfenil)pirrolidin-2,5-diil)bis(4,1-fenilen))bis(azandiil)bis(oxometilen)bis(pirrolidin-2,1-diil))bis(3-metil-1-oxobutan-2,1-diil)dicarbamato de dimetilo

El producto del Ejemplo 34D (29,0 mg, 0,050 mmol), ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico (19,27 mg, 0,110 mmol), EDAC (21,09 mg, 0,110 mmol), HOBT (16,85 mg, 0,110 mmol) y N-metilmorfolina (0,027 ml, 0,250 mmol) se combinaron en DMF (2 ml). La mezcla de la reacción se agitó a temperatura ambiente por 3 h. La mezcla se particionó con acetato de etilo y agua. La capa orgánica se lavó con salmuera dos veces, se secó con sulfato de sodio, se filtró y se evaporó. El residuo se purificó mediante cromatografía sobre gel de sílice eluyendo con acetato de etilo en hexano (50% a 80%) para dar un sólido. El sólido se trituró con acetato de etilo/hexano para dar el compuesto del título (13 mg, 29%). ^{1}H RMN (400 MHz, DMSO-D6) δ ppm 0,85 - 0,95 (m, 12 H) 1,11 (s, 9 H) 1,59 - 1,65 (m, 2 H) 1,79 - 2,04 (m, 8 H) 2,10 - 2,18 (m, 2 H) 2,41-2,46 (m, 2H) 3,52 (s, 6 H) 3,57 - 3,67 (m, 2 H) 3,76 - 3,86 (m, 2 H) 4,00 (t, J=7,56 Hz, 2 H) 4,39 - 4,46 (m, 2 H) 5,15 (d, J=7,00 Hz, 2 H) 6,17 (d, J=7,70 Hz, 2 H) 6,94 (d, J=8,78 Hz, 2 H) 7,13 (d, J=7,37 Hz, 4 H) 7,30 (d, J=8,20 Hz, 2 H) 7,50 (d, J=8,24 Hz, 4 H) 9,98 (s, 2 H); (ESI+) m/z 895 (M+H)+. El compuesto del título mostró un valor de EC_{50} inferior a aproximadamente 0,1 nM en ensayos de replicones del VHC 1b-Con1 en presencia de FBS al 5%.

Ejemplo 35

(2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-((2S,5S)-1-(4-tert-butilfenil)pirrolidin-2,5-diil)bis(4,1-fenilen))bis(azandiil)bis(oxometilen)bis(pirrolidin-2,1-diil))bis(3-metil-1-oxobutan-2,1-diil)dicarbamato de dimetilo



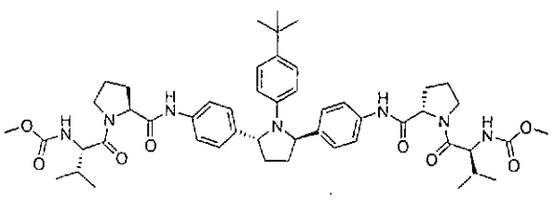
El producto del Ejemplo 34E se purificó mediante cromatografía quiral en una columna semipreparativa Chiralpak AD-H eluyendo con una mezcla 2:1 de hexano:(2:1 alcohol isopropílico:EtOH). El compuesto del título fue el primero de los 2 diastereómeros en eluir. ^{1}H RMN (400 MHz, DMSO-D6) δ ppm 0,88 (d, J=6,61 Hz, 6 H) 0,93 (d, J=6,72 Hz, 6 H) 1,11 (s, 9 H) 1,63 (d, J=5,42 Hz, 2 H) 1,80 - 2,04 (m, 8 H) 2,09 - 2,19 (m, 2 H) 2,44 - 2,47 (m, 2 H) 3,52 (s, 6 H) 3,59 - 3,66 (m, 2 H) 3,77 - 3,84 (m, 2 H) 4,02 (t, J=8,40 Hz, 2 H) 4,42 (dd, J=7,86, 4,83 Hz, 2 H) 5,14 (d, J=6,18 Hz, 2 H) 6,17 (d, J=8,67 Hz, 2 H)

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6,94 (d, J=8,78 Hz, 2 H) 7,13 (d, J=8,46 Hz, 4 H) 7,31 (d, J=8,35 Hz, 2 H) 7,50 (d, J=8,35 Hz, 4 H) 9,98 (s, 2 H). El compuesto del título mostró un valor de EC_{50} inferior a aproximadamente 0,1 nM en ensayos de replicones del VHC 1b-Con1 en presencia de FBS al 5%.

Ejemplo 36

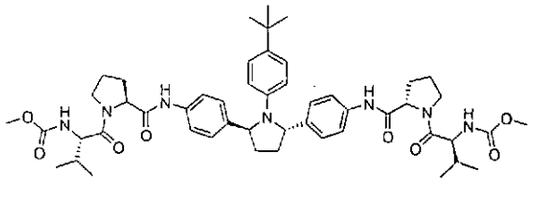
(2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-((2R,5R)-1-(4-tert-butilfenil)pirrolidin-2,5-diil)bis(4,1-fenilen))bis(azandiil)bis(oxometilen)bis(pirrolidin-2,1-diil))bis(3-metil-1-oxobutan-2,1-diil)dicarbamato de dimetilo



El producto del Ejemplo 34E se purificó mediante cromatografía quiral en una columna semipreparativa Chiralpak AD-H eluyendo con una mezcla 2:1 de hexano:(2:1 alcohol isopropílico:EtOH). El compuesto del título fue el segundo de 2 diastereómeros en eluir. ^{1}H RMN (400 MHz, DMSO-D6) δ ppm 0,87 (d, J=6,51 Hz, 6 H) 0,92 (d, J=6,72 Hz, 6 H) 1,11 (s, 9 H) 1,63 (d, J=5,53 Hz, 2 H) 1,82 - 2,04 (m, 8 H) 2,09-2,18 (m, 2 H) 2,41 - 2,47 (m, 2 H) 3,52 (s, 6 H) 3,58 - 3,67 (m, 2 H) 3,75 - 3,84 (m, 2 H) 4,02 (t, J=7,26 Hz, 2 H) 4,43 (dd, J=7,92, 4,88 Hz, 2 H) 5,14 (d, J=6,18 Hz, 2 H) 6,17 (d, J=8,78 Hz, 2 H) 6,94 (d, J=8,67 Hz, 2 H) 7,12 (d, J=8,46 Hz, 4 H) 7,31 (d, J=8,35 Hz, 2 H) 7,49 (d, J=8,46 Hz, 4 H) 9,98 (s, 2 H). El compuesto del título mostró un valor de EC_{50} inferior a aproximadamente 0,1 nM en ensayos de replicones del VHC 1b-Con1 en presencia de FBS al 5%.

Ejemplo 37

(2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-((2S,5S)-1-(4-tert-butilfenil)pirrolidin-2,5-diil)bis(4,1-fenilen))bis(azandiil)bis(oxometilen)bis(pirrolidin-2,1-diil))bis(3-metil-1-oxobutan-2,1-diil)dicarbamato de dimetilo



Ejemplo 37A

2-(metoxicarbonilamino)-3-metilbutanoato de (S)-2,5-dioxopirrolidin-1-ilo

A una mezcla de ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico (19,66 g, 112 mmol) y N-hidroxisuccinimida (13,29g, 116 mmol) se agregó acetato de etilo (250 ml), y la mezcla se enfrió a 0-5 °C. Se agregó diisopropilcarbodiimida (13,88 g, 110 mmol) y la

mezcla de la reacción se agitó a 0-5 °C por aproximadamente 1 hora. La mezcla de la reacción se calentó a temperatura ambiente. Los sólidos (subproducto diisopropilurea) se filtraron y se enjuagó con acetato de etilo. El material filtrado se concentró al vacío para dar un aceite. Se agregó alcohol isopropílico (200 ml) al aceite y la mezcla se calentó a aproximadamente 50 °C para obtener una solución homogénea. Luego de enfriar, se formaron sólidos cristalinos. Los sólidos se filtraron y se lavó con alcohol isopropílico (3 x 20 ml) y se secó para dar el compuesto del título como un sólido blanco (23,2 g, 77% de rendimiento).

Ejemplo 37B

ácido (S)-1-((S)-2-(metoxicarbonilamino)-3-metilbutanoil)pirrolidin-2-carboxílico

A una mezcla de L-prolina (4,44g, 38,6 mmol), agua (20 ml), acetonitrilo (20 ml) y DIEA (9,5 g, 73,5 mmol) se agregó una solución del producto del Ejemplo 37A (10g, 36,7 mmol) en acetonitrilo (20 ml) a lo largo de 10 minutos. La mezcla de la reacción se agitó durante la noche a temperatura ambiente. La solución se concentró bajo vacío para eliminar el acetonitrilo. A la solución en agua traslúcida resultante se agregó HCl 6N (9 ml) hasta pH ~ 2 .La solución se transfirió a un embudo de separación y se agregó NaCl al 25% (10 ml) y la mezcla se extrajo con acetato de etilo (75 ml), y luego nuevamente con acetato de etilo (6 x 20 ml), y los extractos combinados se lavaron con NaCl al 25% (2 x 10ml). El solvente se evaporó para dar un aceite espeso. Se agregó heptano y el solvente se evaporó para dar una espuma, la cual se secó bajo alto vacío. Se agregó éter dietílico y el solvente se evaporó para dar una espuma, la cual se secó bajo alto vacío para dar el compuesto del título (10,67g) como un sólido blanco.

Ejemplo 37C

(1R,4R)-dimetansulfonato de 1,4-Bis(4-nitrofenil)butan-1,4-diilo

El producto del Ejemplo 32 (5,01 g, 13,39 mmol) se combinó con 2-metiltetrahidrofurano (70 ml) y se enfrió a -5 °C, y se agregó N,N-diisopropiletilamina (6,81 g, 52,7 mmol) durante 30 segundos. En forma separada, se preparó una solución de anhídrido metansulfónico (6,01 g, 34,5 mmol) en 2-metiltetrahidrofurano (30 ml) y se agregó a la lechada de diol a lo largo de 3 min., manteniendo la temperatura interna entre -15 °C y -25 °C. Luego de mezclar por 5 min a -15 °C, el baño de frío se retiró y la reacción se dejó calentar lentamente a 23 °C y se mezcló por 30 minutos. Luego de completarse la reacción, la lechada cruda se llevó inmediatamente al siguiente paso.

Ejemplo 37D

(2S,5S)-1-(4-tert-butilfenil)-2,5-bis(4-nitrofenil)pirrolidina

a la solución cruda del producto del Ejemplo 37C (7,35 g, 13,39 mmol) se agregó 4-tert-butilanilina (13,4 g, 90 mmol) a 23 °C durante 1 minuto. La reacción se calentó a 65

°C por 2 h. Luego de completarse, la mezcla de la reacción se enfrió a 23 °C y se diluyó con 2-metiltetrahidrofurano (100 ml) y HCl 1 M (150 ml). Luego de particionar las fases, la fase orgánica se trató con HCl 1 M (140 ml), 2-metiltetrahidrofurano (50 ml), y NaCl acuoso al 25 p% (100 ml), y las fases se particionaron. La fase orgánica se lavó con NaCl acuoso al 25 p% (50 ml), se secó sobre $MgSO_4$, se filtró, y se concentró al vacío a aproximadamente 20 ml. Se agregó heptano (30 ml) y 2-metiltetrahidrofurano adicional para inducir cristalización. La lechada se concentró adicionalmente, y se agregó heptano adicional (40 ml) lentamente y la lechada se filtró, lavando con 2-metiltetrahidrofurano:heptano (1:4, 20 ml). Los sólidos se suspendieron en MeOH (46 ml) por 3 h, se filtró, y el sólido húmedo se lavó con MeOH adicional (18 ml). El sólido se secó a 45 °C en un horno de vacío por 16 h para dar el compuesto del título (3,08 g, 51% 2-paso rendimiento).

Ejemplo 37E

4,4'-((2S,5S)-1-(4-tert-butilfenil)pirrolidin-2,5-diil)dianilina

A un recipiente de hidrogenación con un agitador Parr de 160 ml se agregó el producto del Ejemplo 37D (2 g, 4,49 mmol), seguido por 60 ml de THF, y Níquel de Raney Grace 2800 (1 g, 50 p% (base seca)) bajo una corriente de nitrógeno. El reactor se ensambló y se purgó con nitrógeno (8 x 20 psig) seguido por la purga con hidrógeno (8 x 30 psig). El reactor luego se presurizó a 30 psig con hidrógeno y la agitación (700 rpm) comenzó y se continuó por un total de 16 h a temperatura ambiente. La lechada se filtró mediante filtración al vacío usando n filtro de fibra de vidrio GF/F Whatman. La evaporación del material filtrado dio el compuesto crudo del título, el cual se usó directamente en el siguiente paso.

Ejemplo 37F

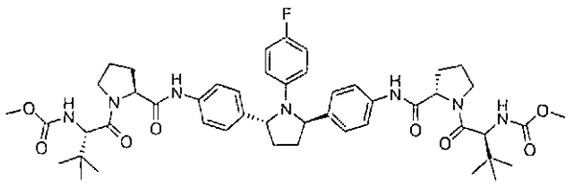
(2S,2'R)-1,1'-((2S,2'S)-2,2'-(4,4'-((2S,5S)-1-(4-tert-butilfenil)pirrolidin-2,5-diil)bis(4,1-fenilen)bis(azandiil)bis(oxometilen))bis(pirrolidin-2,1-diil))bis(3-metil-1-oxobutan-2,1-diil)dicarbamato de dimetilo

A una solución del producto del Ejemplo 37E (1,64 g, 4,25 mmol) en DMF (20 ml), el producto del Ejemplo 37B (2,89 g, 10,63 mmol), y HATU (4,04 g, 10,63 mmol) en DMF (150mL) se agregó trietilamina (1,07 g, 10,63 mmol), y la solución se agitó a temperatura ambiente por 90 min. A la mezcla de la reacción se vertió 20 ml de agua, y el precipitado blanco obtenido se filtró, y el sólido se lavó con agua (3x5 ml). El sólido se secó con un secador de aire por 1h. El material crudo se cargó en una columna de gel de sílice y se eluyó con un gradiente comenzando con acetato de etilo/ heptano (3/7), y finalizando con acetato de etilo puro. Las fracciones deseadas se combinaron el solvente se eliminó por destilación para dar un sólido amarillo muy claro, el cual se secó a 45 °C en un horno de

vacío con purga de nitrógeno por 15 h para dar el compuesto del título (2,3 g, 61% de rendimiento). ^{1}H RMN (400 MHz, DMSO-D6) δ ppm 0,88 (d, J=6,61 Hz, 6 H) 0,93 (d, J=6,72 Hz, 6 H) 1,11 (s, 9 H) 1,63 (d, J=5,42 Hz, 2 H) 1,80 - 2,04 (m, 8 H) 2,09 - 2,19 (m, 2 H) 2,44 - 2,47 (m, 2 H) 3,52 (s, 6 H) 3,59 - 3,66 (m, 2 H) 3,77 - 3,84 (m, 2 H) 4,02 (t, J=8,40 Hz, 2 H) 4,42 (dd, J=7,86, 4,83 Hz, 2 H) 5,14 (d, J=6,18 Hz, 2 H) 6,17 (d, J=8,67 Hz, 2 H) 6,94 (d, J=8,78 Hz, 2 H) 7,13 (d, J=8,46 Hz, 4 H) 7,31 (d, J=8,35 Hz, 2 H) 7,50 (d, J=8,35 Hz, 4 H) 9,98 (s, 2 H). El compuesto del título mostró un valor de EC_{50} inferior a aproximadamente 0,1 nM en ensayos de replicones del VHC 1b-Con1 en presencia de FBS al 5%.

Ejemplo 38

(2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-((2R,5R)-1-(4-fluorofenil)pirrolidin-2,5-diil)bis(4,1-fenilen))bis(azandiil)bis(oxometilen)bis(pirrolidin-2,1-diil))bis(3,3-dimetil-1-oxobutan-2,1-diil)dicarbamato de dimetilo



Ejemplo 38A

(1S,4S)-dimetansulfonato de 1,4-Bis(4-nitrofenil)butan-1,4-diilo

El compuesto del título se preparó usando los métodos del Ejemplo 37C, utilizando el producto del Ejemplo 33 en lugar del producto del Ejemplo 32.

Ejemplo 38B

(2R,5R)-1-(4-fluorofenil)-2,5-bis(4-nitrofenil)pirrolidina

El compuesto del título se preparó usando los métodos del Ejemplo 37D, utilizando 4-fluoroanilina en lugar de 4-*tert*-butilanilina.

Ejemplo 38C

4,4'-((2R,5R)-1-(4-fluorofenil)pirrolidin-2,5-diil)dianilina

A una solución del producto del Ejemplo 38B (2,34 g, 5,74 mmol) en 1:1 etanol:THF (60 ml) en una botella de presión de acero inoxidable de 250 ml se agregó PtO_2 (0,47 g, 2,06 mmol) y la mezcla resultante se colocó bajo presión de H_2 (30 psi) y se agitó a temperatura ambiente por 90 min. La mezcla se filtró a través de una membrana de nylon y el material filtrado se concentró al vacío. El producto crudo se purificó mediante cromatografía de columna sobre gel de sílice usando un gradiente de solvente de 0-65% acetato de etilo en hexanos para dar el compuesto del título como un sólido (0,736 g, 37%).

Ejemplo 38D

(2S,2'S)-2,2'-(4,4'-((2R,5R)-1-(4-fluorofenil)pirrolidin-2,5-diil)bis(4,1-fenilen))bis(azandiil)bis(oxometilen)dipirrolidin-1-carboxilato de tert-butilo

A una solución del producto del Ejemplo 38C (3,54 g, 10,19 mmol), ácido (S)-1-(tert-butoxicarbonil)pirrolidin-2-carboxílico (5,48 g, 25,5 mmol), y HATU (9,69 g, 25,5 mmol) en NMP anhidro (50mL) se agregó N,N-diisopropiletilamina (5,29 ml, 30,6 mmol), y la mezcla de reacción se agitó a temperatura ambiente por 30-45 minutos. La mezcla de la reacción se diluyó con agua (500mL). El producto precipitado se filtró y se lavó con agua (3x100mL), solución de bicarbonato de sodio (50mL), y agua (50mL). El producto se secó a 40 °C por 15 h. Este material (8,5g) se pasó a través de una almohadilla de gel de sílice y se eluyó con acetato de etilo para dar el producto sólido blanco (7,9g, 99%).

Ejemplo 38E

(2S,2'S)-N,N'-(4,4'-((2R,5R)-1-(4-fluorofenil)pirrolidin-2,5-diil)bis(4,1-fenilen))dipirrolidin-2-carboxamida

A una solución del producto del Ejemplo 38D (7,9 g, 10,65 mmol) en diclorometano (50mL), se agregó solución 5M de HCl en alcohol isopropílico (50mL) y la mezcla de la reacción se agitó a temperatura ambiente por 16 h. El solvente se evaporó mediante rotavap bajo vacío y el material crudo se recogió con diclorometano con 20% de metanol (200mL). La solución se lavó con solución al 5% de hidróxido de amonio (90mL), salmuera (50mL) y se secó sobre $MgSO_4$. La solución se filtró y se concentró para dar 6,5g de producto crudo. Este material se recristalizó a partir de acetato de etilo /heptano (8/2) para dar el compuesto del título (5,0 g, 87% de rendimiento).

Ejemplo 38F

(2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-((2R,5R)-1-(4-fluorofenil)pirrolidin-2,5-diil)bis(4,1-fenilen))bis(azandiil)bis(oxometilen)bis(pirrolidin-2,1-diil))bis(3,3-dimetil-1-oxobutan-2,1-diil)dicarbamato de dimetilo

A una solución del producto del Ejemplo 38E (4,14 g, 7,64 mmol), ácido (S)-2-metoxicarbonilamino-3,3-dimetil-butírico (3,62 g, 19,11 mmol), y EDAC (3,66 g, 19,11 mmol) en DMF anhidro (80mL) se agregó N,N-diisopropiletilamina (2,96 g, 22,93 mmol) y la solución se agitó a temperatura ambiente por 4 h. La mezcla de la reacción se vertió sobre 400 ml de agua, y el precipitado blanco obtenido se filtró y se lavó con agua (3x50mL), bicarbonato de sodio (50mL), agua (50ML), y se secó a 45 °C en un horno de vacío con purga de nitrógeno por 15 h para dar 7,0 g del producto crudo. El material crudo se cargó sobre columna de gel de sílice (150g de sílice) y se eluyó con un gradiente comenzando con acetato de etilo/ heptano (7/3), y finalizando con acetato de etilo. Las fracciones deseadas se combinaron el solvente se eliminó por destilación para dar un aceite amarillo muy claro, el cual se trituró con MTBE /heptano(1:9) por 1h. El sólido

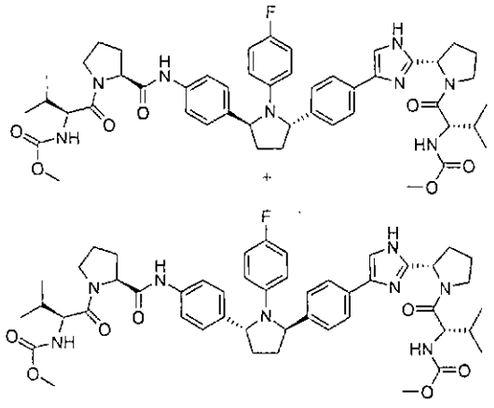
blanco así obtenido se filtró y se secó en un horno de vacío con purga de nitrógeno para dar 6,1g de producto. El sólido 5,5 g se disolvió en 16mL de metanol y esta solución se agregó a agua (220 ml) en un recipiente de 500mL. La lechada se agitó por 30 minutos, y el sólido se recogió mediante filtración, se secó a 45 ^{0}C con purga de nitrógeno por 15 h para dar el compuesto del título (5,4 g). ^{1}H RMN (400 MHz, DMSO-D6) δ ppm 0,96 (s, 18 H) 1,64 (d, *J*=5,53 Hz, 2 H) 1,78 – 1,93 (m, 6 H) 1,94 – 2,06 (m, 2 H) 2,09 – 2,21 (m, 2 H) 3,54 (s, 6 H) 3,59 – 3,69 (m, 2 H) 3,72 – 3,83 (m, 2 H) 4,20 (d, *J*=8,89 Hz, 2 H) 4,43 (dd, *J*=7,92, 5,42 Hz, 2 H) 5,16 (d, *J*=6,29 Hz, 2 H) 6,20 (dd, *J*=9,16, 4,39 Hz, 2 H) 6,77 (t, *J*=8,95 Hz, 2 H) 7,12 (d, *J*=8,57 Hz, 4 H) 7,50 (d, *J*=8,57 Hz, 4 H) 9,99 (s, 2 H). El compuesto del título mostró un valor de EC_{50} inferior a aproximadamente 0,1 nM en ensayos de replicones del VHC 1b-Con1 en presencia de FBS al 5%.

Ejemplo 39

N-(metoxicarbonil)-L-valil-*N*-(4-{(2*S*,5*S*)-1-(4-fluorofenil)-5-[4-(2-{(2*S*)-1-[*N*-(metoxicarbonil)-L-valil]pirrolidin-2-il}-1*H*-imidazol-4-il)fenil]pirrolidin-2-il}fenil)-L-prolinamida (ACD v12)

y

N-(metoxicarbonil)-L-valil-*N*-(4-{(2*R*,5*R*)-1-(4-fluorofenil)-5-[4-(2-{(2*S*)-1-[*N*-(metoxicarbonil)-L-valil]pirrolidin-2-il}-1*H*-imidazol-4-il)fenil]pirrolidin-2-il}fenil)-L-prolinamida (ACD v12)



Ejemplo 39A

1-(4-bromofenil)-4-(4-nitrofenil)butan-1,4-diona

Se agregó benceno (108 ml) a cloruro de cinc(II) anhidro (19,62 g, 144 mmol), seguido por la adición de dietilamina (11,16 ml, 108 mmol) y 2-metilpropan-2-ol (10,32 ml, 108 mmol) y se agitó a temperatura ambiente por 2 h. Se agregó 2-bromo-1-(4-bromofenil)etanona (20 g, 72,0 mmol) y 1-(4-nitrofenil)etanona (17,83 g, 108 mmol) conjuntamente y se agitó la mezcla por 18 h. Se agregó ácido sulfúrico acuoso al 5% (50 ml) y se agitó enérgicamente, luego el producto se recogió mediante filtración, se enjuagó

con benceno, agua, metanol, diclorometano y se secó bajo vacío para dar el producto (15,0 g, 58% de rendimiento, polvo incoloro).

Ejemplo 39B

1-(4-bromofenil)-4-(4-nitrofenil)butan-1,4-diol

Se disolvió el producto del Ejemplo 39A (3,64 g, 10,05 mmol) en etanol (67 ml) y se agregó borhidruro de sodio (0,837 g, 22,11 mmol) por porciones. Luego de agitar por 1 h a temperatura ambiente, la mezcla se filtró a través de celite y se lavó con metanol y acetato de etilo y el material filtrado se concentró para dar un sólido. El sólido se disolvió en acetato de etilo (200 ml) y se extrajo con HCl 1N acuoso (200 ml), luego salmuera y la capa orgánica se secó y se concentró para dar un aceite incoloro (3,68 g, 100%) que se usó directamente en la siguiente reacción.

Ejemplo 39C

dimetansulfonato de 1-(4-bromofenil)-4-(4-nitrofenil)butan-1,4-diilo

Se disolvió el producto del Ejemplo 39B (3,68 g, 10,05 mmol) en diclorometano (167 ml) y se enfrió la solución en un baño de hielo seguido por la adición de trietilamina (4,20 ml, 30,1 mmol) y cloruro de metansulfonilo (1,96 ml, 25,1 mmol) por goteo. Luego de agitar por 15 min, la solución se concentró para dar un sólido (5,25 g, 100%) que se usó directamente en la siguiente reacción.

Ejemplo 39D

2-(4-bromofenil)-1-(4-fluorofenil)-5-(4-nitrofenil)pirrolidina

Se disolvió el producto del Ejemplo 39C (5,25 g, 10,05 mmol) en DMF (31 ml) y luego se agregó 4-fluoroanilina (9,65 ml, 101 mmol) y se calentó la solución a 50 ^{0}C por 18 h. La solución se enfrió a temperatura ambiente y se agregó HCl 1N acuoso (100 ml) luego se extrajo con acetato de etilo (2 x 200 ml), luego los extractos orgánicos combinados se lavaron con salmuera, se secó y se concentró para dar un aceite ámbar al cual se agregó metanol (10 ml) y luego de 3 h resultó un sólido amarillo (1,05 g, 24%) como el compuesto del título como una mezcla 1/1 de isómeros trans pirrolidina.

Ejemplo 39E

1-(4-fluorofenil)-2-(4-nitrofenil)-5-(4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)pirrolidina

Se disolvió el producto del Ejemplo 39D (1,05 g, 2,38 mmol), 4,4,4',4',5,5,5',5'-octametil-2,2'-bi(1,3,2-dioxaborolano) (0,725 g, 2,86 mmol), [1,1'-bis(difenilfosfino)ferrocen]dicloropaladio(II) (0,194 g, 0,238 mmol), y acetato de potasio (0,35 g, 3,57 mmol) en dioxano (20 ml) y luego se burbujeó nitrógeno gaseoso a través de la solución por 10 min, luego se calentó a 100 ^{0}C por 1,5 h. La solución se enfrió a temperatura ambiente luego se filtró a través de celite y se lavó con acetato de etilo (20

ml). El material filtrado se secó, se concentró y el residuo se purificó mediante cromatografía de columna sobre gel de sílice, eluyendo con un gradiente de solvente de acetato de etilo al 10-50% en hexano para dar el compuesto del título (1,09 g, 94%) como un sólido amarillo y una mezcla 1/1 de estereoisómeros trans.

Ejemplo 39F

(2S)-2-(4-(4-(1-(4-fluorofenil)-5-(4-nitrofenil)pirrolidin-2-il)fenil)-1H-imidazol-2-il)pirrolidin-1-carboxilato de tert-butilo

Se disolvió el producto del Ejemplo 39E (1,05 g, 2,15 mmol), el producto del Ejemplo 26D (0,748 g, 2,365 mmol), [1,1'-bis(difenilfosfino)ferrocen]dicloropaladio(II) (0,176 g, 0,215 mmol) en una mezcla de tolueno (10 ml), etanol (10 ml) y una solución acuosa 1N de bicarbonato de sodio (2,58 ml, 2,58 mmol) y se burbujeó nitrógeno gaseoso a través de la solución por 10 min, luego se calentó a 90°C por 3 h. La solución se enfrió a temperatura ambiente y se agregó agua (20 ml) luego se extrajo con diclorometano (50 ml), luego se secó, se concentró y el residuo se purificó mediante cromatografía de columna sobre gel de sílice, eluyendo con un gradiente de solvente de 0-100% acetato de etilo en hexano para dar el compuesto del título (0,28 g, 72%) como un sólido amarillo y una mezcla 1/1 de estereoisómeros trans.

Ejemplo 39G

(2S)-2-(4-(4-(5-(4-aminofenil)-1-(4-fluorofenil)pirrolidin-2-il)fenil)-1H-imidazol-2-il)pirrolidin-1-carboxilato de tert-butilo

Se disolvió el producto del Ejemplo 39F (300 mg, 0,502 mmol) en etanol (5 ml) y THF (5 ml) luego se agregó óxido de platino(IV) (22,8 mg, 0,1 mmol) y un globo de hidrógeno y se agitó la solución a temperatura ambiente por 2,5 h. La solución se filtró a través de celite y se lavó con metanol (10 ml), luego se concentró para dar el compuesto del título (285 mg, 100%) como un semisólido incoloro y una mezcla 1/1 de estereoisómeros.

Ejemplo 39H

(2S)-2-(4-(5-(4-(2-((S)-1-(tert-butoxicarbonil)pirrolidin-2-il)-1H-imidazol-4-il)fenil)-1-(4-fluorofenil)pirrolidin-2-il)fenilcarbamoil)pirrolidin-1-carboxilato de tert-butilo

Se disolvió el producto del Ejemplo 39G (285 mg, 0,502 mmol), ácido (S)-1-(tert-butoxicarbonil)pirrolidin-2-carboxílico (162 mg, 0,753 mmol), HATU (305 mg, 0,803 mmol) y base de Hunig (0,263 ml, 1,506 mmol) en DMSO (5 ml) y se agitó a temperatura ambiente por 1 h. Se agregó diclorometano (50 ml) seguido por extracción con agua (2 x 50 ml), el extracto orgánico se secó, se concentró y el residuo se disolvió en metanol (10 ml) seguido por la adición de carbonato de potasio (400 mg, 2,89 mmol) y se agitó la solución amarillo brillante solución a temperatura ambiente por 30 min. La solución luego

se filtró y el material filtrado se concentró para dar un aceite, el cual se disolvió en una mezcla 95/5 de diclorometano/metanol (50 ml) y se extrajo con agua (20 ml). El extracto orgánico se secó y se concentró para dar el producto del título (350 mg, 91%) como un sólido amarillo claro y una mezcla 1/1 de estereoisómeros.

Ejemplo 39I

(2S)-N-(4-(1-(4-fluorofenil)-5-(4-(2-((S)-pirrolidin-2-il)-1H-imidazol-4-il)fenil)pirrolidin-2-il)fenil)pirrolidin-2-carboxamida sal clorhidrato

Se disolvió el producto del Ejemplo 39H (350 mg, 0,458 mmol) en ácido clorhídrico 4M en solución de dioxano (6 ml) y se agitó la solución a temperatura ambiente por 30 min luego se concentró la mezcla bajo alto vacío para dar un sólido (aprox. 310 mg) como una sal clorhidrato que se usó directamente en la siguiente reacción.

Ejemplo 39J

N-(metoxicarbonil)-L-valil-*N*-(4-{(2*S*,5*S*)-1-(4-fluorofenil)-5-[4-(2-{(2*S*)-1-[*N*-(metoxicarbonil)-L-valil]pirrolidin-2-il}-1*H*-imidazol-4-il)fenil]pirrolidin-2-il}fenil)-L-prolinamida (ACD v12)

y

N-(metoxicarbonil)-L-valil-*N*-(4-{(2*R*,5*R*)-1-(4-fluorofenil)-5-[4-(2-{(2*S*)-1-[*N*-(metoxicarbonil)-L-valil]pirrolidin-2-il}-1*H*-imidazol-4-il)fenil]pirrolidin-2-il}fenil)-L-prolinamida (ACD v12)

A una mezcla del producto del Ejemplo 39I (300 mg, 0,45 mmol), ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico (173 mg, 0,99 mmol), y HATU (428 mg, 1,125 mmol) en DMSO (5 ml) se agregó base de Hunig (0,786 ml, 4,5 mmol), y la reacción se agitó a temperatura ambiente por 1 h. Se agregó diclorometano (50 ml) seguido por extracción con agua (2 x 25 ml), el extracto orgánico se secó, se concentró y el residuo se disolvió en metanol (15 ml) seguido por la adición de carbonato de potasio (300 mg, 2,17 mmol) y se agitó a temperatura ambiente por 20 min. La solución luego se filtró y el material filtrado se concentró para dar un aceite, el cual se disolvió en una mezcla 95/5 de diclorometano/metanol (50 ml) y se extrajo con agua (20 ml). El extracto orgánico se secó y se concentró, y el residuo se purificó mediante cromatografía de columna sobre gel de sílice, eluyendo con un gradiente de solvente de metanol al 0-25% en diclorometano para dar los compuestos del título (0,13 g, 33%) como un sólido incoloro y como una mezcla 1/1 de diastereómeros. ^{1}H RMN (400 MHz, DMSO-D6) δ ppm 11,64 (s, 1H), 9,94 (s, 1H), 7,57 (d, J=8,1 Hz, 2H), 7,47 (m, 3H), 7,33 (d, J=1,7 Hz, 1H), 7,24 (m, 2H), 7,08 (m, 4H), 6,72 (m, 2H), 6,17 (m, 2H), 5,15 (m, 2H), 5,01 (m, 1H), 4,38 (m, 1H), 4,0 (m, 2H), 3,75 (m, 2H), 3,56 (m, 1H), 3,48 (s, 3H), 3,47 (s, 3H), 2,06 (m, 2H), 1,87 (m, 8H), 1,63 (m, 2H), 0,82 (m, 12H). El compuesto del título mostró un valor de EC_{50} inferior a aproximadamente 0,1

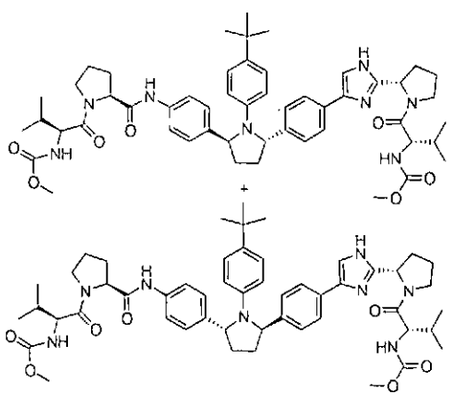
nM en ensayos de replicones del VHC 1b-Con1 en presencia de FBS al 5%.

Ejemplo 40

N-(metoxicarbonil)-L-valil-*N*-(4-{(2*S*,5*S*)-1-(4-*tert*-butilfenil)-5-[4-(2-{(2*S*)-1-[*N*-(metoxicarbonil)-L-valil]pirrolidin-2-il}-1*H*-imidazol-4-il)fenil]pirrolidin-2-il}fenil)-L-prolinamida (ACD v12)

y

N-(metoxicarbonil)-L-valil-*N*-(4-{(2*R*,5*R*)-1-(4-*tert*-butilfenil)-5-[4-(2-{(2*S*)-1-[*N*-(metoxicarbonil)-L-valil]pirrolidin-2-il}-1*H*-imidazol-4-il)fenil]pirrolidin-2-il}fenil)-L-prolinamida (ACD v12)



Ejemplo 40A

2-(4-bromofenil)-1-(4-tert-butilfenil)-5-(4-nitrofenil)pirrolidina

El producto del Ejemplo 39C (10,86 g, 20,79 mmol), DMF (65 ml) y 4-tert-butilanilina (26,5 ml, 166 mmol) se hizo reaccionar de acuerdo al procedimiento en Ejemplo 39D para dar el compuesto del título (5,0 g, 50%, sólido amarillo) como una mezcla de estereoisómeros pirrolidina cis y trans.

Ejemplo 40B

1-(4-tert-butilfenil)-2-(4-nitrofenil)-5-(4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)pirrolidina

El producto del Ejemplo 40A (2,0 g, 4,17 mmol), 4,4,4',4',5,5,5',5'-octametil-2,2'-bi(1,3,2-dioxaborolano) (1,27 g, 5,01 mmol), [1,1'-bis(difenilfosfino)ferrocen]dicloropaladio(II) (0,681 g, 0,834 mmol), y acetato de potasio (0,614 g, 6,26 mmol) en dioxano (35 ml) se hizo reaccionar de acuerdo al procedimiento en Ejemplo 39E para dar el compuesto del título (1,5 g, 68%, sólido amarillo) como una mezcla de estereoisómeros.

Ejemplo 40C

(2S)-2-(4-(4-(1-(4-tert-butilfenil)-5-(4-nitrofenil)pirrolidin-2-il)fenil)-1H-imidazol-2-il)pirrolidin-1-carboxilato de tert-butilo

El producto del Ejemplo 40B (0,7 g, 1,33 mmol), (S)-2-(4-bromo-1H-imidazol-2-il)pirrolidin-1-carboxilato de tert-butilo (0,462 g, 1,463 mmol), [1,1'-bis(difenilfosfino)ferrocen]dicloropaladio(II) (0,109 g, 0,133 mmol) en una mezcla de tolueno (6 ml), etanol (6 ml) y una solución acuosa 1N de bicarbonato de sodio (1,6 ml, 1,6 mmol) se hizo reaccionar de acuerdo al procedimiento en Ejemplo 39F para dar el compuesto del título (0,66 g, 78%, sólido amarillo) como una mezcla de estereoisómeros.

Ejemplo 40D

(2S)-2-(4-(4-(5-(4-aminofenil)-1-(4-tert-butilfenil)pirrolidin-2-il)fenil)-1H-imidazol-2-il)pirrolidin-1-carboxilato de tert-butilo

Al producto del Ejemplo 40C (1,37 g, 2,153 mmol), en etanol (10 ml) y THF (10 ml) luego se agregó óxido de platino(IV) (196 mg, 0,862 mmol) y un globo de hidrógeno y se agitó la solución a temperatura ambiente por 48 h. La reacción luego se trató de acuerdo al procedimiento en Ejemplo 39G para dar el compuesto del título (1,3 g, 100%) como una mezcla de estereoisómeros.

Ejemplo 40E

(2R)-2-(4-(5-(4-(2-((S)-1-(tert-butoxicarbonil)pirrolidin-2-il)-1H-imidazol-4-il)fenil)-1-(4-tert-butilfenil)pirrolidin-2-il)fenilcarbamoil)pirrolidin-1-carboxilato de tert-butilo

El producto del Ejemplo 40D (1,3 g, 2,146 mmol), ácido (S)-1-(tert-butoxicarbonil)pirrolidin-2-carboxílico (1,386 g, 6,44 mmol), HATU (1,305 g, 3,43 mmol) y base de Hunig (1,124 ml, 6,44 mmol) en DMSO (20 ml) se hizo reaccionar de acuerdo al procedimiento en Ejemplo 39H para dar el compuesto del título (1,01 g, 59%) como una mezcla de estereoisómeros.

Ejemplo 40F

(2R)-N-(4-(1-(4-tert-butilfenil)-5-(4-(2-((S)-pirrolidin-2-il)-1H-imidazol-4-il)fenil)pirrolidin-2-il)fenil)pirrolidin-2-carboxamida sal clorhidrato

El producto del Ejemplo 40E (610 mg, 0,76 mmol), en ácido clorhídrico 2M en solución de dioxano (10 ml) se hizo reaccionar de acuerdo al procedimiento en Ejemplo 39I para dar el compuesto del título (495 mg) como una sal clorhidrato y una mezcla de estereoisómeros.

Ejemplo 40G

N-(metoxicarbonil)-L-valil-*N*-(4-{(2*S*,5*S*)-1-(4-*tert*-butilfenil)-5-[4-(2-{(2*S*)-1-[*N*-(metoxicarbonil)-L-valil]pirrolidin-2-il}-1*H*-imidazol-4-il)fenil]pirrolidin-2-il}fenil)-L-prolinamida (ACD v12)

y

N-(metoxicarbonil)-L-valil-*N*-(4-{(2*R*,5*R*)-1-(4-*tert*-butilfenil)-5-[4-(2-{(2*S*)-1-[*N*-(metoxicarbonil)-L-valil]pirrolidin-2-il}-1*H*-imidazol-4-il)fenil]pirrolidin-2-il}fenil)-L-prolinamida

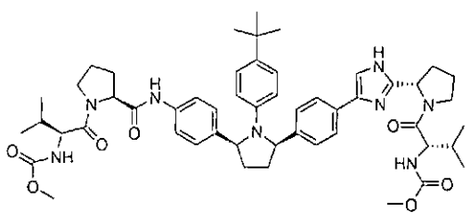
(ACD v12)

El producto del Ejemplo 40F (372 mg, 0,617 mmol), ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico (324 mg, 1,851 mmol), HATU (821 mg, 2,16 mmol) en DMSO (6 ml) y base de Hunig (1,078 ml, 6,17 mmol) se hizo reaccionar de acuerdo al procedimiento en Ejemplo 39J luego la reacción se diluyó con acetonitrilo y agua (TFA al 0,1%) y se purificó mediante cromatografía de fase inversa (C18), eluyendo con 10-100% acetonitrilo en agua (TFA al 0,1%) para dar los compuestos del título (68 mg, 12% de rendimiento, sólido blanco) como una mezcla 1/1 de diastereómeros . ^{1}H RMN (base libre) (400 MHz, DMSO-D6) δ ppm 0,80 - 0,96 (m, 12 H), 1,10 (s, 9 H), 1,65 (d, *J*=6,07 Hz, 2 H), 1,82 - 2,04 (m, 8 H), 2,07 - 2,20 (m, 3 H), 3,52 (s, 3 H), 3,53 (s, 3 H), 3,58 - 3,66 (m, 2 H), 3,73 - 3,85 (m, 3 H), 3,99 - 4,08 (m, 2 H), 4,43 (dd, *J*=7,97, 4,93 Hz, 1 H), 5,06 (dd, *J*=6,99, 2,87 Hz, 1 H), 5,17 (d, *J*=6,40 Hz, 2 H), 6,20 (d, *J*=8,89 Hz, 2 H), 6,93 (d, *J*=8,89 Hz, 2 H), 7,14 (dd, *J*=8,51, 2,87 Hz, 4 H), 7,30 (t, *J*=9,11 Hz, 2 H), 7,37 (d, *J*=1,84 Hz, 1 H), 7,50 (d, *J*=8,02 Hz, 2 H), 7,61 (d, *J*=8,13 Hz, 2 H), 9,98 (s, 1 H), 11,68 (s, 1 H). El compuesto del título mostró un valor de EC_{50} inferior a aproximadamente 0,1 nM en ensayos de replicones del VHC 1b-Con1 en presencia de FBS al 5%.

Ejemplo 41

N-(metoxicarbonil)-L-valil-*N*-(4-{(2*S*,5*R*)-1-(4-*tert*-butilfenil)-5-[4-(2-{(2*S*)-1-[*N*-(metoxicarbonil)-L-valil]pirrolidin-2-il}-1*H*-imidazol-4-il)fenil]pirrolidin-2-il}fenil)-L-prolinamida

(ACD v12)



Al producto del Ejemplo 40F (493 mg, 0,818 mmol), ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico (430 mg, 2,454 mmol), HATU (1088 mg, 2,86 mmol) en DMSO (8,2 ml) y base de Hunig (1,5 ml, 8,59 mmol) se hizo reaccionar de acuerdo al procedimiento en Ejemplo 39J luego el residuo se diluyó con acetonitrilo y agua (TFA al 0,1%) y se purificó mediante cromatografía de fase inversa (C18), eluyendo con 10-100% acetonitrilo en agua (TFA al 0,1%) para dar el compuesto del título (80 mg, 11% de rendimiento, sólido blanco). ^{1}H RMN (base libre) (400 MHz, DMSO-D6) δ ppm 0,89 - 1,04 (m, 12 H), 1,20 (s, 9 H), 1,86 - 2,12 (m, 10 H), 2,15 - 2,27 (m, 3 H), 2,43 - 2,49 (m, 2 H), 3,60 (s, 3 H), 3,61 (s, 3 H), 3,66 - 3,74 (m, 1 H), 3,81 - 3,93 (m, 2 H), 4,06 - 4,15 (m, 2 H), 4,52 (dd, *J*=7,86, 4,61 Hz, 1 H), 4,74 (d, *J*=5,20 Hz, 2 H), 5,14 (dd, *J*=6,99, 3,31 Hz, 1 H), 6,40 (d, *J*=8,78 Hz, 2 H), 7,06 - 7,11 (m, 2 H), 7,32 - 7,41 (m, 2 H), 7,47 (d,

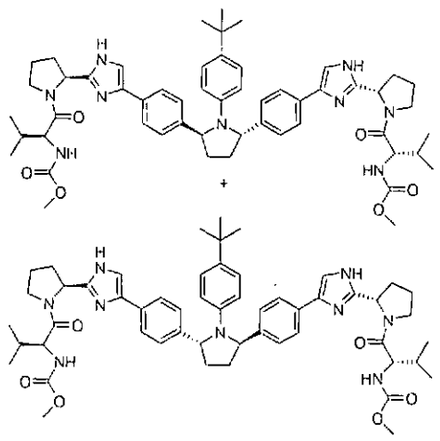
J=1,73 Hz, 1 H), 7,51 (d, *J*=7,81 Hz, 4 H), 7,65 (d, *J*=8,46 Hz, 2 H), 7,77 (d, *J*=8,24 Hz, 2 H), 10,10 (s, 1 H) ,11,76 (s, 1 H). El compuesto del título mostró un valor de EC_{50} inferior a aproximadamente 0,1 nM en ensayos de replicones del VHC 1b-Con1 en presencia de FBS al 5%.

Ejemplo 42

(2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-(4,4'-((2S,5S)-1-(4-tert-butilfenil)pirrolidin-2,5-diil)bis(4,1-fenilen))bis(1H-imidazol-4,2-diil))bis(pirrolidin-2,1-diil))bis(3-metil-1-oxobutan-2,1-diil)dicarbamato de dimetilo

y

(2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-(4,4'-((2R,5R)-1-(4-tert-butilfenil)pirrolidin-2,5-diil)bis(4,1-fenilen))bis(1H-imidazol-4,2-diil))bis(pirrolidin-2,1-diil))bis(3-metil-1-oxobutan-2,1-diil)dicarbamato de dimetilo



Ejemplo 42A

1,4-bis(4-bromofenil)butan-1,4-diol

El producto del Ejemplo 26E (3,42 g, 8,63 mmol) se sometió a las condiciones descritas en Ejemplo 39B para dar el producto del título (3,45 g, 100% de rendimiento, aceite incoloro).

Ejemplo 42B

dimetansulfonato de 1,4-bis(4-bromofenil)butan-1,4-diilo

El producto del Ejemplo 42A (3,45 g, 8,63 mmol) se sometió a las condiciones descritas en Ejemplo 39C para dar el producto del título (4,8 g, 100%).

Ejemplo 42C

2,5-bis(4-bromofenil)-1-(4-tert-butilfenil)pirrolidina

El producto del Ejemplo 42B (5,2 g, 9,35 mmol) se sometió a las condiciones descritas en Ejemplo 39D, utilizando 4-tert-butilanilina (11,91 ml, 74,8 mmol) en lugar de 4-fluoroanilina para dar el producto del título (3,89 g, 81%) como una mezcla de isómeros.

Ejemplo 42D

1-(4-tert-butilfenil)-2,5-bis(4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)pirrolidina

Se disolvió el producto del Ejemplo 42C (3,88 g, 7,56 mmol), 4,4,4',4',5,5,5',5'-octametil-2,2'-bi(1,3,2-dioxaborolano) (6,72 g, 26,5 mmol), [1,1'-bis(difenilfosfino)ferrocen]dicloropaladio(II) (0,617 g, 0,756 mmol), y acetato de potasio (3,34 g, 34,0 mmol) en dimetoxietano (70 ml) y se burbujeó nitrógeno gaseoso a través de la solución por 10 min, luego se calentó a 85 ^{0}C por 1 h. La solución se enfrió a temperatura ambiente luego se filtró a través de celite y se lavó con acetato de etilo (20 ml), el material filtrado se secó, luego se concentró y el residuo se purificó mediante cromatografía de columna sobre gel de sílice, eluyendo con un gradiente de solvente de 0-10% acetato de etilo en hexano seguido por trituración del sólido resultante con éter dietílico para dar el compuesto del título (1,14 g, 25%) como una mezcla 1/1 de estereoisómeros trans.

Ejemplo 42E

(2S,2'S)-2,2'-(4,4'-(4,4'-(1-(4-tert-butilfenil)pirrolidin-2,5-diil)bis(4,1-fenilen))bis(1H-imidazol-4,2-diil))dipirrolidin-1-carboxilato de tert-butilo

Se disolvieron los productos del Ejemplo 42D (0,915 g, 1,506 mmol), el producto del Ejemplo 26D (1,429 g, 4,52 mmol), [1,1'-bis(difenilfosfino)ferrocen]dicloropaladio(II) (0,123 g, 0,151 mmol) en una mezcla de tolueno (7 ml), etanol (7 ml) y una solución acuosa 2N de bicarbonato de sodio (2,64 ml, 5,28 mmol) y se burbujeó nitrógeno gaseoso a través de la solución por 10 min, luego se calentó a 100 ^{0}C por 3 h. La solución se enfrió a temperatura ambiente y se agregó agua (20 ml) luego se extrajo con diclorometano (50 ml), luego se secó, se concentró y el residuo se purificó mediante cromatografía de columna sobre gel de sílice, eluyendo con un gradiente de solvente de 0-80% acetato de etilo en hexano para dar el compuesto del título (0,93 g, 75%) como una mezcla 1/1 de estereoisómeros trans.

Ejemplo 42F

sal clorhidrato de (S)-4,4'-(4,4'-(1-(4-tert-butilfenil)pirrolidin-2,5-diil)bis(4,1-fenilen))bis(2-((S)-pirrolidin-2-il)-1H-imidazol)

Al producto del Ejemplo 42E (1,11 g, 1,344 mmol), en ácido clorhídrico 4M en solución de dioxano (5 ml) se hizo reaccionar de acuerdo al procedimiento en Ejemplo 39I para dar el compuesto del título (1,12 g) como una sal clorhidrato y una mezcla de estereoisómeros.

Ejemplo 42G

(2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-(4,4'-((2S,5S)-1-(4-tert-butilfenil)pirrolidin-2,5-diil)bis(4,1-fenilen))bis(1H-imidazol-4,2-diil))bis(pirrolidin-2,1-diil))bis(3-metil-1-oxobutan-2,1-

diil)dicarbamato de dimetilo

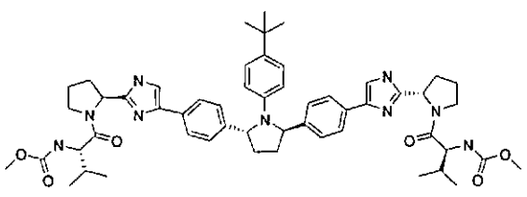
y

(2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-(4,4'-((2R,5R)-1-(4-tert-butilfenil)pirrolidin-2,5-diil)bis(4,1-fenilen))bis(1H-imidazol-4,2-diil))bis(pirrolidin-2,1-diil))bis(3-metil-1-oxobutan-2,1-diil)dicarbamato de dimetilo

A una mezcla de los productos del Ejemplo 42F (1,04 g, 1,662 mmol), ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico (0,728 g, 4,15 mmol), y HATU (1,295 g, 3,41 mmol) en DMSO (20 ml) se agregó base de Hunig (2,322 ml, 13,29 mmol), y la reacción se agitó a temperatura ambiente por 1 h. Se agregó agua (20 ml) para formar un sólido que se disolvió en diclorometano y se purificó mediante cromatografía de columna sobre gel de sílice, eluyendo con un gradiente de solvente de metanol al 0-5% en diclorometano para dar un sólido que se diluyó con acetonitrilo y agua (TFA al 0,1%) y se purificó adicionalmente mediante cromatografía de fase inversa (C18), eluyendo con 10-100% acetonitrilo en agua (TFA al 0,1%) para dar el compuesto del título (92 mg, 6% de rendimiento, sólido blanco) como una mezcla 1/1 de diastereómeros. ^{1}H RMN (base libre) (400 MHz, DMSO-D6) δ ppm 0,78 - 0,92 (m, 12 H), 1,09 (s, 9 H), 1,63 - 1,74 (m, 2 H), 1,85 - 2,00 (m, 6 H), 2,05 - 2,16 (m, 2 H), 3,44 - 3,50 (m, 4 H), 3,52 (s, 6 H), 3,70 - 3,82 (m, 4 H), 4,02 - 4,09 (m, 2 H), 5,04 (dd, J=6,67, 3,20 Hz, 2 H), 5,19 (t, J=6,18 Hz, 2 H), 6,21 (d, J=8,57 Hz, 2 H), 6,91 (dd, J=7,16, 1,63 Hz, 2 H), 7,14 (dd, J=8,19, 2,22 Hz, 4 H), 7,20 - 7,30 (m, 2 H), 7,36 (d, J=1,19 Hz, 2 H), 7,61 (d, J=8,13 Hz, 4 H), 11,67 (d, J=4,01 Hz, 2 H). El compuesto del título mostró un valor de EC_{50} inferior a aproximadamente 0,1 nM en ensayos de replicones del VHC 1b-Con1 en presencia de FBS al 5%.

Ejemplo 43

(2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-(4,4'-((2R,5R)-1-(4-tert-butilfenil)pirrolidin-2,5-diil)bis(4,1-fenilen))bis(1H-imidazol-4,2-diil))bis(pirrolidin-2,1-diil))bis(3-metil-1-oxobutan-2,1-diil)dicarbamato de dimetilo

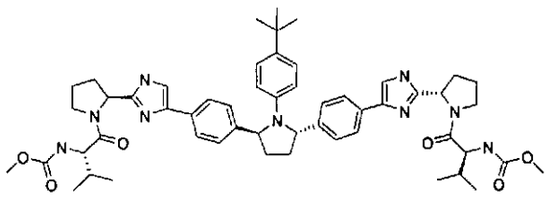


El producto del Ejemplo 42G se purificó mediante cromatografía quiral en una columna Chiralpak IB eluyendo con una mezcla de hexano/THF/MeOH (80/10/10). El compuesto del título fue el primero de 2 diastereómeros en eluir. ^{1}H RMN (400 MHz, DMSO-D6) δ ppm 0,78 - 0,92 (m, 12 H), 1,09 (s, 9 H), 1,63 - 1,74 (m, 2 H), 1,85 - 2,00 (m, 6 H), 2,05 - 2,16 (m, 2 H), 3,44 - 3,50 (m, 4 H), 3,52 (s, 6 H), 3,70 - 3,82 (m, 4 H), 4,02 - 4,09 (m, 2 H), 5,04 (dd, J=6,67, 3,20 Hz, 2 H), 5,19 (t, J=6,18 Hz, 2 H), 6,21 (d, J=8,57 Hz,

2 H), 6,91 (dd, J=7,16, 1,63 Hz, 2 H), 7,14 (dd, J=8,19, 2,22 Hz, 4 H), 7,20 - 7,30 (m, 2 H), 7,36 (d, J=1,19 Hz, 2 H), 7,61 (d, J=8,13 Hz, 4 H), 11,67 (d, J=4,01 Hz, 2 H). El compuesto del título mostró un valor de EC_{50} inferior a aproximadamente 0,1 nM en ensayos de replicones del VHC 1b-Con1 en presencia de FBS al 5%.

Ejemplo 44

(2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-(4,4'-((2S,5S)-1-(4-tert-butilfenil)pirrolidin-2,5-diil)bis(4,1-fenilen))bis(1H-imidazol-4,2-diil))bis(pirrolidin-2,1-diil))bis(3-metil-1-oxobutan-2,1-diil)dicarbamato de dimetilo



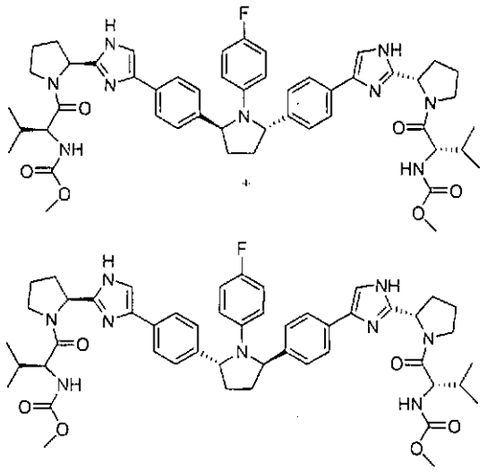
El producto del Ejemplo 42G se purificó mediante cromatografía quiral en una columna Chiralpak IB eluyendo con una mezcla de hexano/THF/MeOH (80/10/10). El compuesto del título fue el segundo de 2 diastereómeros en eluir. ^{1}H RMN (400 MHz, DMSO-D6) δ ppm 0,78 - 0,92 (m, 12 H), 1,09 (s, 9 H), 1,63 - 1,74 (m, 2 H), 1,85 - 2,00 (m, 6 H), 2,05 - 2,16 (m, 2 H), 3,44 - 3,50 (m, 4 H), 3,52 (s, 6 H), 3,70 - 3,82 (m, 4 H), 4,02 - 4,09 (m, 2 H), 5,04 (dd, J=6,67, 3,20 Hz, 2 H), 5,19 (t, J=6,18 Hz, 2 H), 6,21 (d, J=8,57 Hz, 2 H), 6,91 (dd, J=7,16, 1,63 Hz, 2 H), 7,14 (dd, J=8,19, 2,22 Hz, 4 H), 7,20 - 7,30 (m, 2 H), 7,36 (d, J=1,19 Hz, 2 H), 7,61 (d, J=8,13 Hz, 4 H), 11,67 (d, J=4,01 Hz, 2 H). El compuesto del título mostró un valor de EC_{50} inferior a aproximadamente 0,1 nM en ensayos de replicones del VHC 1b-Con1 en presencia de FBS al 5%.

Ejemplo 45

(2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-(4,4'-((2S,5S)-1-(4-fluorofenil)pirrolidin-2,5-diil)bis(4,1-fenilen))bis(1H-imidazol-4,2-diil))bis(pirrolidin-2,1-diil))bis(3-metil-1-oxobutan-2,1-diil)dicarbamato de dimetilo

y

(2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-(4,4'-((2R,5R)-1-(4-fluorofenil)pirrolidin-2,5-diil)bis(4,1-fenilen))bis(1H-imidazol-4,2-diil))bis(pirrolidin-2,1-diil))bis(3-metil-1-oxobutan-2,1-diil)dicarbamato de dimetilo



Ejemplo 45A

2,5-bis(4-bromofenil)-1-(4-fluorofenil)pirrolidina

El producto del Ejemplo 42B (5,2 g, 9,35 mmol) se sometió a las condiciones descritas en Ejemplo 39D para dar el producto del título (6,41 g, 48%) como una mezcla de isómeros cis y trans.

Ejemplo 45B

1-(4-fluorofenil)-2,5-bis(4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)pirrolidina

El producto del Ejemplo 45A (2,17 g, 4,57 mmol) se sometió a las condiciones descritas en Ejemplo 42D y se purificó mediante cromatografía de columna sobre gel de sílice, eluyendo con un gradiente de solvente de 0-15% acetato de etilo en hexano para dar el compuesto del título (1,65 g, 64%) como una mezcla de estereoisómeros cis y trans.

Ejemplo 45C

(2S,2'S)-2,2'-(4,4'-(4,4'-(1-(4-fluorofenil)pirrolidin-2,5-diil)bis(4,1-fenilen))bis(1H-imidazol-4,2-diil))dipirrolidin-1-carboxilato de tert-butilo

El producto del Ejemplo 45B (1,0 g, 1,756 mmol) se sometió a las condiciones descritas en Ejemplo 42E para dar el producto del título (1,0 g, 72%) como una mezcla de isómeros cis y trans.

Ejemplo 45D

(S)-4,4'-(4,4'-(1-(4-fluorofenil)pirrolidin-2,5-diil)bis(4,1-fenilen))bis(2-((S)-pirrolidin-2-il)-1H-imidazol)

Se disolvió el producto del Ejemplo 45C (150 mg, 0,19 mmol) en diclorometano (1 ml) y TFA (1 ml) y se agitó la solución a temperatura ambiente por 1 h luego se concentró la mezcla bajo alto vacío para dar un sólido que se diluyó con acetonitrilo y agua (TFA al 0,1%) y se purificó mediante cromatografía de fase inversa (C18), eluyendo con 10-100% acetonitrilo en agua (TFA al 0,1%) para dar el compuesto del título (62 mg, 55% de

rendimiento) como una mezcla 1/1 de diastereómeros trans que eluyó antes que el isómero cis.

Ejemplo 45E

(2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-(4,4'-((2S,5S)-1-(4-fluorofenil)pirrolidin-2,5-diil)bis(4,1-fenilen))bis(1H-imidazol-4,2-diil))bis(pirrolidin-2,1-diil))bis(3-metil-1-oxobutan-2,1-diil)dicarbamato de dimetilo

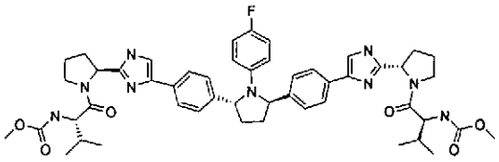
y

(2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-(4,4'-((2R,5R)-1-(4-fluorofenil)pirrolidin-2,5-diil)bis(4,1-fenilen))bis(1H-imidazol-4,2-diil))bis(pirrolidin-2,1-diil))bis(3-metil-1-oxobutan-2,1-diil)dicarbamato de dimetilo

A una mezcla del producto del Ejemplo 45D (47 mg, 0,08 mmol), ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico (29 mg, 0,168 mmol), y HATU (61 mg, 0,16 mmol) en DMSO (0,8 ml) se agregó base de Hunig (0,035 ml, 0,2 mmol) se hizo reaccionar de acuerdo al procedimiento en Ejemplo 39J luego el residuo se diluyó con acetonitrilo y agua (TFA al 0,1%) y se purificó mediante cromatografía de fase inversa (C18), eluyendo con 10-100% acetonitrilo en agua (TFA al 0,1%) para dar el compuesto del título (54 mg, 75% de rendimiento, sólido blanco) como una mezcla 1/1 de diastereómeros . ^{1}H RMN (base libre) (400 MHz, DMSO-D6) δ ppm 11,62 - 12,13 (m, 2 H), 7,59 - 7,71 (m, *J*=8,13 Hz, 3 H), 7,46 - 7,57 (m, *J*=8,24 Hz, 1 H), 7,38 (d, *J*=1,84 Hz, 2 H), 7,10 - 7,32 (m, 6 H), 6,72 - 6,83 (m, 2 H), 6,19 - 6,31 (m, 2 H), 5,17 - 5,28 (m, 2 H), 5,02 - 5,11 (m, *J*=6,72 Hz, 2 H), 4,05 (t, *J*=8,40 Hz, 2 H), 3,71 - 3,85 (m, 4 H), 3,53 (s, 6 H), 2,05 - 2,21 (m, 4 H), 1,94 (s, 6 H), 1,64 - 1,78 (m, 2 H), 0,77 - 0,95 (m, 12 H). El compuesto del título mostró un valor de EC_{50} inferior a aproximadamente 0,1 nM en ensayos de replicones del VHC 1b-Con1 en presencia de FBS al 5%.

Ejemplo 46

(2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-(4,4'-((2R,5R)-1-(4-fluorofenil)pirrolidin-2,5-diil)bis(4,1-fenilen))bis(1H-imidazol-4,2-diil))bis(pirrolidin-2,1-diil))bis(3-metil-1-oxobutan-2,1-diil)dicarbamato de dimetilo

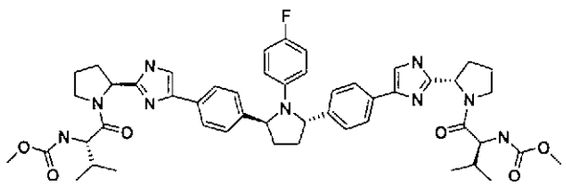


El producto del Ejemplo 45E se purificó mediante cromatografía quiral en una columna Chiralpak IB eluyendo con una mezcla de hexano/THF/MeOH (85/7,5/7,5). ^{1}H RMN (400 MHz, DMSO-D6) δ ppm 11,62 - 12,13 (m, 2 H), 7,59 - 7,71 (m, *J*=8,13 Hz, 3 H), 7,46 - 7,57 (m, *J*=8,24 Hz, 1 H), 7,38 (d, *J*=1,84 Hz, 2 H), 7,10 - 7,32 (m, 6 H), 6,72 - 6,83

(m, 2 H), 6,19 - 6,31 (m, 2 H), 5,17 - 5,28 (m, 2 H), 5,02 - 5,11 (m, *J*=6,72 Hz, 2 H), 4,05 (t, *J*=8,40 Hz, 2 H), 3,71 - 3,85 (m, 4 H), 3,53 (s, 6 H), 2,05 - 2,21 (m, 4 H), 1,94 (s, 6 H), 1,64 - 1,78 (m, 2 H), 0,77 - 0,95 (m, 12 H). El compuesto del título mostró un valor de EC_{50} inferior a aproximadamente 0,1 nM en ensayos de replicones del VHC 1b-Con1 en presencia de FBS al 5%.

Ejemplo 47

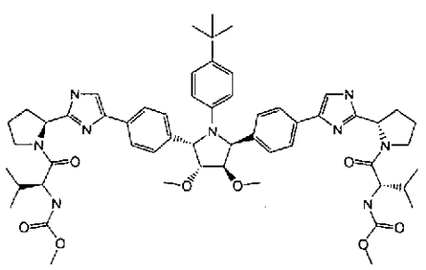
(2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-(4,4'-((2S,5S)-1-(4-fluorofenil)pirrolidin-2,5-diil)bis(4,1-fenilen))bis(1H-imidazol-4,2-diil))bis(pirrolidin-2,1-diil))bis(3-metil-1-oxobutan-2,1-diil)dicarbamato de dimetilo



El producto del Ejemplo 45E se purificó mediante cromatografía quiral en una columna Chiralpak IB eluyendo con una mezcla de hexano/THF/MeOH (85/7,5/7,5). ^{1}H RMN (400 MHz, DMSO-D6) δ ppm 11,62 - 12,13 (m, 2 H), 7,59 - 7,71 (m, *J*=8,13 Hz, 3 H), 7,46 - 7,57 (m, *J*=8,24 Hz, 1 H), 7,38 (d, *J*=1,84 Hz, 2 H), 7,10 - 7,32 (m, 6 H), 6,72 - 6,83 (m, 2 H), 6,19 - 6,31 (m, 2 H), 5,17 - 5,28 (m, 2 H), 5,02 - 5,11 (m, *J*=6,72 Hz, 2 H), 4,05 (t, *J*=8,40 Hz, 2 H), 3,71 - 3,85 (m, 4 H), 3,53 (s, 6 H), 2,05 - 2,21 (m, 4 H), 1,94 (s, 6 H), 1,64 - 1,78 (m, 2 H), 0,77 - 0,95 (m, 12 H). El compuesto del título mostró un valor de EC_{50} inferior a aproximadamente 0,1 nM en ensayos de replicones del VHC 1b-Con1 en presencia de FBS al 5%.

Ejemplo 48

(2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-(4,4'-((2S,3R,4R,5S)-1-(4-tert-butilfenil)-3,4-dimetoxipirrolidin-2,5-diil)bis(4,1-fenilen))bis(1H-imidazol-4,2-diil))bis(pirrolidin-2,1-diil))bis(3-metil-1-oxobutan-2,1-diil)dicarbamato de dimetilo



Ejemplo 48A

(2S,3R,4R,5S)-2,5-bis(4-(benciloxi)fenil)-1-(4-tert-butilfenil)pirrolidin-3,4-diol

A una solución de (1R,1'R)-1,1'-((4R,5R)-2,2-dimetil-1,3-dioxolan-4,5-diil)dietan-1,2-diol (200 mg, 0,90 mmol) en metanol (6 ml) y diclorometano (3 ml) se agregó diacetato

de yodobenceno (696 mg, 2,16 mmol) y la solución se agitó a temperatura ambiente por 5 h. La solución se concentró y al residuo se agregó H_2SO_4 al 0,1M (4 ml) y la agitación se continuó a temperatura ambiente por 18 h. El pH se ajustó a ~6 con $NaHCO_3$ sólido, y se agregó 4-tert-butilanilina (287 µl, 1,80 mmol) seguido por ácido 4-benciloxifenilborónico (369 mg, 1,62 mmol) y alcohol hexafluoroisopropílico (4 ml) y se agitó a 60 °C por 2 h. El solvente se concentró y el residuo se disolvió en acetato de etilo, se lavó con H_2O, K_3PO_4 0,33M, salmuera, se secó (Na_2SO_4), se filtró y se concentró para dar producto crudo el cual se purificó mediante cromatografía sobre gel de sílice eluyendo con 0-20% acetato de etilo/diclorometano para dar compuesto del título (249 mg, 46%).

Ejemplo 48B

(2S,3R,4R,5S)-2,5-bis(4-(benciloxi)fenil)-1-(4-tert-butilfenil)-3,4-dimetoxipirrolidina

A una solución del producto del Ejemplo 48A (200 mg, 0,33 mmol) en THF (2,1 ml) y DMF (0,7 ml) a 0 °C se agregó, en porciones, hidruro de sodio, 60% en aceite mineral (40,0 mg, 1,0 mmol) y la agitación se continuó a 0 °C por 20 min. Se agregó yodometano (0,046 ml, 0,734 mmol) y la agitación se continuó a temperatura ambiente durante la noche. Se diluyó con acetato de etilo, se lavó con NH_4Cl saturado, H_2O, salmuera, se secó (Na_2SO_4), se filtró y se concentró para dar producto crudo el cual se purificó mediante cromatografía sobre gel de sílice eluyendo con 0-20% acetato de etilo/diclorometano para dar compuesto del título (170 mg, 80%).

Ejemplo 48C

4,4'-((2S,3R,4R,5S)-1-(4-tert-butilfenil)-3,4-dimetoxipirrolidin-2,5-diil)difenol

A una solución del producto del Ejemplo 48B (168 mg, 0,268mmol) en acetato de etilo (3 ml) se agregó paladio sobre carbono al 10% (17 mg) y el recipiente se evacuó y se llenó con gas H_2. La solución se agitó bajo un globo de gas H_2 gas por 20 h, se filtró a través de Celite, y se lavó con acetato de etilo y metanol. El material filtrado se concentró y el residuo se azeotropeó con éter para dar compuesto del título (120 mg, 100%) como un sólido blanco.

Ejemplo 48D

4,4'-((2S,3R,4R,5S)-1-(4-tert-butilfenil)-3,4-dimetoxipirrolidin-2,5-diil)bis(4,1-fenileno) bis(1,1,2,2,3,3,4,4,4-nonafluorobutan-1-sulfonato)

A una solución del producto del Ejemplo 48C (117 mg, 0,261 mmol) en DMF (1,3 ml) se agregó K_2CO_3 (81 mg, 0,588 mmol) y fluoruro de 1,1,2,2,3,3,4,4,4-nonafluorobutan-1-sulfonilo (0,101 ml, 0,575 mmol) y la solución se agitó a 100 °C por 1 h. La solución fría se diluyó con acetato de etilo, se lavó con H_2O, salmuera, se secó (Na_2SO_4), se filtró y se concentró para dar un aceite el cual se purificó mediante cromatografía sobre gel de sílice eluyendo con 0-20% acetato de etilo/hexano para dar compuesto del título (195 mg, 73,7

000598

% de rendimiento).

Ejemplo 48E

(2S,3R,4R,5S)-1-(4-tert-butilfenil)-3,4-dimetoxi-2,5-bis(4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)pirrolidina

A un tubo de presión se agregó el producto del Ejemplo 48D (193 mg, 0,191 mmol), 4,4,4',4',5,5,5',5'-octametil-2,2'-bi(1,3,2-dioxaborolano) (102 mg, 0,401 mmol), diciclohexil(2',4',6'-triisopropilbifenil-2-il)fosfina (X-Phos) (14,55 mg, 0,031 mmol), acetato de potasio (112 mg, 1,145 mmol), y dioxano (1,5 ml) y la solución se desgasificó con gas N_2 por 30 min. Se agregó tris(dibencilidenacetona)dipaladio(0) (6,99 mg, 7,63 µmol) y la desgasificación se continuó otros 10 min. El tubo se selló y se calentó con agitación a 100 °C durante la noche. La solución fría se diluyó con acetato de etilo, se lavó con H_2O, salmuera, se secó (Na_2SO_4), se filtró y el material filtrado se trató con 3-(mercaptopropilo) gel de sílice por 1 h. La solución se filtró y el solvente se eliminó para dar un sólido amarillo el cual se purificó mediante cromatografía sobre gel de sílice eluyendo con 0-20% acetato de etilo/hexano para dar compuesto del título (99 mg, 78 % de rendimiento) como un sólido blanco.

Ejemplo 48F

(2S,2'S)-2,2'-(4,4'-(4,4'-((2S,3R,4R,5S)-1-(4-tert-butilfenil)-3,4-dimetoxipirrolidin-2,5-diil)bis(4,1-fenilen))bis(1H-imidazol-4,2-diil))dipirrolidin-1-carboxilato de tert-butilo

En un tubo sellado se combinó el producto del Ejemplo 48E (97 mg, 0,145 mmol), el producto del Ejemplo 26D (115 mg, 0,363 mmol), 1 M Na_2CO_3 (0,363 ml, 0,363 mmol), EtOH (1,0 ml) y tolueno (1,0 ml) y la solución se desgasificó con N2 gas por 30 min. Se agregó complejo 1,1'-Bis(difenilfosfino)ferrocenodicloro paladio(II) diclorometano (10,63 mg, 0,015 mmol) y la desgasificación se continuó otros 10 min. El tubo se selló y se calentó a 100 °C por 3 h. La solución fría se diluyó con acetato de etilo, se filtró a través de Celite y el residuo se lavó con acetato de etilo. El material filtrado se concentró al vacío y el material resultante se purificó con cromatografía sobre gel de sílice usando una columna de 12g de sílice eluyendo con 0-2% metanol/diclorometano para dar compuesto del título (85 mg, 66,1 % de rendimiento).

Ejemplo 48G

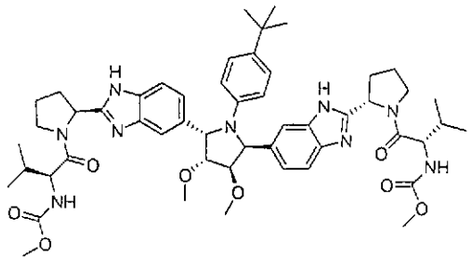
(2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-(4,4'-((2S,3R,4R,5S)-1-(4-tert-butilfenil)-3,4-dimetoxipirrolidin-2,5-diil)bis(4,1-fenilen))bis(1H-imidazol-4,2-diil))bis(pirrolidin-2,1-diil))bis(3-metil-1-oxobutan-2,1-diil)dicarbamato de dimetilo

A una solución del producto del Ejemplo 48F (83 mg, 0,094 mmol) en diclorometano (1,0 ml) se agregó TFA (1,0 ml, 12,98 mmol) y la solución se agitó a temperatura ambiente por 1 h. El solvente se concentró y el residuo se azeotropeó 2

veces con diclorometano. El residuo se colocó bajo vacío por 1 h para eliminar los restos finales de TFA. A este residuo (64,2 mg, 0,094 mmol) se agregó DMSO (500 µl) seguido por ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico (41,1 mg, 0,234 mmol), HATU (89 mg, 0,234 mmol) y base de hunig (82 µl, 0,469 mmol). se verificó el pH y se agregó más base de Hunig para ajustar el pH a ~9. La agitación se continuó a temperatura ambiente por 1 h. La solución se diluyó con acetato de etilo, se lavó con H_2O, salmuera, se secó (Na_2SO_4), se filtró y se concentró para dar un residuo crudo. La purificación se llevó a cabo mediante cromatografía sobre gel de sílice eluyendo con 0-4% metanol/diclorometano a lo largo de 60 min para dar compuesto del título (7,5 mg, 8,01 % de rendimiento). 1H RMN (400 MHz, CDCl3) δ ppm 0,86 (s, 12H) 1,13 (s, 9H) 1,86-2,02 (m, 2H) 2,02-2,12 (m, 2H) 2,12-2,25 (m, 2H) 2,25-2,41 (m, 1H) 2,90-3,17 (m, 2H) 3,43 (s, 6H) 3,53-3,65 (m, 2H) 3,70 (s, 6H) 3,74-3,89 (m, 2H) 4,16-4,26 (m, 2H) 4,26-4,37 (m, 1H) 5,18-5,26 (m, 2H) 5,26-5,32 (m, 2H) 5,33-5,41 (m, 2H) 6,28 (d, J=8,78 Hz, 2H) 6,89-6,99 (m, 2H) 7,16 (s, 2H) 7,20 (s, 2H) 7,22 (s, 2H) 7,26 (s, 4H) 7,30-7,48 (br s, 1H) 7,58-7,82 (br s, 2H) 10,08-10,42 (br s, 1H). El compuesto del título mostró un valor de EC_{50} inferior a aproximadamente 0,1 nM en ensayos de replicones del VHC 1b-Con1 en presencia de FBS al 5%.

Ejemplo 49

(2S,2'S)-1,1'-((2S,2'S)-2,2'-(5,5'-((2S,3R,4R,5S)-1-(4-tert-butilfenil)-3,4-dimetoxipirrolidin-2,5-diil)bis(1H-benzo[d]imidazol-5,2-diil))bis(pirrolidin-2,1-diil))bis(3-metil-1-oxobutan-2,1-diil)dicarbamato de dimetilo



Ejemplo 49A

(S)-2-(2-amino-5-bromofenilcarbamoil)pirrolidin-1-carboxilato de tert-butilo

Una solución de la 2-amino-4-bromoanilina (6,0 g, 32,1 mmol), Boc-Pro-OH (6,90 g, 32,1 mmol) y HATU (13,42 g, 35,3 mmol) en DMSO seco (160 ml) se trató con diisopropiletilamina (14,0 ml, 10,4 g, 80 mmol) seguido por agitación a temperatura ambiente por 18 h. La mezcla se diluyó con acetato de etilo y se extrajo con agua (3 x) y solución saturada de cloruro de sodio. El secado (Na_2SO_4) y concentración al vacío dio un sólido marrón el cual se usó directamente en el siguiente paso.

Ejemplo 49B

(S)-2-(5-bromo-1H-benzo[d]imidazol-2-il)pirrolidin-1-carboxilato de tert-butilo

Se calentó una solución del compuesto de Ejemplo 49A en ácido acético glacial (75 ml) a 60 °C por 3 h. La mezcla se enfrió y se diluyó con tolueno y se concentró al vacío. El resto del ácido acético se retiró azeotropizando con tolueno (2 x) y el residuo se cromatografió sobre un cartucho de 360 g de gel de sílice, eluyendo con 25-75% acetato de etilo en diclorometano. Estos procedimientos dieron el producto (10,0 g, 85%) como una espuma rígida beige claro.

Ejemplo 49C

(S)-2-(6-bromo-1-((2-(trimetilsilil)etoxi)metil)-1H-benzo[d]imidazol-2-il)pirrolidin-1-carboxilato de tert-butilo

Una solución del compuesto de Ejemplo 49B (2,25 g, 6,14 mmol) en THF seco (25 ml) se trató con hidruro de sodio (295 mg de 60% en aceite, 177 mg, 7,37 mmol) seguido por agitación a temperatura ambiente por 1 h. La solución luego se trató con SEM-cloruro (1,20 ml, 1,13 g, 6,76 mmol) seguido por agitación a temperatura ambiente por 18 h. La mezcla se detuvo mediante la adición de agua y la mezcla se diluyó con acetato de etilo. La mezcla se extrajo con agua y solución saturada de cloruro de sodio. El secado (Na_2SO_4) y concentración al vacío dio un aceite, el cual se cromatografió sobre un cartucho de gel de sílice de 100 g, eluyendo con 20-75% acetato de etilo en hexanos. Estos procedimientos dieron el producto (2,24 g, 73%) como un aceite pesado, el cual solidificó luego de reposar por varios días. Esta mezcla de ambos derivados SEM regioisoméricos no se separó para su uso en el siguiente paso.

Ejemplo 49D

(S)-2-(6-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1-((2-(trimetilsilil)etoxi)metil)-1H-benzo[d]imidazol-2-il)pirrolidin-1-carboxilato de tert-butilo

En un tubo de presión resellable, se desgasificó una solución del compuesto de Ejemplo 49C (2,24 g, 4,51 mmol), bis(pinacolato)diboro (1,26 g, 4,96 mmol), y acetato de potasio (1,33 g, 13,53 mmol) en dioxano seco (23 ml) rociando con nitrógeno por 30 min. La solución se trató con complejo cloruro de 1,1'-bis(difenilfosfino)ferrocenopaladio (II) diclorometano (111 mg, 0,14 mmol) seguido por desgasificación por otros 5 min. El tubo de presión se selló y se calentó a 90 °C por 4 h. La mezcla se enfrió y se diluyó con acetato de etilo, seguido por extracción con agua y solución saturada de cloruro de sodio. La solución se secó (Na_2SO_4) y se agitó por 1 h con 3-mercaptopropilo) gel de sílice. Luego de la filtración y concentración al vacío el aceite marrón se cromatografió sobre un cartucho de gel de sílice de 100 g, eluyendo con 15-70% acetato de etilo en diclorometano. Estos procedimientos dieron el producto (1,99 g, 81%) como una espuma rígida blanca.

Ejemplo 49E

(S)-2-(6-((2S,3R,4R,5S)-5-(2-((S)-1-(tert-butoxicarbonil)pirrolidin-2-il)-1-((2-(trimetilsilil)etoxi)metil)-1H-benzo[d]imidazol-5-il)-1-(4-tert-butilfenil)-3,4-dihidroxipirrolidin-2-il)-1-((2-(trimetilsilil)etoxi)metil)-1H-benzo[d]imidazol-2-il)pirrolidin-1-carboxilato de tert-butilo

Una solución de 2,3-O-isopropiliden-D-mannitol (144 mg, 0,65 mmol) y iodobencenodiacetato (501 mg, 1,56 mmol) en 2:1 metanol-diclorometano (3 ml) se agitó a temperatura ambiente por 5 h. La mezcla se concentró al vacío para dar una pasta blanca y luego se suspendió en solución 0,1 M de ácido sulfúrico (1,0 ml) seguido por agitación a temperatura ambiente por 18 h. La solución se ajustó a pH 6 mediante la adición de bicarbonato de sodio sólido seguido por la adición de 4-tert-butilanilina (206 µL, 193 mg, 1,30 mmol) el producto del Ejemplo 49D (634 mg, 1,17 mmol) y alcohol hexafluoroisopropílico (2,6 ml). La solución luego se calentó a 70 °C por 5 h. La solución se enfrió y se concentró al vacío. El residuo se disolvió en acetato de etilo y se extrajo con solución de fosfato de potasio tribásico 0,33 M y solución saturada de cloruro de sodio. El secado (Na_2SO_4) y concentración al vacío dio un aceite marrón, el cual se cromatografió sobre un cartucho de 50g de gel de sílice, eluyendo con 15-85% acetato de etilo en diclorometano. Estos procedimientos dieron el boronato recuperado (208 mg) como un aceite marrón viscoso. La columna luego se eluyó nuevamente con 0-20% metanol en diclorometano para dar el producto (159 mg, 23%) como un sólido marrón.

Ejemplo 49F

(S)-2-(6-((2S,3R,4R,5S)-5-(2-((S)-1-(tert-butoxicarbonil)pirrolidin-2-il)-1-((2-(trimetilsilil)etoxi)metil)-1H-benzo[d]imidazol-5-il)-1-(4-tert-butilfenil)-3,4-dimetoxipirrolidin-2-il)-1-((2-(trimetilsilil)etoxi)metil)-1H-benzo[d]imidazol-2-il)pirrolidin-1-carboxilato de tert-butilo

Una solución del producto del Ejemplo 49E (154 mg, 0,14 mol) en THF seco se trató con hidruro de sodio (13 mg de 60% en aceite, 8 mg, 0,33 mmol) seguido por agitación a temperatura ambiente por 30 min. La mezcla se trató con yoduro de metilo (19 µL, 43 mg, 0,30 mmol) seguido por agitación a temperatura ambiente por 2 h. La mezcla se diluyó con acetato de etilo y se detuvo mediante la adición de agua. La mezcla se extrajo con agua y solución saturada de cloruro de sodio. El secado (Na_2SO_4) y concentración al vacío dio un aceite marrón, el cual se cromatografió sobre un cartucho de 25 g de gel de sílice, eluyendo con metanol al 0-15% en diclorometano. Estos procedimientos dieron el producto (121 mg, 77%) como una espuma beige.

Ejemplo 49G

(S)-5,5'-((2S,3R,4R,5S)-1-(4-tert-butilfenil)-3,4-dimetoxipirrolidin-2,5-diil)bis(2-((S)-

pirrolidin-2-il)-1H-benzo[d]imidazol)

Una solución del compuesto de Ejemplo 49F (111 mg, 0,10 mmol) en etanol (1 ml) se trató con solución 4 N de ácido clorhídrico (2,0 ml) seguido por calentamiento a 60 °C por 18 h. La solución se enfrió y se concentró al vacío con mezclas de etanol-tolueno (2 x) para dar el tetraclorhidrato como un sólido amarillo claro. Este material se disolvió en metanol (3 ml) y se agitó con Amberlyte IRA 400 (forma OH-, 1,4 equivalentes molares/g, 577 mg, 0,81 equivalentes molares) por 1 h. La resina se retiró mediante filtración y el material filtrado se concentró al vacío para dar el producto (29 mg, 45%) como un vidrio ámbar claro.

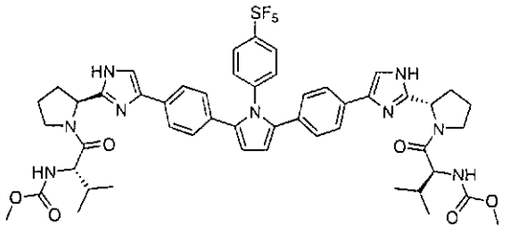
Ejemplo 49H

(2S,2'S)-1,1'-((2S,2'S)-2,2'-(5,5'-((2S,3R,4R,5S)-1-(4-tert-butilfenil)-3,4-dimetoxipirrolidin-2,5-diil)bis(1H-benzo[d]imidazol-5,2-diil))bis(pirrolidin-2,1-diil))bis(3-metil-1-oxobutan-2,1-diil)dicarbamato de dimetilo

Una solución del compuesto de Ejemplo 49G (29 mg, 0,046 mmol), hidrato de HOBt (18 mg, 0,114 mmol), EDAC (22 mg, 0,114 mmol) y ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico (20 mg, 0,114 mmol) en DMF seco (0,5 ml) a 0 °C se trató con N-metilmorfolina (15 µL, 14 mg, 0,137 mmol) seguido por agitación a 0 °C por 30 min y calentamiento a temperatura ambiente por 2 h. La mezcla se diluyó con acetato de etilo y se extrajo con agua (3 x) y solución saturada de cloruro de sodio. El secado (Na_2SO_4) y concentración al vacío dio un aceite el cual se disolvió en metanol y se trató con una pequeña cantidad de carbonato de potasio. Luego de agitar 1 h, la mezcla se filtró y se concentró al vacío para dar un aceite amarillo, el cual se cromatografió sobre un cartucho de 25 g de gel de sílice, eluyendo con metanol al 0-15% en diclorometano para dar el producto (14 mg, 32%) como un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d6) δ 7,39 (m, 4 H), 7,30 (m, 4 H), 7,07 (t, J = 9,1 Hz, 2 H), 6,87 (m, 2 H), 6,31 (d, J = 8,9 Hz, 1 H), 5,54 (m, 2 H), 5,14 (dd, J = 7,6, 4,6 Hz, 2 H), 4,14 (m, 2 H), 3,77 (m, 4 H), 3,51 (m, 6 H), 3,28 (m, 6 H), 2,15 (m, 4 H), 1,04 (s, 9 H), 0,86 (m, 12 H). El compuesto del título mostró un valor de EC_{50} de entre aproximadamente 0,1 y aproximadamente 1 nM en ensayos de replicones del VHC 1b-Con1 en presencia de FBS al 5%.

Ejemplo 50

(2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-(4,4'-(1-(4-(pentafluorotio)fenil)-1H-pirrol-2,5-diil)bis(4,1-fenilen))bis(1H-imidazol-4,2-diil))bis(pirrolidin-2,1-diil))bis(3-metil-1-oxobutan-2,1-diil)dicarbamato de dimetilo



Ejemplo 50A

2,5-bis(4-bromofenil)-1-(4-(pentafluorotio)fenil)-1H-pirrol

El compuesto del título se preparó a partir del producto del Ejemplo 26E usando los métodos del Ejemplo 26F sustituyendo pentafluoruro de 4-aminofenilazufre en lugar de 4-tert-butilanilina para dar el compuesto deseado.

Ejemplo 50B

1-(4-(pentafluorotio)fenil)-2,5-bis(4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)-1H-pirrol

El compuesto del título se preparó usando los métodos del Ejemplo 26G utilizando el producto del Ejemplo 50A en lugar del producto del Ejemplo 26F para dar el compuesto deseado.

Ejemplo 50C

2,2'-(4,4'-(4,4'-(1-(4-(pentafluorotio)fenil)-1H-pirrol-2,5-diil)bis(4,1-fenilen))bis(1H-imidazol-4,2-diil))dipirrolidin-1-carboxilato de tert-butilo

El compuesto del título se preparó usando los métodos del Ejemplo 26H utilizando el producto del Ejemplo 50B en lugar del producto del Ejemplo 26G para dar el compuesto deseado.

Ejemplo 50D

4,4'-(4,4'-(1-(4-(pentafluortio)fenil)-1H-pirrol-2,5-diil)bis(4,1-fenilen))bis(2-(pirrolidin-2-il)-1H-imidazol)

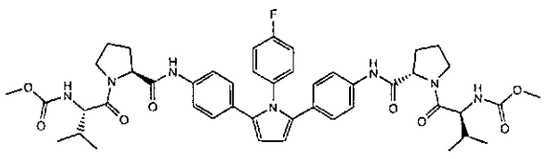
Compuesto del título se preparó usando los métodos del Ejemplo 26I utilizando el producto del Ejemplo 50C en lugar del producto del Ejemplo 26H para dar el compuesto deseado.

Ejemplo 50E

(2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-(4,4'-(1-(4-(pentafluorotio)fenil)-1H-pirrol-2,5-diil)bis(4,1-fenilen))bis(1H-imidazol-4,2-diil))bis(pirrolidin-2,1-diil))bis(3-metil-1-oxobutan-2,1-diil)dicarbamato de dimetilo

Compuesto del título se preparó usando los métodos del Ejemplo 26J utilizando el producto del Ejemplo 50D en lugar del producto del Ejemplo 26I para dar el compuesto deseado. ^{1}HNMR (DMSO-d6; 400 MHz): δ 11,75 (br s, 2H), 7,88 (m, 2H), 7,56 (app d, J=8,35 Hz, 4H), 7,45 (br s, 2H), 7,27 (m, 4H), 6,96 (app d, J=8,35 Hz, 4H), 6,50 (s, 2H),

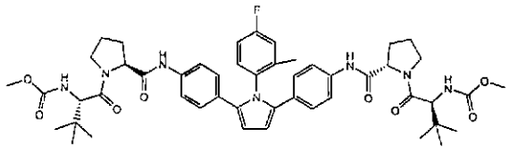
5,04 (m, 2H), 4,03 (m, 2H), 3,78 (m, 4H), 3,53 (s, 6H), 2,11-1,85 (m, 10H), 0,86 (d, J=6,72 Hz, 6H), 0,82 (d, J=6,72 Hz, 6H). El compuesto del título mostró un valor de EC_{50} inferior a aproximadamente 0,1 nM en ensayos de replicones del VHC 1b-Con1 en presencia de FBS al 5%.



Ejemplo 51

([1-(4-fluorofenil)-1H-pirrol-2,5-diil]bis{bencen-4,1-diilcarbamoil(2S)pirrolidin-2,1-diil[(2S)-3-metil-1-oxobutan-1,2-diil]})biscarbamato de dimetilo

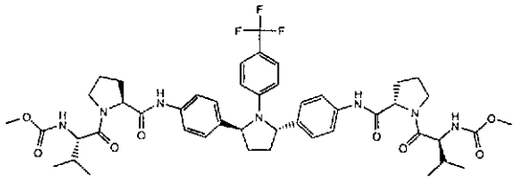
Se procesó Ejemplo 19D (150 mg) y ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico usando el método de Ejemplo 19E (utilizando DMF como solvente) para dar el compuesto del título el cual se purificó usando cromatografía sobre gel de sílice con gradiente (30-70% EtOAc en hexanos)(70 mg). ^{1}H RMN (500 MHz, DMSO-D6) δ 9,76 (s, 2H), 7,16 (d, *J* = 8,7, 4H), 7,06 (d, *J* = 8,4, 2H), 6,92 (t, *J* = 8,7, 2H), 6,83 (dd, *J* = 5,0, 8,9, 2H), 6,71 (d, *J* = 8,7, 4H), 6,14 (s, 2H), 4,15 (dd, *J* = 5,1, 7,9, 2H), 3,77 (t, *J* = 8,5, 2H), 3,59 – 3,50 (m, 2H), 3,40 – 3,31 (m, 2H), 3,27 (s, 6H), 1,95 – 1,82 (m, 2H), 1,79 – 1,52 (m, 8H), 0,67 (d, *J* = 6,8, 6H), 0,62 (d, *J* = 6,7, 6H). MS (ESI; M+H) m/z = 853.



Ejemplo 52

([1-(4-fluoro-2-metilfenil)-1H-pirrol-2,5-diil]bis{bencen-4,1-diilcarbamoil(2S)pirrolidin-2,1-diil[(2S)-3,3-dimetil-1-oxobutan-1,2-diil]})biscarbamato de dimetilo

Se procesó Ejemplo 1A usando 4-fluoro-2-metilanilina y los métodos de los Ejemplos 19A, 19B, 19C, 19D, y 51 (se usó ácido (S)-2-(metoxicarbonilamino)-3,3-dimetilbutanoico) para dar el compuesto del título. ^{1}H RMN (400 MHz, DMSO-D6) δ 9,98 (s, 2H), 7,44 – 7,36 (m, 5H), 7,09 – 6,96 (m, 8H), 6,42 (s, 2H), 4,39 (dd, *J* = 5,5, 8,1, 2H), 4,19 (d, *J* = 8,7, 2H), 3,80 – 3,70 (m, 2H), 3,65 – 3,56 (m, 2H), 3,52 (s, 6H), 2,20 – 2,06 (m, 2H), 1,97 – 1,91 (m, 2H), 1,90 – 1,76 (m, 4H), 1,63 (s, 3H), 0,94 (s, 18H). MS (ESI; M+H) m/z = 895.



Ejemplo 53

({(2S,5S)-1-[4-(trifluorometil)fenil]pirrolidin-2,5-diil}bis{bencen-4,1-diilcarbamoil(2S)pirrolidin-2,1-diil[(2S)-3-metil-1-oxobutan-1,2-diil]})biscarbamato de dimetilo

Ejemplo 53A

({(2S,5S)-1-[4-(trifluorometil)fenil]pirrolidin-2,5-diil}bis{bencen-4,1-diilcarbamoil(2S)pirrolidin-2,1-diil[(2S)-3-metil-1-oxobutan-1,2-diil]})biscarbamato de dimetilo y

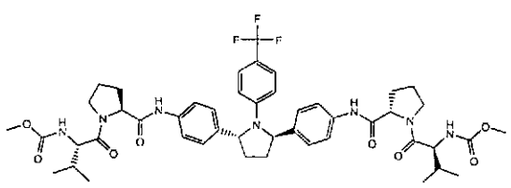
({(2R,5R)-1-[4-(trifluorometil)fenil]pirrolidin-2,5-diil}bis{bencen-4,1-diilcarbamoil(2S)pirrolidin-2,1-diil[(2S)-3-metil-1-oxobutan-1,2-diil]})biscarbamato de dimetilo

A una solución del producto del Ejemplo 23B (84 mg, 0,142 mmol) en DMSO (1,5 ml) se agregó ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico (62,2 mg, 0,355 mmol), HATU (135 mg, 0,355 mmol), y base de Hunig (0,074 ml, 0,426 mmol), y la mezcla resultante se agitó a temperatura ambiente por 90 min y luego se particionó entre H_2O (1 ml) y EtOAc (2 x 2 ml). Las capas orgánicas combinadas se secaron sobre Na_2SO_4, se filtró y se concentró al vacío. El agente de secado se retiró por filtración, y el producto crudo se purificó mediante cromatografía de columna sobre gel de sílice usando un gradiente de solvente de 1-3% MeOH en CH_2Cl_2 para dar los compuestos del título como una mezcla 1:1.

Ejemplo 53B

({(2S,5S)-1-[4-(trifluorometil)fenil]pirrolidin-2,5-diil}bis{bencen-4,1-diilcarbamoil(2S)pirrolidin-2,1-diil[(2S)-3-metil-1-oxobutan-1,2-diil]})biscarbamato de dimetilo

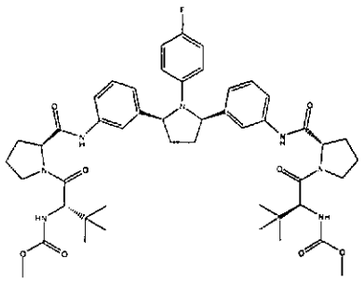
El producto del Ejemplo 53A se separó en una columna Chiralpak AD-H usando 1:1 hexanos:(1:1 EtOH:2-PrOH). El compuesto del título fue el primer componente en eluir. ^{1}H RMN (400 MHz, DMSO-D6) δ ppm 0,88 (d, *J*=6,61 Hz, 6 H), 0,93 (d, *J*=6,61 Hz, 6 H), 1,63 - 1,72 (m, 2 H), 1,78 - 2,06 (m, 8 H), 2,06 - 2,20 (m, 2 H), 3,52 (s, 6 H), 3,56 - 3,67 (m, 2 H), 3,73 - 3,86 (m, 2 H), 4,03 (t, *J*=8,51 Hz, 2 H), 4,42 (dd, *J*=7,92, 4,88 Hz, 2 H), 5,27 (d, *J*=6,61 Hz, 2 H), 6,36 (d, *J*=8,67 Hz, 2 H), 7,14 (d, *J*=8,57 Hz, 4 H), 7,25 (d, *J*=8,89 Hz, 2 H), 7,31 (d, *J*=8,35 Hz, 2 H), 7,52 (d, *J*=8,57 Hz, 4 H), 10,01 (s, 2 H); MS (ESI) m/z 906,3 $(M+H)^+$.



Ejemplo 54

({(2R,5R)-1-[4-(trifluorometil)fenil]pirrolidin-2,5-diil}bis{bencen-4,1-diilcarbamoil(2S)pirrolidin-2,1-diil[(2S)-3-metil-1-oxobutan-1,2-diil]})biscarbamato de dimetilo

El producto del Ejemplo 53A se separó en una columna Chiralpak AD-H usando 1:1 hexanos:(1:1 EtOH:2-PrOH). El compuesto del título fue el segundo componente en eluir. ^{1}H RMN (400 MHz, DMSO-D6) δ ppm 0,87 (d, *J*=6,61 Hz, 6 H), 0,92 (d, *J*=6,72 Hz, 6 H), 1,64 - 1,74 (m, 2 H), 1,78 - 2,06 (m, 8 H), 2,06 - 2,22 (m, 2 H), 3,52 (s, 6 H), 3,56 - 3,67 (m, 2 H), 3,75 - 3,86 (m, 2 H), 3,97 - 4,08 (m, 2 H), 4,37 - 4,48 (m, 2 H), 5,28 (d, *J*=6,51 Hz, 2 H), 6,36 (d, *J*=8,78 Hz, 2 H), 7,14 (d, *J*=8,57 Hz, 4 H), 7,25 (d, *J*=8,89 Hz, 2 H), 7,30 (d, *J*=8,24 Hz, 2 H), 7,52 (d, *J*=8,57 Hz, 4 H), 10,01 (s, 2 H); MS (ESI) m/z 906,3 $(M+H)^+$.



Ejemplo 55

([(2R,5S)-1-(4-fluorofenil)pirrolidin-2,5-diil]bis{bencen-3,1-diilcarbamoil(2S)pirrolidin-2,1-diil[(2S)-3,3-dimetil-1-oxobutan-1,2-diil]})biscarbamato de dimetilo

Ejemplo 55A

1,4-bis(3-nitrofenil)butan-1,4-diona

Se agitó cloruro de cinc(II) anhidro (5,42 g, 39,7 mmol) en benceno seco (50 ml) bajo nitrógeno mientras se agregaba dietilamina (3,10 ml, 29,8 mmol) y t-butanol (2,85 ml, 29,8 mmol). La mezcla resultante se agitó a temperatura ambiente por 90 min para dar una solución turbia. A esto se agregó 1-(3-nitrofenil)etanona (4,97g, 29,8mmol) seguido por 2-bromo-1-(3-nitrofenil)etanona (5,00g, 19,87mmol) y la mezcla resultante se dejó agitar a temperatura ambiente durante la noche. Luego se eliminó una gran porción del benceno por decantación. La mezcla resultante luego se trató con ácido sulfúrico al 5% (25mL) en un embudo de separación y la fase acuosa se retiró. La fase orgánica se lavó con agua (2x25mL). Un tercer lavado resultó en una emulsión. Los contenidos del embudo se vaciaron en un volumen grande de agua (750mL) al cual se agregó cloruro de sodio y la mezcla de aceite en agua se agitó rápidamente. Se agregó metanol (75mL) en porciones para intentar dispersar el aceite y promover la solidificación del producto. Luego de casi cuarenta y ocho horas de agitación el producto solidificó y se recogió mediante filtración al vacío. La torta de filtrado se lavó con agua, se secó primero en aire y luego en un horno de vacío a 55 °C para dar el compuesto del título (5,85g, 90% de rendimiento) como un

sólido amarillo pálido que se usó directamente en el siguiente paso.

Ejemplo 55B

1,4-bis(3-nitrofenil)butan-1,4-diol

Se agregó borhidruro de sodio (0,6173 g, 17,74 mmol) a una suspensión de Ejemplo 55A (2,71 g, 8,26 mmol) en etanol (150 ml) y se agitó a temperatura ambiente por 3 horas. La reacción se detuvo con agua (~50 ml) y se concentró para dar una pasta la cual se colocó en 1:1 MeOH:THF. Esta suspensión se filtró a través de un tapón de celite y se concentró. El residuo se colocó en tolueno y se calentó con agitación para formar una pasta blanca la cual luego se sonicó y raspó hasta que se formó un sólido filtrable. Esto se filtró, se enjuagó con tolueno y se secó bajo vacío para dar 2,84 g (100%) del compuesto del título como un sólido blanco opaco. MS (DCI) *m/z* 350 $(M+NH_4)^+$.

Ejemplo 55C

dimetansulfonato de 1,4-bis(3-nitrofenil)butan-1,4-diilo

Se agregó cloruro de metansulfonilo (0,3 ml, 3,87 mmol) por goteo a una solución fría (0 °C) de Ejemplo 55B (0,5089 g, 1,531 mmol) y trietilamina (0,65 ml, 4,66 mmol) en THF (10 ml). La reacción se retiró del baño de hielo y se agitó a temperatura ambiente por 30 minutos. El solvente se eliminó bajo vacío para dar el compuesto del título como un sólido que se usó sin purificación.

Ejemplo 55D

1-(4-fluorofenil)-2,5-bis(3-nitrofenil)pirrolidina

Se mezcló Ejemplo 55C (0,733 g, 1,5 mmol) con 4-fluoroanilina (1,5 ml, 15,63 mmol) y DMF (3 ml). La reacción se agitó a 50 °C por 24 horas. La mezcla de la reacción se particionó entre EtOAc y agua. La porción orgánica se lavó con agua (2 x), salmuera (1 x), se secó ($MgSO_4$), se concentró. La purificación mediante cromatografía flash (gel de sílice, EtOAc al 0-50%/Hexanos). El material se disolvió en EtOAc y se lavó con HCl 1 M (2 x) para eliminar anilina residual, agua (1 x), NaHCO3 acuoso saturado (1 x) y salmuera (1 x) se secó ($MgSO_4$) y se concentró para dar el compuesto del título como una mezcla de isómeros cis y trans (0,45 g, 73%).

Ejemplo 55E

3,3'-(1-(4-fluorofenil)pirrolidin-2,5-diil)dianilina

Una suspensión de Pd/C (0,0527 g, 0,050 mmol) en THF (2 ml) se agregó a una solución de Ejemplo 55D (0,45 g, 1,105 mmol) en THF (7 ml)/EtOH (7 ml) bajo N_2. Se hizo pasar H_2 por recipiente y se agitó bajo 1 atm de H_2 por 20 horas. La reacción se filtró a través de un tapón de celite, se enjuagó con ~100 ml (1:1 EtOH:THF) y el solvente se eliminó bajo vacío. El material se usó sin purificación. MS (DCI) *m/z* 348 $(M+H)^+$.

Ejemplo 55F

(2S,2'S)-2,2'-(3,3'-((2S,5R)-1-(4-fluorofenil)pirrolidin-2,5-diil)bis(3,1-fenilen))bis(azandiil)bis(oxometilen)dipirrolidin-1-carboxilato de tert-butilo

Se agregó diisopropiletilamina (0,8 ml, 4,58 mmol) a una mezcla de Ejemplo 55E (0,382 g, 1,1 mmol), ácido (S)-1-(tert-butoxicarbonil)pirrolidin-2-carboxílico (0,5950 g, 2,76 mmol) y HATU (0,9196 g, 2,419 mmol) en diclorometano (12 ml). La reacción se agitó a temperatura ambiente por 1 hr, se diluyó con diclorometano, se lavó con agua (2 x), salmuera (1 x), se secó ($MgSO_4$) y se concentró para dar un residuo marrón. El residuo se colocó en éter, se sonicó y se filtró para dar el compuesto del título como un sólido color tostado. Los isómeros trans permanecieron en la solución de éter y se describen más adelante en Ejemplo 83. LC/MS temperatura ambiente 2,27 *m/z* 742 $(M+H)^+$.

Ejemplo 55G

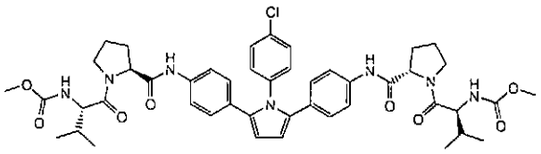
(2S,2'S)-N,N'-(3,3'-((2S,5R)-1-(4-fluorofenil)pirrolidin-2,5-diil)bis(3,1-fenilen))dipirrolidin-2-carboxamida

Se agregó TFA (3 ml, 38,9 mmol) a una solución de Ejemplo 55F (0,4033 g, 0,544 mmol) en diclorometano (10 ml). Luego de 90 minutos la reacción se concentró. El residuo se disolvió en forma consecutiva en y se concentró al vacío a partir de los siguientes solventes: diclorometano (2x), metanol (2x), y éter (1x). El semisólido se colocó en diclorometano y se lavó con $NaHCO_3$ acuoso saturado (2 x) agua (1x) salmuera (1x) se secó ($MgSO_4$) y se filtró para dar el compuesto del título. LC/MS temperatura ambiente 1,31 *m/z* 542 $(M+H)^+$.

Ejemplo 55H

([(2R,5S)-1-(4-fluorofenil)pirrolidin-2,5-diil]bis{bencen-3,1-diilcarbamoil(2S)pirrolidin-2,1-diil[(2S)-3,3-dimetil-1-oxobutan-1,2-diil]})biscarbamato de dimetilo

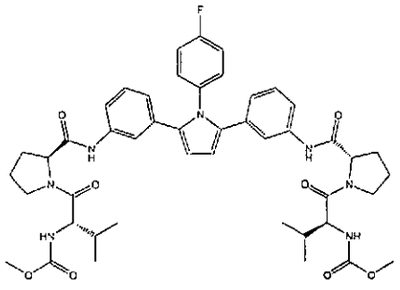
Se agregó diisopropiletilamina (0,5 ml, 2,86 mmol) a una mezcla de Ejemplo 55G, ácido (S)-2-metoxicarbonilamino-3,3-dimetil-butírico (0,2600 g, 1,374 mmol) y HATU (0,4527 g, 1,191 mmol) en diclorometano(15 ml). La reacción se agitó a temperatura ambiente por 18 horas. La reacción se diluyó con diclorometano, se lavó con agua (2x), salmuera (1x), se secó ($MgSO_4$), se concentró y se purificó mediante cromatografía flash (gel de sílice, 0-30% EtOAc/diclorometano) para dar 0,14 g (30%) del compuesto del título. ^1H RMN (400 MHz, DMSO-d6) δ 0,96 (s, 9H), 0,98 (s, 9H), 2,06 - 1,71 (m, 8H), 2,25 - 2,07 (m, 2H), 2,42 (t, J = 7,1, 2H), 3,54 (d, J = 3,2, 6H), 3,72 - 3,59 (m, 2H), 3,86 - 3,72 (m, 2H), 4,22 (d, J = 8,9, 2H), 4,51 - 4,37 (m, 2H), 4,69 (t, J = 11,9, 2H), 6,42 - 6,28 (m, 2H), 6,96 - 6,83 (m, 2H), 7,08 (t, J = 8,5, 2H), 7,39 - 7,18 (m, 4H), 7,76 - 7,54 (m, 4H), 10,03 (d, J = 9,8, 2H). MS (ESI) *m/z* 884 $(M+H)^+$, 882 $(M-H)^+$.



Ejemplo 56

([1-(4-clorofenil)-1H-pirrol-2,5-diil]bis{bencen-4,1-diilcarbamoil(2S)pirrolidin-2,1-diil[(2S)-3-metil-1-oxobutan-1,2-diil]})biscarbamato de dimetilo

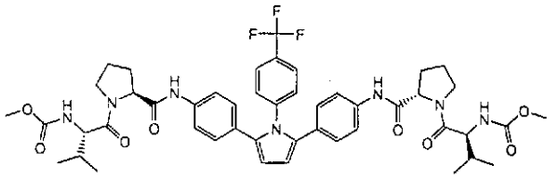
Se procesó Ejemplo 1A usando 4-cloroanilina y los métodos de los Ejemplos 19A, 19B, 19C, 19D, y 51 para dar el compuesto del título (72 mg). ^{1}H RMN (400 MHz, DMSO-d6) δ 10,00 (s, 2H), 7,45 – 7,36 (m, 6H), 7,31 (d, *J* = 8,3, 2H), 7,04 (d, *J* = 8,4, 2H), 6,96 (d, *J* = 8,6, 4H), 6,39 (s, 2H), 4,44 – 4,37 (m, 2H), 4,06 – 3,99 (m, 2H), 3,85 – 3,74 (m,2H), 3,67 – 3,56 (m, 2H), 3,52 (s, 6H), 2,20 – 2,06 (m, 2H), 2,04 – 1,79 (m, 8H), 0,92 (d, *J* = 6,7, 6H), 0,88 (d, *J* = 6,7, 6H). MS (ESI; M+H) m/z = 869.



Ejemplo 57

([1-(4-fluorofenil)-1H-pirrol-2,5-diil]bis{bencen-3,1-diilcarbamoil(2S)pirrolidin-2,1-diil[(2S)-3-metil-1-oxobutan-1,2-diil]})biscarbamato de dimetilo

Ejemplo 55A se procesó usando los métodos de Ejemplo 19A, 19B, 19C, 19D, y 19E para dar el compuesto del título. ^{1}H RMN (400 MHz, DMSO-d6) δ 0,99 - 0,84 (m, 12H), 2,05 - 1,76 (m, 8H), 2,22 - 2,05 (m, 2H), 3,53 (s, 6H), 3,70 - 3,56 (m, 2H), 3,88 - 3,71 (m, 2H), 4,11 - 3,93 (m, 2H), 4,42 (dd, J = 4,9, 7,9, 2H), 6,40 (s, 2H), 6,54 (d, J = 7,9, 2H), 7,18 - 6,98 (m, 6H), 7,34 (dd, J = 8,3, 15,4, 4H), 7,55 (s, 2H), 9,96 (d, J = 11,2, 2H). MS (ESI) *m/z* 852 $(M+H)^+$.



Ejemplo 58

({1-[4-(trifluorometil)fenil]-1H-pirrol-2,5-diil}bis{bencen-4,1-diilcarbamoil(2S)pirrolidin-2,1-diil[(2S)-3-metil-1-oxobutan-1,2-diil]})biscarbamato de dimetilo

Ejemplo 58A

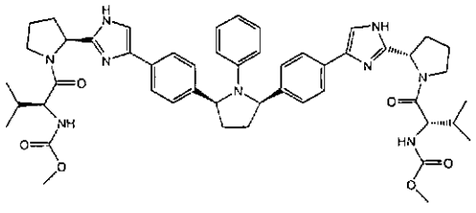
2,5-bis(4-nitrofenil)-1-(4-(trifluorometil)fenil)-1H-pirrol

A una lechada del producto del Ejemplo 1A (1,00 g, 3,05 mmol) en ácido acético (30 ml) se agregó 4-(trifluorometil)anilina (1,9 ml, 15 mmol). La mezcla se calentó a 170 °C por 15 minutos bajo irradiación de microondas. La mezcla fría se diluyó con agua y éter dietílico y se agitó enérgicamente por 15 minutos y luego se filtró. El producto crudo se purificó mediante cromatografía sobre gel de sílice eluyendo con un gradiente de solvente de acetato de etilo al 0-30% en hexano. Las fracciones que contenían el producto se combinaron y se concentró bajo presión reducida y luego se trituró con éter dietílico para dar el compuesto del título (110 mg, 8% de rendimiento).

Ejemplo 58B

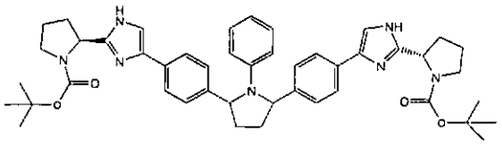
({1-[4-(trifluorometil)fenil]-1H-pirrol-2,5-diil}bis{bencen-4,1-diilcarbamoil(2S)pirrolidin-2,1-diil[(2S)-3-metil-1-oxobutan-1,2-diil]})biscarbamato de dimetilo

Ejemplo 58A se procesó usando los métodos de Ejemplos 19B, 19C, 19D, y 51 para dar el compuesto del título (44 mg). ^{1}H RMN (400 MHz, DMSO-d6) δ 10,01 (s, 2H), 7,71 (d, *J* = 8,6, 2H), 7,42 (d, *J* = 8,7, 4H), 7,31 (d, *J* = 8,2, 2H), 7,22 (d, *J* = 8,3, 2H), 6,95 (d, *J* = 8,6, 4H), 6,43 (s, 2H), 4,39 (dd, *J* = 5,2, 8,1, 2H), 4,03 (d, *J* = 8,3, 2H), 3,85 – 3,75 (m, 2H), 3,66 – 3,56 (m, 2H), 3,52 (s, 6H), 2,18 – 2,08 (m, 2H), 2,01 – 1,79 (m, 8H), 0,92 (d, *J* = 6,7, 6H), 0,87 (d, *J* = 6,6, 6H). MS (ESI; M+H) m/z = 903.



Ejemplo 59

{(2S)-1-[(2S)-2-(4-{4-[(2R,5S)-5-(4-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-4-il}fenil)-1-fenilpirrolidin-2-il]fenil}-1H-imidazol-2-il)pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo



Ejemplo 59A

(2S,2'S)-2,2'-(4,4'-(4,4'-(1-fenilpirrolidin-2,5-diil)bis(4,1-fenilen))bis(1H-imidazol-4,2-diil))dipirrolidin-1-carboxilato de tert-butilo

Ejemplo 42B y anilina se procesaron usando los métodos de Ejemplos 39D, 42D, y 42E para dar el compuesto del título como una mezcla de estereoisómeros. MS (ESI) m/z 770 (M+H)+.

Ejemplo 59B

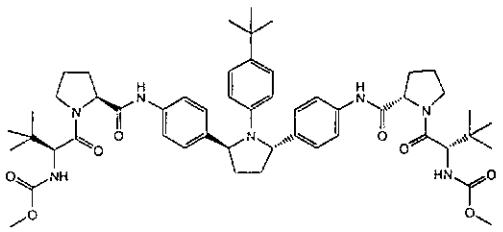
4,4'-{[(2*R*,5*S*)-1-fenilpirrolidin-2,5-diil]dibencen-4,1-diil}bis{2-[(2*S*)-pirrolidin-2-il]-1*H*-imidazol} (ACD v12)

Al producto de Ejemplo 59A (30 mg, 0,039 mmol) se agregó dimetoxietano (1,5 ml) y una solución 4N de ácido clorhídrico en dioxano (3 ml) y la solución resultante se agitó a temperatura ambiente por 1,5 hr. El solvente luego se eliminó bajo vacío y el residuo resultante se diluyó con acetonitrilo y agua (TFA al 0,1%) y se purificó mediante cromatografía de fase inversa (C18), eluyendo con 10-100% acetonitrilo en agua (TFA al 0,1%) para dar 9,8 mg (44%) del compuesto del título y 8,5 mg de una mezcla de los diastereómeros trans (MS (ESI) m/z 570 (M+H)+) que se procesaron adicionalmente como se describe en Ejemplo 89. Para el compuesto del título: MS (ESI) m/z 570 (M+H)+.

Ejemplo 59C

{(2S)-1-[(2S)-2-(4-{4-[(2R,5S)-5-(4-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-4-il}fenil)-1-fenilpirrolidin-2-il]fenil}-1H-imidazol-2-il)pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

El producto del Ejemplo 59B (9,8 mg, 0,012 mmol), ácido (S)-2-(metoxicarbonilamino)-3,3-dimetilbutanoico (5,4 mg, 0,031 mmol) y HATU (10,3 mg, 0,027 mmol) en DMSO (1 ml) se agregó base de Hunig (0,017 ml, 0,098 mmol), y la mezcla de la reacción se agitó a temperatura ambiente por 1 hr. La mezcla de la reacción se particionó entre agua y acetato de etilo, y la capa orgánica se secó sobre $MgSO_4$, se filtró y se concentró al vacío. El producto crudo se purificó mediante cromatografía de fase inversa (C18), eluyendo con 10-100% acetonitrilo en agua (TFA al 0,1%) para dar 4,5 mg (41%) del compuesto del título. 1H RMN (Sal TFA) (400 MHz, DMSO-D6) δ ppm 14,50 (bs, 2 H), 7,99 (s, 2 H), 7,78 (m, 4 H), 7,65 (m, 4H), 7,32 (m, 2H), 7,02 (t, *J*=8,0 Hz, 2 H), 6,63 (t, *J*=7,4 Hz, 1 H), 6,40 (d, *J*=8,2 Hz, 2 H), 5,11 (t, *J*=6,9 Hz, 2 H), 4,83 (m, 2H), 4,10 (t, *J*=7,7 Hz, 2 H), 3,82 (m, 6 H), 3,48 (s, 6 H), 2,40 (m, 2 H), 2,08 (m, 2 H), 2,00 (m, 6 H), 1,85 (m, 2 H), 0,85 (m, 2 H), 0,80 (m, 12 H); MS (ESI) m/z 884 (M+H)+.



Ejemplo 60

([(2S,5S)-1-(4-tert-butilfenil)pirrolidin-2,5-diil]bis{bencen-4,1-diilcarbamoil(2S)pirrolidin-2,1-diil[(2S)-3,3-dimetil-1-oxobutan-1,2-diil]})biscarbamato de dimetilo

Ejemplo 60A

000612

([(2S,5S)-1-(4-tert-butilfenil)pirrolidin-2,5-diil]bis{bencen-4,1-diilcarbamoil(2S)pirrolidin-2,1-diil[(2S)-3,3-dimetil-1-oxobutan-1,2-diil]})biscarbamato de dimetilo

y

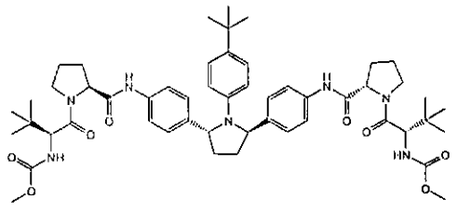
([(2R,5R)-1-(4-tert-butilfenil)pirrolidin-2,5-diil]bis{bencen-4,1-diilcarbamoil(2S)pirrolidin-2,1-diil[(2S)-3,3-dimetil-1-oxobutan-1,2-diil]})biscarbamato de dimetilo

El producto del Ejemplo 34D (29,0 mg, 0,05 mmol), ácido (S)-2-(metoxicarbonilamino)-3,3-dimetilbutanoico (20,81 mg, 0,110 mmol), EDC (21,09 mg, 0,110 mmol), HOBT (16,85 mg, 0,110 mmol) y N-metilmorfolina (0,027 ml, 0,250 mmol) se combinaron en DMF (2 ml). La mezcla se agitó a temperatura ambiente por 3 horas. La mezcla de la reacción se particionó entre acetato de etilo y agua. La capa orgánica se lavó con salmuera dos veces, se secó con sulfato de sodio, se filtró y se evaporó. El residuo se purificó mediante cromatografía sobre gel de sílice eluyendo con acetato de etilo/hexano (50% a 80%) para dar el compuesto del título (32 mg, 69%) como una mezcla de trans diastereómeros.

Ejemplo 60B

([(2S,5S)-1-(4-tert-butilfenil)pirrolidin-2,5-diil]bis{bencen-4,1-diilcarbamoil(2S)pirrolidin-2,1-diil[(2S)-3,3-dimetil-1-oxobutan-1,2-diil]})biscarbamato de dimetilo

El producto del Ejemplo 60A se purificó mediante cromatografía quiral en una columna semipreparativa Chiralpak AD-H eluyendo con una mezcla 3:1 de hexano:(2:1 IPA:EtOH). El compuesto del título fue el primero de los 2 diastereómeros en eluir. ^{1}H RMN (400 MHz, DMSO-D6) δ ppm 0,97 (s, 18 H) 1,11 (s, 9 H) 1,60 - 1,65 (m, 2 H) 1,79 - 1,91 (m, 4 H) 1,94 - 2,03 (m, 2 H) 2,10 - 2,18 (m, 2 H) 2,44 - 2,50 (m, 2 H) 3,54 (s, 6 H) 3,59 - 3,67 (m, 2 H) 3,71 - 3,82 (m, 2 H) 4,21 (d, J=8,89 Hz, 2 H) 4,43 (dd, J=7,92, 5,42 Hz, 2 H) 5,14 (d, J=6,40 Hz, 2 H) 6,18 (d, J=8,89 Hz, 2 H) 6,94 (d, J=8,78 Hz, 2 H) 7,08 (d, J=8,78 Hz, 2 H) 7,13 (d, J=8,57 Hz, 4 H) 7,50 (d, J=8,46 Hz, 4 H) 9,99 (s, 2 H); MS (ESI+) m/z 923 (M+H)+.



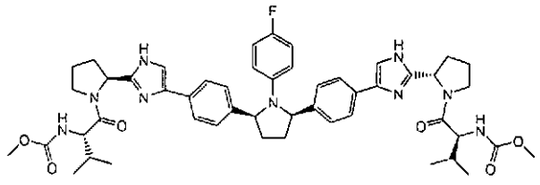
Ejemplo 61

([(2R,5R)-1-(4-tert-butilfenil)pirrolidin-2,5-diil]bis{bencen-4,1-diilcarbamoil(2S)pirrolidin-2,1-diil[(2S)-3,3-dimetil-1-oxobutan-1,2-diil]})biscarbamato de dimetilo

El producto del Ejemplo 60A se purificó mediante cromatografía quiral en una columna semipreparativa Chiralpak AD-H eluyendo con una mezcla 3:1 de hexano:(2:1 IPA:EtOH). El compuesto del título fue el segundo de los 2 diaestereoisómeros en eluir. ^{1}H RMN (400

000013

MHz, DMSO-D6) δ ppm 0,96 (s, 18 H) 1,11 (s, 9 H) 1,60 - 1,66 (m, 2 H) 1,78 - 1,92 (m, 4 H) 1,94 - 2,04 (m, 2 H) 2,08 - 2,19 (m, 2 H) 2,42 - 2,50 (m, 2 H) 3,54 (s, 6 H) 3,59 - 3,67 (m, 2 H) 3,74 - 3,81 (m, 2 H) 4,20 (d, J=8,89 Hz, 2 H) 4,43 (dd, J=7,97, 5,37 Hz, 2 H) 5,15 (d, J=6,29 Hz, 2 H) 6,17 (d, J=8,89 Hz, 2 H) 6,94 (d, J=8,89 Hz, 2 H) 7,07 (d, J=8,89 Hz, 2 H) 7,13 (d, J=8,46 Hz, 4 H) 7,50 (d, J=8,57 Hz, 4 H) 9,99 (s, 2 H); MS (ESI+) m/z 923 (M+H)+.



Ejemplo 62

{(2S)-1-[(2S)-2-(4-{4-[(2R,5S)-1-(4-fluorofenil)-5-(4-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-4-il}fenil)pirrolidin-2-il]fenil}-1H-imidazol-2-il)pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

Ejemplo 62A

4,4'-{[(2*R*,5*S*)-1-(4-fluorofenil)pirrolidin-2,5-diil]dibencen-4,1-diil}bis{2-[(2*S*)-pirrolidin-2-il]-1*H*-imidazol} (ACD v12)

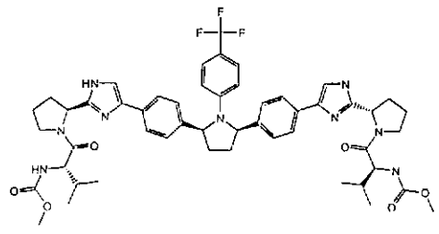
El producto del Ejemplo 45C (0,15 g, 0,190 mmol) en CH_2Cl_2 (1 ml) se trató con TFA (1 ml), y la mezcla resultante se agitó a temperatura ambiente por 1h y luego se concentró al vacío. El producto crudo se purificó mediante cromatografía de columna en una columna de sílice C18 usando un gradiente de solvente de 10-100% CH_3CN en TFA acuoso al 0,1%. El isómero cis-pirrolidina deseado fue el segundo de 2 componentes en eluir. Las fracciones que contenían isómero cis puro se juntaron y se concentró al vacío. El residuo se particionó entre $NaHCO_3$ acuoso saturado y una mezcla 3:1 de CH_2Cl_2:2-PrOH (3x). Las capas orgánicas combinadas se secaron sobre Na_2SO_4, se filtró y se concentró al vacío para dar el compuesto del título (32 mg, 28%).

Ejemplo 62B

{(2S)-1-[(2S)-2-(4-{4-[(2R,5S)-1-(4-fluorofenil)-5-(4-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-4-il}fenil)pirrolidin-2-il]fenil}-1H-imidazol-2-il)pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

El producto del Ejemplo 62A (32 mg, 54 mmol) se sometió al método descrito en Ejemplo 5D, utilizando ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico en lugar de ácido (S)-2-(metoxicarbonilamino)butanoico, para dar el compuesto del título (34 mg, 69%). ^{1}H RMN (400 MHz, DMSO-D6) δ ppm 0,78 - 0,93 (m, 12 H), 1,78 - 2,24 (m, 12 H), 2,37 - 2,46 (m, 2 H), 3,54 (s, 6 H), 3,68 - 3,87 (m, 4 H), 4,66 - 4,79 (m, 2 H), 5,02 - 5,13 (m, 2 H), 6,39 (dd, *J*=9,16, 4,50 Hz, 2 H), 6,81 - 6,92 (m, 2 H), 7,23 - 7,34 (m, 2 H), 7,39 - 7,80 (m, 12 H),

11,67 - 12,12 (m, 2 H); MS (ESI) m/z 902,7 $(M+H)^+$.



Ejemplo 63

[(2S)-1-{(2S)-2-[4-(4-{(2R,5S)-5-(4-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-4-il}fenil)-1-[4-(trifluorometil)fenil]pirrolidin-2-il}fenil)-1H-imidazol-2-il]pirrolidin-1-il}-3-metil-1-oxobutan-2-il]carbamato de metilo

Ejemplo 63A

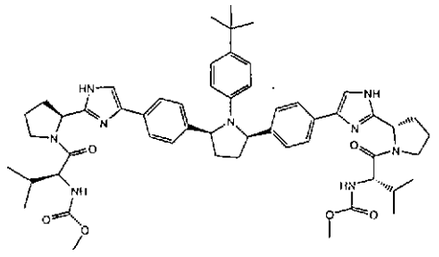
(2R,5S)-2,5-bis(4-bromofenil)-1-(4-(trifluorometil)fenil)pirrolidina

El producto del Ejemplo 42B (11,13 g, 20,0 mmol) y 4-(trifluorometil)anilina (Aldrich, 32,2 g, 200 mmol) se combinaron en DMF (50 ml), se agitó a 50 °C bajo nitrógeno por 16 horas, se enfrió y se concentró. El residuo se diluyó con acetato de etilo, se trató con HCl 1M, se agitó por 10 minutos y se filtró para eliminar los sólidos. La capa orgánica del material filtrado se lavó con salmuera, se secó (Na_2SO_4), se filtró y se concentró. El residuo se purificó mediante cromatografía flash (gel de sílice, 0-1% acetato de etilo/hexano) para dar el compuesto del título (1,0 g, 10 %) como el segundo estereoisómero en eluir. MS (ESI+) m/z 526 $(M+H)^+$.

Ejemplo 63B

[(2S)-1-{(2S)-2-[4-(4-{(2R,5S)-5-(4-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-4-il}fenil)-1-[4-(trifluorometil)fenil]pirrolidin-2-il}fenil)-1H-imidazol-2-il]pirrolidin-1-il}-3-metil-1-oxobutan-2-il]carbamato de metilo

El producto del Ejemplo 63A (1,0 g, 1,90 mmol) se procesó usando los métodos descritos en Ejemplo 42D, 42E, 42F, y 42G para dar el compuesto del título. ^1H RMN (base libre) (400 MHz, DMSO-d_6) δ 0,80 - 0,95 (m, 12 H) 1,83 - 2,18 (m, 14 H) 3,54 (s, 6 H) 3,79 (d, J=6,18 Hz, 3 H) 3,97 - 4,15 (m, 3 H) 4,87 (d, J=4,88 Hz, 2 H) 5,02 - 5,14 (m, 2 H) 6,54 (d, J=8,67 Hz, 2 H) 7,15 - 7,80 (m, 14 H) 11,56 - 12,30 (m, 2 H); MS (ESI+) m/z 953 $(M+H)^+$.



Ejemplo 64

000015

{(2S)-1-[(2S)-2-(4-{4-[(2R,5S)-1-(4-tert-butilfenil)-5-(4-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-4-il}fenil)pirrolidin-2-il]fenil}-1H-imidazol-2-il)pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

Ejemplo 64A

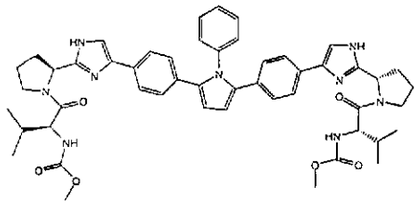
(2S,2'R)-2,2'-(4,4'-(4,4'-(1-(4-tert-butilfenil)pirrolidin-2,5-diil)bis(4,1-fenilen))bis(1H-imidazol) bis sal trifluoroacetato

Ejemplo 42C se procesó usando los métodos de Ejemplos 42D, 42E, y 42F para dar una mezcla de isómeros cis/trans pirrolidina. La mezcla de estereoisómeros se disolvió en 10 ml de 80% (TFA al 0,1%/agua):20% CH_3CN y se aplicó a una columna C18 de 13 g de sílice. La columna se eluyó con un gradiente de TFA al 0,1%(ac):CH3CN; 80/20 a 50:50 a lo largo de 25 minutos, para dar el estereoisómero cis del compuesto del título como una sal trifluoroacetato sólida amarillo claro, 88,6 mg, 58%.

Ejemplo 64B

{(2S)-1-[(2S)-2-(4-{4-[(2R,5S)-1-(4-tert-butilfenil)-5-(4-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-4-il}fenil)pirrolidin-2-il]fenil}-1H-imidazol-2-il)pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

El producto del Ejemplo 64A se disolvió en 1 ml de DMF y se agregó por goteo a una solución fría (0-5 °C) con ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico (0,41g, 0,232 mmol), HOBt (0,036g, 0,232 mmol), EDAC (0,045 g, 0,232 mmol) y 4-metilmorfolina (0,138g, 0,150 ml, 1,364 mmol) en 0,5 ml de DMF. El pH de la solución se midió y era de 8. La reacción se agitó a total de 3,5 hr en el baño de hielo. La mezcla de la reacción se diluyó con 50 ml de EtOAc y se lavó con $NaHCO_3$ al 10%, NaCl al 10%, se secó sobre Na_2SO_4 anhidro(s), se filtró y el solvente se eliminó al vacío para dar un aceite rosáceo. El aceite se disolvió en 5 ml de CH_2Cl_2 y se aplicó a una columna de 12g de gel de sílice. La columna se eluyó con un gradiente de CH_2Cl_2/MeOH, 99/1 a 94/6 a lo largo de 25 minutos para dar el compuesto del título como un sólido blanco, 12,5 mg, 11%. 1H RMN (400 MHz, DMSO-D6) d ppm 0,85 (s, 12 H) 1,13 (s, 9 H) 1,95 (s, 6 H) 2,15 (s, 4 H) 2,50 (s, 3 H) 3,43 (s, 1 H) 3,54 (s, 5 H) 3,80 (s, 4 H) 4,05 (s, 2 H) 4,70 (s, 2 H) 5,07 (s, 1 H) 6,36 (d, J=8,78 Hz, 2 H) 7,01 (s, 2 H) 7,28 (s, 2 H) 7,47 (s, 6 H) 7,70 (s, 4 H) 11,71 (s, 2 H) 12,09 (s, 2 H)ESI+:940,8



Ejemplo 65

{(2S)-1-[(2S)-2-(4-{4-[5-(4-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-4-il}fenil)-1-fenil-1H-pirrol-2-il]fenil}-1H-imidazol-2-il)pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

Ejemplo 65A

(2S,2'R)-2,2'-(4,4'-(4,4'-(1-fenil-1H-pirrol-2,5-diil)bis(4,1-fenilen))bis(1H-imidazol-4,2-diil))dipirrolidin-1-carboxilato de tert-butilo

Ejemplo 26E y anilina se procesaron usando los métodos de Ejemplos 19A, 26G, y 26H para dar el compuesto del título (150 mg).

Ejemplo 65B

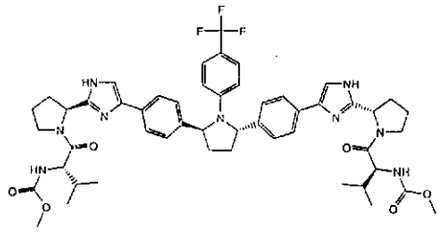
(S)-4,4'-(4,4'-(1-fenil-1H-pirrol-2,5-diil)bis(4,1-fenilen))bis(2-((S)-pirrolidin-2-il)-1H-imidazol)

A una suspensión del producto del Ejemplo 65A (186 mg, 0,243 mmol) en dioxano (5 ml) se agregó HCl/dioxano (5 ml, 20 mmol). La mezcla se agitó por 30 minutos y luego se concentró bajo presión reducida para dar el compuesto del título como una sal clorhidrato.

Ejemplo 65C

{(2S)-1-[(2S)-2-(4-{4-[5-(4-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-4-il}fenil)-1-fenil-1H-pirrol-2-il]fenil}-1H-imidazol-2-il)pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

Una solución que consistía en clorhidrato de N1-((etilimino)metilen)-N3,N3-dimetilpropan-1,3-diamina (90 mg, 0,47 mmol), hidrato de 1H-benzo[d][1,2,3]triazol-1-ol (72 mg, 0,47 mmol), ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico (82 mg, 0,47 mmol) y 4-metilmorfolina (0,28 ml, 2,6 mmol) en DMF (1,6 ml) se enfrió en un baño de hielo. A esta mezcla se agregó por goteo una solución del producto del Ejemplo 65B (150 mg, 0,23 mmol) en DMF (0,5 ml). Se agregó 4-metilmorfolina adicional a la mezcla hasta que el pH se ajustó a 8. La reacción se agitó por 3,5 horas y luego el baño de hielo se retiró y la reacción se agitó por otras 16 horas. Luego se agregó agua a la mezcla de la reacción y el precipitado resultante se recuperó mediante filtración. El residuo se lavó con cantidades copiosas de agua seguido por éter dietílico. El producto crudo se purificó mediante cromatografía sobre gel de sílice eluyendo con un gradiente de solvente de metanol al 0-5% en CH_2Cl_2 para dar el compuesto del título. ^{1}H RMN (400 MHz, DMSO-d6) δ 12,12 – 11,64 (m, 2H), 7,57 – 7,45 (m, 4H), 7,42 – 7,36 (m, 2H), 7,36 – 7,29 (m, 3H), 7,29 – 7,05 (m,4H), 7,04 – 6,91 (m, 4H), 6,54 – 6,43 (m, 2H), 5,06 – 4,96 (m, 2H), 4,06 – 3,96 (m, 2H), 3,84 – 3,67 (m, 4H), 3,52 (s, 6H), 2,17 – 1,80 (m, 10H), 0,91 – 0,76 (m, 12H). MS (ESI; M+H) m/z = 881.



Ejemplo 66

[(2S)-1-{(2S)-2-[4-(4-{(2S,5S)-5-(4-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-4-il}fenil)-1-[4-(trifluorometil)fenil]pirrolidin-2-il}fenil)-1H-imidazol-2-il]pirrolidin-1-il}-3-metil-1-oxobutan-2-il]carbamato de metilo

Ejemplo 66A

(2R,5R)-2,5-bis(4-bromofenil)-1-(4-(trifluorometil)fenil)pirrolidina

y

(2S,5S)-2,5-bis(4-bromofenil)-1-(4-(trifluorometil)fenil)pirrolidina

El producto del Ejemplo 42B (11,13 g, 20,0 mmol) y 4-(trifluorometil)anilina (32,2 g, 200 mmol) se combinaron en DMF (50 ml). La mezcla se agitó a 50 °C bajo nitrógeno durante la noche. La mezcla de la reacción se evaporó y el residuo se diluyó con acetato de etilo, se trató con HCl 1M, se agitó por 10 minutos, y se filtró para eliminar el sólido. La capa orgánica del material filtrado se lavó con salmuera, se secó con sulfato de sodio, se filtró y se evaporó. El residuo se purificó mediante cromatografía sobre gel de sílice eluyendo con acetato de etilo/hexano (0 a 1%). Los compuestos del título (500 mg, 5%) se eluyeron como el primero de 2 estereoisómeros y se obtuvieron como una mezcla de diastereómeros trans.

Ejemplo 66B

(2R,5R)-2,5-bis(4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)-1-(4-(trifluorometil)fenil)pirrolidina

y

(2S,5S)-2,5-bis(4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)-1-(4-(trifluorometil)fenil)pirrolidina

Los productos del Ejemplo 66A (500 mg, 0,952 mmol), bis(pinacolato)diboro (725 mg, 2,86 mmol), acetato de potasio (374 mg, 3,81 mmol) y cloruro de bis(trifenilfosfin)paladio(II) (66,8 mg, 0,095 mmol) se combinaron en 1,2-dimetoxietano (10 ml). La mezcla se purgó con nitrógeno por 15 minutos y se agitó a 85 °C por 2 horas. La mezcla de la reacción se particionó entre acetato de etilo y HCl 1M. La capa orgánica se lavó con bicarbonato de sodio saturado, salmuera, se secó con sulfato de sodio, se filtró y se evaporó. El residuo se purificó mediante cromatografía sobre gel de sílice eluyendo con hexano a acetato de etilo/hexano (10%) para dar un sólido el cual se trituró con

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diclorometano/hexano (1:3) para dar los compuestos del título (370 mg, 63%).

Ejemplo 66C

(2S,2'S)-2,2'-(4,4'-(4,4'-((2R,5R)-1-(4-(trifluorometil)fenil)pirrolidin-2,5-diil)bis(4,1-fenilen))bis(1H-imidazol-4,2-diil))dipirrolidin-1-carboxilato de tert-butilo

y

(2S,2'S)-2,2'-(4,4'-(4,4'-((2S,5S)-1-(4-(trifluorometil)fenil)pirrolidin-2,5-diil)bis(4,1-fenilen))bis(1H-imidazol-4,2-diil))dipirrolidin-1-carboxilato de tert-butilo

Los productos del Ejemplo 66B (257 mg, 0,415 mmol), el producto del Ejemplo 26D (341 mg, 1,079 mmol), fosfato de potasio tribásico (352 mg, 1,660 mmol) y dicloruro de 1,1'-bis(di-tert-butilfosfin)ferrocenopaladio (27,0 mg, 0,041 mmol) se combinaron en THF (4,5 ml)/ agua (1,5 ml). La mezcla se purgó con nitrógeno por 15 minutos y se agitó a 70 °C por 6 horas. La mezcla de la reacción se particionó entre acetato de etilo y bicarbonato de sodio saturado. La capa orgánica se lavó con salmuera, se secó con sulfato de sodio, se filtró y se evaporó. El residuo se purificó mediante cromatografía sobre gel de sílice eluyendo con metanol/diclorometano (1% a 3%) para dar los compuestos del título (286 mg, 82%) como un sólido.

Ejemplo 66D

(S)-4,4'-(4,4'-((2R,5R)-1-(4-(trifluorometil)fenil)pirrolidin-2,5-diil)bis(4,1-fenilen))bis(2-((S)-pirrolidin-2-il)-1H-imidazol)

y

(S)-4,4'-(4,4'-((2S,5S)-1-(4-(trifluorometil)fenil)pirrolidin-2,5-diil)bis(4,1-fenilen))bis(2-((S)-pirrolidin-2-il)-1H-imidazol)

A los productos del Ejemplo 66C (385 mg, 0,459 mmol) en dioxano (6 ml) se agregó ácido clorhídrico 4M en dioxano (10 ml, 40,0 mmol) y la reacción se agitó a temperatura ambiente por 1 hora. El solvente se evaporó bajo alto vacío para dar los compuestos del título (aprox. 360 mg) como sales clorhidrato.

Ejemplo 66E

[(2S)-1-{(2S)-2-[4-(4-{(2S,5S)-5-(4-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-4-il}fenil)-1-[4-(trifluorometil)fenil]pirrolidin-2-il}fenil)-1H-imidazol-2-il]pirrolidin-1-il}-3-metil-1-oxobutan-2-il]carbamato de metilo

y

[(2S)-1-{(2S)-2-[4-(4-{(2R,5R)-5-(4-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-4-il}fenil)-1-[4-(trifluorometil)fenil]pirrolidin-2-il}fenil)-1H-imidazol-2-il]pirrolidin-1-il}-3-metil-1-oxobutan-2-il]carbamato de metilo

El producto del Ejemplo 66D (360 mg, 0,459 mmol), ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico (161 mg, 0,919 mmol), 4-metilmorfolina (0,404 ml, 3,68 mmol), clorhidrato

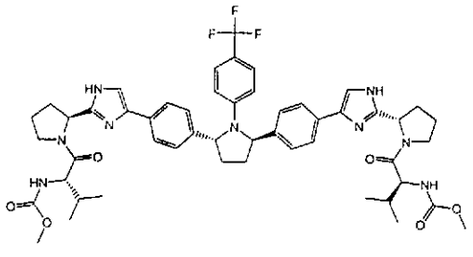
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de N1-((etilimino)metilen)-N3,N3-dimetilpropan-1,3-diamina (194 mg, 1,011 mmol) y hidrato de 1H-benzo[d][1,2,3]triazol-1-ol (155 mg, 1,011 mmol) se combinaron en DMF (10 ml). La mezcla se agitó a temperatura ambiente por 20 horas. La mezcla de la reacción se particionó entre acetato de etilo y agua. La capa orgánica se lavó con bicarbonato de sodio saturado, salmuera dos veces, se secó con sulfato de sodio, se filtró y se evaporó. El residuo se purificó mediante cromatografía sobre gel de sílice eluyendo con metanol/diclorometano (1% a 6%) para dar los compuestos del título (223 mg, 51%) como un sólido.

Ejemplo 66F

[(2S)-1-{(2S)-2-[4-(4-{(2S,5S)-5-(4-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-4-il}fenil)-1-[4-(trifluorometil)fenil]pirrolidin-2-il}fenil)-1H-imidazol-2-il]pirrolidin-1-il}-3-metil-1-oxobutan-2-il]carbamato de metilo

El producto del Ejemplo 66E se purificó mediante cromatografía quiral en una columna Chiralpak IB eluyendo con una mezcla de hexano/THF/metanol (8/1/1). El compuesto del título fue el primero de los 2 diastereómeros en eluir. ^{1}H RMN (400 MHz, DMSO-D6) δ ppm 0,78 - 0,90 (m, 12 H) 1,71 - 1,77 (m, 2 H) 1,86 - 2,02 (m, 6 H) 2,09 - 2,18 (m, 4 H) 2,51 - 2,54 (m, 2 H) 3,53 (s, 6 H) 3,74 - 3,84 (m, 4 H) 4,04 (t, J=8,35 Hz, 2 H) 5,06 (dd, J=6,83, 3,14 Hz, 2 H) 5,28 - 5,41 (m, 2 H) 6,41 (d, J=8,67 Hz, 2 H) 7,12 - 7,33 (m, 8 H) 7,36 - 7,72 (m, 6 H) 11,62 - 12,13 (m, 2 H); MS (ESI+) m/z 953 (M+H)+.

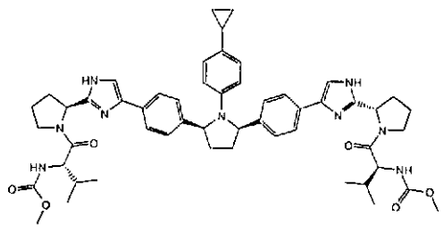


Ejemplo 67

[(2S)-1-{(2S)-2-[4-(4-{(2R,5R)-5-(4-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-4-il}fenil)-1-[4-(trifluorometil)fenil]pirrolidin-2-il}fenil)-1H-imidazol-2-il]pirrolidin-1-il}-3-metil-1-oxobutan-2-il]carbamato de metilo

El producto del Ejemplo 66E se purificó mediante cromatografía quiral en una columna Chiralpak IB eluyendo con una mezcla de hexano/THF/metanol (8/1/1). El compuesto del título fue el segundo de los 2 diaestereoisómeros en eluir. ^{1}H RMN (400 MHz, DMSO-D6) δ ppm 0,79 - 0,91 (m, 12 H) 1,71 - 1,77 (m, 2 H) 1,88 - 2,01 (m, 6 H) 2,08 - 2,17 (m, 4 H) 2,51 - 2,54 (m, 2 H) 3,53 (s, 6 H) 3,74 - 3,82 (m, 4 H) 4,05 (t, J=8,40 Hz, 2 H) 5,00 - 5,13 (m, 2 H) 5,29 - 5,40 (m, 2 H) 6,40 (d, J=8,57 Hz, 2 H) 7,12 - 7,31 (m, 8 H) 7,36 - 7,72 (m, 6 H) 11,52 - 12,15 (m, 2 H); MS (ESI+) m/z 953 (M+H)+.

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Ejemplo 68

{(2S)-1-[(2S)-2-(4-{4-[(2R,5S)-1-(4-ciclopropilfenil)-5-(4-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-4-il}fenil)pirrolidin-2-il]fenil}-1H-imidazol-2-il)pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

Ejemplo 68A

2,5-bis(4-bromofenil)-1-(4-ciclopropilfenil)pirrolidina

El producto del Ejemplo 42B (3,14 g, 5,64 mmol) y 4-ciclopropilanilina (6,01 g, 45,2 mmol) se combinaron en DMF (20 ml). La mezcla se agitó a 50 °C bajo nitrógeno por 3 horas. La mezcla de la reacción se particionó entre HCl 1M y acetato de etilo. La capa orgánica se lavó con salmuera tres veces, se secó con sulfato de sodio, se filtró y se evaporó. El residuo se purificó mediante cromatografía sobre gel de sílice eluyendo con acetato de etilo/hexano (0,5% a 1%) para dar el compuesto del título (2,12g, 76%) como una mezcla de estereoisómeros como un sólido pegajoso.

Ejemplo 68B

1-(4-ciclopropilfenil)-2,5-bis(4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)pirrolidina

El producto del Ejemplo 68A (2,12 g, 4,26 mmol), bis(pinacolato)diboro (3,25 g, 12,79 mmol), acetato de potasio (1,674 g, 17,05 mmol) y cloruro de bis(trifenilfosfin)paladio(II) (0,299 g, 0,426 mmol) se combinaron en 1,2-dimetoxietano (40 ml). La mezcla se purgó con nitrógeno por 15 minutos y se agitó a 85 °C por 2 horas. La mezcla de la reacción se particionó entre acetato de etilo y HCl 1M. La capa orgánica se lavó con bicarbonato de sodio saturado, salmuera, se secó con sulfato de sodio, se filtró y se evaporó. El residuo se purificó mediante cromatografía sobre gel de sílice eluyendo con hexano a acetato de etilo/hexano (10%) para dar un sólido el cual se trituró con éter dietílico/hexano (1/3) para dar el compuesto del título (1,05, 42%) como una mezcla de estereoisómeros como un sólido blanco.

Ejemplo 68C

(2S,2'S)-2,2'-(4,4'-(4,4'-(1-(4-ciclopropilfenil)pirrolidin-2,5-diil)bis(4,1-fenilen))bis(1H-imidazol-4,2-diil))dipirrolidin-1-carboxilato de tert-butilo

El producto del Ejemplo 68B (1,04 g, 1,759 mmol), el producto del Ejemplo 26D (1,446 g, 4,57 mmol), $PdCl_2$(dppf) (0,129g, 0,176 mmol) y carbonato de sodio 1,0 M (4,57 ml, 4,57 mmol) se combinaron en la mezcla de solventes de etanol (5 ml)/tolueno (5 ml). La mezcla

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se purgó con nitrógeno por 15 minutos y se agitó a 80 °C por 2 horas. La mezcla de la reacción se particionó entre acetato de etilo y bicarbonato de sodio saturado, salmuera, se secó con sulfato de sodio, se filtró y se evaporó. El residuo se purificó mediante cromatografía sobre gel de sílice eluyendo con metanol/diclorometano (1% a 3%) para dar el compuesto del título (1,28 g, 90%) como una mezcla de estereoisómeros como un sólido.

Ejemplo 68D

(S)-4,4'-(4,4'-((2R,5S)-1-(4-ciclopropilfenil)pirrolidin-2,5-diil)bis(4,1-fenilen))bis(2-((S)-pirrolidin-2-il)-1H-imidazol)

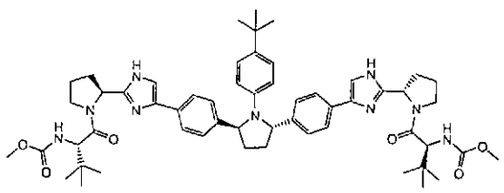
El producto del Ejemplo 68C (1,27 g, 1,568 mmol) se disolvió en diclorometano (12 ml). La mezcla se enfrió a 0 °C y ácido trifluoroacético (8 ml, 104 mmol) se agregó lentamente. La mezcla se calentó a temperatura ambiente y se agitó por 1h. El solvente se evaporó y el residuo se purificó mediante cromatografía sobre gel de sílice eluyendo con metanol/diclorometano (1% a 10%). El compuesto del título (310 mg, 32%) eluyó como el segundo de 2 estereoisómeros.

Ejemplo 68E

{(2S)-1-[(2S)-2-(4-{4-[(2R,5S)-1-(4-ciclopropilfenil)-5-(4-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-4-il}fenil)pirrolidin-2-il]fenil}-1H-imidazol-2-il)pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

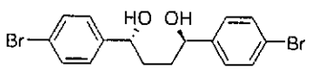
El producto de Ejemplo 68D (90 mg, 0,148 mmol), ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico (51,7 mg, 0,295 mmol), 4-metilmorfolina (0,130 ml, 1,181 mmol), clorhidrato de N1-((etilimino)metilen)-N3,N3-dimetilpropan-1,3-diamina (62,2 mg, 0,325 mmol) y hidrato de 1H-benzo[d][1,2,3]triazol-1-ol (49,7 mg, 0,325 mmol) se combinaron en DMF (10 ml). La mezcla se agitó a temperatura ambiente por 2 horas. La mezcla de la reacción se particionó entre acetato de etilo y agua. La capa orgánica se lavó con bicarbonato de sodio saturado, salmuera dos veces, se secó con sulfato de sodio, se filtró y se evaporó. El residuo se purificó mediante cromatografía sobre gel de sílice eluyendo con metanol/diclorometano (1% a 4%) para dar el compuesto del título (40 mg, 29%) como un sólido. ^{1}H RMN (400 MHz, DMSO-D6) δ ppm 0,39-0,47 (m, 2 H) 0,71 - 0,78 (m, 2 H) 0,82 - 0,92 (m, 12 H) 1,65 - 1,72 (m, 1 H) 1,82 - 2,03 (m, 8 H) 2,09 - 2,17 (m, 4 H) 2,40 - 2,45 (m, 2 H) 3,54 (s, 6 H) 3,75 - 3,83 (m, 4 H) 4,02 - 4,09 (m, 2 H) 4,64 - 4,75 (m, 2 H) 5,03 - 5,11 (m, 2 H) 6,32 (d, J=8,67 Hz, 2 H) 6,73 (d, J=8,35 Hz, 2 H) 7,29 (d, J=8,02 Hz, 2 H) 7,37 - 7,81 (m, 10 H) 11,47 - 12,17 (m, 2 H); MS (ESI+) m/z 924,7 (M+H)+.

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Ejemplo 69

{(2S)-1-[(2S)-2-(4-{4-[(2S,5S)-1-(4-tert-butilfenil)-5-(4-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3,3-dimetilbutanoil}pirrolidin-2-il]-1H-imidazol-4-il}fenil)pirrolidin-2-il]fenil}-1H-imidazol-2-il)pirrolidin-1-il]-3,3-dimetil-1-oxobutan-2-il}carbamato de metilo



Ejemplo 69A

(1R,4R)-1,4-bis(4-bromofenil)butan-1,4-diol

A (S)-(-)-alfa, alfa-difenil-2-pirrolidinmetanol (3,81 g, 15,04 mmol) se agregó THF (140 ml) a 23 °C. La lechada delgada se trató con borato de trimetilo (2,189 ml, 19,63 mmol) para formar una solución traslúcida. Luego de agitar por 1,5 h, la solución se enfrió a 10-15 °C, y se agregó N,N-dietilanilina borano (33,1 ml, 186 mmol) durante 5-10 min con una jeringa. Se observó una leve reacción exotérmica y evolución de H_2. A un recipiente separado se cargó Ejemplo 26E (35,045 g, 88 mmol), seguido por THF (140 ml), para formar una lechada. La lechada se enfrió a 10 °C. La solución fría de borano se transfirió mediante cánulos a la lechada de diona a lo largo de aproximadamente 5 minutos, manteniendo la temperatura interna <25 °C. Luego de completarse la transferencia, la lechada se mantuvo a 15 °C por 5 min y luego la temperatura se mantuvo a 23 °C por 3 h. Luego de completarse la reacción, la solución se enfrió a 5 °C, y se agregó metanol (31,6 ml, 780 mmol) lentamente para mantener una temperatura <20 °C (*nota: evolución enérgica de hidrógeno).* La solución brumosa se mezcló por 1 h adicional para asegurar la detención total. La solución brumosa se diluyó con EtOAc (500 ml) y HCl 1 M (220 ml). Las fases se particionaron, y la fase orgánica se lavó en forma sucesiva con HCl 1 M (2 x 220 ml), H_2O (110 ml), y NaCl acuoso al 25% (110 ml). La capa orgánica se concentró al vacío, luego se disolvió en EtOAc, se filtró, se concentró y se cristalizó a partir de EtOAc/hexano para dar el compuesto del título (16,92 g; 100% ee; 47% de rendimiento aislado).

Ejemplo 69B

(2S,5S)-2,5-bis(4-bromofenil)-1-(4-tert-butilfenil)pirrolidina

A una mezcla del producto del Ejemplo 69A (0,60 g, 1.500 mmol) en CH_2Cl_2 anhidro (15

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ml) a 0 °C se agregó Et_3N (0,627 ml, 4,50 mmol), y la mezcla resultante se agitó a 0 °C por 10 min hasta que se obtuvo una solución homogénea. A la solución fría se agregó cloruro de metansulfonilo (0,292 ml, 3,75 mmol) por goteo, y la mezcla resultante se agitó a 0 °C por 1,5 h hasta que se completó la reacción según se determinó mediante TLC (1:1 EtOAc:hexanos). El solvente se eliminó al vacío para dar un sólido, el cual se secó al vacío. El sólido se disolvió en DMF anhidro (5 ml), y se agregó 4-tert-butilanilina (2,39 ml, 15 mmol). La mezcla resultante se agitó a 40 °C por 4h y luego se particionó entre HCl 1N acuoso (30 ml) y EtOAc (30 ml). La capa orgánica se lavó con H_2O y se secó sobre Na_2SO_4. El agente de secado se retiró por filtración, el solvente se eliminó al vacío, y el producto crudo se purificó mediante cromatografía de columna sobre gel de sílice usando un gradiente de solvente de EtOAc al 0-20% en hexanos. El compuesto del título se obtuvo como un sólido incoloro (0,71 g, 92%). ^1H RMN indicó este material era una mezcla 87:13 de isómeros pirrolidina trans:cis.

Ejemplo 69C

(2S,5S)-1-(4-tert-butilfenil)-2,5-bis(4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)pirrolidina

El producto del Ejemplo 69B (0,71 g, 1,38 mmol) se sometió a las condiciones descritas en Ejemplo 42D para dar el compuesto del título como un sólido incoloro (0,56 g, 66%).

Ejemplo 69D

(2S,2'S)-2,2'-(4,4'-(4,4'-((2S,5S)-1-(4-tert-butilfenil)pirrolidin-2,5-diil)bis(4,1-fenilen))bis(1H-imidazol-4,2-diil))dipirrolidin-1-carboxilato de tert-butilo

El producto del Ejemplo 69C (0,55 g, 0,91 mmol) se sometió a las condiciones descritas en Ejemplo 42E para dar el compuesto del título (0,27 g, 36%).

Ejemplo 69E

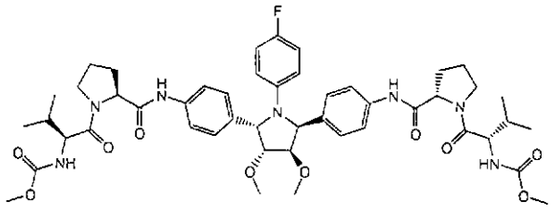
(S)-4,4'-(4,4'-((2S,5S)-1-(4-tert-butilfenil)pirrolidin-2,5-diil)bis(4,1-fenilen))bis(2-((S)-pirrolidin-2-il)-1H-imidazol)

Una solución del producto del Ejemplo 69D (0,27 g, 0,33 mmol) en una mezcla 1:1 de CH_2Cl_2:TFA (4 ml) se agitó a temperatura ambiente por 40 min y luego se concentró al vacío. El residuo se particionó entre $NaHCO_3$ acuoso saturado y una mezcla 3:1 de CH_2Cl_2:2-PrOH (2x), y las capas orgánicas combinadas se secaron sobre Na_2SO_4. El agente de secado se retiró por filtración, y el solvente se eliminó al vacío para dar el compuesto del título como un sólido amorfo (0,18 g, 87%).

Ejemplo 69F

{(2S)-1-[(2S)-2-(4-{4-[(2S,5S)-1-(4-tert-butilfenil)-5-(4-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3,3-dimetilbutanoil}pirrolidin-2-il]-1H-imidazol-4-il}fenil)pirrolidin-2-il]fenil}-1H-imidazol-2-il)pirrolidin-1-il]-3,3-dimetil-1-oxobutan-2-il}carbamato de metilo

A una mezcla del producto del Ejemplo 69E (0,10 g, 0,16 mmol) y ácido (S)-2-(metoxicarbonilamino)-3,3-dimetilbutanoico (76 mg, 0,40 mmol) en DMSO anhidro (1,6 ml) se agregó HATU (152 mg, 0,40 mmol) y base de Hunig (84 µL, 0,48 mmol). La mezcla resultante se agitó a temperatura ambiente por 90 min, y luego se particionó entre H_2O (5 ml) y EtOAc (2 x 5mL). Las capas orgánicas combinadas se concentraron al vacío, y el residuo se disolvió en MeOH (1 ml). A la solución se agregó K_2CO_3 sólido (1-2 mg) y la mezcla resultante se agitó a temperatura ambiente por 30 min. La mezcla se filtró y se concentró al vacío, y el producto crudo se purificó mediante cromatografía de columna sobre gel de sílice usando un gradiente de solvente de 0-5% MeOH en CH_2Cl_2 para dar el compuesto del título (0,12 g, 78%). ^{1}H RMN (400 MHz, DMSO-D6) δ ppm 0,94 (s, 18 H), 1,10 (s, 9 H), 1,63 - 1,77 (m, 2 H), 1,84 - 2,25 (m, 10 H), 3,55 (s, 6 H), 3,66 - 3,87 (m, 2 H), 4,16 - 4,28 (m, 2 H), 5,03 - 5,12 (m, 2 H), 5,15 - 5,28 (m, 2 H), 6,22 (d, *J*=8,46 Hz, 2 H), 6,93 (d, *J*=8,67 Hz, 2 H), 7,07 (d, 2 H), 7,15 (d, *J*=8,13 Hz, 4 H), 7,23 (d, 1 H), 7,38 (d, *J*=1,41 Hz, 2 H), 7,52 (d, 1 H), 7,62 (d, *J*=8,02 Hz, 4 H), 11,66 - 12,10 (m, 2 H). MS (ESI) m/z 969,1 $(M+H)^+$.



Ejemplo 70

([(2S,3R,4R,5S)-1-(4-fluorofenil)-3,4-dimetoxipirrolidin-2,5-diil]bis{bencen-4,1-diilcarbamoil(2S)pirrolidin-2,1-diil[(2S)-3-metil-1-oxobutan-1,2-diil]})biscarbamato de dimetilo

Ejemplo 70A

4,4'-((2S,3R,4R,5S)-1-(4-fluorofenil)-3,4-dihidroxipirrolidin-2,5-diil)bis(4,1-fenilen)dicarbamato de tert-butilo

Una solución de 3,4-O-isopropiliden-D-mannitol (444 mg, 2,0 mmol) en 2:1 metanol-diclorometano (8 ml) se trató con diacetato de yodobenceno (1,54 g, 4,79 mmol) seguido por agitación a temperatura ambiente por 5 h. La mezcla se concentró al vacío para eliminar solventes orgánicos, y el residuo se suspendió en solución 0,1 M de ácido sulfúrico (4 ml) seguido por agitación a temperatura ambiente por 18 h. La mezcla se ajustó a pH 6 mediante la adición de bicarbonato de sodio sólido. La mezcla luego se trató en forma consecutiva con 4-fluoroanilina (383 µL, 444 mg, 4,00 mmol), ácido 4-(tert-butoxicarbonilamino)fenilborónico (853 mg, 3,60 mmol) y alcohol hexafluoroisopropílico (8 ml). La mezcla se calentó a 50 °C por 2 h. La solución se enfrió y se concentró al vacío.

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La mezcla se disolvió en acetato de etilo y se extrajo con agua, solución de fosfato de potasio tribásico 0,33 M, y solución saturada de cloruro de sodio. El secado (Na_2SO_4) y concentración al vacío dio un sólido marrón, el cual se cromatografió sobre un cartucho de gel de sílice de 100 g, eluyendo con 5-70% acetato de etilo en diclorometano. Estos procedimientos dieron el compuesto del título (770 mg, 67%) como un sólido casi blanco. ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,35 (d, J = 8,3 Hz, 4 H), 7,11 (d, J = 8,4 Hz, 4 H), 6,67 (t, J = 8,8 Hz, 2 H), 6,51 (s, 2 H), 6,22 (dd, J = 9,1, 4,3 Hz, 2 H), 5,15 (d, J = 6,3 Hz, 2 H), 4,26 (d, J = 5,7 Hz, 2 H), 1,51 (s, 18 H). MS +ESI m/z (abundancia relativa) 580 (100, M+H), 602 (15, M+Na), 1159 (18, 2M+H).

Ejemplo 70B

diacetato de (2S,3R,4R,5S)-2,5-bis(4-(tert-butoxicarbonilamino)fenil)-1-(4-fluorofenil)pirrolidin-3,4-diilo

Una solución del compuesto de Ejemplo 70A (314 mg, 0,54 mmol), trietilamina (227 µL, 164 mg, 1,65 mmol), y DMAP (13 mg, 0,11 mmol) en 1:1 acetato de etilo-tetrahidrofurano (2,8 ml) se trató con anhídrido acético (128 µL, 138 mg, 1,35 mmol) seguido por agitación a temperatura ambiente por 1 h. La mezcla se trató con agua seguido por agitación a temperatura ambiente por 30 min. La mezcla se diluyó con acetato de etilo y se extrajo con agua, solución saturada de bicarbonato de sodio y solución saturada de cloruro de sodio. El secado (Na_2SO_4) y concentración al vacío dio el compuesto del título (330 mg, 92%) como un sólido color crema, suficientemente puro para su uso posterior. ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,32 (d, J = 8,4 Hz, 4 H), 7,07 (d, J = 8,5 Hz, 4 H), 6,66 (t, J = 8,8 Hz, 2 H), 6,47 (s, 2 H), 6,25 (dd, J = 9,2, 4,3 Hz, 2 H), 5,53 (dd, J = 5,5, 1,9 Hz, 2 H), 5,46 (d, J = 7,2 Hz, 2 H), 1,83 (s, 6 H), 1,51 (s, 18 H). MS +ESI m/z (abundancia relativa) 664 (100, M+H).

Ejemplo 70C

diclorhidrato de diacetato de (2S,3R,4R,5S)-2,5-bis(4-aminofenil)-1-(4-fluorofenil)pirrolidin-3,4-diilo

Una solución de cloruro de hidrógeno 4 N en dioxano (8 ml) se trató con el compuesto de Ejemplo 70B (136 mg, 0,21 mmol) seguido por agitación a temperatura ambiente por 2 h. (Durante este tiempo, el producto de la mono-desprotección producto comenzó a precipitar, y se agregó aproximadamente 4 ml de diclorometano para acelerar la reacción solubilizando el mono-clorhidrato) La mezcla se agregó a exceso de éter y el producto se recogió mediante filtración y se lavó con éter. Luego de secar en un horno de vacío a 50 °C por 18 h, estos procedimientos dieron el compuesto del título (92 mg, 84%) como un polvo blanco opaco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 7,28 (m, 8 H), 6,81 (t, J = 8,9 Hz, 2 H), 6,33 (m, 2 H), 5,63 (m, 2 H), 5,51 (dd, J = 5,5, 1,9 Hz, 2 H), 1,79 (s, 6 H).

Ejemplo 70D

(2S,3R,4R,5S)-2,5-bis(4-aminofenil)-1-(4-fluorofenil)pirrolidin-3,4-diol

En un balón de 25 ml, se disolvió Ejemplo 70C(160,5 mg, 0,299 mmol) en MeOH (3 ml), se agregó carbonato de potasio (165 mg, 1,197 mmol), y se agitó a 25 °C por 1,5 hr. Se filtró los sólidos, se lavó con MeOH, y se concentró el material filtrado mediante evaporación por rotación hasta secar. Se purificó mediante cromatografía flash (gel de sílice, columna Alltech Extract-Clean de 10g, 8% MeOH/CH_2Cl_2) para dar el compuesto del título como un sólido amarillo (85 mg, 75%). ^{1}H RMN (400 MHz, DMSO-D6) δ ppm 4,10 - 4,19 (m, 2 H), 4,73 (d, *J*=2,71 Hz, 2 H), 4,80 - 4,88 (m, 2 H), 4,84 (s, 4 H), 6,21 (dd, *J*=9,22, 4,55 Hz, 2 H), 6,45 (d, *J*=8,35 Hz, 4 H), 6,72 (t, *J*=8,95 Hz, 2 H), 6,77 (d, *J*=8,24 Hz, 4 H); MS (DCI+) 380 $(M+H)^+$.

Ejemplo 70E

4,4'-((2S,3R,4R,5S)-1-(4-fluorofenil)-3,4-dimetoxipirrolidin-2,5-diil)dianilina

en un balón de 25 ml secado en horno, se disolvió el producto de Ejemplo 70D (83,6 mg, 0,220 mmol) en THF anhidro (3 ml) bajo nitrógeno, se enfrió a 0 °C en un baño de hielo y agua, se agregó dispersión de NaH al 60 p% en aceite mineral (18,51 mg, 0,463 mmol), y se agitó a 0 °C por 15 min. Luego se agregó yodometano (0,028 ml, 0,441 mmol) con microjeringas y se agitó a 0 °C por 1 hr, luego a 25 °C por 3 hr. Se eliminó el solvente por evaporación por rotación y se secó el residuo al vacío. Se purificó mediante cromatografía flash (gel de sílice, columna Alltech Extract-Clean de 10g, gradiente de 1% a 2% MeOH/CH_2Cl_2) para dar el compuesto del título como un sólido amarillo (59 mg, 66%). ^{1}H RMN (400 MHz, DMSO-D6) δ ppm 3,25 (s, 6 H), 3,92 - 4,17 (m, 2 H), 4,91 (s, 4 H), 5,07 - 5,24 (m, 2 H), 6,28 (dd, *J*=9,16, 4,50 Hz, 2 H), 6,47 (d, *J*=8,46 Hz, 4 H), 6,73 (t, *J*=8,95 Hz, 2 H), 6,86 (d, *J*=8,35 Hz, 4 H); MS (DCI+) m/z 408 $(M+H)^+$.

Ejemplo 70F

(2S,2'S)-2,2'-(4,4'-((2S,3R,3R,5S)-1-(4-fluorofenil)-3,4-dimetoxipirrolidin-2,5-diil)bis(4,1-fenilen))bis(azandiil)bis(oxometilen)dipirrolidin-1-carboxilato de *tert*-butilo

En un balón de 10 ml, se disolvió el producto de Ejemplo 70E (57 mg, 0,140 mmol) en DMSO anhidro (1,2 ml) bajo nitrógeno, se agregó ácido (S)-1-(tert-butoxicarbonil)pirrolidin-2-carboxílico (76 mg, 0,350 mmol), HATU (137 mg, 0,350 mmol), y diisopropiletilamina (0,073 ml, 0,420 mmol), y se agitó la solución amarillo brillante a 25 °C por 1 hr. Se diluyó la reacción con EtOAc (50 ml), se lavó con H_2O (3 x 25 ml) y salmuera (15 ml), se secó la fase orgánica sobre $MgSO_4$ anhidro, se filtró, y se concentró mediante evaporación por rotación para dar un residuo amarillo. Se purificó mediante cromatografía flash (gel de sílice, columna Alltech Extract-Clean de 10g, 3% MeOH/CH_2Cl_2) para dar el compuesto del título como un sólido amarillo (118 mg). ^{1}H RMN (400 MHz, DMSO-D6) δ ppm 1,29 (s,

11 H), 1,39 (s, 7 H), 1,72 - 1,95 (m, 6 H), 2,08 - 2,25 (m, 2 H), 3,29 (s, 6 H), 3,35 - 3,49 (m, 3 H), 4,12 (d, J=0,87 Hz, 2 H), 4,15 - 4,29 (m, 2 H), 5,30 - 5,45 (m, 2 H), 6,28 (dd, *J*=9,22, 4,45 Hz, 2 H), 6,75 (t, *J*=8,89 Hz, 2 H), 7,19 (d, *J*=8,35 Hz, 4 H), 7,50 (t, *J*=8,89 Hz, 4 H), 9,70 - 10,14 (m, 2 H); MS (APCI+) m/z 802 $(M+H)^+$.

Ejemplo 70G

(2S,2'S)-N,N'-(4,4'-((2S,3R,4R,5S)-1-(4-fluorofenil)-3,4-dimetoxipirrolidin-2,5-diil)bis((4,1-fenilen))dipirrolidin-2-carboxamida

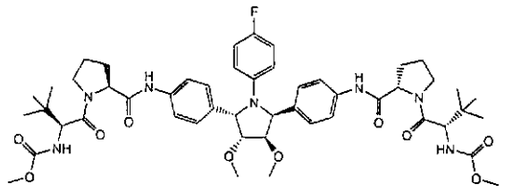
Se disolvió el producto de Ejemplo 70F (112 mg, 0,140 mmol) en CH_2Cl_2 anhidro (1 ml) bajo nitrógeno, se agregó TFA (1 ml), y se agitó a 25 °C por 30 min. Se eliminó el solvente por evaporación por rotación, se disolvió nuevamente en 1:5 v/v CH_2Cl_2/hexanos, y se concentró al vacío. Se recogió el residuo con EtOAc (50 ml), se lavó con $NaHCO_3$ acuoso saturado (2 x 15 ml), se secó la fase orgánica sobre $MgSO_4$ anhidro, se filtró, y se concentró por evaporación por rotación para dar el compuesto del título como un sólido amarillo (72 mg, 84%). ^{1}H RMN (400 MHz, DMSO-D6) δ ppm 1,57 - 1,69 (m, 4 H), 1,70 - 1,85 (m, 2 H), 1,96 - 2,10 (m, 2 H), 2,82 - 2,95 (m, 4 H), 3,28 (s, 6 H), 3,66 (dd, *J*=8,84, 5,58 Hz, 2 H), 4,07 - 4,17 (m, 2 H), 5,30 - 5,49 (m, 2 H), 6,28 (dd, *J*=9,16, 4,39 Hz, 2 H), 6,75 (t, *J*=8,89 Hz, 2 H), 7,18 (d, *J*=8,57 Hz, 4 H), 7,56 (d, *J*=8,57 Hz, 4 H), 9,90 (s, 2 H); MS (ESI+) m/z 602 $(M+H)^+$.

Ejemplo 70H

([(2S,3R,4R,5S)-1-(4-fluorofenil)-3,4-dimetoxipirrolidin-2,5-diil]bis{bencen-4,1-diilcarbamoil(2S)pirrolidin-2,1-diil[(2S)-3-metil-1-oxobutan-1,2-diil]})biscarbamato de dimetilo

Se disolvió el producto de Ejemplo 70G (69,3 mg, 0,115 mmol) en DMF anhidro (1,2 ml) bajo nitrógeno, se enfrió a 0 °C, luego se agregó en forma consecutiva ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico (50,4 mg, 0,288 mmol), monohidrato de HOBT (44,1 mg, 0,288 mmol), EDAC (56,3 mg, 0,288 mmol), y N-metilmorfolina (0,038 ml, 0,346 mmol). Se eliminó el baño de frío y se agitó a 25 °C por 13 hr. Se diluyó la reacción con EtOAc (50 ml), se lavó con $NaHCO_3$ acuoso saturado (25 ml), H_2O (2 x 25 ml), y salmuera (25 ml). Se secó la fase orgánica sobre $MgSO_4$ anhidro, se filtró, y se concentró por evaporación por rotación. Se purificó mediante cromatografía flash (gel de sílice, 2,5 cm x 15 cm, 6% MeOH/CH_2Cl_2) para dar el compuesto del título como un sólido blanco (48 mg, 85%). ^{1}H RMN (400 MHz, DMSO-D6) δ ppm 0,88 (d, *J*=6,61 Hz, 6 H), 0,93 (d, *J*=6,72 Hz, 6 H), 1,80 - 2,05 (m, 8 H), 2,08 - 2,22 (m, 2 H), 3,28 (s, 6 H), 3,52 (s, 6 H), 3,56 - 3,69 (m, 2 H), 3,77 - 3,88 (m, 2 H), 4,03 (t, *J*=8,51 Hz, 2 H), 4,07 - 4,16 (m, 2 H), 4,43 (dd, *J*=7,97, 4,83 Hz, 2 H), 5,29 - 5,44 (m, 2 H), 6,27 (dd, *J*=9,22, 4,45 Hz, 2 H), 6,75 (t, *J*=8,89 Hz, 2 H), 7,17 (d, *J*=8,46 Hz, 4 H), 7,31 (d, *J*=8,46 Hz, 2 H), 7,49 (d, *J*=8,57 Hz, 4 H), 9,99 (s, 2

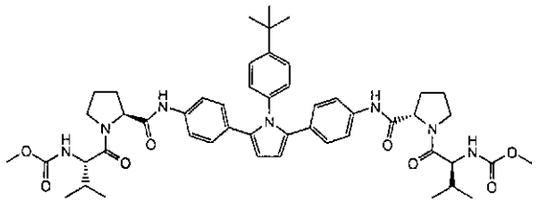
H); MS (ESI+) m/z 408 $(M+H)^+$.



Ejemplo 71

([(2S,3R,4R,5S)-1-(4-fluorofenil)-3,4-dimetoxipirrolidin-2,5-diil]bis{bencen-4,1-diilcarbamoil(2S)pirrolidin-2,1-diil[(2S)-3,3-dimetil-1-oxobutan-1,2-diil]})biscarbamato de dimetilo

Se disolvió el producto de Ejemplo 70D (58,5 mg, 0,097 mmol) en DMF anhidro (1 ml) bajo nitrógeno, se enfrió a 0 °C, luego se agregó en forma consecutiva ácido (S)-2-(metoxicarbonilamino)-3,3-dimetilbutanoico (46,0 mg, 0,243 mmol), monohidrato de HOBt (37,2 mg, 0,243 mmol), EDAC (47,5 mg, 0,243 mmol), y 4-metilmorfolina (0,032 ml, 0,292 mmol). Se eliminó el baño de frío y se agitó durante la noche a 25 °C por 16 hr . Se diluyó la reacción con EtOAc (50 ml), se lavó con $NaHCO_3$ acuoso saturado (25 ml), H_2O (2 x 25 ml), y salmuera (25 ml). Se secó la fase orgánica sobre $MgSO_4$ anhidro, se filtró, y se concentró por evaporación por rotación. Se purificó mediante cromatografía flash (gel de sílice, 2,5 cm x 15 cm, 4% $MeOH/CH_2Cl_2$) para dar el compuesto del título como un sólido color crema (66 mg, 72%). ^1H RMN (400 MHz, DMSO-D6) δ ppm 0,96 (s, 18 H), 1,79 - 1,94 (m, 4 H), 1,94 - 2,06 (m, 2 H), 2,10 - 2,22 (m, 2 H), 3,28 (s, 6 H), 3,54 (s, 6 H), 3,58 - 3,70 (m, 2 H), 3,71 - 3,86 (m, 2 H), 4,06 - 4,15 (m, 2 H), 4,21 (d, *J*=8,89 Hz, 2 H), 4,44 (dd, *J*=7,92, 5,31 Hz, 2 H), 5,31 - 5,39 (m, 2 H), 6,27 (dd, *J*=9,22, 4,45 Hz, 2 H), 6,75 (t, *J*=8,89 Hz, 2 H), 7,08 (d, *J*=8,78 Hz, 2 H), 7,17 (d, *J*=8,57 Hz, 4 H), 7,49 (d, *J*=8,57 Hz, 4 H), 9,99 (s, 2 H); MS (ESI+) m/z 945 $(M+H)^+$.



Ejemplo 72

([1-(4-tert-butilfenil)-1H-pirrol-2,5-diil]bis{bencen-4,1-diilcarbamoil(2S)pirrolidin-2,1-diil[(2S)-3-metil-1-oxobutan-1,2-diil]})biscarbamato de dimetilo

Ejemplo 72A

4,4'-(1-(4-tert-butilfenil)-1H-pirrol-2,5-diil)dianilina

Ejemplo 1A se procesó usando los métodos descritos de manera general en Ejemplos 26F y 19B para dar el compuesto del título. MS (ESI; M+H) m/z = 382.

Ejemplo 72B

(2S,2'S)-2,2'-(4,4'-(1-(4-tert-butilfenil)-1H-pirrol-2,5-diil)bis(4,1-fenilen)bis(azandiil)bis(oxometilen))dipirrolidin-1-carboxilato de tert-butilo

A una solución del producto del Ejemplo 72A (0,310 g, 0,813 mmol) en DMF (5 ml) se agregó ácido (S)-1-(tert-butoxicarbonil)pirrolidin-2-carboxílico (0,385 g, 1,79 mmol) hidrato de 1-hidroxibenzotriazol (0,274 g; 1,79 mmol) y clorhidrato de N-(3-dimetilaminopropil)-N'-etilcarbodiimida (0,343 g, 1,79 mmol) y la mezcla se agitó durante la noche. La mezcla se vertió en agua y se extrajo CH_2Cl_2. El extracto orgánico se secó (Na_2SO_4), se filtró y se concentró para dar un producto crudo que se purificó mediante trituración con éter para dar 325 mg (51%) del compuesto del título. ^{1}H RMN (400 MHz, DMSO-D6) δ 1,25 (s, 24 H) 1,83 (s, 6 H) 2,15 (s, 2 H) 3,45 (m, 4 H) 4,18 (s, 2 H) 6,40 (s, 2 H) 6,98 (s, 6 H) 7,37 (s, 6 H) 9,98 (s, 2 H).

Ejemplo 72C

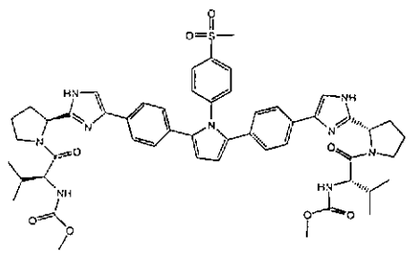
(2S,2'S)-N,N'-(4,4'-(1-(4-tert-butilfenil)-1H-pirrol-2,5-diil)bis(4,1-fenilen))dipirrolidin-2-carboxamida

A una solución del producto del Ejemplo 72B (0,325 g, 0,419 mmol) en CH_2Cl_2 (5 ml) a temperatura ambiente se agregó TFA (1,0 ml) y la agitación se continuó por 5 h. La reacción se concentró y el residuo se particionó entre agua y 25% alcohol isopropílico-$CHCl_3$. La fase orgánica se secó (Na_2SO_4), se filtró y se concentró para dar el compuesto del título se usó directamente en la siguiente reacción. MS (DCI; M+H) m/z = 576.

Ejemplo 72D

([1-(4-tert-butilfenil)-1H-pirrol-2,5-diil]bis{bencen-4,1-diilcarbamoil(2S)pirrolidin-2,1-diil[(2S)-3-metil-1-oxobutan-1,2-diil]})biscarbamato de dimetilo

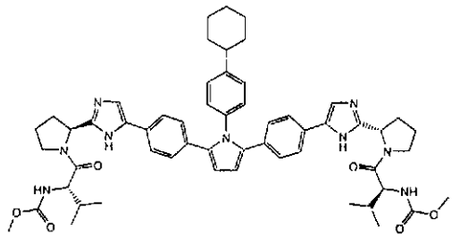
El producto del Ejemplo 72C y el producto de ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico se procesaron usando el método descrito en Ejemplo 72B. El residuo crudo se purificó mediante cromatografía sobre gel de sílice (1% gradiente de elución entre 0% y 4% MeOH:CH_2Cl_2) para dar 129 mg (35%) del compuesto del título. ^{1}H RMN (400 MHz, DMSO-D6) δ0,89 (s, 12 H) 1,25 (s, 9 H) 1,89 (s, 6 H) 1,98 (s, 2 H) 2,13 (s, 2 H) 3,52 (s, 6 H) 3,61 (s, 2 H) 3,80 (s, 2 H) 4,00 (s, 2 H) 4,39 (s, 2 H) 6,38 (s, 2 H) 6,95 (s, 6 H) 7,34 (s, 8 H) 9,96 (s, 2 H).



Ejemplo 73

[(2S)-1-{(2S)-2-[4-(4-{5-(4-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-4-il}fenil)-1-[4-(metilsulfonil)fenil]-1H-pirrol-2-il}fenil)-1H-imidazol-2-il]pirrolidin-1-il}-3-metil-1-oxobutan-2-il]carbamato de metilo

Ejemplo 26E y 4-(metilsulfonil)anilina se procesaron usando los métodos de Ejemplos 26F, 26G, 26H, 65B, y 65C para dar el compuesto del título (78 mg). ^{1}H RMN (400 MHz, DMSO-d6) δ 12,17 – 11,67 (m, 2H), 7,92 – 7,82 (m, 2H), 7,62 – 7,49 (m, 4H), 7,48 – 7,40 (m, 2H), 7,39 – 7,15 (m, 4H), 7,08 – 6,92 (m, 4H), 6,59 – 6,47 (m, 2H), 5,08 – 4,99 (m, 2H), 4,08 – 3,98 (m, 2H), 3,84 – 3,69 (m, 4H), 3,53 (s, 6H), 3,24 (d, *J* = 1,9, 3H), 2,20 – 1,81 (m, 10H), 0,91 – 0,77 (m, 12H). MS (ESI; M+H) m/z = 959.



Ejemplo 74

{(2S)-1-[(2S)-2-(5-{4-[1-(4-ciclohexilfenil)-5-(4-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-5-il}fenil)-1H-pirrol-2-il]fenil}-1H-imidazol-2-il)pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

Ejemplo 74A

2,5-bis(4-bromofenil)-1-(4-ciclohexilfenil)-1H-pirrol

El producto del Ejemplo 26E y 4-ciclohexilanilina (Alfa) se procesaron usando el método descrito en Ejemplo 26F para dar 1,23 g (91%) del compuesto del título. ^{1}H RMN (400 MHz, bencen-D6) δ1,09 (s, 5 H) 1,60 (s, 5 H) 2,14 (s, 1 H) 6,52 (s, 2 H) 6,67 (s, 4 H) 6,84 (s, 4 H) 7,11 (s, 4 H).

Ejemplo 74B

1-(4-ciclohexilfenil)-2,5-bis(4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)-1H-pirrol

El producto del Ejemplo 74A se procesó usando el método descrito en Ejemplo 26G para dar 1,58 g (60%) del compuesto del título. MS (ESI; M+H) m/z = 630.

Ejemplo 74C

(2S,2'S)-2,2'-(5,5'-(4,4'-(1-(4-ciclohexilfenil)-1H-pirrol-2,5-diil)bis(4,1-fenilen))bis(1H-imidazol-5,2-diil))dipirrolidin-1-carboxilato de tert-butilo

Una solución del producto del Ejemplo 74B (0,400 g, 0,635 mmol) y el producto del Ejemplo 26D (0,442 g, 1,40 mmol) en tolueno (3 ml) y etanol (3 ml) se trató con carbonato de sodio 1 M (2 ml) seguido por complejo dicloruro de 1,1'-bis(difenilfosfino)ferrocen-

paladio(II) diclorometano (0,052 g, 0,064 mmol), la mezcla se desgasificó (3 x vacío/purga N_2) y luego se calentó a 90 °C por 4 h. La reacción se concentró y el residuo se particionó entre alcohol isopropílico al 25%-$CHCl_3$. La fase orgánica se secó (Na_2SO_4), se concentró y el residuo se recogió con éter, se sonicó, se filtró y se secó para dar 499 mg (93%) del compuesto del título. MS (ESI; M+H) m/z = 848.

Ejemplo 74D

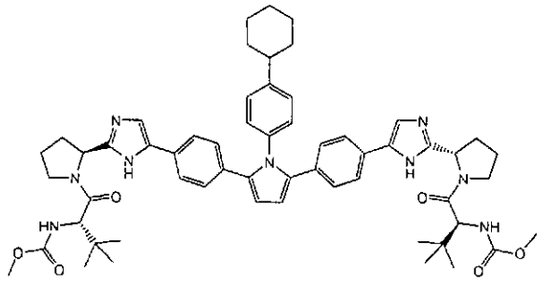
(S)-5,5'-(4,4'-(1-(4-ciclohexilfenil)-1H-pirrol-2,5-diil)bis(4,1-fenilen))bis(2-((S)-pirrolidin-2-il)-1H-imidazol)

El producto del Ejemplo 74C se procesó usando el método descrito en Ejemplo 19D para dar el compuesto del título. MS (ESI; M+H) m/z = 648.

Ejemplo 74E

{(2S)-1-[(2S)-2-(5-{4-[1-(4-ciclohexilfenil)-5-(4-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-5-il}fenil)-1H-pirrol-2-il]fenil}-1H-imidazol-2-il)pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

A una solución del producto del Ejemplo 74D (0,190 g, 0,293 mmol) en DMF (5 ml) se agregó ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico (0,113 g, 0,645 mmol), hidrato de 1-hidroxibenzotriazol (0,099 g; 0,645 mmol) y clorhidrato de N-(3-dimetilaminopropil)-N'-etilcarbodiimida (0,124 g, 0,645 mmol) y la mezcla se agitó por 3 h. La mezcla se vertió en agua y se extrajo con CH_2Cl_2. La capa orgánica se concentró y el residuo se purificó mediante cromatografía (gradiente de elución entre 0% y 4% MeOH-CH_2Cl_2) para dar 100 mg (35%) del compuesto del título. ^{1}H RMN (400 MHz, DMSO-D6) δ 0,84 (d, J=6,62 Hz, 6 H) 0,87 (d, J=6,72 Hz, 6 H) 1,20 (m, 2 H) 1,35 (m, 4 H) 1,78 (m, 4 H) 1,92 (m, 6 H) 2,10 (m, 4 H) 3,52 (s, 6 H) 3,76 (m, 4 H) 4,02 (m, 2 H) 5,03 (m, 2 H) 6,47 (m, 2 H) 6,99 (m, 6 H) 7,18 (m, 3 H) 7,27 (m, 2 H) 7,41 (m, 2 H) 7,51 (m, 4 H) 11,74 (s, 2 H).

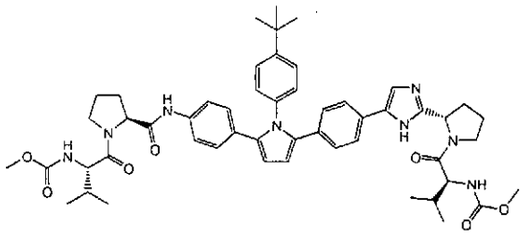


Ejemplo 75

{(2S)-1-[(2S)-2-(5-{4-[1-(4-ciclohexilfenil)-5-(4-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3,3-dimetilbutanoil}pirrolidin-2-il]-1H-imidazol-5-il}fenil)-1H-pirrol-2-il]fenil}-1H-imidazol-2-il)pirrolidin-1-il]-3,3-dimetil-1-oxobutan-2-il}carbamato de metilo

El producto del Ejemplo 74D y ácido (S)-2-metoxicarbonilamino-3,3-dimetil-butírico (Org.

Process Res. Develop. 2008, 12, 69) se procesó usando el método descrito en Ejemplo 74E para dar 165 mg (57%) del compuesto del título. ^{1}H RMN (400 MHz, DMSO-D6) δ 0,86 - 0,96 (m, 18 H) 1,23 (m, 2 H) 1,36 (m, 4 H) 1,78 (m, 4 H) 1,88 - 2,00 (m, 4 H) 2,10 (m, 4 H) 3,54 (s, 6 H) 3,77 (m, 4 H) 4,21 (m, 2 H) 5,05 (m, 2 H) 6,46 (s, 2 H) 6,96 - 7,03 (m, 6 H) 7,19 (m, 2 H) 7,38 - 7,55 (m, 7 H) 7,70 (d, J=8,35 Hz, 1 H) 7,97 (d, J=8,46 Hz, 1 H) 11,76 (s, 2 H).



Ejemplo 76

N-(metoxicarbonil)-L-valil-N-(4-{1-(4-tert-butilfenil)-5-[4-(2-{(2S)-1-[N-(metoxicarbonil)-L-valil]pirrolidin-2-il}-1H-imidazol-5-il)fenil]-1H-pirrol-2-il}fenil)-L-prolinamida

Ejemplo 76A

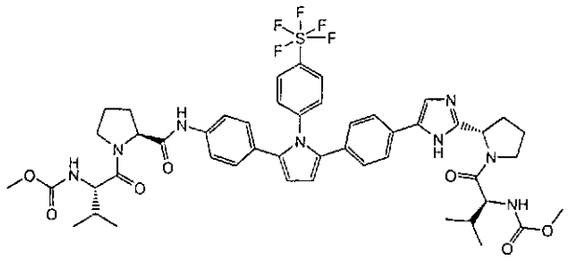
2-(4-bromofenil)-1-(4-tert-butilfenil)-5-(4-nitrofenil)-1H-pirrol

Se agregó TFA (0,6 ml, 7,79 mmol) a una mezcla del producto del Ejemplo 39A (1,2335 g, 3,41 mmol) y 4-tert-butilanilina (0,8 ml, 5,07 mmol) en tolueno (30 ml) y se calentó a 110 °C por 17 horas. La mezcla de reacción fría se vertió en éter/agua y se agitó hasta que se formó un buen sólido. La mezcla se filtró para dar el compuesto del título. ^{1}H RMN (400 MHz, BENCEN-D6) δ 1,02 (s, 9H), 6,48 (d, *J* = 3,8, 1H), 6,52 (d, *J* = 3,8, 1H), 6,63 (d, *J* = 8,5, 2H), 6,80 (d, *J* = 8,5, 2H), 6,84 (d, *J* = 8,9, 2H), 6,89 (d, *J* = 8,5, 2H), 7,10 (d, *J* = 8,5, 2H), 7,70 (d, *J* = 8,9, 2H).

Ejemplo 76B

N-(metoxicarbonil)-L-valil-N-(4-{1-(4-tert-butilfenil)-5-[4-(2-{(2S)-1-[N-(metoxicarbonil)-L-valil]pirrolidin-2-il}-1H-imidazol-5-il)fenil]-1H-pirrol-2-il}fenil)-L-prolinamida

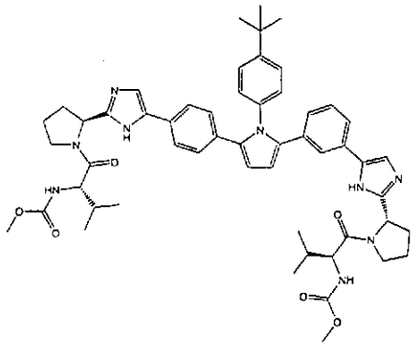
El Ejemplo 76A se procesó usando en forma consecutiva los métodos de Ejemplos 19B, 55F, 39E (temperatura de la reacción = 85 °C), 39F, 55G, y 26J (solvente de reacción = diclorometano) para dar el compuesto del título (0,14 g). ^{1}H RMN (400 MHz, METANOL-D4) δ 0,94 (ddd, *J* = 21,1, 19,5, 6,7, 12H), 1,30 (s, 10H), 2,36 - 1,92 (m, 10H), 3,63 (s, 6H), 3,76 - 3,67 (m, 1H), 3,89 - 3,78 (m, 1H), 4,02 - 3,89 (m, 2H), 4,19 (d, *J* = 7,9, 2H), 4,50 (dd, *J* = 8,1, 5,3, 1H), 5,11 (dd, *J* = 7,6, 5,5, 1H), 6,39 (d, *J* = 3,7, 1H), 6,43 (d, *J* = 3,6, 1H), 7,01 (dt, *J* = 28,2, 8,3, 6H), 7,20 (s, 1H), 7,40 (ddd, *J* = 19,1, 11,9, 5,7, 6H). MS (ESI) *m/z* 913 $(M+H)^+$.



Ejemplo 77

N-(metoxicarbonil)-L-valil-N-(4-{5-[4-(2-{(2S)-1-[N-(metoxicarbonil)-L-valil]pirrolidin-2-il}-1H-imidazol-5-il)fenil]-1-[4-(pentafluoro-lambda~6~-sulfanil)fenil]-1H-pirrol-2-il}fenil)-L-prolinamida

Ejemplo 39A y pentafluoruro de 4-aminofenilazufre se procesaron usando en forma consecutiva los métodos de Ejemplos 76A, 19B, 55F, 39E (temperatura de la reacción = 85 °C), 39F, 55G, y 26J (solvente de reacción = DMF) para dar el compuesto del título (0,36 g). ^{1}H RMN (400 MHz, DMSO-D6) δ 0,86 (ddd, J = 6,9, 15,8, 21,6, 12H), 2,04 - 1,76 (m, 7H), 2,24 - 2,04 (m, 3H), 3,53 (d, J = 3,0, 6H), 3,61 (dd, J = 6,7, 16,0, 1H), 3,88 - 3,67 (m, 3H), 4,03 (dd, J = 8,3, 14,1, 2H), 4,40 (dd, J = 5,0, 8,0, 1H), 5,12 - 4,92 (m, 1H), 6,49 (ddd, J = 3,6, 14,2, 18,1, 2H), 7,09 - 6,84 (m, 4H), 7,38 - 7,12 (m, 4H), 7,50 - 7,38 (m, 3H), 7,58 (dd, J = 8,3, 16,7, 2H), 7,89 (t, J = 8,7, 2H), 10,01 (d, J = 20,9, 1H), 12,16 - 11,66 (m, 1H). MS (ESI) *m/z* 983 $(M+H)^+$, 981 $(M-H)^+$.

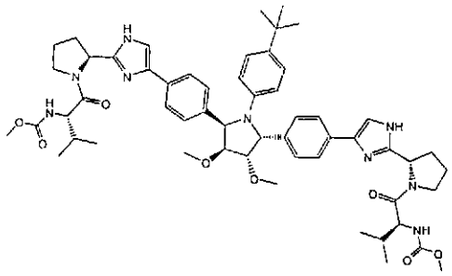


Ejemplo 78

{(2S)-1-[(2S)-2-(5-{3-[1-(4-tert-butilfenil)-5-(4-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-5-il}fenil)-1H-pirrol-2-il]fenil}-1H-imidazol-2-il)pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

2,4'-Dibromoacetofenona y 3'-bromoacetofenona se procesaron usando en forma consecutiva los métodos de Ejemplos 26E, 26F, 26G, 74C, 19D, y 74E para dar el compuesto del título (232 mg). ^{1}H RMN (400 MHz, DMSO-D6) δ 0,81 - 0,91 (m, 12 H) 1,25 (s, 9 H) 1,93 (m, 4 H) 2,11 (m, 4 H) 3,53 (s, 6 H) 3,78 (m, 4 H) 4,04 (m, 2 H) 5,03 (m, 2 H) 6,49 (m, 2 H) 6,90 - 7,08 (m, 5 H) 7,11 - 7,21 (m, 1 H) 7,27 - 7,55 (m, 9 H) 7,71 (d, J=8,35

Hz, 1 H) 7,94 - 8,01 (m, 2 H) 11,72 (br s, 2 H).



Ejemplo 79

{(2S)-1-[(2S)-2-(4-{4-[(2R,3S,4S,5R)-1-(4-tert-butilfenil)-3,4-dimetoxi-5-(4-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-4-il}fenil)pirrolidin-2-il]fenil}-1H-imidazol-2-il)pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

Ejemplo 79A

1,2:3,4:5,6-Tri-O-isopropiliden-L-mannitol

Una solución de γ-lactona de ácido L-mannónico (9,87 g, 55,4 mmol) en metanol (150 ml) a 0 °C se trató con borhidruro de litio (2,1 g, 97 mmol) a lo largo de 30 min. Luego de completarse la adición, la mezcla se calentó a temperatura ambiente por 30 min. La mezcla luego se trató cuidadosamente con una solución de cloruro de hidrógeno en dioxano (4 N, 2 ml). La solución luego se concentró al vacío, primero en el evaporador rotatorio y luego bajo alto vacío (0,3 mm Hg) mientras se calentaba con una pistola de calor para eliminar los últimos restos de metanol. El sólido obtenido luego se suspendió en acetona (50 ml) y se trató con 2,2-dimetoxipropano (41 ml, 34,6 g, 332 mmol) y una solución de cloruro de hidrógeno en dioxano (4 N, 42 ml, 166 mmol) seguido por agitación a temperatura ambiente por 18 h. La mezcla se concentró al vacío a aproximadamente 20% de original volumen, y a la mezcla heterogénea se agregó una solución saturada de bicarbonato de sodio (200 ml) seguido por agitación por 48 h. El precipitado se recogió mediante filtración y se lavó con agua y se secó con aire. El sólido blanco se disolvió en etanol (grado de ensayo 200, 175 ml) y se filtró a través de celite para eliminar el material particulado. La solución se enfrió a -78 °C para producir cristalización. El sólido se recogió mediante filtración, y los licores madre se concentraron a aproximadamente la mitad del volumen, y se enfrió nuevamente a -78 °C. La segunda cosecha de cristales se recogió mediante filtración y se lavó con etanol. Luego de secar en un horno de vacío a 50 °C por 3 h, estos procedimientos dieron el compuesto del título (9,88 g, 59%) como un sólido blanco aireado. ^{1}H RMN (400 MHz, $CDCl_3$) δ 4,19 (dt, *J* = 6,0, 3,0 Hz, 2 H), 4,08 (dd, *J* = 8,3, 6,4 Hz, 2 H), 3,99 (m, 2 H), 3,95 (m, 2 H), 1,43 (s, 6 H), 1,39 (s, 6 H), 1,36 (s, 6 H). MS (+ESI) *m/z* (abundancia relativa) 303 (100, M+H), 320 (43, M+NH4).

000035

Ejemplo 79B

3,4-O-Isopropiliden-L-mannitol

El compuesto de Ejemplo 79A (9,88 g, 32,7 mmol) se suspendió en ácido acético al 60% (v/v) en agua (150 ml) en un balón de 1 L y el recipiente se colocó en el evaporador rotatorio y se hizo girar en el baño de calentamiento a 45 °C por 1,5 h. El baño de calentamiento se redujo en temperatura a 40 °C y se fijó una línea a la bomba de vacío al evaporador rotatorio. La mezcla se concentró bajo aproximadamente 1 mm Hg de presión para dar un sólido húmedo. Este material se diluyó con diclorometano (100 ml) y se agitó a temperatura ambiente por 10 min. La solución se filtró a través de celite, y el material filtrado se concentró al vacío. El residuo se disolvió en tolueno y se concentró al vacío (2 x) para eliminar ácido acético residual. El sólido blanco luego se trituró con éter (60 ml) y se recogió mediante filtración. Luego de secar en un horno de vacío por 18 h, estos procedimientos dieron el compuesto del título (2,46 g, 34%) como un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 5,07 (d, J = 4,5 Hz, 2 H), 4,45 (t, J = 5,7 Hz, 2 H), 3,86 (dd, J = 4,9, 1,5 Hz, 2 H), 3,54 (ddd, J = 10,9, 5,5, 3,1 Hz, 2 H), 3,48 (d, J = 4,6 Hz, 2 H), 3,37 (m, 2 H), 1,28 (s, 6 H).

Ejemplo 79C

(2R,3S,4S,5R)-1-(4-tert-butilfenil)-2,5-bis(4-(4-metoxibenciloxi)fenil)-pirrolidin-3,4-diol

A una solución de Ejemplo 79B (1,0g, 4,5 mmol) en CH_3OH (12,0 ml) y CH_2Cl_2 (6,0 ml) se agregó diacetato de yodobenceno (3,48g, 10,8 mmol) y la solución se agitó a temperatura ambiente por 5 h. El solvente se eliminó al vacío y al residuo se agregó H_2SO_4 0,1 M (4 ml) y la solución se agitó a temperatura ambiente por 18 h. El pH se ajustó a ~6 con $NaHCO_3$ sólido, y se agregó 4-tert-butilanilina (1,43 ml, 9,0 mmol) seguido por ácido 4-(4-metoxibenciloxi)fenilborónico (2,09g, 8,1 mmol) y alcohol hexafluoroisopropílico (8 ml). La solución se calentó a 50 °C por 2 h, se enfrió y el solvente se eliminó al vacío para dar la capa acuosa la cual contenía algo de material sólido. La mezcla se diluyó con H_2O y se agregó K_3PO_4 0,33 M y la mezcla se agitó enérgicamente. El sólido blanco resultante se recogió mediante filtración y se secó en un horno de vacío para dar compuesto del título (1,49g, 2,26 mmol, 50%),1H RMN (400 MHz, DMSO-*d6*) δ ppm 1,10 (s, 9H) 3,75 (s, 6H) 4,21 (s, 2H) 4,95 (s, 2H) 5,02 (d, J=6,9 Hz, 2H) 5,75 (s, 2H) 6,20 (d, J=8,9 Hz, 2H) 6,85-6,97 (m, 10H) 7,05 (d, J=8,6 Hz, 4H) 7,37 (d, J=8,7 Hz, 4H).

Ejemplo 79D

(2R,3S,4S,5R)-1-(4-tert-butilfenil)-3,4-dimetoxi-2,5-bis-(4-(4-metoxibenciloxi)fenil)pirrolidina

A una solución de Ejemplo 79C (1,49g, 2,26 mmol) en THF (17 ml) y DMF (5,7 ml) a 0 °C

se agregó, en porciones, NaH, 60% en aceite mineral (0,27g, 6,77 mmol) y la mezcla se agitó a 0 °C por 20 min. Se agregó yodometano (0,31 ml, 4,97 mmol) y la mezcla de la reacción se agitó a temperatura ambiente por 18 h, se diluyó con EtOAc, se lavó con NH_4Cl saturado, H_2O, y salmuera, se secó (Na_2SO_4), se filtró y el solvente se eliminó al vacío para dar un producto oleoso. El aceite se diluyó con un mínimo de éter y el aceite comenzó a solidificarse y el compuesto del título se aisló como un sólido incoloro (1,55g, 2,25 mmol, 100%). ^{1}H RMN (400 MHz, $CDCl_3$) δ ppm 1,16 (s, 6H) 3,44 (s, 6H) 3,82 (s, 6H) 4,12-4,17 (m, 2H) 4,94 (s, 4H) 5,22 (dd, J=5,2, 1,63 Hz, 2H) 6,29 (d, J=8,9 Hz, 2H) 6,88-7,00 (m, 10H) 7,12 (d, J=8,6 Hz, 4H) 7,34 (d, J=8,6 Hz, 4H). MS (ESI) m/z 688 $(M+H)^+$.

Ejemplo 79E

4,4'-((2R,3S,4S,5R)-1-(4-tert-butilfenil)-3,4-dimetoxipirrolidin-2,5-diil)difenol

A una solución de Ejemplo 79D (1,55g, 2,25 mmol) en CH_2Cl_2 (9 ml) se agregó ácido trifluoroacético (9 ml, 117 mmol) y la agitación se continuó a temperatura ambiente por 1 h. El solvente se eliminó y el residuo crudo se disolvió en 1:1 EtOAc/ $NaHCO_3$ saturado. La capa orgánica se separó, se lavó con salmuera, se secó (Na_2SO_4), se filtró y el solvente se eliminó al vacío para dar compuesto del título (1,0 g, 2,23 mmol, 99%). MS (ESI) m/z 448 $(M+H)^+$.

Ejemplo 79F

4,4'-((2R,3S,4S,5R)-1-(4-tert-butilfenil)-3,4-dimetoxipirrolidin-2,5-diil)bis(4,1-fenilen)bis(1,1,2,2,3,3,4,4,4-nonafluorobutan-1-sulfonato)

A una solución de Ejemplo 79E (1,0g, 2,23 mmol) en DMF (12 ml) se agregó K_2CO_3 (0,695 g, 5,0 mmol) y fluoruro de 1,1,2,2,3,3,4,4,4-nonafluorobutan-1-sulfonilo (0,86 ml, 4,9 mmol) y la solución se agitó a 100 °C por 1 h. La solución fría se diluyó con EtOAc, se lavó con H_2O, salmuera, se secó (Na_2SO_4), se filtró y el solvente se eliminó al vacío para dar producto crudo el cual se purificó mediante cromatografía flash sobre gel de sílice eluyendo con EtOAc al 0-20%/hexano para dar el compuesto del título (1,63 g, 1,61 mmol, 72%). ^{1}H RMN (400 MHz, $CDCl_3$) δ ppm 1,17 (s, 9H) 3,42 (s, 6H) 4,10 (dd, J=5,3, 1,90 Hz, 2H) 5,30 (dd, J=5,2, 1,9 Hz, 2H) 6,19 (d, J=8,8 Hz, 2H) 6,99-7,03 (m, 2H) 7,21-7,29 (m, 8H). MS (ESI) m/z 1012 $(M+H)^+$.

Ejemplo 79G

(2R,3S,4S,5R)-1-(4-tert-butilfenil)-3,4-dimetoxi-2,5-bis(4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)pirrolidina

En un tubo de presión se combinó Ejemplo 79F (216 mg, 0,21 mmol), 4,4,4',4',5,5,5',5'-octametil-2,2'-bi(1,3,2-dioxaborolano) (114 mg, 0,45 mmol), diciclohexil(2',4',6'-triisopropilbifenil-2-il)fosfina (16,3 mg, 0,034 mmol), acetato de potasio (126 mg, 1,28 mmol) y dioxano (2 ml) y la mezcla se desgasificó con N_2 gaseoso por 30 min. Se agregó

tris(dibencilidenacetona)dipaladio(0) (7,8 mg, 8,54 mmol) y la desgasificación se continuó por 10 min. El tubo se selló y se calentó a 100 °C por 30 min. La solución fría se diluyó con EtOAc, se lavó con H_2O, salmuera, se secó (Na_2SO_4), se filtró y el material filtrado se trató con gel de sílice funcionalizado con 3-mercaptopropilo por 1 h, se filtró y el solvente se eliminó al vacío para dar el compuesto del título (143 mg, 100%).

Ejemplo 79H

(2S,2'S)-2,2'-(4,4'-(4,4'-((2R,3S,4S,5R)-1-(4-tert-butilfenil)-3,4-dimetoxipirrolidin-2,5-diil)bis(4,1-fenilen)bis(1H-imidazol-4,2-diil))dipirrolidin-1-carboxilato de tert-butilo

A un tubo de presión se combinó Ejemplo 79G (140 mg, 0,21 mmol), (S)-2-(4-bromo-1H-imidazol-2-il)pirrolidin-1-carboxilato de tert-butilo (Ejemplo 26D) (166 mg, 0,524 mmol), Na_2CO_3 1 M (0,524 ml, 0,524 mmol), EtOH (1 ml), y tolueno (1 ml) y la mezcla se desgasificó con N_2 gaseoso por 30 min. Se agregó complejo 1,1'-Bis(difenilfosfino)ferrocenodicloro paladio(II) diclorometano (15,3 mg, 0,021 mmol) y la desgasificación se continuó por 10 min. El tubo se selló y se calentó a 100 °C por 3 h, luego se agitó a temperatura ambiente por 16 h. La solución se diluyó con EtOAc, se filtró a través de Celite y el material filtrado se lavó con salmuera, se secó (Na_2SO_4), se filtró y el solvente se eliminó al vacío. Se purificó mediante cromatografía flash sobre gel de sílice eluyendo con EtOAc al 0-100%/hexano para dar compuesto del título (119 mg, 0,135 mmol, 64%). ^1H RMN (400 MHz, $CDCl_3$) δ ppm 1,13 (s, 9H) 1,49 (s, 18H) 1,88-2,02 (m, 2H) 2,06-2,22 (m, 4H) 2,99 (s, 2H) 3,33-3,48 (m, 4H) 3,43 (s, 6H) 4,23 (s, 2H) 4,96 (d, J=5,3 Hz, 2H) 5,29 (d, J=6,9 Hz, 2H) 6,29 (d, J=8,9 Hz, 2H) 6,94 (d, J=8,4 Hz, 2H) 7,13-7,29 (m, 8H). MS (ESI) m/z 886 $(M+H)^+$.

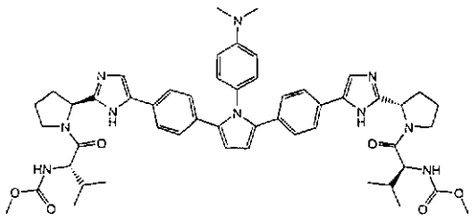
Ejemplo 79I

{(2S)-1-[(2S)-2-(4-{4-[(2R,3S,4S,5R)-1-(4-tert-butilfenil)-3,4-dimetoxi-5-(4-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-4-il}fenil)pirrolidin-2-il]fenil}-1H-imidazol-2-il)pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

A una solución de Ejemplo 79H (30 mg, 0,034 mmol) en CH_2Cl_2 (1 ml) se agregó ácido trifluoroacético (1 ml) y la solución se agitó a temperatura ambiente por 1 h. El solvente se eliminó al vacío y luego se disolvió en DMSO (0,5 ml). Se agregó N,N-diisopropiletilamina hasta pH 9-10, luego se agregó ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico (14,8 mg, 0,085 mmol) seguido por HATU (32 mg, 0,085 mmol) y la solución se agitó a temperatura ambiente por 1 h. La solución se diluyó con EtOAc, se lavó con H_2O, salmuera, se secó (Na_2SO_4), se filtró y el solvente se eliminó al vacío. Se disolvió el residuo en CH_3OH (2 ml), se agregó K_2CO_3 sólido y se agitó a temperatura ambiente por 30 min. El sólido se retiró por filtración y el material filtrado se concentró al vacío y el residuo se purificó mediante cromatografía flash sobre gel de sílice eluyendo con 0-5%

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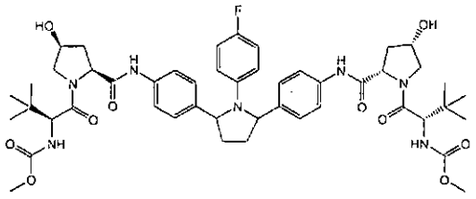
CH_3OH/CH_2Cl_2 para dar compuesto del título (21,6 mg, 0,022 mmol, 63%). ^1H RMN (400 MHz, $CDCl_3$) δ ppm 0,85 (s, 12H) 1,13 (s, 9H) 1,82-2,03 (m, 2H) 2,02-2,24 (m, 4H) 2,32 (br s, 2H) 3,04 (br s, 2H) 3,43 (s, 6H) 3,53-3,65 (m, 2H) 3,70 (s, 6H) 3,75-3,90 (m, 2H) 4,22 (s, 2H) 4,31 (d, J=15,7 Hz, 2H) 5,16-5,33 (m, 4H) 5,37 (d, J=9,1 Hz, 2H) 6,29 (d, J=8,9 Hz, 2H) 6,94 (s, 2H) 7,16 (s, 2H) 7,22 (d, J=8,0 Hz, 4H) 7,31-7,52 (m, 2H) 7,60-7,87 (m, 2H) 10,26 (s, 1H) 10,64 (s, 1H). MS (ESI) m/z 1000 $(M+H)^+$.



Ejemplo 80

[(2S)-1-{(2S)-2-[5-(4-{1-[4-(dimetilamino)fenil]-5-(4-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-5-il}fenil)-1H-pirrol-2-il}fenil)-1H-imidazol-2-il]pirrolidin-1-il}-3-metil-1-oxobutan-2-il]carbamato de metilo

Se procesó Ejemplo 26E y N,N-dimetil-p-fenilendiamina se procesaron usando en forma consecutiva los métodos de Ejemplos 76A, 39E, 39F, 55G (se usó 25% isopropilalcohol/cloroformo para la extracción), y 26J (solvente de reacción = diclorometano) para dar el compuesto del título (5,6 mg). ^1H RMN (400 MHz, DMSO-d6) δ 0,94 - 0,75 (m, 12H), 2,04 - 1,78 (m, 6H), 2,21 - 2,03 (m, 4H), 2,89 (s, 6H), 3,38 (s, 1H), 3,53 (s, 6H), 3,84 - 3,68 (m, 3H), 4,10 - 3,96 (m, 2H), 5,04 (dd, J = 2,9, 6,7, 2H), 6,53 - 6,37 (m, 2H), 6,70 - 6,54 (m, 2H), 7,12 - 6,85 (m, 6H), 7,33 - 7,12 (m, 2H), 7,46 - 7,34 (m, 2H), 7,60 - 7,46 (m, 4H), 12,11 - 11,64 (m, 2H). MS (ESI) *m/z* 923 $(M+H)^+$.



Ejemplo 81

([(2*S*,5*S*)-1-(4-fluorofenil)pirrolidin-2,5-diil]bis{bencen-4,1-diilcarbamoil[(2*S*,4*S*)-4-hidroxipirrolidin-2,1-diil][(2*S*)-3,3-dimetil-1-oxobutan-1,2-diil]})biscarbamato de dimetilo

y

([(2*R*,5*R*)-1-(4-fluorofenil)pirrolidin-2,5-diil]bis{bencen-4,1-diilcarbamoil[(2*S*,4*S*)-4-hidroxipirrolidin-2,1-diil][(2*S*)-3,3-dimetil-1-oxobutan-1,2-diil]})biscarbamato de dimetilo

Ejemplo 81A

ácido (2S,4S)-1-(tert-butoxicarbonil)-4-hidroxipirrolidin-2-carboxílico

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A una solución de ácido (2S,4S)-4-hidroxipirrolidin-2-carboxílico (3,9 g, 29,7 mmol) en THF (26,7 ml) y agua (13,3 ml) dicarbonato de di-tert-butilo (7,14 g, 32,7 mmol) y hidróxido de sodio (2,0 N, 22,9 ml, 45,8 mmol) y la mezcla se agitó a temperatura ambiente durante la noche. A la mezcla luego se agregó ácido cítrico al 10% (50 ml) seguido por EtOAc y extracción con agua y salmuera. El extracto orgánico se secó, se filtró y se concentró para dar 5,31 g (77%) del compuesto del título. MS (ESI) m/z 232 (M+H)+.

Ejemplo 81B

(2S,4S)-1-(tert-butoxicarbonil)-4-(tert-butildimetilsililoxi)pirrolidin-2-ácido carboxílico

A una solución de Ejemplo 81A (5,31, 22,96 mmol) e imidazol (7,82 g, 115 mmol) en diclorometano (106 ml) y DMF (21,3 ml) se agregó cloruro de *tert*-butildimetilsililo (7,61 g, 50,5 mmol) y la mezcla se agitó a temperatura ambiente durante la noche. A la mezcla luego se agregó agua (425 ml) y la solución se extrajo con EtOAc y el extracto orgánico se concentró para dar un residuo que se disolvió en EtOAc al 25% y hexanos al 75% luego se extrajo con salmuera y el extracto orgánico se concentró para dar un sólido. El sólido resultante se disolvió en metanol (65 ml) y agua (85 ml) luego se agregó hidróxido de litio monohidratado (1,93 g, 46 mmol) y la solución se agitó a temperatura ambiente por 2 h. Luego se agregó agua (106 ml) y una solución de ácido clorhídrico acuoso 1N hasta alcanzar un pH de 2. La mezcla luego se extrajo con una mezcla de EtOAc al 25% y hexanos al 75%, el extracto orgánico se secó, se filtró y se concentró para dar un sólido incoloro. MS (ESI) m/z 346 (M+H)+.

Ejemplo 81C

(3S,3'S,5S,5'S)-5,5'-(4,4'-((2S,5S)-1-(4-fluorofenil)pirrolidin-2,5-diil)bis(4,1-fenilen))bis(azandiil)bis(oxometilen)bis(3-(tert-butildimetilsililoxi)pirrolidin-1-carboxilato) de tert-butilo

y

(3S,3'S,5S,5'S)-5,5'-(4,4'-((2R,5R)-1-(4-fluorofenil)pirrolidin-2,5-diil)bis(4,1-fenilen))bis(azandiil)bis(oxometilen)bis(3-(tert-butildimetilsililoxi)pirrolidin-1-carboxilato) de tert-butilo

El producto de Ejemplo 81B (149 mg, 0,432 mmol) y el producto del Ejemplo 5A (50 mg, 0,144 mmol) se procesaron usando el método descrito en Ejemplo 1F para dar 74 mg (51%) del compuesto del título como una mezcla 1:1 de diastereómeros. MS (ESI) m/z 1002 (M+H)+.

Ejemplo 81D

(2S,2'S,4S,4'S)-N,N'-(4,4'-((2S,5S)-1-(4-fluorofenil)pirrolidin-2,5-diil)bis(4,1-fenilen))bis(4-hidroxipirrolidin-2-carboxamida)

y

(2S,2'S,4S,4'S)-N,N'-(4,4'-((2R,5R)-1-(4-fluorofenil)pirrolidin-2,5-diil)bis(4,1-fenilen))bis(4-hidroxipirrolidin-2-carboxamida)

El producto de Ejemplo 81C (74 mg, 0,074 mmol) se disolvió en ácido trifluoroacético (4 ml), agua (0,2 ml) y diclorometano (0,2 ml) y la mezcla se agitó a temperatura ambiente por 3 horas. Luego la mezcla se concentró para dar un aceite el cual se disolvió en $CHCl_3$ al 75% y alcohol isopropílico al 25% luego se extrajo con una solución saturada acuosa de bicarbonato de sodio, el extracto orgánico se separó, se secó, se filtró y se concentró para dar un sólido incoloro. MS (ESI) m/z 574 (M+H)+.

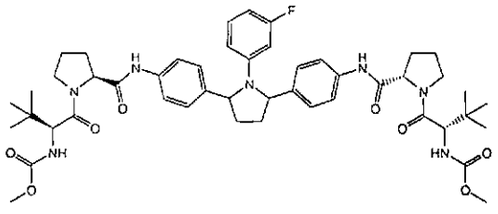
Ejemplo 81E

([(2S,5S)-1-(4-fluorofenil)pirrolidin-2,5-diil]bis{bencen-4,1-diilcarbamoil[(2S,4S)-4-hidroxipirrolidin-2,1-diil][(2S)-3,3-dimetil-1-oxobutan-1,2-diil]})biscarbamato de dimetilo

y

([(2*R*,5*R*)-1-(4-fluorofenil)pirrolidin-2,5-diil]bis{bencen-4,1-diilcarbamoil[(2*S*,4*S*)-4-hidroxipirrolidin-2,1-diil][(2*S*)-3,3-dimetil-1-oxobutan-1,2-diil]})biscarbamato de dimetilo

Al producto del Ejemplo 81D (40 mg, 0,072 mmol), ácido (S)-2-(metoxicarbonilamino)-3,3-dimetilbutanoico (34,1 mg, 0,18 mmol) y HATU (60,2 mg, 0,158 mmol) en DMSO (3 ml) se agregó base de Hunig (0,063 ml, 0,36 mmol), y la mezcla de la reacción se agitó a temperatura ambiente por 1 hr. La mezcla de la reacción se particionó entre agua y acetato de etilo, y la capa orgánica se secó sobre $MgSO_4$, se filtró y se concentró al vacío. El producto crudo se purificó mediante cromatografía de columna sobre gel de sílice usando un gradiente de solvente de 0-MeOH al 10% en diclorometano para dar el compuesto del título como una mezcla 1:1 de estereoisómeros (21 mg, 32% de rendimiento): ^{1}H RMN (400 MHz, DMSO-D6) δ ppm 9,94 (s, 2 H), 7,44 (d, *J*=8,4 Hz, 4 H), 7,07 (m, 6 H) 6,74 (t, *J*=8,9 Hz, 2 H), 6,15 (dd, *J*=9,1, 4,4 Hz, 2 H), 5,26 (dd, *J*=6,1, 3,3 Hz, 2 H), 5,11 (d, *J*=5,5 Hz, 2 H), 4,33 (t, *J*=7,8 Hz, 2H), 4,19 (m, 2 H), 4,07 (m, 2 H), 3,93 (m, 2 H), 3,48 (s, 6 H), 2,34 (m, 2 H), 1,66 (m, 2 H), 1,59 (m, 2 H), 1,20 (m, 2 H), 0,91 (m, 18 H).



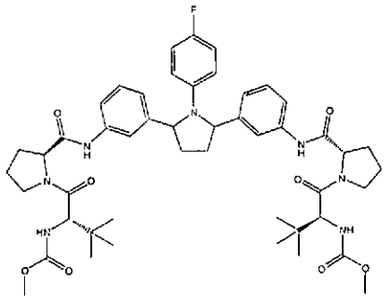
Ejemplo 82

([(2*S*,5*S*)-1-(3-fluorofenil)pirrolidin-2,5-diil]bis{bencen-4,1-diilcarbamoil(2*S*)pirrolidin-2,1-diil[(2*S*)-3,3-dimetil-1-oxobutan-1,2-diil]})biscarbamato de dimetilo

y

([(2*R*,5*R*)-1-(3-fluorofenil)pirrolidin-2,5-diil]bis{bencen-4,1-diilcarbamoil(2*S*)pirrolidin-2,1-diil[(2*S*)-3,3-dimetil-1-oxobutan-1,2-diil]})biscarbamato de dimetilo

Se procesó Ejemplo 1C y 3-fluoroanilina usando en forma consecutiva los métodos de Ejemplos 1D, 1E, 1F, 1G, y 1H para dar los compuestos del título. Los diastereómeros trans se separaron del diastereómero cis en la etapa de 4,4'-(1-(3-fluorofenil)pirrolidin-2,5-diil)dianilina. Datos para los compuestos del título. ^{1}H RMN (base libre) (400 MHz, DMSO-d_6) δ ppm 0,96 (d, *J*=2,17 Hz, 18 H), 1,75 - 1,92 (m, 7 H), 1,93 - 2,05 (m, 2 H), 2,10 - 2,21 (m, 2 H), 2,31 - 2,44 (m, 2 H), 3,43 - 3,51 (m, 4 H), 3,53 (s, 6 H), 3,59 - 3,73 (m, 6 H), 3,73 - 3,82 (m, 2 H), 4,21 (d, *J*=8,89 Hz, 2 H), 4,46 (dd, *J*=7,92, 5,31 Hz, 2 H), 4,70 (t, *J*=4,66 Hz, 2 H), 6,07 (d, *J*=12,90 Hz, 1 H), 6,19 (dd, *J*=8,35, 1,63 Hz, 1 H), 6,37 (dt, *J*=8,35, 2,06 Hz, 1 H), 6,97 - 7,05 (m, 2 H), 7,08 (d, *J*=8,67 Hz, 2 H), 7,41 (d, *J*=7,26 Hz, 4 H), 7,60 (d, *J*=8,57 Hz, 4 H), 10,07 (s, 2 H). MS (ESI) m/z 885 $(M+H)^+$.



Ejemplo 83

([(2*S*,5*S*)-1-(4-fluorofenil)pirrolidin-2,5-diil]bis{bencen-3,1-diilcarbamoil(2*S*)pirrolidin-2,1-diil[(2*S*)-3,3-dimetil-1-oxobutan-1,2-diil]})biscarbamato de dimetilo

y

([(2*R*,5*R*)-1-(4-fluorofenil)pirrolidin-2,5-diil]bis{bencen-3,1-diilcarbamoil(2*S*)pirrolidin-2,1-diil[(2*S*)-3,3-dimetil-1-oxobutan-1,2-diil]})biscarbamato de dimetilo

Ejemplo 83A

(2S,2'S)-2,2'-(3,3'-((2S,5S)-1-(4-fluorofenil)pirrolidin-2,5-diil)bis(3,1-fenilen))bis(azandiil)bis(oxometilen)dipirrolidin-1-carboxilato de tert-butilo

y

(2S,2'S)-2,2'-(3,3'-((2R,5R)-1-(4-fluorofenil)pirrolidin-2,5-diil)bis(3,1-fenilen))bis(azandiil)bis(oxometilen)dipirrolidin-1-carboxilato de tert-butilo

La fracción éter de la preparación de Ejemplo 55F se purificó usando cromatografía flash (gel de sílice, 0-30%EtOAc/diclorometano) para dar el compuesto del título como una mezcla de diastereómeros trans. MS (ESI) *m/z* 742 $(M+H)^+$.

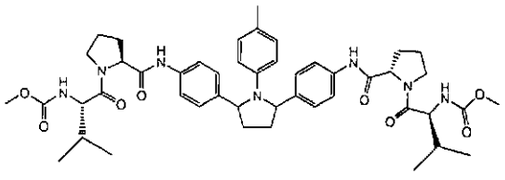
Ejemplo 83B

([(2*S*,5*S*)-1-(4-fluorofenil)pirrolidin-2,5-diil]bis{bencen-3,1-diilcarbamoil(2*S*)pirrolidin-2,1-diil[(2*S*)-3,3-dimetil-1-oxobutan-1,2-diil]})biscarbamato de dimetilo

y

([(2*R*,5*R*)-1-(4-fluorofenil)pirrolidin-2,5-diil]bis{bencen-3,1-diilcarbamoil(2*S*)pirrolidin-2,1-diil[(2*S*)-3,3-dimetil-1-oxobutan-1,2-diil]})biscarbamato de dimetilo

El producto del Ejemplo 83A se procesó usando los métodos descritos en Ejemplos 55G y 55H para dar el compuesto del título (0,18 g, 27%). ^{1}H RMN (400 MHz, DMSO-D6) δ 0,97 (d, J = 4,5, 18H), 1,73 - 1,60 (m, 2H), 1,92 - 1,75 (m, 5H), 2,05 - 1,92 (m, 3H), 2,23 - 2,05 (m, 2H), 3,54 (d, J = 1,5, 6H), 3,71 - 3,59 (m, 2H), 3,85 - 3,71 (m, 2H), 4,21 (d, J = 8,9, 2H), 4,50 - 4,37 (m, 2H), 5,14 (d, J = 5,7, 2H), 6,30 - 6,19 (m, 2H), 6,85 - 6,75 (m, 2H), 6,88 (d, J = 7,7, 2H), 7,09 (d, J = 8,7, 2H), 7,23 (t, J = 7,9, 2H), 7,40 - 7,30 (m, 2H), 7,58 (d, J = 8,1, 2H), 10,07 - 9,96 (m, 2H). MS (ESI) *m/z* 884 $(M+H)^+$, 882 $(M-H)^+$.



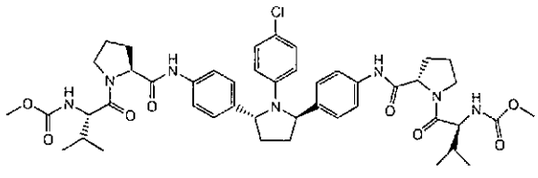
Ejemplo 84

([(2S,5S)-1-(4-metilfenil)pirrolidin-2,5-diil]bis{bencen-4,1-diilcarbamoil(2S)pirrolidin-2,1-diil[(2S)-3-metil-1-oxobutan-1,2-diil]})biscarbamato de dimetilo

y

([(2R,5R)-1-(4-metilfenil)pirrolidin-2,5-diil]bis{bencen-4,1-diilcarbamoil(2S)pirrolidin-2,1-diil[(2S)-3-metil-1-oxobutan-1,2-diil]})biscarbamato de dimetilo

El compuesto del título se preparó usando los procedimientos descritos para la síntesis de Ejemplos 34A, 34B, 34C, 34D, y 34E, utilizando 4-metilanilina en lugar de 4-*tert*-butilanilina. 1H RMN (500 MHz, DMSO-D6) δ ppm 0,85 - 0,90 (m, 6 H), 0,90 - 0,95 (m, 6 H), 1,61 - 1,65 (m, 2 H), 1,82 - 2,01 (m, 8 H), 2,03 (s, 3 H), 2,09 - 2,16 (m, 2 H), 3,52 (s, 6 H), 3,58 - 3,66 (m, 2 H), 3,77 - 3,84 (m, 2 H), 4,02 (t, 2 H), 4,40 - 4,45 (m, 2 H), 5,14 (d, *J*=6,6 Hz, 2 H), 6,13 - 6,18 (m, 2 H), 6,72 (d, *J*=8,4 Hz, 2 H), 7,08 - 7,14 (m, 4 H), 7,29 - 7,34 (m, 2 H), 7,46 - 7,51 (m, 4 H), 9,98 (s, 2 H); MS m/z 852,3 $(M+H)^+$.



Ejemplo 85

([(2S,5S)-1-(4-clorofenil)pirrolidin-2,5-diil]bis{bencen-4,1-diilcarbamoil(2S)pirrolidin-2,1-diil[(2S)-3-metil-1-oxobutan-1,2-diil]})biscarbamato de dimetilo

y

([(2R,5R)-1-(4-clorofenil)pirrolidin-2,5-diil]bis{bencen-4,1-diilcarbamoil(2S)pirrolidin-2,1-diil[(2S)-3-metil-1-oxobutan-1,2-diil]})biscarbamato de dimetilo

Ejemplo 85A

1-(4-clorofenil)-2,5-bis(4-nitrofenil)pirrolidina

El producto de Ejemplo 1B (0,50 g, 1,51 mmol) se suspendió en CH_2Cl_2 (15 ml). Se agregó trietilamina (0,626 ml, 4,51 mmol) a 0 °C, la mezcla resultante se agitó por 30 min, y se agregó cloruro de metansulfonilo (0,293 ml, 3,76 mmol). La mezcla se agitó a temperatura ambiente por 1 hr y luego se concentró al vacío para dar un sólido amarillo claro. El sólido se disolvió en DMF (6 ml), se agregó 4-cloroanilina (1,92 g, 15,05 mmol), y la mezcla resultante se agitó a 50 °C durante la noche. La mezcla se particionó entre EtOAc y HCl acuoso 1N, y la capa orgánica se secó sobre Na_2SO_4, se filtró y se concentró al vacío. El producto crudo se purificó mediante cromatografía de columna sobre gel de sílice usando un gradiente de solvente de 0-12% EtOAc en hexano para dar el compuesto del título (0,226 g, 35%).

Ejemplo 85B

4,4'-(trans-1-(4-clorofenil)pirrolidin-2,5-diil)dianilina

A una solución del producto de ejemplo 85A (0,214 g, 0,505 mmol) en EtOH (2,52 ml) y THF (2,52 ml) se agregó óxido de platino(IV) (0,115 g, 0,505 mmol), y la mezcla resultante se agitó a temperatura ambiente bajo 1 atm H_2 durante la noche. La mezcla se filtró a través de celite, y el material filtrado se concentró al vacío. El producto crudo se purificó mediante cromatografía de columna sobre gel de sílice usando un gradiente de solvente de 0-12% EtOAc en hexano para dar una mezcla del compuesto del título y algo de producto desclorado (4,4'-(trans-1-fenilpirrolidin-2,5-diil)dianilina).

Ejemplo 85C

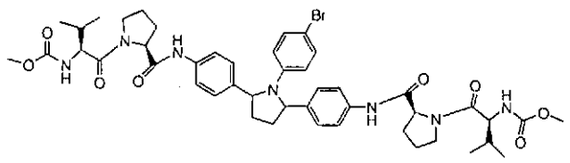
([(2S,5S)-1-(4-clorofenil)pirrolidin-2,5-diil]bis{bencen-4,1-diilcarbamoil(2S)pirrolidin-2,1-diil[(2S)-3-metil-1-oxobutan-1,2-diil]})biscarbamato de dimetilo

y

([(2R,5R)-1-(4-clorofenil)pirrolidin-2,5-diil]bis{bencen-4,1-diilcarbamoil(2S)pirrolidin-2,1-diil[(2S)-3-metil-1-oxobutan-1,2-diil]})biscarbamato de dimetilo

Una mezcla del producto del Ejemplo 85B se sometió a los procedimientos descritos en Ejemplos 34C, 34D, y 34E para dar los compuestos del título libres de producto desclorado. 1H RMN (Sal TFA) (400 MHz, DMSO-D6) δ ppm 0,84 - 0,89 (m, 6 H), 0,89 - 0,94 (m, 6 H), 1,61 - 1,66 (m, 2 H), 1,80 - 2,03 (m, 8 H), 2,06 - 2,18 (m, 2 H), 3,51 (s, 6 H),

3,56 - 3,65 (m, 2H), 3,74 - 3,84 (m, 2 H), 4,01 (t, *J*=8,4 Hz, 2 H), 4,36 - 4,44 (m, 2 H), 5,16 (d, *J*=6,3 Hz, 2 H), 6,21 (d, *J*=8,9 Hz, 2 H), 6,93 (d, *J*=9,0 Hz, 2 H), 7,08 - 7,13 (m, 4 H), 7,26 - 7,31 (m, 2 H), 7,46 - 7,51 (m, 4 H), 9,99 (s, 2 H). MS m/z 872,3 $(M+H)^+$.



Ejemplo 86

([(2*S*,5*S*)-1-(4-bromofenil)pirrolidin-2,5-diil]bis{bencen-4,1-diilcarbamoil(2*S*)pirrolidin-2,1-diil[(2*S*)-3-metil-1-oxobutan-1,2-diil]})biscarbamato de dimetilo

y

([(2*R*,5*R*)-1-(4-bromofenil)pirrolidin-2,5-diil]bis{bencen-4,1-diilcarbamoil(2*S*)pirrolidin-2,1-diil[(2*S*)-3-metil-1-oxobutan-1,2-diil]})biscarbamato de dimetilo

Ejemplo 86A

1-(4-bromofenil)-2,5-bis(4-nitrofenil)pirrolidina

El producto del Ejemplo 1C (0,7 g, 1,433 mmol) y 4-bromoanilina (2,54 g, 14,33 mmol) se suspendieron en DMF (6mL) y se agitó a 50 °C durante la noche. La mezcla resultante se particionó entre acetato de etilo (100 ml) y agua (50 ml). La fase orgánica se lavó con HCl 1N (2x50mL) seguido por un lavado con salmuera luego se secó sobre $MgSO_4$, se filtró y se concentró. El producto crudo se purificó mediante cromatografía sobre gel de sílice.usando un gradiente de solvente de acetato de etilo al 2-50% en hexano para dar el compuesto del título como una mezcla de estereoisómeros (74,4mg, 11% de rendimiento).

Ejemplo 86B

(2S,2'S)-N,N'-(4,4'-(1-(4-bromofenil)pirrolidin-2,5-diil)bis(4,1-fenilen))dipirrolidin-2-carboxamida

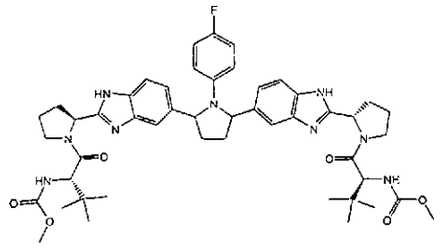
Ejemplo 86A se procesó usando los métodos de Ejemplos 1E, 1F, y 1G para dar el compuesto del título como una mezcla de estereoisómeros.

Ejemplo 86C

([1-(4-bromofenil)pirrolidin-2,5-diil]bis{bencen-4,1-diilcarbamoil(2S)pirrolidin-2,1-diil[(2S)-3-metil-1-oxobutan-1,2-diil]})biscarbamato de dimetilo

El producto del Ejemplo 86B (78,0mg, 0,129mmole) se combinó con EDAC (67,0mg, 0,347 mmol), hidrato de 1-hidroxibenzotriazol (49,0mg, 0,323mmole) y ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico (61,0mg, 0,346mmole) en dimetilformamida (1,4mL) a temperatura ambiente bajo una atmósfera de nitrógeno. A esta solución se agregó diisopropiletilamina (0,113 ml, 0,645 mmol). La mezcla se dejó agitar durante la noche a temperatura ambiente seguido por la partición entre acetato de etilo (20mL) y

agua (5mL). La fase orgánica se lavó con agua (3x5mL) luego se secó sobre $MgSO_4$, se filtró y se evaporó hasta secar. El producto crudo se cromatografió mediante HPLC de fase inversa (C_{18}) para dar el compuesto del título como una mezcla 1:1 de (trans) diastereómeros (0,045g, 38% de rendimiento) como un sólido blanco opaco. 1H RMN (base libre) (400 MHz, DMSO-D6) δ ppm 0,72 - 1,03 (m, 12 H) 1,65 (s, 2 H) 1,79 - 2,19 (m, 11 H) 3,52 (s, 6 H) 3,58 - 3,67 (m, 2 H) 3,75 - 3,86 (m, 2 H) 3,95 - 4,09 (m, 2 H) 4,43 (dd, *J*=7,92, 4,88 Hz, 2 H) 5,08 - 5,25 (m, 2 H) 6,19 (d, *J*=8,89 Hz, 2 H) 7,06 (d, *J*=8,89 Hz, 2 H) 7,12 (d, *J*=7,16 Hz, 4 H) 7,31 (dd, *J*=8,29, 3,96 Hz, 2 H) 7,51 (dd, *J*=8,46, 1,52 Hz, 4 H) 10,00 (s, 2 H). MS ESI(+) m/z@916,6 (M+H)+.



Ejemplo 87

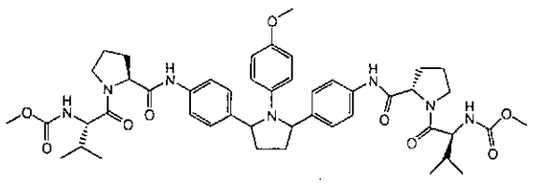
{(2*S*)-1-[(2*S*)-2-{5-[(2*S*,5*S*)-1-(4-fluorofenil)-5-{2-[(2*S*)-1-{(2*S*)-2-[(metoxicarbonil)amino]-3,3-dimetilbutanoil}pirrolidin-2-il]-1*H*-bencimidazol-5-il}pirrolidin-2-il]-1*H*-bencimidazol-2-il}pirrolidin-1-il]-3,3-dimetil-1-oxobutan-2-il}carbamato de metilo

y

{(2*S*)-1-[(2*S*)-2-{5-[(2*R*,5*R*)-1-(4-fluorofenil)-5-{2-[(2*S*)-1-{(2*S*)-2-[(metoxicarbonil)amino]-3,3-dimetilbutanoil}pirrolidin-2-il]-1*H*-bencimidazol-5-il}pirrolidin-2-il]-1*H*-bencimidazol-2-il}pirrolidin-1-il]-3,3-dimetil-1-oxobutan-2-il}carbamato de metilo

El producto del Ejemplo 29G (0,045 g, 0,084 mmol), ácido (S)-2-metoxicarbonilamino-3,3-dimetil-butírico (0,037 g, 0,193 mmol), 4-metilmorfolina (0,037 ml, 0,336 mmol), hidrato de 1H-benzo[d][1,2,3]triazol-1-ol (0,028 g, 0,185 mmol) y clorhidrato de N1-((etilimino)metilen)-N3,N3-dimetilpropan-1,3-diamina (0,035 g, 0,185 mmol) se combinaron en 2 ml de DMF y se agitó por 2 horas. La mezcla de la reacción se particionó entre EtOAc y agua. La capa orgánica se lavó 3 X 20 ml con salmuera, se secó (Na_2SO_4), se filtró y se concentró. El material crudo se sometió a cromatografía flash en un cartucho de sílice Isco Gold de 4 g eluyendo con 1,5-8% MeOH en cloruro de metileno. Una segunda cromatografía preparativa C-18 de fase inversa eluyendo con 9:1 agua/acetonitrilo --> 100% acetonitrilo dio los compuestos del título (29 mg, 28%; mezcla de diastereómeros trans) como un polvo color tostado claro. ^{1}H RMN (Sal TFA) (400 MHz, DMSO-d_6) δ 0,84 - 0,95 (m, 18 H) 1,21 - 1,46 (m, 4 H) 1,75 - 2,27 (m, 8 H) 3,56 (s, 6 H) 3,86 (t, J=5,26 Hz, 4 H) 4,22 (dd, J=8,57, 4,45 Hz, 2 H) 5,15 - 5,24 (m, 2 H) 5,53 (d,

J=4,88 Hz, 2 H) 6,30 (dd, J=9,11, 4,34 Hz, 2 H) 6,75 - 6,83 (m, 2 H) 7,29 (d, J=8,57 Hz, 2 H) 7,35 (d, J=8,46 Hz, 2 H) 7,48 (d, J=7,92 Hz, 2 H) 7,69 (d, J=7,37 Hz, 2 H). MS (ESI+) m/z 879 $(M+H)^+$.



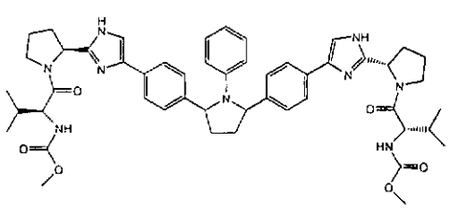
Ejemplo 88

([(2S,5S)-1-(4-metoxifenil)pirrolidin-2,5-diil]bis{bencen-4,1-diilcarbamoil(2S)pirrolidin-2,1-diil[(2S)-3-metil-1-oxobutan-1,2-diil]})biscarbamato de dimetilo

y

([(2R,5R)-1-(4-metoxifenil)pirrolidin-2,5-diil]bis{bencen-4,1-diilcarbamoil(2S)pirrolidin-2,1-diil[(2S)-3-metil-1-oxobutan-1,2-diil]})biscarbamato de dimetilo

El compuesto del título se preparó usando los procedimientos descritos para la síntesis de Ejemplos 34A, 34B, 34C, 34D, y 34E, utilizando 4-metoxianilina en lugar de 4-*tert*-butilanilina. 1H RMN (Sal TFA) (400 MHz, DMSO-D6) δ ppm 0,85 - 0,90 (m, 6 H), 0,90 - 0,95 (m, 6 H), 1,60 - 1,66 (m, 2 H), 1,81 - 2,04 (m, 8 H), 2,08 - 2,19 (m, 2 H), 3,52 (s, 9 H), 3,57 - 3,66 (m, 2 H), 3,77 - 3,85 (m, 2 H), 4,02 (t, 2 H), 4,39 - 4,46 (m, 2 H), 5,12 (d, *J*=6,3 Hz, 2 H), 6,18 (d, *J*=9,0 Hz, 2 H), 6,56 (d, *J*=9,0 Hz, 2 H), 7,09 - 7,15 (m, 4 H), 7,28 - 7,34 (m, 2 H), 7,46 - 7,52 (m, 4 H), 9,97 (s, 2 H); MS m/z 868,5 $(M+H)^+$.



Ejemplo 89

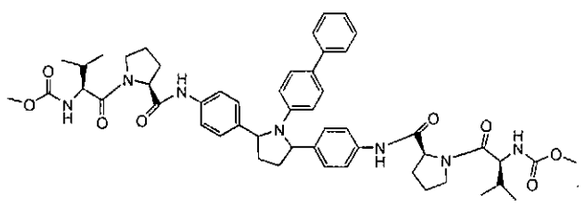
{(2*S*)-1-[(2*S*)-2-(4-{4-[(2*S*,5*S*)-5-(4-{2-[(2*S*)-1-{(2*S*)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1*H*-imidazol-4-il}fenil)-1-fenilpirrolidin-2-il]fenil}-1*H*-imidazol-2-il)pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

y

{(2*S*)-1-[(2*S*)-2-(4-{4-[(2*R*,5*R*)-5-(4-{2-[(2*S*)-1-{(2*S*)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1*H*-imidazol-4-il}fenil)-1-fenilpirrolidin-2-il]fenil}-1*H*-imidazol-2-il)pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

A los diastereómeros trans obtenidos en Ejemplo 59B (8,5 mg, 0,0107 mmol), ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico (4,67 mg, 0,027 mmol) y HATU (8,9 mg, 0,023 mmol) en DMSO (1 ml) se agregó base de Hunig (0,015 ml, 0,085 mmol), y la

mezcla de la reacción se agitó a temperatura ambiente por 1 hr. La mezcla de la reacción se particionó entre agua y acetato de etilo, y la capa orgánica se secó sobre $MgSO_4$, se filtró y se concentró al vacío. El producto crudo se purificó mediante cromatografía de fase inversa (C18), eluyendo con 10-100% acetonitrilo en agua (TFA al 0,1%) para dar 5,0 mg (53%) del compuesto del título como una mezcla de diastereómeros trans. 1H RMN (Sal TFA) (400 MHz, DMSO-D6) δ ppm 14,45 (bs, 2 H), 7,97 (s, 2 H), 7,66 (m, 4 H), 7,38 (m, 4H), 7,31 (d, *J*=7,4 Hz, 2 H), 6,92 (t, *J*=7,6 Hz, 2 H), 6,43 (m, 1 H), 6,28 (d, *J*=8,1 Hz, 2 H), 5,37 (m, 2H), 5,09 (t, *J*=6,7 Hz, 2 H), 4,09 (t, *J*=7,7 Hz, 2 H), 3,81 (m, 6 H), 3,53 (s, 6 H), 2,40 (m, 2 H), 2,08 (m, 2 H), 2,02 (m, 6 H), 1,85 (m, 2 H), 0,85 (m, 2 H), 0,80 (m, 12 H); MS (ESI) m/z 884 (M+H)+.



Ejemplo 90

([(2*S*,5*S*)-1-(bifenil-4-il)pirrolidin-2,5-diil]bis{bencen-4,1-diilcarbamoil(2*S*)pirrolidin-2,1-diil[(2*S*)-3-metil-1-oxobutan-1,2-diil]})biscarbamato de dimetilo

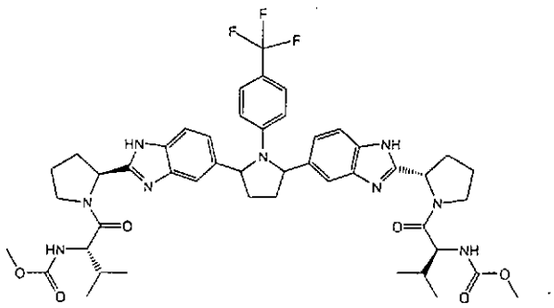
y

([(2*R*,5*R*)-1-(bifenil-4-il)pirrolidin-2,5-diil]bis{bencen-4,1-diilcarbamoil(2*S*)pirrolidin-2,1-diil[(2*S*)-3-metil-1-oxobutan-1,2-diil]})biscarbamato de dimetilo

El producto del Ejemplo 86C (24,9mg, 0,027mmole) disuelto en una solución de THF (1mL) y agua (0,3mL) se combinó en un tubo de microondas con ácido fenilborónico (6,90mg, 0,054mmole), fosfato de potasio tribásico (13,37mg, 0,063mmole) y dicloruro de 1,1'-bis(di-tert-butilfosfino)ferrocenopaladio (1,42mg, 2,17µmol). El tubo se selló y se burbujeó nitrógeno a temperatura ambiente por cinco minutos. Luego se retiraron todas las líneas de gas y el recipiente de la reacción se sumergió en un baño de aceite a 50 °C y se calentó por dos horas y media. Los contenidos del tubo se particionaron entre acetato de etilo (5mL) y salmuera (1mL). La fase orgánica se lavó con salmuera (2 x 1mL) luego se secó sobre $MgSO_4$, se filtró y se concentró. El producto crudo se purificó mediante cromatografía sobre gel de sílice eluyendo con 5% EtOAc – hexano y se progresó a (75% EtOAc-hexano) + 3% metanol para dar el compuesto del título como una mezcla 1:1 de (trans) diastereómeros (18,6mg, 75% de rendimiento) como un sólido color crema. 1H RMN (400 MHz, DMSO-D6) δ ppm 0,76 - 0,99 (m, 12 H) 1,67 (s, 2 H) 1,77 - 2,19 (m, 11 H) 3,52 (s, 6 H) 3,58 - 3,65 (m, 2 H) 3,74 - 3,86 (m, 2 H) 3,96 - 4,08 (m, 2 H) 4,44 (d, *J*=4,99 Hz, 2 H) 5,25 (s, 2 H) 6,35 (d, *J*=8,02 Hz, 2 H) 7,17 (d, *J*=7,26 Hz, 5 H) 7,24 - 7,34

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(m, 6 H) 7,45 (d, *J*=7,92 Hz, 2 H) 7,52 (d, *J*=7,81 Hz, 4 H) 10,00 (s, 2 H). MS ESI(+) m/z@ 915,1 (M+H)+, m/z@ 972,3 ($M+CH_3CN+NH_4$)+.



Ejemplo 91

{(2*S*)-1-[(2*S*)-2-(5-{(2*S*,5*S*)-5-{2-[(2*S*)-1-{(2*S*)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1*H*-bencimidazol-5-il}-1-[4-(trifluorometil)fenil]pirrolidin-2-il}-1*H*-bencimidazol-2-il)pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

y

{(2*S*)-1-[(2*S*)-2-(5-{(2*R*,5*R*)-5-{2-[(2*S*)-1-{(2*S*)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1*H*-bencimidazol-5-il}-1-[4-(trifluorometil)fenil]pirrolidin-2-il}-1*H*-bencimidazol-2-il)pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

Ejemplo 91A

cloruro de (2S,2'S)-2,2'(6,6'-(1-(4-(trifluorometil)fenil)pirrolidin-2,5-diil)bis(1H-benzo[d]imidazol-6,2-diil))dipirrolidinio

Se procesó Ejemplo 28C y 4-trifluorometilanilina usando los métodos de Ejemplos 28D-28J para dar el compuesto del título como una mezcla de estereoisómeros cis y trans.

Ejemplo 91B

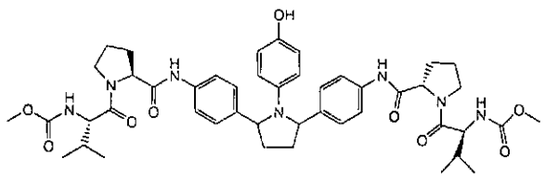
{(2*S*)-1-[(2*S*)-2-(5-{(2*S*,5*S*)-5-{2-[(2*S*)-1-{(2*S*)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1*H*-bencimidazol-5-il}-1-[4-(trifluorometil)fenil]pirrolidin-2-il}-1*H*-bencimidazol-2-il)pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

y

{(2*S*)-1-[(2*S*)-2-(5-{(2*R*,5*R*)-5-{2-[(2*S*)-1-{(2*S*)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1*H*-bencimidazol-5-il}-1-[4-(trifluorometil)fenil]pirrolidin-2-il}-1*H*-bencimidazol-2-il)pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

El producto del Ejemplo 91A (1: 1 mezcla de isómeros cis y trans), 0,018 g, 0,027 mmol), HOBt (0,013 g, 0,082 mmol), EDAC (0,016 g, 0,082 mmol) y ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico (0,014 g, 0,082 mmol) se combinaron en un balón de 20 ml y se disolvió en 1 ml de DMF a temperatura ambiente, se agregó 4-metilmorfolina (0,015 ml, 0,137 mmol) y la solución ligeramente marrón traslúcida resultante se agitó a temperatura ambiente por 2 hr. La mezcla de la reacción se analizó

mediante LC-MS y se determinó que se había completado. La mezcla de la reacción se diluyó con 50 ml de EtOAc, se lavó con $NaHCO_3$ al 10% y NaCl al 10%, se secó sobre Na_2SO_4 anhidro(s), se filtró y el solvente se eliminó al vacío para dar el compuesto del título como un sólido marrón claro. El material se purificó mediante HPLC preparativa en una columna Fenomenex Luna C8(2) 5 um 100Å AXIA (30mm x 75mm). Se usó un gradiente de acetonitrilo (A) y ácido trifluoroacético al 0,1% en agua (B), a una velocidad de flujo de 50mL/min (0-0,5 min 10% A, gradiente lineal de 0,5-7,0 min 10-95% A, 7,0-10,0 min 95% A, gradiente lineal de 10,0-12,0 min 95-10% A). Las fracciones del producto se recogieron y se evaporó hasta secar al vacío para dar el compuesto del título como un sólido color tostado, (11 mg, 44%) y una mezcla de isómeros trans diastereoméricos. 1H RMN (Sal TFA) (400 MHz, DMSO-D6) d ppm 0,67 - 0,94 (m, 12 H) 1,95 (m, 18 H) 3,79 - 3,89 (m, 6 H) 4,10 (s, 2 H) 5,19 (s, 1 H) 5,64 (s, 2 H) 6,45 (s, 2 H) 7,28 (s, 4 H) 7,47 (s, 4 H) 7,69 (s, 4 H), 12,1 (b, 2H)ESI+(m/z):900,6, ESI-(m/z):898,8.



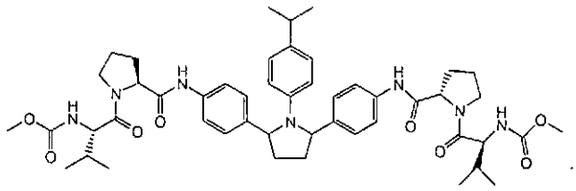
Ejemplo 92

([(2S,5S)-1-(4-hidroxifenil)pirrolidin-2,5-diil]bis{bencen-4,1-diilcarbamoil(2S)pirrolidin-2,1-diil[(2S)-3-metil-1-oxobutan-1,2-diil]})biscarbamato de dimetilo

y

([(2R,5R)-1-(4-hidroxifenil)pirrolidin-2,5-diil]bis{bencen-4,1-diilcarbamoil(2S)pirrolidin-2,1-diil[(2S)-3-metil-1-oxobutan-1,2-diil]})biscarbamato de dimetilo

A una solución del producto del Ejemplo 88 (0,050 g, 0,058 mmol) en CH_2Cl_2 (1 ml) a –78 °C se agregó una solución 1,0 M de tribromuro de boro en CH_2Cl_2 (0,29 ml, 0,29 mmol). La solución color rojo oscuro resultante se agitó a –78 °C por 4 h, y luego se calentó a temperatura ambiente y se lavó con agua. La capa orgánica se secó sobre sulfato de sodio, se filtró, y se concentró al vacío. El producto crudo se purificó mediante cromatografía de columna sobre gel de sílice usando un gradiente de solvente de 0-7,5% MeOH en CH_2Cl_2 para dar el compuesto del título (5,5 mg, 12%) como una mezcla de diastereómeros trans. 1H RMN (400 MHz, DMSO-D6) δ ppm 0,86 - 0,90 (m, 6 H), 0,90 - 0,95 (m, 6 H), 1,58 - 1,63 (m, 2 H), 1,82 - 2,04 (m, 8 H), 2,08 - 2,19 (m, 2 H), 3,52 (s, 6 H), 3,58 - 3,66 (m, 2 H), 3,77 - 3,84 (m, 2 H), 4,02 (t, *J*=8,5 Hz, 2 H), 4,40 - 4,46 (m, 2 H), 5,08 (d, *J*=6,3 Hz, 2 H), 6,08 (d, *J*=8,8 Hz, 2 H), 6,38 (d, *J*=8,8 Hz, 2 H), 7,08 - 7,13 (m, 4 H), 7,29 - 7,34 (m, 2 H), 7,45 - 7,51 (m, 4 H), 8,27 (d, *J*=1,2 Hz, 1 H), 9,96 (s, 2 H); MS m/z 854,4 $(M+H)^+$.



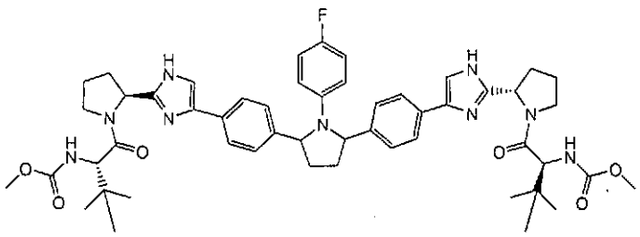
Ejemplo 93

{{(2S,5S)-1-[4-(propan-2-il)fenil]pirrolidin-2,5-diil}bis{bencen-4,1-diilcarbamoil(2S)pirrolidin-2,1-diil[(2S)-3-metil-1-oxobutan-1,2-diil]})biscarbamato de dimetilo

y

({(2R,5R)-1-[4-(propan-2-il)fenil]pirrolidin-2,5-diil}bis{bencen-4,1-diilcarbamoil(2S)pirrolidin-2,1-diil[(2S)-3-metil-1-oxobutan-1,2-diil]})biscarbamato de dimetilo

El compuesto del título se preparó como una mezcla de diastereómeros trans usando los procedimientos descritos para la síntesis de Ejemplos 34A, 34B, 34C, 34D, y 34E, utilizando 4-isopropilanilina en lugar de 4-*tert*-butilanilina. 1H RMN (Sal TFA) (400 MHz, DMSO-D6) δ ppm 0,85 - 0,90 (m, *J*=5,8, 5,8 Hz, 6 H), 0,90 - 0,96 (m, 6 H), 1,02 - 1,06 (m, 6 H), 1,60 - 1,65 (m, 2 H), 1,81 - 2,04 (m, 8 H), 2,08 - 2,19 (m, 2 H), 2,56 - 2,65 (m, 1 H), , 3,52 (s, 6 H), 3,58 - 3,66 (m, 2 H), 3,76 - 3,85 (m, 2 H), 4,02 (t, *J*=8,3 Hz, 2 H), 4,40 - 4,45 (m, 2 H), 5,14 (d, *J*=6,5 Hz, 2 H), 6,15 - 6,20 (m, 2 H), 6,79 (d, *J*=8,7 Hz, 2 H), 7,09 - 7,16 (m, 4 H), 7,29 - 7,34 (m, 2 H), 7,47 - 7,52 (m, 4 H), 9,97 (s, 2 H); MS m/z 880,5 $(M+H)^+$.



Ejemplo 94

{(2*S*)-1-[(2*S*)-2-(4-{4-[(2*S*,5*S*)-1-(4-fluorofenil)-5-(4-{2-[(2*S*)-1-{(2*S*)-2-[(metoxicarbonil)amino]-3,3-dimetilbutanoil}pirrolidin-2-il]-1*H*-imidazol-4-il}fenil)pirrolidin-2-il]fenil}-1*H*-imidazol-2-il)pirrolidin-1-il]-3,3-dimetil-1-oxobutan-2-il}carbamato de metilo

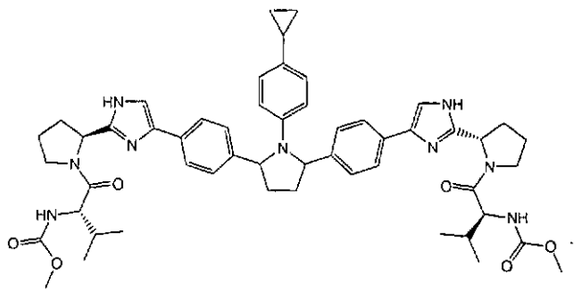
y

{(2*S*)-1-[(2*S*)-2-(4-{4-[(2*R*,5*R*)-1-(4-fluorofenil)-5-(4-{2-[(2*S*)-1-{(2*S*)-2-[(metoxicarbonil)amino]-3,3-dimetilbutanoil}pirrolidin-2-il]-1*H*-imidazol-4-il}fenil)pirrolidin-2-il]fenil}-1*H*-imidazol-2-il)pirrolidin-1-il]-3,3-dimetil-1-oxobutan-2-il}carbamato de metilo

El producto del Ejemplo 45D (28 mg, 0,048 mmol) se sometió a las condiciones descritas en ejemplo 45E, utilizando ácido (S)-2-(metoxicarbonilamino)-3,3-dimetilbutanoico en lugar de ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico, para dar el compuesto del

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título (18 mg, 41%) como una mezcla de diastereómeros. 1H RMN (Sal TFA) (400 MHz, DMSO-D6) δ ppm 0,86 (s, 9 H), 0,87 (s, 9 H), 1,70 - 1,81 (m, 2 H), 1,94 - 2,25 (m, 6 H), 2,34 - 2,44 (m, 2 H), 3,55 (s, 6 H), 3,72 - 3,95 (m, 4 H), 4,19 (d, *J*=8,7 Hz, 2 H), 5,09 (t, *J*=7,2 Hz, 2 H), 5,35 (d, *J*=6,1 Hz, 2 H), 6,26 (dd, *J*=9,1, 4,4 Hz, 2 H), 6,81 (t, *J*=8,9 Hz, 2 H), 7,29 (d, *J*=8,0 Hz, 2 H), 7,37 (d, *J*=7,2 Hz, 4 H), 7,68 (dd, *J*=7,8, 5,4 Hz, 4 H), 7,97 (s, 2 H), 14,46 (br s, 2 H); MS m/z 930,8 $(M+H)^+$.



Ejemplo 95

{(2*S*)-1-[(2*S*)-2-(4-{4-[(2*S*,5*S*)-1-(4-ciclopropilfenil)-5-(4-{2-[(2*S*)-1-{(2*S*)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1*H*-imidazol-4-il}fenil)pirrolidin-2-il]fenil}-1*H*-imidazol-2-il)pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

y

{(2*S*)-1-[(2*S*)-2-(4-{4-[(2*R*,5*R*)-1-(4-ciclopropilfenil)-5-(4-{2-[(2*S*)-1-{(2*S*)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1*H*-imidazol-4-il}fenil)pirrolidin-2-il]fenil}-1*H*-imidazol-2-il)pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

Ejemplo 95A

(S)-4,4'-(4,4'-((2R,5R)-1-(4-ciclopropilfenil)pirrolidin-2,5-diil)bis(4,1-fenilen))bis(2-((S)-pirrolidin-2-il)-1H-imidazol)

y

(S)-4,4'-(4,4'-((2S,5S)-1-(4-ciclopropilfenil)pirrolidin-2,5-diil)bis(4,1-fenilen))bis(2-((S)-pirrolidin-2-il)-1H-imidazol)

El producto del Ejemplo 68C (1,27 g, 1,568 mmol) se disolvió en diclorometano (12 ml). La mezcla se enfrió a 0 °C y ácido trifluroacético (8 ml, 104 mmol) se agregó lentamente. La mezcla se calentó a temperatura ambiente y se agitó por 1h. El solvente se evaporó y el residuo se purificó mediante cromatografía sobre gel de sílice eluyendo con metanol/diclorometano (1% a 10%). El compuesto del título se eluyó como el primero de 2 estereoisómeros y se obtuvo como una mezcla de diastereómeros trans (510 mg, 53%).

Ejemplo 95B

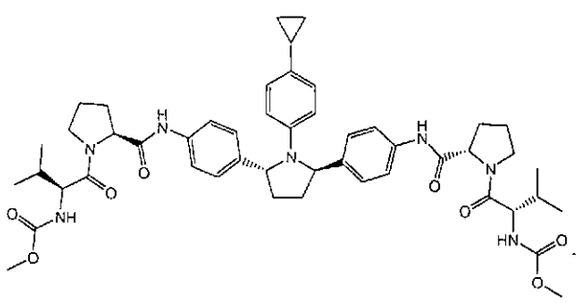
{(2*S*)-1-[(2*S*)-2-(4-{4-[(2*S*,5*S*)-1-(4-ciclopropilfenil)-5-(4-{2-[(2*S*)-1-{(2*S*)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1*H*-imidazol-4-il}fenil)pirrolidin-2-

il]fenil}-1*H*-imidazol-2-il)pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

y

{(2*S*)-1-[(2*S*)-2-(4-{4-[(2*R*,5*R*)-1-(4-ciclopropilfenil)-5-(4-{2-[(2*S*)-1-{(2*S*)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1*H*-imidazol-4-il}fenil)pirrolidin-2-il]fenil}-1*H*-imidazol-2-il)pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

El producto del Ejemplo 95A (150 mg, 0,246 mmol), ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico (86 mg, 0,492 mmol), 4-metilmorfolina (0,216 ml, 1,968 mmol), clorhidrato de N1-((etilimino)metilen)-N3,N3-dimetilpropan-1,3-diamina (104 mg, 0,541 mmol) y hidrato de 1H-benzo[d][1,2,3]triazol-1-ol (83 mg, 0,541 mmol) se combinaron en DMF (10 ml). La mezcla se agitó a temperatura ambiente por 2 horas. La mezcla de la reacción se particionó entre acetato de etilo y agua. La capa orgánica se lavó con bicarbonato de sodio saturado, salmuera dos veces, se secó con sulfato de sodio, se filtró y se evaporó. El residuo se purificó mediante cromatografía sobre gel de sílice eluyendo con metanol/diclorometano (1% a 4%) para dar el compuesto del título (78 mg, 34%) como un sólido. 1H RMN (400 MHz, DMSO-D6) δ ppm 0,35 - 0,41 (m, 2 H) 0,65 - 0,72 (m, 2 H) 0,81 - 0,92 (m, 12 H) 1,58 - 1,64 (m, 1 H) 1,66 - 1,72 (m, 2 H) 1,86 - 2,03 (m, 6 H) 2,07 - 2,17 (m, 4 H) 2,24 - 2,30 (m, 2 H) 3,53 (s, 6 H) 3,74 - 3,82 (m, 4 H) 4,04 (t, J=7,86 Hz, 2 H) 5,06 (dd, J=6,72, 2,93 Hz, 2 H) 5,14 - 5,26 (m, 2 H) 6,19 (d, J=8,67 Hz, 2 H) 6,64 (d, J=8,24 Hz, 2 H) 7,10 - 7,30 (m, 6 H) 7,34 - 7,69 (m, 6 H) 11,64 - 12,11 (m, 2 H); MS (ESI+) m/z 924,8 (M+H)+.

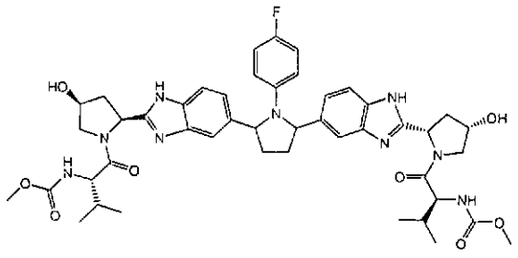


Ejemplo 96

([(2R,5R)-1-(4-ciclopropilfenil)pirrolidin-2,5-diil]bis{bencen-4,1-diilcarbamoil(2S)pirrolidin-2,1-diil[(2S)-3-metil-1-oxobutan-1,2-diil]})biscarbamato de dimetilo

Se procesó Ejemplo 38A y 4-ciclopropilanilina usando en forma consecutiva los métodos de Ejemplos 34A, 34B, 34C, 66D, y 66E para dar el compuesto del título (62 mg). ^{1}H RMN (400 MHz, DMSO-d_6) δ 0,36 - 0,46 (m, 2 H) 0,63 - 0,77 (m, 2 H) 0,87 (d, J=6,61 Hz, 6 H) 0,92 (d, J=6,72 Hz, 6 H) 1,52 - 2,46 (m, 15 H) 3,52 (s, 6 H) 3,57 - 3,66 (m, 2 H) 3,75 - 3,85 (m, 2 H) 4,02 (t, J=8,46 Hz, 2 H) 4,42 (dd, J=8,02, 4,88 Hz, 2 H) 5,14 (d, J=6,40 Hz, 2 H) 6,14 (d, J=8,78 Hz, 2 H) 6,65 (d, J=8,67 Hz, 2 H) 7,10 (d, J=8,57 Hz, 4 H)

7,30 (d, J=8,35 Hz, 2 H) 7,48 (d, J=8,57 Hz, 4 H) 9,97 (s, 2 H). MS (APCI) m/z 878 $(M+H)^+$.

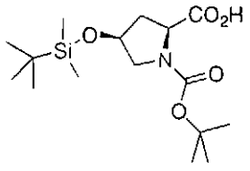


Ejemplo 97

{(2*S*)-1-[(2*S*,4*S*)-2-{5-[(2*S*,5*S*)-1-(4-fluorofenil)-5-{2-[(2*S*,4*S*)-4-hidroxi-1-{(2*S*)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1*H*-bencimidazol-5-il}pirrolidin-2-il]-1*H*-bencimidazol-2-il}-4-hidroxipirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

y

{(2*S*)-1-[(2*S*,4*S*)-2-{5-[(2*R*,5*R*)-1-(4-fluorofenil)-5-{2-[(2*S*,4*S*)-4-hidroxi-1-{(2*S*)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1*H*-bencimidazol-5-il}pirrolidin-2-il]-1*H*-bencimidazol-2-il}-4-hidroxipirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo



Ejemplo 97A

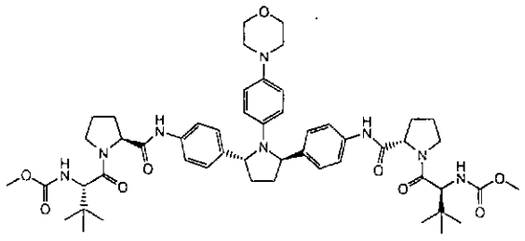
ácido (2S,4S)-1-(tert-butoxicarbonil)-4-(tert-butildimetilsililoxi)pirrolidin-2-carboxílico

Se combinó ácido (2S,4S)-1-(tert-butoxicarbonil)-4-hidroxipirrolidin-2-carboxílico (5,31 g, 22,96 mmol) e imidazol (7,82 g, 115 mmol) en diclorometano (106 ml) y dimetilformamida (22 ml) a temperatura ambiente y se trató con la adición por porciones de tert-butilclorodimetilsilano (7,61 g, 50,5 mmol). La mezcla se agitó por 18 horas luego se diluyó con agua y se extrajo con acetato de etilo y se concentró para dar el compuesto del título.

Ejemplo 97B

El producto del Ejemplo 29D (0,906 g, 2,62 mmol) se procesó como en Ejemplos 29E, 29F, 29G, y 29H, utilizando Ejemplo 97A en lugar de S-Boc-prolina en paso 29E para dar los compuestos del título (0,012 g, 13%),1H RMN (400 MHz, DMSO-D6) δ ppm 0,69 - 0,85 (m, 12 H) 1,27 - 1,39 (m, 1 H) 1,53 (dt, J=21,31, 6,64 Hz, 1 H) 1,71 (s, 4 H) 1,80 - 1,90 (m, 2 H) 2,02 (d, J=7,70 Hz, 2 H) 2,54 - 2,62 (m, 2 H) 3,53 (s, 6 H) 3,68 (t, J=10,63 Hz, 2 H) 3,93 - 4,00 (m, 2 H) 4,39 (s, 2 H) 5,13 (s, 2 H) 5,38 (s, 2 H) 6,19 - 6,38 (m, 4 H) 6,74 (d, J=2,60 Hz, 2 H) 7,08 (s, 2 H) 7,21 - 7,36 (m, 4 H) 7,40 - 7,51 (m, 2 H)

12,21 - 12,38 (m, 2 H); MS TFA+ m/z 882,5 (M+H)+.



Ejemplo 98

({(2R,5R)-1-[4-(morfolin-4-il)fenil]pirrolidin-2,5-diil}bis{bencen-4,1-diilcarbamoil(2S)pirrolidin-2,1-diil[(2S)-3,3-dimetil-1-oxobutan-1,2-diil]})biscarbamato de dimetilo

Ejemplo 98A

4-(4-((2R,5R)-2,5-bis(4-nitrofenil)pirrolidin-1-il)fenil)morfolina

El producto del Ejemplo 38A y 4-morfolinoanilina se procesaron usando el método descrito en Ejemplo 1D usando NMP como solvente para dar el compuesto del título. MS (ESI) *m/z* 475 $(M+H)^+$.

Ejemplo 98B

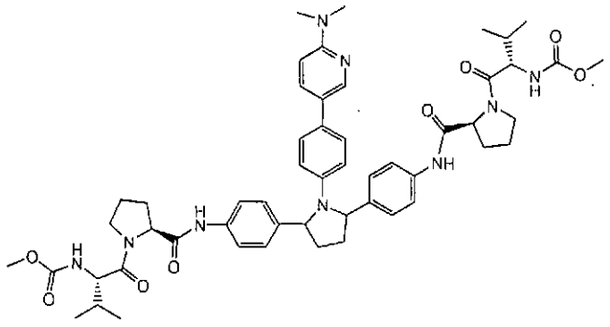
4,4'-((2R,5R)-1-(4-morfolinofenil)pirrolidin-2,5-diil)dianilina

El producto del Ejemplo 98A en tetrahidrofurano (20 ml) se agregó a Ra-Ni (humedecido con agua, A-7000, 0,8 g, 12,63 mmol) en una botella de presión de 50 ml y se agitó por 2 horas a temperatura ambiente bajo 30 psi de hidrógeno. La mezcla se filtró a través de una membrana de nylon y se concentró para dar el compuesto del título (0,31 g, 44%). MS (DCI) *m/z* 415 $(M+H)^+$.

Ejemplo 98C

(2S,2'S)-2,2'-(4,4'-((2R,5R)-1-(4-morfolinofenil)pirrolidin-2,5-diil)bis(4,1-fenilen))bis(azandiil)bis(oxometilen)dipirrolidin-1-carboxilato de tert-butilo

El producto del Ejemplo 98B se procesó usando en forma consecutiva los métodos de Ejemplos 55F, 55G, y 26J (con ácido (S)-2-(metoxicarbonilamino)-3,3-dimetilbutanoico) para dar el compuesto del título (0,13 g). ^{1}H RMN (400 MHz, DMSO-D6) δ 0,93 (d, *J* = 20,5, 17H), 1,92 - 1,79 (m, 4H), 2,05 - 1,93 (m, 3H), 2,21 - 2,08 (m, 2H), 2,43 (t, *J* = 6,1, 3H), 2,84 - 2,75 (m, 4H), 3,54 (s, 6H), 3,68 - 3,58 (m, 6H), 3,83 - 3,70 (m, 2H), 4,20 (d, *J* = 8,9, 2H), 4,43 (dd, *J* = 7,9, 5,3, 2H), 5,12 (d, *J* = 6,3, 2H), 6,17 (d, *J* = 9,1, 2H), 6,60 (d, *J* = 9,1, 2H), 7,07 (d, *J* = 8,8, 2H), 7,11 (d, *J* = 8,5, 4H), 7,48 (d, *J* = 8,5, 4H), 9,98 (s, 2H). Impureza ^{1}H RMN (400 MHz, DMSO-D6) δ 1,63 (d, *J* = 5,6, 2H), 3,17 (d, *J* = 5,3, 3H), 4,09 (q, *J* = 5,3, 1H). MS (ESI) *m/z* 952 $(M+H^+)$.



Ejemplo 99

([(2*S*,5*S*)-1-{4-[6-(dimetilamino)piridin-3-il]fenil}pirrolidin-2,5-diil]bis{bencen-4,1-diilcarbamoil(2*S*)pirrolidin-2,1-diil[(2*S*)-3-metil-1-oxobutan-1,2-diil]})biscarbamato de dimetilo

y

([(2*R*,5*R*)-1-{4-[6-(dimetilamino)piridin-3-il]fenil}pirrolidin-2,5-diil]bis{bencen-4,1-diilcarbamoil(2*S*)pirrolidin-2,1-diil[(2*S*)-3-metil-1-oxobutan-1,2-diil]})biscarbamato de dimetilo

Ejemplo 99A

5-(4-(2,5-bis(4-nitrofenil)pirrolidin-1-il)fenil)-N,N-dimetilpiridin-2-amina

El producto del Ejemplo 86A (25,7mg, 0,055mmole) se combinó en un tubo de microondas con ácido 6-(dimetilamino)piridin-3-ilborónico (17,49mg, 0,105mmole), fosfato de potasio tribásico (24,70mg, 0,116mole) y dicloruro de 1,1'-bis(di-tert-butilfosfino)ferrocenopaladio (2,504mg, 3,84µmol). El tubo se selló y se agregó una mezcla de solventes de THF (2mL) y agua (0,6mL) mediante una jeringa. La mezcla de la reacción se roció con nitrógeno a temperatura ambiente por tres minutos durante los cuales la solución se volvió de color negro. El análisis cromatográfico indicó que la reacción se había completado. Los contenidos del tubo de microondas se particionaron entre salmuera (3mL) y acetato de etilo (3mL). El agua se retiró y la fase orgánica se secó sobre $MgSO_4$, se filtró y se concentró. El producto crudo se purificó mediante cromatografía sobre gel de sílice de 2 hasta 20% acetato de etilo en hexano para dar el compuesto del título (26,8mg, 96% de rendimiento) como un sólido anaranjado como una mezcla de estereoisómeros. MS ESI(+) m/z @ 510,4 (M+H)+.

Ejemplo 99B

4,4'-(1-(4-(6-(dimetilamino)piridin-3-il)fenil)pirrolidin-2,5-diil)dianilina

El producto del Ejemplo 99A (26,8mg, 0,053mmole) se disolvió en THF (526µL) en un balón al cual se agregó subsiguientemente etanol (526µL) para dar un precipitado amarillo. A esta suspensión se agregó óxido de platino (IV) (3,16mg, 0,014mmole). El recipiente se tapó con un septo y los contenidos se desgasificaron al vacío tres veces. Se

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introdujo hidrógeno por medio de un globo y la mezcla se dejó agitar a temperatura ambiente por dos horas y media. La mezcla de la reacción se filtró al vacío a través de un tapón de arena y celite, el cual se enjuagó con THF y metanol hasta que el material filtrado fue u.v.(-). El material filtrado se concentró al vacío para dar el compuesto del título en rendimiento cuantitativo como un sólido blanco como una mezcla de estereoisómeros. MS ESI(+), m/z @ 450,7 (M+H)+.

Ejemplo 99C

(2S,2'S)-2,2'-(4,4'-(1-(4-(6-(dimetilamino)piridin-3-il)fenil)pirrolidin-2,5-diil)bis(4,1-fenilen))bis(azandiil)bis(oxometilen)dipirrolidin-1-carboxilato de tert-butilo

El producto del Ejemplo 99B (23,83mg, 0,053mmole) se hizo reaccionar con ácido (S)-1-(tert-butoxicarbonil)pirrolidin-2-carboxílico (27,8mg, 0,129mmole) como se describe en Ejemplo 1F con modificaciones menores. El producto crudo se recuperó mediante partición de la mezcla de la reacción entre acetato de etilo(10mL) y agua(3mL). La fase orgánica se lavó con agua (3x3mL), se secó sobre $MgSO_4$, se filtró y se concentró. La cromatografía sobre gel de sílice usando un gradiente de solvente de 2-100% acetato de etilo en hexano dio el compuesto del título (32,6mg, 73% de rendimiento) como un sólido color crema como una mezcla de estereoisómeros.

Ejemplo 99D

(2S,2'S)-N,N'-(4,4'-(1-(4-(6-(dimetilamino)piridin-3-il)fenil)pirrolidin-2,5-diil)bis(4,1-fenilen))dipirrolidin-2-carboxamida

El producto del Ejemplo 99C (32,6mg, 0,039mmole) se hizo reaccionar con ácido trifluoroacético (0,071mL, 0,927mmole) como se describe en Ejemplo 1G para dar el compuesto del título (22,5mg, 90% de rendimiento) como un sólido color crema como una mezcla de estereoisómeros.

Ejemplo 99E

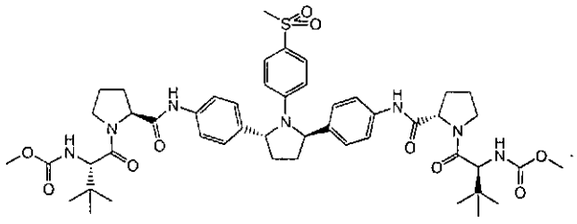
([(2*S*,5*S*)-1-{4-[6-(dimetilamino)piridin-3-il]fenil}pirrolidin-2,5-diil]bis{bencen-4,1-diilcarbamoil(2*S*)pirrolidin-2,1-diil[(2*S*)-3-metil-1-oxobutan-1,2-diil]})biscarbamato de dimetilo

y

([(2*R*,5*R*)-1-{4-[6-(dimetilamino)piridin-3-il]fenil}pirrolidin-2,5-diil]bis{bencen-4,1-diilcarbamoil(2*S*)pirrolidin-2,1-diil[(2*S*)-3-metil-1-oxobutan-1,2-diil]})biscarbamato de dimetilo

El producto del Ejemplo 99D (22,5mg, 0,035mmole) se hizo reaccionar con ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico (19,41mg, 0,111mmole) como se describe en Ejemplo 86C. La cromatografía sobre gel de sílice (10% acetato de etilo / 90% hexano a 100% acetato de etilo / 4% metanol) dio el compuesto del título (14,5mg, 43,3% de

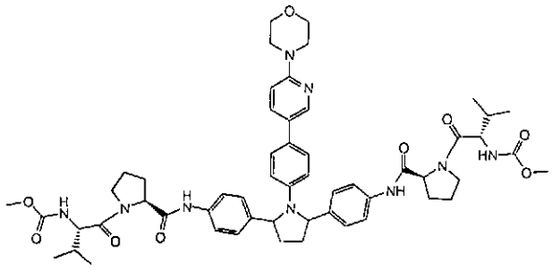
rendimiento), un sólido anaranjado amarillo que se oscureció algo con el reposo, como una mezcla 1:1 de diastereómeros trans. 1H RMN (400 MHz, DMSO-D6) δ ppm 0,77 - 0,99 (m, 12 H) 1,67 (s, 2 H) 1,76 - 2,24 (m, 11 H) 2,98 (s, 6 H) 3,52 (s, 6 H) 3,58 - 3,65 (m, 2 H) 3,76 - 3,90 (m, *J*=9,54 Hz, 2 H) 3,95 - 4,11 (m, 2 H) 4,36 - 4,47 (m, 2 H) 5,19 - 5,27 (m, 2 H) 6,30 (s, 2 H) 6,58 (d, *J*=9,00 Hz, 1 H) 7,17 (t, *J*=8,08 Hz, 4 H) 7,30 (d, *J*=8,02 Hz, 3 H) 7,52 (d, *J*=7,37 Hz, 4 H) 7,57 - 7,63 (m, 1 H) 7,63 - 7,68 (m, 1 H) 7,91 (s, 1 H) 8,18 - 8,22 (m, 1 H) 10,00 (s, 2 H). MS ESI(+) m/z @ 959,4 (M+H)+.



Ejemplo 100

({(2*R*,5*R*)-1-[4-(metilsulfonil)fenil]pirrolidin-2,5-diil}bis{bencen-4,1-diilcarbamoil(2*S*)pirrolidin-2,1-diil[(2*S*)-3,3-dimetil-1-oxobutan-1,2-diil]})biscarbamato de dimetilo

Se procesó Ejemplo 38A y 4-(metilsulfonil)anilina usando en forma consecutiva los métodos de Ejemplos 98A, 98B, 55F, 55G, y 26J (con ácido (S)-2-(metoxicarbonilamino)-3,3-dimetilbutanoico; solvente de reacción = diclorometano) para dar el compuesto del título (55 mg). ^{1}H RMN (400 MHz, DMSO-D6) δ0,96 (d, *J* = 5,1, 18H), 1,24 (s, 1H), 1,69 (d, *J* = 5,7, 2H), 2,04 - 1,74 (m, 7H), 2,22 - 2,07 (m, 2H), 2,98 (s, 3H), 3,54 (s, 6H), 3,70 - 3,58 (m, 2H), 3,83 - 3,70 (m, 2H), 4,20 (d, *J* = 8,9, 2H), 4,43 (dd, *J* = 7,8, 5,4, 2H), 5,32 (d, *J* = 6,1, 2H), 6,39 (d, *J* = 9,0, 2H), 7,08 (d, *J* = 8,8, 2H), 7,15 (d, *J* = 8,6, 4H), 7,43 (d, *J* = 9,0, 2H), 7,53 (d, *J* = 8,6, 4H), 10,03 (s, 2H). MS (ESI) *m/z* 966 $(M+Na)^+$, 943 $(M-H)^+$.



Ejemplo 101

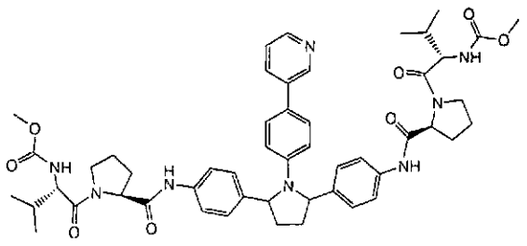
([(2*S*,5*S*)-1-{4-[6-(morfolin-4-il)piridin-3-il]fenil}pirrolidin-2,5-diil]bis{bencen-4,1-diilcarbamoil(2*S*)pirrolidin-2,1-diil[(2*S*)-3-metil-1-oxobutan-1,2-diil]})biscarbamato de dimetilo

y

([(2*R*,5*R*)-1-{4-[6-(morfolin-4-il)piridin-3-il]fenil}pirrolidin-2,5-diil]bis{bencen-4,1-

diilcarbamoil(2*S*)pirrolidin-2,1-diil[(2*S*)-3-metil-1-oxobutan-1,2-diil]})biscarbamato de dimetilo

Se procesó Ejemplo 86A y 4-(5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)piridin-2-il)morfolina usando en forma consecutiva los métodos de Ejemplos 99A, 99B, 1F, 1G, y 86C para dar el compuesto del título como una mezcla 1:1 de diastereómeros trans. 1H RMN (base libre) (400 MHz, DMSO-D6) δ ppm 0,78 - 1,00 (m, 12 H) 1,67 (s, 2 H) 1,75 - 2,20 (m, 11 H) 3,36 - 3,41 (m, 4 H) 3,52 (s, 6 H) 3,57 - 3,65 (m, 2 H) 3,65 - 3,72 (m, 4 H) 3,79 (s, 2 H) 4,02 (s, 2 H) 4,36 - 4,48 (m, 2 H) 5,24 (s, 2 H) 6,32 (d, *J*=7,70 Hz, 2 H) 6,78 (d, *J*=9,00 Hz, 1 H) 7,12 - 7,18 (m, 4 H) 7,21 (d, *J*=8,78 Hz, 2 H) 7,31 (d, *J*=8,35 Hz, 2 H) 7,52 (d, *J*=7,48 Hz, 4 H) 7,63 - 7,69 (m, 1 H) 8,22 - 8,27 (m, 1 H) 10,00 (s, 2 H). MS ESI(+) m/z @1000,6 (M+H)+.



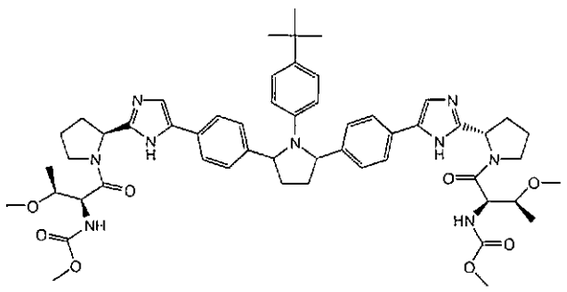
Ejemplo 102

({(2S,5S)-1-[4-(piridin-3-il)fenil]pirrolidin-2,5-diil}bis{bencen-4,1-diilcarbamoil(2S)pirrolidin-2,1-diil[(2S)-3-metil-1-oxobutan-1,2-diil]})biscarbamato de dimetilo

y

({(2*R*,5*R*)-1-[4-(piridin-3-il)fenil]pirrolidin-2,5-diil}bis{bencen-4,1-diilcarbamoil(2*S*)pirrolidin-2,1-diil[(2*S*)-3-metil-1-oxobutan-1,2-diil]})biscarbamato de dimetilo

Se procesó Ejemplo 86A y ácido piridin-3-ilborónico usando en forma consecutiva los métodos de Ejemplos 99A, 99B, 1F, 1G, y 86C para dar el compuesto del título como una mezcla 1:1 de diastereómeros trans (35,8mg). 1H RMN (base libre) (400 MHz, DMSO-D6) δ ppm 0,71 - 1,05 (m, 11 H) 1,68 (s, 2 H) 1,87 (s, 8 H) 2,06 - 2,21 (m, 2 H) 3,52 (s, 6 H) 3,56 - 3,67 (m, 2 H) 3,80 (s, 2 H) 4,02 (d, *J*=1,73 Hz, 2 H) 4,43 (dd, *J*=7,97, 4,93 Hz, 2 H) 5,26 (d, *J*=6,29 Hz, 2 H) 6,37 (d, *J*=7,92 Hz, 2 H) 7,17 (dd, *J*=8,57, 1,95 Hz, 4 H) 7,28 - 7,36 (m, 5 H) 7,52 (d, *J*=7,81 Hz, 4 H) 7,82 - 7,87 (m, 1 H) 8,36 (dd, *J*=4,72, 1,36 Hz, 1 H) 8,69 (s, 1 H) 10,00 (s, 2 H). MS ESI(+) m/z @ 915,6 (M+H)+



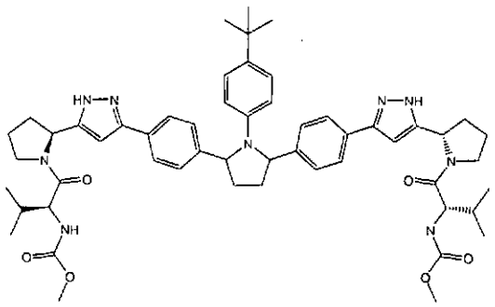
Ejemplo 103

[(2*S*,3*S*)-1-{(2*S*)-2-[5-(4-{(2*S*,5*S*)-1-(4-*tert*-butilfenil)-5-[4-(2-{(2*S*)-1-[*N*-(metoxicarbonil)-*O*-metil-D-treonil]pirrolidin-2-il}-1*H*-imidazol-5-il)fenil]pirrolidin-2-il}fenil)-1*H*-imidazol-2-il]pirrolidin-1-il}-3-metoxi-1-oxobutan-2-il]carbamato de metilo

y

[(2*S*,3*S*)-1-{(2*S*)-2-[5-(4-{(2*R*,5*R*)-1-(4-*tert*-butilfenil)-5-[4-(2-{(2*S*)-1-[*N*-(metoxicarbonil)-*O*-metil-D-treonil]pirrolidin-2-il}-1*H*-imidazol-5-il)fenil]pirrolidin-2-il}fenil)-1*H*-imidazol-2-il]pirrolidin-1-il}-3-metoxi-1-oxobutan-2-il]carbamato de metilo

El producto del Ejemplo 201A (0,122 g, 0,639 mmol), y HOBt (0,098 g, 0,639 mmol) se combinaron y se disolvió en 2 ml de DMF luego se enfrió en un baño de hielo entre 0-5 °C. A esta solución se agregó EDAC (0,123g, 0,639 mmol) seguido por 4-metilmorfolina (0,211 ml, 1,917 mmol) y la mezcla se agitó 5 minutos, luego se agregó por goteo la mezcla de los productos del Ejemplo 42F (0,2 g, 0,320 mmol), en DMF (2 ml) con un lavado con DMF (1 ml). El pH de la solución se ajustó con 4-metilmorfolina adicional (0,1 ml, 0,96 mmol) y la mezcla se agitó a total de 90 minutos en el baño de hielo. La mezcla de la reacción se analizó mediante LC-MS a 90 min y se determinó que la reacción se había completado. La mezcla de la reacción se diluyó con 100 ml EtOAc y se lavó con 25 ml de agua. Las capas se separaron y la capa acuosa se extrajo con otros 100 ml de EtOAc. Los extractos orgánicos combinados se lavaron con $NaHCO_3$ al 10% y NaCl al 10%, se secó sobre Na_2SO_4 anhidro(s), se filtró y el solvente se eliminó al vacío para dar un aceite morado. El aceite se disolvió en 10 ml de CH_2Cl_2 y se aplicó a una columna de 12g de gel de sílice. La columna se eluyó con un gradiente de CH_2Cl_2/MeOH, 99/1 a 95/5 a lo largo de 25 minutos. Los compuestos del título se aislaron como un sólido amarillo claro, 60 mg, 19%,1H RMN (400 MHz, DMSO-D6) d ppm 0,86 (m, 2 H) 1,00 - 1,18 (m, 15 H) 1,27 (m, 2 H) 1,70 (m, s H) 1,99 (m, 2H) 2,15 (m, 4 H) 3,18 (d, J=10,08 Hz, 6 H) 3,54 (s, 6 H) 3,81 (m, 4 H) 4,27 (m, 2 H) 5,06 (m, 2 H) 5,21 (d, 2 H) 6,21 (d, 2 H) 6,94 (d, 2 H) 7,17 (d, 2 H) 7,29 (d, 2 H) 7,38 (d, J=1,73 Hz, 2 H) 7,51 (d, 2 H) 7,62 (d, J=8,02 Hz, 2 H) 11,68 (s, 2 H), 12,01 (m, 2H);ESI+:972,6



Ejemplo 105

{(2*S*)-1-[(2*S*)-2-(3-{4-[(2*S*,5*S*)-1-(4-*tert*-butilfenil)-5-(4-{5-[(2*S*)-1-{(2*S*)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1*H*-pirazol-3-il}fenil)pirrolidin-2-il]fenil}-1*H*-pirazol-5-il)pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

y

{(2*S*)-1-[(2*S*)-2-(3-{4-[(2*R*,5*R*)-1-(4-*tert*-butilfenil)-5-(4-{5-[(2*S*)-1-{(2*S*)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1*H*-pirazol-3-il}fenil)pirrolidin-2-il]fenil}-1*H*-pirazol-5-il)pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

Ejemplo 105A

1-(4-*tert*-butilfenil)-2,5-bis(4-((trimetilsilil)etinil)fenil)pirrolidina

A un tubo de microondas secado en horno (tamaño M, 5 ml) purgado con nitrógeno, se agregó el producto de Ejemplo 42C (340 mg, 0,662 mmol), dicloruro de bis(trifenilfosfin)paladio(II) (18,60 mg, 0,026 mmol), THF (2 ml), y trietilamina (2 ml). Se agitó a temperatura ambiente por 5 min, luego se agregó yoduro de cobre(I) (2,52 mg, 0,013 mmol), se agitó la mezcla amarilla por 2 min, luego se burbujeó nitrógeno por 15 min. Se agregó trimetilsililacetileno (0,374 ml, 2,65 mmol), se selló el tubo con un tapón alabeado de aluminio, y se calentó en un baño de aceite a 70 °C por 20 hr. Se enfrió la reacción a temperatura ambiente, se agregó más dicloruro de bis(trifenilfosfin)paladio(II) (18,60 mg, 0,026 mmol) y yoduro de cobre(I) (2,52 mg, 0,013 mmol), se agregó trimetilsililacetileno adicional (0,374 ml, 2,65 mmol), y se continuó agitando a 80 °C por 24 hr. Se enfrió la reacción a temperatura ambiente, se diluyó con Et_2O (50 ml), se lavó con H_2O (2 x 25 ml) y salmuera (25 ml), se secó la fase orgánica sobre $MgSO_4$ anhidro, se filtró, y se concentró mediante evaporación por rotación para dar una espuma color tostado claro (470 mg). Se purificó mediante cromatografía flash (gel de sílice, 2,5 cm x 10 cm, 2% Et_2O/hexanos) para dar el producto del título como una espuma amarilla (324 mg, 89%) como una mezcla de estereoisómeros. MS (ESI+) m/z 548 $(M+H)^+$.

Ejemplo 105B

1-(4-*tert*-butilfenil)-2,5-bis(4-etinilfenil)pirrolidina

Se disolvió el producto de Ejemplo 105A (322 mg, 0,588 mmol) en THF anhidro (5 ml)

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bajo nitrógeno, se agregó TBAF 1M en THF (1,322 ml, 1,322 mmol), y se agitó a 25 °C por 30 min. La reacción se oscureció inmediatamente luego de la adición y permaneció un color marrón a lo largo de la reacción. Se eliminó el solvente por evaporación por rotación, se disolvió el residuo en Et_2O (50 ml), se lavó con H_2O (2 x 25 ml) y salmuera (25 ml), se secó la fase orgánica sobre $MgSO_4$ anhidro, se filtró, y se concentró mediante evaporación por rotación para dar una espuma color tostado claro (289 mg). Se purificó mediante cromatografía flash (gel de sílice, 3,8 cm x 14 cm, 20% CH_2Cl_2/hexanos) para dar el compuesto del título como una espuma amarillo claro (176 mg, 74%) como una mezcla de estereoisómeros. MS (ESI+) m/z 404 $(M+H)^+$.

Ejemplo 105C

(S)-3,3'-(4,4'-(1-(4-tert-butilfenil)pirrolidin-2,5-diil)bis(1-(4,1-fenilen))bis(1-(N-Boc-(S)-pirrolidin-2-il)prop-2-en-1-ona

En un balón de 10 ml secado bajo llama, se disolvió el producto de Ejemplo 105B (94,3 mg, 0,234 mmol) en THF anhidro (2 ml) bajo nitrógeno y se enfrió a -78 °C, se agregó n-BuLi 1,6 M en hexanos (0,365 ml, 0,584 mmol) lentamente por goteo usando una jeringa hermética a los gases, y se agitó la solución verdosa-amarilla por 1 hr a -78 °C. En otro balón de 10 ml secado bajo llama purgado con nitrógeno, se preparó una solución de N-(tert-butoxicarbonil)-L-prolina N'-metoxi-N'-metilamida (166 mg, 0,631 mmol) en THF anhidro (1 ml), y se enfrió a -78 °C. Se agregó la mezcla de dianión por goteo usando una jeringa hermética a los gases equipada con una aguja 16G a la solución de amida Weinreb y se agitó a -78 °C por 30 min, se reemplazó el baño de hielo seco-acetona con un baño de agua-hielo, y se agitó a 0 °C por 1 hr. Se eliminó el baño de frío y se agitó a temperatura ambiente por 1 hr, la mezcla amarilla turbia se volvió una solución amarilla oscura. Se detuvo la reacción con NH_4Cl acuoso saturado (10 ml), se extrajo con Et_2O (2 x 25 ml), se lavó los extractos de éter combinados con H_2O (2 x 25 ml) y salmuera (25 ml), se secó la fase orgánica sobre $MgSO_4$ anhidro, se filtró, y se concentró mediante evaporación por rotación para dar un aceite amarillo (214 mg). Se purificó mediante cromatografía flash (gel de sílice, columna Alltech Extract-Clean de 10g, gradiente de 5% hasta 7% EtOAc/CH_2Cl_2) para dar el compuesto del título como un sólido amarillo (77 mg, 41%) como una mezcla de estereoisómeros. MS (ESI+) m/z 798 $(M+H)^+$, 1595 $(2M+H)^+$.

Ejemplo 105D

(2S,2'S)-2,2'-(3,3'-(4,4'-(1-(4-*tert*-butilfenil)pirrolidin-2,5-diil)bis(4,1-fenilen))bis(1*H*-pirazol-5,3-diil))dipirrolidin-1-carboxilato de *tert*-butilo

Se disolvió el producto de Ejemplo 105C (75 mg, 0,094 mmol) en EtOH absoluto anhidro (1 ml) bajo nitrógeno, se agregó hidrato de hidrazina (0,023 ml, 0,235 mmol), y se agitó la solución amarilla a temperatura ambiente por 1 hr. Se eliminó el solvente por evaporación

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por rotación, se azeotropeó el aceite amarillo con tolueno (2 x 5 ml), se disolvió nuevamente en 1:5 v/v CH_2Cl_2/hexanos, se concentró, y se secó el sólido amarillo claro al vacío. Se purificó mediante cromatografía flash (gel de sílice, 2,5 cm x 15 cm, 4% MeOH/CH_2Cl_2) para dar el compuesto del título como un sólido blanco (59 mg, 76%) como una mezcla de estereoisómeros. MS (ESI+) m/z 826 (M+H)+, 848 $(M+Na)^+$.

Ejemplo 105E

(S)-3,3'-(4,4'-(1-(4-*tert*-butilfenil)pirrolidin-2,5-diil)bis(4,1-fenilen))bis(5-((S)-pirrolidin-2-il)-1*H*-pirazol

Se disolvió el producto de Ejemplo 105D (57,5 mg, 0,070 mmol) en CH_2Cl_2 anhidro (2 ml) bajo nitrógeno, se agregó TFA (1 ml, 12,98 mmol), y se agitó a 25 °C por 30 min. Se eliminó el solvente por evaporación por rotación, se recogió el residuo con 1:5 v/v CH_2Cl_2/hexanos, se concentró para dar un residuo amarillo, y se secó al vacío (83 mg). La sal TFA se disolvió en MeOH anhidro (7 ml) bajo nitrógeno, se trató con lavado previo (H_2O y MeOH) y se secó resina Amberlite IRA-400(OH) (750 mg, ~15 equivs de OH^- en base a ~1,4 equivalentes molares/g de resina seca) y se agitó a 25 °C por 2 hr. Se filtró a vacío en un embudo Büchner y se lavó la resina a fondo con MeOH. El material filtrado se concentró por evaporación por rotación, el residuo se recogió con 1:5 v/v CH_2Cl_2/hexanos, y se concentró al vacío para dar el compuesto del título como un sólido amarillo claro (41 mg, 94%) como una mezcla de estereoisómeros. MS (ESI+) m/z 626 $(M+H)^+$, 1251 $(2M+H)^+$.

Ejemplo 105F

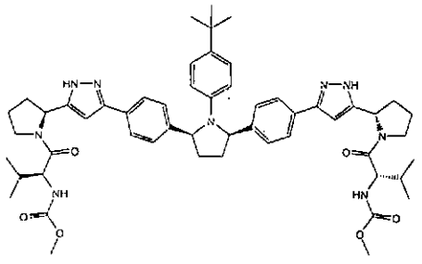
{(2*S*)-1-[(2*S*)-2-(3-{4-[(2*S*,5*S*)-1-(4-*tert*-butilfenil)-5-(4-{5-[(2*S*)-1-{(2*S*)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1*H*-pirazol-3-il}fenil)pirrolidin-2-il]fenil}-1*H*-pirazol-5-il)pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

y

{(2*S*)-1-[(2*S*)-2-(3-{4-[(2*R*,5*R*)-1-(4-*tert*-butilfenil)-5-(4-{5-[(2*S*)-1-{(2*S*)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1*H*-pirazol-3-il}fenil)pirrolidin-2-il]fenil}-1*H*-pirazol-5-il)pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

En un balón de 10 ml secado en horno purgado con nitrógeno, se disolvió el producto de Ejemplo 105E (39,7 mg, 0,063 mmol) en DMF anhidro (1 ml) y se enfrió a 0 °C. Se agregó en forma consecutiva ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico (23,89 mg, 0,136 mmol), hidrato de HOBt (21,37 mg, 0,140 mmol), EDAC (27,3 mg, 0,140 mmol), y N-metilmorfolina (0,021 ml, 0,190 mmol). Se eliminó el baño de frío y se agitó la solución amarilla oscura a 25 °C por 1 hr. Se diluyó la reacción con EtOAc (50 ml), se lavó con H_2O (3 x 25 ml) y salmuera (25 ml), se secó la fase orgánica sobre $MgSO_4$ anhidro, se filtró, y se concentró mediante evaporación por rotación para dar un sólido color durazno claro

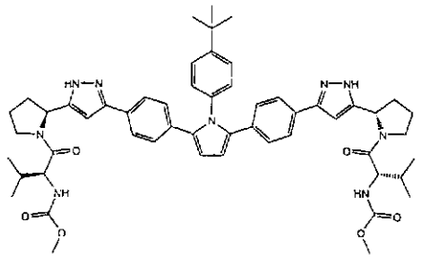
(63 mg). Se disolvió el material crudo en CH_2Cl_2 y se purificó mediante cromatografía flash (gel de sílice, 2,5 cm x 10 cm, 5% MeOH/CH_2Cl_2) para dar una mezcla 1:1,25 de producto trans:cis (34 mg, 94% de pureza). Se disolvió el residuo en 1:1 v/v DMSO/MeOH (2 ml) y se purificó mediante RP-C_{18} HPLC (Waters Prep LC, 40mm Module con un cartucho Nova Pak HR C_{18} 6µm 40x100mm Prep Pak) eluyendo con un gradiente de 30 min de 90:10 TFA al 0,1% en H_2O/AcCN a 100% AcCN a 20 ml/min. Las fracciones que contenían una mezcla de los diastereómeros trans se concentraron por evaporación por rotación, el residuo se recogió con 1:5 v/v CH_2Cl_2/hexanos y se evaporó (5 veces), y se secó al vacío para dar los compuestos del título como un sólido color crema (12 mg, 16%). ^{1}H RMN (Sal TFA) (400 MHz, DMSO-D6) δ ppm 0,76 - 0,94 (m, 12 H), 1,10 (s, 9 H), 1,13 - 1,31 (m, 3 H), 1,71 (d, *J*=5,42 Hz, 2 H), 1,82 - 2,17 (m, 9 H), 3,53 (s, 6 H), 3,70 - 3,85 (m, 4 H), 4,05 (t, *J*=8,08 Hz, 2 H), 5,09 - 5,19 (m, 2 H), 5,26 (d, *J*=5,96 Hz, 2 H), 6,22 (d, *J*=8,78 Hz, 2 H), 6,39 (d, *J*=1,30 Hz, 2 H), 6,94 (d, *J*=8,67 Hz, 2 H), 7,20 - 7,31 (m, 6 H), 7,62 (d, *J*=7,92 Hz, 4 H); MS (ESI+) m/z 940 $(M+H)^+$.



Ejemplo 106

{(2S)-1-[(2S)-2-(3-{4-[(2R,5S)-1-(4-tert-butilfenil)-5-(4-{5-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-pirazol-3-il}fenil)pirrolidin-2-il]fenil}-1H-pirazol-5-il)pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

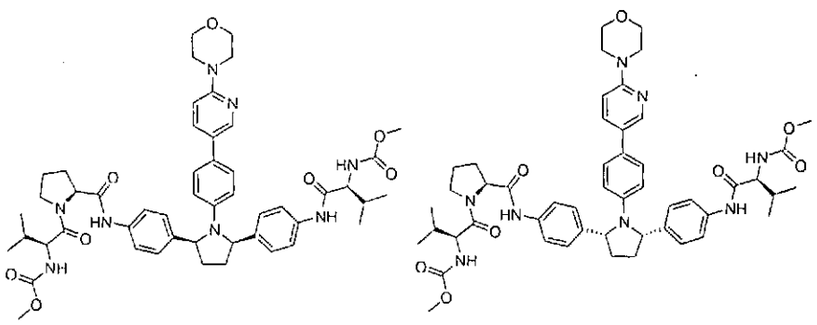
A partir de la separación HPLC preparativa de Ejemplo 105F se obtuvo el compuesto del título (cis) como un sólido amarillo (16 mg, 21%). ^{1}H RMN (Sal TFA) (400 MHz, DMSO-D6) δ ppm 0,77 - 0,93 (m, 12 H), 1,14 (s, 9 H), 1,17 - 1,31 (m, 2 H), 1,80 - 2,18 (m, 11 H), 3,35 (d, *J*=8,02 Hz, 1 H), 3,54 (s, 6 H), 3,72 - 3,85 (m, 4 H), 4,06 (t, *J*=8,29 Hz, 2 H), 4,71 - 4,79 (m, 2 H), 5,13 - 5,20 (m, 2 H), 6,35 (d, *J*=8,78 Hz, 2 H), 6,43 (s, 2 H), 7,03 (d, *J*=8,78 Hz, 2 H), 7,28 (d, *J*=8,35 Hz, 2 H), 7,55 (d, *J*=8,24 Hz, 4 H), 7,71 (d, *J*=7,59 Hz, 4 H); MS (ESI+) m/z 940 $(M+H)^+$.



Ejemplo 107

{(2S)-1-[(2S)-2-(3-{4-[1-(4-tert-butilfenil)-5-(4-{5-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-pirazol-3-il}fenil)-1H-pirrol-2-il]fenil}-1H-pirazol-5-il)pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

En un balón de 5 ml secado en horno purgado con nitrógeno, se disolvió el producto de Ejemplo 105E (5,1 mg, 8,15 µmol) en DMF anhidro (400 µL) y se enfrió a 0 °C. Se agregó en forma consecutiva ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico (3,07 mg, 0,018 mmol), hidrato de HOBt (2,75 mg, 0,018 mmol), EDAC (3,51 mg, 0,018 mmol), y N-metilmorfolina (2,69 µL, 0,024 mmol). Se eliminó el baño de frío y se agitó la solución amarilla oscura a 25 °C por 18 hr. Se diluyó la reacción en EtOAc (50 ml), se lavó con H_2O (2 x 10 ml) y salmuera (10 ml), se secó la capa orgánica sobre $MgSO_4$ anhidro, se filtró, y se concentró mediante evaporación por rotación a un sólido amarillo (9,6 mg). Se disolvió en 1:1 v/v MeOH/DMSO (1,5 ml) y se purificó mediante RP-C_{18} HPLC (Waters Prep LC, 40mm Module con un cartucho Nova Pak HR C_{18} 6µm 40x100mm Prep Pak) eluyendo con un gradiente de 30 min de 90:10 TFA al 0,1% en H_2O/AcCN a 100% AcCN a 20 ml/min. Las fracciones puras se concentraron por evaporación por rotación, se azeotropeó con tolueno (25 ml), el residuo se colocó en 1:5 v/v CH_2Cl_2/hexanos y se evaporó (3 veces), luego se secó al vacío para dar el compuesto del título como un sólido blanco opaco (2,5 mg, 25%). ^{1}H RMN (Sal TFA) (400 MHz, DMSO-D6) δ ppm 0,76 - 0,92 (m, 12 H), 1,27 (s, 9 H), 1,80 - 2,15 (m, 10 H), 3,53 (s, 6 H), 3,69 - 3,84 (m, 4 H), 4,05 (t, *J*=8,24 Hz, 2 H), 5,08 - 5,16 (m, 2 H), 6,39 (s, 2 H), 6,53 (s, 2 H), 7,06 (dd, *J*=8,29, 2,87 Hz, 6 H), 7,26 (d, *J*=8,35 Hz, 2 H), 7,37 (d, *J*=8,46 Hz, 2 H), 7,44 - 7,55 (m, 4 H), 12,92 (s, 2 H); MS (ESI+) m/z 936 $(M+H)^+$.



000665

Ejemplo 108

N-(metoxicarbonil)-L-valil-*N*-{4-[(2*S*,5*R*)-5-(4-{[*N*-(metoxicarbonil)-L-valil]amino}fenil)-1-{4-[6-(morfolin-4-il)piridin-3-il]fenil}pirrolidin-2-il]fenil}-L-prolinamida

y

N-(metoxicarbonil)-L-valil-*N*-{4-[(2*R*,5*S*)-5-(4-{[*N*-(metoxicarbonil)-L-valil]amino}fenil)-1-{4-[6-(morfolin-4-il)piridin-3-il]fenil}pirrolidin-2-il]fenil}-L-prolinamida

Ejemplo 108A

4-(5-(4-(2,5-bis(4-nitrofenil)pirrolidin-1-il)fenil)piridin-2-il)morfolina

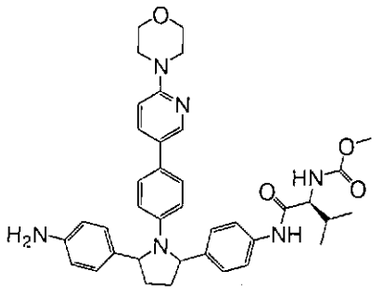
En un tubo de microondas (tamaño L, 20 ml) purgado con nitrógeno y sellado con un septo de goma, se disolvió el producto de Ejemplo 86A (160 mg, 0,342 mmol) y 4-[5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)piridin-2-il]morfolina (153 mg, 0,512 mmol) en THF (6 ml), se agregó una solución de fosfato de potasio (176 mg, 0,803 mmol) en agua (2 ml), y se roció la solución de la reacción con nitrógeno por 5 min. Se agregó dicloruro de 1,1'-bis(di-tert-butilfosfino)ferrocenopaladio (12,02 mg, 0,018 mmol) y se agitó a 25 °C por 15 min . A lo largo de este proceso, la reacción se oscureció velozmente a un color marrón. Se diluyó la reacción con EtOAc (50 ml), se lavó con salmuera (10 ml), se secó la fase orgánica sobre $MgSO_4$ anhidro, se filtró, y se concentró por evaporación por rotación. Se disolvió el residuo en CH_2Cl_2 y se purificó mediante cromatografía flash (gel de sílice, columna Alltech Extract-Clean de 10g, EtOAc al 20%/CH_2Cl_2) para dar el compuesto del título como un sólido (176 mg, 93%) como una mezcla de estereoisómeros. ^{1}H RMN (400 MHz, DMSO-D6) δ ppm 1,82 - 1,94 (m, 2 H), 2,53 - 2,62 (m, 2 H), 3,37 - 3,47 (m, 4 H), 3,64 - 3,74 (m, 4 H), 5,03 (t, *J*=5,37 Hz, 2 H), 6,40 (d, *J*=8,89 Hz, 2 H), 6,82 (d, *J*=9,00 Hz, 1 H), 7,34 (d, *J*=8,78 Hz, 2 H), 7,69 (dd, *J*=8,84, 2,55 Hz, 1 H), 7,83 (d, *J*=8,78 Hz, 4 H), 8,28 (d, *J*=8,78 Hz, 4 H), 8,29 - 8,31 (m, 1 H); MS (ESI+) m/z 552 $(M+H)^+$.

Ejemplo 108B

4,4'-(1-(4-(6-morfolinopiridin-3-il)fenil)pirrolidin-2,5-diil)dianilina

Se cargó un balón de 100 ml con el producto de Ejemplo 108A (174,7 mg, 0,317 mmol), se disolvió parcialmente en THF (12,50 ml) y EtOH absoluto (2,50 ml), se evacuó en vacío de la casa y se llenó el recipiente con nitrógeno, luego se agregó óxido de platino (IV) (14,38 mg, 0,063 mmol), se evacuó recipiente en vacío de la casa y se llenó con hidrógeno a partir de un globo, se repitió el ciclo de evacuación/llenado 3 veces, y se agitó la mezcla de reacción heterogénea enérgicamente bajo hidrógeno (1 atm). Luego de 2 hr, se cargó la reacción con óxido de platino (IV) adicional (14,38 mg, 0,063 mmol) y se continuó agitando enérgicamente bajo hidrógeno a 25 °C. Luego de 5 hr, se agregó óxido de platino (IV) adicional (14,38 mg, 0,063 mmol). La mezcla de la reacción luego se filtró al vacío a través de una cama de Celite 545 en un embudo Büchner, la almohadilla del

filtro se lavó con $CHCl_3$ (100 ml) y $CHCl_3$ caliente (2 x 50 ml), y el material filtrado se concentró por evaporación por rotación para dar el compuesto del título como un sólido amarillo (101 mg, 65%) como una mezcla de estereoisómeros. ^1H RMN (400 MHz, DMSO-D6) δ ppm 1,71 - 1,87 (m, 2 H), 2,24 - 2,31 (m, 1 H), 3,37 - 3,45 (m, 4 H), 3,64 - 3,74 (m, 4 H), 4,57 (t, *J*=4,99 Hz, 2 H), 4,95 (s, 4 H), 6,42 - 6,53 (m, 3 H), 6,57 (d, *J*=8,35 Hz, 4 H), 6,76 - 6,89 (m, 2 H), 7,15 (d, *J*=8,35 Hz, 4 H), 7,26 (d, *J*=8,78 Hz, 2 H), 7,68 (dd, *J*=8,84, 2,44 Hz, 1 H), 8,29 (d, *J*=2,39 Hz, 1 H); MS (ESI+) m/z 492 $(M+H)^+$.



Ejemplo 108C

(2S)-1-(4-(5-(4-aminofenil)-1-(4-(6-morfolinopiridin-3-il)fenil)pirrolidin-2-il)fenilamino)-3-metil-1-oxobutan-2-ilcarbamato de metilo

En un balón de 5 ml secado en horno purgado con nitrógeno, se disolvió el producto de Ejemplo 108B (70 mg, 0,142 mmol) y ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico (26,2 mg, 0,150 mmol) en DMSO anhidro (1,5 ml), se agregó HATU (58,6 mg, 0,150 mmol) y diisopropiletilamina (0,050 ml, 0,285 mmol), y se agitó la solución amarilla oscura a 25 °C por 15 min. Se diluyó la reacción con MeOH (1,5 ml) y se purificó mediante RP-C_{18} HPLC (Waters Prep LC, 40mm Module con Cartucho Nova Pak HR C18 6µm 40x100mm Prep Pak) eluyendo con un gradiente de 30 min de 95:5 TFA al 0,1% en H_2O/AcCN a 25:75 TFA al 0,1% en H_2O/AcCN, luego 10 min a 100% AcCN a 20 ml/min. Las fracciones puras se concentraron por evaporación por rotación (baño de agua 35°) a un volumen pequeño, se particionó entre iPrOH al 20%/$CHCl_3$ (50 ml), y $NaHCO_3$ acuoso saturado (15 ml), se separaron las capas, se secó el extracto orgánico sobre $MgSO_4$ anhidro, se filtró, y se concentró por evaporación por rotación para dar el compuesto del título como un sólido amarillo claro (48 mg, 52%). 1H RMN mostró que el material era una mezcla ~3:1 trans:cis; MS (ESI+) m/z 649 $(M+H)^+$, 1297 $(2M+H)^+$.

Ejemplo 108D

N-(metoxicarbonil)-L-valil-*N*-{4-[(2*S*,5*R*)-5-(4-{[*N*-(metoxicarbonil)-L-valil]amino}fenil)-1-{4-[6-(morfolin-4-il)piridin-3-il]fenil}pirrolidin-2-il]fenil}-L-prolinamida-ACD v12

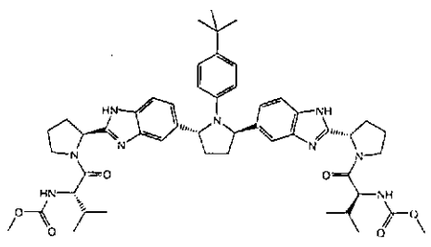
y

N-(metoxicarbonil)-L-valil-*N*-{4-[(2*R*,5*S*)-5-(4-{[*N*-(metoxicarbonil)-L-valil]amino}fenil)-1-{4-

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[6-(morfolin-4-il)piridin-3-il]fenil}pirrolidin-2-il]fenil}-L-prolinamida ACD v12

En un balón de 5 ml secado en horno purgado con nitrógeno, se disolvió una mezcla 3:1 trans/cis de Ejemplo 108C (44 mg, 0,068 mmol) y el producto de Ejemplo 37B (20,31 mg, 0,075 mmol) en DMSO anhidro (1 ml), se agregó HATU (29,2 mg, 0,075 mmol) y diisopropiletilamina (0,024 ml, 0,136 mmol), y se agitó la solución amarilla a 25 °C por 30 min. Se diluyó la reacción con MeOH (1 ml) y se purificó mediante RP-C_{18} HPLC (Waters Prep LC, 40mm Module con cartucho Nova Pak HR C18 6µm 40x100mm Prep Pak) eluyendo con un gradiente de 30 min de 95:5 TFA al 0,1% en H_2O/AcCN hasta 25:75 TFA al 0,1% en H_2O/AcCN, luego 10 min hasta 100% AcCN a 20 ml/min. Se determinó mediante ^{1}H RMN que el compuesto de elución más temprana (18,8 mg, 31%) era los diastereómeros trans. Las fracciones del último pico de la elución se concentraron por evaporación por rotación (baño de agua 35 °C) a un volumen más pequeño, se particionó entre 20% iPrOH/$CHCl_3$ (50 ml) y $NaHCO_3$ acuoso saturado (15 ml), se separaron las capas, se secó la fase orgánica sobre $MgSO_4$ anhidro, se filtró, y se concentró por evaporación por rotación para dar una mezcla 2:3 trans:cis como un sólido blanco opaco (10 mg). La mezcla se disolvió en 1:1 v/v MeOH/DMSO (1,5 ml) y se purificó mediante RP-C_{18} HPLC (columna Fenomenex Luna C_8(2) 5 µm 100Å AXIA (30mm × 75mm)) eluyendo con un gradiente de 90:10 10 mM NH_4OAc:MeOH hasta 100% MeOH para dar los compuestos cis del título como un sólido beige (2 mg, 3%). ^{1}H RMN (400 MHz, DMSO-D6) δ ppm 0,85 - 0,98 (m, 12 H), 1,77 - 2,06 (m, 7 H), 2,09 - 2,21 (m, 1 H), 2,36 - 2,45 (m, 1 H), 3,37 - 3,42 (m, 4 H), 3,51 (s, 3 H), 3,53 (s, 3 H), 3,59 - 3,70 (m, 6 H), 3,75 - 3,86 (m, 1 H), 3,95 (t, *J*=8,13 Hz, 1 H), 4,02 (t, *J*=8,57 Hz, 1 H), 4,44 (dd, *J*=8,19, 4,72 Hz, 1 H), 4,73 (s, 2 H), 6,43 (d, *J*=8,89 Hz, 2 H), 6,80 (d, *J*=8,89 Hz, 1 H), 7,27 (d, *J*=8,78 Hz, 2 H), 7,29 - 7,38 (m, 2 H), 7,44 (dd, *J*=8,57, 2,71 Hz, 4 H), 7,54 - 7,64 (m, 4 H), 7,67 (dd, *J*=8,89, 2,49 Hz, 1 H), 8,27 (d, J=2,49 Hz, 1 H), 10,04 (s, 2 H); MS (ESI+) m/z 903 $(M+H)^+$, 920 $(M+NH4)^+$, 961 $(M+AcCN+NH4)^+$.



Ejemplo 109

{(2S)-1-[(2S)-2-{5-[(2R,5R)-1-(4-tert-butilfenil)-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-bencimidazol-5-il}pirrolidin-2-il]-1H-bencimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

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Ejemplo 109A

2-bromo-1-(4-cloro-3-nitrofenil)etanona

Método A:

A un recipiente equipado con una barra de agitación magnética y bajo una atmósfera de N_2 se agregó 4'-cloro-3'-nitroacetofenona (10,0 g, 50,1 mmol) y THF (100 ml). A esa mezcla en agitación se agregó por porciones tribromuro de feniltrimetilamonio (19,78 g, 52,6 mmol) durante un periodo de 15 minutos. La mezcla resultante luego se agitó con monitoreo cada hora con LCMS. Luego de 3 hr la mezcla luego se filtró y los sólidos resultantes se lavaron con EtOAc. La solución orgánica luego se concentró, se agregó H_2O y $NaHCO_3$ acuoso al 10% y se lavó con EtOAc (2 x 300 ml). Las capas orgánicas combinadas luego se lavaron con salmuera, se secó ($MgSO_4$), se filtró y se concentró. El residuo material luego se sometió a purificación mediante cristalización (se disolvió el material en 100 ml de EtOAc y se agregó lentamente hexanos hasta enturbecer – se dejó reposar por unas pocas horas) para dar 9,81 g (70%) de 2-bromo-1-(4-cloro-3-nitrofenil)etanona como un producto sólido color blanco opaco. 1H RMN (500 MHz, DMSO-D6) δ ppm 5,00 (s, 2 H) 7,98 (d, J=8,54 Hz, 1 H) 8,24 (dd, J=8,54, 2,14 Hz, 1 H) 8,61 (d, J=1,98 Hz, 1 H).

Método B:

En un balón de 500 ml se agregó 1-(4-cloro-3-nitrofenil)etanona (11,98 g, 60 mmol) en benceno (75 ml) para dar una suspensión blanca. Se agregó bromo (9,59 g, 60,0 mmol) por goteo a lo largo de 5 minutos para dar una solución rojo profundo. Se agitó por 1 hora para dar una solución amarilla que se concentró al vacío para dar un sólido amarillo. Se recristalizó a partir de 9:1 hexano/acetato de etilo para dar 2-bromo-1-(4-cloro-3-nitrofenil)etanona como agujas amarillas.

Ejemplo 109B

1,4-bis(4-cloro-3-nitrofenil)butan-1,4-diona

Se agregó cloruro de cinc (II) (14,68 g, 108 mmol) a tolueno (81 ml), luego se agregó dietilamina (8,35 ml, 81 mmol) y tert-butanol (7,73 ml, 81 mmol) y la solución heterogénea resultante se agitó a temperatura ambiente por aprox. 2 h. Luego se agregó Ejemplo 109A (15,0 g, 53,9 mmol) y 4'-cloro-3'-nitroacetofenona (16,13 g, 81 mmol) a la solución en una porción, y la mezcla resultante se agitó a temperatura ambiente por 42 h). La reacción luego se detuvo con ácido sulfúrico acuoso al 5% (500 ml) y se agitó enérgicamente para inducir la formación de sólido. El sólido resultante se filtró al vacío, luego se lavó con tolueno, agua, y metanol en forma consecutiva. Luego el sólido se agregó a una solución de acetato de etilo caliente y la solución heterogénea resultante se agitó por 30 minutos y

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luego el sólido se recogió y se secó durante la noche en un horno de vacío para dar 16,6 g (78%) del compuesto del título. ^{1}H RMN (400 MHz, DMSO-d6) δ 8,61 (d, J = 1,9 Hz, 2H), 8,27 (dd, J = 8,4, 1,9 Hz, 2H), 7,96 (d, J = 8,3 Hz, 2H), 3,48 (s, 4H).

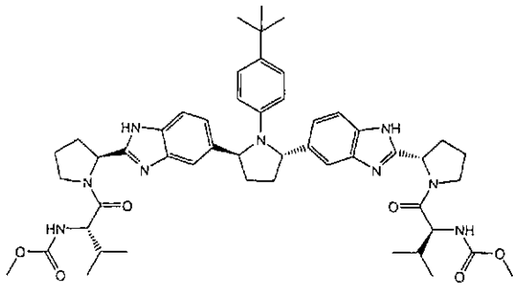
Ejemplo 109C

(1S,4S)-1,4-bis(4-cloro-3-nitrofenil)butan-1,4-diol

Se disolvió (R)-(+)-alfa,alfa-difenil-2-pirrolidinmetanol (1,08g, 4,28mmol) en 70 ml de THF a temperatura ambiente en un recipiente seco bajo nitrógeno y el borato de timetilo (650 uL, 5,54 mmol) se agregó por goteo. La solución resultante se agitó por 1 hr. La solución se enfrió en un baño frío a ~ 10 °C y se agregó N,N-dietilanilina borano (9,18 ml, 51,6 mmol) por goteo con algo de burbujeo. Luego de 15 min, esta solución se transfirió a un embudo de adición y se agregó por goteo a 1,4-bis(4-cloro-3-nitrofenil)butan-1,4-diona (Ejemplo 109B) (10,0g, 25,2 mmol), se suspendió en 200 ml de THF y se enfrió a ~ 10 °C. Se observó burbujeo. Luego de la adición, mezcla se agitó a temperatura ambiente por 4 horas. La mezcla se enfrió en un baño de hielo y se agregó 30 ml de MeOH por goteo hasta que se detuvo el burbujeo, luego la mezcla se dejó agitar a temperatura ambiente por 30 min. La mezcla se filtró para eliminar un resto de material de partida sin reaccionar insoluble. El material filtrado se concentró, se vertió en HCl 1 M y se extrajo con acetato de etilo, se secó sobre sulfato de sodio; se concentró para dar el compuesto del título (9,9g, 99%) como un sólido ceroso amarillo. HPLC quiral e.e. >99,9% (RR diol fue indetectable). ^{1}H RMN (400 MHz, DMSO-d6) δ 7,94 (d, J = 1,9 Hz, 2H), 7,69 (d, J = 8,4 Hz, 2H), 7,60 (dd, J = 8,4, 1,9 Hz, 2H), 4,65 (m, 2H), 1,62 (m, 4H).

Ejemplo 109D

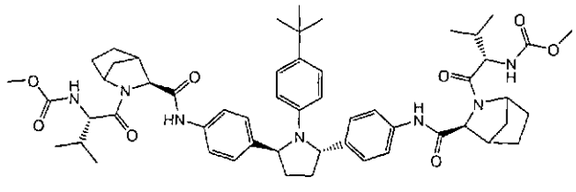
El producto de Ejemplo 109C se procesó como en Ejemplo 113A, 113B, 113C, y 113D, utilizando 4-t-butilanilina en lugar de 4-ciclohexilanilina en el procedimiento del paso 113A para dar 0,212 g (22%) del compuesto del título. 1H RMN (400 MHz, DMSO-D6) δ ppm 0,74 - 0,92 (m, 12 H) 1,07 (s, 9 H) 1,69 (d, J=4,01 Hz, 2 H) 1,86 - 2,05 (m, 6 H) 2,13 - 2,24 (m, 4 H) 2,54 (d, J=2,60 Hz, 2 H) 3,51 - 3,56 (m, 6 H) 3,81 (s, 4 H) 4,05 (t, J=8,13 Hz, 2 H) 5,09 - 5,18 (m, 2 H) 5,35 (d, J=3,47 Hz, 2 H) 6,25 (d, J=8,78 Hz, 2 H) 6,86 - 6,96 (m, 2 H) 7,07 (t, J=7,81 Hz, 2 H) 7,20 (s, 1 H) 7,26 - 7,32 (m, 3 H) 7,38 (d, J=8,24 Hz, 1 H) 7,46 (d, J=8,24 Hz, 1 H) 11,98 - 12,08 (m, 2 H); MS TFA+ m/z 889.



Ejemplo 110

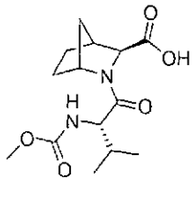
{(2S)-1-[(2S)-2-{5-[(2S,5S)-1-(4-tert-butilfenil)-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-bencimidazol-5-il}pirrolidin-2-il]-1H-bencimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

El producto del Ejemplo 28K se purificó mediante cromatografía quiral en una columna Chiralpak IA eluyendo con una mezcla de hexano/metanol/tetrahidrofurano (3:1:1) para dar el compuesto del título. 1H RMN (400 MHz, DMSO-D6) δ ppm 0,78 - 0,91 (m, 12 H) 1,07 (s, 9 H) 1,64 - 1,73 (m, 2 H) 1,89 - 2,00 (m, 6 H) 2,12 - 2,23 (m, 4 H) 3,14 - 3,24 (m, 2 H) 3,52 (s, 6 H) 3,76 - 3,85 (m, 4 H) 4,05 (td, J=8,38, 2,33 Hz, 2 H) 5,07 - 5,16 (m, 2 H) 5,30 - 5,39 (m, 2 H) 6,23 (d, J=8,78 Hz, 2 H) 6,90 (ddd, J=8,95, 4,72, 4,55 Hz, 2 H) 7,06 (t, J=9,22 Hz, 2 H) 7,17 (s, 1 H) 7,23 - 7,31 (m, 3 H) 7,37 (d, J=8,13 Hz, 1 H) 7,44 (d, J=8,24 Hz, 1 H) 12,02 (d, J=23,42 Hz, 2 H); MS ESI+ m/z 888 (M+H)+.



Ejemplo 111

([(2S,5S)-1-(4-tert-butilfenil)pirrolidin-2,5-diil]bis{bencen-4,1-diilcarbamoil(3S)-2-azabiciclo[2,2,1]heptan-3,2-diil[(2S)-3-metil-1-oxobutan-1,2-diil]})biscarbamato de dimetilo



Ejemplo 111A

ácido (3S)-2-((S)-2-(metoxicarbonilamino)-3-metilbutanoil)-2-azabiciclo[2,2,1]heptan-3-carboxílico

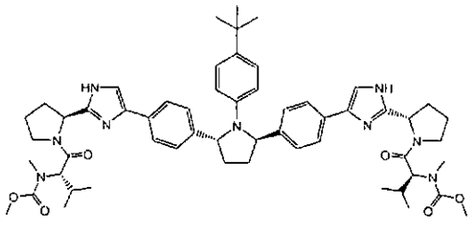
Se combinó (3S)-2-azabiciclo[2,2,1]heptan-3-carboxilato de etilo (1,25 g, 7,39 mmol), ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico (1,42 g, 8,13 mmol), diisopropiletilamina (6,45 ml, 36,9 mmol), y HATU (2,95 g, 7,76 mmol) en

dimetilformamida (40 ml) a temperatura ambiente y se agitó por 2 horas. La solución se diluyó con agua y el producto se filtró y se secó. El éster seco (1,0g, 3,06 mmol) se colocó en agua (15 ml) y etanol (15 ml) y se trató con hidróxido de sodio (0,5 g, 12,5 mmol) a temperatura ambiente por 17 horas. La solución se lavó con éter luego la capa acuosa se neutralizó con HCl concentrado a pH 7 y el producto se extrajo con acetato de etilo, se secó sobre sulfato de sodio, y se concentró para dar el compuesto del título como un sólido ceroso.

Ejemplo 111B

([(2S,5S)-1-(4-tert-butilfenil)pirrolidin-2,5-diil]bis{bencen-4,1-diilcarbamoil(3S)-2-azabiciclo[2,2,1]heptan-3,2-diil[(2S)-3-metil-1-oxobutan-1,2-diil]})biscarbamato de dimetilo

El producto del Ejemplo 37E (0,05g, 0,13 mmol), el producto del Ejemplo 111A (0,097 g, 0,324 mmol), diisopropiletilamina (0,113 ml, 0,648 mmol), y HATU (0,104 g, 0,272 mmol) se combinaron en dimetilformamida (2 ml) a temperatura ambiente y se agitó por 3 horas. La solución se vertió en salmuera, se extrajo con acetato de etilo, se concentró, y se purificó mediante columna combi-flash de 12g de sílice, eluyendo con 0-6% metanol en diclorometano para dar el compuesto del título como un sólido. 1H RMN (400 MHz, DMSO-D6) δ ppm 0,91 (d, J=6,72 Hz, 6 H) 0,98 (d, J=6,72 Hz, 6 H) 1,11 (s, 9 H) 1,32 (d, J=8,89 Hz, 2 H) 1,36 - 1,46 (m, 2 H) 1,59 - 1,74 (m, 6 H) 1,76 - 1,84 (m, 2 H) 1,90 (td, J=13,88, 6,94 Hz, 2 H) 2,01 - 2,09 (m, 2 H) 2,40 - 2,47 (m, 2 H) 2,60 (d, J=1,19 Hz, 2 H) 3,52 (s, 6 H) 3,94 (s, 2 H) 4,04 - 4,15 (m, 2 H) 4,46 (s, 2 H) 5,15 (d, J=6,51 Hz, 2 H) 6,17 (d, J=8,78 Hz, 2 H) 6,94 (d, J=8,78 Hz, 2 H) 7,13 (d, J=8,57 Hz, 4 H) 7,22 (d, J=8,46 Hz, 2 H) 7,49 (d, J=8,57 Hz, 4 H) 9,95 (s, 2 H)



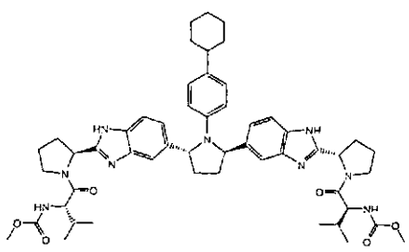
Ejemplo 112

{(2S)-1-[(2S)-2-(4-{4-[(2R,5R)-1-(4-tert-butilfenil)-5-(4-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)(metil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-4-il}fenil)pirrolidin-2-il]fenil}-1H-imidazol-2-il)pirrolidin-1-il]-3-metil-1-oxobutan-2-il}metilcarbamato de metilo

El producto del Ejemplo 126H se procesó como en Ejemplo 42B-42G, utilizando ácido (S)-2-(metoxicarbonil(metil)amino)-3-metilbutanoico en lugar de ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico en paso 42G, para dar 0,07 g (40%) del compuesto del título como un sólido blanco. 1H RMN (base libre) (400 MHz, DMSO-D6) δ ppm 0,76 (d, J=6,61 Hz, 6 H) 0,83 (d, J=6,51 Hz, 6 H) 1,09 (s, 9 H) 1,63 - 1,75 (m, 2 H)

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1,86 - 2,00 (m, 4 H) 2,03 - 2,21 (m, 6 H) 2,77 (s, 6 H) 3,10 - 3,22 (m, 4 H) 3,63 (s, 6 H) 3,74 - 3,84 (m, 2 H) 4,98 - 5,07 (m, 2 H) 5,16 - 5,23 (m, 2 H) 6,21 (d, J=8,78 Hz, 2 H) 6,88 - 6,96 (m, 2 H) 7,15 (d, J=8,24 Hz, 4 H) 7,22 (d, J=8,35 Hz, 1 H) 7,36 (d, J=1,52 Hz, 2 H) 7,51 (d, J=8,24 Hz, 1 H) 7,61 (d, J=8,13 Hz, 4 H) 11,70 (s, 2 H); MS ESI+ m/z 968,7 (M+H)+; MS ESI+ m/z 968,7 (M+H)+.



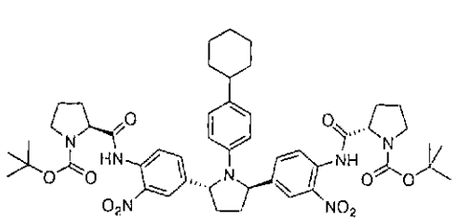
Ejemplo 113

{(2S)-1-[(2S)-2-{5-[(2R,5R)-1-(4-ciclohexilfenil)-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-bencimidazol-5-il}pirrolidin-2-il]-1H-bencimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

Ejemplo 113A

(2R,5R)-2,5-bis(4-cloro-3-nitrofenil)-1-(4-ciclohexilfenil)pirrolidina

El producto de Ejemplo 109C (2,0g, 4,99mmol) y trietilamina (1,51 ml, 14,96 mmol) se disolvieron en diclorometano (50 ml) y se enfrió en un baño de hielo. Se agregó cloruro de metansulfonilo (0,855 ml, 10,97 mmol) en diclorometano (2 ml) por goteo y la mezcla resultante se agitó a temperatura ambiente por 2 horas. La solución se concentró hasta secar y se disolvió en dimetilformamida (8 ml). Se agregó 4-ciclohexilanilina (5,24 g, 29,9 mmol) y la solución se calentó a 65 °C por 2 horas luego se vertió en HCl 1 M y se extrajo con diclorometano, se concentró, y se purificó mediante columna combi-flash de 80g de sílice, eluyendo con 0-20% acetato de etilo en hexanos para dar 1,38 g (51%) del compuesto del título.



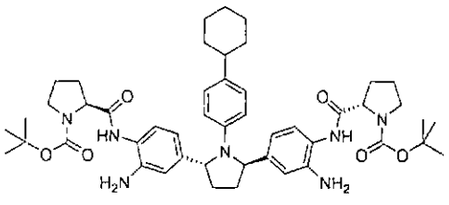
Ejemplo 113B

(2S,2'S)-2,2'-(4,4'-((2R,5R)-1-(4-ciclohexilfenil)pirrolidin-2,5-diil)bis(2-nitro-4,1-fenilen))bis(azandiil)bis(oxometilen)dipirrolidin-1-carboxilato de tert-butilo

El producto del Ejemplo 113A (1,29 g, 2,39 mmol), (S)-2-carbamoilpirrolidin-1-carboxilato de tert-butilo (1,53 g, 7,16 mmol), carbonato de cesio (2,33g, 7,16 mmol), 4,5-bis(difenilfosfino)-9,9-dimetilxanteno (0,33 g, 0,573 mmol), y

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tris(dibencilidenacetona)dipaladio(0) (0,328 g, 0,358 mmol) se combinaron en dioxano (18 ml) y se burbujeó nitrógeno a través de la solución por 15 min, luego el recipiente se tapó con un condensador de reflujo y la solución se calentó a 100 °C por 8 horas. Luego de filtrar a través de celite y concentrar, el residuo se purificó mediante columna combi-flash de 80g de sílice, eluyendo con 0-20% acetato de etilo en diclorometano para dar 1,71 g (80%) del compuesto del título.



Ejemplo 113C

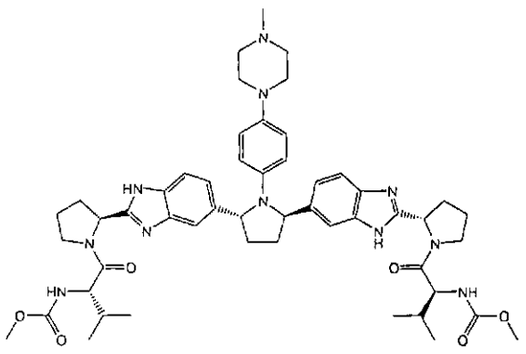
(2S,2'S)-2,2'-(4,4'-((2R,5R)-1-(4-ciclohexilfenil)pirrolidin-2,5-diil)bis(2-amino-4,1-fenilen))bis(azandiil)bis(oxometilen)dipirrolidin-1-carboxilato de tert-butilo

El producto del Ejemplo 113B (1,71 g, 1,91 mmol) se disolvió en tetrahidrofurano (10 ml) y etanol (10 ml) a temperatura ambiente y se trató con óxido de platino (IV) (0,11 g, 0,48 mmol). El recipiente se evacuó y se abrió a un globo de hidrógeno y se agitó por 18 horas luego se filtró a través de celite y se concentró para dar el compuesto del título.

Ejemplo 113D

{(2S)-1-[(2S)-2-{5-[(2R,5R)-1-(4-ciclohexilfenil)-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-bencimidazol-5-il}pirrolidin-2-il]-1H-bencimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

Ejemplo 113C se procesó usando los métodos de Ejemplos 28I, 28J, y 28K para dar el compuesto del título. 1H RMN (400 MHz, DMSO-D6) δ ppm 0,76 - 0,91 (m, 12 H) 1,03 - 1,29 (m, 6 H) 1,55 - 1,74 (m, 7 H) 1,84 - 2,06 (m, 6 H) 2,11 - 2,25 (m, 6 H) 3,53 (s, 6 H) 3,81 (s, 4 H) 4,02 - 4,13 (m, 2 H) 5,08 - 5,18 (m, 2 H) 5,32 - 5,38 (m, 2 H) 6,24 (d, J=8,57 Hz, 2 H) 6,68 - 6,77 (m, 2 H) 7,06 (t, J=7,54 Hz, 2 H) 7,19 (s, 1 H) 7,26 - 7,32 (m, 3 H) 7,37 (d, J=8,24 Hz, 1 H) 7,45 (d, J=8,35 Hz, 1 H) 11,98 - 12,05 (m, 2 H); MS ESI+ m/z 914,5.

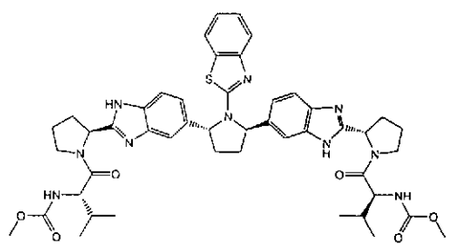


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Ejemplo 114

{(2S)-1-[(2S)-2-(6-{(2R,5R)-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-bencimidazol-5-il}-1-[4-(4-metilpiperazin-1-il)fenil]pirrolidin-2-il}-1H-bencimidazol-2-il)pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

El producto de Ejemplo 109C (1,0g, 2,49mmol) se procesó como en Ejemplos 113A-113D, utilizando 4-(4-metilpiperazin-1-il)anilina en lugar de 4-ciclohexilanilina en el procedimiento de Ejemplo 113A y utilizando Níquel de Raney en tetrahidrofurano en lugar de óxido de platino(IV) en tetrahidrofurano y etanol en el procedimiento de Ejemplo 113C para dar 0,028 g (50%) del compuesto del título como un sólido. 1H RMN (400 MHz, DMSO-D6) δ ppm 0,77 - 0,90 (m, 12 H) 1,65 - 1,72 (m, 2 H) 1,85 - 2,04 (m, 8 H) 2,13 (s, 3 H) 2,15 - 2,23 (m, 4 H) 2,32 (s, 2 H) 2,77 (s, 6 H) 3,54 (s, 6 H) 3,82 (d, J=4,66 Hz, 4 H) 4,02 - 4,08 (m, 2 H) 5,09 - 5,18 (m, 2 H) 5,28 - 5,37 (m, 2 H) 6,23 (d, J=8,78 Hz, 2 H) 6,54 (ddd, J=9,00, 4,66, 4,55 Hz, 2 H) 7,02 - 7,08 (m, 2 H) 7,19 (s, 1 H) 7,26 - 7,31 (m, 3 H) 7,36 (d, J=8,13 Hz, 1 H) 7,44 (d, J=8,35 Hz, 1 H) 12,01 (s, 2 H); MS ESI+ m/z 556 (M+H)+.



Ejemplo 115

{(2S)-1-[(2S)-2-{6-[(2R,5R)-1-(1,3-benzotiazol-2-il)-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-bencimidazol-5-il}pirrolidin-2-il]-1H-bencimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

Ejemplo 115A

(2R,5R)-1-alil-2,5-bis(4-cloro-3-nitrofenil)pirrolidina

El producto del Ejemplo 109C (5,0 g , 12,46 mmol) y alilamina se procesaron como en Ejemplo 113A para dar 1,5 g (39%) del compuesto del título como un aceite espeso.

Ejemplo 115B

(2R,5R)-2,5-bis(4-cloro-3-nitrofenil)pirrolidina

El producto del Ejemplo 115A (2,0 g, 4,74 mmol) se disolvió en acetonitrilo (40 ml) y agua (4 ml) y se trató con cloruro de Tris(trifenilfosfin)rodio(I) (0,219 g, 0,237 mmol). La mezcla se calentó a 100 ºC y se burbujeó nitrógeno a través de la solución por 3 horas. La mezcla se particionó entre solución de bicarbonato de sodio al 5% y acetato de etilo, luego los orgánicos se concentraron y el producto se purificó mediante columna

combiflash de 80g de sílice eluyendo con diclorometano para dar 1,33 g (74%) del compuesto del título.

Ejemplo 115C

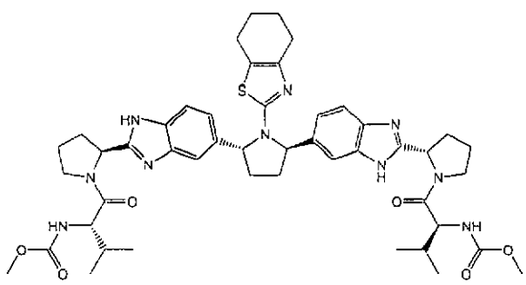
2-((2R,5R)-2,5-bis(4-cloro-3-nitrofenil)pirrolidin-1-il)benzo[d]tiazol

El producto del Ejemplo 115B (0,335 g, 0,877mmol), 2-bromobenzo[d]tiazol (0,281 g, 1,32 mmol), tris(dibencilidenacetona)dipaladio(0) 0,08 g (0,088 mmol), BINAP (0,055 g, 0,088 mmol), y tert-butóxido de sodio (0,126 g, 1,32 mmol) se combinaron en dioxano (8 ml) y se burbujeó nitrógeno a través de la solución por 10 minutos. El tubo se selló y se calentó a 100 ºC por 18 horas. La mezcla de la reacción se particionó entre salmuera y diclorometano y los orgánicos se concentraron y se purificó mediante columna combi-flash de 24 g de sílice, eluyendo con 1:1 hexanos: diclorometano, seguido por 100% diclorometano para dar 0,165 g (37%) del compuesto del título.

Ejemplo 115D

{(2S)-1-[(2S)-2-{6-[(2R,5R)-1-(1,3-benzotiazol-2-il)-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-bencimidazol-5-il}pirrolidin-2-il]-1H-bencimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

El producto del Ejemplo 115C se procesó como en Ejemplos 113B, 113C, y 113D para dar 0,040 g (38%) del compuesto del título. 1H RMN (400 MHz, DMSO-D6) δ ppm 0,74 - 0,88 (m, 12 H) 1,76 - 1,84 (m, 2 H) 1,85 - 1,94 (m, 3 H) 1,95 - 2,07 (m, 4 H) 2,14 - 2,26 (m, 4 H) 2,61 - 2,71 (m, 2 H) 3,53 (s, 6 H) 3,76 - 3,85 (m, 4 H) 4,05 (t, J=8,51 Hz, 2 H) 5,10 - 5,18 (m, 2 H) 6,90 (t, J=7,54 Hz, 2 H) 7,07 - 7,16 (m, 3 H) 7,22 - 7,35 (m, 4 H) 7,40 (d, J=8,13 Hz, 2 H) 7,47 (d, J=8,35 Hz, 1 H) 7,52 - 7,59 (m, 1 H) 12,07 (s, 2 H); MS ESI+ m/z 889.



Ejemplo 116

{(2S)-1-[(2S)-2-{6-[(2R,5R)-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-bencimidazol-5-il}-1-(4,5,6,7-tetrahidro-1,3-benzotiazol-2-il)pirrolidin-2-il]-1H-bencimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

Ejemplo 116A

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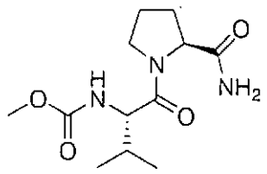
(S)-pirrolidin-2-carboxamida sal clorhidrato

A (S)-2-carbamoilpirrolidin-1-carboxilato de tert-butilo (29,8 g, 139 mmol) se agregó una solución de HCl 4N en dioxano (209 ml, 836 mmol) y la mezcla resultante se agitó a temperatura ambiente por 18 hrs. La mezcla luego se concentró y se trituró con éter dietílico luego se filtró al vacío y se secó bajo vacío para dar 21,6 g (104%) del producto del título como un sólido incoloro.

Ejemplo 116B

ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico

A ácido (S)-2-amino-3-metilbutanoico (57 g, 487 mmol) disuelto en dioxano (277 ml) se agregó una solución acuosa 2N de hidróxido de sodio (803 ml, 1606 mmol) seguido por la adición por goteo de cloroformato de metilo (75 ml, 973 mmol) a lo largo de 1 hr lo cual ocasionó el calentamiento de la solución. Luego de la adición, la mezcla se calentó a 60 °C por 22 hrs, luego se enfrió y se extrajo con diclorometano (400 ml). La capa acuosa resultante se enfrió en un baño de hielo luego se agregó ácido clorhídrico 12N por goteo hasta que el pH fue 2. La mezcla resultante se agitó a 0 °C por 2 hrs luego el sólido resultante se filtró al vacío y se secó en un horno de vacío para dar 80g (94%) del compuesto del título como un sólido incoloro. ^{1}H RMN (400 MHz, DMSO-d6) δ 12,50 (bs, 1H), 7,34 (d, J = 8,6 Hz, 1H), 3,84 (dd, J = 8,6, 6,0 Hz, 1H), 3,54 (s, 3H), 2,03 (m, 1H), 0,86 (t, J = 7,0 Hz, 6H).

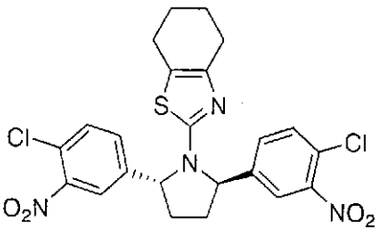


Ejemplo 116C

(S)-1-((S)-2-carbamoilpirrolidin-1-il)-3-metil-1-oxobutan-2-ilcarbamato de metilo

Al producto de Ejemplo 116A (21,6 g, 144 mmol), el producto de Ejemplo 116B (29,1 g, 166 mmol), hidrato de 1H-benzo[d][1,2,3]triazol-1-ol (27,6 g, 180 mmol), clorhidrato de N1-((etilimino)metilen)-N3,N3-dimetilpropan-1,3-diamina (34,6 g, 180 mmol) y 4-metilmorfolina (63,5 ml, 578 mmol) se disolvió en diclorometano (960 ml) y se agitó a temperatura ambiente por 18 hrs. La solución resultante luego se concentró para dar un residuo, luego se agregó agua y la solución se extrajo con una solución al 25% de isopropanol en cloroformo (2 x 2000 ml) la capa orgánica se lavó con salmuera luego el extracto orgánico se secó sobre $MgSO_4$, luego se concentró para dar un aceite amarillo el cual se purificó mediante cromatografía de columna eluyendo con un gradiente de 0-10% metanol en diclorometano para dar 25 g (64%) del compuesto del título como un sólido incoloro. ^{1}H RMN (400 MHz, DMSO-d6) δ 7,28 (m, 2H), 6,81 (s, 1H), 4,24 (dd, J = 8,1, 4,4

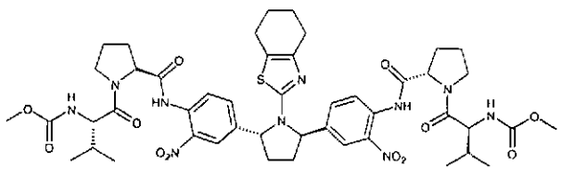
Hz, 1H), 4,00 (t, J = 8,4 Hz, 1H), 3,75 (m, 1H), 3,55 (m, 1H), 3,50 (s, 3H), 2,02 (m, 1H), 1,97 (m, 2H), 1,80 (m, 2H), 0,92 (d, J = 6,7 Hz, 3H), 0,86 (d, J = 8,6 Hz, 3H).



Ejemplo 116D

2-((2R,5R)-2,5-bis(4-cloro-3-nitrofenil)pirrolidin-1-il)-4,5,6,7-tetrahidrobenzo[d]tiazol

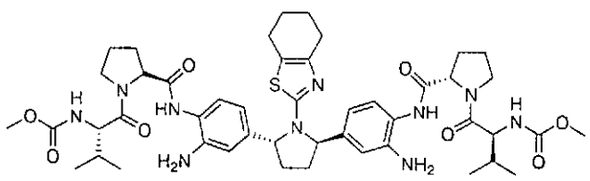
El producto del Ejemplo 109C (0,80 g, 1,489mmol) y 4,5,6,7-tetrahidrobenzo[d]tiazol-2-amina se procesaron usando el método de Ejemplo 113A para dar 0,375 g (50%) del compuesto del título



Ejemplo 116E

([(2*R*,5*R*)-1-(4,5,6,7-tetrahidro-1,3-benzotiazol-2-il)pirrolidin-2,5-diil]bis{(2-nitrobencen-4,1-diil)carbamoil(2*S*)pirrolidin-2,1-diil[(2*S*)-3-metil-1-oxobutan-1,2-diil]})biscarbamato de dimetilo (ACD v12))

El producto del Ejemplo 116D (0,375 g, 0,722 mmol) se procesó como en Ejemplo 113B, utilizando el producto del Ejemplo 116C en lugar de (S)-2-carbamoilpirrolidin-1-carboxilato de tert-butilo para dar 0,59 g (83%) del compuesto del título.



Ejemplo 116F

([(2*R*,5*R*)-1-(4,5,6,7-tetrahidro-1,3-benzotiazol-2-il)pirrolidin-2,5-diil]bis{(2-aminobencen-4,1-diil)carbamoil(2*S*)pirrolidin-2,1-diil[(2*S*)-3-metil-1-oxobutan-1,2-diil]})biscarbamato de dimetilo (ACD v12))

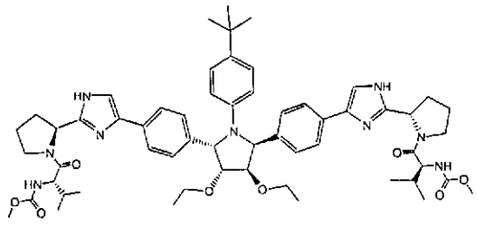
El producto del Ejemplo 116E (0,59 g, 0,596 mmol) se disolvió en tetrahidrofurano (15 ml) y se trató con lechada de níquel de Raney en agua (0,25 ml). El recipiente se evacuó y se abrió a un globo de hidrógeno y se agitó a temperatura ambiente por 1 hora. La solución se filtró a través de un tapón de sílice y se concentró hasta secar para dar el

compuesto del título.

Ejemplo 116G

{(2S)-1-[(2S)-2-{6-[(2R,5R)-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-bencimidazol-5-il}-1-(4,5,6,7-tetrahidro-1,3-benzotiazol-2-il)pirrolidin-2-il]-1H-bencimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

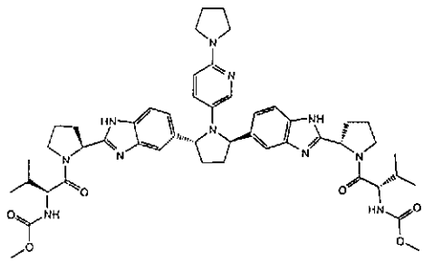
El producto del Ejemplo 116F (0,55 g, 0,592 mmol) se disolvió en tolueno (6 ml) y se trató con ácido acético (0,34 ml, 5,92 mmol) y se calentó a 65 °C por 4 horas. La solución se concentró hasta secar y se purificó mediante columna combi-flash de 12g de sílice, eluyendo con 0-6% metanol en diclorometano para dar 0,245 g (48%) del compuesto del título. 1H RMN (400 MHz, DMSO-D6) δ ppm 0,78 - 0,92 (m, 12 H) 1,53 - 1,61 (m, 4 H) 1,67 - 1,75 (m, 2 H) 1,88 - 2,07 (m, 6 H) 2,15 - 2,27 (m, 6 H) 2,41 - 2,47 (m, 2 H) 2,59 (d, J=1,63 Hz, 2 H) 3,54 (s, 6 H) 3,79 - 3,87 (m, 4 H) 4,07 (t, J=8,57 Hz, 2 H) 5,12 - 5,20 (m, 2 H) 5,38 - 5,46 (m, 2 H) 7,05 (dd, J=12,79, 9,00 Hz, 2 H) 7,22 - 7,33 (m, 4 H) 7,39 (d, J=8,46 Hz, 1 H) 7,46 (d, J=8,46 Hz, 1 H) 12,06 (d, J=6,83 Hz, 2 H); MS ESI+ m/z 893,5.



Ejemplo 117

{(2S)-1-[(2S)-2-(4-{4-[(2S,3R,4R,5S)-1-(4-tert-butilfenil)-3,4-dietoxi-5-(4-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-4-il}fenil)pirrolidin-2-il]fenil}-1H-imidazol-2-il)pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

Se procesó 3,4-O-isopropiliden-D-mannitol usando los métodos de Ejemplos 79C, 79D, 79E, 79F, 79G, 79H, y 79I para dar el compuesto del título, donde se usó yodoetano el paso de O-alquilación (método de Ejemplo 79D) en lugar de yodometano. ^{1}H RMN (400 MHz, $CDCl_3$) δ ppm 0,86 (t, J=7,4 Hz, 12H) 1,04 (t, J=7,0 Hz, 6H) 1,13 (s, 9H) 1,85-2,03 (m, 4H) 2,03-2,13 (m, 2H) 2,13-2,24 (m, 2H) 2,24-2,40 (m, 2H) 3,03 (m, 2H) 3,54-3,89 (m, 9H) 3,69 (d, J=1,7 Hz, 6H) 4,25 (d, J=5,3 Hz, 2H) 4,31 (br s, 2H) 5,19-5,29 (m, 4H) 5,36 (br s, 2H) 6,28 (d, J=8,8 Hz, 2H) 6,90-6,98 (m, 4H) 7,12-7,23 (m, 6H). MS (ESI) m/z 1029 $(M+H)^+$.



Ejemplo 118

{(2S)-1-[(2S)-2-(5-{(2R,5R)-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-bencimidazol-5-il}-1-[6-(pirrolidin-1-il)piridin-3-il]pirrolidin-2-il}-1H-bencimidazol-2-il)pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

Ejemplo 118A

5-nitro-2-(pirrolidin-1-il)piridina

A una lechada de 2-cloro-5-nitropiridina (10 g, 63,1 mmol) en EtOH (100 ml) a temperatura ambiente se agregó pirrolidina (15,72 ml, 189 mmol) y la mezcla se calentó a 70 °C por 18 h. La solución fría se concentró al vacío y el residuo se particionó entre CH_2Cl_2 y NaOH 1M. La capa orgánica se secó (Na_2SO_4), se filtró y el solvente se eliminó al vacío para dar compuesto del título (9,52g, 78%). MS (ESI) m/z 194 $(M+H)^+$.

Ejemplo 118B

6-(pirrolidin-1-il)piridin-3-amina

Se disolvió material del Ejemplo 118A (9,52 g, 49,3 mmol) en THF (50 ml) y DMF (40 ml) y se agregó a una botella de presión con níquel de Raney 2800, lechada en agua (45%) (9,52g, 162 mmol) agitando por 2 h a 30 psi bajo gas H_2. La solución se filtró a través de una membrana de nylon, se lavó con CH_3OH y el material filtrado se concentró al vacío para dar el compuesto del título (7,78 g, 97%). ^{1}H RMN (400 MHz, DMSO-*d6*) δ ppm 1,81-1,91 (m, 4H) 3,17-3,29 (m, 4H) 4,30 (s, 2H) 6,25 (d, J=8,7, 1H), 6,90 (dd, J=2,8, 8,7, 1H), 7,55 (d, J=2,6, 1H). MS (ESI) m/z 164 $(M+H)^+$.

Ejemplo 118C

(2S,2'S)-2,2'-(5,5'-((2R,5R)-1-(6-(pirrolidin-1-il)piridin-3-il)pirrolidin-2,5-diil)bis(1H-benzo[d]imidazol-5,2-diil)dipirrolidin-1-carboxilato de tert-butilo

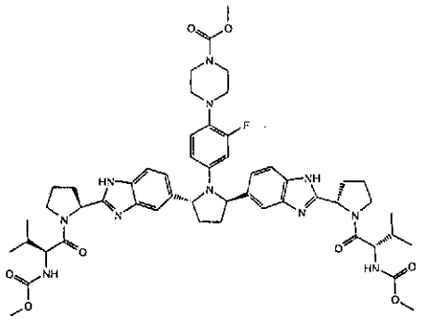
Se procesó Ejemplo 118B y Ejemplo 109C usando en forma consecutiva los métodos de Ejemplos 113A, 113B, 116F, y 28I para dar el compuesto del título.

Ejemplo 118D

{(2S)-1-[(2S)-2-(5-{(2R,5R)-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-bencimidazol-5-il}-1-[6-(pirrolidin-1-il)piridin-3-il]pirrolidin-2-il}-1H-bencimidazol-2-il)pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

A una solución de Ejemplo 118C (741 mg, 0,94 mmol) en dioxano (4 ml) se agregó HCl 4

M en dioxano (4,0 ml) y la solución se agitó a temperatura ambiente por 30 min. El solvente se elimina al vacío y el residuo se disuelve en DMF (9,4 ml). Se agregó N,N-diisopropiletilamina (0,99 ml, 5,65 mmol) seguido por ácido (S)-2-(metoxicarbonil-amino)-3-metilbutanoico (379 mg, 2,16 mmol), HOBT (331 mg, 2,16 mmol), y EDC (415 mg, 2,16 mmol) y se agitó a temperatura ambiente por 18 h. Se vertió en EtOAc, se lavó con H_2O, salmuera, se secó (Na_2SO_4), se filtró y se eliminó el solvente al vacío para dar producto crudo el cual se purificó mediante cromatografía flash sobre gel de sílice eluyendo con 0-6% CH_3OH/CH_2Cl_2 para dar el compuesto del título (165 mg, 0,183 mmol, 19%). 1H RMN (400 MHz, DMSO-d6) δ 0,73-0,95 (m, 12H) 1,66-2,27 (m, 12H) 3,09 (br s, 5H) 3,53 (s, 6H) 3,81 (br s, 4H) 4,06 (t, J=8,4 Hz, 2H) 5,13 (br s, 2H) 5,33 (br s, 2H) 6,12 (br s, 1H) 6,64 (br s, 1H) 7,00-7,47 (m, 10H) 12,02 (s, 2H). MS (ESI) m/z 903 $(M+H)^+$.



Ejemplo 119

4-{4-[(2R,5R)-2,5-bis(2-{(2S)-1-[N-(metoxicarbonil)-L-valil]pirrolidin-2-il}-1H-bencimidazol-5-il)pirrolidin-1-il]-2-fluorofenil}piperazin-1-carboxilato de metilo

Ejemplo 119A

1-(2-fluoro-4-nitrofenil)piperazina

A una solución caliente de piperazina (7,78 g, 90 mmol) en DMSO (40 ml) se agregó por goteo 1,2-difluoro-4-nitrobenceno (2,0 ml, 18,07 mmol). La solución se agitó a 70 °C por 2 h, se enfrió a temperatura ambiente, se diluyó con EtOAc, se lavó con H_2O, salmuera, se secó (Na_2SO_4), se filtró y el solvente se eliminó al vacío para dar el compuesto del título (4,05 g, 17,98 mmol, 100%). ^1H RMN (400 MHz, $CDCl_3$) δ ppm 3,03-3,09 (m, 4H) 3,26-3,29 (m, 4H) 6,91 (t, J=8,8 Hz, 1H) 7,91 (dd, J=13,1, 2,6 Hz, 1H) 7,96-8,01 (m, 1H). MS (ESI) m/z 226 $(M+H)^+$.

Ejemplo 119B

4-(2-fluoro-4-nitrofenil)piperazin-1-carboxilato de metilo

A una solución de Ejemplo 119A (4,0 g, 17,76 mmol) en dioxano (40 ml) a 0 °C se agregó NaOH 2 M (29,3 ml, 58,6 mmol) seguido por la adición por goteo de cloroformato de metilo (2,75 ml, 35,5 mmol). La solución se calentó a temperatura ambiente y se agitó por 2 h. Se diluyó con EtOAc y se agregó HCl 1 N hasta que se disolvió todo el sólido, se

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separó las fases y se lavó la fase orgánica con HCl 1 N, H_2O, salmuera, se secó (Na_2SO_4), se filtró y se eliminó el solvente al vacío para dar el compuesto del título (4,69 g, 16,56 mmol, 93%). ^{1}H RMN (400 MHz, $CDCl_3$) δ ppm 3,20-3,31 (m, 4H) 3,62-3,71 (m, 4H) 3,75 (s, 3H) 6,92 (t, J=8,8 Hz, 1H) 7,93 (dd, J=12,9, 2,6 Hz, 1H) 7,98-8,02 (m, 1H). MS (ESI) m/z 284 $(M+H)^+$.

Ejemplo 119C

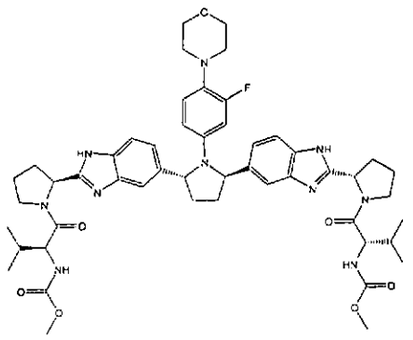
4-(4-amino-2-fluorofenil)piperazin-1-carboxilato de metilo

A una solución de Ejemplo 119B (3,0 g, 10,59 mmol) en EtOAc (40 ml) se agregó paladio sobre carbono al 10% (300 mg) y la solución se agitó bajo un globo de gas H_2 por 1,5 h. La solución se filtró a través de Celite, el catalizador se lavó con EtOAc, y el material filtrado se concentró al vacío para dar el compuesto del título (2,68g, 10,59 mmol, 100%).

Ejemplo 119D

4-{4-[(2R,5R)-2,5-bis(2-{(2S)-1-[N-(metoxicarbonil)-L-valil]pirrolidin-2-il}-1H-bencimidazol-5-il)pirrolidin-1-il]-2-fluorofenil}piperazin-1-carboxilato de metilo

Ejemplo 119C y Ejemplo 109C se procesaron usando en forma consecutiva los métodos de Ejemplos 113A-113C, 26I, y 118D para dar el compuesto del título. ^{1}H RMN (400 MHz, DMSO-*d6*) δ ppm 0,75-0,93 (m, 12H) 1,69 (br s, 2H) 1,82-2,07 (m, 7H) 2,10-2,28 (m, 4H) 2,61-2,73 (m, 5H) 3,54 (s, 6H) 3,56 (s, 3H) 3,82 (br s, 4H) 3,99-4,11 (m, 2H) 5,09-5,19 (m, 2H) 5,29-5,41 (m, 2H) 6,01-6,13 (m, 2H) 6,61-6,72 (m, 1H) 7,06 (s, 2H) 7,20 (s, 1H) 7,29 (d, J=9,1 Hz, 3H) 7,38 (d, J=8,1 Hz, 1H) 7,46 (d, 1H) 12,04 (s, 2H). MS (ESI) m/z 993 $(M+H)^+$.



Ejemplo 120

{(2S)-1-[(2S)-2-{5-[(2R,5R)-1-[3-fluoro-4-(morfolin-4-il)fenil]-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-bencimidazol-5-il}pirrolidin-2-il]-1H-bencimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

Ejemplo 120A

4-(2-Fluoro-4-nitrofenil)morfolina

Una suspensión de morfolina (4,72 ml, 4,72 g, 54,2 mmol) y fosfato de potasio dibásico

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(9,44 g, 54,2 mmol) en DMSO (27 ml) se trató con 3,4-difluoronitrobenceno (3,0 ml, 4,31 g, 27,1 mmol) se calentó a 60 °C por 18 h. La solución se enfrió y se diluyó con acetato de etilo y se extrajo con agua (3 x) y solución saturada de cloruro de sodio. El secado (Na_2SO_4) y concentración al vacío dio el compuesto del título (6,32 g, aproximadamente 100%) como un sólido amarillo. ^{1}H RMN (400 MHz, $CDCl_3$) δ 8,00 (ddd, J = 9,0, 2,6, 0,9 Hz, 1 H), 7,92 (dd, J = 13,1, 2,6 Hz, 1 H), 6,92 (t, J = 8,8 Hz, 1 H), 3,88 (m, 4 H), 3,29 (dd, J = 5,5, 4,0 Hz, 4 H). MS +DCI m/z (abundancia relativa) 227 (10, M+H), 244 (100, M+NH4).

Ejemplo 120B

3-Fluoro-4-morfolinoanilina

Una solución del compuesto de Ejemplo 120A (2,26 g, 10,00 mmol) en acetato de etilo (35 ml) se trató con paladio sobre carbono al 10% (300 mg) seguido por hidrogenación bajo presión de una atmósfera por 6 h. La mezcla se filtró a través de celite y se concentró al vacío para dar el compuesto del título como un sólido blanco.

Ejemplo 120C

4-(4-((*2R,5R*)-2,5-bis(4-cloro-3-nitrofenil)pirrolidin-1-il)-2-fluorofenil)morfolina

Una solución del compuesto de Ejemplo 109C (2,00 g, 4,99 mmol) y trietilamina (4,17 ml, 3,03 g, 29,9 mmol) en diclorometano seco (25 ml) a 0 °C se trató con cloruro de metansulfonilo (1,17 ml, 1,71 g, 14,96 mmol) seguido por agitación a 0 °C por 30 min. La solución se calentó a temperatura ambiente y luego se concentró al vacío. El residuo se combinó con el compuesto de Ejemplo 120B y N,N-dimetilanilina (1,26 ml, 1,21 g, 9,98 mmol) y se disolvió en DMF seco (14 ml) seguido por calentamiento a 50 °C por 2 h. La solución se enfrió y se diluyó con acetato de etilo, seguido por extracción con agua (3 x) y solución 1 N de ácido clorhídrico (2 x) y solución saturada de cloruro de sodio. El secado (Na_2SO_4) y concentración al vacío dio un aceite anaranjado, el cual se cromatografió sobre un cartucho de 340 g de gel de sílice, eluyendo con 10-80% acetato de etilo en hexanos. Estos procedimientos dieron el compuesto del título (1,39 g, 50%) como una espuma rígida anaranjada. ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,92 (m, 2 H), 7,58 (m, 9 H), 7,31 (dd, *J* = 8,3, 2,1 Hz, 2 H), 6,69 (s, 1 H), 5,99 (m, 2 H), 5,20 (d, *J* = 7,1 Hz, 2 H), 3,79 (m, 4 H), 2,92 (m, 6 H), 2,54 (m, 2 H), 1,88 (m, 2 H).

Ejemplo 120D

(2R,2'R)-1,1'-((*2S,2'S*)-2,2'-(4,4'-((*2R,5R*)-1-(3-fluoro-4-morfolinofenil)pirrolidin-2,5-diil)bis(2-nitro-4,1-fenilen))bis(azandiil)bis(oxometilen)bis(pirrolidin-2,1-diil))bis(3-metil-1-oxobutan-2,1-diil)dicarbamato de dimetilo

En un tubo de microondas, a suspensión del Ejemplo 120C (1,39 g, 2,48 mmoL), el

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compuesto de Ejemplo 116C (2,02 g, 7,43 mmol), XantPhos (129 mg, 0,22 mmol) y carbonato de cesio (2,42 g, 7,43 mmoL) en dioxano (14 ml) se desgasificó rociando con nitrógeno por 30 min. La mezcla se trató con tris(dibencilidenacetona)dipaladio (0) (68 mg, 0,074 mmol) seguido por desgasificación por otros 5 min. El tubo de microondas se selló y la mezcla se calentó a 100 °C por 2 h. La mezcla se enfrió y se diluyó con acetato de etilo y se extrajo con agua (3 x) y solución saturada de cloruro de sodio. La solución se secó (Na_2SO_4) y se agitó durante la noche con 3-(mercaptopropilo) gel de sílice. El filtrado y concentración al vacío dio un sólido, el cual se cromatografió sobre un cartucho de 340 g de gel de sílice, eluyendo con 0-10% metanol en diclorometano. Estos procedimientos dieron el compuesto del título como un sólido anaranjado. ^{1}H RMN (400 MHz, DMSO-*d6*) δ ppm 0,80-0,90 (m, 12H) 1,74 (br s, 2H) 1,82-2,03 (m, 10H) 2,08-2,20 (m, 2H) 2,71-2,81 (m, 4H) 3,52 (s, 6H) 3,62 (m, 4H) 3,76 (s, 2H) 4,02 (m, 2H) 4,50 (d, J=4,4 Hz, 2H) 5,39 (s, 2H) 6,04-6,19 (m, 2H) 6,72-6,81 (m, 1H) 7,32 (d, J=8,4 Hz, 2H) 7,47-7,60 (m, 4H) 7,80 (d, J=1,5 Hz, 2H) 10,41 (s, 2H). MS (ESI) m/z 1031 $(M+H)^+$.

Ejemplo 120E

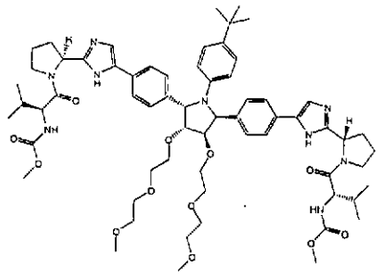
(2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-((2R,5R)-1-(3-fluoro-4-morfolinofenil)pirrolidin-2,5-diil)bis(2-amino-4,1-fenilen)bis(azandiil)bis(oxometilen)bis(pirrolidin-2,1diil)bis(3-metil-1-oxobutan-2,1-diil)dicarbamato de dimetilo

A una solución de Ejemplo 120D (640 mg, 0,621 mmol) en EtOH (4 ml) y THF (4 ml) se agregó PtO_2 (35 mg) y la solución se agitó bajo un globo de gas H_2 por 16 h. La solución se filtró a través de Celite y se lavó con EtOAc. El material filtrado se concentró al vacío para dar el compuesto del título (322 mg, 0,332 mmol, 53%).

Ejemplo 120F

{(2S)-1-[(2S)-2-{5-[(2R,5R)-1-[3-fluoro-4-(morfolin-4-il)fenil]-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-bencimidazol-5-il}pirrolidin-2-il]-1H-bencimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

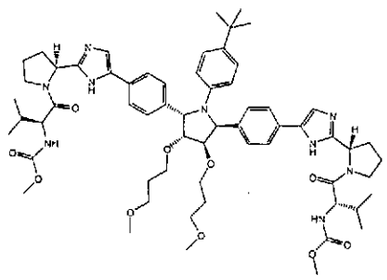
A una solución de Ejemplo 120E (320 mg, 0,33 mmol) en tolueno (1,5 ml) se agregó ácido acético glacial (0,057 ml, 0,99 mmol) y la solución se agitó a 50 °C por 3 h. La solución fría se concentró al vacío y se azeotropeó 2 veces con tolueno. El producto crudo se purificó mediante cromatografía flash sobre gel de sílice eluyendo con 0-4% CH_3OH/CH_2Cl_2 para dar el compuesto del título (100 mg, 0,107 mmol, 32%). ^{1}H RMN (400 MHz, DMSO-*d6*) δ ppm 0,72-0,92 (m, 12H) 1,69 (br s, 2H) 1,81-2,10 (m, 8H) 2,11-2,28 (m, 4H) 2,64-2,78 (m, 4H) 3,54 (s, 6H) 3,59 (s, 4H) 3,73-3,92 (m, 4H) 4,06 (s, 2H) 5,02-5,21 (m, 2H) 5,36 (s, 2H) 6,03-6,14 (m, 2H) 6,60-6,73 (m, 1H) 7,00-7,15 (m, 2H) 7,15-7,37 (m, 4H) 7,36-7,61 (m, 2H) 12,06 (br s, 2H). MS (ESI) m/z 935 $(M+H)^+$.



Ejemplo 121

[(2S)-1-{(2S)-2-[5-(4-{(2S,3R,4R,5S)-1-(4-tert-butilfenil)-5-(4-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-5-il}fenil)-3,4-bis[2-(2-metoxietoxi)etoxi]pirrolidin-2-il}fenil)-1H-imidazol-2-il]pirrolidin-1-il}-3-metil-1-oxobutan-2-il]carbamato de metilo

Se procesó 3,4-O-isopropiliden-D-mannitol usando en forma consecutiva los métodos de Ejemplos 79C, 79D (1-bromo-2-(2-metoxietoxi)etano como el agente alquilante con la adición de yoduro de sodio), 79E-79G, 79H (tiempo de reacción 18 hora), 66D, y 66E para dar el compuesto del título (46 mg) como un sólido amarillo claro. ^{1}H RMN (400 MHz, DMSO-d_6) δ 7,60 (d, J = 7,9 Hz, 4 H), 7,50 (d, J = 8,4 Hz, 2 H), 7,38 (s, 2 H), 7,29 (d, J = 8,6 Hz, 2 H), 7,19 (s, 4 H), 6,90 (m, 2 H), 6,27 (d, J = 8,6 Hz, 2 H), 5,37 (s, 2 H), 5,07 (d, J = 3,6 Hz, 2 H), 4,32 (s, 2 H), 4,06 (m, 2 H), 3,78 (d, J = 6,0 Hz, 2 H), 3,66 (d, J = 4,2 Hz, 4 H), 3,53 (s, 6 H), 3,17 (s, 6 H), 2,10 (m, 4 H), 1,93 (m,4 H), 1,07 (s, 9 H), 0,86 (m, 12 H). MS (+ESI) *m/z* (abundancia relativa) 1177 (100, M+H), 1199 (5, M+Na).



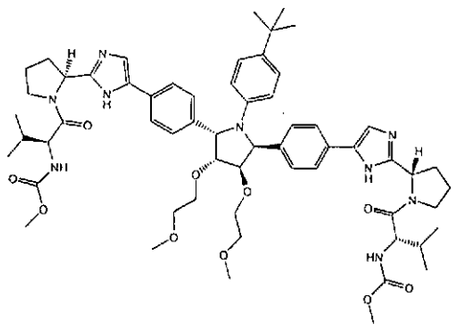
Ejemplo 122

{(2S)-1-[(2S)-2-(5-{4-[(2S,3R,4R,5S)-1-(4-tert-butilfenil)-5-(4-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-5-il}fenil)-3,4-bis(3-metoxipropoxi)pirrolidin-2-il]fenil}-1H-imidazol-2-il)pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

Se procesó 3,4-O-isopropiliden-D-mannitol usando en forma consecutiva los métodos de Ejemplos 79C, 79D (1-bromo-3-metoxipropano como el agente alquilante con la adición de yoduro de sodio), 79E-79H, 66D, y 66E para dar el compuesto del título. ^{1}H RMN (400 MHz, DMSO-d_6) δ 7,60 (s, 4 H), 7,52 (m, 2 H), 7,37 (m, 2 H), 7,30 (m, 4 H), 7,18 (d, J = 7,1 Hz, 4 H), 6,91 (m, 2 H), 6,24 (m, 2 H), 5,40 (m, 2 H), 5,06 (m, 2 H), 4,31

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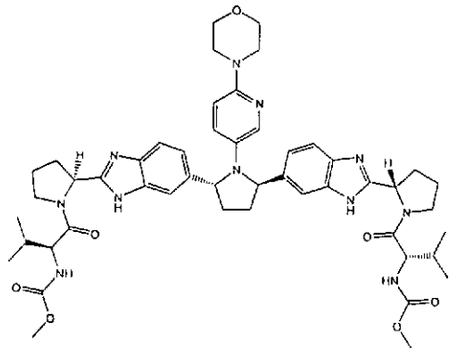
(m, 2 H), 4,11 (m, 2 H), 3,78 (s, 4 H), 3,66 (m, 4 H), 3,56 (m, 10 H), 3,14 (m, 14 H), 2,14 (m, 6 H), 1,94 (d, *J* = 3,5 Hz, 8 H), 1,43 (m, 6 H), 1,07 (s, 10 H), 0,89 (d, *J* = 6,1 Hz, 6 H), 0,84 (d, *J* = 5,9 Hz, 6H).



Ejemplo 123

{(2S)-1-[(2S)-2-(5-{4-[(2S,3R,4R,5S)-1-(4-tert-butilfenil)-5-(4-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-5-il}fenil)-3,4-bis(2-metoxietoxi)pirrolidin-2-il]fenil}-1H-imidazol-2-il)pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

3,4-O-isopropiliden-D-mannitol se procesó usando en forma consecutiva los métodos de Ejemplos 79C, 79D (1-bromo-2-metoxietano como el agente alquilante con la adición de yoduro de sodio), 79E, 79F, 79G, y 79H, donde Ejemplo 126G reemplaza al (S)-2-(4-bromo-1H-imidazol-2-il)pirrolidin-1-carboxilato de tert-butilo en la aplicación del método de Ejemplo 79H, para dar el compuesto del título (43 mg) como un sólido beige. ^{1}H RMN (400 MHz, DMSO-d_6) δ 7,60 (d, *J* = 8,0 Hz, 4 H), 7,47 (m, 2 H), 7,37 (m, 2 H), 7,27 (m, 4 H), 7,19 (s, 4 H), 6,90 (d, *J* = 8,6 Hz, 2 H), 6,26 (d, *J* = 8,7 Hz, 2 H), 5,37 (s, 2 H), 5,06 (d, *J* = 3,7 Hz, 2 H), 4,30 (s, 2 H), 4,03 (m, 2 H), 3,79 (s, 4 H), 3,66 (m, 6 H), 3,53 (s, 6 H), 3,25 (m, 6 H), 3,12 (s, 6 H), 2,13 (m, 4 H), 1,94 (m, 6 H), 1,07 (s, 9 H), 0,89 (d, *J* = 6,6 Hz, 6 H), 0,84 (d, *J* = 6,6 Hz, 6 H). MS +ESI *m/z* (abundancia relativa) 1088 (100, M+H).



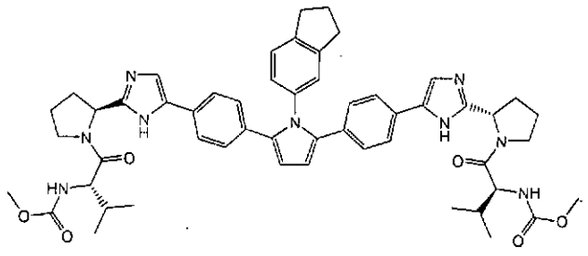
Ejemplo 124

{(2S)-1-[(2S)-2-(6-{(2R,5R)-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-bencimidazol-6-il}-1-[6-(morfolin-4-il)piridin-3-il]pirrolidin-2-

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il}-1H-bencimidazol-2-il)pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

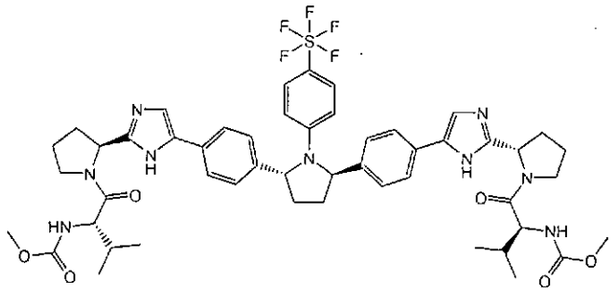
Ejemplo 109C y Ejemplo 154B se procesaron usando los métodos de Ejemplos 113A, 113B, 116F, 28I (la reacción se llevó a cabo a 50 °C por 4 h), 66D, y 66E para dar el compuesto del título (120 mg) como un sólido beige. ^{1}H RMN (400 MHz, DMSO-d_6) δ 12,03 (s, 1 H), 7,46 (d, J = 8,2 Hz, 1 H), 7,45 (s, 1 H), 7,31 (d, J = 6,4 Hz, 3 H), 7,21 (s, 1 H), 7,06 (t, J = 8,0 Hz, 2 H), 6,64 (m, 1 H), 6,49 (m, 1 H), 5,36 (d, J = 6,2 Hz, 2 H), 5,13 (s, 2 H), 4,04 (m, 2 H), 3,77 (m, 3 H), 3,55 (m, 9 H), 3,04 (s, 4 H), 2,19 (s, 3 H), 1,95 (m, 5 H), 1,73 (s, 3 H), 0,82 (m, 12 H). MS +ESI *m/z* (abundancia relativa) 918 (100, M+H).



Ejemplo 125

{(2S)-1-[(2S)-2-(5-{4-[1-(2,3-dihidro-1H-inden-5-il)-5-(4-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-5-il}fenil)-1H-pirrol-2-il]fenil}-1H-imidazol-2-il)pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

Ejemplo 26E y 5-aminoindan se procesaron usando los métodos de Ejemplos 76A, 39E, 39F, 55G, y 26J (solvente de reacción = diclorometano) para dar el compuesto del título (0,1446 g). ^{1}H RMN (400 MHz, DMSO-D6) δ 0,91 - 0,79 (m, 12H), 2,18 - 1,87 (m, 12H), 2,74 (t, J = 6,7, 2H), 2,86 (t, J = 6,8, 2H), 3,53 (s, 6H), 3,84 - 3,68 (m, 4H), 4,10 - 3,98 (m, 2H), 5,03 (dd, J = 6,8, 2,9, 2H), 6,54 - 6,40 (m, 2H), 7,10 - 6,86 (m, 5H), 7,22 - 7,13 (m, 2H), 7,33 - 7,22 (m, 2H), 7,45 - 7,35 (m, 2H), 7,53 (dd, J = 13,7, 8,5, 4H), 11,70 (s, 1H), 12,07 - 11,96 (m, 1H). MS (ESI) *m/z* 920 $(M+H)^+$, 918 $(M-H)^+$.



Ejemplo 126

[(2S)-1-{(2S)-2-[5-(4-{(2R,5R)-5-(4-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-5-il}fenil)-1-[4-(pentafluoro-lambda~6~-sulfanil)fenil]pirrolidin-2-il}fenil)-1H-imidazol-2-il]pirrolidin-1-il}-3-metil-1-oxobutan-2-

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il]carbamato de metilo

Ejemplo 126A

ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico

Una mezcla de ácido (S)-2-amino-3-metilbutanoico (10,0 g, 85,0 mmol), NaOH (3,41 g, 85,0 mmol) y $NaHCO_3$ (4,7 g, 44,4 mmol) en H_2O (85 ml) se enfrió a 0 °C. Una mezcla de cloroformato de metilo (7,3 ml, 94,0 mmol) disuelto en Et_2O (40 ml) se agregó lentamente a la mezcla acuosa y se agitó por 20 horas alcanzando temperatura ambiente. La mezcla se ajustó a pH 2,0 con HCl (*conc*). La mezcla se extrajo con CH_2Cl_2 (3 x 100 ml) y luego se secó ($MgSO_4$), se filtró y se concentró para dar 7,5 g (50%) del compuesto del título. MS (ESI) m/z 176 $(M+H)^+$.

Ejemplo 126B

(S)-2-formilpirrolidin-1-carboxilato de tert-butilo

Una mezcla de cloruro de oxalilo (14,1 ml, 161 mmol) en CH_2Cl_2 (331 ml) se enfrió a -75 °C. Se agregó sulfóxido de dimetilo (19,4 ml, 273 mmol) en CH_2Cl_2 (70 ml) lentamente a lo largo de 30 minutos seguido por agitación a -75 °C por otros 15 minutos. A -75 °C se agregó (S)-2-(hidroximetil)pirrolidin-1-carboxilato de tert-butilo (25,0 g, 124 mmol) en CH_2Cl_2 (132 ml) lentamente a lo largo de una hora, seguido por otros 15 minutos de agitación. Luego, aun a -75 °C, se agregó Et_3N (87 ml, 621 mmol) a lo largo de 30 minutos seguido por otros 15 minutos de agitación. La mezcla luego se dejó agitar a 0 °C por 90 minutos. Mezcla se detuvo con ácido cítrico acuoso al 10% a 0 °C. La mezcla se diluyó con ácido cítrico acuoso al 10% y se particionó. El orgánico se lavó con H_2O (5 x 150 ml) y salmuera. El orgánico luego se secó ($MgSO_4$), se filtró y se concentró para dar 24,7g (100%) del compuesto del título. MS (ESI) m/z 200 $(M+H)^+$.

Ejemplo 126C

(S)-2-(1H-imidazol-2-il)pirrolidin-1-carboxilato de tert-butilo

Una mezcla de Ejemplo 126B (24,7g, 124,0 mmol) y NH_4OH (62,0 ml, 497 mmol) en metanol (62 ml) se agitó a 0 °C seguido por adición lenta de hidrato de glioxal (29,9 ml, 262 mmol) a lo largo de 10 minutos. La mezcla se agitó por 16 horas a temperatura ambiente. La mezcla se concentró, se diluyó con H_2O y se extrajo con EtOAc (3 x 200 ml). El orgánico luego se secó ($MgSO_4$), se filtró y se concentró. La purificación mediante trituración con *t*BuOMe dio 15,5g (53%) del compuesto del título. MS (ESI) m/z 238 $(M+H)^+$.

Ejemplo 126D

(S)-2-(4,5-dibromo-1H-imidazol-2-il)pirrolidin-1-carboxilato de tert-butilo

Una mezcla de Ejemplo 126C (15,5 g, 65,4 mmol) en CH_2Cl_2 (260 ml) se agitó a 0 °C

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seguido por la adición por goteo de 1-bromopirrolidin-2,5-diona (24,5, 137,0 mmol) a lo largo de 10 minutos. La mezcla se agitó 0 °C por 90 minutos. La mezcla se concentró, se diluyó con EtOAc (600 ml) y se lavó con H_2O (3 x 200 ml) y salmuera. El orgánico luego se secó ($MgSO_4$), se filtró y se concentró. La purificación mediante trituración con Et_2O dio 24,9 g (96%) del compuesto del título. MS (ESI) m/z 396 $(M+H)^+$.

Ejemplo 126E

(S)-2-(5-bromo-1H-imidazol-2-il)pirrolidin-1-carboxilato de tert-butilo

A una mezcla de Ejemplo 126D (12,5 g, 31,5 mmol) en dioxano (400 ml) y H_2O (400 ml) se agregó una solución de Na_2SO_3 (43,7 g, 347 mmol) en H_2O (400 ml) y se calentó a reflujo por 21 horas. La mezcla se concentró a la mitad del volumen y se extrajo con CH_2Cl_2 (3 x 200 ml). El orgánico luego se lavó con salmuera, se secó ($MgSO_4$), se filtró y se concentró. La purificación mediante trituración (CH_2Cl_2, *t*BuOMe, y Hexanos) dio 5,2 g (52%) del compuesto del título. MS (ESI) m/z 317 $(M+H)^+$.

Ejemplo 126F

clorhidrato de (S)-5-bromo-2-(pirrolidin-2-il)-1H-imidazol

Una mezcla de Ejemplo 126E (5,0g, 15,8 mmol) en HCl 4M/Dioxano (40 ml) se dejó agitar por una hora. La mezcla se concentró para dar 3,99g (100%) del compuesto del título. MS (ESI) m/z 217 $(M+H)^+$.

Ejemplo 126G

(S)-1-((S)-2-(5-bromo-1H-imidazol-2-il)pirrolidin-1-il)-3-metil-1-oxobutan-2-ilcarbamato de metilo

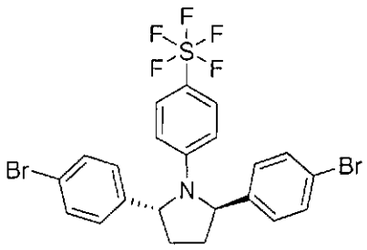
Una mezcla de Ejemplo 126F (3,99g, 15,8 mmol), Ejemplo 126A (2,77 g, 15,8 mmol), clorhidrato de N-(3-dimetilaminopropil)-N'-etilcarbodiimida (3,63 g, 19,0 mmol), hidrato de 1-hidroxi-benzotriazol (2,90 g, 19,0 mmol) y N-metilmorfolina (12,2 ml, 111,0 mmol) en DMF (150 ml) se dejó agitar durante la noche. Mezcla se diluyó con H_2O y se extrajo con EtOAc (3 x 300 ml). El orgánico se lavó con H_2O y salmuera. El orgánico luego se secó ($MgSO_4$), se filtró y se concentró. La purificación mediante cromatografía (gel de sílice, 75% EtOAc en Hexanos) dio 5,2 g (88%) del compuesto del título: ^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 0,79 (dd, *J*=6,67, 3,63 Hz, 6 H), 1,84 - 1,96 (m, 3 H), 2,02 - 2,14 (m, 2 H), 3,51 (s, 3 H), 3,66 - 3,80 (m, 2 H), 3,96 - 4,03 (m, 1 H), 4,91 - 4,99 (m, 1 H), 7,06 (d, *J*=1,52 Hz, 1 H), 7,26 (d, *J*=8,46 Hz, 1 H), 12,01 (s, 1 H). MS (ESI) m/z 373 $(M+H)^+$.

Ejemplo 126H

(1S,4S)-1,4-bis(4-bromofenil)butan-1,4-diol

Se preparó (1S,4S)-1,4-bis(4-bromofenil)butan-1,4-diol usando el método de Ejemplo 69A y (R)-alfa, alfa-difenil-2-pirrolidinmetanol).

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Ejemplo 126I

(2R,5R)-2,5-bis(4-bromofenil)-1-(4-sulfopentafluorofenil)pirrolidina

Una solución de anhídrido metansulfónico (2,95 ml, 23,02 mmol) en 2-Me THF (15 ml) se enfrió en baño de hielo/sal a ~0°C. A esta solución fría se agregó una solución de Ejemplo 126H (4,0524 g, 10,13 mmol) y N,N-diisopropiletilamina (5,5 ml, 31,8 mmol) en 2-Me THF (40 ml) por goteo a lo largo de 40 minutos. La reacción se calentó lentamente a 20 °C. Luego de este tiempo se agregó pentafluoruro de 4-aminofenilsulfuro (7,1238 g, 32,5 mmol) y la mezcla se calentó a 38 °C por 17 horas. La reacción se enfrió y se particionó entre EtOAc y agua. La fracción orgánica se lavó con agua (2 x) salmuera (1 x) y se concentró. La purificación mediante cromatografía flash (gel de sílice, EtOAc/hexano) dio el compuesto del título (1,95 g, 33%). LC/MS temperatura ambiente 2,38 *m/z* 584 $(M+H)^+$.

Ejemplo 126J

(2R,5R)-1-(4-pentafluoruro de azufre fenil)-2,5-bis(4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)pirrolidina

El producto del Ejemplo 126I se procesó usando el método descrito en Ejemplo 39E para dar el compuesto del título (1,67 g, 74%). MS (ESI) *m/z* 678 $(M+H)^+$.

Ejemplo 126K

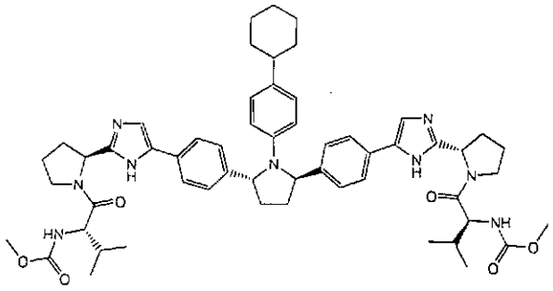
[(2S)-1-{(2S)-2-[5-(4-{(2R,5R)-5-(4-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-5-il}fenil)-1-[4-(pentafluoro-lambda~6~-sulfanil)fenil]pirrolidin-2-il}fenil)-1H-imidazol-2-il]pirrolidin-1-il}-3-metil-1-oxobutan-2-il]carbamato de metilo

El producto del Ejemplo 126J y Ejemplo 126G se procesaron usando el método descrito en Ejemplo 39F para dar el compuesto del título (0,75 g, 30%). ^{1}H RMN (400 MHz, DMSO-d6) δ 0,85 (dd, *J* = 6,7, 15,8, 12H), 2,26 – 1,66 (m, 14H), 3,53 (s, 6H), 3,87 – 3,63 (m, 4H), 4,14 – 3,91 (m, 2H), 5,06 (dd, *J* = 3,0, 6,7, 2H), 5,34 (s, 2H), 6,34 (d, *J* = 9,1, 2H), 7,17 (d, *J* = 8,2, 4H), 7,26 (dd, *J* = 8,4, 17,3, 2H), 7,75 – 7,34 (m, 8H), 12,22 – 11,46 (m, 2H). MS (ESI) *m/z* 1010 $(M+H)^+$, 1008 $(M-H)^-$.

Ejemplo 127

[(2S)-1-{(2S)-2-[5-(4-{1-[4-(azepan-1-il)fenil]-5-(4-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-5-il}fenil)-1H-pirrol-2-il}fenil)-1H-imidazol-2-il]pirrolidin-1-il}-3-metil-1-oxobutan-2-il]carbamato de metilo

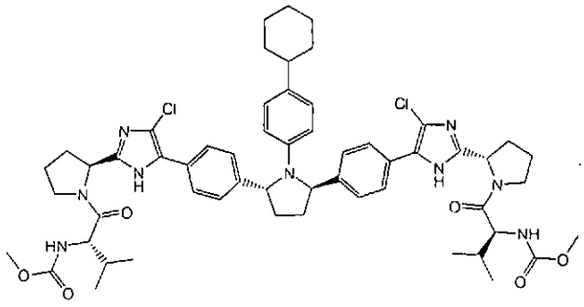
Se procesó Ejemplo 26E y 4-(1-azepanil)anilina usando los métodos de Ejemplos 76A, 39E, 39F, 55G, y 26J (solvente de reacción = diclorometano) para dar el compuesto del título (6,1 mg). MS (ESI) *m/z* 977 $(M+H)^+$.



Ejemplo 128

{(2S)-1-[(2S)-2-(5-{4-[(2R,5R)-1-(4-ciclohexilfenil)-5-(4-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-5-il}fenil)pirrolidin-2-il]fenil}-1H-imidazol-2-il)pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

Ejemplo 126H y 4-ciclohexilanilina se procesaron usando los métodos de Ejemplos 126I, 126J, y 126K para dar el compuesto del título (0,14 g),1H RMN (400 MHz, DMSO-D6) δ 0,85 (dd, *J* = 16,6, 6,9, 12H), 1,32 - 1,06 (m, 8H), 1,65 (dd, *J* = 19,1, 6,2, 7H), 2,27 - 1,82 (m, 13H), 3,53 (s, 6H), 3,78 (d, *J* = 6,8, 2H), 4,10 - 3,95 (m, 2H), 5,06 (dd, *J* = 6,9, 3,1, 2H), 5,19 (t, *J* = 6,7, 2H), 6,21 (d, *J* = 8,7, 2H), 6,76 (dd, *J* = 8,6, 3,7, 2H), 7,19 - 7,08 (m, 4H), 7,34 - 7,19 (m, 2H), 7,37 (d, *J* = 1,8, 1H), 7,50 (t, *J* = 11,3, 1H), 7,65 - 7,57 (m, 3H), 11,68 (s, 1H), 12,10 - 11,93 (m, 1H). MS (ESI) *m/z* 966 $(M+H)^+$.



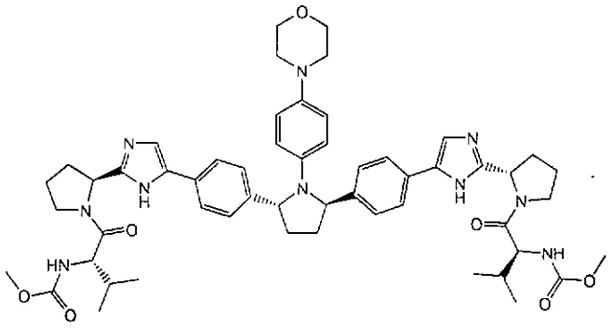
Ejemplo 129

{(2S)-1-[(2S)-2-(4-cloro-5-{4-[(2R,5R)-5-(4-{4-cloro-2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-5-il}fenil)-1-(4-

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ciclohexilfenil)pirrolidin-2-il]fenil}-1H-imidazol-2-il)pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

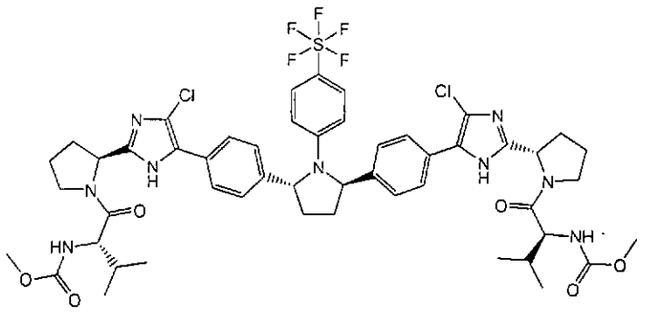
Se agregó N-clorosuccinimida (0,046 g, 0,342 mmol) a una solución del producto del Ejemplo 128 (0,1435 g, 0,149 mmol) en diclorometano (7 ml) y se agitó a temperatura ambiente por 17 horas. La reacción se diluyó con diclorometano y se lavó con NaHCO3 acuoso saturado (2 x) y se concentró. El residuo se purificó mediante cromatografía flash (gel de sílice, MeOH/diclorometano) luego mediante HPLC preparativa para dar el compuesto del título (20,4 mg, 13%). ^{1}H RMN (base libre) (400 MHz, DMSO-D6) δ 0,94 - 0,73 (m, 12H), 1,39 - 0,99 (m, 8H), 1,75 - 1,41 (m, 6H), 2,27 - 1,77 (m, 12H), 3,53 (s, 6H), 3,86 - 3,66 (m, 3H), 4,08 - 3,96 (m, 2H), 5,11 - 4,89 (m, 2H), 5,30 - 5,12 (m, 1H), 5,55 - 5,33 (m, 1H), 6,21 (d, J = 8,7, 1H), 6,88 - 6,67 (m, 2H), 6,94 (dd, J = 4,3, 8,4, 1H), 7,42 - 7,02 (m, 6H), 7,56 - 7,42 (m, 3H), 7,61 (t, J = 8,5, 1H), 11,68 (d, J = 10,7, 1H), 12,49 - 12,26 (m, 1H). MS (ESI) *m/z* 1034 $(M+H)^+$.



Ejemplo 130

[(2S)-1-{(2S)-2-[5-(4-{(2R,5R)-5-(4-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-5-il}fenil)-1-[4-(morfolin-4-il)fenil]pirrolidin-2-il}fenil)-1H-imidazol-2-il]pirrolidin-1-il}-3-metil-1-oxobutan-2-il]carbamato de metilo

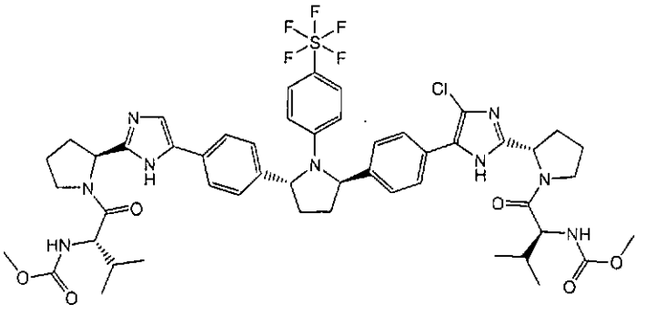
Se procesó Ejemplo 126H y 4-morfolinoanilina usando en forma consecutiva los métodos de Ejemplos 126I, 39E, 39F, 39I, y 26J (solvente de reacción = diclorometano) para dar el compuesto del título (0,16 g). ^{1}H RMN (300 MHz, DMSO-D6) δ 0,86 (dd, *J* = 12,2, 6,6, 12H), 1,77 - 1,55 (m, 2H), 2,03 - 1,77 (m, 6H), 2,21 - 2,03 (m, 4H), 2,45 - 2,39 (m, 1H), 2,58 - 2,54 (m, 1H), 2,82 - 2,74 (m, 4H), 3,53 (s, 6H), 3,67 - 3,57 (m, 4H), 3,77 (d, *J* = 6,1, 3H), 4,04 (t, *J* = 8,3, 2H), 5,06 (dd, *J* = 6,7, 3,0, 2H), 5,18 (t, *J* = 5,0, 2H), 6,22 (d, *J* = 9,0, 2H), 6,58 (dd, *J* = 9,0, 1,9, 2H), 7,14 (d, *J* = 8,4, 4H), 7,32 - 7,17 (m, 3H), 7,37 (d, *J* = 1,8, 2H), 7,55 - 7,41 (m, 1H), 7,63 (t, *J* = 10,0, 4H), 11,68 (s, 1H), 12,15 - 11,90 (m, 1H). MS (ESI) *m/z* 969 $(M+H)^+$.



Ejemplo 131

[(2S)-1-{(2S)-2-[4-cloro-5-(4-{(2R,5R)-5-(4-{4-cloro-2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-5-il}fenil)-1-[4-(pentafluoro-lambda~6~-sulfanil)fenil]pirrolidin-2-il}fenil)-1H-imidazol-2-il]pirrolidin-1-il}-3-metil-1-oxobutan-2-il]carbamato de metilo

El producto del Ejemplo 126K se procesó usando el método descrito en Ejemplo 129. La mezcla de productos mono y diclorados se purificó mediante HPLC de fase inversa para dar el compuesto del título (90,9 mg, 19%). ^{1}H RMN (base libre) (500 MHz, DMSO-D6) δ 0,84 (dd, *J* = 6,8, 16,1, 12H), 2,23 – 1,70 (m, 13H), 3,53 (s, 6H), 3,85 – 3,66 (m, 4H), 4,02 (ddd, *J* = 4,8, 10,8, 16,1, 3H), 5,05 – 4,91 (m, 2H), 5,43 (d, *J* = 5,8, 2H), 6,36 (d, *J* = 9,1, 2H), 7,28 (d, *J* = 8,4, 2H), 7,34 (d, *J* = 8,3, 4H), 7,46 (d, *J* = 9,4, 2H), 7,72 – 7,58 (m, 4H), 12,43 (s, 2H). MS(ESI) *m/z* 1078 $(M+H)^+$.



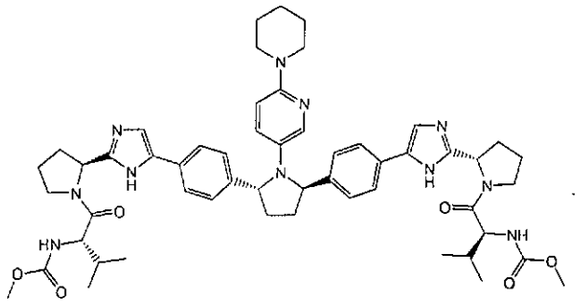
Ejemplo 132

[(2S)-1-{(2S)-2-[4-cloro-5-(4-{(2R,5R)-5-(4-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-5-il}fenil)-1-[4-(pentafluoro-lambda~6~-sulfanil)fenil]pirrolidin-2-il}fenil)-1H-imidazol-2-il]pirrolidin-1-il}-3-metil-1-oxobutan-2-il]carbamato de metilo

El producto del Ejemplo 126K se procesó usando el método descrito en Ejemplo 129. La mezcla de productos mono y diclorados se purificó mediante HPLC de fase inversa para dar el compuesto del título (33,3 mg, 7%). ^{1}H RMN (base libre) (500 MHz, DMSO-D6) δ 0,94 – 0,76 (m, 12H), 2,24 – 1,63 (m, 13H), 3,53 (d, *J* = 1,2, 6H), 3,86 – 3,68 (m, 4H), 4,10 – 3,98 (m, 2H), 5,02 – 4,93 (m, 1H), 5,06 (dd, *J* = 3,2, 7,1, 1H), 5,48 – 5,30

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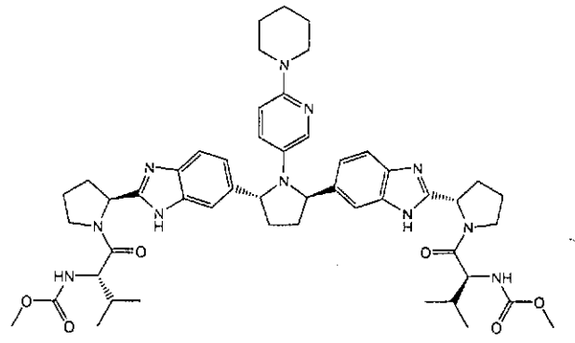
(m, 2H), 6,35 (d, *J* = 9,1, 2H), 7,21 – 7,10 (m, 2H), 7,36 – 7,21 (m, 4H), 7,58 – 7,38 (m, 4H), 7,73 – 7,59 (m, 4H), 12,50 – 11,65 (m, 2H). MS (ESI) *m/z* 1044 $(M+H)^+$, 1042 $(M-H)^+$.



Ejemplo 133

[(2S)-1-{(2S)-2-[5-(4-{(2R,5R)-5-(4-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-5-il}fenil)-1-[6-(piperidin-1-il)piridin-3-il]pirrolidin-2-il}fenil)-1H-imidazol-2-il]pirrolidin-1-il}-3-metil-1-oxobutan-2-il]carbamato de metilo

Se procesó Ejemplo 126H y 6-(piperidin-1-il)piridin-3-amina usando en forma consecutiva los métodos de Ejemplos 126I, 39E, 39F, 39I, y 26J (solvente de reacción = diclorometano) para dar el compuesto del título (91,4 mg). ^{1}H RMN (400 MHz, DMSO-D6) δ 0,85 (dt, *J* = 7,1, 14,3, 12H), 1,24 (s, 2H), 1,44 (s, 6H), 1,70 (d, *J* = 5,2, 2H), 2,04 – 1,82 (m, 6H), 2,23 – 2,04 (m, 4H), 3,21 – 3,03 (m, 4H), 3,53 (s, 6H), 3,87 – 3,67 (m, 4H), 4,12 – 3,96 (m, 2H), 5,06 (dd, *J* = 3,2, 7,0, 2H), 5,20 (t, *J* = 6,8, 2H), 6,49 (dd, *J* = 3,1, 9,1, 1H), 6,60 (dd, *J* = 2,9, 9,2, 1H), 7,20 – 7,10 (m, 4H), 7,33 – 7,20 (m, 3H), 7,38 (d, *J* = 1,8, 2H), 7,51 (t, *J* = 10,4, 1H), 7,64 (dd, *J* = 8,1, 15,7, 3H), 11,69 (s, 1,4H), 12,06 (t, *J* = 32,1, 0,6H).

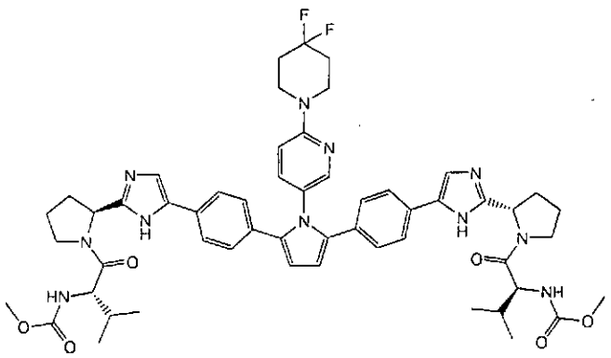


Ejemplo 134

{(2S)-1-[(2S)-2-(6-{(2R,5R)-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-bencimidazol-6-il}-1-[6-(piperidin-1-il)piridin-3-il]pirrolidin-2-il}-1H-bencimidazol-2-il)pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

Ejemplo 109C y 6-(piperidin-1-il)piridin-3-amina se procesaron usando en forma consecutiva los métodos de Ejemplos 113A, 113B, 116F (Reducción con Ra-Ni llevada a cabo en una botella de presión SS por 120 min a 30 psi a temperatura ambiente), 28I (reacción llevada a cabo a 50 °C por 4 horas), 39I, y 26J (solvente de reacción =

diclorometano) para dar el compuesto del título (71 mg). ^{1}H RMN (400 MHz, METANOL-D4) δ 0,89 (ddd, *J* = 6,5, 20,7, 26,0, 12H), 1,62 – 1,43 (m, 6H), 2,48 – 1,80 (m, 13H), 2,72 – 2,60 (m, 2H), 3,10 – 2,97 (m, 4H), 3,64 (s, 6H), 3,93 – 3,78 (m, 2H), 4,09 – 3,94 (m, 2H), 4,22 (d, *J* = 7,3, 2H), 5,21 (dd, *J* = 5,2, 7,6, 1H), 5,44 – 5,30 (m, 2H), 6,50 (d, *J* = 9,1, 1H), 6,83 – 6,71 (m, 1H), 7,59 – 7,15 (m, 7H). MS (ESI) *m/z* 916 $(M+H)^+$, 914 $(M-H)^+$.



Ejemplo 135

[(2S)-1-{(2S)-2-[5-(4-{1-[6-(4,4-difluoropiperidin-1-il)piridin-3-il]-5-(4-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-5-il}fenil)-1H-pirrol-2-il}fenil)-1H-imidazol-2-il]pirrolidin-1-il}-3-metil-1-oxobutan-2-il]carbamato de metilo

Ejemplo 135A

2-(4,4-difluoropiperidin-1-il)-5-nitropiridina

A una lechada de 2-cloro-5-nitropiridina (5 g, 31,5 mmol) y clorhidrato de 4,4-difluoropiperidina (4,97 g) en etanol (40 ml) a temperatura ambiente se agregó N,N-diisopropiletilamina (12,00 ml, 69,4 mmol) y la mezcla se calentó a 70 °C por 18 horas. La reacción se concentró, se particionó entre CH2Cl2 y NaOH 1M. La fase orgánica se concentró y se purificó mediante cromatografía (elución con 2% MeOH-CH2Cl2 luego 3% MeOH-CH2Cl2) para dar el compuesto del título como un aceite amarillo. MS (DCI) *m/z* 261 $(M+NH_4)^+$.

Ejemplo 135B

6-(4,4-difluoropiperidin-1-il)piridin-3-amina

El producto del Ejemplo 135A (4,56 g, 18,75 mmol) y solvente THF (20 ml)/DMF se agregaron a Ra-Ni 2800, lechada de agua (4,56 g, 78 mmol) en una botella de presión SS de 250 ml y se agitó por 2 hr a 30 psi y temperatura ambiente. La mezcla se filtró a través de una membrana de nylon y se lavó con MeOH. El material filtrado se concentró y se secó bajo vacío para dar el compuesto del título (3,40 g, 85%). ^{1}H RMN (400 MHz, DMSO-D6) δ 2,03 – 1,88 (m, 4H), 3,49 – 3,38 (m, 4H), 4,61 (s, 2H), 6,73 (d, *J* = 8,8, 1H), 6,93 (dd, *J* = 2,9, 8,8, 1H), 7,61 (d, *J* = 2,6, 1H). MS (ESI) *m/z* 214 $(M+H^+)$.

Ejemplo 135C

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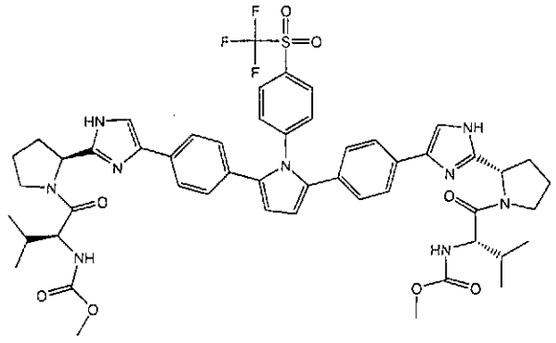
5-(2,5-bis(4-(2-((S)-pirrolidin-2-il)-1H-imidazol-5-il)fenil)-1H-pirrol-1-il)-2-(4,4-difluoropiperidin-1-il)piridina

Se agregó TFA (0,046 ml, 0,596 mmol) a una mezcla del producto del Ejemplo 138B (0,2114 g, 0,298 mmol) y el producto del Ejemplo 135B (0,095 g, 0,447 mmol) en tolueno (2,98 ml). La mezcla se calentó a 110 °C por 18 horas. La reacción se enfrió y se agregó TFA adicional (0,023 ml, 0,298 mmol) y se agitó por otra hora. El solvente se eliminó bajo presión reducida y se azeotropeó con tolueno para dar el compuesto del título.

Ejemplo 135D

[(2S)-1-{(2S)-2-[5-(4-{1-[6-(4,4-difluoropiperidin-1-il)piridin-3-il]-5-(4-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-5-il}fenil)-1H-pirrol-2-il}fenil)-1H-imidazol-2-il]pirrolidin-1-il}-3-metil-1-oxobutan-2-il]carbamato de metilo

El producto del Ejemplo 135C se procesó usando el método descrito en Ejemplo 26J para dar el compuesto del título. ^{1}H RMN (400 MHz, DMSO-D6) δ 0,94 - 0,73 (m, 12H), 2,03 - 1,82 (m, 10H), 2,20 - 2,04 (m, 4H), 3,53 (s, 6H), 3,64 (s, 4H), 3,86 - 3,69 (m, 4H), 4,04 (dd, 2H), 5,04 (dd, *J* = 3,0, 7,0, 2H), 6,53 - 6,39 (m, 2H), 6,93 - 6,79 (m, 1H), 7,06 (d, *J* = 8,4, 3H), 7,13 (dd, *J* = 10,9, 19,3, 1H), 7,30 - 7,21 (m, 2H), 7,39 - 7,30 (m, 1H), 7,42 (d, *J* = 1,7, 1H), 7,48 - 7,43 (m, 1H), 7,66 - 7,49 (m, 4H), 7,85 (dd, *J* = 2,7, 9,7, 1H), 12,16 - 11,64 (m, 2H). MS (ESI) *m/z* 1000 $(M+H)^+$, 998 $(M-H)^+$.



Ejemplo 136

{(2S)-1-[(2S)-2-(4-{4-[5-(4-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-4-il}fenil)-1-{4-[(trifluorometil)sulfonil]fenil}-1H-pirrol-2-il]fenil}-1H-imidazol-2-il)pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

Ejemplo 136A

2,5-bis(4-bromofenil)-1-(4-(trifluorometilsulfonil)fenil)-1H-pirrol

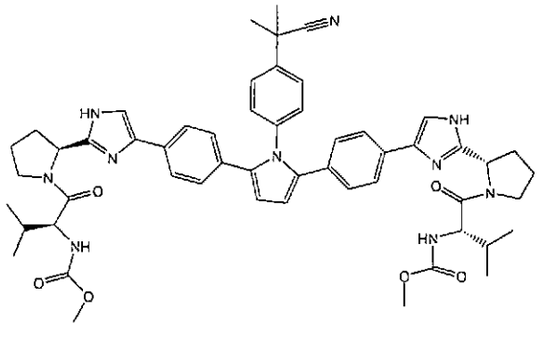
A una lechada del producto del Ejemplo 26E (0,60 g, 1,52 mmol) y 4-(trifluorometilsulfonil)anilina (0,51 g, 2,27 mmol) en tolueno (12 ml) se agregó una solución 1N de cloruro de titanio(IV) (1,6 ml, 1,6 mmol) en tolueno. La mezcla se agitó durante la

noche a temperatura ambiente y luego se calentó a reflujo por 3 horas. La mezcla fría se filtró y el residuo sólido se suspendió en una mezcla de agua y éter dietílico. El sólido se diluyó con agua y éter y se agitó enérgicamente por 15 minutos. La mezcla se filtró y luego se lavó a fondo con éter dietílico para dar el compuesto del título como una mezcla cruda que se usó en reacciones subsiguientes sin purificación adicional (0,60g, 68% de rendimiento crudo).

Ejemplo 136B

{(2S)-1-[(2S)-2-(4-{4-[5-(4-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-4-il}fenil)-1-{4-[(trifluorometil)sulfonil]fenil}-1H-pirrol-2-il]fenil}-1H-imidazol-2-il)pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

Ejemplo 136A se procesó usando en forma consecutiva los métodos de Ejemplos 26G, 26H, 65B, y 65C para dar el compuesto del título (90 mg). ^{1}H RMN (400 MHz, DMSO-D6) δ 12,20 – 11,68 (m, 2H), 8,17 – 8,04 (m, 2H), 7,63 – 7,42 (m, 8H), 7,31 – 7,15 (m, 2H), 7,02 – 6,90 (m, 4H), 6,64 – 6,53 (m, 2H), 5,08 – 4,97 (m, 2H), 4,05 – 3,97 (m, 2H), 3,83 – 3,69 (m, 4H), 3,53 (s, 6H), 2,18 – 1,79 (m, 10H), 0,90 – 0,78 (m, 12H). MS (ESI; M+H) m/z = 1013.

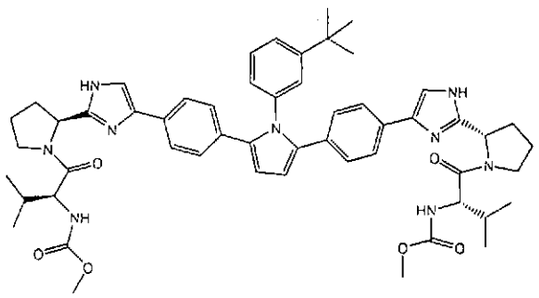


Ejemplo 137

[(2S)-1-{(2S)-2-[4-(4-{1-[4-(2-cianopropan-2-il)fenil]-5-(4-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-4-il}fenil)-1H-pirrol-2-il}fenil)-1H-imidazol-2-il]pirrolidin-1-il}-3-metil-1-oxobutan-2-il]carbamato de metilo

Ejemplo 26E y 2-(4-aminofenil)-2-metilpropanonitrilo se procesaron usando en forma consecutiva los métodos de Ejemplos 26F, 26G, 26H, 65B, y 65C para dar el compuesto del título (100 mg). ^{1}H RMN (400 MHz, DMSO-D6) δ 12,15 – 11,68 (m, 0H), 7,58 – 7,44 (m, 0H), 7,44 – 7,36 (m, 0H), 7,30 – 7,12 (m, 0H), 7,07 – 6,91 (m, 0H), 6,55 – 6,42 (m, 0H), 5,06 – 4,96 (m, 0H), 4,02 (t, *J* = 8,3, 0H), 3,81 – 3,67 (m, 0H), 3,52 (s, 0H), 2,15 – 1,82 (m, 0H), 1,65 (s, 0H), 0,90 – 0,74 (m, 1H). MS (ESI; M+H) m/z = 948.

000697



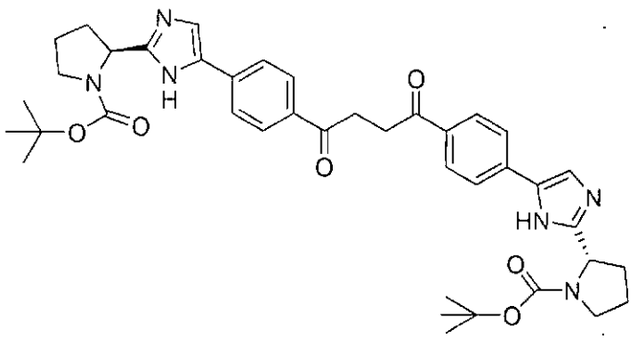
Ejemplo 138

{(2S)-1-[(2S)-2-(4-{4-[1-(3-tert-butilfenil)-5-(4-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-4-il}fenil)-1H-pirrol-2-il]fenil}-1H-imidazol-2-il)pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

Ejemplo 138A

1,4-bis(4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)butan-1,4-diona

A una solución del producto del Ejemplo 26E (2,00 g, 5,05 mmol), bis(pinacolato)diborano (3,85 g, 15,15 mmol), acetato de potasio (1,982 g, 20,20 mmol) en dimetoxietano (50 ml) a temperatura ambiente se agregó $PdCl_2(dppf)$-CH_2Cl_2 aducto (0,412 g, 0,505 mmol) y la mezcla se desgasificó (purga con N_2). La mezcla se calentó a reflujo por 1 hora. La mezcla fría se filtró a través de celite y se lavó con acetato de etilo. El material filtrado se lavó con agua, salmuera y se secó (Na_2SO_4). Luego de la filtración y la eliminación de solvente, el residuo se purificó mediante cromatografía (80 g columna; gradiente de elución entre 0% y acetato de etilo al 40%-hexanos) para dar el compuesto del título (2,22 g; 90%) como un sólido blanco. ^{1}HNMR ($CDCl_3$; 400 MHz): δ 8,02 (AA'XX', J=8,24 Hz, 4H), 7,91 (AA'XX', J=8,13 Hz, 4H), 3,47 (s, 4H), 1,36 (s, 24H).



Ejemplo 138B

(2*S*,2'*S*)-2,2'-[(1,4-dioxobutan-1,4-diil)bis(bencen-4,1-diil-1*H*-imidazol-5,2-diil)]dipirrolidin-1-carboxilato de di-*tert*-butilo

Una solución del producto del Ejemplo 138A (2,22 g, 4,53 mmol), $PdCl_2(dppf)$-CH_2Cl_2 aducto (0,37 g, 0,45 mmol), carbonato de sodio 1 M (18 ml, 18 mmol) y el producto del Ejemplo 26D (4,30 g, 13,6 mmol) en etanol (23 ml)/tolueno (23 ml) se desgasificó

000093

(purga N_2) y se calentó en baño de aceite a 90 °C durante la noche. La mezcla fría se concentró y el residuo se particionó entre agua y acetato de etilo. La fase orgánica se concentró y el residuo se purificó mediante cromatografía (gradiente de elución entre 30% y 100% acetato de etilo-hexano) para dar el compuesto del título (1,90 g, 59%) como un sólido color tostado claro. ^{1}HNMR (DMSO-d_6; 400 MHz): δ 12,06 (m, 2H), 8,04-7,96 (m, 4H), 7,89-7,78 (m, 4H), 7,69 (m, 2H), 4,85-4,75 (m, 2H), 3,53 (m, 2H), 3,35 (m, 4H), 2,24-1,87 (m, 10H), 1,39 (br s, 8H), 1,14 (br s, 10H). MS (ESI; M+H) m/z = 709.

Ejemplo 138C

(S)-4,4'-(4,4'-(1-(3-tert-butilfenil)-1H-pirrol-2,5-diil)bis(4,1-fenilen))bis(2-((S)-pirrolidin-2-il)-1H-imidazol)

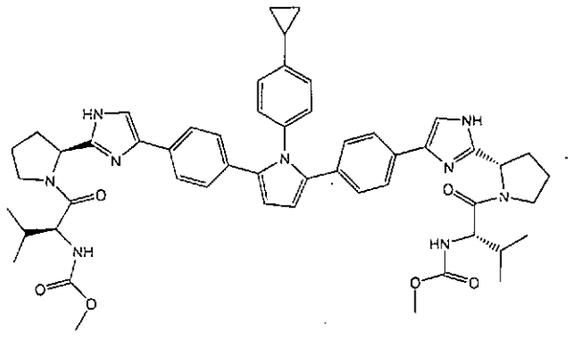
A una solución del producto del Ejemplo 138B (180 mg, 0,25 mmol) y 3-tert-butilanilina (57 mg, 0,38 mmol) en tolueno (2,0 ml) se agregó ácido trifluoroacético (39 µL 0,50 mmol). La mezcla se calentó a 110 °C durante la noche. A la mezcla fría se agregó ácido trifluoroacético (0,4 ml) y la mezcla se agitó por 1 hora a temperatura ambiente. La mezcla se concentró bajo presión reducida. El residuo se particionó entre alcohol isopropílico al 25% en $CHCl_3$ y solución saturada de bicarbonato de sodio. La capa orgánica se separó y se secó sobre Na_2SO_4, se filtró y se concentró bajo presión reducida para dar el compuesto del título.

Ejemplo 138D

{(2S)-1-[(2S)-2-(4-{4-[1-(3-tert-butilfenil)-5-(4-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-4-il}fenil)-1H-pirrol-2-il]fenil}-1H-imidazol-2-il)pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

Una solución de clorhidrato de N1-((etilimino)metilen)-N3,N3-dimetilpropan-1,3-diamina (109 mg, 0,57 mmol), hidrato de 1H-benzo[d][1,2,3]triazol-1-ol (87 mg, 0,57 mmol), ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico (100 mg, 0,57 mmol) y 4-metilmorfolina (0,14 ml, 1,0 mmol) en DMF (2,6 ml) se enfrió en un baño de hielo. A esta mezcla se agregó el producto del Ejemplo 138C (161 mg, 0,26 mmol). Se agregó 4-metilmorfolina adicional a la mezcla hasta que el pH se ajustó a 8. La reacción se agitó por 3,5 horas y luego el baño de hielo se retiró y la reacción se agitó por otras 16 horas. Luego se agregó agua a la mezcla de la reacción y el precipitado resultante se recuperó mediante filtración. El residuo se lavó con cantidades copiosas de agua seguido por éter dietílico. El producto crudo se purificó mediante cromatografía sobre gel de sílice eluyendo con un gradiente de solvente de metanol al 0-5% en CH_2Cl_2 para dar el compuesto del título (15 mg, 6% de rendimiento). ^{1}H RMN (400 MHz, DMSO-D6) δ 12,04 – 11,65 (m, 2H), 7,57 – 7,45 (m, 4H), 7,43 – 7,35 (m, 2H), 7,33 – 7,08 (m, 5H), 7,05 – 6,91 (m, 4H), 6,79 (t, *J* = 7,5, 1H), 6,53 – 6,40 (m, 2H), 5,05 – 4,99 (m, 2H), 4,02 (t, *J* = 8,3, 2H), 3,82 –

3,68 (m, 4H), 3,56 – 3,47 (m, 6H), 2,18 – 1,79 (m, 10H), 1,09 (s, 9H), 0,89 – 0,75 (m, 12H). MS (ESI; M+H) m/z = 937.



Ejemplo 139

{(2S)-1-[(2S)-2-(4-{4-[1-(4-ciclopropilfenil)-5-(4-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-4-il}fenil)-1H-pirrol-2-il]fenil}-1H-imidazol-2-il)pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

Ejemplo 139A

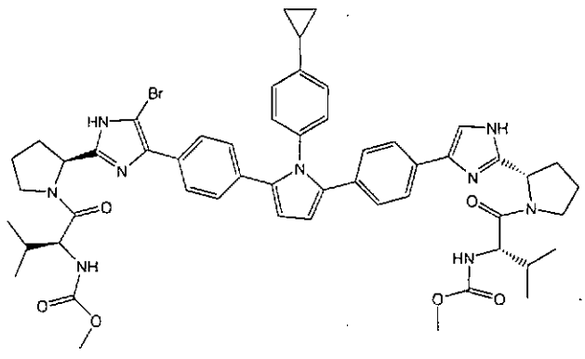
tetrakis(2,2,2-trifluoroacetato) de (S)-4,4'-(4,4'-(1-(4-ciclopropilfenil)-1H-pirrol-2,5-diil)bis(4,1-fenilen))bis(2-((S)-pirrolidin-2-il)-1H-imidazol)

A una solución del producto del Ejemplo 138B (0,30g 0,43 mmol) y 4-ciclopropilanilina (85 mg, 0,64 mmol) en tolueno (3,4 ml) se agregó ácido trifluoroacético (65 µL 0,85 mmol). La mezcla se calentó a 110 °C durante la noche. A la mezcla fría se agregó ácido trifluoroacético (1,0 ml) y la mezcla se agitó por 1 hora a temperatura ambiente. La mezcla se concentró bajo presión reducida y luego se trituró con éter dietílico para dar el compuesto del título (0,42g, 28% de rendimiento).

Ejemplo 139B

{(2S)-1-[(2S)-2-(4-{4-[1-(4-ciclopropilfenil)-5-(4-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-4-il}fenil)-1H-pirrol-2-il]fenil}-1H-imidazol-2-il)pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

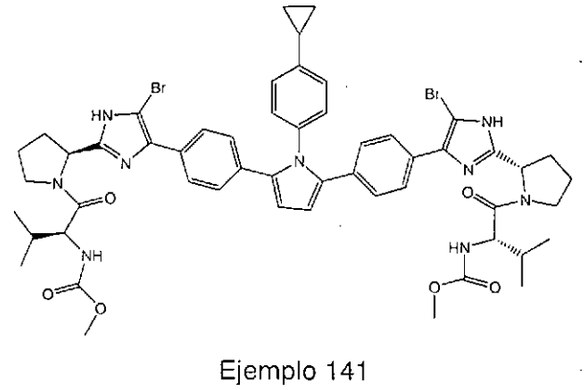
El compuesto del título se preparó usando los métodos del Ejemplo 138D utilizando el producto del Ejemplo 139A en lugar del producto del Ejemplo 138C para dar el compuesto del título (150 mg, 40% de rendimiento). ^{1}H RMN (400 MHz, DMSO-D6) δ 12,09 – 11,63 (m, 2H), 7,56 – 7,46 (m, 4H), 7,44 – 7,35 (m, 2H), 7,30 – 7,11 (m, 2H), 7,07 – 6,88 (m, 8H), 6,54 – 6,39 (m, 2H), 5,07 – 4,97 (m, 2H), 4,03 (t, *J* = 8,3, 2H), 3,83 – 3,66 (m, 4H), 3,52 (s, 6H), 2,18 – 1,79 (m, 10H), 1,26 – 1,19 (m, 1H), 0,98 – 0,90 (m, 2H), 0,90 – 0,74 (m, 12H), 0,69 – 0,60 (m, 2H). MS (ESI; M+H) m/z = 921.



Ejemplo 140

[(2S)-1-{(2S)-2-[5-bromo-4-(4-{1-(4-ciclopropilfenil)-5-[4-(2-{(2S)-1-[N-(metoxicarbonil)-L-valil]pirrolidin-2-il}-1H-imidazol-4-il)fenil]-1H-pirrol-2-il}fenil)-1H-imidazol-2-il]pirrolidin-1-il}-3-metil-1-oxobutan-2-il]carbamato de metilo

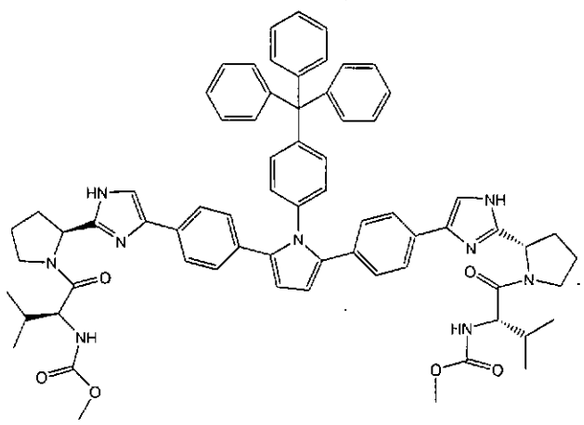
A una suspensión del producto del Ejemplo 139 (47 mg, 0,051 mmol) en CH_2Cl_2 (0,5 ml) se agregó una mezcla de 1-bromopirrolidin-2,5-diona (9,1 mg, 0,051 mmol) en CH_2Cl_2 (0,5 ml). La mezcla se agitó durante la noche a temperatura ambiente luego se concentró bajo presión reducida y se trituró con éter dietílico para dar una mezcla de compuestos bromados que se sometió a purificación HPLC de fase inversa eluyendo con un gradiente de 10-100% CH_3CN en ácido trifluoroacético acuoso al 0,1% para dar el compuesto del título (8 mg, 13% de rendimiento). ^{1}H RMN (Sal TFA) (400 MHz, DMSO-D6) δ 14,32 (s, 1H), 12,44 (s, 1H), 7,97 (s, 1H), 7,62 – 7,48 (m, 4H), 7,31 (d, *J* = 8,4, 1H), 7,24 (d, *J* = 8,5, 1H), 7,18 – 7,08 (m, 4H), 7,09 – 7,00 (m, 4H), 6,61 (d, *J* = 3,7, 1H), 6,57 (d, *J* = 3,7, 1H), 5,07 (t, *J* = 7,0, 1H), 4,98 – 4,91 (m, 1H), 4,08 (t, *J* = 7,9, 1H), 4,02 (t, *J* = 8,3, 1H), 3,90 – 3,67 (m, 4H), 3,52 (s, 3H), 3,51 (s, 3H), 2,18 – 1,83 (m, 10H), 1,22 (s, 1H), 1,01 – 0,93 (m, 2H), 0,89 – 0,72 (m, 12H), 0,70 – 0,62 (m, 2H). MS (ESI; M+H) m/z = 1000.



Ejemplo 141

{(2S)-1-[(2S)-2-(5-bromo-4-{4-[5-(4-{5-bromo-2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-4-il}fenil)-1-(4-ciclopropilfenil)-1H-pirrol-2-il]fenil}-1H-imidazol-2-il)pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

El compuesto del título se formó como un producto adicional en Ejemplo 140. La mezcla de productos se sometió a purificación HPLC de fase inversa eluyendo con un gradiente de 10-100% CH_3CN en ácido trifluoroacético acuoso al 0,1% para dar el compuesto del título (15 mg, 23% de rendimiento). ^{1}H RMN (Sal TFA) (400 MHz, DMSO-D6) δ 12,43 (s, 2H), 7,54 (dd, 4H), 7,25 (d, *J* = 8,4, 2H), 7,15 – 7,08 (m, 4H), 7,08 – 7,00 (m, 4H), 6,55 (s, 2H), 4,99 – 4,89 (m, 2H), 4,02 (t, *J* = 8,3, 2H), 3,82 – 3,68 (m, 4H), 3,51 (s, 6H), 2,22 – 2,03 (m, 4H), 2,00 – 1,81 (m, 6H), 1,27 – 1,19 (m, 1H), 1,02 – 0,92 (m, 2H), 0,90 – 0,77 (m, 12H), 0,70 – 0,61 (m, 2H). MS (ESI; M+H) m/z = 1078.



Ejemplo 142

{(2S)-1-[(2S)-2-(4-{4-[5-(4-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-4-il}fenil)-1-(4-tritilfenil)-1H-pirrol-2-il]fenil}-1H-imidazol-2-il)pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

Ejemplo 142A

tetrakis(2,2,2-trifluoroacetato) de (S)-4,4'-(4,4'-(1-(4-tritilfenil)-1H-pirrol-2,5-diil)bis(4,1-fenilen))bis(2-((S)-pirrolidin-2-il)-1H-imidazol)

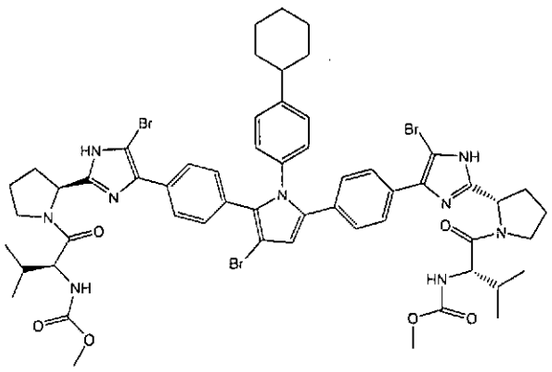
El compuesto del título se preparó usando los métodos del Ejemplo 139A utilizando 4-tritilanilina en lugar de 4-ciclopropilanilina para dar el compuesto del título.

Ejemplo 142B

{(2S)-1-[(2S)-2-(5-bromo-4-{4-[5-(4-{5-bromo-2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-4-il}fenil)-1-(4-ciclopropilfenil)-1H-pirrol-2-il]fenil}-1H-imidazol-2-il)pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

El compuesto del título se preparó usando los métodos del Ejemplo 138D utilizando el producto del Ejemplo 142A en lugar del producto del Ejemplo 138C para dar el compuesto del título (71 mg, 43% de rendimiento). ^{1}H RMN (400 MHz, DMSO-D6) δ 12,15 – 11,69 (m, 2H), 7,61 – 7,48 (m, 4H), 7,46 – 7,37 (m, 2H), 7,35 – 7,15 (m, 11H), 7,10 – 6,91 (m, 14H), 6,55 – 6,44 (m, 2H), 5,11 – 5,00 (m, 2H), 4,03 (t, *J* = 8,5, 2H), 3,86 – 3,70 (m, 4H), 3,52 (s, 6H), 2,21 – 1,83 (m, 10H), 0,92 – 0,76 (m, 12H). MS (ESI; M+H) m/z

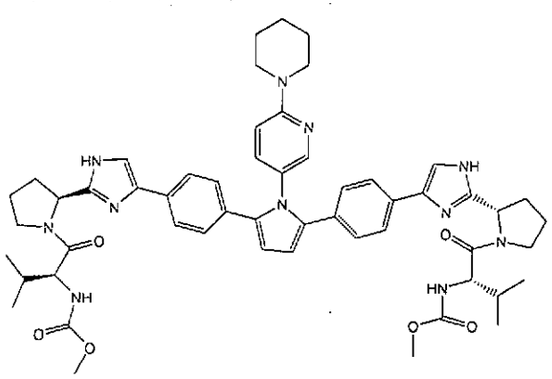
= 1123.



Ejemplo 143

{(2S)-1-[(2S)-2-(5-bromo-4-{4-[4-bromo-5-(4-{5-bromo-2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-4-il}fenil)-1-(4-ciclohexilfenil)-1H-pirrol-2-il]fenil}-1H-imidazol-2-il)pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

A una suspensión del producto del Ejemplo 74 (100 mg, 0,10 mmol) en CH_2Cl_2 (1,0 ml) a -78 °C se agregó una mezcla de 1-bromopirrolidin-2,5-diona (59 mg, 0,33 mmol) en CH_2Cl_2 (1,0 ml). La mezcla se agitó por 3 horas, se calentó a temperatura ambiente, luego se concentró bajo presión reducida y se trituró con éter dietílico para dar el compuesto del título (103 mg, 83% de rendimiento). ^{1}H RMN (400 MHz, DMSO-D6) δ 12,47 (s, 1H), 11,02 (s, 1H), 7,54 (d, *J* = 26,1, 4H), 7,29 – 6,98 (m, 10H), 6,71 (s, 1H), 5,01 – 4,90 (m, 2H), 4,02 (t, *J* = 8,1, 2H), 3,86 – 3,67 (m, 4H), 3,52 (s, 6H), 2,18 – 1,58 (m, 16H), 1,35 – 1,20 (m, 5H), 0,90 – 0,76 (m, 12H). MS (ESI; M+H) m/z = 1200.



Ejemplo 144

[(2S)-1-{(2S)-2-[4-(4-{5-(4-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-4-il}fenil)-1-[6-(piperidin-1-il)piridin-3-il]-1H-pirrol-2-il}fenil)-1H-imidazol-2-il]pirrolidin-1-il}-3-metil-1-oxobutan-2-il]carbamato de metilo

Ejemplo 144A

5-nitro-2-(piperidin-1-il)piridina

000703

A una lechada de 2-cloro-5-nitropiridina (100 g, 632 mmol) en etanol (2000 ml) a temperatura ambiente se agregó piperidina (206 ml, 2,08 mol) y la mezcla se calentó a 60 °C por 30 minutos. La mezcla fría se concentró y el residuo se recogió con CH_2Cl_2, luego se lavó con $NaHCO_3$ saturado y salmuera. La mezcla se secó (Na_2SO_4), se filtró, y se concentró para dar el compuesto del título como un sólido amarillo (130,4g, 99% de rendimiento). ^{1}H RMN (400 MHz, DMSO-D6) δ 8,94 (d, *J* = 2,9, 1H), 8,17 (dd, *J* = 9,6, 2,9, 1H), 6,93 (d, *J* = 9,6, 1H), 3,79 – 3,73 (m, 4H), 1,69 – 1,64 (m, 2H), 1,61 – 1,51 (m, 4H).

Ejemplo 144B

6-(piperidin-1-il)piridin-3-ilcarbamato de tert-butilo

A una solución del producto del Ejemplo 144A (130,4g, 629 mmol) y dicarbonato de di-tert-butilo (165g, 755 mmol) en etanol (750 ml) se agregó PtO_2 (5,4g, 24 mmol). La mezcla se presurizó a 40 psi con H_2 y se agitó durante la noche a temperatura ambiente. Para asegurar una reacción completa se agregó PtO_2 adicional (3,2g, 14 mmol) y la mezcla presurizada se calentó a 50 °C por 1 hora. La mezcla luego se filtró, se concentró bajo presión reducida y se adsorbió en gel de sílice y se colocó por encima de un tapón de entre 4 y 5" de sílice en un embudo de vidrio sinterizado de 3000 ml. El material se eluyó con éter dietílico al 15% en CH_2Cl_2 y el material filtrado se concentró bajo presión reducida y el residuo se trituró con hexanos en ebullición. S recuperó producto adicional con la concentración del material filtrado, el cual luego se cromatografió sobre gel de sílice eluyendo con éter dietílico al 10% en CH_2Cl_2. Las fracciones apropiadas se recogieron y se concentró luego se trituró con hexanos en ebullición. Los dos lotes de sólidos color lavanda se combinaron para dar el compuesto del título (100g, 57% de rendimiento). ^{1}H RMN (400 MHz, DMSO) δ 9,02 (bs, 1H), 8,11 (s, 1H), 7,63 – 7,54 (m, 1H), 6,74 (d, *J* = 9,1, 1H), 3,42 – 3,37 (m, 4H), 1,57 – 1,49 (m, 6H), 1,45 (9, 1H).

Ejemplo 144C

diclorhidrato de 6-(piperidin-1-il)piridin-3-amina

El producto del Ejemplo 144B (1,00 g, 3,62 mmol) se agregó lentamente a ácido clorhídrico 4 M (10 ml, 40 mmol) y se agitó a temperatura ambiente. Luego de agitar durante la noche, se agregó éter y el sólido se filtró. Se secó en horno de vacío a un sólido blanco (0,817 g; 84%). ^{1}H RMN (400 MHz, metanol-d4) δ 1,77 (s, 6H), 3,65 (s, 4H), 7,41 (d, J=9,8 Hz, 1H), 7,70 (d, J=2,6 Hz, 1H), 7,79 (dd, J=2,7, 9,8 Hz, 1H).

Ejemplo 144D

5-(2,5-bis(4-(2-((S)-pirrolidin-2-il)-1H-imidazol-4-il)fenil)-1H-pirrol-1-il)-2-(piperidin-1-il)piridina

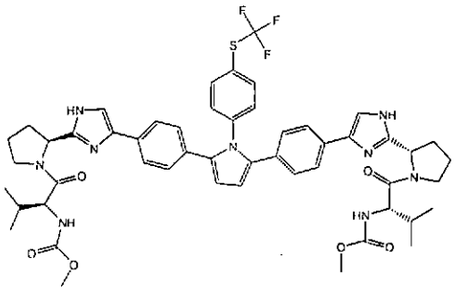
A una solución del producto del Ejemplo 138B (0,20 g, 0,28 mmol) y el producto

del Ejemplo 144C (0,11 g, 0,42 mmol) en tolueno (2,8 ml) se agregó TFA (22 µL, 0,28 mmol). La mezcla se agitó a 110 °C por 3 horas. A la mezcla fría se agregó TFA (0,5 ml) y la mezcla se agitó por 1 h a temperatura ambiente. El solvente luego se eliminó bajo presión reducida y se trituró con éter dietílico y se secó para dar 0,31 g del compuesto deseado como una sal TFA. ^{1}HNMR (DMSO-d_6; 400 MHz): δ 9,78 (br s, 2H), 7,84 (d, J=2,71 Hz, 1H), 7,75 (s, 2H), 7,67 (AA'XX', J=8,34 Hz, 4H), 7,35 (dd, J=9,11, 2,71 Hz, 1H), 7,18 (AA'XX', J=8,46 Hz, 4H), 6,79 (d, J=9,11 Hz, 1H), 6,53 (s, 2H), 4,79 (app t, J=7,81 Hz, 2H), 3,4-3,2 (m, 4H), 2,44-2,36 (m, 2H), 2,25-1,98 (m, 6H), 1,65-1,45 (m, 6H).

Ejemplo 144E

[(2S)-1-{(2S)-2-[4-(4-{5-(4-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-4-il}fenil)-1-[6-(piperidin-1-il)piridin-3-il]-1H-pirrol-2-il}fenil)-1H-imidazol-2-il]pirrolidin-1-il}-3-metil-1-oxobutan-2-il]carbamato de metilo

A una solución de clorhidrato de N1-((etilimino)metilen)-N3,N3-dimetilpropan-1,3-diamina (0,17 g, 0,89 mmol), hidrato de 1H-benzo[d][1,2,3]triazol-1-ol (0,14 g, 0,89 mmol), ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico (0,16 g, 0,89 mmol) en DMF (1,0 ml) se agregó 4-metilmorfolina (0,3 ml, 2,7 mmol). Esta mezcla se agitó a temperatura ambiente por 15 minutos y luego se agregó a una solución del producto del Ejemplo 144D (0,31 g, 0,25 mmol) y 4-metilmorfolina (0,2 ml, 1,8 mmol) en DMF (0,7 ml). Luego de agitar 4 h, se agregó agua a esta mezcla y el sólido se recogió mediante filtración luego se lavó con agua y éter dietílico. El residuo se purificó sobre gel de sílice eluyendo con 60% THF/Hexanos para dar 100 mg del compuesto del título. ^{1}H RMN (400 MHz, DMSO) δ 12,17 – 11,70 (m, 2H), 7,84 – 7,76 (m, 1H), 7,64 – 7,50 (m, 4H), 7,49 – 7,40 (m, 2H), 7,31 – 7,02 (m, 7H), 6,76 – 6,69 (m, 1H), 6,52 – 6,41 (m, 2H), 5,09 – 5,01 (m, 2H), 4,04 (t, *J* = 8,3, 2H), 3,83 – 3,71 (m, 4H), 3,53 (s, 6H), 3,50 – 3,44 (m, 4H), 2,18 – 2,04 (m, 4H), 2,03 – 1,86 (m, 6H), 1,61 – 1,46 (m, 6H), 0,90 – 0,79 (m, 12H). MS (ESI; M+H) m/z = 965.

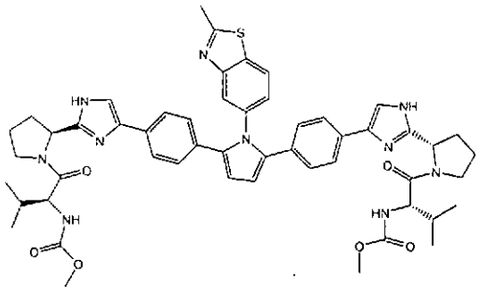


Ejemplo 145

{(2S)-1-[(2S)-2-(4-{4-[5-(4-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-4-il}fenil)-1-{4-[(trifluorometil)sulfanil]fenil}-1H-pirrol-2-il]fenil}-1H-imidazol-2-il)pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

000705

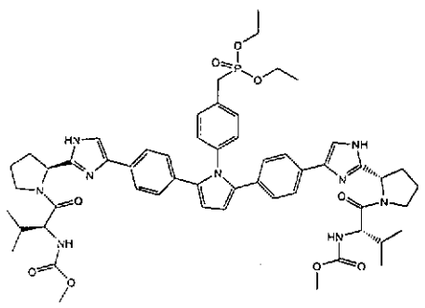
Ejemplo 138B y 4-(trifluorometiltio)anilina se procesaron usando los métodos de Ejemplos 139A y 138D para dar el compuesto del título (19 mg). ^{1}H RMN (400 MHz, DMSO-D6) δ 12,18 – 11,65 (m, 2H), 7,73 – 7,63 (m, 2H), 7,60 – 7,48 (m, 4H), 7,45 – 7,39 (m, 2H), 7,31 – 7,15 (m, 4H), 7,06 – 6,92 (m, 4H), 6,58 – 6,46 (m, 2H), 5,08 – 5,00 (m, 2H), 4,03 (t, *J* = 8,4, 2H), 3,85 – 3,69 (m, 4H), 3,53 (s, 6H), 2,23 – 1,79 (m, 10H), 0,93 – 0,77 (m, 12H). MS (ESI; M+H) m/z = 981.



Ejemplo 146

{(2S)-1-[(2S)-2-(4-{4-[5-(4-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-4-il}fenil)-1-(2-metil-1,3-benzotiazol-5-il)-1H-pirrol-2-il]fenil}-1H-imidazol-2-il)pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

Se procesó Ejemplo 138B y diclorhidrato de 2-metilbenzo[d]tiazol-5-amina se procesaron usando los métodos de Ejemplos 139A y 138D para dar el compuesto del título (19 mg). ^{1}H RMN (400 MHz, DMSO-D6) δ 12,04 – 11,63 (m, 2H), 8,02 – 6,85 (m, 15H), 6,58 – 6,45 (m, 2H), 5,07 – 4,96 (m, 2H), 4,02 (t, *J* = 8,4, 2H), 3,86 – 3,67 (m, 4H), 3,53 (s, 6H), 2,75 (s, 3H), 2,21 – 1,78 (m, 10H), 0,93 – 0,76 (m, 12H). MS (ESI; M+H) m/z = 952.



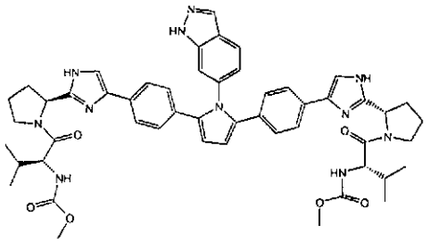
Ejemplo 147

(4-{2,5-bis[4-(2-{(2S)-1-[N-(metoxicarbonil)-L-valil]pirrolidin-2-il}-1H-imidazol-4-il)fenil]-1H-pirrol-1-il}bencil)fosfonato de dietilo

Se procesó Ejemplo 138B y 4-aminobencilfosfonato de dietilo usando los métodos de Ejemplos 139A y 138D para dar el compuesto del título. ^{1}H RMN (400 MHz, DMSO-D6) δ 12,19 – 11,63 (m, 2H), 7,56 – 7,44 (m, 4H), 7,42 – 7,34 (m, 2H), 7,32 – 7,10 (m, 4H), 7,10 – 6,91 (m, 6H), 6,53 – 6,40 (m, 2H), 5,10 – 4,98 (m, 2H), 4,03 (t, *J* = 8,4, 2H), 3,91 –

000706

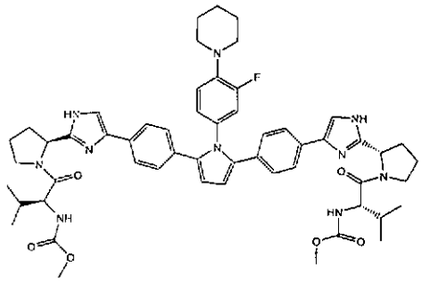
3,67 (m, 8H), 3,53 (s, 6H), 3,23 (d, *J* = 21,8, 2H), 2,22 – 1,80 (m, 10H), 1,15 – 1,04 (m, 6H), 0,92 – 0,77 (m, 12H). MS (ESI; M+H) m/z = 1031.



Ejemplo 148

{(2S)-1-[(2S)-2-(4-{4-[1-(1H-indazol-6-il)-5-(4-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-4-il}fenil)-1H-pirrol-2-il]fenil}-1H-imidazol-2-il)pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

Se procesó Ejemplo 138B y 1H-indazol-6-amina usando los métodos de Ejemplos 139A y 138D para dar el compuesto del título (24 mg). ^{1}H RMN (400 MHz, DMSO-D6) δ 13,08 – 12,99 (m, 1H), 12,05 – 11,62 (m, 2H), 8,13 – 8,04 (m, 1H), 7,74 – 7,66 (m, 1H), 7,54 – 7,42 (m, 4H), 7,41 – 7,34 (m, 2H), 7,31 – 7,09 (m, 3H), 7,05 – 6,77 (m, 5H), 6,58 – 6,47 (m, 2H), 5,06 – 4,97 (m, 2H), 4,02 (t, *J* = 8,4, 2H), 3,83 – 3,66 (m, 4H), 3,53 (s, 6H), 2,20 – 1,78 (m, 10H), 0,89 – 0,76 (m, 12H). MS (ESI; M+H) m/z = 921.

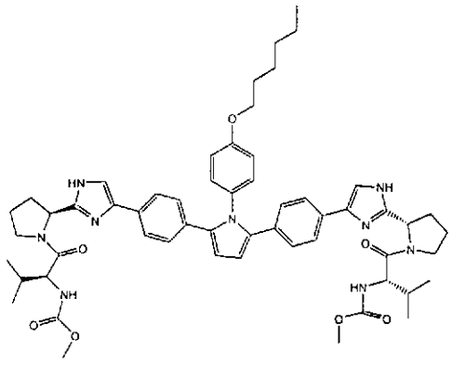


Ejemplo 149

[(2S)-1-{(2S)-2-[4-(4-{1-[3-fluoro-4-(piperidin-1-il)fenil]-5-(4-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-4-il}fenil)-1H-pirrol-2-il}fenil)-1H-imidazol-2-il]pirrolidin-1-il}-3-metil-1-oxobutan-2-il]carbamato de metilo

Ejemplo 138B y 3-fluoro-4-(piperidin-1-il)anilina se procesaron usando los métodos de Ejemplos 139A y 138D para dar el compuesto del título. ^{1}H RMN (400 MHz, DMSO-D6) δ 12,15 – 11,69 (m, 2H), 7,62 – 7,49 (m, 4H), 7,48 – 7,39 (m, 2H), 7,32 – 7,15 (m, 2H), 7,12 – 6,77 (m, 7H), 6,52 – 6,42 (m, 2H), 5,08 – 4,99 (m, 2H), 4,04 (t, *J* = 8,4, 2H), 3,84 – 3,70 (m, 4H), 3,53 (s, 6H), 3,01 – 2,89 (m, 4H), 2,19 – 1,82 (m, 10H); 1,68 – 1,43 (m, 6H), 0,92 – 0,75 (m, 12H). MS (ESI; M+H) m/z = 982.

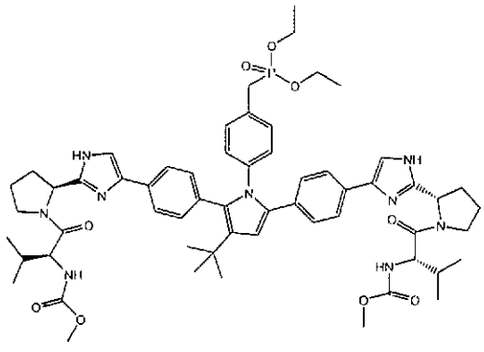
000707



Ejemplo 150

[(2S)-1-{(2S)-2-[4-(4-{1-[4-(hexiloxi)fenil]-5-(4-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-4-il}fenil)-1H-pirrol-2-il}fenil)-1H-imidazol-2-il]pirrolidin-1-il}-3-metil-1-oxobutan-2-il]carbamato de metilo

Se procesó Ejemplo 138B y 4-(hexiloxi)anilina usando los métodos de Ejemplos 139A y 138D para dar el compuesto del título (15 mg). ^{1}H RMN (400 MHz, DMSO-D6) δ 12,12 – 11,67 (m, 2H), 7,59 – 7,48 (m, 4H), 7,45 – 7,39 (m, 2H), 7,30 – 7,13 (m, 2H), 7,08 – 6,96 (m, 6H), 6,90 – 6,83 (m, 2H), 6,52 – 6,42 (m, 2H), 5,07 – 5,01 (m, 2H), 4,04 (t, *J* = 8,5, 2H), 3,92 (t, *J* = 6,4, 2H), 3,83 – 3,70 (m, 4H), 3,53 (s, 6H), 2,19 – 1,83 (m, 10H), 1,73 – 1,63 (m, 2H), 1,45 – 1,21 (m, 6H), 0,92 – 0,77 (m, 15H). MS (ESI; M+H) m/z = 981.

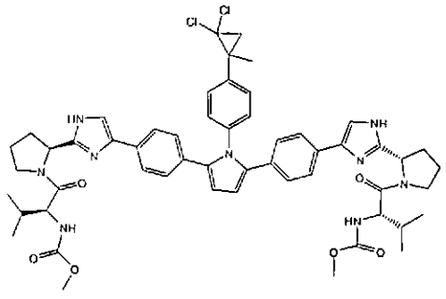


Ejemplo 151

(4-{3-tert-butil-2,5-bis[4-(2-{(2S)-1-[N-(metoxicarbonil)-L-valil]pirrolidin-2-il}-1H-imidazol-4-il)fenil]-1H-pirrol-1-il}bencil)fosfonato de dietilo

El compuesto del título se formó como un producto adicional del Ejemplo 147. La mezcla de productos se purificó mediante cromatografía sobre gel de sílice eluyendo con un gradiente de solvente de metanol al 0-5% en CH_2Cl_2 para dar el compuesto del título. ^{1}H RMN (400 MHz, DMSO-D6) δ 11,68 (d, *J* = 13,5, 2H), 7,55 – 7,39 (m, 5H), 7,37 – 7,23 (m, 3H), 7,21 – 6,90 (m, 8H), 6,43 (s, 1H), 5,07 – 4,99 (m, 2H), 4,06 – 3,97 (m, 2H), 3,83 – 3,58 (m, 8H), 3,53 (s, 6H), 3,07 (d, *J* = 21,5, 2H), 2,20 – 1,81 (m, 10H), 1,15 (s, 9H), 0,98 (t, *J* = 7,0, 6H), 0,90 – 0,78 (m, 12H). MS (ESI; M+H) m/z = 1087.

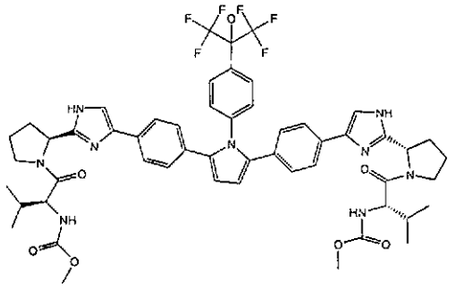
000708



Ejemplo 152

[(2S)-1-{(2S)-2-[4-(4-{1-[4-(2,2-dicloro-1-metilciclopropil)fenil]-5-(4-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-4-il}fenil)-1H-pirrol-2-il}fenil)-1H-imidazol-2-il]pirrolidin-1-il}-3-metil-1-oxobutan-2-il]carbamato de metilo

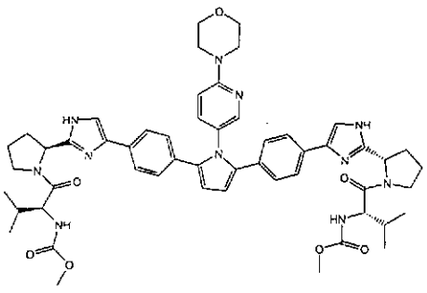
Ejemplo 138B y 4-(2,2-dicloro-1-metilciclopropil)anilina se procesaron usando los métodos de Ejemplos 139A y 138D para dar el compuesto del título (36 mg). ^{1}H RMN (400 MHz, DMSO-D6) δ 12,18 – 11,68 (m, 2H), 7,55 – 7,42 (m, 4H), 7,41 – 7,22 (m, 6H), 7,17 – 6,90 (m, 6H), 6,57 – 6,44 (m, 2H), 5,08 – 5,00 (m, 2H), 4,03 (t, *J* = 8,3, 2H), 3,86 – 3,69 (m, 4H), 3,53 (s, 6H), 2,22 (t, *J* = 8,5, 1H), 2,18 – 1,81 (m, 10H), 1,79 – 1,72 (m, 1H), 1,65 (s, 3H), 0,92 – 0,77 (m, 12H). MS (ESI; M+H) m/z = 1003.



Ejemplo 153

[(2S)-1-{(2S)-2-[4-(4-{1-[4-(1,1,1,3,3,3-hexafluoro-2-hidroxipropan-2-il)fenil]-5-(4-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-4-il}fenil)-1H-pirrol-2-il}fenil)-1H-imidazol-2-il]pirrolidin-1-il}-3-metil-1-oxobutan-2-il]carbamato de metilo

Se procesó Ejemplo 138B y 2-(4-aminofenil)-1,1,1,3,3,3-hexafluoropropan-2-ol usando los métodos de Ejemplos 139A y 138D para dar el compuesto del título (45 mg). ^{1}H RMN (400 MHz, DMSO-D6) δ 12,08 – 11,71 (m, 2H), 8,80 (s, 1H), 8,01 – 7,37 (m, 8H), 7,33 – 7,13 (m, 4H), 7,06 – 6,89 (m, 4H), 6,57 – 6,47 (m, 2H), 5,03 (d, *J* = 6,8, 2H), 4,03 (t, *J* = 8,4, 2H), 3,77 (d, *J* = 6,2, 4H), 3,53 (s, 6H), 2,21 – 1,80 (m, 10H), 0,92 – 0,76 (m, 12H). MS (ESI; M+H) m/z = 1047.



Ejemplo 154 [(2S)-1-{(2S)-2-[4-(4-{5-(4-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-4-il}fenil)-1-[6-(morfolin-4-il)piridin-3-il]-1H-pirrol-2-il}fenil)-1H-imidazol-2-il]pirrolidin-1-il}-3-metil-1-oxobutan-2-il]carbamato de metilo

Ejemplo 154A

4-(5-nitropiridin-2-il)morfolina

El compuesto del título se preparó usando los métodos del Ejemplo 144A utilizando morfolina en lugar de piperidina para dar el compuesto del título.

Ejemplo 154B

6-morfolinopiridin-3-amina

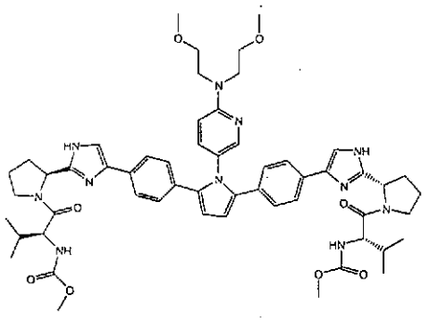
A una solución del producto del Ejemplo 154A (12,5, 59,5 mmol) en THF (150 ml) se agregó a Ra-Ni 2800, lechada de agua (12,5 g, 212 mmol) en una botella SS de presión de 500 ml. La mezcla se presurizó (H_2, 30 psi) y se agitó por 2 horas a temperatura ambiente. La mezcla se filtró y luego se concentró bajo presión reducida para dar el compuesto del título.

Ejemplo 154C

[(2S)-1-{(2S)-2-[4-(4-{5-(4-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-4-il}fenil)-1-[6-(morfolin-4-il)piridin-3-il]-1H-pirrol-2-il}fenil)-1H-imidazol-2-il]pirrolidin-1-il}-3-metil-1-oxobutan-2-il]carbamato de metilo

Ejemplo 138B y Ejemplo 154B se procesaron usando los métodos de Ejemplos 139A y 138D para dar el compuesto del título. ^{1}H RMN (400 MHz, DMSO-D6) δ 12,16 – 11,69 (m, 2H), 7,89 – 7,80 (m, 1H), 7,63 – 7,50 (m, 4H), 7,50 – 7,40 (m, 2H), 7,39 – 7,02 (m, 7H), 6,80 – 6,71 (m, 1H), 6,52 – 6,41 (m, 2H), 5,10 – 5,00 (m, 2H), 4,04 (t, *J* = 8,7, 2H), 3,85 – 3,72 (m, 4H), 3,69 – 3,59 (m, 4H), 3,53 (s, 6H), 3,45 – 3,37 (m, 4H), 2,20 – 1,82 (m, 10H), 0,94 – 0,77 (m, 12H). MS (ESI; M+H) m/z = 967.

000710



Ejemplo 155

{(2S)-1-[(2S)-2-(4-{4-[1-{6-[bis(2-metoxietil)amino]piridin-3-il}-5-(4-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-4-il}fenil)-1H-pirrol-2-il]fenil}-1H-imidazol-2-il)pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

Ejemplo 155A

N,N-bis(2-metoxietil)-5-nitropiridin-2-amina

El compuesto del título se preparó usando los métodos del Ejemplo 144A utilizando bis(2-metoxietil)amina en lugar de piperidina para dar el compuesto del título.

Ejemplo 155B

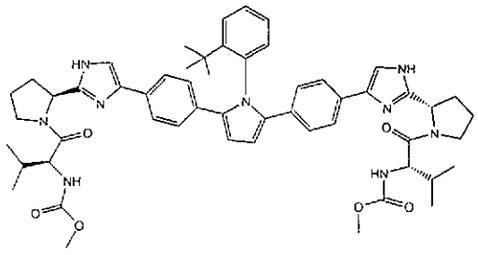
N2,N2-bis(2-metoxietil)piridin-2,5-diamina

Ejemplo 155A se procesó usando los métodos de Ejemplo 154B para dar el compuesto del título.

Ejemplo 155C

{(2S)-1-[(2S)-2-(4-{4-[1-{6-[bis(2-metoxietil)amino]piridin-3-il}-5-(4-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-4-il}fenil)-1H-pirrol-2-il]fenil}-1H-imidazol-2-il)pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

Se procesó Ejemplo 138B y Ejemplo 155B usando los métodos de Ejemplos 139A y 138D para dar el compuesto del título. ^{1}H RMN (400 MHz, DMSO-D6) δ 12,17 – 11,67 (m, 2H), 7,86 – 7,77 (m, 1H), 7,63 – 7,49 (m, 4H), 7,49 – 7,38 (m, 2H), 7,34 – 7,20 (m, 3H), 7,20 – 7,03 (m, 4H), 6,64 – 6,56 (m, 1H), 6,52 – 6,40 (m, 2H), 5,09 – 5,00 (m, 2H), 4,04 (t, *J* = 8,2, 2H), 3,84 – 3,69 (m, 4H), 3,65 – 3,57 (m, 4H), 3,53 (s, 6H), 3,47 – 3,40 (m, 4H), 3,21 (s, 6H), 2,20 – 1,84 (m, 10H), 0,84 (m, 12H). MS (ESI; M+H) m/z = 1013.

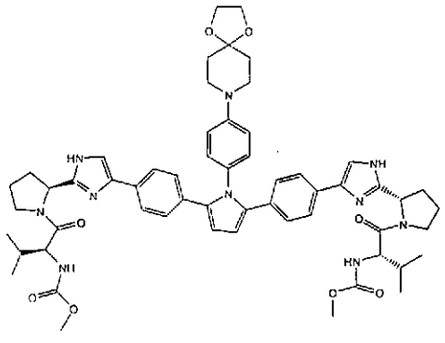


Ejemplo 156

000711

{(2S)-1-[(2S)-2-(4-{4-[1-(2-tert-butilfenil)-5-(4-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-4-il}fenil)-1H-pirrol-2-il]fenil}-1H-imidazol-2-il)pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

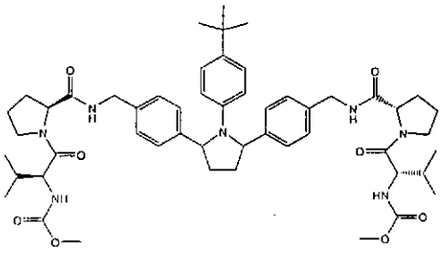
Ejemplo 138B y 2-tert-butilanilina se procesaron usando los métodos de Ejemplos 139A y 138D para dar el compuesto del título (10 mg). ^{1}H RMN (400 MHz, DMSO-D6) δ 12,07 – 11,64 (m, 2H), 7,61 – 7,11 (m, 12H), 7,06 – 6,93 (m, 4H), 6,65 – 6,49 (m, 2H), 5,08 – 4,97 (m, 2H), 4,04 (t, *J* = 7,2, 2H), 3,82 – 3,69 (m, 4H), 3,53 (s, 6H), 2,17 – 1,83 (m, 10H), 0,92 – 0,77 (m, 21H). MS (ESI; M+H) m/z = 937.



Ejemplo 157

[(2S)-1-{(2S)-2-[4-(4-{1-[4-(1,4-dioxa-8-azaespiro[4,5]dec-8-il)fenil]-5-(4-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-4-il}fenil)-1H-pirrol-2-il}fenil)-1H-imidazol-2-il]pirrolidin-1-il}-3-metil-1-oxobutan-2-il]carbamato de metilo

Se procesó Ejemplo 138B y 4-(1,4-dioxa-8-azaespiro[4,5]decan-8-il)anilina usando los métodos de Ejemplos 139A y 138D para dar el compuesto del título (156 mg). ^{1}H RMN (400 MHz, DMSO-D6) δ 12,06 – 11,65 (m, 2H), 7,59 – 7,46 (m, 4H), 7,44 – 7,36 (m, 2H), 7,30 – 7,13 (m, 2H), 7,09 – 6,96 (m, 4H), 6,90 (p, 4H), 6,53 – 6,39 (m, 2H), 5,08 – 4,98 (m, 2H), 4,04 (t, *J* = 8,4, 2H), 3,90 (s, 4H), 3,86 – 3,71 (m, 4H), 3,53 (s, 6H), 3,29 – 3,20 (m, 4H), 2,19 – 1,83 (m, 10H), 1,73 – 1,64 (m, 4H), 0,93 – 0,77 (m, 12H). MS (ESI; M+H) m/z = 1022.



Ejemplo 158

([1-(4-tert-butilfenil)pirrolidin-2,5-diil]bis{bencen-4,1-diilmetandiilcarbamoil(2S)pirrolidin-2,1-diil[(2S)-3-metil-1-oxobutan-1,2-diil]})biscarbamato de dimetilo

Ejemplo 158A

000712

4,4'-(1-(4-tert-butilfenil)pirrolidin-2,5-diil)dibenzonitrilo

Una solución de Ejemplo 42C (2,0 g, 3,9 mmol) y cianuro de cobre(I) (1,047 g, 11,69 mmol) en DMF (19 ml) se calentó en a microondas por 7 horas a 160 °C. Luego la mezcla se vertió en agua (700 ml) y luego se concentró hidróxido de amonio (40 ml) se agregó y la solución se extrajo con EtOAc. El extracto orgánico se secó, se filtró, se concentró y el residuo se purificó mediante cromatografía flash (gel de sílice, EtOAc/hexanos) para dar 1,23 g (78%) del compuesto del título. MS (ESI) m/z 406 (M+H)+.

Ejemplo 158B

4,4'-(1-(4-tert-butilfenil)pirrolidin-2,5-diil)bis(4,1-fenilen)dimetanamina

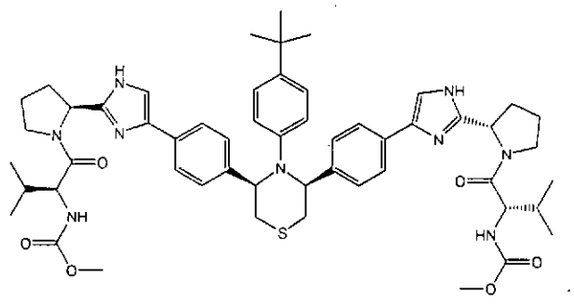
A una solución de Ejemplo 158A (0,63 g, 1,554 mmol) en THF (21 ml) se agregó hidruro de litio y aluminio (0,236 g, 6,21 mmol) luego se agitó a temperatura ambiente por 20 minutos y a 70 °C por 1 hora. La mezcla luego se enfrió en un baño de hielo y una solución de cloruro de amonio acuoso saturado se agregó seguido por extracción con EtOAc y la capa orgánica se extrajo con solución de Rochelle. La solución orgánica luego se secó, se filtró y se concentró para dar el compuesto del título. MS (ESI) m/z 414 (M+H)+.

Ejemplo 158C

([1-(4-tert-butilfenil)pirrolidin-2,5-diil]bis{bencen-4,1-diilmetanediilcarbamoil(2S)pirrolidin-2,1-diil[(2S)-3-metil-1-oxobutan-1,2-diil]})biscarbamato de dimetilo

El producto del Ejemplo 158B (45 mg, 0,109 mmol), el producto del Ejemplo 37B (62,2 mg, 0,228 mmol) y HATU (91 mg, 0,239 mmol) en DMSO (3 ml) se agregó base de Hunig (0,095 ml, 0,544 mmol), y la mezcla de la reacción se agitó a temperatura ambiente por 1 hr. La mezcla de la reacción se particionó entre agua y diclorometano, y la capa orgánica se secó sobre $MgSO_4$, se filtró y se concentró. La purificación mediante cromatografía flash (gel de sílice, 0-10% metanol/diclorometano) dio 55 mg (55%) del compuesto del título como una mezcla de estereoisómeros. 1H RMN (400 MHz, DMSO-D6) δ ppm 8,11 (m, 2 H), 7,08 (s, 2 H), 6,95 (m, 8 H), 6,74 (d, *J*=8,8 Hz, 2 H), 5,97 (d, *J*=8,7 Hz, 2 H), 5,01 (m, 2H), 4,15 (m, 4H), 4,05 (m, 4 H), 3,80 (m, 2 H), 3,31 (s, 6 H), 2,40 (m, 2 H), 1,90 (m, 2 H), 1,85 (m, 4 H), 1,80 (m, 4 H), 0,95 (s, 9 H), 0,70 (m, 2H), 0,65 (m, 12 H); MS (ESI) m/z 923 (M+H)+.

000713



Ejemplo 159

{(2S)-1-[(2S)-2-(4-{4-[(3S,5R)-4-(4-tert-butilfenil)-5-(4-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-4-il}fenil)tiomorfolin-3-il]fenil}-1H-imidazol-2-il)pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

Ejemplo 159A

2,2'-tiobis(1-(4-bromofenil)etanona)

Una solución de 2-bromo-1-(4-bromofenil)etanona (27,8 g, 100 mmol) se disolvió en acetona, la solución se enfrió en un baño de hielo luego se agregó sulfuro de sodio nonahidratado (12,01 g, 50 mmol) disuelto en agua (100 ml) por goteo a lo largo de 45 minutos. La solución resultante se agitó otras 2 horas a temperatura ambiente, el sólido formado en la reacción se recogió y luego se lavó con agua luego etanol y se secó en un horno de vacío para dar 18,5 g (43%) del compuesto del título.

Ejemplo 159B

2,2'-tiobis(1-(4-bromofenil)etanol)

A una solución de Ejemplo 159A (5,0 g, 11,68 mmol) en etanol (78 ml) se agregó borhidruro de sodio (0,972 g, 25,7 mmol) por porciones y la mezcla se agitó a temperatura ambiente por 20 minutos. Luego la solución se concentró, luego se agregó una solución de ácido clorhídrico acuoso 1N (100 ml) y se extrajo con EtOAc. El extracto orgánico se secó, se filtró y se concentró a 5,05 g (100%) de un líquido incoloro como el compuesto del título.

Ejemplo 159C

N,N'-(2,2'-tiobis(1-(4-bromofenil)etan-2,1-diil))bis(4-tert-butilanilina)

A una solución de Ejemplo 159B (5,05 g, 11,68 mmol) en THF (145 ml) y diclorometano (145 ml) se agregó trietilamina (4,86 ml, 35,1 mmol) y la mezcla se enfrió en un baño de hielo. A esta solución se agregó cloruro de metansulfonilo (2,276 ml, 29,2 mmol) por goteo seguido por agitación a 0 °C por 30 minutos adicionales seguido por concentración a temperatura ambiente para dar un residuo. El residuo resultante se disolvió en DMF (39 ml) seguido por la adición de 4-tert-butilanilina (18,62 ml, 117 mmol) y la mezcla se calentó a 50 °C por 5 horas. Luego se agregó ácido clorhídrico acuoso 1N

000714

seguido por extracción con EtOAc. El extracto orgánico se secó, se filtró y se concentró. La purificación mediante cromatografía flash (gel de sílice, 0-30% EtOAc/hexanos) dio 2,67g (42%) del compuesto del título.

Ejemplo 159D

3,5-bis(4-bromofenil)-4-(4-tert-butilfenil)tiomorfolina

A una solución de Ejemplo 159C (350 mg, 0,504 mmol) en tolueno (5 ml) se agregó gel de sílice (1,0 g) que se había deshidratado calentando a 180°C en un horno de vacío por 3 horas, y ácido trifluorometansulfónico (0,045 ml, 0,504 mmol) y se calentó a 100°C por 3 horas. Luego de enfriar a temperatura ambiente, se agregó diclorometano y el gel de sílice se retiró mediante filtración y la solución se extrajo con solución semisaturada acuosa de bicarbonato de sodio. El extracto orgánico se secó, se filtró y se concentró para dar 220 mg (80%) del compuesto del título como una mezcla de isómeros. MS (ESI) m/z 546 (M+H)+.

Ejemplo 159E

4-(4-tert-butilfenil)-3,5-bis(4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)tiomorfolina

El producto de Ejemplo 159D (200 mg, 0,367 mmol) se procesó usando el método descrito en Ejemplo 42D para dar 105 mg (45%) del compuesto del título como una mezcla de isómeros. MS (ESI) m/z 640 (M+H)+.

Ejemplo 159F

(2S,2'S)-2,2'-(4,4'-(4,4'-(4-(4-tert-butilfenil)tiomorfolina-3,5-diil)bis(4,1-fenilen))bis(1H-imidazol-4,2-diil))dipirrolidin-1-carboxilato de tert-butilo

El producto de Ejemplo 159E (190 mg, 0,297 mmol) y el producto del Ejemplo 26D (282 mg, 0,891 mmol) se procesaron usando el método descrito en Ejemplo 42E para dar 110 mg (43%) del compuesto del título como una mezcla de isómeros. MS (ESI) m/z 859 (M+H)+.

Ejemplo 159G

4-(4-tert-butilfenil)-3,5-bis(4-(2-((S)-pirrolidin-2-il)-1H-imidazol-4-il)fenil)tiomorfolina

Al producto de Ejemplo 159F (110 mg, 0,128 mmol) se agregó dimetoxietano (5 ml) y una solución de ácido clorhídrico 4N en dioxano (5 ml) y la solución resultante se agitó a temperatura ambiente por 1 hr. El solvente luego se eliminó bajo vacío y el residuo resultante se diluyó con acetonitrilo y agua (TFA al 0,1%) y se purificó mediante cromatografía de fase inversa (C18), eluyendo con 10-100% acetonitrilo en agua (TFA al 0,1%) para dar 12 mg (14%) del compuesto del título como una mezcla de estereoisómeros. MS (ESI) m/z 658 (M+H)+.

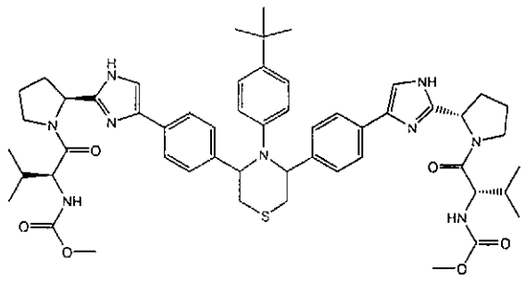
Ejemplo 159H

{(2S)-1-[(2S)-2-(4-{4-[(3S,5R)-4-(4-tert-butilfenil)-5-(4-{2-[(2S)-1-{(2S)-2-

000715

[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-4-il}fenil)tiomorfolin-3-il]fenil}-1H-imidazol-2-il)pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

El producto del Ejemplo 159G (10 mg, 0,015 mmol), ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico (5,86 mg, 0,033 mmol) y HATU (12,71 mg, 0,033 mmol) en DMSO (0,5 ml) se agregó base de Hunig (0,013 ml, 0,076 mmol), y la mezcla de la reacción se agitó a temperatura ambiente por 1,5 hr. La mezcla de la reacción se particionó entre agua y diclorometano, y la capa orgánica se secó sobre $MgSO_4$, se filtró y se concentró al vacío. El producto crudo se disolvió nuevamente en metanol (5 ml) luego se agregó carbonato de potasio (50 mg) luego se agitó a temperatura ambiente por 20 minutos, los sólidos se eliminaron mediante filtración, el material filtrado se concentró y se purificó mediante cromatografía (gel de sílice, 0-10% metanol/diclorometano) para dar 7 mg (47%) del compuesto del título. 1H RMN (400 MHz, DMSO-D6) δ ppm 11,65 (m, 2 H), 7,47 (m, 2 H), 7,32 (m, 4 H), 7,23 (m, 4H), 6,85 (m, 4 H), 5,02 (m, 2 H), 4,38 (m, 2H), 4,02 (m, 2 H), 3,75 (m, 4 H), 3,52 (s, 6 H), 3,10 (m, 2 H), 2,66 (m, 2 H), 2,08 (m, 4 H), 1,91 (m, 4 H), 0,97 (s, 9 H), 0,82 (m, 12 H); MS (ESI) m/z 973 (M+H)+.



Ejemplo 160

{(2*S*)-1-[(2*S*)-2-(4-{4-[(3*S*,5*S*)-4-(4-*tert*-butilfenil)-5-(4-{2-[(2*S*)-1-{(2*S*)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1*H*-imidazol-4-il}fenil)tiomorfolin-3-il]fenil}-1*H*-imidazol-2-il)pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

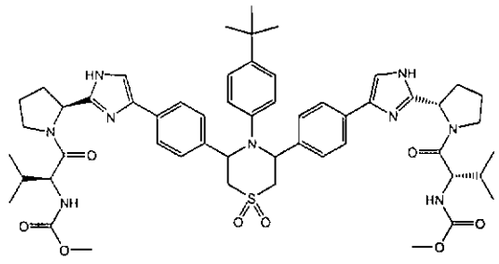
y

{(2*S*)-1-[(2*S*)-2-(4-{4-[(3*R*,5*R*)-4-(4-*tert*-butilfenil)-5-(4-{2-[(2*S*)-1-{(2*S*)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1*H*-imidazol-4-il}fenil)tiomorfolin-3-il]fenil}-1*H*-imidazol-2-il)pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

El producto del Ejemplo 159E (100 mg, 0,156 mmol), el producto del Ejemplo 126G (146 mg, 0,391 mmol), y [1,1'-bis(difenilfosfino)ferrocen]dicloropaladio(II) diclorometano aducto (25,5 mg, 0,031 mmol) en una mezcla de tolueno (3 ml), etanol (3 ml) y una solución acuosa 1N de bicarbonato de sodio (0,469 ml, 4,69 mmol) y se burbujeó nitrógeno gaseoso a través de la solución por 10 min, luego se calentó a 80 °C por 18 h. La solución se enfrió a temperatura ambiente y se agregó agua (20 ml) luego se extrajo con diclorometano (50 ml), luego se secó, se concentró y el residuo se purificó

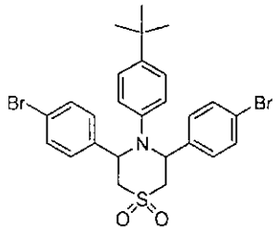
000718

mediante cromatografía de fase inversa (C18), eluyendo con 10-100% acetonitrilo en agua (TFA al 0,1%) para dar 8,5 mg (6%) del compuesto del título como una mezcla de estereoisómeros. 1H RMN (base libre) (400 MHz, DMSO-D6) δ ppm 11,70 (bs, 2 H), 7,64 (m, 4 H), 7,45 (m, 2 H), 7,37 (m, 4H), 7,28 (m, 2 H), 7,01 (m, 2 H), 6,46 (d, *J*=8,7 Hz, 2 H), 5,38 (m, 2 H), 5,07 (m, 2H), 4,03 (m, 2 H), 3,52 (s, 6 H), 3,10 (m, 2 H), 2,12 (m, 4 H), 1,91 (m, 4 H), 1,12 (s, 9 H), 0,86 (m, 12 H); MS (ESI) m/z 973 (M+H)+.



Ejemplo 161

{(2S)-1-[(2S)-2-(4-{4-[4-(4-tert-butilfenil)-5-(4-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-4-il}fenil)-1,1-dioxidotiomorfolin-3-il]fenil}-1H-imidazol-2-il)pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo



Ejemplo 161A

1,1-dióxido de 3,5-bis(4-bromofenil)-4-(4-*tert*-butilfenil)tiomorfolina (ACD v12)

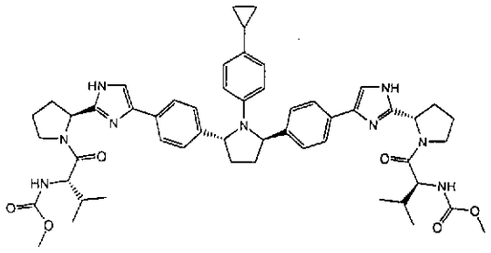
Una solución de Ejemplo 159D (850 mg, 1,56 mmol) en mezcla de acetona (15 ml), agua (5 ml) y THF (5 ml) se agregó una solución de tetróxido de osmio (2,5% en tert-butanol, 0,587 ml, 0,047 mmol) y la mezcla se agitó a temperatura ambiente por 1,5 hr. La solución luego se diluyó con agua y se extrajo con EtOAc, el extracto orgánico se secó, se filtró y se concentró para dar 900 mg (100%) del compuesto del título. MS (ESI) m/z 578 (M+H)+.

Ejemplo 161B

{(2S)-1-[(2S)-2-(4-{4-[4-(4-tert-butilfenil)-5-(4-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-4-il}fenil)-1,1-dioxidotiomorfolin-3-il]fenil}-1H-imidazol-2-il)pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

Ejemplo 161A se procesó usando en forma consecutiva los métodos de Ejemplos 42D, 42E, 159G, y 159H para dar el compuesto del título como una mezcla de estereoisómeros trans. 1H RMN (400 MHz, DMSO-D6) δ ppm 11,73 (bs, 2 H), 7,64 (m, 4

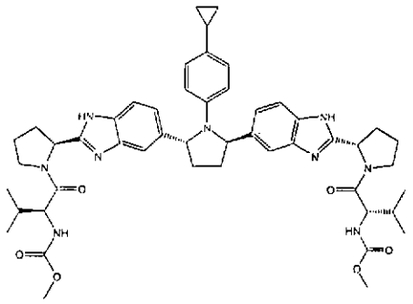
H), 7,55 (m, 2 H), 7,44 (m, 4H), 7,24 (m, 2 H), 7,04 (m, 2 H), 6,60 (m, 2 H), 5,48 (m, 2 H), 5,06 (m, 2H), 4,04 (m, 2 H), 3,78 (m, 6 H), 3,52 (s, 6 H), 2,11 (m, 4 H), 1,92 (m, 6 H), 1,13 (s, 9 H), 0,92 (m, 12 H); MS (ESI) m/z 1005 (M+H)+.



Ejemplo 162

{(2S)-1-[(2S)-2-(4-{4-[(2R,5R)-1-(4-ciclopropilfenil)-5-(4-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-4-il}fenil)pirrolidin-2-il]fenil}-1H-imidazol-2-il)pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

El producto del Ejemplo 95B se purificó mediante cromatografía quiral en una columna Chiralpak IB eluyendo con una mezcla de hexano/THF/metanol (85/10/5). El compuesto del título fue el primero de los 2 diastereómeros en eluir. 1H RMN (400 MHz, DMSO-D6) δ ppm 0,33 - 0,43 (m, 2 H) 0,65 - 0,72 (m, 2 H) 0,79 - 0,91 (m, 12 H) 1,56 - 1,64 (m, 1 H) 1,66 - 1,72 (m, 2 H) 1,84 - 2,03 (m, 6 H) 2,06 - 2,19 (m, 4 H) 3,53 (s, 6 H) 3,73 - 3,84 (m, 4 H) 4,04 (t, J=8,35 Hz, 2 H) 5,06 (dd, J=6,89, 3,09 Hz, 2 H) 5,14 - 5,23 (m, 2 H) 6,19 (d, J=8,67 Hz, 2 H) 6,60 - 6,67 (m, 2 H) 7,09 - 7,31 (m, 6 H) 7,34 - 7,68 (m, 6 H) 11,62 - 12,11 (m, 2 H); MS (ESI+) m/z 924,6 (M+H).

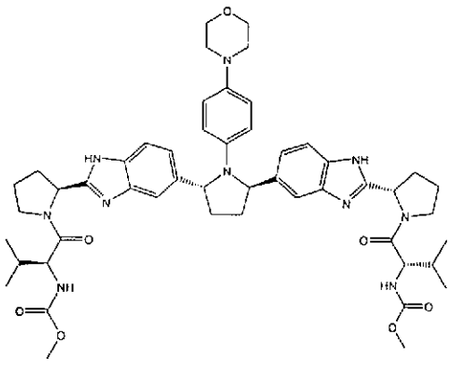


Ejemplo 163

{(2S)-1-[(2S)-2-{5-[(2R,5R)-1-(4-ciclopropilfenil)-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-bencimidazol-5-il}pirrolidin-2-il]-1H-bencimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

Se procesó Ejemplo 109C y 4-ciclopropilanilina usando en forma consecutiva los métodos de Ejemplos 113A (la reacción de ciclización se llevó a cabo a temperatura ambiente durante la noche), 113B, 113C, 28I (reacción llevada a cabo a 50 °C por 3 horas), 28J, y 66E para dar el compuesto del título (122 mg) como un sólido. 1H RMN

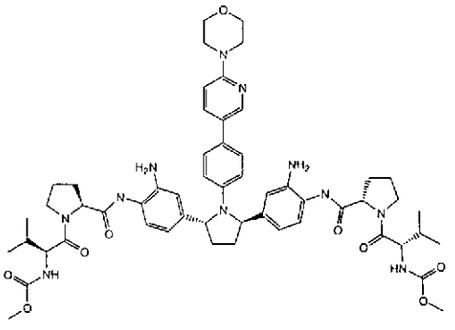
(400 MHz, DMSO-D6) δ ppm 0,32 - 0,39 (m, 2 H) 0,63-0,69 (m, 2 H) 0,77 - 0,90 (m, 12 H) 1,53 - 1,61 (m, 1 H) 1,66 - 1,74 (m, 2 H) 1,86 - 2,04 (m, 8 H) 2,14 - 2,23 (m, 4 H) 3,54 (s, 6 H) 3,78 - 3,87 (m, 4 H) 4,00 - 4,07 (m, 2 H) 5,10 - 5,18 (m, 2 H) 5,31 - 5,39 (m, 2 H) 6,22 (d, J=8,67 Hz, 2 H) 6,57 - 6,65 (m, 2 H) 7,00 - 7,07 (m, 2 H) 7,16 - 7,32 (m, 4 H) 7,36 (d, J=8,13 Hz, 1 H) 7,44 (d, J=8,24 Hz, 1 H) 11,97 - 12,27 (m, 2 H); MS (ESI+) m/z 872,5 (M+H)+.



Ejemplo 164

{(2S)-1-[(2S)-2-(5-{(2R,5R)-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-bencimidazol-5-il}-1-[4-(morfolin-4-il)fenil]pirrolidin-2-il}-1H-bencimidazol-2-il)pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

Se procesó Ejemplo 109C y 4-morfolinoanilina usando en forma consecutiva los métodos de Ejemplos 113A (la reacción de ciclización se llevó a cabo a temperatura ambiente durante la noche), 113B, 113C, 28I (reacción llevada a cabo a 50 °C por 2 horas), 28J, y 28K para dar el compuesto del título (100 mg) como un sólido. 1H RMN (400 MHz, DMSO-D6) δ ppm 0,76 - 0,91 (m, 12 H) 1,66 - 1,72 (m, 2 H) 1,87 - 2,03 (m, 8 H) 2,15 - 2,22 (m, 4 H) 2,72 - 2,78 (m, 4 H) 3,53 (s, 6 H) 3,57 - 3,62 (m, 4 H) 3,78 - 3,86 (m, 4 H) 4,00 - 4,12 (m, 2 H) 5,09 - 5,18 (m, 2 H) 5,30 - 5,37 (m, 2 H) 6,25 (d, J=8,78 Hz, 2 H) 6,52 - 6,59 (m, 2 H) 7,05 (t, J=7,54 Hz, 2 H) 7,18 - 7,32 (m, 4 H) 7,36 (d, J=8,13 Hz, 1 H) 7,44 (d, J=8,24 Hz, 1 H) 11,91 - 12,28 (m, 2 H); MS (ESI+) m/z 917,5 (M+H)+.



Ejemplo 165

{[(2R,5R)-1-{4-[6-(morfolin-4-il)piridin-3-il]fenil}pirrolidin-2,5-diil]bis{(2-aminobencen-4,1-

diil)carbamoil(2S)pirrolidin-2,1-diil[(2S)-3-metil-1-oxobutan-1,2-diil]})biscarbamato de dimetilo

Ejemplo 165A

(2R,5R)-2,5-bis(4-cloro-3-nitrofenil)-1-(4-yodofenil)pirrolidina

Ejemplo 109C (3,34 g, 6,0 mmol) y 4-yodoanilina (7,88 g, 36,0 mmol) se procesaron usando el método de Ejemplo 113A dejando proceder la reacción por 4 días a temperatura ambiente para dar el compuesto del título (2,01 g, 57%) como un sólido amarillo.

Ejemplo 165B

4-(5-(4-((2R,5R)-2,5-bis(4-cloro-3-nitrofenil)pirrolidin-1-il)fenil)piridin-2-il)morfolina

El producto de 165A (1,869 g, 3,2 mmol), 4-(5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)piridin-2-il)morfolina (0,929 g, 3,20 mmol), fosfato de potasio (1,359 g, 6,40 mmol), tris(dibencilidenacetona)dipaladio(0) (0,029 g, 0,032 mmol) y 1,3,5,7-tetrametil-6-fenil-2,4,8-trioxa-6-fosfaadamanto (0,028 g, 0,096 mmol) se combinaron en THF (18 ml)/agua (6 ml). La mezcla se purgó con nitrógeno por 15 minutos y se agitó a temperatura ambiente por 24 horas. La mezcla de la reacción se particionó entre acetato de etilo y bicarbonato de sodio saturado. La capa orgánica se lavó con salmuera, se secó con sulfato de sodio, se filtró y se evaporó. El residuo se purificó mediante cromatografía sobre gel de sílice eluyendo con acetato de etilo/hexano (20% a 40%) para dar el compuesto del título (1,01 g, 51%) como un sólido.

Ejemplo 165C

(2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-((2R,5R)-1-(4-(6-morfolinopiridin-3-il)fenil)pirrolidin-2,5-diil)bis(2-nitro-4,1-fenilen))bis(azandiil)bis(oxometilen)bis(pirrolidin-2,1-diil))bis(3-metil-1-oxobutan-2,1-diil)dicarbamato de dimetilo

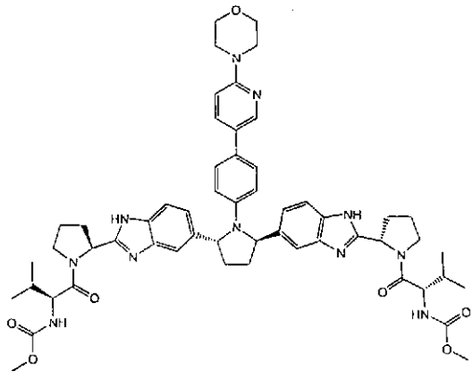
El producto del Ejemplo 165B (683 mg, 1,10 mmol), el producto del Ejemplo 116C (895 mg, 3,30 mmol), carbonato de cesio (1004 mg, 3,08 mmol), tris(dibencilidenacetona)dipaladio(0) (60,4 mg, 0,066 mmol) y (9,9-dimetil-9H-xanten-4,5-diil)bis(difenilfosfina) (115 mg, 0,198 mmol) se combinaron en dioxano (15 ml). La mezcla se purgó con nitrógeno por 15 minutos y se agitó a 100 °C por 3 horas. La mezcla se particionó entre acetato de etilo y bicarbonato de sodio saturado. La capa orgánica se lavó con salmuera, se secó con sulfato de sodio, se filtró y se evaporó. El residuo se purificó mediante cromatografía sobre gel de sílice eluyendo con metanol/diclorometano (1% a 3%) para dar el compuesto del título (631 mg, 53%) como un sólido.

Ejemplo 165D

([(2R,5R)-1-{4-[6-(morfolin-4-il)piridin-3-il]fenil}pirrolidin-2,5-diil]bis{(2-aminobencen-4,1-diil)carbamoil(2S)pirrolidin-2,1-diil[(2S)-3-metil-1-oxobutan-1,2-diil]})biscarbamato de

dimetilo

El producto del Ejemplo 165C (628 mg, 0,576 mmol) y Ra-Ni 2800 (628 mg) se combinaron en THF (40 ml). La mezcla se hidrogenó a 30psi por 4 horas. La mezcla se filtró y el material filtrado se evaporó. El residuo se purificó mediante cromatografía sobre gel de sílice eluyendo con metanol/diclorometano (2% a 5%) para dar el compuesto del título (590 g, 99%) como un sólido. 1H RMN (400 MHz, DMSO-D6) δ ppm 0,88 (d, J=6,61 Hz, 6 H) 0,91 (d, J=6,72 Hz, 6 H) 1,62 - 1,69 (m, 2 H) 1,82 - 2,04 (m, 8 H) 2,10 - 2,20 (m, 2 H) 2,52 - 2,56 (m, 2 H) 3,37 - 3,41 (m, 4 H) 3,52 (s, 6 H) 3,56 - 3,62 (m, 2 H) 3,65 - 3,70 (m, 4 H) 3,78 - 3,85 (m, 2 H) 3,98 - 4,07 (m, 2 H) 4,36 - 4,44 (m, 2 H) 4,87 (s, 4 H) 5,06 (d, J=6,32 Hz, 2 H) 6,36 (d, J=8,78 Hz, 2 H) 6,42 (d, J=8,02 Hz, 2 H) 6,57 (d, J=1,19 Hz, 2 H) 6,78 (d, J=8,89 Hz, 1 H) 6,96 (d, J=8,02 Hz, 2 H) 7,23 (d, J=8,78 Hz, 2 H) 7,36 (d, J=8,24 Hz, 2 H) 7,68 (dd, J=8,78, 2,49 Hz, 1 H) 8,27 (d, J=2,49 Hz, 1 H) 9,24 (s, 2 H); MS (ESI+) m/z 1030,6 (M+H)+.

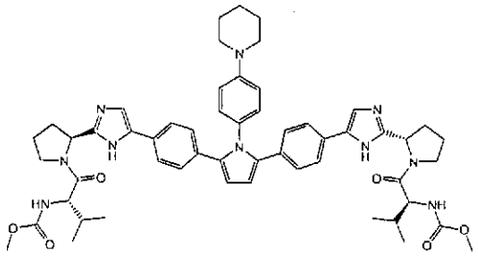


Ejemplo 166

{(2S)-1-[(2S)-2-{5-[(2R,5R)-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-bencimidazol-5-il}-1-{4-[6-(morfolin-4-il)piridin-3-il]fenil}pirrolidin-2-il]-1H-bencimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

El producto del Ejemplo 165D (520 g, 0,505 mmol) y ácido acético (0,087 ml, 1,514 mmol) se combinaron en tolueno (10 ml). La mezcla se agitó a 50 °C durante 4 horas. El solvente se evaporó y el residuo se purificó mediante cromatografía sobre gel de sílice eluyendo con metanol/diclorometano (2% a 5%) para dar el compuesto del título (309 mg, 62%) como un sólido. 1H RMN (400 MHz, DMSO-D6) δ ppm 0,73 - 0,90 (m, 12 H) 1,70 - 1,76 (m, 2 H) 1,84 - 2,05 (m, 8 H) 2,14 - 2,21 (m, 2 H) 2,55 - 2,60 (m, 2 H) 3,34 - 3,39 (m, 4 H) 3,53 (s, 6 H) 3,62 - 3,69 (m, 4 H) 3,75 - 3,87 (m, 4 H) 4,02 - 4,08 (m, 2 H) 5,06 - 5,17 (m, 2 H) 5,40 - 5,47 (m, 2 H) 6,40 (d, J=8,67 Hz, 2 H) 6,75 (d, J=8,89 Hz, 1 H) 7,02 - 7,20 (m, 4 H) 7,25 (s, 1 H) 7,28 (d, J=8,46 Hz, 2 H) 7,34 (s, 1 H) 7,39 (d, J=8,13 Hz, 1 H) 7,47 (d, J=8,24 Hz, 1 H) 7,60 (d, J=8,60 Hz,1 H) 8,21 (s, 1 H) 11,96 - 12,11 (m, 2 H); MS (ESI+)

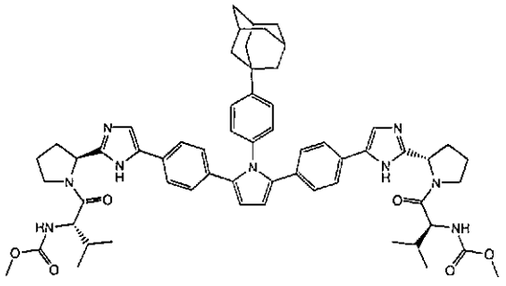
m/z 994,5 (M+H)+.



Ejemplo 167

[(2S)-1-{(2S)-2-[5-(4-{5-(4-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-5-il}fenil)-1-[4-(piperidin-1-il)fenil]-1H-pirrol-2-il}fenil)-1H-imidazol-2-il]pirrolidin-1-il}-3-metil-1-oxobutan-2-il]carbamato de metilo

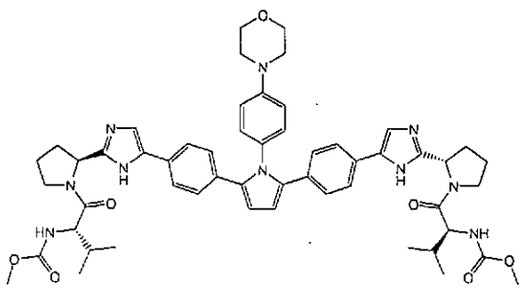
Se procesaron el Ejemplo 26E y 4-piperidinanilina (Maybridge) utilizando en forma consecutiva los métodos de los Ejemplos 26F, 26G, 74C, 19D, y 74E para dar el compuesto del título (106 mg). ^{1}H RMN (400 MHz, DMSO-D6) δ 0,83 (d, J=6,73 Hz, 6 H) 0,87 (d, J=6,73 Hz, 6 H) 1,50 – 1,62 (m, 6 H) 1,90 – 2,15 (m, 10 H) 3,13 (m, 4 H) 3,53 (s, 6 H) 3,77 (m, 4 H) 4,04 (m, 2 H) 5,04 (m, 2 H) 6,47 (m, 2 H) 6,80 – 7,35 (m, 10 H) 7,42 (m, 2 H) 7,53 (m, 4 H) 11,73 (s, 2 H).



Ejemplo 168

[(2S)-1-{(2S)-2-[5-(4-{5-(4-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-5-il}fenil)-1-[4-(triciclo[3,3,1,1~3,7~]dec-1-il)fenil]-1H-pirrol-2-il}fenil)-1H-imidazol-2-il]pirrolidin-1-il}-3-metil-1-oxobutan-2-il]carbamato de metilo

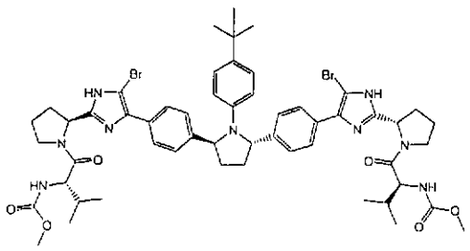
Se procesaron el Ejemplo 26E y clorhidrato de 4-(1-adamantanil)anilina (Enamina) utilizando en forma consecutiva los métodos de los Ejemplos 26F, 26G, 74C, 19D, y 74E para dar el compuesto del título (320 mg). ^{1}H RMN (400 MHz, metanol-D4) δ 0,91 (m, 12 H) 1,75 – 2,35 (m, 25 H) 3,64 (s, 6 H) 3,84 (m, 2 H) 4,00 (m, 2 H) 4,20 (m, 2 H) 5,12 (m, 2 H) 6,48 (s, 2 H) 7,02 (m, 6 H) 7,31 (m, 4 H) 7,46 (m, 6 H) 7,72 (d, J=8,13 Hz, 1 H) 7,82 (d, J=8,24 Hz, 1 H).



Ejemplo 169

[(2S)-1-{(2S)-2-[5-(4-{5-(4-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-5-il}fenil)-1-[4-(morfolin-4-il)fenil]-1H-pirrol-2-il}fenil)-1H-imidazol-2-il]pirrolidin-1-il}-3-metil-1-oxobutan-2-il]carbamato de metilo

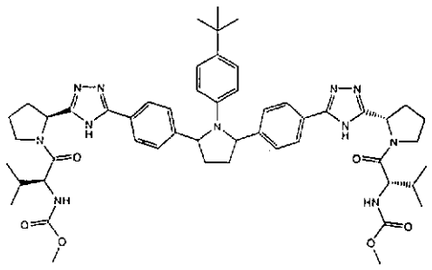
Se procesaron el Ejemplo 26E y 4-morfolinoanilina (Aldrich) utilizando en forma consecutiva los métodos de los Ejemplos 26F, 26G, 74C, 19D, y 74E para dar el compuesto del título (133 mg). ^{1}H RMN (400 MHz, DMSO-D6) δ 0,83 (d, J=6,83 Hz, 6 H) 0,87 (d, J=6,61 Hz, 6 H) 1,88 - 2,17 (m, 10 H) 3,11 (m, 4 H) 3,53 (s, 6 H) 3,70 – 3,80 (m, 8 H) 3,97 - 4,08 (m, 2 H) 5,04 (m, 2 H) 6,41 - 6,51 (m, 2 H) 6,84 – 7,35 (m, 10 H) 6,93 - 7,02 (m, 6 H) 11,71 – 12,03 (m, 2 H).



Ejemplo 170

{(2S)-1-[(2S)-2-(5-bromo-4-{4-[(2S,5S)-5-(4-{5-bromo-2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-4-il}fenil)-1-(4-tert-butilfenil)pirrolidin-2-il]fenil}-1H-imidazol-2-il)pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

A una solución del Ejemplo 44 (0,100 g, 0,106 mmol) en CH_2Cl_2 (5 ml) a temperatura ambiente se agregó N-bromosuccinimida (0,019 ml, 0,223 mmol). Luego de 15 min, la reacción se lavó con $NaHCO_3$ saturado y se concentró. El residuo se purificó mediante cromatografía (1% gradiente de elución entre 0% y 4% MeOH-CH_2Cl_2; columna de 12 g) para dar 60 mg (51%) del compuesto del título como un sólido amarillo claro. ^{1}H RMN (400 MHz, DMSO-D6) δ 0,8 (d, J=6,61 Hz, 6 H) 0,87 (d, J=6,56 Hz, 6 H) 1,11 (s, 9 H) 1,72 – 1,75 (m, 2 H) 1,87 - 1,98 (m, 7 H) 2,10 – 2,15 (m, 5 H) 3,53 (s, 6 H) 3,70 -3,75 (m, 4 H) 4,00 = 4,06 (m, 2 H) 4,96 – 5,00 (m, 2 H) 5,27 – 5,35 (m, 2 H) 6,24 (d, J=8,78 Hz, 2 H) 6,97 (d, J=8,78 Hz, 2 H) 7,24 - 7,35 (m, 6 H) 7,60 – 7,65 (m, 4 H) 12,41 (m, 2 H).



Ejemplo 171

{(2S)-1-[(2S)-2-(5-{4-[(2S,5S)-1-(4-tert-butilfenil)-5-(4-{5-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-4H-1,2,4-triazol-3-il}fenil)pirrolidin-2-il]fenil}-4H-1,2,4-triazol-3-il)pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

y

{(2S)-1-[(2S)-2-(5-{4-[(2R,5R)-1-(4-tert-butilfenil)-5-(4-{5-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-4H-1,2,4-triazol-3-il}fenil)pirrolidin-2-il]fenil}-4H-1,2,4-triazol-3-il)pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

Ejemplo 171A

4,4'-(1-(4-tert-butilfenil)pirrolidin-2,5-diil)dibenzoato de dimetilo

Una mezcla del Ejemplo 42C (0,5 g, 0,974 mmol), Et_3N (0,407 ml, 2,92 mmol) y [1,1'-Bis(difenilfosfino)ferrocen]dicloropaladio(II) (71,3 mg, 0,097 mmol) en metanol (20 ml) se sometió a una atmósfera de monóxido de carbono gaseoso (60 psi) durante 24 horas a 100 °C. La mezcla se filtró a través de celite y se concentró. La purificación mediante cromatografía (gel de sílice, 25% EtOAc en hexanos) dio 396 mg (86%) del compuesto del título. MS (ESI) m/z 472 $(M+H)^+$.

Ejemplo 171B

4,4'-(1-(4-tert-butilfenil)pirrolidin-2,5-diil)dibenzohidrazida

Una mezcla del Ejemplo 171A (350 mg, 0,742 mmol) e hidrazina (0,140 µL, 4,45 mmol) en metanol (10 ml) se sometió a reflujo durante 72 horas. La mezcla se concentró para dar 350 mg del compuesto del título como una mezcla de estereoisómeros. MS (ESI) m/z 472 $(M+H)^+$.

Ejemplo 171C

(2S,2'S)- 2,2'-(5,5'-(4,4'-(1-(4-tert-butilfenil)pirrolidin-2,5-diil)bis(4,1-fenilen))bis(4H-1,2,4-triazol-5,3-diil))dipirrolidin-1-carboxilato de tert-butilo

Una mezcla del Ejemplo 171B (105 mg, 0,223 mmol), (S)-1-N-Boc-2-ciano-pirrolidina (175 mg, 0,891 mmol), y K_2CO_3 (9,23 mg, 0,067 mmol) en n-butanol (0,5 ml) se calentó a 150 °C durante 90 minutos en un microondas. La mezcla se diluyó con EtOAc y luego se lavó con H_2O y salmuera. La fase orgánica luego se secó ($MgSO_4$), se filtró y se concentró. La purificación mediante cromatografía (gel de sílice, 90% EtOAc en Hexanos)

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dio 59 mg (32%) del compuesto del título como una mezcla de estereoisómeros. MS (ESI) m/z 829 $(M+H)^+$.

Ejemplo 171D

pentaclorhidrato de (S)-5,5'-(4,4'-(1-(4-tert-butilfenil)pirrolidin-2,5-diil)bis(4,1-fenilen))bis(3-((S)-pirrolidin-2-il)-4H-1,2,4-triazol)

Una mezcla del Ejemplo 171C (59 mg, 0,071 mmol) en HCl 4M/Dioxano (2 ml) se dejó agitar durante una hora. La mezcla se concentró para dar 58 mg (100%) del compuesto del título como una mezcla de estereoisómeros. MS (ESI) m/z 628 $(M+H)^+$.

Ejemplo 171E

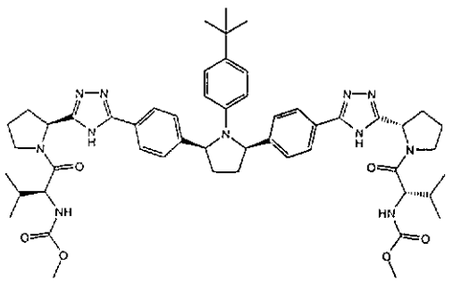
{(2S)-1-[(2S)-2-(5-{4-[(2S,5S)-1-(4-tert-butilfenil)-5-(4-{5-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-4H-1,2,4-triazol-3-il}fenil)pirrolidin-2-il]fenil}-4H-1,2,4-triazol-3-il)pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

y

{(2S)-1-[(2S)-2-(5-{4-[(2R,5R)-1-(4-tert-butilfenil)-5-(4-{5-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-4H-1,2,4-triazol-3-il}fenil)pirrolidin-2-il]fenil}-4H-1,2,4-triazol-3-il)pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

Una mezcla del Ejemplo 171D (58 mg, 0,071 mmol), ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico (25 mg, 0,142 mmol), clorhidrato de N-(3-dimetilaminopropil)-N'-etilcarbodiimida (30 mg, 0,157 mmol), 1-Hidroxi-benzotriazol hidrato (24 mg, 0,157 mmol) y N-metilmorfolina (78 µL, 0,712 mmol) en DMF (1 ml) se dejó en agitación durante la noche. La mezcla se diluyó con EtOAc. La fase orgánica luego se lavó con H_2O y salmuera. La fase orgánica luego se secó ($MgSO_4$), se filtró y se concentró. El compuesto se sometió a purificación por HPLC en una columna de fase reversa C18 semipreparativa usando un gradiente de 10-100% acetonitrilo en TFA ac. 0,1% para dar ambos compuestos del título del Ejemplo 171 (24 mg, 70%) que eluyeron en primer lugar (isómeros trans) y el compuesto del título del Ejemplo 172 que eluyó segundo (isómero cis). ^{1}H RMN (base libre) (400 MHz, DMSO-d_6) δ ppm 0,27 (d, J=6,72 Hz, 2 H), 0,71 (dd, J=6,61, 2,49 Hz, 2 H), 0,78 - 0,95 (m, 9 H), 1,03 (d, J=6,07 Hz, 12 H), 1,09 (s, 9 H), 1,22 (s, 2 H), 1,65 - 1,77 (m, 3 H), 1,82 - 2,30 (m, 10 H), 3,52 (s, 6 H), 3,57 - 3,66 (m, 1 H), 3,71 - 3,92 (m, 3 H), 4,00 - 4,16 (m, 2 H), 5,07 - 5,15 (m, 1 H), 5,25 - 5,34 (m, 2 H), 5,65 (d, J=4,88 Hz, 1 H), 6,21 (dd, J=8,73, 3,20 Hz, 2 H), 6,94 (dd, J=8,78, 2,82 Hz, 2 H), 7,16 - 7,46 (m, 6 H), 7,83 - 7,92 (m, 4 H), 14,01 (s, 1 H); MS (ESI) m/z 943 $(M+H)^+$.

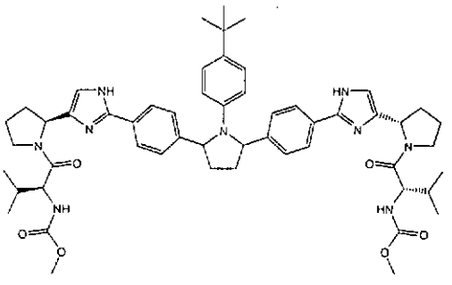
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Ejemplo 172

{(2S)-1-[(2S)-2-(5-{4-[(2R,5S)-1-(4-tert-butilfenil)-5-(4-{5-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-4H-1,2,4-triazol-3-il}fenil)pirrolidin-2-il]fenil}-4H-1,2,4-triazol-3-il)pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

El compuesto del título, Ejemplo 172, fue el segundo compuesto en eluir descrito en los procedimientos por ejemplo 171E. El procedimiento dio 21 mg (61%) del compuesto del título (Cis isómero). ^{1}H RMN (base libre) (400 MHz, DMSO-d_6) δ ppm 0,27 (d, J=6,29 Hz, 2 H), 0,71 (d, J=6,61 Hz, 2 H), 0,81 - 0,96 (m, 9 H), 1,03 (d, J=6,07 Hz, 12 H), 1,12 (s, 9 H), 1,22 (s, 2 H), 1,82 - 2,30 (m, 12 H), 3,52 (s, 6 H), 3,72 - 3,91 (m, 4 H), 4,03 - 4,17 (m, 2 H), 4,33 (d, J=4,23 Hz, 1 H), 4,73 - 4,83 (m, 2 H), 5,09 - 5,18 (m, 2 H), 6,33 (d, J=8,78 Hz, 2 H), 7,03 (dd, J=8,78, 3,04 Hz, 2 H), 7,29 (d, J=7,70 Hz, 1 H), 7,57 - 7,69 (m, 4 H), 7,92 - 8,01 (m, 4 H), 13,84 (s, 2 H); MS (ESI) m/z 943 $(M+H)^+$.



Ejemplo 173

{(2S)-1-[(2S)-2-(2-{4-[(2S,5S)-1-(4-tert-butilfenil)-5-(4-{4-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-2-il}fenil)pirrolidin-2-il]fenil}-1H-imidazol-4-il)pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

y

{(2S)-1-[(2S)-2-(2-{4-[(2R,5R)-1-(4-tert-butilfenil)-5-(4-{4-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-2-il}fenil)pirrolidin-2-il]fenil}-1H-imidazol-4-il)pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

Ejemplo 173A

4,4'-(1-(4-tert-butilfenil)pirrolidin-2,5-diil)dibenzonitrilo

Una mezcla del Ejemplo 42C (1,0 g, 1,948 mmol) y CuCN (523 mg, 5,84 mmol) en

Dimetilformamida (9,5 ml) se calentó a 160 °C durante 4,5 horas en un microondas. La mezcla se volcó en una mezcla de dimetilamina/H_2O (1/10) y se extrajo con EtOAc (3 x 150 ml). Los materiales orgánicos combinados se lavaron con H_2O y salmuera. La fase orgánica luego se secó ($MgSO_4$), se filtró y se concentró. La purificación mediante cromatografía (gel de sílice, EtOAc al 20% en Hexanos) dio 395 mg (50%) del compuesto del título. MS (ESI) m/z 406 $(M+H)^+$.

Ejemplo 173B

4,4'-(1-(4-tert-butilfenil)pirrolidin-2,5-diil)dibencimidato de dimetilo

En una mezcla del Ejemplo 173A (0,5 g, 1,233 mmol) en MeOH anhidro (12 ml) a 0 °C se burbujeó un exceso de HCl (*g*) durante 45 minutos. La mezcla luego se agitó a temperatura ambiente durante 24 horas y luego se concentró para dar el compuesto del título.

Ejemplo 173C

4,4'-(1-(4-tert-butilfenil)pirrolidin-2,5-diil)dibencimidamida

En una mezcla del Ejemplo 173B (0,579 g, 1,233 mmol) en MeOH anhidro (12 ml) a 0 °C se burbujeó un exceso de NH_3 (*g*) durante 45 minutos. La mezcla luego se agitó a temperatura ambiente durante 24 horas y luego se concentró y se sometió a purificación mediante cromatografía (columna C18 en fase reversa usando un gradiente de 10-100% acetonitrilo en TFA ac. 0,1%) para dar el compuesto del título como una mezcla de isómeros trans; el isómero cis se descartó.. MS (ESI) m/z 440 $(M+H)^+$.

Ejemplo 173D

(S)-1-((S)-2-(2-diazoacetil)pirrolidin-1-il)-3-metil-1-oxobutan-2-ilcarbamato de metilo

A una mezcla del Ejemplo 37B (100 mg, 0,367 mmol) y Et_3N (154 µL, 1,102 mmol) en tetrahidrofurano (4 ml) a 0 °C se agregó cloroformato de isobutilo (50 µL, 0,386 mmol). La mezcla luego se agitó a 0 °C durante 30 minutos y luego se agregó un exceso de diazometano en Et_2O. La mezcla se dejó alcanzar lentamente la temperatura ambiente durante 3 horas. La mezcla luego se concentró y se diluyó con EtOAc. El material orgánico luego se lavó con $NaHCO_3$ acuoso saturado y salmuera. El material orgánico se secó ($MgSO_4$), se filtró y se concentró. La purificación mediante cromatografía (gel de sílice, EtOAc al 100%) dio 82 mg (75%) del compuesto del título. MS (ESI) m/z 297 $(M+H)^+$.

Ejemplo 173E

(S)-1-((S)-2-(2-bromoacetil)pirrolidin-1-il)-3-metil-1-oxobutan-2-ilcarbamato de metilo

A una mezcla del Ejemplo 173D (70 mg, 0,236 mmol) en HOAc (0,6 ml) a temperatura ambiente se agregó HBr 48% (80 µL, 0,709 mmol). La mezcla se agitó a temperatura ambiente durante 1 hora. La mezcla se volcó en hielo/H_2O y se extrajo con

CH_2Cl_2 (3 x 75 ml). El material orgánico se secó (Na_2SO_4), se filtró y se concentró para dar 63 mg (76%) del compuesto del título. MS (ESI) m/z 350 $(M+H)^+$.

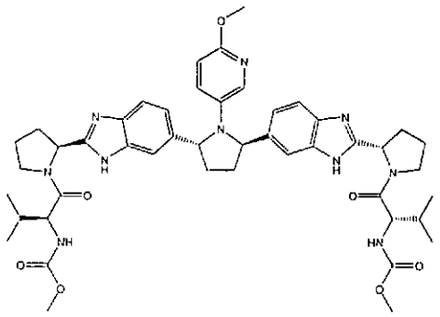
Ejemplo 173F

{(2S)-1-[(2S)-2-(2-{4-[(2S,5S)-1-(4-tert-butilfenil)-5-(4-{4-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-2-il}fenil)pirrolidin-2-il]fenil}-1H-imidazol-4-il)pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

y

{(2S)-1-[(2S)-2-(2-{4-[(2R,5R)-1-(4-tert-butilfenil)-5-(4-{4-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-2-il}fenil)pirrolidin-2-il]fenil}-1H-imidazol-4-il)pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

Una mezcla del Ejemplo 173E (59,6 mg, 0,171 mmol), el Ejemplo 173C (25 mg, 0,057 mmol) y K_2CO_3 (65 mg, 0,470 mmol) en tetrahidrofurano (1 ml) se sometió a reflujo durante 4 horas. La mezcla se diluyó con CH_2Cl_2 y se lavó con H_2O y salmuera. La fase orgánica luego se secó ($MgSO_4$), se filtró y se concentró. El compuesto se sometió a purificación por HPLC en una columna de fase reversa C18 semipreparativa usando un gradiente de 10-100% acetonitrilo en TFA ac. 0,1% para dar 4,5 mg (6,7%) el compuesto del título Ejemplo 173 (isómeros trans). ^1H RMN (base libre) (400 MHz, DMSO-d_6) δ ppm 0,78 - 0,89 (m, 12 H), 1,09 (s, 9 H), 1,68 - 1,74 (m, 4 H), 1,88 - 2,04 (m, 8 H), 3,52 (s, 6 H), 3,70 - 3,78 (m, 4 H), 4,04 (t, *J*=8,19 Hz, 2 H), 5,07 (t, *J*=4,61 Hz, 2 H), 5,26 (s, 2 H), 6,21 (d, *J*=8,46 Hz, 2 H), 6,82 (s, 2 H), 6,93 (d, *J*=8,67 Hz, 2 H), 7,22 (d, *J*=8,89 Hz, 2 H), 7,26 (d, *J*=8,13 Hz, 4 H), 7,78 (d, *J*=8,13 Hz, 4 H), 7,82 (d, *J*=7,70 Hz, 2 H), 12,11 - 12,20 (m, 2 H). MS (ESI) m/z 941 $(M+H)^+$.



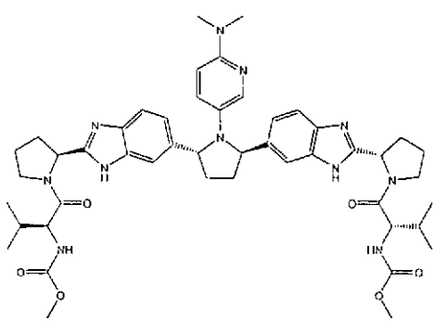
Ejemplo 174

{(2S)-1-[(2S)-2-{6-[(2R,5R)-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-bencimidazol-6-il}-1-(6-metoxipiridin-3-il)pirrolidin-2-il]-1H-bencimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

El Ejemplo 109C y 6-metoxipiridin-3-amina se procesaron utilizando en forma consecutiva los métodos de los Ejemplos 113A (se utilizó diclorometano como solvente y la ciclización se llevó a cabo a temperatura ambiente durante la noche), 165C, 113C, y

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166 para dar el compuesto del título el cual se purificó mediante HPLC en una columna de fase reversa C18 semipreparativa usando un gradiente de 10-100% acetonitrilo en TFA ac. 0,1% para dar 27 mg del compuesto del título. ^{1}H RMN (base libre) (400 MHz, DMSO-d_6) δ ppm 0,76 - 0,86 (m, 12 H), 1,69 - 1,76 (m, 2 H), 1,84 - 2,04 (m, 4 H), 2,13 - 2,22 (m, 4 H), 2,52 - 2,60 (m, 2 H), 3,52 (s, 6 H), 3,55 (s, 3 H), 3,76 - 3,85 (m, 4 H), 4,05 (t, J=8,40 Hz, 2 H), 5,08 - 5,16 (m, 2 H), 5,31 - 5,41 (m, 2 H), 6,36 - 6,45 (m, 2 H), 6,74 (dd, J=9,00, 3,04 Hz, 2 H), 7,05 (t, J=8,57 Hz, 2 H), 7,15 - 7,24 (m, J=17,02 Hz, 3 H), 7,28 (d, J=8,46 Hz, 2 H), 7,31 (s, 1 H), 7,37 (d, J=8,13 Hz, 1 H), 7,45 (d, J=8,13 Hz; 1 H), 12,03 (s, 2 H); MS (ESI) m/z 864 $(M+H)^+$.



Ejemplo 175

{(2S)-1-[(2S)-2-{6-[(2R,5R)-1-[6-(dimetilamino)piridin-3-il]-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-bencimidazol-6-il}pirrolidin-2-il]-1H-bencimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

Ejemplo 175A

N,N-dimetil-5-nitropiridin-2-amina

Una mezcla de 2-cloro-5-nitropiridina (5,0 g, 31,5 mmol) y solución de Dimetilamina 40% (10,66 g, 95 mmol) en etanol (40 ml) se calentó a 75 °C durante 1 hora. La mezcla se enfrió a temperatura ambiente, se diluyó con CH_2Cl_2 y se lavó con $NaHCO_3$ acuoso saturado (3 x 100 ml) y salmuera. La fase orgánica se secó ($MgSO_4$), se filtró y se concentró para dar 5,27 g (100%) del compuesto del título. MS (ESI) m/z 168 $(M+H)^+$.

Ejemplo 175B

N^2,N^2-dimetilpiridin-2,5-diamina

Una mezcla del Ejemplo 175A (5,27 g, 31,5 mmol) y niquel de Raney (5,27 g, 90 mmol) en tetrahidrofurano (60 ml) se sometió a una atmósfera (30 psi) de gas hidrógeno durante 2 horas a temperatura ambiente. La mezcla se filtró y se concentró para dar 4,3 g (100%) del compuesto del título. MS (ESI) m/z 138 $(M+H)^+$.

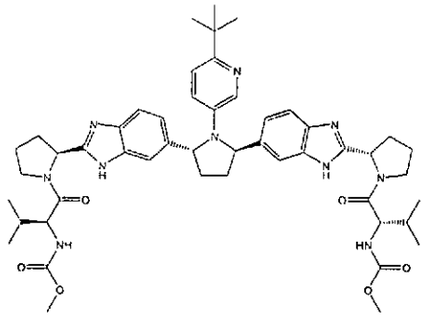
Ejemplo 175C

{(2S)-1-[(2S)-2-{6-[(2R,5R)-1-[6-(dimetilamino)piridin-3-il]-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-bencimidazol-6-il}pirrolidin-2-il]-

000729

1H-bencimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

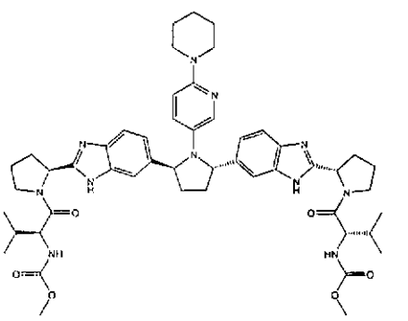
El Ejemplo 175B se procesó usando los métodos a los que se refiere o que se describen en el Ejemplo 174 para dar el compuesto del título (8,5 mg). ^{1}H RMN (base libre) (400 MHz, DMSO-d_6) δ ppm 0,75 - 0,86 (m, 12 H), 1,71 (d, J=4,99 Hz, 2 H), 1,86 - 2,05 (m, 6 H), 2,12 - 2,23 (m, 3 H), 2,55 (s, 2 H), 2,70 (s, 6 H), 3,16 (s, 2 H), 3,52 (s, 6 H), 3,81 (s, 3 H), 4,05 (t, J=8,35 Hz, 2 H), 5,09 - 5,18 (m, 2 H), 5,33 (d, J=5,53 Hz, 2 H), 6,33 (d, J=9,00 Hz, 1 H), 6,63 (dd, J=9,05, 2,98 Hz, 1 H), 7,04 (d, J=7,70 Hz, 2 H), 7,19 - 7,31 (m, 4 H), 7,34 - 7,48 (m, 2 H), 12,02 (s, 2 H); MS (ESI) m/z 877 $(M+H)^+$.



Ejemplo 176

{(2S)-1-[(2S)-2-{6-[(2R,5R)-1-(6-tert-butilpiridin-3-il)-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-bencimidazol-6-il}pirrolidin-2-il]-1H-bencimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

Se procesó 6-tert-Butilpiridin-3-amina usando los métodos a los que se refiere o que se describen en el Ejemplo 174 para dar el compuesto del título (62,5 mg). ^{1}H RMN (base libre) (400 MHz, DMSO-d_6) δ ppm 0,74 - 0,88 (m, 12 H), 1,08 (s, 9 H), 1,68 - 1,77 (m, 2 H), 1,83 - 2,04 (m, 7 H), 2,12 - 2,23 (m, 4 H), 2,53 - 2,61 (m, 2 H), 3,16 (d, J=5,20 Hz, 2 H), 3,52 (s, 6 H), 3,76 - 3,85 (m, 4 H), 4,00 - 4,11 (m, 3 H), 5,08 - 5,16 (m, 2 H), 5,37 - 5,46 (m, 2 H), 6,54 - 6,61 (m, 1 H), 6,88 - 6,96 (m, 2 H), 7,08 (t, J=9,00 Hz, 2 H), 7,20 (s, 1 H), 7,25 - 7,31 (m, 3 H), 7,39 (d, J=8,13 Hz, 1 H), 7,47 (d, J=8,24 Hz, 1 H), 7,60 (d, J=3,25 Hz, 1 H), 12,04 (d, J=27,76 Hz, 2 H); MS (ESI) m/z 890 $(M+H)^+$.



Ejemplo 177

{(2S)-1-[(2S)-2-(6-{(2S,5S)-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-

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metilbutanoil}pirrolidin-2-il]-1H-bencimidazol-6-il}-1-[6-(piperidin-1-il)piridin-3-il]pirrolidin-2-il}-1H-bencimidazol-2-il)pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

Ejemplo 177A

5-((2S,5S)-2,5-bis(4-cloro-3-nitrofenil)pirrolidin-1-il)-2-(piperidin-1-il)piridina

Se procesó (1R,4R)-1,4-bis(4-cloro-3-nitrofenil)butan-1,4-diol (preparado utilizando (S)-(+)-alfa,alfa-difenil-2-pirrolidinmetanol y el método del Ejemplo 109C) (0,60 g, 1,5 mmol) usando el método descrito en el Ejemplo 182A para dar el compuesto del título (0,41 g, 50%).

Ejemplo 177B

(2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-((2S,5S)-1-(6-(piperidin-1-il)piridin-3-il)pirrolidin-2,5-diil)bis(2-nitro-4,1-fenilen))bis(azandiil)bis(oxometilen)bis(pirrolidin-2,1-diil))bis(3-metil-1-oxobutan-2,1-diil)dicarbamato de dimetilo

El producto del Ejemplo 177A (0,20 g, 0,369 mmol) se combinó con el producto del Ejemplo 116C (0,30 g, 1,11 mmol), carbonato de cesio (0,336 g, 1,03 mmol), Xantphos (38 mg, 0,066 mmol) y tris(dibencilidenacetona)dipaladio (20,3 mg, 0,022 mmol). Se agregó 1,4-dioxano anhidro (3,7 ml), y la mezcla se burbujeó con N_2 gaseoso durante 15 min. La mezcla resultante se agitó en un tubo sellado a 100 °C durante 2 h. La mezcla se enfrió a temperatura ambiente, se diluyó con agua y se extrajo con acetato de etilo. El extracto orgánico se lavó con salmuera, se secó ($NaSO_4$), se filtró y se concentró. La purificación mediante cromatografía flash dos veces (gel de sílice, MeOH 0-10%/CH_2Cl_2) dio el compuesto del título (235 mg, 60%).

Ejemplo 177C

(2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-((2S,5S)-1-(6-(piperidin-1-il)piridin-3-il)pirrolidin-2,5-diil)bis(2-amino-4,1-fenilen))bis(azandiil)bis(oxometilen)bis(pirrolidin-2,1-diil))bis(3-metil-1-oxobutan-2,1-diil)dicarbamato de dimetilo

A una solución del producto del Ejemplo 177B (237mg, 0,234 mmol) en etanol (1,2 ml) y tetrahidrofurano (1,2 ml) se agregó óxido de platino(IV) (13,29 mg, 0,059 mmol). La mezcla se colocó bajo una atmósfera de hidrógeno durante aproximadamente 1 hora. La mezcla se filtró sobre celite, lavando con metanol y se concentró. La purificación mediante cromatografía flash (gel de sílice, MeOH 0-10%/CH_2Cl_2) dio el compuesto del título (186 mg, 84%).

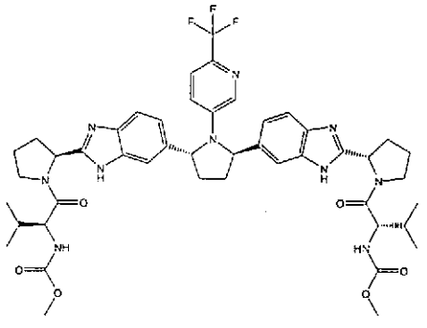
Ejemplo 177D

{(2S)-1-[(2S)-2-(6-{(2S,5S)-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-bencimidazol-6-il}-1-[6-(piperidin-1-il)piridin-3-il]pirrolidin-2-il}-1H-bencimidazol-2-il)pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

A una solución del producto del Ejemplo 177C (113 mg, 0,119 mmol) en tolueno

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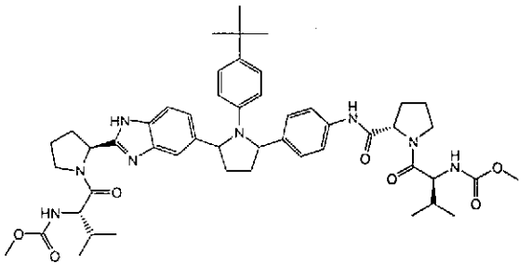
(1,2 ml) se agregó ácido acético (34 µL, 0,593 mmol) y filtros moleculares de 3A. La mezcla se calentó a 60 °C durante 2 horas. La reacción se enfrió a temperatura ambiente y se diluyó con acetato de etilo. La fase orgánica se lavó con $NaHCO_3$ acuoso saturado, se secó (Na_2SO_4), se filtró y se concentró. El producto crudo se purificó mediante HPLC en fase reversa (C18) usando un gradiente de solvente de 10-90% CH_3CN en agua (TFA al 0,1%). Las fracciones que contenían el producto deseado se juntaron y se concentró al vacío, y el residuo se particionó entre $NaHCO_3$ acuoso saturado, y CH_2Cl_2. La capa orgánica se secó (Na_2SO_4), se filtró y se concentró para dar el compuesto del título (9 mg, 8%). 1H RMN (400 MHz, DMSO-D6) δ ppm 0,78 - 0,85 (m, 7 H), 0,87 (dd, *J*=6,7, 3,0 Hz, 6 H), 1,23 (s, 1 H), 1,43 (s, 6 H), 1,72 (s, 2 H), 1,97 (s, 5 H), 2,18 (s, 3 H), 3,09 (s, 4 H), 3,30 (s, 2 H), 3,53 (d, *J*=1,5 Hz, 6 H), 3,81 (s, 4 H), 4,07 (s, 2 H), 5,13 (s, 2 H), 5,33 (s, 2 H), 6,48 (d, *J*=4,4 Hz, 1 H), 6,59 - 6,64 (m, 1 H), 7,05 (s, 2 H), 7,22 (s, 1 H), 7,25 - 7,34 (m, 4 H), 7,37 (s, 1 H), 7,44 (s, 1 H), 12,06 (s, 2 H); MS (ESI) m/z 916 $(M+H)^+$.



Ejemplo 178

{(2S)-1-[(2S)-2-(6-{(2R,5R)-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-bencimidazol-6-il}-1-[6-(trifluorometil)piridin-3-il]pirrolidin-2-il}-1H-bencimidazol-2-il)pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

El Ejemplo 109C y 5-amino-2-(trifluorometil)piridina se procesaron utilizando en forma consecutiva los métodos de los Ejemplos 182A, 177B, 177C, y 177D para dar el compuesto del título. 1H RMN (400 MHz, DMSO-D6) δ ppm 0,79 - 0,89 (m, 15 H), 1,61 (s, 4 H), 1,97 (s, 6 H), 2,19 (s, 5 H), 3,50 - 3,58 (m, 7 H), 3,82 (s, 4 H), 3,99 - 4,10 (m, 2 H), 5,15 (s, 2 H), 6,89 - 6,98 (m, 2 H), 7,19 (s, 1 H), 7,26 - 7,34 (m, 4 H), 7,36 (d, *J*=8,2 Hz, 1 H), 11,94 (d, *J*=12,9 Hz, 2 H). MS m/z 901 $(M+H)^+$.



Ejemplo 179

N-(metoxicarbonil)-L-valil-N-{4-[(2*S*,5*S*)1-(4-tert-butilfenil)-5-(2-{(2S)-1-[N-(metoxicarbonil)-L-valil]pirrolidin-2-il}-1H-bencimidazol-5-il)pirrolidin-2-il]fenil}-L-prolinamida

y

N-(metoxicarbonil)-L-valil-*N*-{4-[(2*R*,5*R*)-1-(4-*tert*-butilfenil)-5-(2-{(2*S*)-1-[*N*-(metoxicarbonil)-L-valil]pirrolidin-2-il}-1*H*-bencimidazol-5-il)pirrolidin-2-il]fenil}-L-prolinamida

Ejemplo 179A

1-(4-cloro-3-nitrofenil)-4-(4-nitrofenil)butan-1,4-diona

A una mezcla de cloruro de cinc (39,1 g, 287 mmol) en benceno (215 ml) se agregó dietilamina (22,24 ml, 215 mmol) y 2-metilpropan-2-ol (20,57 ml, 215 mmol). La mezcla resultante se agitó a temperatura ambiente durante 2h, y se agregaron 2-bromo-1-(4-nitrofenil)etanona (35,0 g, 143 mmol) y 1-(4-cloro-3-nitrofenil)etanona (42,9 g, 215 mmol) en una porción. La mezcla resultante se agitó a temperatura ambiente durante la noche. Se agregó H_2SO_4 ac. 5% (50 ml) y se agitó enérgicamente para inducir la precipitación. El sólido resultante se recogió mediante filtración y se lavó en forma sucesiva con benceno, agua, metanol, y CH_2Cl_2. El sólido se secó al vacío para dar el compuesto del título.

Ejemplo 179B

1-(4-cloro-3-nitrofenil)-4-(4-nitrofenil)butan-1,4-diol

A una solución del producto del Ejemplo 179A (10,0 g, 27,6 mmol) en EtOH (220 ml) se agregó borhidruro de sodio (2,190 g, 57,9 mmol) en varias porciones durante 1 h. La mezcla resultante se agitó a temperatura ambiente durante 1 h, se filtró a través de celite, y se concentró al vacío. El residuo se disolvió en EtOAc y se lavó con HCl ac. 1N. La capa orgánica se secó sobre Na_2SO_4, se filtró y se concentró al vacío para dar el compuesto del título (9,29 g, 92%)

Ejemplo 179C

1-(4-tert-butilfenil)-2-(4-cloro-3-nitrofenil)-5-(4-nitrofenil)pirrolidina

A una solución de producto del Ejemplo 179B (9,29 g, 25,3 mmol) en CH_2Cl_2 anhidro (200 ml) a 0 °C se agregó trietilamina (10,53 ml, 76 mmol), y luego se agregó por goteo cloruro de metansulfonilo (4,93 ml, 63,3 mmol). La mezcla resultante se agitó a 0 °C durante 2 h, y luego se concentró al vacío. El sólido resultante se disolvió en DMF anhidro (70 ml), se agregó 4-tert-butilanilina (40,4 ml, 253 mmol), y la mezcla resultante se agitó a 50 °C durante 1 h. La mezcla resultante se enfrió a temperatura ambiente y se volcó en HCl acuoso 1N helado (500 ml) para dar un precipitado amarillo. El precipitado se recogió mediante filtración y se secó para dar el compuesto del título (13,2 g).

Ejemplo 179D

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4-(1-(4-tert-butilfenil)-5-(4-nitrofenil)pirrolidin-2-il)-N-(4-metoxibencil)-2-nitroanilina

El producto del Ejemplo 179C (13,2 g, 27,5 mmol) y 4-metoxibencilamina (18 ml, 139 mmol) se combinaron y se agitó a 145 °C durante 1,5 h. La mezcla se enfrió a temperatura ambiente, y se agregó CH_2Cl_2. El precipitado resultante se retiró por filtración, y el material filtrado se lavó en forma sucesiva con HCl acuoso 1N y $NaHCO_3$ acuoso saturado. La capa orgánica se secó sobre Na_2SO_4, se filtró y se concentró al vacío. El producto crudo se purificó mediante cromatografía en columna sobre gel de sílice usando un gradiente de solvente de 0-25% de EtOAc en hexano para dar el compuesto del título (5,0 g, 31%).

Ejemplo 179E

4-(5-(4-aminofenil)-1-(4-tert-butilfenil)pirrolidin-2-il)-N1-(4-metoxibencil)bencen-1,2-diamina

A una solución del producto del Ejemplo 179D (2,74 g, 4,72 mmol) en EtOH (25 ml) y THF (25 ml) se agregó óxido de platino(IV) (0,5 g, 2,2 mmol). La mezcla resultante se agitó a temperatura ambiente bajo 1 atm de H_2 durante la noche. La mezcla se filtró a través de celite, se lavó con metanol, y el material filtrado se concentró al vacío. El producto crudo se purificó mediante cromatografía en columna sobre gel de sílice usando un gradiente de solvente de 0-45% de EtOAc en hexano para dar el compuesto del título (1,74 g, 71%).

Ejemplo 179F

(2S)- 2-(4-(5-(3-((S)-1-(tert-butoxicarbonil)pirrolidin-2-carboxamido)-4-(4-metoxibencilamino)fenil)-1-(4-tert-butilfenil)pirrolidin-2-il)fenilcarbamoil)pirrolidin-1-carboxilato de tert-butilo

A una mezcla del producto del Ejemplo 179E (1,74 g, 3,33 mmol), ácido (S)-1-(tert-butoxicarbonil)pirrolidin-2-carboxílico (1,793 g, 8,33 mmol) y HATU (3,17 g, 8,33 mmol) en DMSO (33 ml) se agregó base de Hunig (1,746 ml, 10,00 mmol). La mezcla resultante se agitó a temperatura ambiente durante 1 h y se particionó entre H_2O y CH_2Cl_2. La capa orgánica se secó sobre Na_2SO_4, se filtró y se concentró al vacío. El producto crudo se purificó mediante cromatografía en columna sobre gel de sílice usando un gradiente de solvente de 0-25% de EtOAc en hexano para dar el compuesto del título (2,1 g, 69%).

Ejemplo 179G

(2S)- 2-(4-(5-(4-amino-3-((S)-1-(tert-butoxicarbonil)pirrolidin-2-carboxamido)fenil)-1-(4-tert-butilfenil)pirrolidin-2-il)fenilcarbamoil)pirrolidin-1-carboxilato de tert-butilo

A una solución del producto del Ejemplo 179F (1,06 g, 1,16 mmol) en CH_2Cl_2 (40 ml) y H_2O (2 ml) se agregó 2,3-dicloro-5,6-diciano-1,4-benzoquinona (DDQ) (0,316 g, 1,393 mmol) en varias porciones. La mezcla se agitó a temperatura ambiente durante 20 min y se lavó con $NaHCO_3$ acuoso saturado. La capa orgánica se secó sobre Na_2SO_4, se

filtró y se concentró al vacío. El producto crudo se purificó mediante cromatografía en columna sobre gel de sílice usando un gradiente de solvente de 0-25% de EtOAc en hexano para dar el compuesto del título (0,53 g, 57%).

Ejemplo 179H

(2S)- 2-(4-(5-(2-((S)-1-(tert-butoxicarbonil)pirrolidin-2-il)-1H-benzo[d]imidazol-5-il)-1-(4-tert-butilfenil)pirrolidin-2-il)fenilcarbamoil)pirrolidin-1-carboxilato de tert-butilo

Una solución de producto del Ejemplo 179G (0,526 g, 0,662 mmol) en ácido acético (4,73 ml, 83 mmol) se agitó a 65 °C durante 1 h. La mezcla resultante se particionó entre CH_2Cl_2 y $NaHCO_3$ acuoso saturado. La capa orgánica se secó sobre Na_2SO_4, se filtró y se concentró al vacío. El producto crudo se purificó mediante cromatografía en columna sobre gel de sílice usando un gradiente de solvente de 0-2,5% de MeOH en CH_2Cl_2 para dar el compuesto del título (0,23 g, 45%).

Ejemplo 179I

(S)-N-(4-((2S,5S)-1-(4-tert-butilfenil)-5-(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol-5-il)pirrolidin-2-il)fenil)pirrolidin-2-carboxamida

y

(S)-N-(4-((2R,5R)-1-(4-tert-butilfenil)-5-(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol-5-il)pirrolidin-2-il)fenil)pirrolidin-2-carboxamida

A una solución del producto del Ejemplo 179H (0,302 g, 0,389 mmol) en CH_2Cl_2 (3 ml) se agregó TFA (2,5 ml), y la mezcla resultante se agitó a temperatura ambiente durante 1,5 h. La mezcla se concentró al vacío, y el producto crudo se purificó mediante HPLC en fase reversa (C18) usando un gradiente de solvente de 10-100% de acetonitrilo en H_2O (TFA al 0,1%). El isómero trans-pirrolidina eluyó antes que el isómero cis-pirrolidina. Las fracciones que contenían el isómero trans se concentraron al vacío, y el residuo se particionó entre CH_2Cl_2 y $NaHCO_3$ acuoso saturado. La capa orgánica se secó sobre Na_2SO_4, se filtró y se concentró al vacío para dar el compuesto del título (83 mg, 37%).

Ejemplo 179J

N-(metoxicarbonil)-L-valil-N-{4-[(2*S*,5*S*)1-(4-tert-butilfenil)-5-(2-{(2S)-1-[N-(metoxicarbonil)-L-valil]pirrolidin-2-il}-1H-bencimidazol-5-il)pirrolidin-2-il]fenil}-L-prolinamida

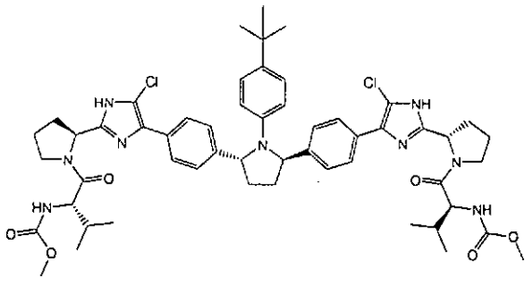
y

N-(metoxicarbonil)-L-valil-*N*-{4-[(2*R*,5*R*)-1-(4-*tert*-butilfenil)-5-(2-{(2*S*)-1-[*N*-(metoxicarbonil)-L-valil]pirrolidin-2-il}-1*H*-bencimidazol-5-il)pirrolidin-2-il]fenil}-L-prolinamida

A una mezcla del producto del Ejemplo 179I (83 mg, 0,144 mmol), ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico (63 mg, 0,361 mmol), y HATU (0,137 g, 0,361 mmol) en DMSO (1,5 ml) se agregó base de Hunig (0,101 ml, 0,578 mmol), y la mezcla

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resultante se agitó a temperatura ambiente durante 1 h. La mezcla se particionó entre CH_2Cl_2 y H_2O. La capa orgánica se secó sobre Na_2SO_4, se filtró y se concentró al vacío. El producto crudo se purificó mediante cromatografía en columna sobre gel de sílice usando un gradiente de solvente de 0-3,5% de MeOH en CH_2Cl_2 para dar los compuestos del título (80 mg, 60%). 1H RMN (400 MHz, DMSO-D6) δ ppm 0,74 - 0,99 (m, 12 H), 1,09 (s, 9 H), 1,59 - 1,73 (m, 2 H), 1,81 - 2,05 (m, 6 H), 2,07 - 2,24 (m, 2 H), 3,50 - 3,56 (m, 6 H), 3,58 - 3,67 (m, 1 H), 3,76 - 3,85 (m, 2 H), 3,99 - 4,10 (m, 2 H), 4,43 (dd, *J*=8,0, 4,9 Hz, 1 H), 5,08 - 5,16 (m, 1 H), 5,16 - 5,25 (m, 1 H), 5,26 - 5,37 (m, 1 H), 6,21 (d, *J*=8,8 Hz, 2 H), 6,88 - 6,97 (m, 2,5 H), 7,00 - 7,08 (m, 1 H), 7,11 - 7,20 (m, *J*=5,7 Hz, 2,5 H), 7,21 - 7,34 (m, 2 H), 7,37 (dd, *J*=8,2, 2,0 Hz, 0,5 H), 7,45 (d, *J*=8,3 Hz, 0,5 H), 7,50 (d, *J*=8,3 Hz, 2 H), 9,98 (s, 1 H), 12,01 (m, 1 H); MS m/z 891,6 $(M+H)^+$.

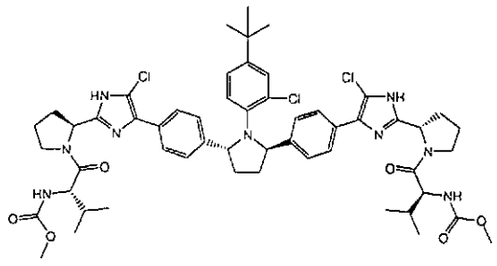


Ejemplo 180

{(2S)-1-[(2S)-2-(4-{4-[(2R,5R)-1-(4-tert-butilfenil)-5-(4-{5-cloro-2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-4-il}fenil)pirrolidin-2-il]fenil}-5-cloro-1H-imidazol-2-il)pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

A una solución del producto del Ejemplo 43 (114 mg, 0,121 mmol) en CH_2Cl_2 (1,2 ml) se agregó N-clorosuccinimida (54 mg, 0,41 mmol), y la mezcla resultante se agitó a temperatura ambiente durante 9 h. La mezcla se diluyó con CH_2Cl_2 y se lavó con $NaHCO_3$ acuoso saturado. La capa orgánica se secó sobre Na_2SO_4, se filtró, y se concentró al vacío. El producto crudo se sometió a HPLC en fase reversa (C18) usando un gradiente de solvente de 40%-100% de acetonitrilo en agua (TFA al 0,1%). Las fracciones que contenían el producto deseado se juntaron y se concentró al vacío. El residuo se purificó en una placa de TLC preparativa, eluyendo con 3% MeOH en CH_2Cl_2 para dar el compuesto del título (3,5 mg, 3%). 1H RMN (400 MHz, DMSO-D6) δ ppm 0,80 - 0,92 (m, 12 H), 1,11 (s, 9 H), 1,72 (d, *J*=5,0 Hz, 2 H), 1,87 - 2,04 (m, 6 H), 2,05 - 2,23 (m, 2 H), 3,53 (s, 6 H), 3,72 - 3,82 (m, 2 H), 4,04 (t, *J*=8,4 Hz, 2 H), 4,98 (dd, *J*=6,8, 3,5 Hz, 2 H), 5,29 (dd, *J*=3,5, 2,5 Hz, 2 H), 6,23 (d, *J*=8,8 Hz, 2 H), 6,96 (d, *J*=8,8 Hz, 2 H), 7,27 (d, *J*=8,6 Hz, 2 H), 7,32 (d, *J*=8,2 Hz, 4 H), 7,61 (d, *J*=8,1 Hz, 4 H), 12,41 (s, 2 H); MS m/z 1009,1 $(M+H)^+$.

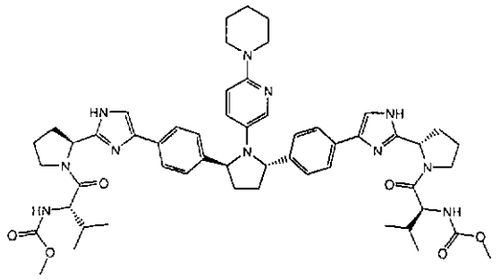
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Ejemplo 181

{(2S)-1-[(2S)-2-(4-{4-[(2R,5R)-1-(4-tert-butil-2-clorofenil)-5-(4-{5-cloro-2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-4-il}fenil)pirrolidin-2-il]fenil}-5-cloro-1H-imidazol-2-il)pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

El producto del Ejemplo 43 (114 mg, 0,121 mmol) se sometió al procedimiento descrito en el Ejemplo 180 para dar el compuesto del título (4,7 mg, 4%). 1H RMN (Sal TFA) (400 MHz, DMSO-D6) δ ppm 0,78 - 0,89 (m, 12 H), 1,05 (s, 9 H), 1,85 - 1,97 (m, 10 H), 2,04 - 2,18 (m, 4 H), 3,52 (s, 6 H), 3,69 - 3,81 (m, 4 H), 4,03 (t, *J*=8,3 Hz, 2 H), 4,95 (dd, *J*=7,0, 4,0 Hz, 2 H), 5,53 (d, *J*=7,5 Hz, 2 H), 6,91 - 6,95 (m, 1 H), 6,96 - 7,02 (m, 2 H), 7,26 (d, *J*=8,5 Hz, 2 H), 7,30 - 7,41 (m, 4 H), 7,49 (d, *J*=7,6 Hz, 4 H), 12,34 (s, 2 H); MS m/z 1045,1 $(M+H)^+$.



Ejemplo 182 [(2S)-1-{(2S)-2-[4-(4-{(2S,5S)-5-(4-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-4-il}fenil)-1-[6-(piperidin-1-il)piridin-3-il]pirrolidin-2-il}fenil)-1H-imidazol-2-il]pirrolidin-1-il}-3-metil-1-oxobutan-2-il]carbamato de metilo

Ejemplo 182A

5-((2S,5S)-2,5-bis(4-bromofenil)pirrolidin-1-il)-2-(piperidin-1-il)piridina

A una suspensión del producto del Ejemplo 69A (0,50 g, 1,25 mmol) en CH_2Cl_2 anhidro (12 ml) a 0 °C se agregó Et_3N (0,52 ml, 3,75 mmol), seguido por cloruro de metansulfonilo (0,243 ml, 3,12 mmol). La mezcla resultante se agitó a 0 °C durante 90 min y luego se evaporó a sequedad. El sólido se disolvió en DMF anhidro (10 ml), y se agregó Ejemplo 144C (1108 mg, 6,25 mmol). La mezcla resultante se agitó a 40 °C durante la noche, y se particionó entre HCl aq 0,2 N y EtOAc. La capa orgánica se secó sobre Na_2SO_4, se filtró y se concentró al vacío. El producto crudo se purificó mediante

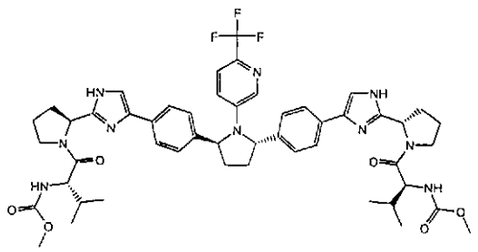
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cromatografía en columna sobre gel de sílice usando un gradiente de solvente de EtOAc y hexano para dar el compuesto del título (107 mg, 16%).

Ejemplo 182B

[(2S)-1-{(2S)-2-[4-(4-{(2S,5S)-5-(4-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-4-il}fenil)-1-[6-(piperidin-1-il)piridin-3-il]pirrolidin-2-il}fenil)-1H-imidazol-2-il]pirrolidin-1-il}-3-metil-1-oxobutan-2-il]carbamato de metilo

El producto del Ejemplo 182A se sometió a los procedimientos descritos en los Ejemplos 42D, 42E, 42F, y 42G para dar el compuesto del título. 1H RMN (base libre) (400 MHz, DMSO-D6) δ ppm 0,80 - 0,94 (m, 12 H), 1,24 (s, 4 H), 1,44 (s, 6 H), 1,89 - 2,04 (m, 6 H), 2,07 - 2,20 (m, 4 H), 3,12 (s, 4 H), 3,53 (s, 6 H), 3,77 (d, *J*=6,7 Hz, 2 H), 4,05 (t, *J*=8,4 Hz, 2 H), 5,06 (dd, *J*=6,7, 3,0 Hz, 2 H), 5,19 (d, *J*=6,4 Hz, 2 H), 6,45 - 6,53 (m, 1 H), 6,56 - 6,63 (m, 1 H), 7,15 (d, *J*=8,2 Hz, 4 H), 7,21 - 7,32 (m, 4 H), 7,38 (d, *J*=1,8 Hz, 2 H), 7,62 (d, *J*=8,0 Hz, 4 H), 11,69 (s, 2 H); MS m/z = 968,8 $(M+H)^+$.



Ejemplo 183

[(2S)-1-{(2S)-2-[4-(4-{(2S,5S)-5-(4-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-4-il}fenil)-1-[6-(trifluorometil)piridin-3-il]pirrolidin-2-il}fenil)-1H-imidazol-2-il]pirrolidin-1-il}-3-metil-1-oxobutan-2-il]carbamato de metilo

Ejemplo 183A

5-((2S,5S)-2,5-bis(4-bromofenil)pirrolidin-1-il)-2-(trifluorometil)piridina

El producto del Ejemplo 69A (1,0 g, 2,5 mmol) se sometió al procedimiento descrito en el Ejemplo 182A, utilizando 6-(trifluorometil)piridin-3-amina en lugar del Ejemplo 144C, para dar el compuesto del título (0,13 g, 10%).

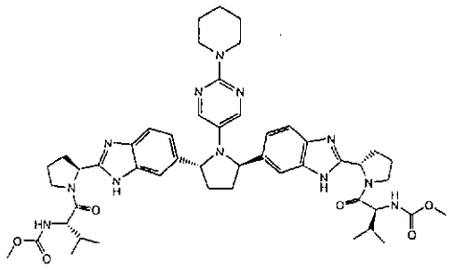
Ejemplo 183B

[(2S)-1-{(2S)-2-[4-(4-{(2S,5S)-5-(4-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-4-il}fenil)-1-[6-(trifluorometil)piridin-3-il]pirrolidin-2-il}fenil)-1H-imidazol-2-il]pirrolidin-1-il}-3-metil-1-oxobutan-2-il]carbamato de metilo

El producto del Ejemplo 183A se sometió a los procedimientos descritos en los Ejemplos 42D, 42E, 42F, y 42G para dar el compuesto del título. 1H RMN (Sal TFA) (400 MHz, DMSO-D6) δ ppm 0,75 - 0,91 (m, 12 H), 1,84 (d, *J*=5,6 Hz, 2 H), 1,96 - 2,10 (m, 6 H), 2,11 - 2,20 (m, *J*=10,8, 5,5 Hz, 2 H), 3,54 (s, 6 H), 3,76 - 3,91 (m, 4 H), 4,10 (t, *J*=7,9

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Hz, 2 H), 5,11 (t, *J*=6,8 Hz, 2 H), 5,56 (d, *J*=5,1 Hz, 2 H), 6,74 (dd, *J*=8,8, 2,5 Hz, 1 H), 7,32 (d, *J*=8,5 Hz, 2 H), 7,41 (d, *J*=7,8 Hz, 4 H), 7,44 - 7,48 (m, *J*=8,8 Hz, 1 H), 7,71 (d, *J*=8,2 Hz, 4 H), 7,76 (d, *J*=2,5 Hz, 1 H), 7,97 (s, 2 H), 14,50 (s, 2 H); MS m/z 953,6 $(M+H)^+$.



Ejemplo 184

{(2S)-1-[(2S)-2-(6-{(2R,5R)-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-bencimidazol-6-il}-1-[2-(piperidin-1-il)pirimidin-5-il]pirrolidin-2-il}-1H-bencimdazol-2-il)pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

Ejemplo 184A

2-(piperidin-1-il)pirimidin-5-amina

A una suspensión de 2-cloro-5-nitropirimidina (1,5 g, 9,40 mmol) en EtOH (15 ml) se agregó piperidina (2,79 ml, 28,2 mmol), y la mezcla resultante se sometió a reflujo durante 2 h. La mezcla fría se concentró al vacío, y el residuo se particionó entre CH_2Cl_2 y $NaHCO_3$ acuoso saturado. La capa orgánica se secó sobre Na_2SO_4, se filtró y se concentró al vacío para dar un sólido (1,65 g, 84%). El sólido se colocó en una botella de presión de acero inoxidable de 250 ml y se disolvió en THF (20 ml). Se agregó Ni Raney 2800 suspendido en agua (1,650 g, 28,1 mmol), y la mezcla se agitó a temperatura ambiente durante 2 h bajo gas H_2 a una presión de 30 psi. La mezcla se filtró a través de una membrana de nylon y se concentró al vacío para dar el compuesto del título (1,4 g, 99%).

Ejemplo 184B

5-((2R,5R)-2,5-bis(4-cloro-3-nitrofenil)pirrolidin-1-il)-2-(piperidin-1-il)pirimidina

El producto del Ejemplo 109C (1,09 g, 2,72 mmol) se sometió a las condiciones descritas en el Ejemplo 182A, utilizando Ejemplo 184A en lugar del Ejemplo 144C, para dar el compuesto del título (0,59 g, 40%).

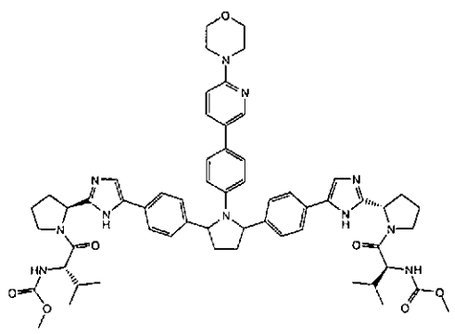
Ejemplo 184C

{(2S)-1-[(2S)-2-(6-{(2R,5R)-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-bencimidazol-6-il}-1-[2-(piperidin-1-il)pirimidin-5-il]pirrolidin-2-il}-1H-bencimdazol-2-il)pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

El producto del Ejemplo 184B se sometió a los procedimientos descritos en los

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Ejemplos 177B, 177C, y 177D para dar el compuesto del título. 1H RMN (Sal TFA) (400 MHz, DMSO-D6) δ ppm 0,71 - 0,91 (m, 12 H), 1,24 (s, 2 H), 1,32 - 1,41 (m, 4 H), 1,44 - 1,52 (m, 2 H), 1,82 (d, *J*=5,1 Hz, 2 H), 1,92 - 2,26 (m, 12 H), 3,86 (s, 6 H), 4,12 (t, *J*=8,0 Hz, 2 H), 5,20 (dd, *J*=8,0, 5,2 Hz, 2 H), 5,54 (d, *J*=6,2 Hz, 2 H), 7,33 (d, *J*=8,3 Hz, 2 H), 7,40 (d, *J*=7,8 Hz, 2 H), 7,51 (s, 2 H), 7,57 - 7,61 (m, 2 H), 7,72 (d, *J*=8,3 Hz, 2 H); MS m/z 917,5 $(M+H)^+$.



Ejemplo 185

{(2*S*)-1-[(2*S*)-2-(5-{4-[(2*S*,5*S*)-5-(4-{2-[(2*S*)-1-{(2*S*)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1*H*-imidazol-5-il}fenil)-1-{4-[6-(morfolin-4-il)piridin-3-il]fenil}pirrolidin-2-il]fenil}-1*H*-imidazol-2-il)pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

y

{(2*S*)-1-[(2*S*)-2-(5-{4-[(2*R*,5*R*)-5-(4-{2-[(2*S*)-1-{(2*S*)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1*H*-imidazol-5-il}fenil)-1-{4-[6-(morfolin-4-il)piridin-3-il]fenil}pirrolidin-2-il]fenil}-1*H*-imidazol-2-il)pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

Ejemplo 185A

2,5-bis(4-bromofenil)-1-(4-yodofenil)pirrolidina

El producto del Ejemplo 42B (1,39 g, 2,499 mmol) en DMF (6,25 ml) se trató con 4-yodoanilina (Aldrich, 4,38 g, 19,99 mmol), se calentó a 40-50 °C durante dos horas, se enfrió y se diluyó con EtOAc. La capa de EtOAc se lavó 3 X 50 ml con HCl 1 M, con agua, salmuera, se secó (Na_2SO_4), se filtró y se concentró. La purificación mediante cromatografía flash en un cartucho de sílice ISCO de 40 g eluyendo con EtOAc al 0-20% en hexano dio el compuesto del título como una espuma color tostado como una mezcla de estereoisómeros (0,96 g, 66 %). MS (ESI) m/z 584 $(M+H)^+$.

Ejemplo 185B

4-(5-(4-(2,5-bis(4-bromofenil)pirrolidin-1-il)fenil)piridin-2-il)morfolina

El producto del Ejemplo 185A (0,1 g, 0,171 mmol), 4-(5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)piridin-2-il)morfolina (0,050 g, 0,171 mmol), fosfato de potasio (0,028 ml,

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0,343 mmol), tris(dibencilidenacetona)dipaladio(0) (1,570 mg, 1,715 µmol) y 1,3,5,7-tetrametil-6-fenil-2,4,8-trioxa-6-fosfadamantano (1,504 mg, 5,14 µmol) se combinaron en THF (1,2 ml) / agua (0,4 ml). La mezcla se burbujeó con nitrógeno durante 15 minutos, se diluyó con EtOAc, se lavó con bicarbonato de sodio 1M, salmuera, se secó (Na_2SO_4), se filtró y se concentró. La purificación mediante cromatografía flash en un cartucho de sílice Isco de 12 g eluyendo con 20-70 % de EtOAc en hexano dio el compuesto del título como un polvo color crema (91 mg, 86%). %). MS (ESI) m/z 620 $(M+H)^+$.

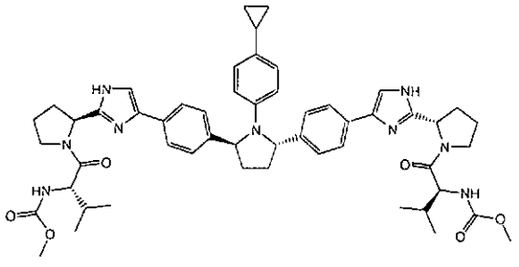
Ejemplo 185C

{(2*S*)-1-[(2*S*)-2-(5-{4-[(2*S*,5*S*)-5-(4-{2-[(2*S*)-1-{(2*S*)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1*H*-imidazol-5-il}fenil)-1-{4-[6-(morfolin-4-il)piridin-3-il]fenil}pirrolidin-2-il]fenil}-1*H*-imidazol-2-il)pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

y

{(2*S*)-1-[(2*S*)-2-(5-{4-[(2*R*,5*R*)-5-(4-{2-[(2*S*)-1-{(2*S*)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1*H*-imidazol-5-il}fenil)-1-{4-[6-(morfolin-4-il)piridin-3-il]fenil}pirrolidin-2-il]fenil}-1*H*-imidazol-2-il)pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

El producto del Ejemplo 185B se procesó como se describe en el Ejemplo 42D, 42E, 42F, y 42G para dar los compuestos del título. ^{1}H RMN (base libre) (400 MHz, DMSO-d_6) δ 0,77 - 0,94 (m, 12 H) 1,71 - 2,47 (m, 16 H) 3,36 - 3,42 (m, 4 H) 3,53 (s, 6 H) 3,63 - 3,71 (m, 4 H) 3,74 - 3,84 (m, 3 H) 4,00 - 4,08 (m, 1 H) 4,79 (d, J=4,23 Hz, 1 H) 5,02 - 5,11 (m, 2 H) 5,24 - 5,32 (m, 1 H) 6,37 (d, J=8,89 Hz, 1 H) 6,49 (d, J=8,78 Hz, 1 H) 6,79 (dd, J=14,91, 8,95 Hz, 1 H) 7,12 - 7,78 (m, 15 H) 8,23 - 8,31 (m, 1 H) 11,64 - 12,11 (m, 2 H). MS (ESI) m/z 1046 $(M+H)^+$.

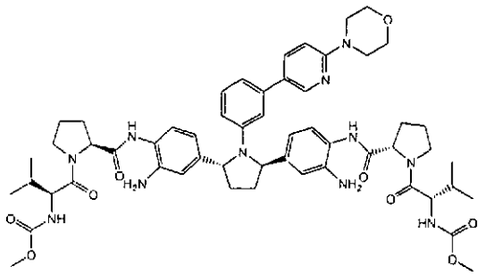


Ejemplo 186

{(2S)-1-[(2S)-2-(4-{4-[(2S,5S)-1-(4-ciclopropilfenil)-5-(4-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-4-il}fenil)pirrolidin-2-il]fenil}-1H-imidazol-2-il)pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

El producto del Ejemplo 95B se purificó mediante cromatografía quiral en una columna Chiralpak IB eluyendo con una mezcla de hexano/THF/metanol (85/10/5). El

compuesto del título fue el segundo de los 2 diaestereoisómeros en eluir. 1H RMN (400 MHz, DMSO-D6) δ ppm 0,35 - 0,42 (m, 2 H) 0,65 - 0,73 (m, 2 H) 0,80 - 0,92 (m, 12 H) 1,58 - 1,65 (m, 1 H) 1,67 - 1,71 (m, 2 H) 1,87 - 2,02 (m, 6 H) 2,07 - 2,17 (m, 4 H) 3,53 (s, 6 H) 3,70 - 3,85 (m, 4 H) 4,05 (t, J=8,35 Hz, 2 H) 5,06 (dd, J=6,72, 2,82 Hz, 2 H) 5,16 - 5,25 (m, 2 H) 6,19 (d, J=8,67 Hz,, 2 H) 6,64 (d, J=8,57 Hz, 2 H) 7,09 - 7,32 (m, 6 H) 7,36 - 7,69 (m, 6 H) 11,60 - 12,09 (m, 2 H); MS (ESI+) m/z 924,6 (M+H).



Ejemplo 187

([(2R,5R)-1-{3-[6-(morfolin-4-il)piridin-3-il]fenil}pirrolidin-2,5-diil]bis{(2-aminobencen-4,1-diil)carbamoil(2S)pirrolidin-2,1-diil[(2S)-3-metil-1-oxobutan-1,2-diil]})biscarbamato de dimetilo

Ejemplo 187A

(2R,5R)-2,5-bis(4-cloro-3-nitrofenil)-1-(3-yodofenil)pirrolidina

El mesilato del Ejemplo 109C (4,17 g, 7,48 mmol) en DMF (15 ml) se trató con 3-yodoanilina (Aldrich, 7,2 ml, 59,8 mmol), se agitó a temperatura ambiente durante 48 horas y se diluyó con EtOAc. La capa de EtOAc se lavó 3 X 50 ml con HCl 1 M, con agua, salmuera, se secó (Na_2SO_4), se filtró y se concentró. La purificación mediante cromatografía flash en un cartucho de sílice Isco de 300 g eluyendo con 10-30% de EtOAc en hexano dio el compuesto del título como una espuma color amarillo intenso (2,6 g, 60 %). MS (ESI) m/z 584 $(M+H)^+$.

Ejemplo 187B

4-(5-(3-((2R,5R)-2,5-bis(4-cloro-3-nitrofenil)pirrolidin-1-il)fenil)piridin-2-il)morfolina

El producto del Ejemplo 187A (1,4 g, 2,396 mmol), 4-(5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)piridin-2-il)morfolina (0,695 g, 2,396 mmol), fosfato de potasio (1,017 g, 4,79 mmol), tris(dibencilidenacetona)dipaladio(0) (0,022 g, 0,024 mmol) y 1,3,5,7-tetrametil-6-fenil-2,4,8-trioxa-6-fosfadamantano (0,021 g, 0,072 mmol) se combinaron en THF (18 ml) / agua (6 ml). La mezcla se burbujeó con nitrógeno durante 15 minutos, se agitó durante 6 horas se diluyó con EtOAc, se lavó con bicarbonato de sodio 1M, salmuera, se secó (Na_2SO_4), se filtró y se concentró. La purificación mediante cromatografía flash en un cartucho de sílice Isco de 120 g eluyendo con 20-60 % EtOAc en hexano dio el compuesto del título como un vidrio color amarillo (1,1 g, 74%). MS (ESI)

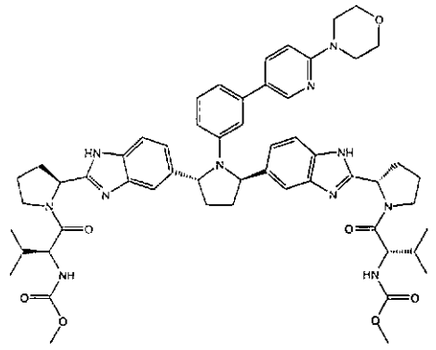
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m/z 620 $(M+H)^+$.

Ejemplo 187C

([(2R,5R)-1-{3-[6-(morfolin-4-il)piridin-3-il]fenil}pirrolidin-2,5-diil]bis{(2-aminobencen-4,1-diil)carbamoil(2S)pirrolidin-2,1-diil[(2S)-3-metil-1-oxobutan-1,2-diil]})biscarbamato de dimetilo

El producto del Ejemplo 187B (0,5 g, 0,806 mmol), se procesó usando los métodos en los Ejemplos 165C y 165D para dar el compuesto del título (400 mg, 45% en dos pasos). ^{1}H RMN (400 MHz, DMSO-d_6) δ 0,89 (dd, *J*=11,82, 6,61 Hz, 12 H) 1,35 - 2,22 (m, 14 H) 3,36 - 3,46 (m, 8 H) 3,52 (s, 6 H) 3,56 - 3,86 (m, 4 H) 3,97 - 4,43 (m, 4 H) 4,85 (s, 4 H) 5,09 (s, 2 H) 6,25 (d, *J*=7,26 Hz, 1 H) 6,42 - 6,51 (m, 3 H) 6,58 (s, 2 H) 6,66 (d, *J*=7,59 Hz, 1 H) 6,81 (d, *J*=8,78 Hz, 1 H) 6,95 - 7,02 (m, 3 H) 7,36 (d, *J*=8,35 Hz, 2 H) 7,51 (dd, *J*=8,73, 2,33 Hz, 1 H) 8,12 (d, *J*=2,06 Hz, 1 H) 9,23 (s, 2 H). MS (ESI) m/z 1031 $(M+H)^+$.

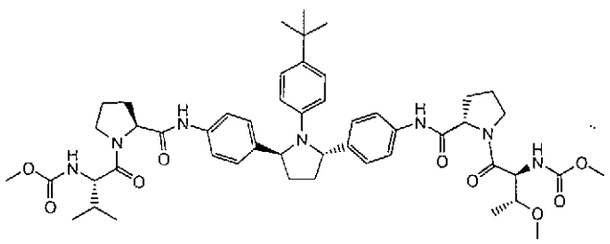


Ejemplo 188

{(2S)-1-[(2S)-2-{5-[(2R,5R)-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-bencimidazol-5-il}-1-{3-[6-(morfolin-4-il)piridin-3-il]fenil}pirrolidin-2-il]-1H-bencimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

El producto del Ejemplo 187C (0,4 g, 0,388 mmol) se trató con ácido acético (0,089 ml, 1,553 mmol) en tolueno (7,77 ml) a 50 °C durante 4 horas, se enfrió y se concentró. El residuo se disolvió en EtOAc, se lavó con bicarbonato de sodio 10%, salmuera, se secó (Na_2SO_4), se filtró y se concentró. La purificación mediante cromatografía flash en un cartucho de sílice Isco Gold de 12 g eluyendo con 1-6% de MeOH en diclorometano dio el compuesto del título (183 mg, 45%). ^{1}H RMN (400 MHz, DMSO-d_6) δ 0,71 - 0,90 (m, 12 H) 1,62 - 2,28 (m, 14 H) 3,37 - 3,43 (m, 4 H) 3,53 (s, 6 H) 3,64 - 3,68 (m, 4 H) 3,80 (s, 4 H) 4,05 (t, J=8,35 Hz, 2 H) 5,08 - 5,19 (m, 2 H) 5,48 (s, 2 H) 6,29 (d, J=8,02 Hz, 1 H) 6,54 - 6,64 (m, 2 H) 6,76 (d, J=8,89 Hz, 1 H) 6,93 (d, J=4,66 Hz, 1 H) 7,11 (d, J=8,13 Hz, 2 H) 7,23 - 7,30 (m, 3 H) 7,34 - 7,40 (m, 2 H) 7,46 (s, 2 H) 8,05 (s, 1 H) 12,01 (s, 2 H). MS (ESI) m/z 995 $(M+H)^+$.

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Ejemplo 189

[(2S,3R)-1-{(2S)-2-[(4-{(2S,5S)-1-(4-tert-butilfenil)-5-[4-({[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]carbonil}amino)fenil]pirrolidin-2-il}fenil)carbamoil]pirrolidin-1-il}-3-metoxi-1-oxobutan-2-il]carbamato de metilo

Ejemplo 189A

(S)- 2-(4-((2S,5S)-1-(4-tert-butilfenil)-5-(4-((S)-1-((S)-2-(metoxicarbonilamino)-3-metilbutanoil)pirrolidin-2-carboxamido)fenil)pirrolidin-2-il)fenilcarbamoil)pirrolidin-1-carboxilato de tert-butilo

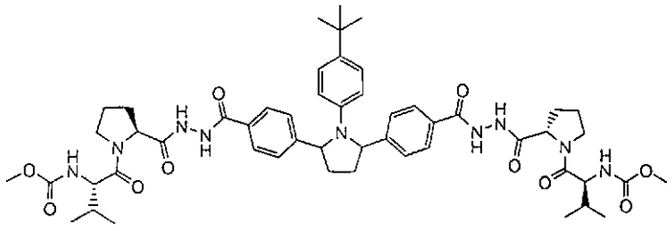
A una solución del producto del Ejemplo 213 (33 mg, 0,052 mmol) en DMSO anhidro (0,5 ml) se agregó ácido (S)-1-(tert-butoxicarbonil)pirrolidin-2-carboxílico (13,3 mg, 0,062 mmol), HATU (23,5 mg, 0,062 mmol) y base de Hunig (18 μL, 0,10 mmol). La mezcla resultante se agitó a temperatura ambiente durante 90 min y luego se particionó entre H_2O y EtOAc. La capa orgánica se secó sobre Na_2SO_4, se filtró, y se concentró al vacío. El producto crudo se purificó mediante cromatografía en columna sobre gel de sílice usando un gradiente de solvente de MeOH 0-10% en CH_2Cl_2 para dar el compuesto del título (33 mg, 76%).

Ejemplo 189B

[(2S,3R)-1-{(2S)-2-[(4-{(2S,5S)-1-(4-tert-butilfenil)-5-[4-({[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]carbonil}amino)fenil]pirrolidin-2-il}fenil)carbamoil]pirrolidin-1-il}-3-metoxi-1-oxobutan-2-il]carbamato de metilo

Una solución del producto del Ejemplo 189A (30 mg, 0,036 mmol) en una mezcla 1:1 de CH_2Cl_2:TFA (0,4 ml) se agitó a temperatura ambiente durante 45 min. La mezcla se concentró al vacío, y el residuo se particionó entre $NaHCO_3$ acuoso saturado y EtOAc (2x). Las capas orgánicas combinadas se secaron sobre Na_2SO_4, se filtró y se concentró al vacío para dar un sólido. El sólido se sometió al procedimiento descrito en el Ejemplo 189A (27 mg), utilizando ácido (2S,3R)-3-metoxi-2-(metoxicarbonilamino)butanoico en lugar de ácido (S)-1-(tert-butoxicarbonil)pirrolidin-2-carboxílico, para dar el compuesto del título (17 mg, 52%). 1H RMN (400 MHz, DMSO-D6) δ ppm 0,85 - 0,97 (m, 6 H), 1,08 - 1,19 (m, 12 H), 1,60 - 1,66 (m, 2 H), 1,80 - 2,05 (m, 8 H), 2,08 - 2,20 (m, 2 H), 3,25 (s, 3 H), 3,42 - 3,50 (m, 2 H), 3,52 (s, 3 H), 3,53 (s, 3 H), 3,58 - 3,72 (m, 2 H), 3,76 - 3,87 (m, 2

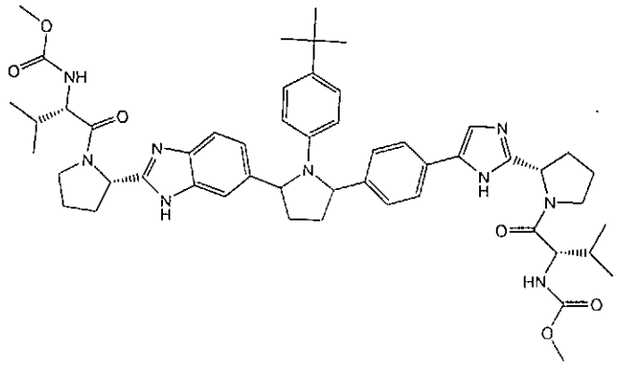
H), 3,98 - 4,06 (m, 1 H), 4,26 (t, *J*=7,81 Hz, 1 H), 4,38 - 4,46 (m, 2 H), 5,15 (d, *J*=6,40 Hz, 2 H), 6,17 (d, *J*=8,78 Hz, 2 H), 6,94 (d, *J*=8,89 Hz, 2 H), 7,13 (d, *J*=8,24 Hz, 4 H), 7,32 (t, *J*=8,84 Hz, 2 H), 7,49 (dd, *J*=8,57, 2,06 Hz, 4 H), 9,96 (d, *J*=15,51 Hz, 2 H). MS (ESI) m/z 910,6 $(M+H)^+$.



Ejemplo 190

([1-(4-tert-butilfenil)pirrolidin-2,5-diil]bis{bencen-4,1-diilcarbonilhidrazin-2,1-diilcarbonil(2S)pirrolidin-2,1-diil[(2S)-3-metil-1-oxobutan-1,2-diil]})biscarbamato) de dimetilo

A una solución del producto del Ejemplo 171B (50 mg, 0,106 mmol) y el producto del Ejemplo 37B (72 mg, 0,27 mmol) en DMSO anhidro (1 ml) se agregó HATU (100 mg, 0,27 mmol) y base de Hunig (56 µL, 0,32 mmol). La mezcla resultante se agitó a temperatura ambiente durante 90 min, y luego se particionó entre H_2O y EtOAc (2x). Las capas orgánicas combinadas se secaron sobre Na_2SO_4, se filtró, y se concentró al vacío. El producto crudo se purificó mediante cromatografía en columna sobre gel de sílice usando un gradiente de solvente de MeOH 0-10% en CH_2Cl_2 para dar el compuesto del título (68 mg, 65%) como una mezcla de estereoisómeros cis y trans. 1H RMN (400 MHz, DMSO-D6) δ ppm 0,81 - 0,98 (m, 12 H), 1,08 - 1,17 (m, 9 H), 1,64 - 1,77 (m, 2 H), 1,78 - 2,06 (m, 8 H), 2,07 - 2,22 (m, 2 H), 3,50 - 3,55 (m, 6 H), 3,58 - 3,69 (m, 2 H), 3,70 - 3,83 (m, 2 H), 3,96 - 4,08 (m, 2 H), 4,38 - 4,49 (m, *J*=8,13 Hz, 2 H), 4,76 - 4,87 (m, 0,7 H), 5,28 - 5,40 (m, 1,3 H), 6,14 - 6,33 (m, 2 H), 6,92 - 7,08 (m, 2 H), 7,27 - 7,38 (m, *J*=8,02 Hz, 5 H), 7,62 (d, *J*=8,35 Hz, 1 H), 7,79 - 7,96 (m, 4 H), 9,87 - 9,98 (m, 2 H), 10,31 - 10,44 (m, 2 H); MS (ESI) m/z 981,1 $(M+H)^+$.



Ejemplo 191

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{(2S)-1-[(2S)-2-(5-{4-[(2S,5S)-1-(4-tert-butilfenil)-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-bencimidazol-6-il}pirrolidin-2-il]fenil}-1H-imidazol-2-il)pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

y

{(2S)-1-[(2S)-2-(5-{4-[(2R,5R)-1-(4-tert-butilfenil)-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-bencimidazol-6-il}pirrolidin-2-il]fenil}-1H-imidazol-2-il)pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

Ejemplo 191A

1-(4-bromofenil)-4-(4-cloro-3-nitrofenil)butan-1,4-diona

Se trató cloruro de cinc (2,73 g, 20 mmol) con benceno anhidro (10 ml) seguido por dietilamina (1,55 ml, 15 mmol) y tert-butanol (1,4 ml, 15 mmol) y la lechada resultante se agitó a temperatura ambiente durante 1,75 hr hasta haberse disuelto todo el sólido. A la suspensión turbia se agregó 4'-cloro-3'-nitroacetofenona seguido por 2,4'-dibromoacetofenona y la suspensión color amarillo claro resultante se agitó a temperatura ambiente durante 68 horas. La lechada blanca espesa resultante se trató con 25 ml de ácido sulfúrico acuoso 5% con agitación y la lechada resultante se filtró. El sólido se lavó con agua (50 ml), MeOH (50 ml) y CH_2Cl_2 (50 ml), luego se secó al vacío a temperatura ambiente durante 1 hr y a 55°C durante 5 hr. dando el compuesto del título como un sólido blanco, 3,4 g, 86%.

Ejemplo 191B

1-(4-bromofenil)-4-(4-cloro-3-nitrofenil)butan-1,4-diol

El producto del Ejemplo 191A (4,62 g, 11,65 mmol) se mezcló con EtOH (100 ml) y la lechada resultante se trató en porciones durante un período de cinco minutos con $NaBH_4$ sólido (0,97 g, 25,6 mmol). La suspensión espumosa resultante se agitó y se calentó a reflujo durante 1 hr. La reacción resultó completa según LC-MS. La mezcla de reacción se enfrió a temperatura ambiente y se concentró al vacío para dar un residuo oleoso. El residuo se disolvió en CH_2Cl_2 y se aplicó a una columna de gel de sílice de 80 g. La columna se eluyó con un gradiente de hexano/acetona, 90/10 a 20/80 a lo largo de 32 minutos. Las fracciones que contenían producto se juntaron y se concentró al vacío dando el compuesto del título como un sólido blanco, 3,14 g, 67%.

Ejemplo 191C

dimetansulfonato de 1-(4-bromofenil)-4-(4-cloro-3-nitrofenil)butan-1,4-diilo

El producto del Ejemplo 191B (3,14 g, 7,84 mmol) se disolvió en 70 ml de CH_2Cl_2 y se enfrió en un baño de hielo-acetona hasta -10 °C. Se agregó trietilamina (3,82 ml, 27,4 mmol) por goteo a la solución fría, y luego se agregó por goteo cloruro de metansulfonilo

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(1,53 ml, 19,59 mmol) en 20 ml de CH_2Cl_2 a lo largo de 10 minutos. La solución transparente resultante se agitó en frío durante 90 min. La reacción resultó completa según el análisis por LC-MS y el solvente se eliminó al vacío dando un sólido amarillo claro como el compuesto del título, (4,36 g, 100%), que se usó directamente en la siguiente reacción.

Ejemplo 191D

2-(4-bromofenil)-1-(4-tert-butilfenil)-5-(4-cloro-3-nitrofenil)pirrolidina

El sólido amarillo claro, obtenido en el Ejemplo 191C (4,36 g, 7,84 mmol) se trató con DMF (15 ml) y luego se agregó por goteo 4-tert-butilanilina (12,47 ml, 78 mmol), luego se colocó en un baño de aceite a 52 °C y se agitó durante un total de 12 hr. La mezcla de reacción se concentró al vacío para dar un residuo oleoso. La mezcla se diluyó con 100 ml de EtOAc y se lavó con 50 ml de HCl 0,5 M. La capa acuosa volvió a extraerse con 100 ml de EtOAc. Los extractos orgánicos combinados se lavaron con $NaHCO_3$ al 10%, NaCl al 10%, se secó sobre Na_2SO_4 (s) anhidro, se filtró y el solvente se eliminó al vacío dando un aceite rojizo. El aceite se disolvió en CH_2Cl_2 (10 ml) y se aplicó a una columna de gel de sílice de 80 g. La columna se eluyó con un gradiente de hexano/Acetona, 90/10 a 30/70 a lo largo de 32 minutos. El compuesto del título se aisló como una mezcla 1:1 de isómeros cis y trans de pirrolidina, 3,13 g, 75%.

Ejemplo 191E

4-(5-(4-bromofenil)-1-(4-tert-butilfenil)pirrolidin-2-il)-N-(2,4-dimetoxibencil)-2-nitroanilina

El producto del Ejemplo 191D (1,1 g, 2,14 mmol) se trató con 2,4-dimetoxibencilamina (3,22 ml, 21,41 mmol) y la lechada resultante se calentó a 140 °C (baño de aceite) durante 1 hr. La mezcla de reacción roja homogénea resultante se concentró al vacío dando un aceite color rojo. El aceite se diluyó con 30 ml de CH_2Cl_2, se filtró el sólido y se aplicó el material filtrado a una columna de gel de sílice de 120 g. La columna se eluyó con CH_2Cl_2 a lo largo de un período de 25 min. Las fracciones se juntaron y se concentró al vacío dando el compuesto del título como un sólido espumoso anaranjado como una mezcla de estereoisómeros (1,18 g).

Ejemplo 191F

4-(5-(4-bromofenil)-1-(4-tert-butilfenil)pirrolidin-2-il)-N1-(2,4-dimetoxibencil)bencen-1,2-diamina

El producto del Ejemplo 191E (1,18 g, 1,831 mmol) se disolvió en una mezcla de THF(10 ml):EtOH(10 ml):EtOAc (10 ml), se trató con PtO_2 (42 mg) y se evacuó durante 10 minutos, y luego se introdujo H_2 (g) a través de un globo. La mezcla de reacción se agitó durante la noche a temperatura ambiente. Al día siguiente, la mezcla de reacción se filtró y el solvente se eliminó al vacío dando un sólido espumoso color verde oscuro. El sólido

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disuelto en 10 ml de CH_2Cl_2 se aplicó a una columna de gel de sílice de 40 g y se eluyó con un gradiente de hexano/EtOAc; 90/10 a 30/70 a lo largo de 20 minutos. El compuesto del título se aisló como un sólido espumoso blanco como una mezcla de isómeros 0,54 g, 48%.

Ejemplo 191G

(2S)-1-((2S)-2-(5-(5-(4-bromofenil)-1-(4-tert-butilfenil)pirrolidin-2-il)-2-(2,4-dimetoxibencilamino)fenilcarbamoil)pirrolidin-1-il)-3-metil-1-oxobutan-2-ilcarbamato de metilo

Se disolvieron ácido (S)-1-((S)-2-(metoxicarbonilamino)-3-metilbutanoil)pirrolidin-2-carboxílico (0,339g, 1,245 mmol) y HOBt (0,191 g, 1,245 mmol) en DMF (4 ml) enfriado en un baño de hielo y se trató con EDAC (0,245 g, 1,245 mmol) y N-Metilmorfolina (NMM) (0,55 ml, 4,98 mmol). La solución resultante se agitó durante 5 minutos en el baño de hielo, se trató por goteo con el producto del Ejemplo 191F en DMF (4 ml) y la mezcla oscura resultante se agitó en el baño de hielo durante 1 hr y luego a temperatura ambiente durante 18 hr. Al día siguiente, la mezcla de reacción se diluyó con EtOAc (50 ml) y la capa orgánica se lavó con $NaHCO_3$ al 10% y NaCl al 10%, se secó sobre Na_2SO_4 (s) anhidro, se filtró y el solvente se eliminó al vacío dando un residuo oleoso como el compuesto del título como una mezcla de isómeros (0,65 g). ESI+ (m/z): 868,2.

Ejemplo 191H

(2S)-1-((2S)-2-(2-amino-5-(5-(4-bromofenil)-1-(4-tert-butilfenil)pirrolidin-2-il)fenilcarbamoil)pirrolidin-1-il)-3-metil-1-oxobutan-2-ilcarbamato de metilo

El producto del Ejemplo 191G (0,65 g, 0,748 mmol) se disolvió en CH_2Cl_2 (10 ml) y luego se agregó ácido trifluoroacético concentrado (2 ml, 26 mmol)) y la mezcla de reacción se agitó durante 10 minutos. El solvente se eliminó al vacío y el residuo volvió a evaporarse dos veces desde CH_2Cl_2 y una vez desde tolueno. El residuo se disolvió en EtOAc (100 ml) se lavó con $NaHCO_3$ al 10%, se secó sobre Na_2SO_4 (s) anhidro, se filtró y el solvente se eliminó al vacío dando un material espumoso color marrón como el compuesto del título como una mezcla de isómeros (0,5 g).

Ejemplo 191I

(2S)-1-((2S)-2-(6-(5-(4-bromofenil)-1-(4-tert-butilfenil)pirrolidin-2-il)-1H-benzo[d]imidazol-2-il)pirrolidin-1-il)-3-metil-1-oxobutan-2-ilcarbamato de metilo

El producto del Ejemplo 191H (0,5 g, 0,696 mmol) se trató con ácido acético (5 ml, 87 mmol) y se calentó en un baño de aceite a 75 °C durante 70 min. La mezcla de reacción se enfrió a temperatura ambiente y se concentró al vacío dando un residuo oleoso. El residuo se disolvió en EtOAc (100 ml) se lavó con $NaHCO_3$ al 10% (20 ml) y NaCl al 10% (20 ml), se secó sobre Na_2SO_4 (s) anhidro, se filtró y el solvente se eliminó al

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vacío dando un sólido espumoso color marrón. El residuo se disolvió en 10 ml de CH_2Cl_2 y se aplicó a una columna de 12g de gel de sílice. La columna se eluyó con un gradiente de CH_2Cl_2/MeOH, 99/1 a 95/5 a lo largo de 15 minutos y el producto se aisló como un sólido color tostado como una mezcla de isómeros (0,31g). ESI(m/z)+: 702,3.

Ejemplo 191J

(2S)-1-((2S)-2-(6-(1-(4-tert-butilfenil)-5-(4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)pirrolidin-2-il)-1H-benzo[d]imidazol-2-il)pirrolidin-1-il)-3-metil-1-oxobutan-2-ilcarbamato de metilo

El producto del Ejemplo 191I (0,31g, 0,442 mmol), bis(pinacolato)diboro (0,34 g, 1,327 mmol) y acetato de potasio (0,17 g, 1,77 mmol) se combinaron y se disolvió en tolueno (5 ml), se agregó complejo 1,1'-Bis(difenilfosfino)ferrocenodicloropaladio(II) diclorometano (32 mg, 0,044 mmol) y la mezcla de reacción se burbujeó con N_2 durante 5 minutos, se selló y se colocó en un baño de aceite a 95°C durante 2 hr. La mezcla se enfrió a temperatura ambiente y se diluyó con EtOAc (100 ml) se lavó con agua (20 ml) y NaCl al 10% (20 ml), se secó sobre Na_2SO_4 (s) anhidro, se filtró y el solvente se eliminó al vacío dando un aceite marrón. El aceite se disolvió en CH_2Cl_2 (10 ml), se aplicó a una columna de 12g de gel de sílice y la columna se eluyó con un gradiente de hexano:EtOAc, 50:50 a 0:100 a lo largo de 18 minutos. El compuesto del título se aisló como un sólido blanco como una mezcla de isómeros (0,23 g).

Ejemplo 191K

(2S)- 2-(5-(4-(1-(4-tert-butilfenil)-5-(2-((S)-1-((S)-2-(metoxicarbonilamino)-3-metilbutanoil)pirrolidin-2-il)-1H-benzo[d]imidazol-6-il)pirrolidin-2-il)fenil)-1H-imidazol-2-il)pirrolidin-1-carboxilato de tert-butilo

El producto del Ejemplo 191J (0,23g, 0,308 mmol) y el producto del Ejemplo 26D (0,195g, 0,615 mmol) se combinaron en un tubo para microondas de 20 ml y se disolvió en tolueno (1,5 ml)/etanol(1,5 ml) . A esta solución se agregó carbonato de sodio acuoso 1M (0,92 ml, 0,92 mmol) seguido por complejo 1,1'-Bis(difenilfosfino)ferrocenodicloro paladio(II) diclorometano (23 mg, 0,036 mmol) y la mezcla resultante se burbujeó con N_2 durante 10 minutos, se selló y se calentó a 100°C durante 2 hr. La mezcla de reacción se enfrió a temperatura ambiente y se diluyó con EtOAc (50 ml). La fase acuosa de carbonato se separó y la capa orgánica se lavó con agua (20 ml) y NaCl al 10% (20 ml), se secó sobre Na_2SO_4 (s) anhidro, se filtró y el solvente se eliminó al vacío dando un sólido espumoso. El sólido se disolvió en 10 ml de CH_2Cl_2 y se aplicó a una columna de 12g de gel de sílice. La columna se eluyó con un gradiente de CH_2Cl_2/MeOH, 99/1 a 95/5 a lo largo de 20 minutos. El compuesto del título se obtuvo como un sólido color tostado como una mezcla de isómeros (0,11g).

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Ejemplo 191L

cloruro de (2S)-2-(5-(4-(1-(4-tert-butilfenil)-5-(2-((S)-1-((S)-2-(metoxicarbonilamino)-3-metilbutanoil)pirrolidin-2-il)-1H-benzo[d]imidazol-6-il)pirrolidin-2-il)fenil)-1H-imidazol-2-il)pirrolidinio

El producto del Ejemplo 191K (0,11 g, 0,28 mmol) se disolvió en dioxano (2 ml), luego se agregó HCl 4N/dioxano (1 ml). El sólido resultante se agitó durante 30 minutos a temperatura ambiente. El solvente se eliminó al vacío dando un sólido color tostado como el compuesto del título como una mezcla de isómeros (0,092g) que se almacenó bajo vacío durante la noche.

Ejemplo 191M

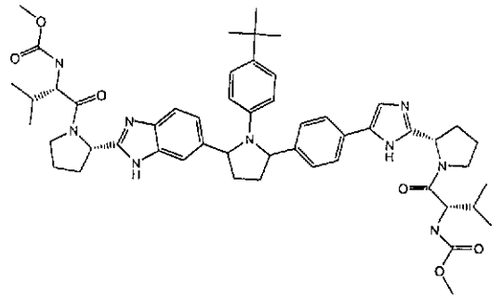
{(2S)-1-[(2S)-2-(5-{4-[(2S,5S)-1-(4-tert-butilfenil)-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-bencimidazol-6-il}pirrolidin-2-il]fenil}-1H-imidazol-2-il)pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

y

{(2S)-1-[(2S)-2-(5-{4-[(2R,5R)-1-(4-tert-butilfenil)-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-bencimidazol-6-il}pirrolidin-2-il]fenil}-1H-imidazol-2-il)pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

El producto del Ejemplo 191L (0,092g, 0,116 mmol), ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico (0,020 g, 0,116 mmol) y HOBt (000,018g, 0,116 mmol) se combinaron en un balón de 25 ml y se disolvió en DMF (1 ml). La mezcla de reacción se colocó en un baño de hielo y se trató con EDAC (0,022g, 0,116 mmol) y N-metilmorfolina (0,12 ml, 1,091 mmol. La mezcla de reacción color amarillo claro se agitó en el baño de hielo durante 1 hr, luego se agitó a temperatura ambiente durante 9 hr. La mezcla de reacción se diluyó con EtOAc (100 ml) se lavó con agua (20 ml) y NaCl al 10% (20 ml), se secó sobre Na_2SO_4 (s) anhidro, se filtró y el solvente se eliminó al vacío dando un residuo oleoso. El residuo se disolvió en 5 ml de CH_2Cl_2 y se aplicó a una columna de 12g de gel de sílice. La columna se eluyó con un gradiente de CH_2Cl_2/MeOH, 99/1 a 95/5 a lo largo de 22 minutos. El compuesto del título se aisló de la primera fracción en eluir de la columna como un sólido blanco que consistía en una mezcla de isómeros trans de pirrolidina, 21 mg, 19%. ^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 0,71 - 0,95 (m, 12 H) 1,11 (s, 9 H) 1,99 (m, 6 H) 2,13 (m, 4 H) 3,53 (s, 6 H) 3,81 (m, 4 H) 4,04 (m, 4 H) 5,06 (m, 2 H) 5,11 - 5,15 (m, 1 H) 5,18 - 5,26 (m, 1 H) 5,32 (m, 1 H) 6,25 (m, 2 H) 6,86 - 6,96 (m, 1 H) 7,05 (m, 2 H) 7,33 (m, 6 H) 7,61 (m, 2 H) 11,53 (s, 1 H) 11,68 (s, 1 H) 12,00 (m, 2 H); ESI+: 914,5.

000730



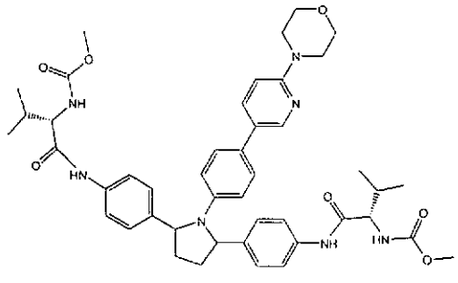
Ejemplo 192

{(2*S*)-1-[(2*S*)-2-(5-{4-[(2*R*,5*S*)-1-(4-*tert*-butilfenil)-5-{2-[(2*S*)-1-{(2*S*)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1*H*-bencimidazol-6-il}pirrolidin-2-il]fenil}-1*H*-imidazol-2-il)pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

y

{(2*S*)-1-[(2*S*)-2-(5-{4-[(2*S*,5*R*)-1-(4-*tert*-butilfenil)-5-{2-[(2*S*)-1-{(2*S*)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1*H*-bencimidazol-6-il}pirrolidin-2-il]fenil}-1*H*-imidazol-2-il)pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

El compuesto del título se aisló de la última fracción en eluir de la columna descrita en el Ejemplo 191M como un sólido blanco como una mezcla de isómeros cis de pirrolidina, 18 mg, 17%. ^{1}H RMN (base libre) (400 MHz, DMSO-d_6) δppm 0,71 - 0,95 (m, 12 H) 1,11 (s, 9 H) 1,99 (m, 6 H) 2,13 (m, 4 H) 3,53 (s, 6 H) 3,81 (m, 4 H) 4,04 (m, 4 H) 4,72 (m, 1H), 4,83 (m, 1 H) 5,11 - 5,15 (m, 1 H) 5,18 - 5,26 (m, 1 H) 5,32 (m, 1 H) 6,25 (m, 2 H) 6,86 - 6,96 (m, 1 H) 7,05 (m, 2 H) 7,33 (m, 6 H) 7,61 (m, 2 H) 11,53 (s, 1 H) 11,68 (s, 1 H) 12,00 (m, 2 H); ESI+: 914,5.



Ejemplo 193

([(2*S*,5*S*)-1-{4-[6-(morfolin-4-il)piridin-3-il]fenil}pirrolidin-2,5-diil]bis{bencen-4,1-diilimino[(2*S*)-3-metil-1-oxobutan-1,2-diil]})biscarbamato de dimetilo

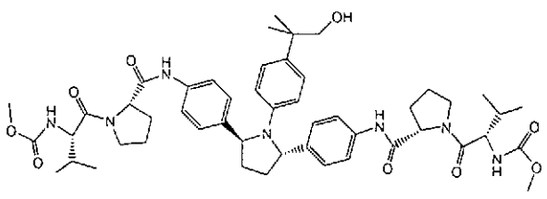
y

([(2*R*,5*R*)-1-{4-[6-(morfolin-4-il)piridin-3-il]fenil}pirrolidin-2,5-diil]bis{bencen-4,1-diilimino[(2*S*)-3-metil-1-oxobutan-1,2-diil]})biscarbamato de dimetilo

El Ejemplo 86A y 4-(5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)piridin-2-il)morfolina se procesaron utilizando en forma consecutiva los métodos de los Ejemplos

000751

99A, 99B, y 1F (utilizando ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico (38,2mg, 0,218mmol) en lugar de ácido (S)-1-(tert-butoxicarbonil)pirrolidin-2-carboxílico). La purificación por HPLC en fase reversa (C_{18}) dio el compuesto del título, un sólido blanco, como una mezcla 1:1 de diastereómeros trans (40,4mg, 50,6% de rendimiento). 1H RMN (base libre) (400 MHz, DMSO-D6) δ ppm 0,89 (d, *J*=6,72 Hz, 12 H) 1,67 (d, *J*=5,64 Hz, 2 H) 1,92 - 2,04 (m, 2 H) 3,37 - 3,41 (m, 4 H) 3,53 (d, *J*=2,06 Hz, 6 H) 3,67 (d, *J*=5,10 Hz, 4 H) 3,94 (t, *J*=8,08 Hz, 2 H) 5,25 (s, 2 H) 6,33 (d, *J*=8,67 Hz, 2 H) 6,78 (d, *J*=8,89 Hz, 1 H) 7,14 - 7,23 (m, 6 H) 7,32 (d, *J*=8,67 Hz, 2 H) 7,54 (d, *J*=7,92 Hz, 4 H) 7,66 (dd, *J*=8,84, 2,55 Hz, 1 H) 8,26 (d, *J*=2,49 Hz, 1 H) 10,01 (s, 2 H). MS ESI(+) m/z @ 806,5 (M+H)+.



Ejemplo 194

({(2S,5S)-1-[4-(1-hidroxi-2-metilpropan-2-il)fenil]pirrolidin-2,5-diil}bis{bencen-4,1-diilcarbamoil(2S)pirrolidin-2,1-diil[(2S)-3-metil-1-oxobutan-1,2-diil]})biscarbamato) de dimetilo

Ejemplo 194A

2-metil-2-(4-nitrofenil)propanoato de etilo

En un recipiente Morton de 500mL equipado para agitación mecánica se agregó a temperatura ambiente bajo nitrógeno 2-(4-nitrofenil)acetato de etilo (10,0g, 55,2mmol), dimetilformamida anhidra (200mL) 18-crown-6 (2,189g, 8,28mmol) y yoduro de metilo (23,13mL, 370mmol). El recipiente se enfrió en un baño de hielo y se agregó hidruro de sodio como dispersión en aceite mineral al 60% (7,73g, 193mmol) en porciones de manera de mantener la temperatura interna menor o igual a +10°C. La adición requirió 53 minutos. Una vez completa la adición la mezcla de reacción se dejó calentar lentamente a temperatura ambiente y se agitó durante la noche. El enfriamiento consecutivo en un baño de hielo se siguió con la adición por goteo de agua (200mL) con agitación vigorosa. La mezcla se particionó entre agua (1200mL) y éter etílico (200mL). La fase acuosa se extrajo con éter etílico (3x200mL cada uno) y los materiales orgánicos combinados se lavaron agua (3x150mL), se secó sobre $MgSO_4$, se filtró y se concentró para dar el compuesto del título con rendimiento casi cuantitativo suficientemente puro para utilizarse como se aisló.

Ejemplo 194B

2-metil-2-(4-nitrofenil)propan-1-ol

000752

A una solución del producto del Ejemplo 194A (12,32g, 55,2mmol) en THF anhidro (300mL) a temperatura ambiente bajo nitrógeno se agregó por goteo mediante cánulos BH_3 1M en THF (200mL) a lo largo de 10,5 minutos. Una vez completa la adición el recipiente se equipó con un condensador y la mezcla se calentó bajo nitrógeno a reflujo en un baño de aceite durante diez horas antes de enfriarse a temperatura ambiente. La reacción se detuvo mediante la adición cautelosa por goteo de metanol (60mL).La mezcla resultante se concentró para dar un aceite el cual luego se disolvió en acetato de etilo (150mL) y se trató con HCl 1N y se dejó agitar a temperatura ambiente durante una hora. La fase orgánica resultante se lavó con salmuera (4x50mL), se secó sobre $MgSO_4$, se filtró y se concentró. El residuo se colocó en tolueno (25mL) y volvió a concentrarse. El sólido aceitoso se suspendió en hexano (50mL) y se recogió mediante filtración al vacío. La almohadilla se lavó con hexano (50mL) y luego se secó bajo vacío para dar el compuesto del título (9,55g, 89% de rendimiento) como un sólido anaranjado claro. MS (DCI+) m/z @ 213,1 $(M+NH_4)+$.

Ejemplo 194C

2-(4-aminofenil)-2-metilpropan-1-ol

El producto del Ejemplo 194B (0,321g, 1,644mmol) se disolvió en una mezcla de THF (10mL) y etanol (2mL). A esto se agregó óxido de platino(IV) (0,030g, 0,131mmol). El recipiente se tapó con un septo y el contenido se desgasificó al vacío tres veces. Se introdujo hidrógeno a través de un globo y la mezcla se agitó a temperatura ambiente. Se agregaron otros 38,2mg (0,167mmol) de catalizador en dos alícuotas antes de que el análisis por cromatografía indicara que se había consumido el material de partida. Luego de agitar durante la noche bajo hidrógeno la mezcla se filtró a través de un tapón de arena / celite y luego se enjuagó con acetato de etilo. El material filtrado se concentró a sequedad y el residuo se purificó mediante cromatografía sobre gel de sílice modificado con amina eluyendo con acetato de etilo – hexano comenzando en 8% y llegando a 66% acetato de etilo para dar el compuesto del título (0,3645g, 68% de rendimiento) como un aceite traslúcido. MS (DCI+) m/z @ 183,1 $(M+NH_4)+$.

Ejemplo 194D

2-(4-((2S,5S)-2,5-bis(4-nitrofenil)pirrolidin-1-il)fenil)-2-metilpropan-1-ol

El producto del Ejemplo 194C (0,595g, 3,60mmol) se combinó en DMF (3mL) con (1R,4R)-dimetansulfonato de 1,4-Bis(4-nitrofenil)butan-1,4-diilo (0,259g, 0,530mmol), preparado como se describe en el Ejemplo 37C, luego se calentó durante la noche bajo nitrógeno en un baño de aceite a 50°C. La mezcla de reacción se particionó entre acetato de etilo (50mL) y agua (50mL). La fase orgánica se lavó con agua (3x25mL), se secó sobre $MgSO_4$, se filtró y se concentró para dar un aceite. La cromatografía sobre gel de

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sílice eluyendo con acetato de etilo – hexano dio el compuesto del título (0,0835g, 34,1% de rendimiento) como un semisólido anaranjado.

Ejemplo 194E

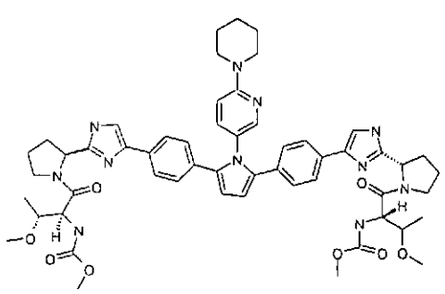
2-(4-((2S,5S)-2,5-bis(4-aminofenil)pirrolidin-1-il)fenil)-2-metilpropan-1-ol

El producto del Ejemplo 194D (83,5mg, 0,181mmol) se hizo reaccionar como se describe en el Ejemplo 99B para dar el compuesto del título en rendimiento cuantitativo como un sólido amarillo claro. MS (DCI+) m/z @ 402,3 (M+H)+.

Ejemplo 194F

({(2S,5S)-1-[4-(1-hidroxi-2-metilpropan-2-il)fenil]pirrolidin-2,5-diil}bis{bencen-4,1-diilcarbamoil(2S)pirrolidin-2,1-diil[(2S)-3-metil-1-oxobutan-1,2-diil]})biscarbamato) de dimetilo

El producto del Ejemplo 194E (73,0mg, 0,181mmol) se hizo reaccionar con el producto del Ejemplo 37B (104,0mg, 0,380mmol) como se describe en el Ejemplo 37F. El compuesto del título se aisló después de la purificación por HPLC en fase reversa (C18) como un sólido blanco opaco (97,4mg, 59% de rendimiento). 1H RMN (base libre) (400 MHz, DMSO-D6) δ ppm 0,79 - 0,96 (m, 12 H) 1,03 (s, 6 H) 1,61 (s, 2 H) 1,76 - 2,04 (m, 8 H) 2,04 - 2,17 (m, 2 H) 3,20 (dd, *J*=5,42, 1,84 Hz, 2 H) 3,51 (s, 6 H) 3,60 (dd, 2 H) 3,78 (s, 2 H) 4,01 (t, *J*=8,46 Hz, 2 H) 4,35 - 4,49 (m, 3 H) 5,14 (s, 2 H) 6,16 (d, *J*=8,78 Hz, 2 H) 6,89 (d, *J*=8,78 Hz, 2 H) 7,12 (d, *J*=8,57 Hz, 4 H) 7,29 (d, *J*=8,35 Hz, 2 H) 7,48 (d, *J*=8,46 Hz, 4 H) 9,97 (s, 2 H). MS ESI(+), m/z @ 910,7 (M+H)+.

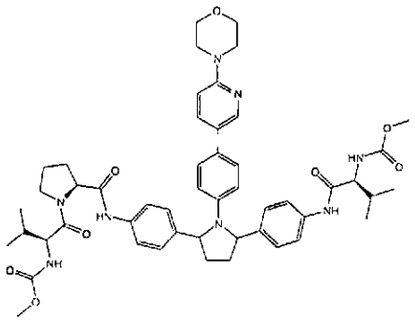


Ejemplo 195

[(1*S*,2*R*)-2-metoxi-1-({(2*S*)-2-[4-(4-{5-[4-(2-{(2*S*)-1-[*N*-(metoxicarbonil)-*O*-metil-L-treonil]pirrolidin-2-il}-1*H*-imidazol-4-il)fenil]-1-(6-piperidin-1-ilpiridin-3-il)-1*H*-pirrol-2-il}fenil)-1*H*-imidazol-2-il]pirrolidin-1-il}carbonil)propil]carbamato de metilo

El compuesto del título se preparó usando los métodos del Ejemplo 144E utilizando ácido (2S,3S)-3-metoxi-2-(metoxicarbonilamino)butanoico en lugar de ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico para dar el compuesto del título (280 mg, 37% de rendimiento). ^{1}H RMN (400 MHz, DMSO-D6) δ 12,12 – 11,70 (m, 2H), 7,85 – 7,76 (m, 1H), 7,63 – 7,49 (m, 4H), 7,49 – 7,39 (m, 2H), 7,34 – 7,03 (m, 7H), 6,77 – 6,69 (m, 1H),

6,54 – 6,41 (m, 2H), 5,08 – 4,99 (m, 2H), 4,27 (t, *J* = 7,6, 2H), 3,86 – 3,75 (m, 4H), 3,54 (s, 6H), 3,50 – 3,43 (m, 4H), 3,17 (s, 6H), 2,19 – 1,88 (m, 10H), 1,61 – 1,44 (m, 6H), 1,12 – 0,99 (m, 6H). MS (ESI; M+H) m/z = 997.

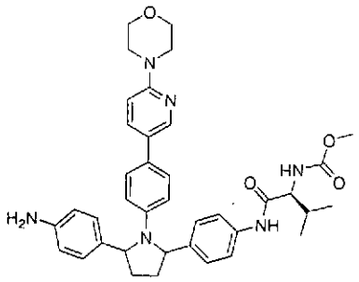


Ejemplo 196

N-(metoxicarbonil)-L-valil-*N*-{4-[(2*S*,5*S*)-5-(4-{[*N*-(metoxicarbonil)-L-valil]amino}fenil)-1-{4-[6-(morfolin-4-il)piridin-3-il]fenil}pirrolidin-2-il]fenil}-L-prolinamida

y

N-(metoxicarbonil)-L-valil-*N*-{4-[(2*R*,5*R*)-5-(4-{[*N*-(metoxicarbonil)-L-valil]amino}fenil)-1-{4-[6-(morfolin-4-il)piridin-3-il]fenil}pirrolidin-2-il]fenil}-L-prolinamida



Ejemplo 196A

(2S)-1-(4-(5-(4-aminofenil)-1-(4-(6-morfolinopiridin-3-il)fenil)pirrolidin-2-il)fenilamino)-3-metil-1-oxobutan-2-ilcarbamato de metilo

En un balón de 5 ml secado al horno purgado con nitrógeno, se disolvió 4,4'-(1-(4-(6-morfolinopiridin-3-il)fenil)pirrolidin-2,5-diil)dianilina (30 mg, 0,061 mmol; preparada a partir del Ejemplo 86A y 4-(5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)piridin-2-il)morfolina usando los métodos de los Ejemplos 99A y 99B), y ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico (11,22 mg, 0,064 mmol) en DMSO anhidro (1 ml), se agregó HATU (26,3 mg, 0,067 mmol) y diisopropiletilamina (0,021 ml, 0,122 mmol), y se agitó la solución amarilla a 25 °C durante 30 min. Se diluyó la reacción con MeOH (1 ml) y se purificó mediante RP-C_{18} HPLC (Waters Prep LC, 40mm Module con cartucho Nova Pak HR C_{18} 6µm 40x100mm Prep Pak) eluyendo con un gradiente de 30 min de 95:5 TFA al 0,1% en H_2O/AcCN a 25:75 TFA al 0,1% en H_2O/AcCN, luego 10 min a 100%

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AcCN a 20 ml/min. Las fracciones puras se concentraron por evaporación por rotación (baño de agua 35º) hasta un pequeño volumen, se particionó entre 20% iPrOH/$CHCl_3$ (50 ml) y $NaHCO_3$ acuoso saturado (15 ml), se separaron las fases, se secó el extracto orgánico sobre $MgSO_4$ anhidro, se filtró, y se concentró por evaporación por rotación para dar el compuesto del título como un sólido blanco opaco (14,6 mg, 37%) como una mezcla de estereoisómeros. MS (ESI+) m/z 649 $(M+H)^+$, 707 $(M+AcCN+NH_4)^+$, 1297 $(2M+H)^+$.

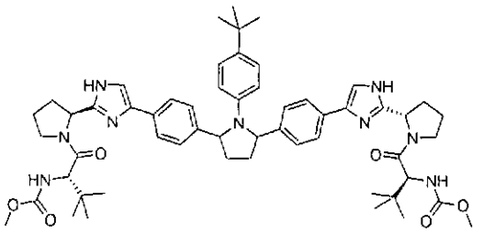
Ejemplo 196B

N-(metoxicarbonil)-L-valil-*N*-{4-[(2*S*,5*S*)-5-(4-{[*N*-(metoxicarbonil)-L-valil]amino}fenil)-1-{4-[6-(morfolin-4-il)piridin-3-il]fenil}pirrolidin-2-il]fenil}-L-prolinamida

y

N-(metoxicarbonil)-L-valil-*N*-{4-[(2*R*,5*R*)-5-(4-{[*N*-(metoxicarbonil)-L-valil]amino}fenil)-1-{4-[6-(morfolin-4-il)piridin-3-il]fenil}pirrolidin-2-il]fenil}-L-prolinamida

En un balón de 5 ml purgado con nitrógeno, se disolvió el producto del Ejemplo 196A (14 mg, 0,022 mmol) en DMSO anhidro (1 ml), se agregó el producto del Ejemplo 37B (6,46 mg, 0,024 mmol), HATU (9,30 mg, 0,024 mmol), y diisopropiletilamina (7,54 µL, 0,043 mmol). Se agitó a 25 °C durante 1 hr, se diluyó la reacción con MeOH (1 ml) y se purificó mediante HPLC RP-C_{18} (Waters Prep LC, 40mm Module con cartucho Nova Pak HR C_{18} 6µm 40x100mm Prep Pak) eluyendo con un gradiente de 30 min de 95:5 TFA al 0,1% en H_2O/AcCN a 25:75 TFA al 0,1% en H_2O/AcCN, luego 10 min a 100% AcCN a 20 ml/min. Las fracciones puras se concentraron por evaporación por rotación (baño de agua 35ºC) hasta casi sequedad, el residuo se recogió con 1:5 v/v CH_2Cl_2/hexanos y se evaporó (3 veces), y el residuo se secó al vacío para dar un sólido amarillo (11mg). La sal TFA se disolvió en 20% iPrOH/$CHCl_3$ (30 ml), se lavó abundantemente con $NaHCO_3$ acuoso saturado (5 ml), se extrajo la fase acuosa con 20% iPrOH/$CHCl_3$ (20 ml), se secaron los extractos orgánicos combinados sobre $MgSO_4$ anhidro, se filtró, y se concentró por evaporación por rotación para dar los compuestos del título como sólidos blancos (7 mg, 35%). ^{1}H RMN (400 MHz, DMSO-D6) δ ppm 0,83 - 0,96 (m, 12 H), 1,60 - 1,71 (m, 2 H), 1,81 - 2,21 (m, 7 H), 3,36 - 3,43 (m, 4 H), 3,49 - 3,56 (m, 6 H), 3,58 - 3,65 (m, 1 H), 3,65 - 3,70 (m, 4 H), 3,75 - 3,85 (m, 1 H), 3,94 (t, *J*=8,08 Hz, 1 H), 4,02 (t, *J*=8,19 Hz, 1 H), 4,42 (dd, *J*=7,86, 4,93 Hz, 1 H), 5,24 (d, *J*=5,31 Hz, 2 H), 6,32 (d, *J*=8,35 Hz, 2 H), 6,78 (d, *J*=9,00 Hz, 1 H), 7,13 - 7,19 (m, 4 H), 7,21 (d, *J*=8,78 Hz, 2 H), 7,26 - 7,35 (m, 2 H), 7,48 - 7,56 (m, 4 H), 7,66 (dd, *J*=7,86, 1,14 Hz, 1 H), 8,25 (d, *J*=2,17 Hz, 1 H), 10,00 (d, *J*=3,47 Hz, 2 H); MS (ESI+) m/z 903 $(M+H)^+$.



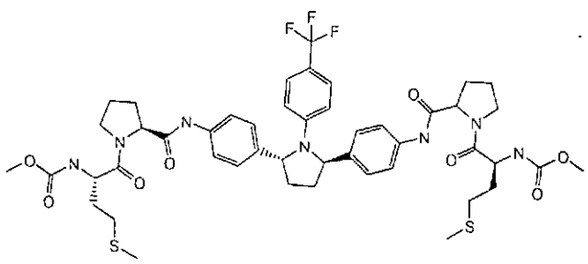
Ejemplo 197

{(2*S*)-1-[(2*S*)-2-(4-{4-[(2*S*,5*S*)-1-(4-*tert*-butilfenil)-5-(4-{2-[(2*S*)-1-{(2*S*)-2-[(metoxicarbonil)amino]-3,3-dimetilbutanoil}pirrolidin-2-il]-1*H*-imidazol-4-il}fenil)pirrolidin-2-il]fenil}-1*H*-imidazol-2-il)pirrolidin-1-il]-3,3-dimetil-1-oxobutan-2-il}carbamato de metilo

y

{(2*S*)-1-[(2*S*)-2-(4-{4-[(2*R*,5*R*)-1-(4-*tert*-butilfenil)-5-(4-{2-[(2*S*)-1-{(2*S*)-2-[(metoxicarbonil)amino]-3,3-dimetilbutanoil}pirrolidin-2-il]-1*H*-imidazol-4-il}fenil)pirrolidin-2-il]fenil}-1*H*-imidazol-2-il)pirrolidin-1-il]-3,3-dimetil-1-oxobutan-2-il}carbamato de metilo

El producto del Ejemplo 42F (0,228 g, 0,364 mmol) se procesó como en el Ejemplo 1H para dar 0,035 g (10%) del compuesto del título como un sólido como una mezcla de isómeros trans. 1H RMN (base libre) (400 MHz, DMSO-D6) δ ppm 0,91 (d, J=7,59 Hz, 18 H) 1,08 (s, 9 H) 1,63 - 1,73 (m, 2 H) 1,83 - 2,24 (m, 12 H) 3,54 (s, 6 H) 3,70 - 3,80 (m, 2 H) 4,21 (d, J=7,92 Hz, 2 H) 5,06 (dd, J=6,99, 3,52 Hz, 2 H) 5,15 - 5,25 (m, 2 H) 6,21 (d, J=8,67 Hz, 2 H) 6,92 (dd, J=8,73, 2,44 Hz, 2 H) 7,05 (d, J=8,78 Hz, 2 H) 7,14 (dd, J=8,24, 3,47 Hz, 4 H) 7,37 (s, 2 H) 7,61 (d, J=8,02 Hz, 4 H) 11,69 (s, 2 H); MS ESI+ m/z 968,8 (M+H)+.



Ejemplo 198

[(2*S*)-1-{(2*S*)-2-[(4-{(2*R*,5*R*)-5-{4-[({1-[(2*S*)-2-[(metoxicarbonil)amino]-4-(metilsulfanil)butanoil]pirrolidin-2-il}carbonil)amino]fenil}-1-[4-(trifluorometil)fenil]pirrolidin-2-il}fenil)carbamoil]pirrolidin-1-il}-4-(metilsulfanil)-1-oxobutan-2-il]carbamato de metilo

Ejemplo 198A

ácido (S)-2-(metoxicarbonilamino)-4-(metiltio)butanoico

A una solución de ácido (S)-2-amino-4-(metiltio)butanoico (1,0 g, 6,7 mmol) en dioxano a 0 °C se agregó NaOH (11,06 g, 22,12 mmol) y luego se agregó por goteo cloroformato de metilo (1,04 ml, 13,4 mmol) y la solución se calentó a temperatura

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ambiente con agitación durante 2 h. La solución se diluyó con EtOAc, se lavó con HCl 1 N, salmuera, se secó (Na_2SO_4), se filtró y el solvente se eliminó al vacío para dar el compuesto del título (1,3 g, 6,27 mmol, 94%). ^{1}H RMN (400 MHz, $CDCl_3$) δ ppm 1,95-2,07 (m, 1H) 2,07-2,13 (m, 3H) 2,14-2,28 (m, 1H) 2,59 (t, J=7,4 Hz, 2H) 3,71 (s, 3H) 4,52 (br s, 1H) 5,33 (br s, 1H).

Ejemplo 198B

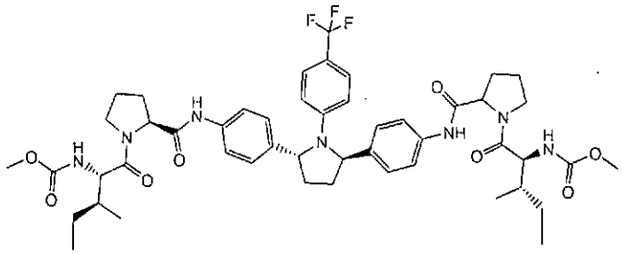
(2S,2'S)-N,N'-(4,4'-((2R,5R)-1-(4-(trifluorometil)fenil)pirrolidin-2,5-diil)bis(4,1-fenilen)dipirrolidin-2-carboxamida

El Ejemplo 38A y 4-trifluorometilanilina se procesaron usando los métodos de los Ejemplos 34A, 34B, 34C, y 34D para dar el compuesto del título.

Ejemplo 198C

[(2*S*)-1-{(2*S*)-2-[(4-{(2*R*,5*R*)-5-{4-[({1-[(2*S*)-2-[(metoxicarbonil)amino]-4-(metilsulfanil)butanoil]pirrolidin-2-il}carbonil)amino]fenil}-1-[4-(trifluorometil)fenil]pirrolidin-2-il}fenil)carbamoil]pirrolidin-1-il}-4-(metilsulfanil)-1-oxobutan-2-il]carbamato de metilo

El Ejemplo 198B y el Ejemplo 198A se procesaron usando el método del Ejemplo 1H para dar el compuesto del título el cual se purificó mediante cromatografía flash sobre gel de sílice eluyendo con 10-80% EtOAc/CH_2Cl_2 (29 mg). ^{1}H RMN (400 MHz, $CDCl_3$) δ ppm 1,78 (d, J=6,1 Hz, 2H) 1,83-2,00 (m, 6H) 2,02 (s, 6H) 2,04-2,26 (m, 4H) 2,43-2,61 (m, 8H) 3,47-3,83 (m, 4H) 3,69 (s, 6H) 4,75 (dd, J=8,0, 2,0 Hz, 4H) 5,15 (d, J=6,7 Hz, 2H) 5,43 (d, 2H) 6,32 (d, J=8,7 Hz, 2H) 7,09 (d, J=8,5 Hz, 4H) 7,18 (d, J=8,8 Hz, 2H) 7,42 (d, J=8,6 Hz, 4H) 9,05 (s, 2H). MS (ESI) m/z 971 $(M+H)^+$.



Ejemplo 199

[(2*S*,3*S*)-1-{(2*S*)-2-[(4-{(2*R*,5*R*)-5-(4-{[(1-{(2*S*,3*S*)-2-[(metoxicarbonil)amino]-3-metilpentanoil}pirrolidin-2-il)carbonil]amino}fenil)-1-[4-(trifluorometil)fenil]pirrolidin-2-il}fenil)carbamoil]pirrolidin-1-il}-3-metil-1-oxopentan-2-il]carbamato de metilo

Ejemplo 199A

ácido (2S,3S)-2-(metoxicarbonilamino)-3-metilpentanoico

A una solución de ácido (2S,3S)-2-amino-3-metilpentanoico (1,0 g, 7,62 mmol) en dioxano (10 ml) a 0 °C se agregó NaOH (12,58 g, 25,2 mmol) y luego se agregó por goteo cloroformato de metilo (1,18 ml, 15,25 mmol). La solución se calentó a temperatura

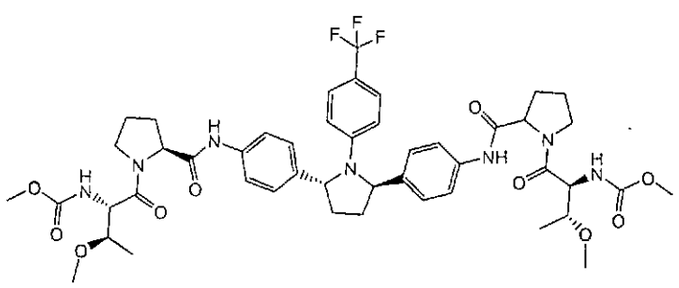
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ambiente con agitación durante 2 h, se diluyó con EtOAc, se lavó con HCl 1 N, salmuera, se secó (Na_2SO_4), se filtró y el solvente se eliminó al vacío para dar el compuesto del título (1,4 g, 7,4 mmol, 97%). ^{1}H RMN (400 MHz, $CDCl_3$) δ ppm 1,27-1,39 (m, 1H) 1,38-1,53 (m, 2H) 1,58-1,72 (m, 3H) 1,82-1,94 (m, 2H) 2,04 (d, J=3,8 Hz, 2H) 3,70 (s, 3H) 4,94 (br s, 1H).

Ejemplo 199B

[(2*S*,3*S*)-1-{(2*S*)-2-[(4-{(2*R*,5*R*)-5-(4-{[(1-{(2*S*,3*S*)-2-[(metoxicarbonil)amino]-3-metilpentanoil}pirrolidin-2-il)carbonil]amino}fenil)-1-[4-(trifluorometil)fenil]pirrolidin-2-il}fenil)carbamoil]pirrolidin-1-il}-3-metil-1-oxopentan-2-il]carbamato de metilo

A una solución del Ejemplo 198B (60 mg, 0,101 mmol) en DMSO (0,5 ml) se agregó el Ejemplo 199A (48 mg, 0,254 mmol), seguido por HATU (96 mg, 0,254 mmol) y N,N-diisopropiletilamina (0,089 ml, 0,507 mmol) y la solución se agitó a temperatura ambiente durante 1 h. Se diluyó con EtOAc, se lavó con H_2O, salmuera, se secó (Na_2SO_4), se filtró y se eliminó el solvente al vacío para dar un producto crudo el cual se purificó mediante cromatografía flash sobre gel de sílice eluyendo con 10-80% EtOAc/CH_2Cl_2 para dar el compuesto del título (11 mg, 0,012 mmol, 12%). ^{1}H RMN (400 Hz, $CDCl_3$) δ ppm 0,78-1,00 (m, 12H) 1,69-1,81 (m, 4H) 1,81-1,94 (m, 2H) 1,99-2,10 (m, 2H) 2,09-2,24 (m, 2H) 2,50 (br s, 2H) 2,53-2,61 (m, 2H) 3,63 (br s, 2H) 3,68 (s, 6H) 3,75-3,87 (m, 2H) 4,34 (t, J=8,5 Hz, 2H) 4,79 (d, J=6,3 Hz, 2H) 5,14 (d, J=6,6 Hz, 2H) 5,28 (d, J=9,3 Hz, 2H) 6,32 (d, J=8,7 Hz, 2H) 7,08 (d, J=8,4 Hz, 4H) 7,18 (d, J=8,8 Hz, 2H) 7,41 (d, J=8,5 Hz, 4H) 9,23 (s, 2H). MS (ESI) m/z 935 $(M+H)^+$.



Ejemplo 200

[(2*S*,3*R*)-3-metoxi-1-{(2*S*)-2-[(4-{(2*R*,5*R*)-5-(4-{[(1-{(2*S*,3*R*)-3-metoxi-2-[(metoxicarbonil)amino]butanoil}pirrolidin-2-il)carbonil]amino}fenil)-1-[4-(trifluorometil)fenil]pirrolidin-2-il}fenil)carbamoil]pirrolidin-1-il}-1-oxobutan-2-il]carbamato de metilo

Ejemplo 200A

ácido *(2S,3R)*-3-Metoxi-2-(metoxicarbonilamino)butanoico

Una solución de O-metil-L-treonina (1,01 g, 7,59 mmol) en solución saturada de bicarbonato (93 ml) se trató por goteo con cloroformato de metilo (900 µL, 1,10 g, 11,61

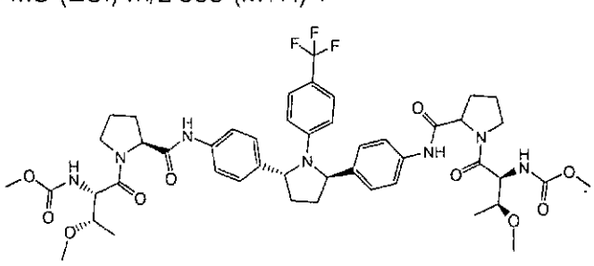
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mmol), seguido por agitación a temperatura ambiente durante 24 h. La mezcla se extrajo con éter metílico t-butílico y se enfrió a 0 °C. La mezcla se ajustó a pH 1-2 mediante la adición de solución concentrada de ácido clorhídrico. La mezcla se extrajo con acetato de etilo (3 x) y los extractos combinados se extrajeron con solución saturada de cloruro de sodio y se secó (Na_2SO_4). La solución se concentró al vacío para dar el compuesto del título (1,31 g, 90%) como un sólido blanco. ^{1}H RMN (400 MHz, $CDCl_3$) δ 5,44 (d, *J* = 8,7 Hz, 1 H), 4,39 (dd, *J* = 8,7, 2,3 Hz, 1 H), 4,00 (dd, *J* = 6,2, 2,4 Hz, 1 H), 3,71 (s, 3 H), 3,36 (s, 3 H), 1,21 (t, *J* = 7,2 Hz, 3 H). MS (+ESI) *m/z* (abundancia relativa) 192 (60, M+H), 209 (100, M+NH4).

Ejemplo 200B

[(2*S*,3*R*)-3-metoxi-1-{(2*S*)-2-[(4-{(2*R*,5*R*)-5-(4-{[(1-{(2*S*,3*R*)-3-metoxi-2-[(metoxicarbonil)amino]butanoil}pirrolidin-2-il)carbonil]amino}fenil)-1-[4-(trifluorometil)fenil]pirrolidin-2-il}fenil)carbamoil]pirrolidin-1-il}-1-oxobutan-2-il]carbamato de metilo

El Ejemplo 198B (60 mg, 0,101 mmol) y el Ejemplo 200A (48,5 mg, 0,254 mmol) se procesaron de la misma manera que en el Ejemplo 199B para dar el compuesto del título (10,5 mg, 0,011 mmol, 11%). ^{1}H RMN (400 MHz, $CDCl_3$) δ ppm 1,19 (s, 3H) 1,21 (s, 3H) 1,78 (d, J=6,1 Hz, 2H) 1,94-2,16 (m, 6H) 2,40-2,57 (m, 4H) 3,36 (s, 6H) 3,66-3,84 (m, 6H) 3,69 (s, 6H) 4,64-4,72 (m, 2H) 4,81 (d, J=8,1 Hz, 2H) 5,14 (d, J=6,7 Hz, 2H) 5,64 (d, J=7,9 Hz, 2H) 6,31 (d, J=8,8 Hz, 2H) 7,08 (d, J=8,6 Hz, 4H) 7,18 (d, J=8,8 Hz, 2H) 7,43(d, J=8,6 Hz, 4H) 8,85 (s, 2H). MS (ESI) m/z 939 $(M+H)^+$.



Ejemplo 201

[(2*S*,3*S*)-3-metoxi-1-{(2*S*)-2-[(4-{(2*R*,5*R*)-5-(4-{[(1-{(2*S*,3*S*)-3-metoxi-2-[(metoxicarbonil)amino]butanoil}pirrolidin-2-il)carbonil]amino}fenil)-1-[4-(trifluorometil)fenil]pirrolidin-2-il}fenil)carbamoil]pirrolidin-1-il}-1-oxobutan-2-il]carbamato de metilo

Ejemplo 201A

ácido *(2S,3S)*-3-Metoxi-2-(metoxicarbonilamino)butanoico

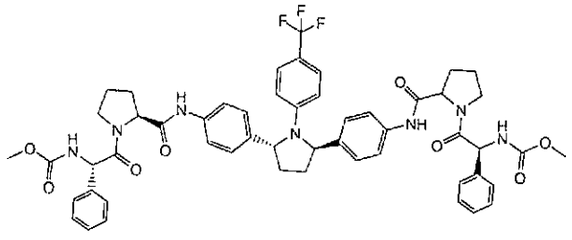
Una solución de alo-O-metil-L-treonina (519 mg, 3,90 mmol) en solución saturada de bicarbonato de sodio (47,6 ml) se trató por goteo con cloroformato de metilo (453 µL,

553 mg, 5,85 mmol) seguido por agitación a temperatura ambiente durante 18 h. La mezcla se extrajo con éter y la fase acuosa se enfrió a 0 °C y se acidificó a pH 2-3 mediante la adición de solución concentrada de ácido clorhídrico. La mezcla se extrajo con acetato de etilo (3 x). Las capas orgánicas combinadas se extrajeron con solución saturada de cloruro de sodio y se secó (Na_2SO_4). La concentración al vacío dio el compuesto del título (640 mg, 86%) como un aceite incoloro. ^{1}H RMN (400 MHz, $CDCl_3$) δ 5,48 (d, *J* = 7,8 Hz, 1 H), 4,52 (d, *J* = 4,7 Hz, 1 H), 3,71 (s, 3 H), 3,39 (s, 3 H), 1,25 (t, *J* = 7,6 Hz, 3 H).

Ejemplo 201B

[(2*S*,3*S*)-3-metoxi-1-{(2*S*)-2-[(4-{(2*R*,5*R*)-5-(4-{[(1-{(2*S*,3*S*)-3-metoxi-2-[(metoxicarbonil)amino]butanoil}pirrolidin-2-il)carbonil]amino}fenil)-1-[4-(trifluorometil)fenil]pirrolidin-2-il}fenil)carbamoil]pirrolidin-1-il}-1-oxobutan-2-il]carbamato de metilo

El Ejemplo 198B (40 mg, 0,068 mmol) y el Ejemplo 201A (32,3 mg, 0,169 mmol) se procesaron de la misma manera que en el Ejemplo 199B para dar el compuesto del título (22 mg, 0,023 mmol, 35%). ^{1}H RMN (400 MHz, $CDCl_3$) δ ppm 1,24 (s, 3H) 1,25 (s, 3H) 1,78 (d, J=6,2 Hz, 2H) 1,87-1,99 (m, 2H) 1,99-2,16 (m, 4H) 2,45-2,58 (m, 4H) 3,20 (s, 6H) 3,46-3,56 (m, 2H) 3,65-3,83 (m, 6H) 3,69 (s, 6H) 4,51-4,59 (m, 2H) 4,78 (d, J=6,7 Hz, 2H) 5,14 (d, J=6,7 Hz, 2H) 5,39 (d, J=9,3 Hz, 2H) 6,30 (d, J=8,7 Hz, 2H) 7,08 (d, J=8,5 Hz, 4H) 7,16 (d, J=8,8 Hz, 2H) 7,40 (d, J=8,5 Hz, 4H) 8,94 (s, 2H). MS (ESI) m/z 939 $(M+H)^+$.



Ejemplo 202

[(1*S*)-2-{(2*S*)-2-[(4-{(2*R*,5*R*)-5-(4-{[(1-{(2*S*)-2-[(metoxicarbonil)amino]-2-fenilacetil}pirrolidin-2-il)carbonil]amino}fenil)-1-[4-(trifluorometil)fenil]pirrolidin-2-il}fenil)carbamoil]pirrolidin-1-il}-2-oxo-1-feniletil]carbamato de metilo

Ejemplo 202A

ácido (S)-2-(metoxicarbonilamino)-2-fenilacético

A una solución de ácido (S)-2-amino-2-fenilacético (0,5 g, 3,31 mmol) en dioxano a 0 °C se agregó NaOH (5,46 g, 10,92 mmol) y luego se agregó por goteo cloroformato de metilo (0,51 ml, 6,62 mmol) y la solución se calentó a temperatura ambiente con agitación durante 1 h. Se diluyó con EtOAc, se lavó con HCl 1 N, salmuera, se secó (Na_2SO_4), se

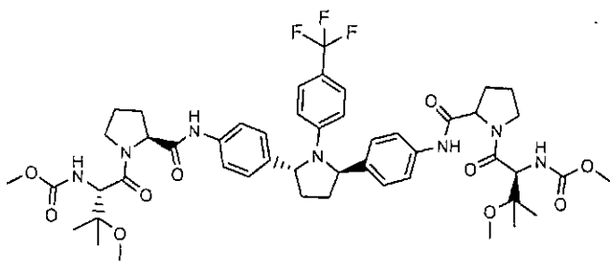
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filtró y se eliminó el solvente al vacío para dar el compuesto del título (0,35 g, 1,673 mmol, 51%).

Ejemplo 202B

[(1*S*)-2-{(2*S*)-2-[(4-{(2*R*,5*R*)-5-(4-{[(1-{(2*S*)-2-[(metoxicarbonil)amino]-2-fenilacetil}pirrolidin-2-il)carbonil]amino}fenil)-1-[4-(trifluorometil)fenil]pirrolidin-2-il}fenil)carbamoil]pirrolidin-1-il}-2-oxo-1-feniletil]carbamato de metilo

El Ejemplo 198B (40 mg, 0,068 mmol) y el Ejemplo 202A (35 mg, 0,169 mmol) se procesaron de la misma manera que en el Ejemplo 199B para dar el compuesto del título (7,5 mg, 7,7 µmol, 11%). ^{1}H RMN (400 MHz, $CDCl_3$) δ ppm 1,76-2,05 (m, 8H) 2,43-2,58 (m, 4H) 3,18-3,29 (m, 2H) 3,57-3,65 (m, 2H) 3,67 (s, 6H) 4,82-4,86 (m, 2H) 5,18 (d, J=6,9 Hz, 2H) 5,48 (d, J=7,7 Hz, 2H) 5,99 (d, J=7,7 Hz, 2H) 6,35 (d, J=8,8 Hz, 2H) 7,11 (d, J=8,5 Hz, 4H) 7,21 (d, J=8,7 Hz, 2H) 7,27-7,32 (m, 4H) 7,32-7,43 (m, 10H) 8,92 (s, 2H). MS (ESI) m/z 975 $(M+H)^+$.



Ejemplo 203

[(2*S*)-3-metoxi-1-{(2*S*)-2-[(4-{(2*R*,5*R*)-5-(4-{[(1-{(2*S*)-3-metoxi-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il)carbonil]amino}fenil)-1-[4-(trifluorometil)fenil]pirrolidin-2-il}fenil)carbamoil]pirrolidin-1-il}-3-metil-1-oxobutan-2-il]carbamato de metilo

Ejemplo 203A

ácido *(S)*-(*tert*-butoxicarbonilamino)-3-hidroxi-3-metilbutanoico

Una solución de ácido *(S)*-2-amino-3-hidroxi-3-metilbutanoico (252 mg, 1,89 mmol) en solución saturada de bicarbonato de sodio (6,3 ml) y tetrahidrofurano (6,3 ml) se trató con dicarbonato de di-tert-butilo (764 mg, 3,50 mmol) seguido por agitación a temperatura ambiente durante 24 h. La mezcla se concentró al vacío para eliminar el tetrahidrofurano y la mezcla se extrajo con hexanos. La fase acuosa se enfrió a 0 °C y se acidificó a pH 3 mediante la adición de solución 1 M de ácido cítrico. La mezcla se extrajo con acetato de etilo y las capas orgánicas combinadas se secaron (Na_2SO_4). La concentración al vacío dio un sólido gomoso, que contenía otras impurezas además del producto deseado. Este material se disolvió en acetato de etilo y la mezcla se filtró a través de un filtro Millipore para eliminar el material no disuelto. El material filtrado se concentró al vacío y después de dejarse en reposo a temperatura ambiente durante una semana, eventualmente

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solidificó para dar el compuesto del título como un sólido blanco. ^{1}H RMN (400 MHz, Metanol-d_4) δ 4,08 (s, 1 H), 1,45 (s, 9 H), 1,29 (s, 3 H), 1,25 (s, 3 H). MS (-ESI) *m/z* (abundancia relativa) 232 (100, M-H).

Ejemplo 203B

ácido (S)-2-(tert-butoxicarbonilamino)-3-metoxi-3-metilbutanoico

A una solución del Ejemplo 203A (363 mg, 1,56 mmol) en THF (7 ml) a 0 °C se agregó NaH (373 mg, 9,34 mmol) y la agitación se continuó durante 15 min. Se agregó yodometano (0,78 ml, 12,45 mmol) y la solución se dejó calentar a temperatura ambiente y se agitó durante 18 h. La solución se detuvo con H_2O, se diluyó con EtOAc, se lavó con H_2O, salmuera, se secó (Na_2SO_4), se filtró y el solvente se eliminó para dar el compuesto del título (165 mg, 0,67 mmol, 43%). MS (ESI) m/z 248 $(M+H)^+$.

Ejemplo 203C

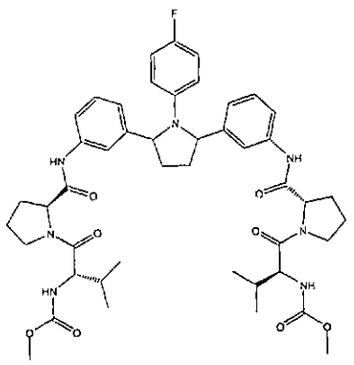
ácido (S)-3-metoxi-2-(metoxicarbonilamino)-3-metilbutanoico

A una solución del Ejemplo 203B (163 mg, 0,66 mmol) en CH_2Cl_2 (2 ml) se agregó ácido trifluoroacético (2 ml) y la solución se agitó a temperatura ambiente durante 1 h. El solvente se eliminó al vacío y el residuo se suspendió en $NaHCO_3$ saturado, se extrajo con EtOAc, los extractos orgánicos se combinaron, se lavó con salmuera, se secó (Na_2SO_4), se filtró y el solvente se eliminó al vacío. El residuo se disolvió en dioxano (1 ml) y se agregó NaOH 1 M (1,1 ml, 2,175 mmol) seguido por la adición por goteo de cloroformato de metilo (0,102 ml, 1,3 mmol). La solución se agitó a temperatura ambiente durante 16 h, se diluyó con EtOAc, se lavó con HCl 1 N, salmuera, se secó (Na_2SO_4), se filtró y el solvente se eliminó al vacío para dar el compuesto del título (96 mg, 0,468 mmol, 71%).

Ejemplo 203D

[(2*S*)-3-metoxi-1-{(2*S*)-2-[(4-{(2*R*,5*R*)-5-(4-{[(1-{(2*S*)-3-metoxi-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il)carbonil]amino}fenil)-1-[4-(trifluorometil)fenil]pirrolidin-2-il}fenil)carbamoil]pirrolidin-1-il}-3-metil-1-oxobutan-2-il]carbamato de metilo

El Ejemplo 198B (80,7 mg, 0,136 mmol) y el Ejemplo 203C (70 mg, 0,341 mmol) se procesaron de la misma manera que en el Ejemplo 199B para dar el compuesto del título (62 mg, 0,064 mmol, 47%). ^{1}H RMN (400 MHz, $CDCl_3$) δ ppm 1,25 (s, 3H) 1,33 (s, 3H) 1,39 (s, 2H) 1,74-1,82 (m,2H) 1,89 (s, 2H) 1,93-2,16 (m, 5H) 2,38-2,59 (m, 4H) 3,16-3,27 (m, 2H) 3,24 (s, 3H) 3,43-3,56 (m, 2H) 3,69 (s, 3H) 3,71-3,78 (m, 2H) 3,80 (s, 3H) 3,84-3,94 (m, 1H) 4,61 (s, 1H) 4,70-4,81 (m, 2H) 5,15 (d, J=6,3 Hz, 2H) 5,58 (s, 1H) 6,32 (d, J=8,7 Hz, 2H) 7,05-7,13 (m, 4H) 7,19 (d, J=8,7 Hz, 2H) 7,33-7,50 (m, 4H) 8,71 (s, 1H) 8,92 (s, 1H). MS (ESI) m/z 967 $(M+H)^+$.



Ejemplo 204

([(2*S*,5*S*)-1-(4-fluorofenil)pirrolidin-2,5-diil]bis{bencen-3,1-diilcarbamoil(2*S*)pirrolidin-2,1-diil[(2*S*)-3-metil-1-oxobutan-1,2-diil]})biscarbamato de dimetilo

y

([(2*R*,5*R*)-1-(4-fluorofenil)pirrolidin-2,5-diil]bis{bencen-3,1-diilcarbamoil(2*S*)pirrolidin-2,1-diil[(2*S*)-3-metil-1-oxobutan-1,2-diil]})biscarbamato de dimetilo

Ejemplo 204A

(2S,2'S)- 2,2'-(3,3'-((2S,5S)-1-(4-fluorofenil)pirrolidin-2,5-diil)bis(3,1-fenilen))bis(azandiil)bis(oxometilen)dipirrolidin-1-carboxilato de tert-butilo

y

(2S,2'S)- 2,2'-(3,3'-((2R,5R)-1-(4-fluorofenil)pirrolidin-2,5-diil)bis(3,1-fenilen))bis(azandiil)bis(oxometilen)dipirrolidin-1-carboxilato de tert-butilo

La fracción en éter de la preparación del Ejemplo 55F se concentró y se purificó mediante cromatografía flash (gel de sílice, diclorometano/EtOAc) para dar el compuesto del título como una mezcla de diastereómeros trans (0,20 g, 10%). MS (ESI) *m/z* 742 $(M+H)^+$.

Ejemplo 204B

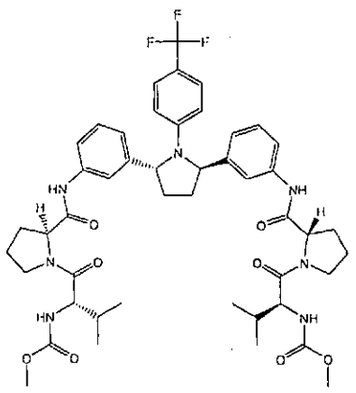
([(2*S*,5*S*)-1-(4-fluorofenil)pirrolidin-2,5-diil]bis{bencen-3,1-diilcarbamoil(2*S*)pirrolidin-2,1-diil[(2*S*)-3-metil-1-oxobutan-1,2-diil]})biscarbamato de dimetilo

y

([(2*R*,5*R*)-1-(4-fluorofenil)pirrolidin-2,5-diil]bis{bencen-3,1-diilcarbamoil(2*S*)pirrolidin-2,1-diil[(2*S*)-3-metil-1-oxobutan-1,2-diil]})biscarbamato de dimetilo

El producto del Ejemplo 204A se procesó usando el método descrito en los Ejemplos 19D y 19E (se utilizó ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico) para dar los compuestos del título (60,5 mg, 22%). ^{1}H RMN (base libre) (400 MHz, DMSO-D6) δ 0,99 - 0,81 (m, 12H), 1,67 (dd, J = 3,4, 5,0, 3H), 2,06 - 1,79 (m, 8H), 2,20 - 2,06 (m, 5H), 3,52 (d, J = 2,3, 6H), 3,63 (q, J = 7,1, 1H), 3,88 - 3,75 (m, 1H), 4,08 - 3,96 (m, 2H), 4,41 (dt, J = 12,8, 25,2, 2H), 5,11 (d, J = 28,1, 2H), 6,24 (dd, J = 6,0, 10,9, 2H), 6,80 (td, J =

4,2, 8,9, 2H), 6,88 (dd, J = 5,5, 6,4, 2H), 7,22 (ddd, J = 5,3, 10,4, 20,8, 2H), 7,32 (d, J = 8,3, 2H), 7,43 - 7,34 (m, 2H), 7,57 (d, J = 7,8, 2H), 10,00 (d, J = 7,8, 2H). MS (ESI) *m/z* 856 $(M+H)^+$.



Ejemplo 205

({(2R,5R)-1-[4-(trifluorometil)fenil]pirrolidin-2,5-diil}bis{bencen-3,1-diilcarbamoil(2S)pirrolidin-2,1-diil[(2S)-3-metil-1-oxobutan-1,2-diil]})biscarbamato de dimetilo

Ejemplo 205A

(1S,4S)-1,4-bis(3-nitrofenil)butan-1,4-diol

El producto del Ejemplo 55A se procesó usando el método descrito en el Ejemplo 33 para dar el compuesto del título (1,74 g, 84%). MS (DCI) *m/z* 350 $(M+NH_4)^+$.

Ejemplo 205B

(2R,5R)-2,5-bis(3-nitrofenil)-1-(4-(trifluorometil)fenil)pirrolidina

El producto del Ejemplo 205A y 4-aminobenzotrifluoruro se procesaron usando el método descrito en los Ejemplos 55C y 55D para dar el compuesto del título (0,27 g, 19%). MS (ESI) *m/z* 858 $(M+H)^+$.

Ejemplo 205C

3,3'-((2R,5R)-1-(4-(trifluorometil)fenil)pirrolidin-2,5-diil)dianilina

El producto del Ejemplo 205B se procesó usando el método descrito en el Ejemplo 55E. El compuesto del título se aisló mediante cromatografía flash (gel de sílice, metanol/diclorometano). MS (ESI) *m/z* 398 $(M+H)^+$, 396 $(M-H)^+$.

Ejemplo 205D

(2S,2'S)- 2,2'-(3,3'-((2R,5R)-1-(4-(trifluorometil)fenil)pirrolidin-2,5-diil)bis(3,1-fenilen))bis(azandiil)bis(oxometilen)dipirrolidin-1-carboxilato de tert-butilo

El producto del Ejemplo 205C se procesó usando el método descrito en el Ejemplo 19C reemplazando DMF por diclorometano para dar el compuesto del título (0,36 g, 77%).

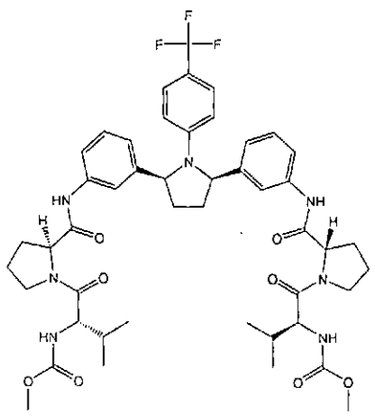
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MS (ESI) *m/z* 792 ($M+H^+$).

Ejemplo 205E

({(2R,5R)-1-[4-(trifluorometil)fenil]pirrolidin-2,5-diil}bis{bencen-3,1-diilcarbamoil(2S)pirrolidin-2,1-diil[(2S)-3-metil-1-oxobutan-1,2-diil]})biscarbamato de dimetilo

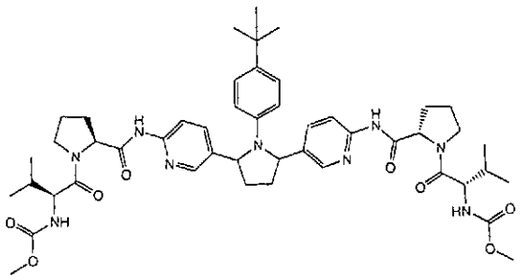
El producto del Ejemplo 205D se procesó usando el método descrito en los Ejemplos 19D y 19E (se utilizó ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico y se reemplazó HATU por HOBt y EDC) para dar el compuesto del título (13,5 mg, 3%). ^1H RMN (Sal TFA) (400 MHz, METANOL-D4) δ 1,08 – 0,89 (m, 12H), 1,88 – 1,73 (m, 2H), 2,32 – 1,93 (m, 10H), 2,62 (t, *J* = 6,9, 2H), 3,64 (s, 6H), 3,77 – 3,67 (m, 2H), 4,00 – 3,90 (m, 2H), 4,20 (d, *J* = 8,0, 2H), 4,56 – 4,45 (m, 2H), 5,26 (d, *J* = 6,5, 2H), 6,42 (d, *J* = 8,8, 2H), 6,98 (d, *J* = 7,6, 2H), 7,17 (d, *J* = 7,4, 2H), 7,27 (t, *J* = 7,8, 2H), 7,52 – 7,37 (m, 4H). MS (ESI) *m/z* 906 $(M+H)^+$, 904 $(M-H)^+$.



Ejemplo 206

({(2R,5S)-1-[4-(trifluorometil)fenil]pirrolidin-2,5-diil}bis{bencen-3,1-diilcarbamoil(2S)pirrolidin-2,1-diil[(2S)-3-metil-1-oxobutan-1,2-diil]})biscarbamato de dimetilo

El producto por ejemplo 206 se aisló de la purificación del Ejemplo 205E (12,5 mg, 3%). ^1H RMN (Sal TFA) (400 MHz, DMSO-D6) δ 0,90 (dt, *J* = 6,2, 10,3, 12H), 2,23 – 1,73 (m, 12H), 2,47 – 2,39 (m, 6H), 3,52 (d, *J* = 3,3, 4H), 3,89 – 3,73 (m, 2H), 4,03 (t, *J* = 8,4, 2H), 4,44 (dd, *J* = 4,9, 7,8, 2H), 4,83 (t, *J* = 5,5, 2H), 6,50 (d, *J* = 8,7, 2H), 7,36 – 7,15 (m, 6H), 7,39 (d, *J* = 8,7, 2H), 7,73 – 7,57 (m, 4H), 10,04 (d, *J* = 10,0, 2H). MS (ESI) *m/z* 906 $(M+H)^+$, 904 $(M-H)^+$.



Ejemplo 207

([(2*S*,5*S*)-1-(4-*tert*-butilfenil)pirrolidin-2,5-diil]bis{piridin-5,2-diilcarbamoil(2*S*)pirrolidin-2,1-diil[(2*S*)-3-metil-1-oxobutan-1,2-diil]})biscarbamato de dimetilo

y

([(2*R*,5*R*)-1-(4-*tert*-butilfenil)pirrolidin-2,5-diil]bis{piridin-5,2-diilcarbamoil(2*S*)pirrolidin-2,1-diil[(2*S*)-3-metil-1-oxobutan-1,2-diil]})biscarbamato de dimetilo

Ejemplo 207A

1,4-bis(6-cloropiridin-3-il)butan-1,4-diona

Se combinaron cloruro de cinc (3,04 g, 22,82 mmol), alcohol tert-butílico (1,576 ml, 16,71 mmol) y dietilamina (1,731 ml, 16,71 mmol) en benceno (12 ml). La lechada resultante se agitó a temperatura ambiente durante 2 horas hasta disolverse los sólidos. A esta suspensión se agregó 1-(6-cloropiridin-3-il)etanona (2,60 g, 16,71 mmol; referencia: *Bioorganic & Medicinal Chemistry Letters,* 1998, 8, 3087-3092), seguida por 2-bromo-1-(6-cloropiridin-3-il)etanona (2,61 g, 11,14 mmol; referencia: *Bioorganic & Medicinal Chemistry Letters,* 1998, 8, 3087-3092). La solución amarilla transparente resultante se agitó a temperatura ambiente durante 88 horas. La mezcla de reacción espesa se trató con H_2SO_4 al 5% (10 ml), se agitó durante 30 minutos, se filtró y se secó para dar el compuesto del título (2,91g, 85%) como un sólido.

Ejemplo 207B

1,4-bis(6-cloropiridin-3-il)butan-1,4-diol

El producto del Ejemplo 207A (2,90 g, 9,38 mmol) y borhidruro de sodio (0,745g, 19,70 mmol) se combinaron en etanol (94 ml) a 0 °C. La mezcla se calentó a temperatura ambiente y se agitó durante 6 horas. El solvente se evaporó y el residuo se particionó entre acetato de etilo y HCl 1M. La capa orgánica se lavó con agua, salmuera, se secó con sulfato de sodio, se filtró y se evaporó para dar el compuesto del título (2,62 g, 89%).

Ejemplo 207C

dimetansulfonato de 1,4-bis(6-cloropiridin-3-il)butan-1,4-diilo

El producto del Ejemplo 207B (2,23 g, 7,12 mmol) y trietilamina (2,98 ml, 21,36 mmol) se combinaron en diclorometano (50 ml). La mezcla se enfrió a -20 °C y se agregó cloruro de metansulfonilo (1,383 ml, 17,80 mmol). La mezcla se agitó a temperatura

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ambiente durante 1 hora. El solvente se evaporó para dar el producto del título (aprox. 3,34 g) que se usó directamente para la siguiente reacción.

Ejemplo 207D

5,5'-(1-(4-tert-butilfenil)pirrolidin-2,5-diil)bis(2-cloropiridina)

El producto del Ejemplo 207C (3,34 g, 7,12 mmol) y 4-tert-butilanilina (6,38 g, 42,7 mmol) se combinaron en DMF (20 ml). La mezcla se agitó a temperatura ambiente durante 24 horas. La mezcla de reacción se particionó entre acetato de etilo y HCl 1M. La capa orgánica se lavó con salmuera dos veces, se secó con sulfato de sodio, se filtró y se evaporó. El residuo se purificó mediante cromatografía sobre gel de sílice eluyendo con acetato de etilo/hexano (5% a 30%) para dar el compuesto del título (2,95 g, 97%) como un sólido amarillo como una mezcla de estereoisómeros.

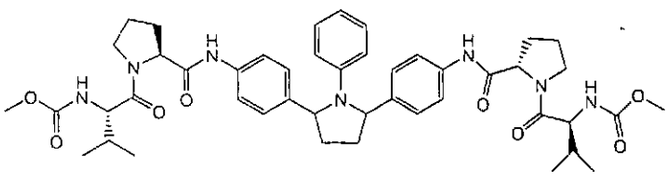
Ejemplo 207E

([(2*S*,5*S*)-1-(4-*tert*-butilfenil)pirrolidin-2,5-diil]bis{piridin-5,2-diilcarbamoil(2*S*)pirrolidin-2,1-diil[(2*S*)-3-metil-1-oxobutan-1,2-diil]})biscarbamato de dimetilo

y

([(2*R*,5*R*)-1-(4-*tert*-butilfenil)pirrolidin-2,5-diil]bis{piridin-5,2-diilcarbamoil(2*S*)pirrolidin-2,1-diil[(2*S*)-3-metil-1-oxobutan-1,2-diil]})biscarbamato de dimetilo

El producto del Ejemplo 207D (0,171 g, 0,40 mmol), el producto del Ejemplo 116C (0,326 g, 1,200 mmol), carbonato de cesio (0,365 g, 1,120 mmol), tris(dibencilidenacetona)dipaladio(0) (0,022 g, 0,024 mmol) y (9,9-dimetil-9H-xanten-4,5-diil)bis(difenilfosfina) (0,042 g, 0,072 mmol) se combinaron en dioxano (4 ml). La mezcla se purgó con nitrógeno durante 15 minutos y se agitó a 100 °C durante 3 horas. La mezcla de reacción se particionó entre acetato de etilo y bicarbonato de sodio saturado. La capa orgánica se lavó con salmuera, se secó con sulfato de sodio, se filtró y se evaporó. El residuo se purificó mediante cromatografía sobre gel de sílice eluyendo con metanol/diclorometano (1% a 4%) para dar el compuesto del título (5 mg, 1%) como una mezcla de diastereómeros trans. 1H RMN (500 MHz, DMSO-D6) δ ppm 0,88 (t, J=6,41 Hz, 6 H) 0,92 (t, J=7,32 Hz, 6 H) 1,12 (s, 9 H) 1,68 - 1,75 (m, 2 H) 1,81 - 1,99 (m, 8 H) 2,07 - 2,18 (m, 2 H) 2,50 - 2,53 (m, 2 H) 3,52 (s, 6 H) 3,57 - 3,64 (m, 2 H) 3,78 - 3,86 (m, 2 H) 3,98 - 4,03 (m, 2 H) 4,55 - 4,63 (m, 2 H) 5,27 (d, J=6,26 Hz, 2 H) 6,18 - 6,27 (m, 2 H) 6,99 (dd, J=8,77, 1,60 Hz, 2 H) 7,28 - 7,37 (m, 2 H) 7,59 (dd, J=8,62, 2,06 Hz, 2 H) 7,96 (d, J=8,39 Hz, 2 H) 8,12 - 8,20 (m, 2 H) 10,53 (s, 2 H); MS (ESI+) m/z 896,6 (M+H)+.



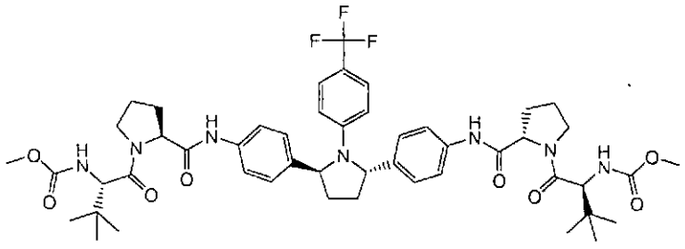
Ejemplo 208

([(2S,5S)-1-fenilpirrolidin-2,5-diil]bis{bencen-4,1-diilcarbamoil(2S)pirrolidin-2,1-diil[(2S)-3-metil-1-oxobutan-1,2-diil]})biscarbamato de dimetilo

y

([(2R,5R)-1-fenilpirrolidin-2,5-diil]bis{bencen-4,1-diilcarbamoil(2S)pirrolidin-2,1-diil[(2S)-3-metil-1-oxobutan-1,2-diil]})biscarbamato de dimetilo

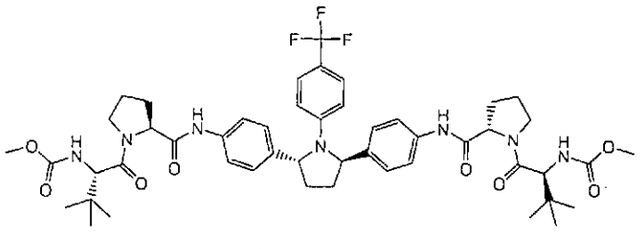
El compuesto del título se aisló del Ejemplo 85C como producto adicional. 1H RMN (Sal TFA) (400 MHz, DMSO-D6) δ ppm 0,83 - 0,88 (m, 6 H), 0,88 - 0,94 (m, 6 H), 1,60 - 1,65 (m, 2 H), 1,79 - 2,02 (m, 8 H), 2,06 - 2,18 (m, 2 H), 3,51 (s, 6 H), 3,55 - 3,64 (m, 2 H), 3,75 - 3,83 (m, 2 H), 4,01 (t, *J*=8,3 Hz, 2 H), 4,38 - 4,43 (m, 2 H), 5,16 (d, *J*=6,4 Hz, 2 H), 6,23 (d, *J*=8,3 Hz, 2 H), 6,39 (t, *J*=7,3 Hz, 1 H), 6,90 (t, *J*=7,9 Hz, 2 H), 7,09 - 7,14 (m, 4 H), 7,25 - 7,31 (m, 2 H), 7,45 - 7,50 (m, 4 H), 9,97 (s, 2 H); MS m/z 838,4 $(M+H)^+$.



Ejemplo 209

({(2S,5S)-1-[4-(trifluorometil)fenil]pirrolidin-2,5-diil}bis{bencen-4,1-diilcarbamoil(2S)pirrolidin-2,1-diil[(2S)-3,3-dimetil-1-oxobutan-1,2-diil]})biscarbamato de dimetilo

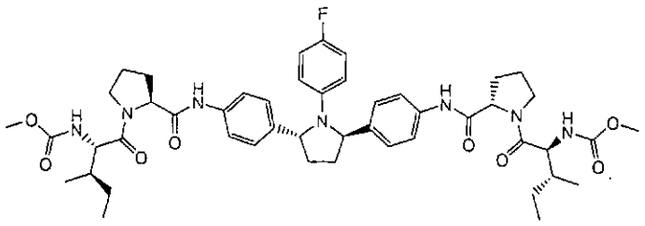
El producto del Ejemplo 23C se separó mediante cromatografía quiral en una columna semipreparativa Chiralpak AD-H eluyendo con 40% 2-PrOH:EtOH (1:1) / 60% hexanos. El compuesto del título fue el primero de 2 componentes en eluir. 1H RMN (400 MHz, DMSO-D6) δ ppm 0,97 (s, 18 H), 1,61 - 1,73 (m, 2 H), 1,75 - 1,93 (m, 4 H), 1,94 - 2,06 (m, 2 H), 2,08 - 2,21 (m, 2 H), 3,54 (s, 6 H), 3,57 - 3,70 (m, 2 H), 3,70 - 3,83 (m, 2 H), 4,21 (d, *J*=8,89 Hz, 2 H), 4,38 - 4,48 (m, 2 H), 5,27 (d, *J*=6,51 Hz, 2 H), 6,37 (d, *J*=8,78 Hz, 2 H), 7,08 (d, *J*=8,89 Hz, 2 H), 7,15 (d, *J*=8,57 Hz, 4 H), 7,25 (d, *J*=8,89 Hz, 2 H), 7,52 (d, *J*=8,57 Hz, 4 H), 10,02 (s, 2 H); MS (ESI) m/z 951,6 $(M+H)^+$.



Ejemplo 210

({(2R,5R)-1-[4-(trifluorometil)fenil]pirrolidin-2,5-diil}bis{bencen-4,1-diilcarbamoil(2S)pirrolidin-2,1-diil[(2S)-3,3-dimetil-1-oxobutan-1,2-diil]})biscarbamato de dimetilo

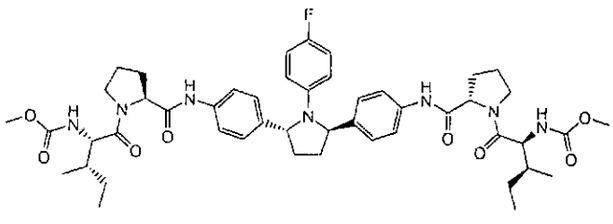
El producto del Ejemplo 23C se separó mediante cromatografía quiral en una columna semipreparativa Chiralpak AD-H eluyendo con 40% 2-PrOH:EtOH (1:1) / 60% hexanos. El compuesto del título fue el segundo de 2 componentes en eluir. 1H RMN (400 MHz, DMSO-D6) δ ppm 0,96 (s, 18 H), 1,64 - 1,75 (m, 2 H), 1,76 - 1,93 (m, 4 H), 1,94 - 2,06 (m, 2 H), 2,07 - 2,21 (m, 2 H), 3,54 (s, 6 H), 3,58 - 3,70 (m, 2 H), 3,70 - 3,86 (m, 2 H), 4,20 (d, *J*=8,89 Hz, 2 H), 4,38 - 4,47 (m, 2 H), 5,28 (d, *J*=6,18 Hz, 2 H), 6,36 (d, *J*=8,89 Hz, 2 H), 7,07 (d, *J*=8,89 Hz, 2 H), 7,14 (d, *J*=8,57 Hz, 4 H), 7,25 (d, *J*=8,78 Hz, 2 H), 7,52 (d, *J*=8,57 Hz, 4 H), 10,03 (s, 2 H); MS (ESI) m/z 951,4 $(M+H)^+$.



Ejemplo 211

([(2R,5R)-1-(4-fluorofenil)pirrolidin-2,5-diil]bis{bencen-4,1-diilcarbamoil(2S)pirrolidin-2,1-diil[(2S,3R)-3-metil-1-oxopentan-1,2-diil]})biscarbamato de dimetilo

El producto del Ejemplo 25 se separó mediante cromatografía quiral en una columna semipreparativa Chiralpak AD-H eluyendo con 50% 2-PrOH:EtOH (1:1) / hexanos al 50%. El compuesto del título fue el segundo de 2 componentes en eluir. 1H RMN (400 MHz, DMSO-D6) δ ppm 0,76 - 0,92 (m, 12 H), 1,05 - 1,19 (m, 2 H), 1,37 - 1,54 (m, 2 H), 1,57 - 1,70 (m, 2 H), 1,69 - 1,96 (m, 6 H), 1,94 - 2,07 (m, 2 H), 2,07 - 2,22 (m, 2 H), 3,53 (s, 6 H), 3,55 - 3,64 (m, 2 H), 3,69 - 3,83 (m, 2 H), 4,17 - 4,28 (m, 2 H), 4,42 (dd, *J*=7,81, 5,20 Hz, 2 H), 5,16 (d, *J*=6,29 Hz, 2 H), 6,20 (dd, *J*=9,22, 4,45 Hz, 2 H), 6,77 (t, *J*=8,95 Hz, 2 H), 7,13 (d, *J*=8,46 Hz, 4 H), 7,49 (d, *J*=8,46 Hz, 2 H), 9,97 (s, 2 H); MS (ESI) m/z 884,4 $(M+H)^+$.

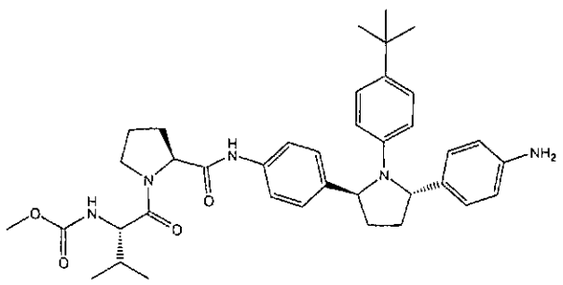


Ejemplo 212

([(2R,5R)-1-(4-fluorofenil)pirrolidin-2,5-diil]bis{bencen-4,1-diilcarbamoil(2S)pirrolidin-2,1-diil[(2S,3S)-3-metil-1-oxopentan-1,2-diil]})biscarbamato de dimetilo

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El producto del Ejemplo 24 se separó mediante cromatografía quiral en una columna semipreparativa Chiralpak AD-H eluyendo con 50% 2-PrOH:EtOH (1:1) / hexanos al 50%. El compuesto del título fue el segundo de 2 componentes en eluir. 1H RMN (400 MHz, DMSO-D6) δ ppm 0,80 (t, *J*=7,37 Hz, 6 H), 0,88 (d, *J*=6,72 Hz, 6 H), 1,02 - 1,18 (m, 2 H), 1,41 - 1,59 (m, 2 H), 1,59 - 1,75 (m, 4 H), 1,80 - 1,95 (m, 4 H), 1,95 - 2,06 (m, 2 H), 2,08 - 2,23 (m, 2 H), 3,52 (s, 6 H), 3,56 - 3,67 (m, 2 H), 3,74 - 3,89 (m, 2 H), 4,07 (t, *J*=8,95 Hz, 2 H), 4,39 - 4,47 (m, 2 H), 5,16 (d, *J*=6,18 Hz, 2 H), 6,20 (dd, *J*=9,22, 4,45 Hz, 2 H), 6,78 (t, *J*=8,95 Hz, 2 H), 7,13 (d, *J*=8,46 Hz, 4 H), 7,35 (d, *J*=8,46 Hz, 2 H), 7,50 (d, *J*=8,57 Hz, 4 H), 9,99 (s, 2 H); MS (ESI) m/z 884,4 $(M+H)^+$.

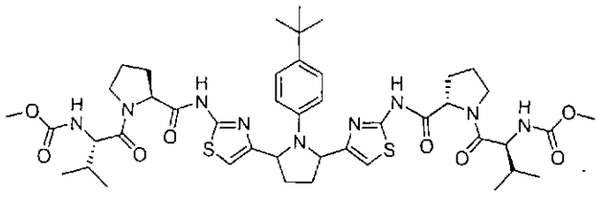


Ejemplo 213

N-(metoxicarbonil)-L-valil-N-{4-[(2S,5S)-5-(4-aminofenil)-1-(4-tert-butilfenil)pirrolidin-2-il]fenil}-L-prolinamida

A una solución del producto del Ejemplo 37B (17,7 mg, 0,065 mmol) y el producto del Ejemplo 37E (50 mg, 0,130 mmol) en DMSO anhidro (1,3 ml) se agregó HATU (27,1 mg, 0,071 mmol) y base de Hunig (0,015 ml, 0,084 mmol). La mezcla resultante se agitó a temperatura ambiente durante 30 min, y luego se particionó entre H_2O (5 ml) y EtOAc (3 x 5 ml). Las capas orgánicas combinadas se secaron sobre Na_2SO_4. El agente de secado se retiró por filtración, y el solvente se eliminó al vacío. El producto crudo se purificó mediante cromatografía en columna sobre gel de sílice usando un gradiente de solvente de 0-5% MeOH en CH_2Cl_2 para dar el compuesto del título (20 mg, 24%). 1H RMN (400 MHz, DMSO-D6) δ ppm 0,88 (d, *J*=6,72 Hz, 3 H), 0,93 (d, *J*=6,72 Hz, 3 H), 1,11 (s, 9 H), 1,52 - 1,66 (m, 2 H), 1,79 - 2,06 (m, 4 H), 2,06 - 2,20 (m, 1 H), 2,34 - 2,47 (m, 2 H), 3,52 (s, 3 H), 3,56 - 3,67 (m, 1 H), 3,74 - 3,87 (m, 1 H), 4,02 (t, *J*=8,51 Hz, 1 H), 4,42 (dd, *J*=8,08, 4,83 Hz, 1 H), 4,83 - 4,94 (m, 2 H), 5,02 (d, *J*=7,16 Hz, 0,5 H), 5,08 (d, *J*=7,59 Hz, 0,5 H), 6,18 (d, *J*=8,78 Hz, 2 H), 6,48 (d, *J*=8,35 Hz, 2 H), 6,84 (d, *J*=8,35 Hz, 2 H), 6,93 (d, *J*=8,89 Hz, 2 H), 7,11 (d, *J*=8,57 Hz, 2 H), 7,31 (d, *J*=8,35 Hz, 1 H), 7,48 (d, *J*=8,57 Hz, 2 H), 9,97 (s, 1 H); MS (ESI) m/z 640,3 $(M+H)^+$.

000771



Ejemplo 214

(2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-((2R,5R)-1-(4-tert-butilfenil)pirrolidin-2,5-diil)bis(tiazol-4,2-diil)bis(azandiil)bis(oxometilen))bis(pirrolidin-2,1-diil))bis(3-metil-1-oxobutan-2,1-diil)dicarbamato de dimetilo

y

(2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-((2S,5S)-1-(4-tert-butilfenil)pirrolidin-2,5-diil)bis(tiazol-4,2-diil)bis(azandiil)bis(oxometilen))bis(pirrolidin-2,1-diil))bis(3-metil-1-oxobutan-2,1-diil)dicarbamato de dimetilo

Ejemplo 214A

1-(4-tert-butilfenil)pirrolidin-2,5-dicarboxilato de dietilo

Una solución de meso-2,5-dibromoadipato de dietilo (2,0 g, 5,55 mmol) y 4-tert-butilanilina (3,32 g, 22,22 mmol) en dimetoxietano (12 ml) se agitó a reflujo durante 10 h. La mezcla fría se particionó entre EtOAc (100 ml) y HCl aq 1N (2x100 ml), y la capa orgánica se secó sobre Na_2SO_4. El agente de secado se retiró por filtración, y el solvente se eliminó al vacío. El producto crudo se purificó mediante cromatografía en columna sobre gel de sílice usando un gradiente de solvente de EtOAc al 0-20% en hexanos para dar el compuesto del título como un aceite (1,95 g, cuant.). El análisis por 1H RMN indicó una mezcla 3:2 de isómeros cis: trans de pirrolidina.

Ejemplo 214B

ácido 1-(4-tert-butilfenil)pirrolidin-2,5-dicarboxílico

A una solución del producto del Ejemplo 214A (1,95 g, 5,61 mmol) en MeOH (50 ml) se agregó una solución de NaOH (0,95 g, 23,8 mmol) en H_2O (10 ml). La mezcla resultante se agitó a temperatura ambiente durante la noche. La mezcla se concentró al vacío para dar aproximadamente 10 ml y se volcó en HCl 1N (50 ml). La mezcla se extrajo con CH_2Cl_2 (3 x 50 ml), y las capas orgánicas combinadas se secaron sobre Na_2SO_4. El agente de secado se retiró por filtración, y el solvente se eliminó al vacío para dar el compuesto del título como un sólido anaranjado claro (1,42 g, 87%) como una mezcla de estereoisómeros.

Ejemplo 214C

ácido trans-1-(4-tert-butilfenil)pirrolidin-2,5-dicarboxílico

El producto del Ejemplo 214B se sometió a cromatografía en columna sobre gel de

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sílice C18 usando un gradiente de solvente de 10-60% acetonitrilo en H_2O (TFA al 0,1%). El compuesto del título fue el primero de 2 componentes principales en eluir.

Ejemplo 214D

1,1'-(trans-1-(4-tert-butilfenil)pirrolidin-2,5-diil)bis(2-diazoetanona)

A una solución del producto del Ejemplo 214C (0,963 g, 3,31 mmol) en CH_2Cl_2 seco (20 ml) a 0 °C se agregó cloruro de oxalilo (1,157 ml, 13,22 mmol), seguido por 2-3 gotas de DMF, y la mezcla resultante se agitó a temperatura ambiente durante 30 min hasta no observarse más burbujeo. La mezcla fría se concentró mediante evaporación con N_2 seco, y el residuo se disolvió en CH_2Cl_2 seco (10 ml). A la solución a 0 °C se agregó una solución de diazometano en Et_2O (~0,6 M, 20 ml) y la mezcla resultante se agitó a 0 °C durante 1h. La mezcla se concentró al vacío, y el producto crudo se purificó mediante cromatografía en columna sobre gel de sílice usando un gradiente de solvente de EtOAc al 0-100% en hexanos para dar el compuesto del título (0,54 g, 48%).

Ejemplo 214E

4,4'-(trans-1-(4-tert-butilfenil)pirrolidin-2,5-diil)ditiazol-2-amina

Una solución del producto del Ejemplo 214D (0,50 g, 1,47 mmol) en Et_2O (10 ml) se trató por goteo con bromuro de hidrógeno ac. 48% (0,500 ml, 4,42 mmol). La mezcla resultante se agitó a temperatura ambiente durante 30 min. Se agregó agua (1 ml), y la mezcla se extrajo con Et_2O (3 x 10 ml). Las capas orgánicas combinadas se secaron sobre Na_2SO_4, se filtró, y se concentró al vacío. El residuo se disolvió en EtOH (15 ml). A la solución resultante se agregó tiourea (0,45 g, 5,89 mmol), y la mezcla resultante se agitó a temperatura ambiente durante 1 h y luego se concentró hasta aproximadamente 1 ml. Se agregó agua (10 ml), y el pH se neutralizó utilizando $NaHCO_3$ acuoso saturado. El sólido resultante se recogió mediante filtración y se secó al vacío para dar el compuesto del título (0,455 g, 77%).

Ejemplo 214F

(2S,2'S)- 2,2'-(4,4'-(trans-1-(4-tert-butilfenil)pirrolidin-2,5-diil)bis(tiazol-4,2-diil)bis(azandiil)bis(oxometilen))dipirrolidin-1-carboxilato de tert-butilo

Una mezcla del producto del Ejemplo 214E (0,2 g, 0,501 mmol), ácido (S)-1-(tert-butoxicarbonil)pirrolidin-2-carboxílico (0,431 g, 2,002 mmol), y clorhidrato de N1-((etilimino)metilen)-N3,N3-dimetilpropan-1,3-diamina (1,151 g, 6,01 mmol) en DMF (4 ml) y piridina (4 ml) se agitó a temperatura ambiente durante la noche. La mezcla se particionó entre HCl acuoso 1N y EtOAc (3x), y las capas orgánicas combinadas se secaron sobre Na_2SO_4. El agente de secado se retiró por filtración, y el solvente se eliminó al vacío. El producto crudo se purificó mediante cromatografía en columna sobre gel de sílice usando un gradiente de solvente de EtOAc al 0-100% en hexanos para dar el

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compuesto del título (0,28 g, 71%) como una mezcla de diastereómeros trans.

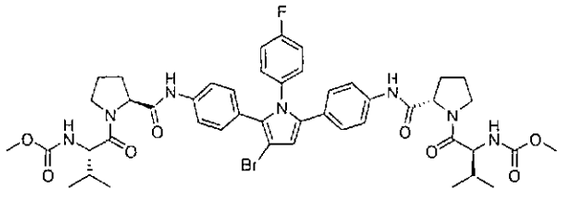
Ejemplo 214G

(2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-((2R,5R)-1-(4-tert-butilfenil)pirrolidin-2,5-diil)bis(tiazol-4,2-diil)bis(azandiil)bis(oxometilen))bis(pirrolidin-2,1-diil))bis(3-metil-1-oxobutan-2,1-diil)dicarbamato de dimetilo

y

(2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-((2S,5S)-1-(4-tert-butilfenil)pirrolidin-2,5-diil)bis(tiazol-4,2-diil)bis(azandiil)bis(oxometilen))bis(pirrolidin-2,1-diil))bis(3-metil-1-oxobutan-2,1-diil)dicarbamato de dimetilo

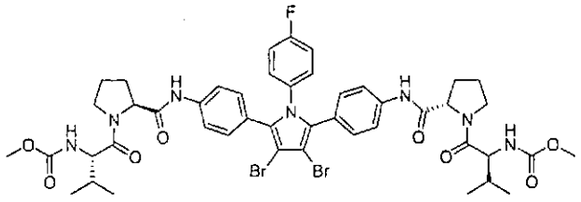
Una solución del producto del Ejemplo 214F se agitó en HCl 2N en dioxano (0,4 ml) durante 1 h y luego se concentró al vacío. El residuo se sometió al procedimiento descrito en el Ejemplo 10 para dar el compuesto del título como una mezcla de diastereómeros trans. 1H RMN (base libre) (400 MHz, DMSO-D6) δ ppm 0,80 - 0,97 (m, 14 H), 1,12 - 1,16 (m, 9 H), 1,69 - 2,06 (m, 8 H), 2,08 - 2,22 (m, 2 H), 3,51 - 3,57 (m, 6 H), 3,57 - 3,68 (m, 2 H), 3,77 - 3,91 (m, 2 H), 3,95 - 4,06 (m, 2 H), 4,47 - 4,59 (m, *J*=7,16 Hz, 1 H), 5,08 - 5,17 (m, 2 H), 6,31 (t, *J*=8,24 Hz, 2 H), 6,70 (d, *J*=21,04 Hz, 2 H), 7,02 (dd, *J*=8,67, 6,40 Hz, 2 H), 7,35 (d, *J*=8,35 Hz, 2 H), 12,24 (s, 2 H).



Ejemplo 215

([3-bromo-1-(4-fluorofenil)-1*H*-pirrol-2,5-diil]bis{bencen-4,1-diilcarbamoil(2*S*)pirrolidin-2,1-diil[(2*S*)-3-metil-1-oxobutan-1,2-diil]})biscarbamato de dimetilo

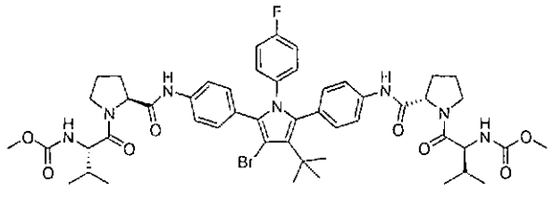
A una suspensión del producto del Ejemplo 51 (455 mg, 0,534 mmol) en CH_2Cl_2 (2,7 ml) se agregó una mezcla de 1-bromopirrolidin-2,5-diona (95 mg, 0,534 mmol) en CH_2Cl_2 (2,7 ml). La mezcla se agitó durante la noche a temperatura ambiente y luego se concentró bajo presión reducida y se trituró con éter dietílico para dar una mezcla de compuestos que se sometió a purificación por HPLC en fase reversa eluyendo con un gradiente de 60-100% MeOH en acetato de amonio 10mM para dar el compuesto del título (84 mg, 17% de rendimiento). ^{1}H RMN (base libre) (400 MHz, DMSO-D6) δ 10,06 (s, 1H), 10,02 (s, 1H), 7,46 (d, *J* = 8,7, 2H), 7,41 (d, *J* = 8,7, 2H), 7,30 (d, *J* = 7,7, 2H), 7,15 – 7,03 (m, 6H), 6,98 (d, *J* = 8,7, 2H), 6,53 (s, 1H), 4,45 – 4,33 (m, 2H), 4,01 (t, *J* = 7,7, 2H), 3,85 – 3,73 (m, 2H), 3,66 – 3,54 (m, 2H), 3,51 (s, 6H), 2,20 – 2,05 (m, 2H), 2,03 – 1,77 (m, 8H), 0,97 – 0,79 (m, 12H). MS (ESI; M+H) m/z = 933.



Ejemplo 216

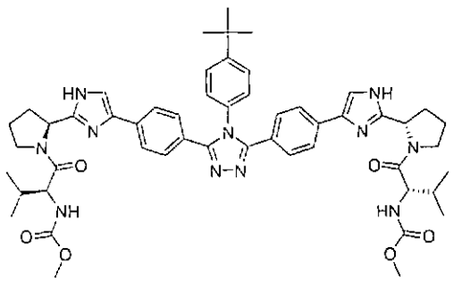
([3,4-dibromo-1-(4-fluorofenil)-1*H*-pirrol-2,5-diil]bis{bencen-4,1-diilcarbamoil(2*S*)pirrolidin-2,1-diil[(2*S*)-3-metil-1-oxobutan-1,2-diil]})biscarbamato de dimetilo

El compuesto del título se obtuvo como producto adicional en el Ejemplo 215. La mezcla de productos se sometió a purificación por HPLC en fase reversa eluyendo con un gradiente de 60-100% MeOH en acetato de amonio 10mM para dar el compuesto del título (125 mg, 23% de rendimiento). ^{1}H RMN (base libre) (400 MHz, DMSO-D6) δ 10,08 (bs, 2H), 7,47 (d, *J* = 8,7, 4H), 7,33 – 7,27 (m, 2H), 7,13 – 7,01 (m, 8H), 4,43 – 4,35 (m, 2H), 4,01 (t, *J* = 8,4, 2H), 3,84 – 3,74 (m, 2H), 3,65 – 3,55 (m, 2H), 3,51 (s, 6H), 2,21 – 2,05 (m, 2H), 2,05 – 1,78 (m, 8H), 0,91 (d, *J* = 6,7, 6H), 0,86 (d, *J* = 6,6, 6H). MS (ESI; M+H) m/z = 1011.



Ejemplo 217

El compuesto del título se obtuvo como subproducto en el Ejemplo 215. La mezcla de productos se sometió a purificación por HPLC en fase reversa eluyendo con un gradiente de 60-100% MeOH en acetato de amonio 10mM para dar el compuesto del título (61 mg, 12% de rendimiento). ^{1}H RMN (base libre) (400 MHz, DMSO-D6) δ 10,00 (s, 2H), 7,41 (d, *J* = 8,7, 2H), 7,38 (d, *J* = 8,9, 2H), 7,29 (d, *J* = 6,6, 2H), 7,14 (d, *J* = 7,3, 1H), 7,11 – 7,05 (m, 3H), 7,01 – 6,93 (m, 2H), 6,89 (t, *J* = 8,7, 2H), 4,37 (dd, *J* = 4,9, 7,4, 2H), 4,00 (t, *J* = 8,4, 2H), 3,84 – 3,74 (m, 2H), 3,64 – 3,55 (m, 2H), 3,51 (s, 6H), 2,19 – 2,05 (m, 2H), 2,03 – 1,78 (m, 8H), 1,23 (s, 9H), 0,91 (dd, *J* = 2,1, 6,6, 6H), 0,86 (d, *J* = 6,4, 6H). MS (ESI; M+H) m/z = 989.



Ejemplo 218

{(2*S*)-1-[(2*S*)-2-(4-{4-[4-(4-*tert*-butilfenil)-5-(4-{2-[(2*S*)-1-{(2*S*)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1*H*-imidazol-4-il}fenil)-4*H*-1,2,4-triazol-3-il]fenil}-1*H*-imidazol-2-il)pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

Ejemplo 218A

4-bromo-N'-(4-bromobenzoil)benzoilhidrazida

Se disolvieron cantidades equimolares de 4-bromobenzohidrazida (1,097 g, 5 mmol) y cloruro de 4-bromobenzoilo (1,120 g, 5 mmol) en piridina anhidra (25 ml) bajo nitrógeno y se calentó a reflujo (baño de aceite 135 °C) durante 6 hr. La reacción se enfrió a temperatura ambiente, se volcó la mezcla sobre EtOH absoluto (100 ml), y se enfrió en un congelador durante la noche para dar cristales blancos. Se recogieron los sólidos mediante filtración al vacío, se lavó con EtOH absoluto (2 x 5 ml), y se secó al vacío para dar el compuesto del título como un sólido blanco (953 mg, 48%). ^{1}H RMN (400 MHz, DMSO-D6) δ ppm 7,75 (d, *J*=8,57 Hz, 4 H), 7,86 (d, *J*=8,46 Hz, 4 H), 10,63 (s, 2 H); MS (ESI-) m/z 395/397/399 $(M-H)^-$ con dos bromos.

Ejemplo 218B

3,5-bis(4-bromofenil)-4-(4-*tert*-butilfenil)-4*H*-1,2,4-triazol

En un balón de 10 ml secado al horno, equipado con un septo y purgado con nitrógeno, se disolvió 4-tert-butilanilina (450 mg, 3,01 mmol) en 1,2-diclorobenceno anhidro (1,5 ml) y la solución se enfrió a 0 °C. Una solución de oxicloruro de fósforo (0,047 ml, 0,502 mmol) en 1,2-diclorobenceno anhidro (0,5 ml) se agregó lentamente por goteo desde una jeringa. Al completarse la adición, se eliminó el baño de frío y se agitó a temperatura ambiente durante 1 hr para formar la fosforiltriamida *in situ* (la reacción se fue tornando turbia). Luego se agregó el producto del Ejemplo 218A (200 mg, 0,502 mmol), se reemplazó el septo con un condensador de reflujo, y se calentó en un baño de aceite a 200 °C durante 4 hr. La solución color marrón claro se enfrió a temperatura ambiente, luego se colocó en un congelador durante 3 días y se recogió un sólido blanco opaco (20 mg, subproducto 4-bromo-N-(4-tert-butilfenil)benzamida) mediante filtración al vacío. El material filtrado se trató con hexanos (~50 ml) y la solución turbia se enfrió en un congelador durante 30 min. Se recogió un sólido blanco opaco (73 mg) mediante filtración al vacío y se concentró el material filtrado por evaporación por rotación a una solución del producto en 1,2-diclorobenceno. Se purificó mediante cromatografía flash (gel de sílice, 3,8 cm x 15 cm, gradiente de CH_2Cl_2 , EtOAc al 20%/CH_2Cl_2, y 30% EtOAc/CH_2Cl_2) para dar el compuesto del título como un sólido liviano blanco (154 mg, 60%). ^{1}H RMN (400 MHz, $CDCl_3$) δ ppm 1,36 (s, 9 H), 7,06 (d, *J*=8,46 Hz, 2 H), 7,29 (d, *J*=8,57 Hz, 4 H), 7,43 (d, *J*=8,57 Hz, 4 H), 7,46 (d, *J*=8,57 Hz, 2 H); MS (ESI+) m/z 510/512/514 $(M+H)^+$ con dos

bromos.

Ejemplo 218C

4-(4-*tert*-butilfenil)-3,5-bis((4(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)-4*H*-1,2,4-triazol

Se cargó un balón de 25 ml secado al horno, purgado con nitrógeno, con el producto del Ejemplo 218B (144,2 mg, 0,282 mmol), bis(pinacalato)diboro (215 mg, 0,846 mmol), acetato de potasio (90 mg, 0,917 mmol), y dioxano anhidro (1,5 ml). Se burbujeó la mezcla con nitrógeno durante 30 min, se agregó complejo dicloruro de 1,1'-bis(difenilfosfino)ferrocen-paladio(II) diclorometano (23,03 mg, 0,028 mmol), volvió a burbujearse con nitrógeno durante 5 min, volvió a colocarse un septo con un tapón de vidrio, y se calentó en un baño de aceite (85 °C) durante 2 hr. Se enfrió la reacción a temperatura ambiente, se filtró al vacío a través de un lecho pequeño de Celite 545, se lavó el catalizador con CH_2Cl_2, y se concentró el material filtrado mediante evaporación por rotación a un aceite marrón oscuro. Se purificó mediante cromatografía flash (gel de sílice, columna Alltech Extract-Clean de 10g, 1:1 EtOAc/CH_2Cl_2) para dar un sólido color beige oscuro (230 mg). Volvió a purificarse mediante cromatografía flash (gel de sílice, columna Alltech Extract-Clean de 10g, 3% MeOH/CH_2Cl_2) para dar el compuesto del título como un sólido beige (171 mg, 100%). ^{1}H RMN (400 MHz, $CDCl_3$) δ ppm 1,27 (s, 9 H), 1,33 (s, 24 H), 7,06 (d, *J*=8,46 Hz, 2 H), 7,38 - 7,47 (m, 6 H), 7,71 (d, *J*=7,92 Hz, 4 H); MS (ESI+) m/z 606 $(M+H)^+$, 1211 $(2M+H)^+$.

Ejemplo 218D

(2S,2'S)- 2,2'-(4,4'-(4,4'-(4-(4-*tert*-butilfenil)-4*H*-1,2,4-triazol-3,5-diil)bis(4,1-fenilen))bis(1*H*-imidazol-4,2-diil))dipirrolidin-1-carboxilato de *tert*-butilo

Se cargó un tubo para microondas purgado con nitrógeno (tamaño M, 5 ml) con el producto del Ejemplo 218C (171 mg, 0,282 mmol), el producto del Ejemplo 26D (223 mg, 0,706 mmol), y una mezcla de EtOH absoluto (1,5 ml) y tolueno (1,5 ml), luego se agregó carbonato de sodio acuoso 1M (0,706 ml, 0,706 mmol) y se burbujeó la mezcla con nitrógeno durante 20 min. Se agregó complejo dicloruro de 1,1'-bis(difenilfosfino)ferrocen-paladio(II) diclorometano (23,07 mg, 0,028 mmol), se roció nuevamente con nitrógeno durante 5 min, se selló el tubo con un tapón alabeado de aluminio, y se calentó en un reactor de microondas (Personal Chemistry Emrys Creator) con agitación a 100 °C durante 1 hr. Se enfrió la reacción a temperatura ambiente, se diluyó en EtOAc (75 ml), se lavó con H_2O (2 x 25 ml) y salmuera (25 ml), se secó la fase orgánica sobre $MgSO_4$ anhidro, se filtró, y se concentró mediante evaporación por rotación a un sólido amarillo (330 mg). Se purificó mediante cromatografía flash (gel de sílice, 3,8 cm x 15 cm, gradiente de 4%, 6%, 8%, y MeOH al 10%/CH_2Cl_2) para dar el compuesto del título como

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un sólido amarillo claro (135 mg, 58%). MS (ESI+) m/z 824 $(M+H)^+$.

Ejemplo 218E

4-(4-*tert*-butilfenil)-3,5-bis(4-(2-((S)-pirrolidin-2-il)-1*H*-imidazol-4-il)fenil)-4*H*-1,2,4-triazol

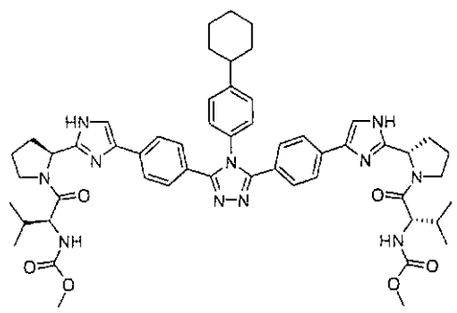
Se disolvió el producto del Ejemplo 218D (131,5 mg, 0,160 mmol) en CH_2Cl_2 anhidro (2 ml) bajo nitrógeno, se agregó ácido trifluoroacético (1 ml, 12,85 mmol), y se agitó a 25 °C durante 30 min. Se eliminó el solvente por evaporación por rotación, se recogió el residuo en 20% iPrOH/$CHCl_3$ (50 ml), se lavó con $NaHCO_3$ acuoso saturado (10 ml), se extrajo la fase acuosa con 20% iPrOH/$CHCl_3$ (2 x 25 ml), se secaron los extractos orgánicos combinados sobre $MgSO_4$ anhidro, se filtró, y se concentró por evaporación por rotación. Se recogió el residuo en 1:5 v/v CH_2Cl_2/hexanos y se concentró al vacío para dar el compuesto del título como un sólido color tostado claro (114 mg). ^{1}H RMN (400 MHz, DMSO-D6) δ ppm 1,30 (s, 9 H), 1,66 - 1,94 (m, 6 H), 1,98 - 2,12 (m, 2 H), 2,80 - 3,07 (m, 4 H), 3,70 - 3,86 (m, 1 H), 4,12 - 4,22 (m, 2 H), 4,34 (d, *J*=4,01 Hz, 1 H), 7,34 (t, *J*=8,08 Hz, 6 H), 7,47 - 7,57 (m, 4 H), 7,68 (d, *J*=8,35 Hz, 4 H), 11,90 (s, 2 H); MS (ESI+) 624 $(M+H)^+$; (ESI-) m/z 622 $(M-H)^-$.

Ejemplo 218F

{(2*S*)-1-[(2*S*)-2-(4-{4-[4-(4-*tert*-butilfenil)-5-(4-{2-[(2*S*)-1-{(2*S*)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1*H*-imidazol-4-il}fenil)-4*H*-1,2,4-triazol-3-il]fenil}-1*H*-imidazol-2-il)pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

En un balón de 5 ml secado al horno purgado con nitrógeno, se disolvió el producto del Ejemplo 218E (50 mg, 0,080 mmol) en DMF anhidro (1 ml), y se enfrió a 0 °C. Se agregó en forma consecutiva ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico (29,5 mg, 0,168 mmol), HOBt hidrato (27,6 mg, 0,180 mmol), EDAC (35,3 mg, 0,180 mmol), y N-metilmorfolina (0,035 ml, 0,321 mmol). Se agitó la solución a 25 °C durante 15 hr. Se diluyó la reacción en EtOAc (50 ml), se lavó con $NaHCO_3$ acuoso saturado (25 ml), H_2O (3 x 25 ml), y salmuera (25 ml), se secó la fase orgánica sobre $MgSO_4$ anhidro, se filtró, y se concentró mediante evaporación por rotación a un sólido blanco opaco (72 mg). Se purificó mediante cromatografía flash (gel de sílice, columna Alltech Extract-Clean de 10g, gradiente de 6% a 8% MeOH/CH_2Cl_2) para dar el compuesto del título como un sólido blanco opaco (49 mg, 65%). ^{1}H RMN (400 MHz, DMSO-D6) δ ppm 0,82 (d, *J*=6,72 Hz, 6 H), 0,86 (d, *J*=6,72 Hz, 6 H), 1,29 (s, 9 H), 1,79 - 2,01 (m, 5 H), 2,03 - 2,22 (m, 4 H), 3,53 (s, 6 H), 3,70 - 3,86 (m, 4 H), 4,04 (t, *J*=8,35 Hz, 2 H), 5,04 (dd, *J*=6,67, 3,20 Hz, 2 H), 7,23 - 7,43 (m, 8 H), 7,48 - 7,60 (m, 4 H), 7,61 - 7,73 (m, 4 H), 11,77 - 12,21 (m, 2 H); MS (ESI+) m/z 939 $(M+H)^+$.

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Ejemplo 219

{(2*S*)-1-[(2*S*)-2-(4-{4-[4-(4-ciclohexilfenil)-5-(4-{2-[(2*S*)-1-{(2*S*)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1*H*-imidazol-4-il}fenil)-4*H*-1,2,4-triazol-3-il]fenil}-1*H*-imidazol-2-il)pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

Ejemplo 219A

3,5-bis(4-bromofenil)-4-(4-ciclohexilfenil)-4*H*-1,2,4-triazol

En un balón de 10 ml secado al horno, equipado con un septo y purgado con nitrógeno, se disolvió 4-ciclohexilanilina (545 mg, 3,01 mmol) en 1,2-diclorobenceno anhidro (1,5 ml) y la solución se enfrió a 0 °C. Una solución de oxicloruro de fósforo (78 mg, 0,502 mmol) en 1,2-diclorobenceno anhidro (0,5 ml) se agregó lentamente por goteo desde una jeringa. La reacción se tornó un gel sólido imposible de agitar; se eliminó el baño de enfriamiento, se agregó más 1,2-diclorobenceno (0,5 ml), se sonicó la mezcla, y se agitó la suspensión espesa a temperatura ambiente durante 1 hr para formar la fosforiltriamida *in situ*. Se agregó el producto del Ejemplo 218A (200 mg, 0,502 mmol), volvió a colocarse el septo con un condensador de reflujo, y se calentó la reacción en un baño de aceite a 200 °C durante 4 hr bajo nitrógeno. La reacción rápidamente se tornó una solución homogénea color dorado al reflujarse. Se enfrió la solución a temperatura ambiente y se purificó mediante cromatografía flash (gel de sílice, 3,8 cm x 15 cm, gradiente de CH_2Cl_2 a EtOAc al 20%/CH_2Cl_2 a 40% EtOAc/CH_2Cl_2) para dar el compuesto del título como un sólido liviano blanco (201 mg, 74%). ^{1}H RMN (400 MHz, $CDCl_3$) δ ppm 1,19 - 1,33 (m, 1 H) 1,35 - 1,50 (m, 4 H) 1,78 (d, *J*=14,42 Hz, 1 H) 1,84 - 1,98 (m, 4 H) 2,51 - 2,65 (m, 1 H) 7,04 (d, *J*=8,35 Hz, 2 H) 7,28 (d, *J*=8,57 Hz, 6 H) 7,43 (d, *J*=8,57 Hz, 4 H); MS (ESI+) m/z 536/538540 $(M+H)^+$, 1072/1074/1076 $(2M+H)^+$ con dos bromos.

Ejemplo 219B

4-(4-ciclohexilfenil)-3,5-bis(4(4,4,5,5-tetrametil-1,3,2-dioxaboralan-2-il)fenil)-4*H*-1,2,4-triazol

Se cargó un balón de 10 ml secado al horno, purgado con nitrógeno, con el producto del Ejemplo 219A (100 mg, 0,186 mmol), bis(pinacalato)diboro (142 mg, 0,558 mmol), acetato de potasio (59,4 mg, 0,605 mmol), y dioxano anhidro (3 ml). Se burbujeó la

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mezcla blanca espesa con nitrógeno durante 30 min, se agregó complejo dicloruro de 1,1'-bis(difenilfosfino)ferrocen-paladio(II) diclorometano (15,20 mg, 0,019 mmol), volvió a burbujearse con nitrógeno durante 5 min, volvió a colocarse el septo con un tapón de vidrio, y se calentó en un baño de aceite (85 °C). La reacción se tornó homogénea al calentarse y se oscureció con el tiempo hasta un color marrón rojizo. TLC (SiO2, 50% EtOAc/CH_2Cl_2). Luego de 2 hr, se enfrió a temperatura ambiente, se agregó más bis(pinacalato)diboro (71 mg, ~1,5 equiv) y acetato de potasio (30 mg, ~1,75 equiv), y se calentó durante 1 hr a 85 °C. Se enfrió la reacción color marrón a temperatura ambiente, se filtró al vacío a través de un lecho pequeño de Celite 545, se lavaron los sólidos recogidos con CH_2Cl_2, y se concentró el material filtrado mediante evaporación por rotación hasta una espuma color marrón. Se purificó mediante cromatografía flash en gel de sílice (columna Alltech Extract-Clean, 10g) eluyendo con 30% EtOAc/CH_2Cl_2 para dar el producto como un aceite marrón claro (190 mg). Volvió a purificarse mediante cromatografía flash en gel de sílice (columna Alltech Extract-Clean, 10g) eluyendo con 3% MeOH/CH_2Cl_2 para dar el compuesto del título como una espuma color beige claro (122 mg, 100%). MS (ESI+) m/z 632 $(M+H)^+$, 1263 $(2M+H)^+$.

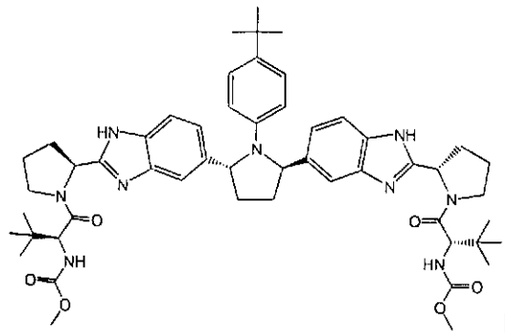
Ejemplo 219C

{(2*S*)-1-[(2*S*)-2-(4-{4-[4-(4-ciclohexilfenil)-5-(4-{2-[(2*S*)-1-{(2*S*)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1*H*-imidazol-4-il}fenil)-4*H*-1,2,4-triazol-3-il]fenil}-1*H*-imidazol-2-il)pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

Se cargó un tubo para microondas purgado con nitrógeno (tamaño M, 5 ml) con el producto del Ejemplo 219B (118 mg, 0,187 mmol), el producto del Ejemplo 126G (174 mg, 0,467 mmol), y una mezcla de EtOH absoluto (1 ml) y tolueno (1 ml), luego se agregó carbonato de sodio acuoso 1M (0,467 ml, 0,467 mmol) y se burbujeó la mezcla con nitrógeno durante 20 min. Se agregó complejo dicloruro de 1,1'-bis(difenilfosfino)ferrocen-paladio(II) diclorometano (15,26 mg, 0,019 mmol), se roció nuevamente con nitrógeno durante 5 min, se selló el tubo con un tapón alabeado de aluminio, y se calentó en un reactor de microondas (Personal Chemistry Emrys Creator) con agitación a 100 °C durante 1 hr. Se enfrió la reacción a temperatura ambiente, se diluyó en EtOAc (50 ml), se lavó con H_2O (2 x 25 ml) y salmuera (25 ml), se secó la fase orgánica sobre $MgSO_4$ anhidro, se filtró, y se concentró mediante evaporación por rotación a un sólido. Se purificó mediante cromatografía flash (gel de sílice, gradiente en pasos 5% a 8% a MeOH al 10%/CH_2Cl_2) para dar el producto como un sólido color tostado (72 mg) que resultó tener ~85% de pureza (2 impurezas principales). Se disolvió el producto impuro en 1,5 ml de 1:1 v/v MeOH/DMSO y se purificó mediante RP-C18 HPLC (Waters Prep LC, 40mm Module con cartucho Nova Pak HR C_{18} 6µm 40x100mm Prep Pak) eluyendo con un

gradiente de 30 min de 95:5 TFA al 0,1% en H_2O/AcCN a 25:75 TFA al 0,1% en H_2O/AcCN, luego 10 min a 100% AcCN a 20 ml/min. Las fracciones puras se concentraron por evaporación por rotación (baño de agua 35ºC) hasta un pequeño volumen, se particionó entre 20% iPrOH/$CHCl_3$ (50 ml) y $NaHCO_3$ acuoso saturado (15 ml), se separaron las fases, se secó el extracto orgánico sobre $MgSO_4$ anhidro, se filtró, y se concentró por evaporación por rotación para dar el compuesto del título como un sólido blanco (34,5 mg, 19%). ^{1}H RMN (400 MHz, DMSO-D6) δ ppm 0,83 (d, *J*=6,72 Hz, 6 H) 0,86 (d, *J*=6,72 Hz, 6 H) 1,29 - 1,47 (m, 5 H) 1,65 - 2,01 (m, 12 H) 2,04 - 2,21 (m, 4 H) 3,53 (s, 6 H) 3,72 - 3,84 (m, 4 H) 4,04 (t, *J*=8,40 Hz, 2 H) 5,04 (dd, *J*=6,89, 3,20 Hz, 2 H) 7,23 - 7,40 (m, 10 H) 7,51 - 7,72 (m, 6 H) 11,84 (s, 2 H); MS (ESI+) m/z 965 $(M+H)^+$.

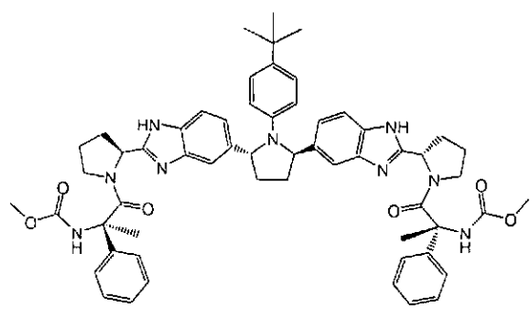
Los Ejemplos 220-308 se prepararon de manera análoga de acuerdo a los métodos y condiciones mencionados en los esquemas y ejemplos precedentes.



Ejemplo 220

{(2S)-1-[(2S)-2-{5-[(2R,5R)-1-(4-tert-butilfenil)-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3,3-dimetilbutanoil}pirrolidin-2-il]-1H-bencimidazol-5-il}pirrolidin-2-il]-1H-bencimidazol-2-il}pirrolidin-1-il]-3,3-dimetil-1-oxobutan-2-il}carbamato de metilo

^{1}H RMN (400 MHz, DMSO-d6) δ ppm 0,88 (d, *J*=13,55 Hz, 18 H), 1,07 (s, 9 H), 1,62 - 1,78 (m, 2 H), 1,91 - 2,09 (m, 4 H), 2,10 - 2,26 (m, 4 H), 2,54 - 2,62 (m, 2 H), 3,55 (s, 6 H), 3,74 - 3,90 (m, 4 H), 4,23 (dd, *J*=8,78, 4,55 Hz, 2 H), 5,09 - 5,23 (m, 2 H), 5,31 - 5,43 (m, 2 H), 6,26 (d, *J*=8,89 Hz, 2 H), 6,84 - 6,97 (m, 2 H), 7,06 (dd, *J*=8,29, 2;55 Hz, 2 H), 7,12 (t, *J*=9,43 Hz, 2 H), 7,20 (s, 1 H), 7,30 (s, 1 H), 7,38 (d, *J*=8,24 Hz, 1 H) 7,45 (d, *J*=8,24 Hz, 1 H), 12,02 (s, 2 H); MS (ESI+) m/z 916 $(M+H)^+$.



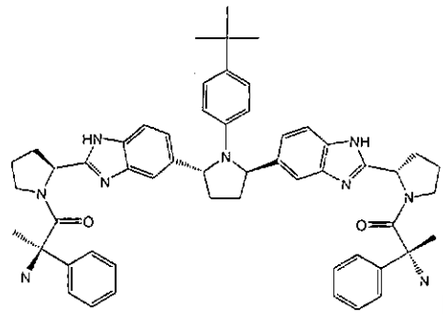
Ejemplo 221

([(2R,5R)-1-(4-tert-butilfenil)pirrolidin-2,5-diil]bis{1H-bencimidazol-5,2-diil(2S)pirrolidin-2,1-

000781

diil[(2R)-1-oxo-2-fenilpropan-1,2-diil]})biscarbamato de dimetilo

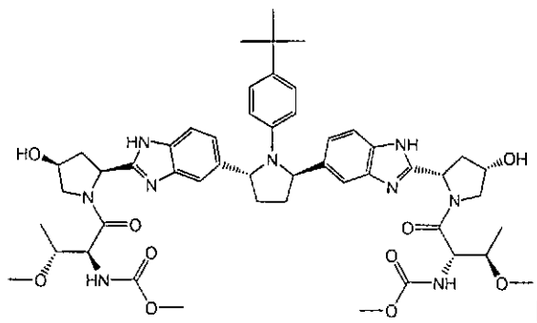
^{1}H RMN (400 MHz, DMSO-d6) δ ppm 1,03 - 1,10 (m, 9 H), 1,49 - 1,58 (m, 2 H), 1,67 (d, *J*=16,70 Hz, 6 H), 1,70 - 1,95 (m, 4 H), 2,04 (s, 3 H), 2,35 - 2,43 (m, 1 H), 2,97 - 3,11 (m, 2 H), 3,22 - 3,29 (m, 1 H), 3,50 (s, 6 H), 3,61 - 3,91 (m, 1 H), 5,08 - 5,22 (m, 2 H), 5,29 - 5,49 (m, 2 H), 6,21 - 6,39 (m, 2 H), 6,84 - 6,99 (m, 2 H), 7,07 - 7,50 (m, 17 H), 7,53 (d, *J*=8,24 Hz, 1 H), 7,61 (s, 2 H), 12,10 (dos s, 2 H); MS (ESI+) m/z 984 $(M+H)^+$.



Ejemplo 222

(2R,2'R)-1,1'-{[(2R,5R)-1-(4-tert-butilfenil)pirrolidin-2,5-diil]bis[1H-bencimidazol-5,2-diil(2S)pirrolidin-2,1-diil]}bis(2-amino-2-fenilpropan-1-ona)

^{1}H RMN (400 MHz, DMSO-d6) δ ppm 1,10 (s, 9 H), 1,55 - 1,66 (m, 3 H), 1,68 - 1,82 (m, 4 H), 1,83 - 2,02 (m, 5 H), 1,93 (s, 6 H), 2,12 - 2,31 (m, 3 H), 2,57 (d, *J*=3,90 Hz, 2 H), 5,26 - 5,36 (m, 2 H), 5,41 - 5,57 (m, 2 H), 6,30 (d, *J*=8,78 Hz, 2 H), 6,93 (d, *J*=8,78 Hz, 2 H), 7,17 - 7,31 (m, 2 H), 7,38 (s, 2 H), 7,47 - 7,66 (m, 13 H), 8,43 (s, 6 H); MS (ESI+) m/z 868 $(M+H)^+$.

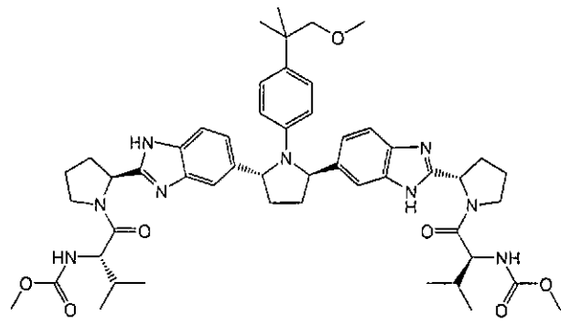


Ejemplo 223

{(2S,3R)-1-[(2S,4S)-2-{5-[(2R,5R)-1-(4-tert-butilfenil)-5-(2-{(2S,4S)-4-hidroxi-1-[N-(metoxicarbonil)-O-metil-L-treonil]pirrolidin-2-il}-1H-bencimidazol-5-il)pirrolidin-2-il]-1H-bencimidazol-2-il}-4-hidroxipirrolidin-1-il]-3-metoxi-1-oxobutan-2-il}carbamato de metilo

^{1}H RMN (400 MHz, DMSO-d6) δ ppm 0,96 (d, *J*=5,96 Hz, 6 H), 1,09 (s, 9 H), 1,74 (d, *J*=5,64 Hz, 2 H), 2,06 - 2,15 (m, 3 H), 2,96 - 3,03 (m, 1 H), 3,10 (s, 6 H), 3,55 (s, 6 H), 3,72 (dd, *J*=9,65, 2,39 Hz, 3 H), 3,94 (dd, *J*=10,25, 4,72 Hz, 2 H), 4,23 - 4,33 (m, 2 H), 4,38 (t, *J*=7,10 Hz, 1 H), 4,44 - 4,53 (m, 2 H), 5,26 (dd, *J*=8,46, 4,23 Hz, 2 H), 5,49 (d, *J*=5,53 Hz, 2 H), 6,25 (d, *J*=8,78 Hz, 2 H), 6,94 (d, *J*=8,78 Hz, 2 H), 7,22 (d, *J*=8,46 Hz, 2 H), 7,37 (d, *J*=7,59 Hz, 2 H), 7,46 (s, 2 H), 7,69 (d, *J*=7,92 Hz, 2 H); MS (ESI+) m/z 952 $(M+H)^+$.

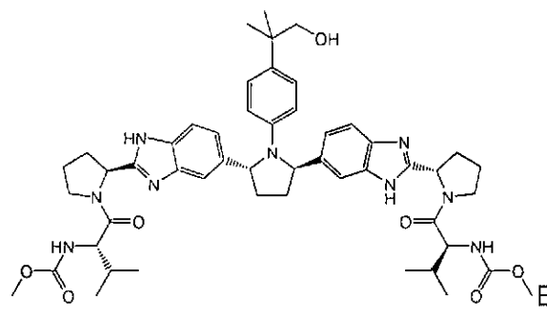
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Ejemplo 224

{(2S)-1-[(2S)-2-(6-{(2R,5R)-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-bencimidazol-5-il}-1-[4-(1-metoxi-2-metilpropan-2-il)fenil]pirrolidin-2-il}-1H-bencimidazol-2-il)pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

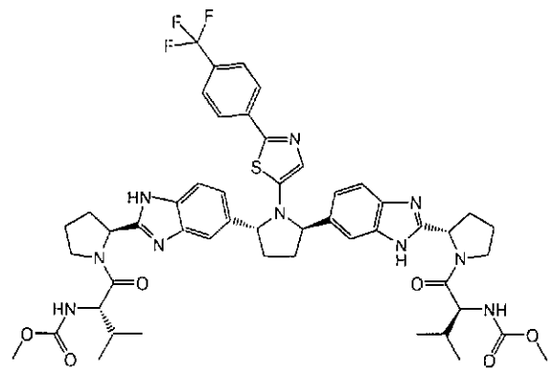
1H RMN (400 MHz, DMSO-D6) δ ppm 0,74 - 0,93 (m, 12 H) 1,04 (s, 6 H) 1,69 (d, J=4,34 Hz, 2 H) 1,85 - 1,94 (m, 2 H) 1,95 - 2,03 (m, 6 H) 2,13 - 2,25 (m, 2 H) 2,53 - 2,63 (m, 4 H) 3,11 (s, 3 H) 3,53 (s, 6 H) 3,81 (s, 4 H) 4,05 - 4,15 (m, 2 H) 5,09 - 5,19 (m, 2 H) 5,32 - 5,41 (m, 2 H) 6,25 (d, J=8,78 Hz, 2 H) 6,87 (ddd, J=8,89, 4,77, 4,55 Hz, 2 H) 7,07 (t, J=7,37 Hz, 2 H) 7,20 (s, 1 H) 7,25 - 7,33 (m, 3 H) 7,38 (d, J=8,24 Hz, 1 H) 7,46 (d, J=8,46 Hz, 1 H) 12,00 - 12,09 (m, 2 H); MS ESI+ 918.



Ejemplo 225

{(2S)-1-[(2S)-2-{6-[(2R,5R)-1-[4-(1-hidroxi-2-metilpropan-2-il)fenil]-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-bencimidazol-5-il}pirrolidin-2-il]-1H-bencimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

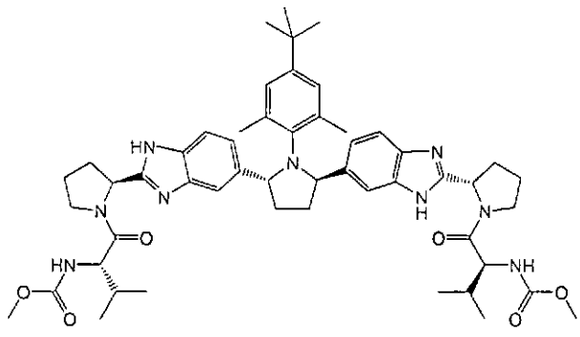
1H RMN (400 MHz, DMSO-D6) d ppm 0,76 - 0,91 (m, 12 H) 1,01 (d, J=2,60 Hz, 6 H) 1,64 - 1,72 (m, 2 H) 1,91 (dd, J=14,42, 6,83 Hz, 2 H) 1,95 - 2,05 (m, 4 H) 2,14 - 2,23 (m, 4 H) 2,54 - 2,60 (m, 2 H) 3,53 (s, 6 H) 3,76 - 3,87 (m, 4 H) 4,11 (q, J=4,77 Hz, 4 H) 4,42 (s, 1 H) 5,09 - 5,17 (m, 2 H) 5,31 - 5,40 (m, 2 H) 6,25 (d, J=8,78 Hz, 2 H) 6,83 - 6,92 (m, 2 H) 7,07 (t, J=7,21 Hz, 2 H) 7,20 (s, 1 H) 7,26 - 7,32 (m, 3 H) 7,38 (d, J=8,13 Hz, 1 H) 7,46 (d, J=8,35 Hz, 1 H) 11,99 - 12,06 (m, 2 H); MS ESI+ m/z 904,5 (M+H)+.



Ejemplo 226

{(2S)-1-[(2S)-2-{6-[(2R,5R)-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-bencimidazol-5-il}-1-{2-[4-(trifluorometil)fenil]-1,3-tiazol-5-il}pirrolidin-2-il]-1H-bencimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

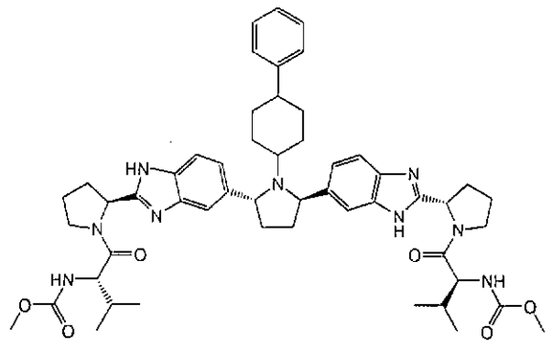
1H RMN (400 MHz, DMSO-D6) d ppm 0,73 - 0,91 (m, 12 H) 1,79 - 1,95 (m, 4 H) 1,96 - 2,06 (m, 4 H) 2,15 - 2,27 (m, 2 H) 2,69 - 2,76 (m, 2 H) 3,43 - 3,50 (m, 2 H) 3,53 (s, 6 H) 3,78 - 3,88 (m, 4 H) 4,01 - 4,10 (m, 2 H) 5,11 - 5,18 (m, 2 H) 5,32 - 5,41 (m, 2 H) 6,43 (s, 1 H) 7,09 - 7,18 (m, 2 H) 7,27 (dd, J=8,24, 2,39 Hz, 2 H) 7,35 (s, 1 H) 7,41 - 7,46 (m, 2 H) 7,51 (d, J=8,35 Hz, 1 H) 7,57 - 7,62 (m, 2 H) 7,64 - 7,70 (m, 2 H) 12,12 (s, 2 H); MS ESI+ m/z 983,4 (M+H)+.



Ejemplo 227

{(2S)-1-[(2S)-2-{6-[(2R,5R)-1-(4-tert-butil-2,6-dimetilfenil)-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-bencimidazol-5-il}pirrolidin-2-il]-1H-bencimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

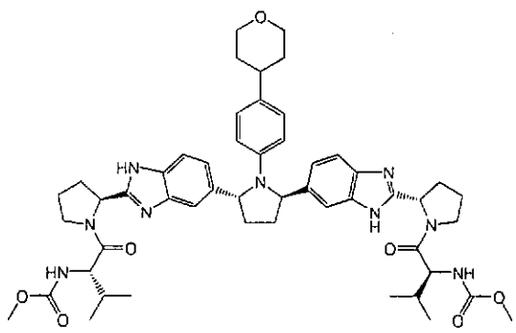
1H RMN (400 MHz, DMSO-D6) d ppm 0,77 - 0,89 (m, 12 H) 1,02 (s, 9 H) 1,84 - 2,05 (m, 10 H) 2,13 - 2,19 (m, 4 H) 2,24 - 2,30 (m, 6 H) 3,53 (s, 6 H) 3,80 (s, 4 H) 4,04 (t, J=8,08 Hz, 2 H) 5,07 - 5,14 (m, 2 H) 5,25 (s, 2 H) 6,61 (dd, J=5,10, 2,71 Hz, 2 H) 7,06 (dd, J=11,87, 8,51 Hz, 2 H) 7,20 - 7,37 (m, 6 H) 11,89 (s, 1 H) 11,99 (s, 1 H); MS ESI+ m/z 916,6 (M+H)+.



Ejemplo 228

{(2S)-1-[(2S)-2-{6-[(2R,5R)-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-bencimidazol-5-il}-1-(4-fenilciclohexil)pirrolidin-2-il]-1H-bencimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

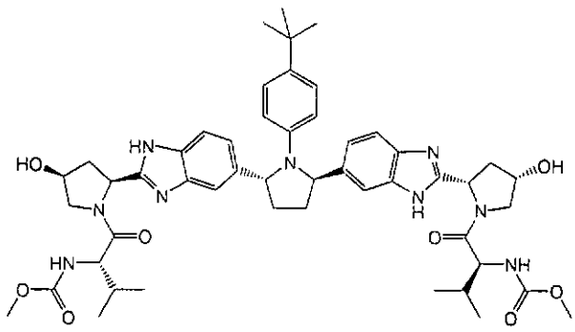
1H RMN (400 MHz, DMSO-D6) d ppm 0,78 - 0,93 (m, 12 H) 1,15 - 1,44 (m, 4 H) 1,46 - 1,59 (m, 2 H) 1,67 - 1,78 (m, 2 H) 1,84 - 1,96 (m, 4 H) 1,98 - 2,10 (m, 4 H) 2,14 - 2,27 (m, 4 H) 2,67 - 2,75 (m, 2 H) 3,07 - 3,21 (m, 1 H) 3,45 - 3,52 (m, 1 H) 3,54 (s, 6 H) 3,78 - 3,91 (m, 4 H) 4,03 - 4,13 (m, 2 H) 4,64 - 4,73 (m, 2 H) 5,17 (d, J=4,88 Hz, 2 H) 7,00 - 7,06 (m, 2 H) 7,09 (t, J=7,32 Hz, 2 H) 7,14 - 7,24 (m, 3 H) 7,30 (d, J=8,46 Hz, 2 H) 7,38 (d, J=8,02 Hz, 1 H) 7,43 - 7,50 (m, 3 H) 12,00 (s, 2 H); MS ESLD+ m/z 914.



Ejemplo 229

{(2S)-1-[(2S)-2-(6-{(2R,5R)-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-bencimidazol-5-il}-1-[4-(tetrahidro-2H-piran-4-il)fenil]pirrolidin-2-il}-1H-bencimidazol-2-il)pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

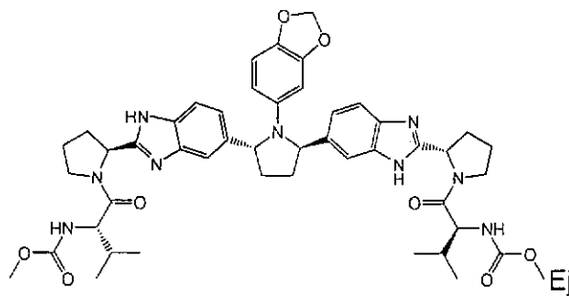
1H RMN (400 MHz, DMSO-D6) d ppm 0,73 - 0,94 (m, 12 H) 1,41 - 1,60 (m, 6 H) 1,65 - 1,75 (m, 2 H) 1,86 - 1,94 (m, 2 H) 1,95 - 2,05 (m, 4 H) 2,14 - 2,24 (m, 4 H) 2,37 - 2,46 (m, 2 H) 3,53 (s, 6 H) 3,77 - 3,86 (m, 7 H) 4,02 - 4,10 (m, 2 H) 5,09 - 5,17 (m, 2 H) 5,32 - 5,39 (m, 2 H) 6,26 (d, J=8,67 Hz, 2 H) 6,72 - 6,81 (m, 2 H) 7,06 (t, J=7,64 Hz, 2 H) 7,20 (s, 1 H) 7,26 - 7,31 (m, 3 H) 7,37 (d, J=8,13 Hz, 1 H) 7,45 (d, J=8,13 Hz, 1 H) 12,00 - 12,05 (m, 2 H); MS ESLD+ m/z 917 (M+H)+.



Ejemplo 230

{(2S)-1-[(2S,4S)-2-{6-[(2R,5R)-1-(4-tert-butilfenil)-5-{2-[(2S,4S)-4-hidroxi-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-bencimidazol-5-il}pirrolidin-2-il]-1H-bencimidazol-2-il}-4-hidroxipirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

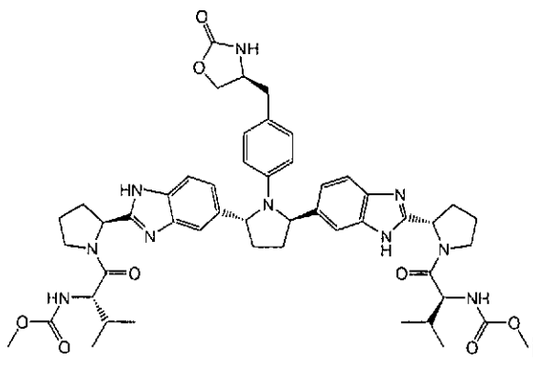
1H RMN (500 MHz, DMSO-D6) d ppm 0,67 - 0,91 (m, 12 H) 1,07 (s, 9 H) 1,69 (d, J=3,97 Hz, 2 H) 1,78 - 1,89 (m, 2 H) 2,01 (d, J=13,12 Hz, 2 H) 2,37 - 2,44 (m, 2 H) 3,53 (s, 6 H) 3,67 (d, J=10,07 Hz, 2 H) 3,95 - 4,07 (m, 4 H) 4,38 (s, 2 H) 5,12 (s, 2 H) 5,37 (s, 2 H) 6,25 (d, J=8,54 Hz, 2 H) 6,34 (s, 2 H) 6,86 - 6,94 (m, 2 H) 7,09 (d, J=7,93 Hz, 2 H) 7,22 - 7,33 (m, 4 H) 7,39 - 7,51 (m, 2 H) 12,27 (d, J=21,05 Hz, 2 H); MS ESLD+ m/z 920.



Ejemplo 231

{(2S)-1-[(2S)-2-{6-[(2R,5R)-1-(1,3-benzodioxol-5-il)-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-bencimidazol-5-il}pirrolidin-2-il]-1H-bencimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

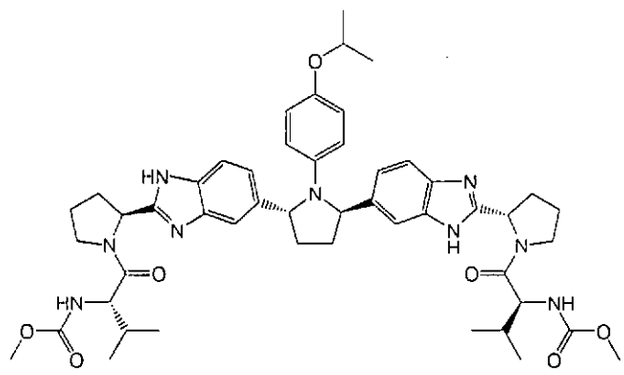
1H RMN (400 MHz, DMSO-D6) d ppm 0,78 - 0,91 (m, 12 H) 1,64 - 1,72 (m, 2 H) 1,86 - 2,04 (m, 6 H) 2,14 - 2,24 (m, 4 H) 3,29 (s, 2 H) 3,54 (s, 6 H) 3,82 (s, 4 H) 4,05 - 4,11 (m, 2 H) 5,10 - 5,18 (m, 2 H) 5,29 - 5,36 (m, 2 H) 5,66 (d, J=2,93 Hz, 1 H) 5,70 - 5,75 (m, 2 H) 5,99 (d, J=2,28 Hz, 1 H) 6,45 - 6,51 (m, 1 H) 7,02 - 7,09 (m, 2 H) 7,21 (s, 1 H) 7,28 (s, 1 H) 7,31 (d, J=6,40 Hz, 2 H) 7,37 (d, J=8,13 Hz, 1 H) 7,45 (d, J=8,24 Hz, 1 H) 12,03 (s, 2 H); MS TFA+ m/z 876,8 (M+H)+.



Ejemplo 232

{(2S)-1-[(2S)-2-{6-[(2R,5R)-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-bencimidazol-5-il}-1-(4-{[(4S)-2-oxo-1,3-oxazolidin-4-il]metil}fenil)pirrolidin-2-il]-1H-bencimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

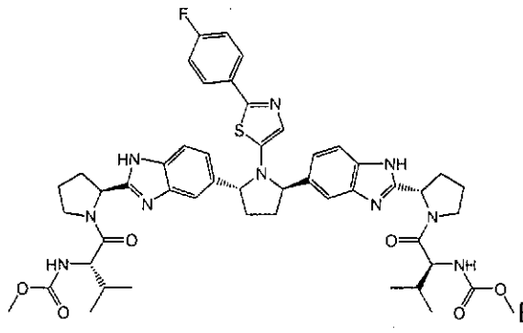
1H RMN (400 MHz, DMSO-D6) d ppm 0,77 - 0,92 (m, 12 H) 1,63 - 1,74 (m, 2 H) 1,86 - 2,04 (m, 6 H) 2,13 - 2,26 (m, 4 H) 2,55 - 2,65 (m, 2 H) 3,25 - 3,33 (m, 2 H) 3,54 (s, 6 H) 3,75 - 3,87 (m, 6 H) 4,05 - 4,17 (m, 3 H) 5,09 - 5,19 (m, 2 H) 5,36 (d, J=5,10 Hz, 2 H) 6,27 (d, J=8,57 Hz, 2 H) 6,71 - 6,79 (m, 2 H) 7,05 (t, J=9,60 Hz, 2 H) 7,20 (s, 1 H) 7,27 - 7,33 (m, 3 H) 7,37 (d, J=8,24 Hz, 1 H) 7,45 (d, J=8,13 Hz, 1 H) 7,63 (s, 1 H) 12,03 (s, 2 H); MS ESI+ m/z 931,5 (M+H)+.



Ejemplo 233

{(2S)-1-[(2S)-2-(6-{(2R,5R)-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-bencimidazol-5-il}-1-[4-(propan-2-iloxi)fenil]pirrolidin-2-il}-1H-bencimidazol-2-il)pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

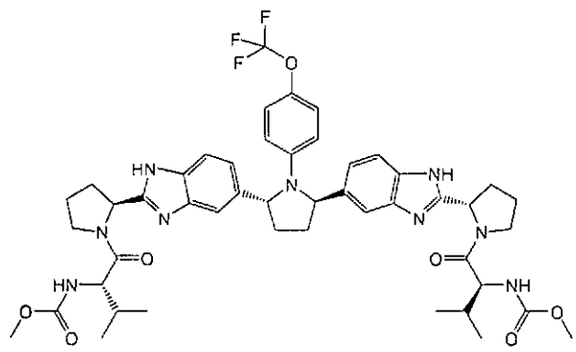
1H RMN (400 MHz, DMSO-D6) d ppm 0,76 - 0,89 (m, 12 H) 1,07 (t, J=5,42 Hz, 6 H) 1,68 (d, J=3,47 Hz, 2 H) 1,85 - 2,05 (m, 6 H) 2,14 - 2,25 (m, 4 H) 2,58 (d, J=4,77 Hz, 2 H) 3,53 (s, 6 H) 3,81 (s, 4 H) 4,05 (t, J=8,40 Hz, 2 H) 4,13 - 4,25 (m, 1 H) 5,08 - 5,20 (m, 2 H) 5,32 (d, J=5,31 Hz, 2 H) 6,23 (d, J=9,00 Hz, 2 H) 6,45 - 6,55 (m, 2 H) 7,05 (t, J=8,19 Hz, 2 H) 7,20 (s, 1 H) 7,26 - 7,33 (m, 3 H) 7,37 (d, J=8,24 Hz, 1 H) 7,44 (d, J=8,35 Hz, 1 H) 12,02 (d, J=4,55 Hz, 2 H); MS ESI+ m/z 890,4 (M+H)+.



Ejemplo 234

{(2S)-1-[(2S)-2-{5-[(2R,5R)-1-[2-(4-fluorofenil)-1,3-tiazol-5-il]-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-bencimidazol-5-il}pirrolidin-2-il]-1H-bencimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

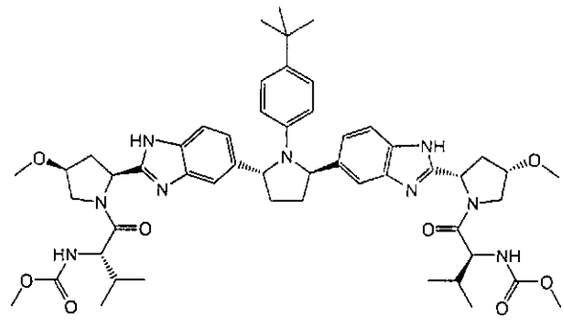
1H RMN (400 MHz, DMSO-D6) d ppm 0,75 - 0,85 (m, 12 H) 1,77 - 1,83 (m, 2 H) 1,87 - 1,93 (m, 2 H) 1,95 - 2,06 (m, 4 H) 2,14 - 2,25 (m, 6 H) 3,53 (s, 6 H) 3,77 - 3,86 (m, 4 H) 4,03 - 4,10 (m, 2 H) 5,12 - 5,18 (m, 2 H) 5,28 - 5,35 (m, 2 H) 7,06 - 7,16 (m, 5 H) 7,28 (dd, J=8,29, 2,01 Hz, 2 H) 7,33 (s, 1 H) 7,40 - 7,45 (m, 2 H) 7,47 - 7,55 (m, 3 H) 12,10 (s, 2 H); MS ESI+ m/z 933,4 (M+H)+.



Ejemplo 235

{(2S)-1-[(2S)-2-(5-{(2R,5R)-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-bencimidazol-5-il}-1-[4-(trifluorometoxi)fenil]pirrolidin-2-il}-1H-bencimidazol-2-il)pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

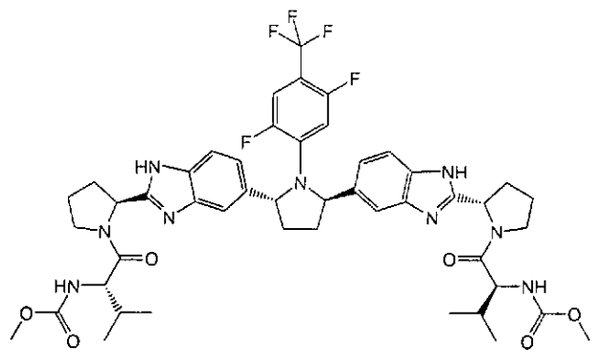
1H RMN (400 MHz, DMSO-D6) d ppm 0,74 - 0,87 (m, 12 H) 1,67 - 1,76 (m, 2 H) 1,86 - 1,92 (m, 2 H) 1,96 - 2,06 (m, 4 H) 2,15 - 2,23 (m, 6 H) 3,53 (s, 6 H) 3,77 - 3,88 (m, 4 H) 4,05 (t, J=8,84 Hz, 2 H) 5,12 (t, J=7,05 Hz, 2 H) 5,37 - 5,46 (m, 2 H) 6,34 (d, J=9,11 Hz, 2 H) 6,89 (q, J=7,30 Hz, 2 H) 7,02 - 7,11 (m, 2 H) 7,21 (s, 1 H) 7,26 - 7,33 (m, 3 H) 7,39 (d, J=8,35 Hz, 1 H) 7,47 (d, J=8,13 Hz, 1 H) 12,06 (d, J=17,02 Hz, 2 H); MS ESI+ m/z 916,4 (M+H)+.



Ejemplo 236

{(2S)-1-[(2S,4S)-2-{5-[(2R,5R)-1-(4-tert-butilfenil)-5-{2-[(2S,4S)-4-metoxi-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-bencimidazol-5-il}pirrolidin-2-il]-1H-bencimidazol-2-il}-4-metoxipirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

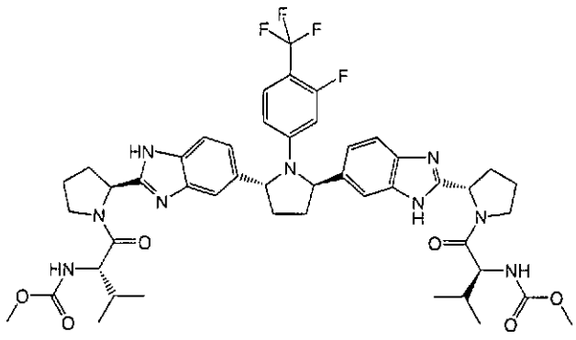
1H RMN (400 MHz, DMSO-D6) d ppm 0,75 - 0,88 (m, 12 H) 1,07 (s, 9 H) 1,67 - 1,76 (m, 2 H) 1,88 - 2,00 (m, 4 H) 2,06 - 2,16 (m, 2 H) 3,12 - 3,21 (m, 2 H) 3,25 (d, J=4,23 Hz, 6 H) 3,54 (s, 6 H) 3,59 - 3,69 (m, 2 H) 4,02 - 4,13 (m, 4 H) 4,16 - 4,28 (m, 2 H) 5,11 (td, J=9,38, 6,51 Hz, 2 H) 5,35 (t, J=5,37 Hz, 2 H) 6,23 - 6,28 (m, 2 H) 6,90 (d, J=8,89 Hz, 2 H) 7,06 (d, J=10,19 Hz, 2 H) 7,22 (d, J=3,25 Hz, 1 H) 7,25 - 7,32 (m, 3 H) 7,38 (d, J=8,35 Hz, 1 H) 7,45 (d, J=8,24 Hz, 1 H) 11,79 (d, J=18,32 Hz, 2 H); MS ESI+ m/z 948,5 (M+H)+.



Ejemplo 237

{(2S)-1-[(2S)-2-{5-[(2R,5R)-1-[2,5-difluoro-4-(trifluorometil)fenil]-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-bencimidazol-5-il}pirrolidin-2-il]-1H-bencimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

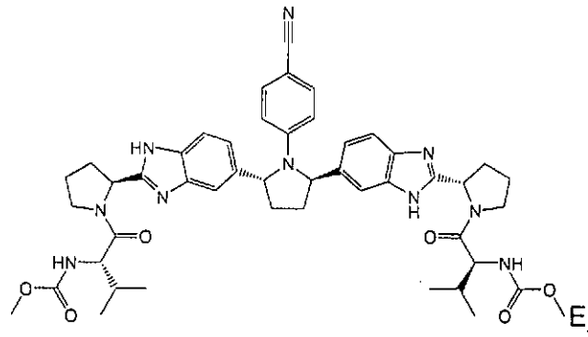
1H RMN (400 MHz, DMSO-D6) d ppm 0,74 - 0,90 (m, 12 H) 1,74 - 1,83 (m, 2 H) 1,86 - 1,93 (m, 2 H) 1,94 - 2,05 (m, 4 H) 2,13 - 2,25 (m, 4 H) 3,44 - 3,48 (m, 2 H) 3,53 (s, 6 H) 3,77 - 3,88 (m, 4 H) 4,06 (t, J=4,23 Hz, 2 H) 5,10 - 5,16 (m, 2 H) 5,63 - 5,74 (m, 2 H) 6,60 - 6,73 (m, 1 H) 7,04 - 7,20 (m, 4 H) 7,24 - 7,31 (m, 3 H) 7,38 (d, J=8,46 Hz, 1 H) 7,46 (d, J=8,13 Hz, 1 H) 12,08 (d, J=27,11 Hz, 2 H); MS ESI+ m/z 936,4 (M+H)+.



Ejemplo 238

{(2S)-1-[(2S)-2-{6-[(2R,5R)-1-[3-fluoro-4-(trifluorometil)fenil]-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-bencimidazol-5-il}pirrolidin-2-il]-1H-bencimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

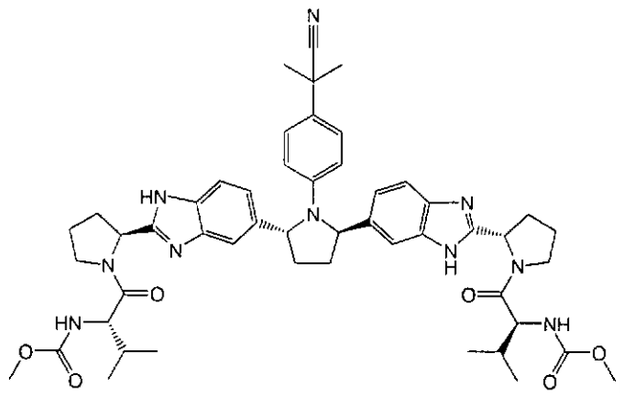
1H RMN (400 MHz, DMSO-D6) d ppm 0,75 - 0,90 (m, 12 H) 1,71 - 1,79 (m, 2 H) 1,87 - 1,95 (m, 2 H) 1,97 - 2,04 (m, 4 H) 2,13 - 2,25 (m, 6 H) 3,53 (s, 6 H) 3,77 - 3,86 (m, 4 H) 4,04 - 4,11 (m, 2 H) 5,11 - 5,18 (m, 2 H) 5,46 - 5,56 (m, 2 H) 6,24 (dd, J=8,24, 2,39 Hz, 2 H) 7,04 - 7,11 (m, 2 H) 7,19 - 7,25 (m, 2 H) 7,28 (dd, J=8,46, 3,69 Hz, 2 H) 7,32 (s, 1 H) 7,41 (d, J=8,13 Hz, 1 H) 7,49 (d, J=8,24 Hz, 1 H) 12,09 (dd, J=15,72, 2,17 Hz, 2 H); MS ESI+ m/z 918,4 (M+H)+.



Ejemplo 239

{(2S)-1-[(2S)-2-{6-[(2R,5R)-1-(4-cianofenil)-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-bencimidazol-5-il}pirrolidin-2-il]-1H-bencimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

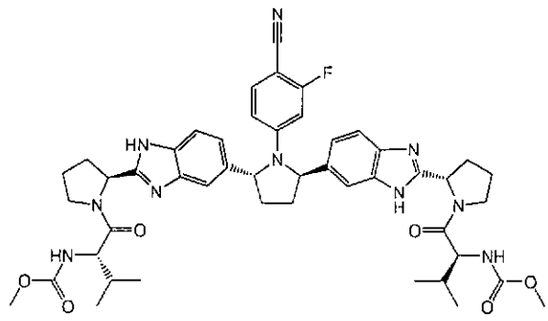
1H RMN (400 MHz, DMSO-D6) d ppm 0,76 - 0,90 (m, 12 H) 1,70 - 1,79 (m, 2 H) 1,90 (dd, J=12,25, 6,40 Hz, 2 H) 1,95 - 2,02 (m, 4 H) 2,15 - 2,24 (m, 6 H) 3,54 (s, 6 H) 3,78 - 3,85 (m, 4 H) 4,06 (t, J=8,29 Hz, 2 H) 5,10 - 5,16 (m, 2 H) 5,46 - 5,55 (m, 2 H) 6,42 (d, J=8,67 Hz, 2 H) 7,05 (dd, J=12,90, 8,57 Hz, 2 H) 7,22 (s, 1 H) 7,25 - 7,34 (m, 5 H) 7,40 (d, J=8,24 Hz, 1 H) 7,47 (d, J=8,24 Hz, 1 H) 12,09 (s, 2 H); MS ESI+ m/z 857,4 (M+H)+.



Ejemplo 240

{(2S)-1-[(2S)-2-{6-[(2R,5R)-1-[4-(2-cianopropan-2-il)fenil]-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-bencimidazol-5-il}pirrolidin-2-il]-1H-bencimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

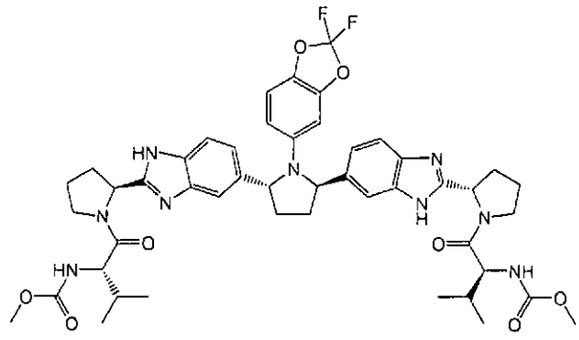
1H RMN (400 MHz, DMSO-D6) d ppm 0,75 - 0,91 (m, 12 H) 1,47 (s, 6 H) 1,67 - 1,76 (m, 2 H) 1,85 - 1,95 (m, 2 H) 1,96 - 2,03 (m, 4 H) 2,15 - 2,24 (m, 6 H) 3,53 (s, 6 H) 3,77 - 3,85 (m, 4 H) 4,05 (t, J=8,46 Hz, 2 H) 5,10 - 5,17 (m, 2 H) 5,37 - 5,45 (m, 2 H) 6,34 (d, J=8,89 Hz, 2 H) 6,97 - 7,04 (m, 2 H) 7,07 (t, J=8,35 Hz, 2 H) 7,21 (s, 1 H) 7,28 (d, J=10,52 Hz, 3 H) 7,39 (d, J=8,13 Hz, 1 H) 7,47 (d, J=8,24 Hz, 1 H) 12,05 (d, J=13,01 Hz, 2 H); MS ESI+ m/z 899,4 (M+H)+.



Ejemplo 241

{(2S)-1-[(2S)-2-{6-[(2R,5R)-1-(4-ciano-3-fluorofenil)-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-bencimidazol-5-il}pirrolidin-2-il]-1H-bencimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

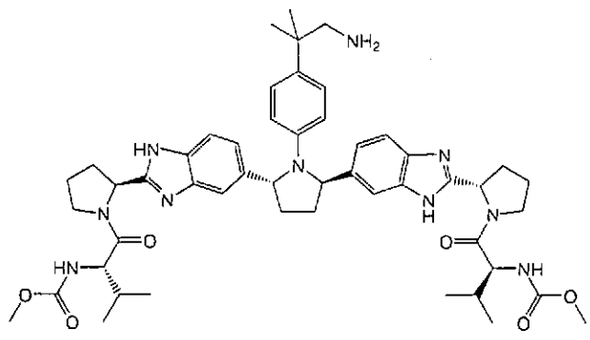
1H RMN (400 MHz, DMSO-D6) d ppm 0,74 - 0,92 (m, 12 H) 1,74 (t, J=9,00 Hz, 2 H) 1,87 - 1,94 (m, 2 H) 1,96 - 2,06 (m, 4 H) 2,15 - 2,25 (m, 4 H) 2,55 - 2,63 (m, 2 H) 3,54 (s, 6 H) 3,82 (s, 4 H) 4,06 (t, J=8,40 Hz, 2 H) 5,14 (d, J=2,28 Hz, 2 H) 5,55 (dd, J=16,26, 6,07 Hz, 2 H) 6,18 - 6,33 (m, 2 H) 7,01 - 7,15 (m, 2 H) 7,23 (s, 1 H) 7,25 - 7,35 (m, 4 H) 7,42 (d, J=7,70 Hz, 1 H) 7,49 (d, J=8,46 Hz, 1 H) 12,10 (s, 2 H); MS ESI+ m/z 875,4 (M+H)+.



Ejemplo 242

{(2S)-1-[(2S)-2-{6-[(2R,5R)-1-(2,2-difluoro-1,3-benzodioxol-5-il)-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-bencimidazol-5-il}pirrolidin-2-il]-1H-bencimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

1H RMN (400 MHz, DMSO-D6) d ppm 0,75 - 0,91 (m, 12 H) 1,69 - 1,77 (m, 2 H) 1,91 (dd, J=14,26, 6,67 Hz, 2 H) 1,96 - 2,07 (m, 4 H) 2,14 - 2,24 (m, 4 H) 2,54 - 2,60 (m, 2 H) 3,53 (s, 6 H) 3,78 - 3,86 (m, 4 H) 4,06 (t, J=8,40 Hz, 2 H) 5,10 - 5,17 (m, 2 H) 5,36 - 5,44 (m, 2 H) 6,05 (dd, J=9,11, 2,17 Hz, 1 H) 6,29 (d, J=2,60 Hz, 1 H) 6,89 - 6,95 (m, 1 H) 7,06 (t, J=8,51 Hz, 2 H) 7,22 (s, 1 H) 7,26 - 7,33 (m, 3 H) 7,39 (d, J=8,35 Hz, 1 H) 7,47 (d, J=7,59 Hz, 1 H) 12,03 - 12,09 (m, 2 H); MS ESI+ m/z 912,8 (M+H)+.

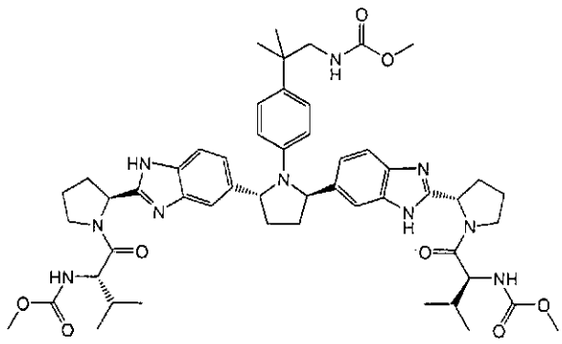


Ejemplo 243

{(2S)-1-[(2S)-2-{6-[(2R,5R)-1-[4-(1-amino-2-metilpropan-2-il)fenil]-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-bencimidazol-5-il}pirrolidin-2-il]-1H-bencimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

1H RMN (400 MHz, DMSO-D6) d ppm 0,74 - 0,92 (m, 12 H) 1,01 (d, J=5,20 Hz, 6 H) 1,65 - 1,76 (m, 2 H) 1,86 - 1,93 (m, 2 H) 1,98 (d, J=4,01 Hz, 4 H) 2,13 - 2,25 (m, 4 H) 2,41 (s, 2 H) 2,53 - 2,61 (m, 2 H) 3,53 (s, 6 H) 3,81 (s, 4 H) 4,05 (t, J=8,35 Hz, 2 H) 5,08 - 5,17 (m, 2 H) 5,32 - 5,41 (m, 2 H) 6,27 (d, J=8,89 Hz, 2 H) 6,81 - 6,92 (m, 2 H) 7,07 (t, J=7,97 Hz, 2 H) 7,20 (s, 1 H) 7,25 - 7,32 (m, 3 H) 7,38 (d, J=8,13 Hz, 1 H) 7,46 (d, J=8,13 Hz, 1 H) 12,02 (d, J=19,63 Hz, 2 H); MS ESI+ m/z 903,4 (M+H)+.

000792

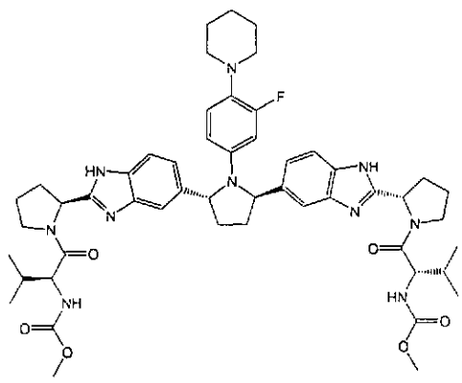


Ejemplo 244

(2-{4-[(2R,5R)-2-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-bencimidazol-5-il}-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-bencimidazol-6-il}pirrolidin-1-il]fenil}-2-metilpropil)carbamato de metilo

1H RMN (400 MHz, DMSO-D6) d ppm 0,75 - 0,91 (m, 12 H) 1,00 (d, J=6,07 Hz, 6 H) 1,64 - 1,75 (m, 2 H) 1,83 - 1,94 (m, 2 H) 1,96 - 2,05 (m, 4 H) 2,14 - 2,23 (m, 4 H) 2,89 - 3,00 (m, 2 H) 3,17 (d, J=5,20 Hz, 2 H) 3,42 (s, 3 H) 3,53 (s, 6 H) 3,77 - 3,87 (m, 4 H) 3,99 - 4,07 (m, 2 H) 5,08 - 5,20 (m, 2 H) 5,32 - 5,42 (m, 2 H) 6,27 (d, J=8,46 Hz, 2 H) 6,72 - 6,80 (m, 1 H) 6,83 - 6,93 (m, 2 H) 7,07 (t, J=8,62 Hz, 2 H) 7,20 (s, 1 H) 7,26 - 7,33 (m, 3 H) 7,38 (d, J=8,13 Hz, 1 H) 7,45 (d, J=8,57 Hz, 1 H) 12,03 (d, J=12,36 Hz, 2 H)

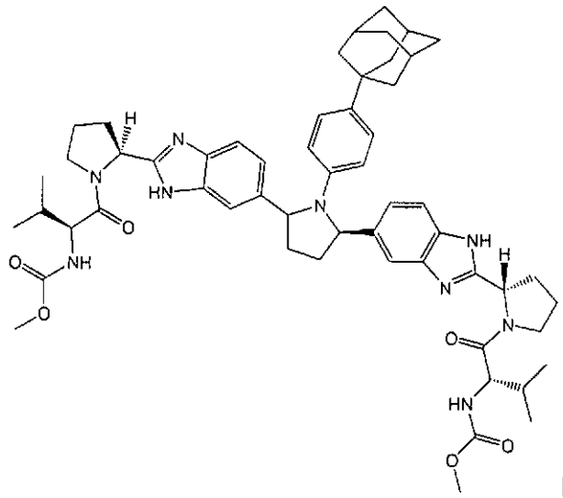
MS ESI+ m/z 961,4 (M+H)+



Ejemplo 245

{(2S)-1-[(2S)-2-{5-[(2R,5R)-1-[3-fluoro-4-(piperidin-1-il)fenil]-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-bencimidazol-5-il}pirrolidin-2-il]-1H-bencimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

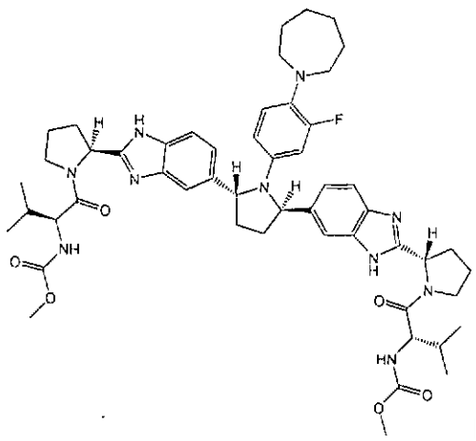
MS (ESI) m/z 934 $(M+H)^+$



Ejemplo 248

{(2S)-1-[(2S)-2-(6-{(5R)-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-bencimidazol-5-il}-1-[4-(triciclo[3,3,1,1~3,7~]dec-1-il)fenil]pirrolidin-2-il}-1H-bencimidazol-2-il)pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

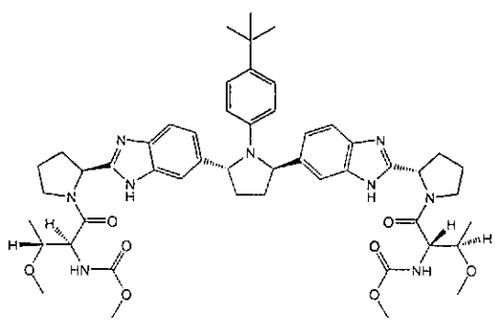
+ESI m/z (abundancia relativa) 967 (100, M+H)



Ejemplo 249

{(2S)-1-[(2S)-2-{6-[(2R,5R)-1-[4-(azepan-1-il)-3-fluorofenil]-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-bencimidazol-5-il}pirrolidin-2-il]-1H-bencimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

+ESI m/z (abundancia relativa) 948 (100, M+H)

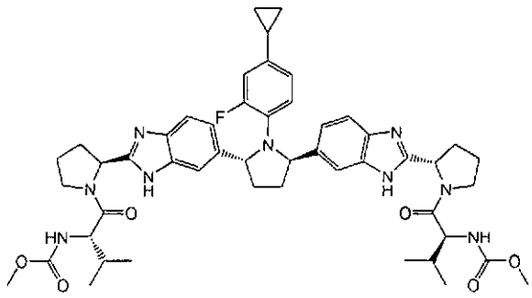


Ejemplo 250

000795

{(2*S*,3*R*)-1-[(2*S*)-2-{6-[(2*R*,5*R*)-1-(4-*tert*-butilfenil)-5-(2-{(2*S*)-1-[*N*-(metoxicarbonil)-*O*-metil-L-treonil]pirrolidin-2-il}-1*H*-bencimidazol-6-il)pirrolidin-2-il]-1*H*-bencimidazol-2-il}pirrolidin-1-il]-3-metoxi-1-oxobutan-2-il}carbamato de metilo

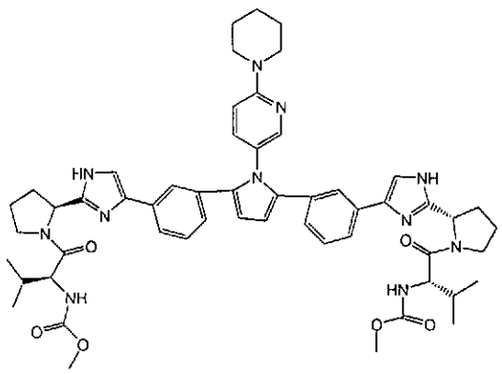
MS (ESI) *m/z* 920 $(M+H)^+$.



Ejemplo 251

{(2S)-1-[(2S)-2-{6-[(2R,5R)-1-(4-ciclopropil-2-fluorofenil)-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-bencimidazol-6-il}pirrolidin-2-il]-1H-bencimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

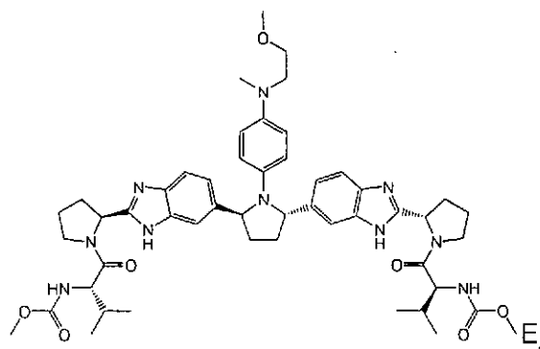
MS (ESI) *m/z* 890 $(M+H)^+$.



Ejemplo 252

[(2S)-1-{(2S)-2-[4-(3-{5-(3-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-4-il}fenil)-1-[6-(piperidin-1-il)piridin-3-il]-1H-pirrol-2-il}fenil)-1H-imidazol-2-il]pirrolidin-1-il}-3-metil-1-oxobutan-2-il]carbamato de metilo

MS (ESI; M+H) m/z = 964,5.

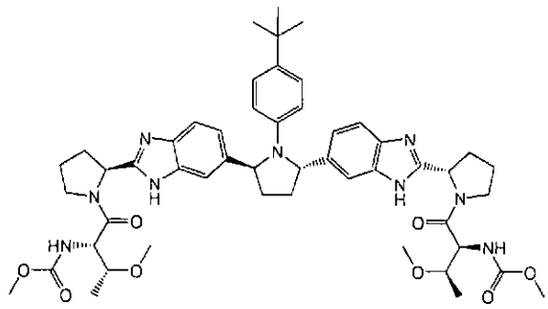


Ejemplo 253

{(2S)-1-[(2S)-2-{6-[(2S,5S)-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-bencimidazol-6-il}-1-{4-[(2-

metoxietil)(metil)amino]fenil}pirrolidin-2-il]-1H-bencimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

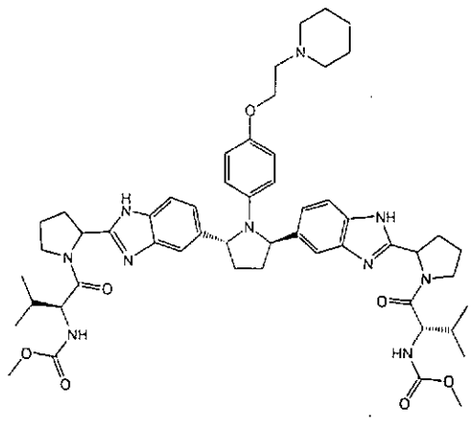
MS (ESI; M+H) m/z = 919,4



Ejemplo 254

{(2S,3R)-1-[(2S)-2-{6-[(2S,5S)-1-(4-tert-butilfenil)-5-(2-{(2S)-1-[N-(metoxicarbonil)-O-metil-L-treonil]pirrolidin-2-il}-1H-bencimidazol-6-il)pirrolidin-2-il]-1H-bencimidazol-2-il}pirrolidin-1-il]-3-metoxi-1-oxobutan-2-il}carbamato de metilo

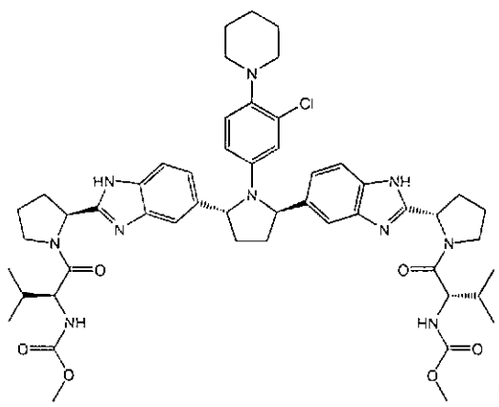
MS (ESI; M+H) m/z = 920,5



Ejemplo 255

[(2*S*)-1-(2-{5-[(2*R*,5*R*)-5-[2-(1-{(2*S*)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il)-1*H*-bencimidazol-5-il]-1-{4-[2-(piperidin-1-il)etoxi]fenil}pirrolidin-2-il]-1*H*-bencimidazol-2-il}pirrolidin-1-il)-3-metil-1-oxobutan-2-il]carbamato de metilo

MS (ESI; M+H) m/z = 959,6

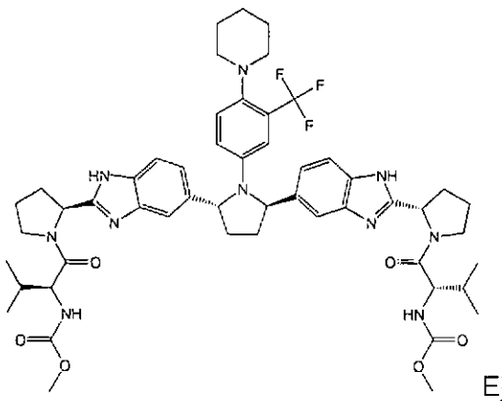


Ejemplo 256

{(2S)-1-[(2S)-2-{5-[(2R,5R)-1-[3-cloro-4-(piperidin-1-il)fenil]-5-{2-[(2S)-1-{(2S)-2-

[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-bencimidazol-5-il}pirrolidin-2-il]-1H-bencimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

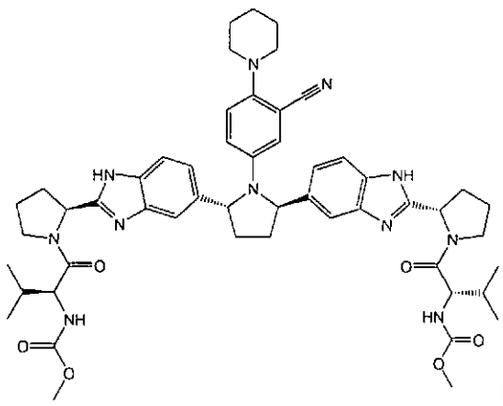
(ESI+) m/z 949,5 (M+H)+



Ejemplo 257

{(2S)-1-[(2S)-2-(5-{(2R,5R)-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-bencimidazol-5-il}-1-[4-(piperidin-1-il)-3-(trifluorometil)fenil]pirrolidin-2-il}-1H-bencimidazol-2-il)pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

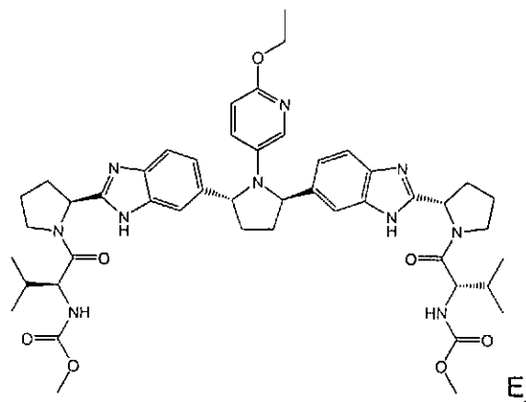
(ESI+) m/z 983,5 (M+H)+



Ejemplo 258

{(2S)-1-[(2S)-2-{5-[(2R,5R)-1-[3-ciano-4-(piperidin-1-il)fenil]-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-bencimidazol-5-il}pirrolidin-2-il]-1H-bencimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

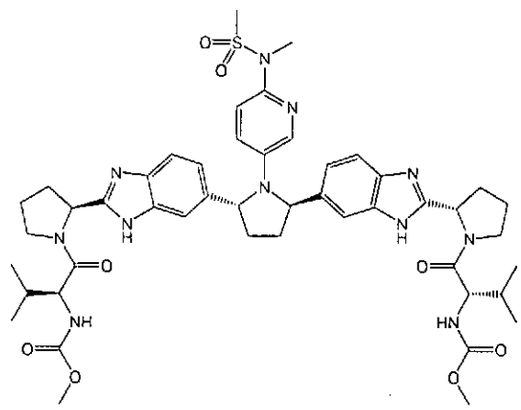
ESI+) m/z 940,4 (M+H)+



Ejemplo 259

{(2S)-1-[(2S)-2-{6-[(2R,5R)-1-(6-etoxipiridin-3-il)-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-bencimidazol-6-il}pirrolidin-2-il]-1H-bencimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

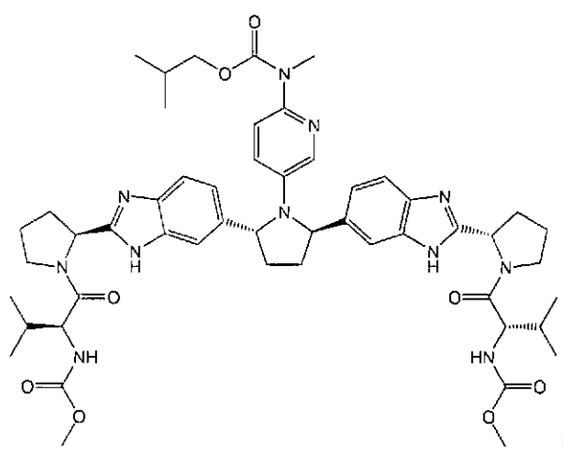
ESI+m/z 878 (M+H)+



Ejemplo 260

{(2S)-1-[(2S)-2-{6-[(2R,5R)-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-bencimidazol-6-il}-1-{6-[metil(metilsulfonil)amino]piridin-3-il}pirrolidin-2-il]-1H-bencimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

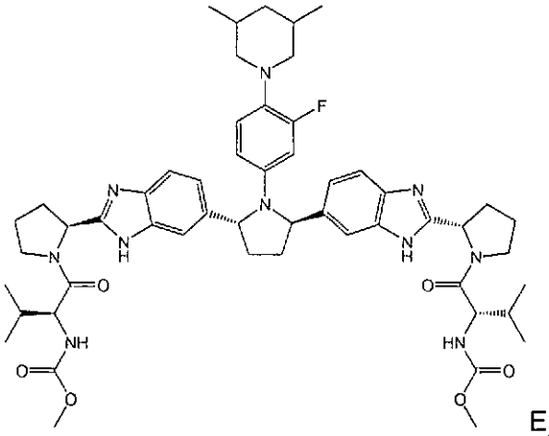
ESI+m/z 940 (M+H)+



Ejemplo 261

{5-[(2R,5R)-2,5-bis(2-{(2S)-1-[N-(metoxicarbonil)-L-valil]pirrolidin-2-il}-1H-bencimidazol-6-il)pirrolidin-1-il]piridin-2-il}metilcarbamato de2-metilpropilo

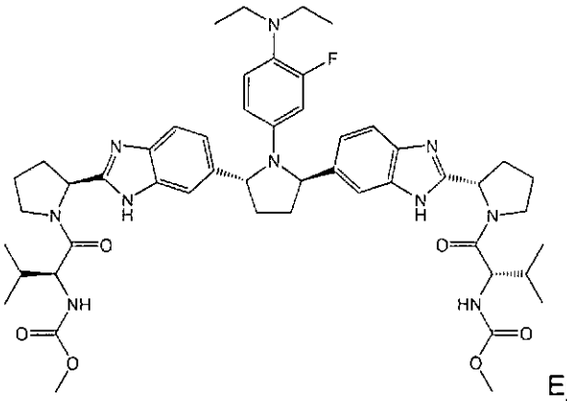
ESI+m/z 963 (M+H)+



Ejemplo 262

{(2S)-1-[(2S)-2-{6-[(2R,5R)-1-[4-(3,5-dimetilpiperidin-1-il)-3-fluorofenil]-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-bencimidazol-6-il}pirrolidin-2-il]-1H-bencimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

ESI+m/z 962 (M+H)+

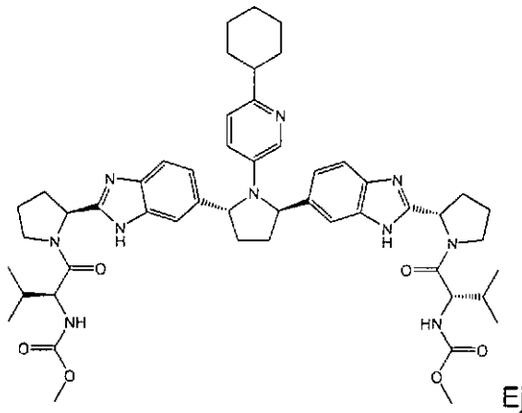


Ejemplo 263

{(2S)-1-[(2S)-2-{6-[(2R,5R)-1-[4-(dietilamino)-3-fluorofenil]-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-bencimidazol-6-il}pirrolidin-2-il]-1H-bencimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

ESI+m/z 922 (M+H)+

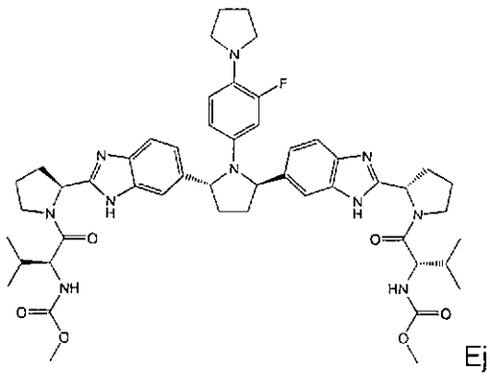
000800



Ejemplo 264

{(2S)-1-[(2S)-2-{6-[(2R,5R)-1-(6-ciclohexilpiridin-3-il)-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-bencimidazol-6-il}pirrolidin-2-il]-1H-bencimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

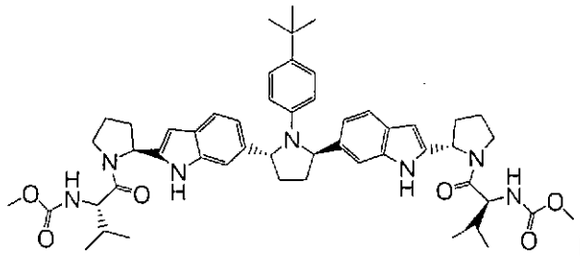
LC/MS : m/z 916,4 método TFA



Ejemplo 265

{(2S)-1-[(2S)-2-{6-[(2R,5R)-1-[3-fluoro-4-(pirrolidin-1-il)fenil]-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-bencimidazol-6-il}pirrolidin-2-il]-1H-bencimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

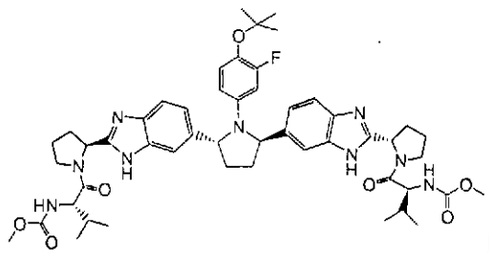
ESI+ (m/z): 919,4 (m+H)



Ejemplo 266

{(2*S*)-1-[(2*S*)-2-{6-[(2*R*,5*R*)-1-(4-*tert*-butilfenil)-5-{2-[(2*S*)-1-{(2*S*)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1*H*-indol-6-il}pirrolidin-2-il]-1*H*-indol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

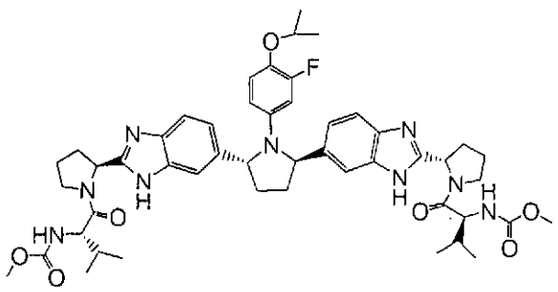
m/z= 886,5 (LC/MS)



Ejemplo 267

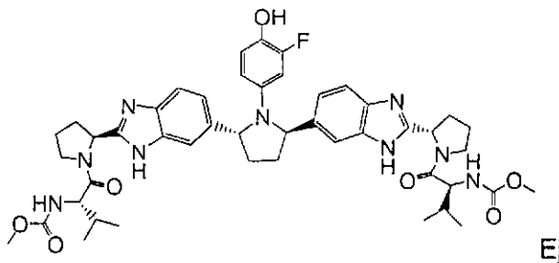
{(2S)-1-[(2S)-2-{6-[(2R,5R)-1-(4-tert-butoxi-3-fluorofenil)-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-bencimidazol-6-il}pirrolidin-2-il]-1H-bencimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

(ESI; M+H) m/z = 922,4



Ejemplo 268 {(2S)-1-[(2S)-2-{6-[(2R,5R)-1-[3-fluoro-4-(propan-2-iloxi)fenil]-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-bencimidazol-6-il}pirrolidin-2-il]-1H-bencimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

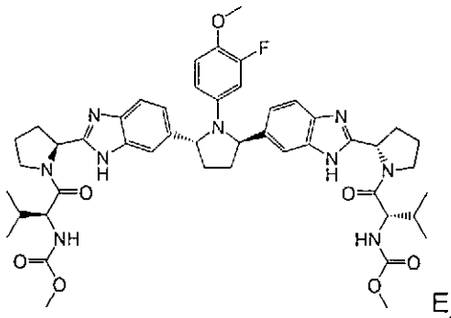
(ESI; M+H) m/z = 908,5



Ejemplo 269

{(2S)-1-[(2S)-2-{6-[(2R,5R)-1-(3-fluoro-4-hidroxifenil)-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-bencimidazol-6-il}pirrolidin-2-il]-1H-bencimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

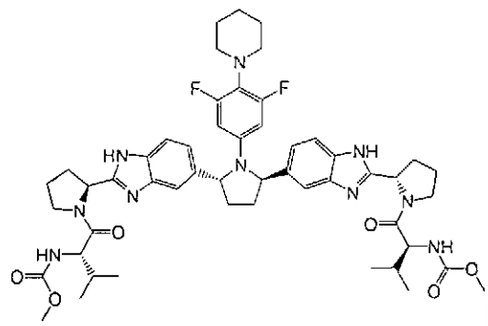
(ESI; M+H) m/z = 866,3



Ejemplo 270

{(2S)-1-[(2S)-2-{6-[(2R,5R)-1-(3-fluoro-4-metoxifenil)-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-bencimidazol-6-il}pirrolidin-2-il]-1H-bencimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

(ESI; M+H) m/z = 880

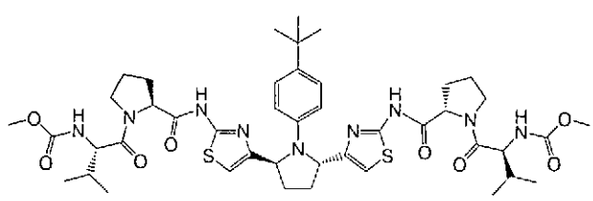


Ejemplo 271

{(2S)-1-[(2S)-2-{5-[(2R,5R)-1-[3,5-difluoro-4-(piperidin-1-il)fenil]-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-bencimidazol-5-il}pirrolidin-2-il]-1H-bencimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

(ESI; M+H) m/z = 952

1H RMN (400 MHz, DMSO-D6) □ ppm 0,73 - 0,90 (m, 12 H) 1,32 - 2,28 (m, 20 H) 2,76 (s, 4 H) 3,54 (s, 6 H) 3,82 (s, 4 H) 3,99 - 4,12 (m, 2 H) 5,10 - 5,20 (m, 2 H) 5,36 (d, J=7,59 Hz, 2 H) 5,83 - 5,95 (m, 2 H) 7,01 - 7,14 (m, 2 H) 7,20 (s, 1 H) 7,26 - 7,33 (m, 3 H) 7,41 (d, J=8,24 Hz, 1 H) 7,49 (d, J=8,24 Hz, 1 H) 12,01 - 12,31 (m, 2 H); MS (ESI; M+H) m/z = 951,5.

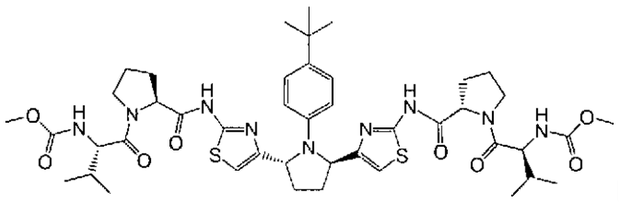


Ejemplo 272

([(2S,5S)-1-(4-tert-butilfenil)pirrolidin-2,5-diil]bis{1,3-tiazol-4,2-diilcarbamoil(2S)pirrolidin-2,1-diil[(2S)-3-metil-1-oxobutan-1,2-diil]})biscarbamato de dimetilo

ESI m/z 908,4 (M+H)

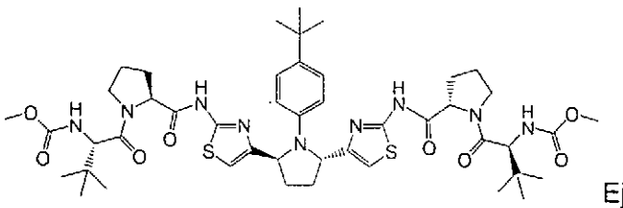
000003



Ejemplo 273

([(2R,5R)-1-(4-tert-butilfenil)pirrolidin-2,5-diil]bis{1,3-tiazol-4,2-diilcarbamoil(2S)pirrolidin-2,1-diil[(2S)-3-metil-1-oxobutan-1,2-diil]})biscarbamato de dimetilo

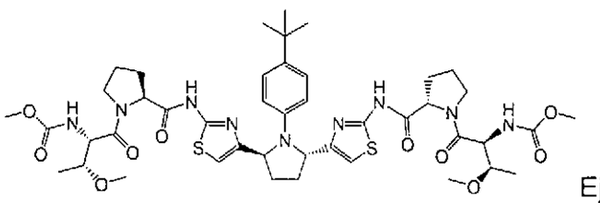
ESI m/z 908,4 (M+H)



Ejemplo 274

([(2S,5S)-1-(4-tert-butilfenil)pirrolidin-2,5-diil]bis{1,3-tiazol-4,2-diilcarbamoil(2S)pirrolidin-2,1-diil[(2S)-3,3-dimetil-1-oxobutan-1,2-diil]})biscarbamato de dimetilo

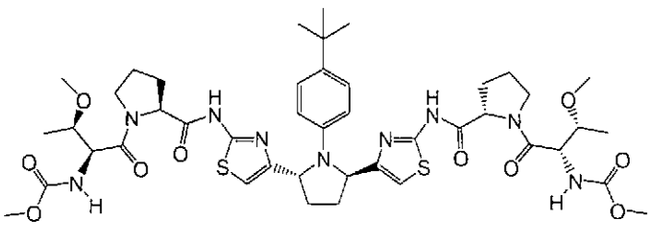
ESI m/z 936,5 (M+H)



Ejemplo 275

([(2S,5S)-1-(4-tert-butilfenil)pirrolidin-2,5-diil]bis{1,3-tiazol-4,2-diilcarbamoil(2S)pirrolidin-2,1-diil[(2S,3R)-3-metoxi-1-oxobutan-1,2-diil]})biscarbamato de dimetilo

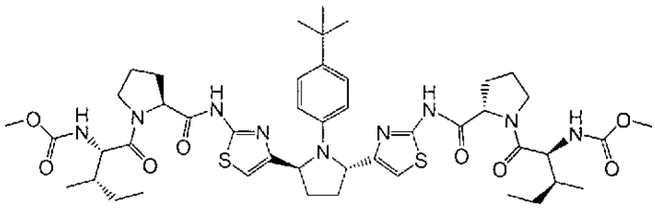
ESI m/z 940,5 (M+H)



Ejemplo 276

([(2R,5R)-1-(4-tert-butilfenil)pirrolidin-2,5-diil]bis{1,3-tiazol-4,2-diilcarbamoil(2S)pirrolidin-2,1-diil[(2S,3R)-3-metoxi-1-oxobutan-1,2-diil]})biscarbamato de dimetilo

ESI m/z 940,5 (M+H)

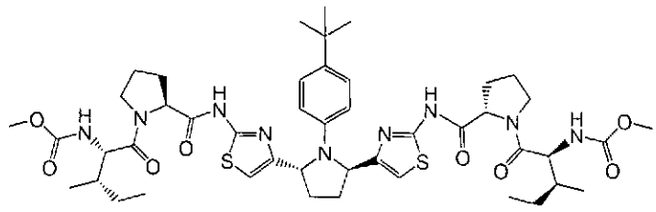


Ejemplo 277

([(2S,5S)-1-(4-tert-butilfenil)pirrolidin-2,5-diil]bis{1,3-tiazol-4,2-diilcarbamoil(2S)pirrolidin-

2,1-diil[(2S,3S)-3-metil-1-oxopentan-1,2-diil]})biscarbamato de dimetilo

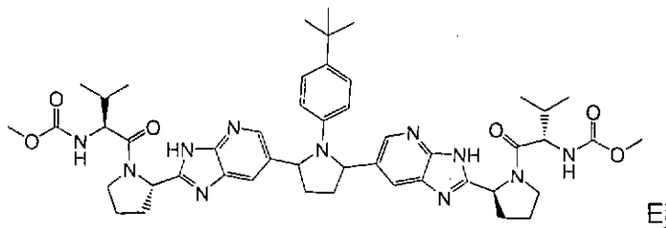
ESI m/z 936,5 (M+H)



Ejemplo 278

([(2R,5R)-1-(4-tert-butilfenil)pirrolidin-2,5-diil]bis{1,3-tiazol-4,2-diilcarbamoil(2S)pirrolidin-2,1-diil[(2S,3S)-3-metil-1-oxopentan-1,2-diil]})biscarbamato de dimetilo

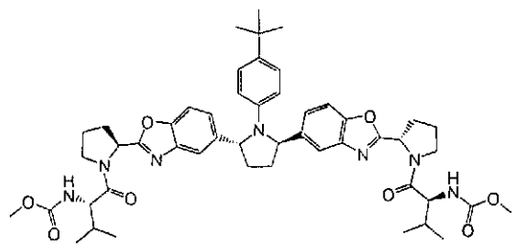
ESI m/z 936,5 (M+H)



Ejemplo 279

{(2S)-1-[(2S)-2-{6-[1-(4-tert-butilfenil)-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-3H-imidazo[4,5-b]piridin-6-il}pirrolidin-2-il]-3H-imidazo[4,5-b]piridin-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

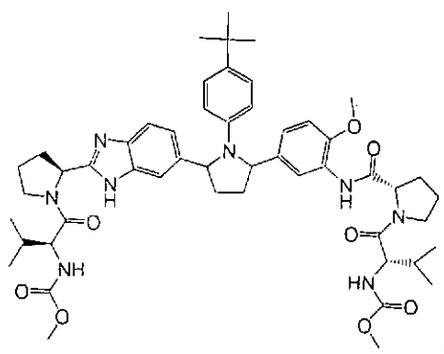
LCMS m/z 890 (M+H)



Ejemplo 280

{(2S)-1-[(2S)-2-{6-[(2R,5R)-1-(4-tert-butilfenil)-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1,3-benzoxazol-6-il}pirrolidin-2-il]-1,3-benzoxazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

ESI+:(M+H): 890,5

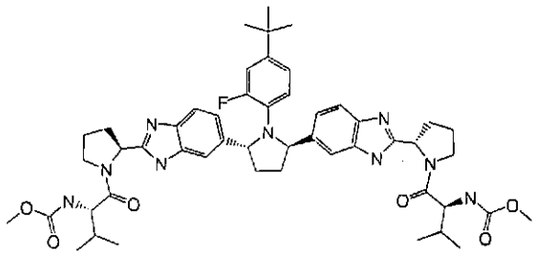


Ejemplo 281

000605

N-(metoxicarbonil)-L-valil-N-{5-[1-(4-tert-butilfenil)-5-(2-{(2S)-1-[N-(metoxicarbonil)-L-valil]pirrolidin-2-il}-1H-bencimidazol-6-il)pirrolidin-2-il]-2-metoxifenil}-L-prolinamida

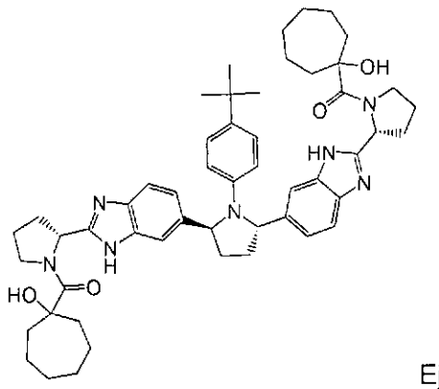
ESI+:(M+H): 921,5



Ejemplo 282

{(2S)-1-[(2S)-2-{6-[(2R,5R)-1-(4-tert-butil-2-fluorofenil)-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-bencimidazol-6-il}pirrolidin-2-il]-1H-bencimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

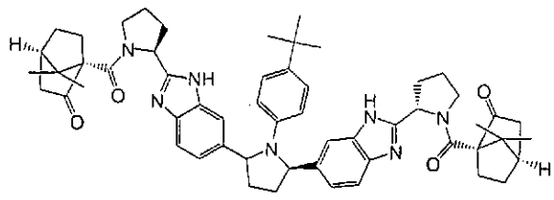
ESI+:(M+H): 906,4



Ejemplo 283

{[(2R,5R)-1-(4-tert-butilfenil)pirrolidin-2,5-diil]bis[1H-bencimidazol-6,2-diil(2S)pirrolidin-2,1-diil]}bis[(1-hidroxiciclohepti)metanona]

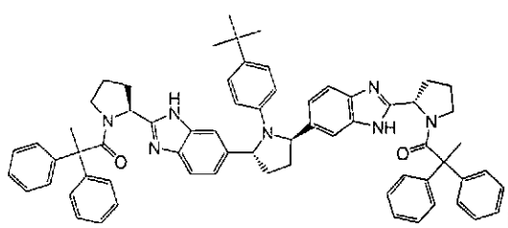
MS (ESI) ion positivo 854 $(M+H)^+$.



Ejemplo 284

(1S,4R,1'S,4'R)-1,1'-{[(2R)-1-(4-tert-butilfenil)pirrolidin-2,5-diil]bis[1H-bencimidazol-6,2-diil(2S)pirrolidin-2,1-diilcarbonil]}bis(7,7-dimetilbiciclo[2,2,1]heptan-2-ona)

MS (ESI) ion positivo 902 $(M+H)^+$.



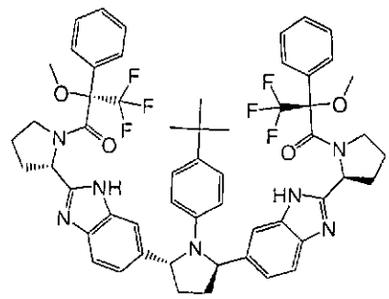
Ejemplo 285

000606

1,1'-{[(2R,5R)-1-(4-tert-butilfenil)pirrolidin-2,5-diil]bis[1H-bencimidazol-6,2-diil(2S)pirrolidin-2,1-diil]}bis(2,2-difenilpropan-1-ona)

MS (ESI) ion positivo $(M+H)^+$. no se observa pero

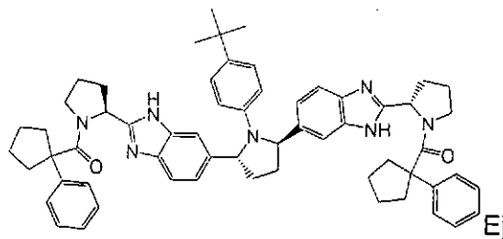
MS (APCI) ion positivo 990 $(M+H)^+$ se observa



Ejemplo 286

(2S,2'S)-1,1'-{[(2R,5R)-1-(4-tert-butilfenil)pirrolidin-2,5-diil]bis[1H-bencimidazol-6,2-diil(2S)pirrolidin-2,1-diil]}bis(3,3,3-trifluoro-2-metoxi-2-fenilpropan-1-ona)

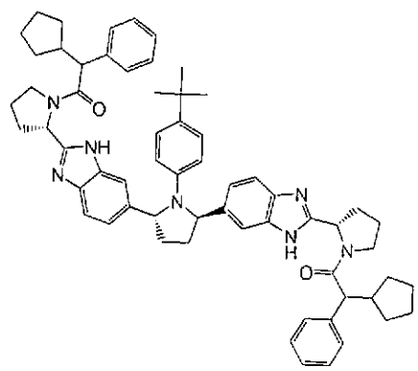
MS (ESI) ion positivo 1006 $(M+H)^+$.



Ejemplo 287

{[(2R,5R)-1-(4-tert-butilfenil)pirrolidin-2,5-diil]bis[1H-bencimidazol-6,2-diil(2S)pirrolidin-2,1-diil]}bis[(1-fenilciclopentil)metanona]

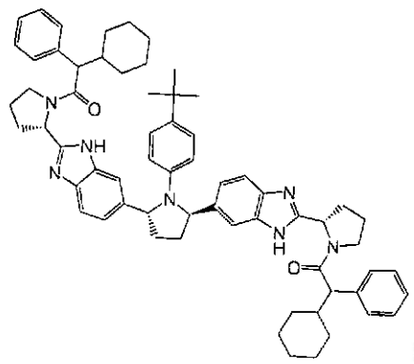
MS (ESI) ion positivo 918,6 $(M+H)^+$.



Ejemplo 288

1,1'-{[(2R,5R)-1-(4-tert-butilfenil)pirrolidin-2,5-diil]bis[1H-bencimidazol-6,2-diil(2S)pirrolidin-2,1-diil]}bis(2-ciclopentil-2-feniletanona)

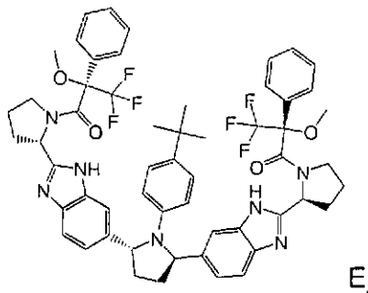
MS (ESI) ion positivo 946 $(M+H)^+$.



Ejemplo 289

1,1'-{[(2R,5R)-1-(4-tert-butilfenil)pirrolidin-2,5-diil]bis[1H-bencimidazol-6,2-diil(2S)pirrolidin-2,1-diil]}bis(2-ciclohexil-2-feniletanona)

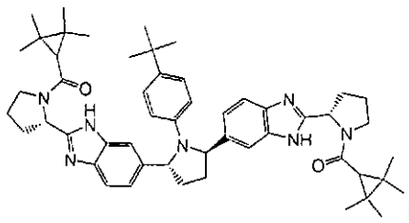
MS (ESI) ion positivo 974 $(M+H)^+$.



Ejemplo 290

(2R,2'R)-1,1'-{[(2R,5R)-1-(4-tert-butilfenil)pirrolidin-2,5-diil]bis[1H-bencimidazol-6,2-diil(2S)pirrolidin-2,1-diil]}bis(3,3,3-trifluoro-2-metoxi-2-fenilpropan-1-ona)

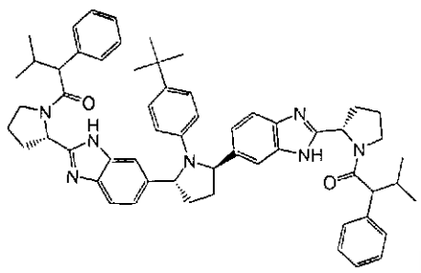
MS (ESI) ion positivo 1006 $(M+H)^+$.



Ejemplo 291

{[(2R,5R)-1-(4-tert-butilfenil)pirrolidin-2,5-diil]bis[1H-bencimidazol-6,2-diil(2S)pirrolidin-2,1-diil]}bis[(2,2,3,3-tetrametilciclopropil)metanona]

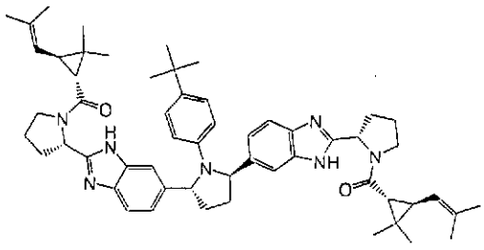
MS (ESI) ion positivo 822 $(M+H)^+$.



Ejemplo 292

1,1'-{[(2R,5R)-1-(4-tert-butilfenil)pirrolidin-2,5-diil]bis[1H-bencimidazol-6,2-diil(2S)pirrolidin-2,1-diil]}bis(3-metil-2-fenilbutan-1-ona)

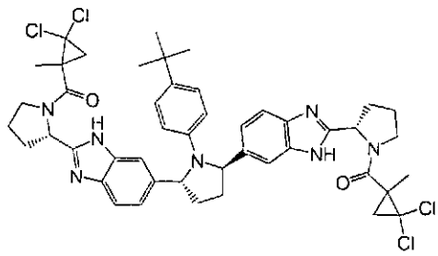
MS (ESI) ion positivo 893 $(M+NH_4-H_2O)^+$.



Ejemplo 293

{[(2R,5R)-1-(4-tert-butilfenil)pirrolidin-2,5-diil]bis[1H-bencimidazol-6,2-diil(2S)pirrolidin-2,1-diil]}bis{[(1R,3R)-2,2-dimetil-3-(2-metilprop-1-en-1-il)ciclopropil]metanona}

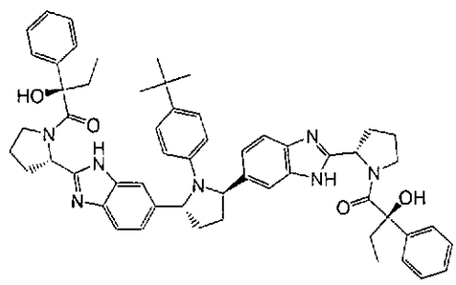
MS (ESI) ion positivo 874 $(M+H)^+$.



Ejemplo 294

{[(2R,5R)-1-(4-tert-butilfenil)pirrolidin-2,5-diil]bis[1H-bencimidazol-6,2-diil(2S)pirrolidin-2,1-diil]}bis[(2,2-dicloro-1-metilciclopropil)metanona]

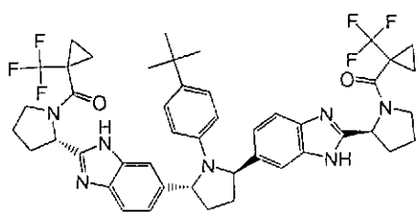
MS (ESI) ion positivo 874 $(M+H)^+$.



Ejemplo 295

(2R,2'R)-1,1'-{[(2R,5R)-1-(4-tert-butilfenil)pirrolidin-2,5-diil]bis[1H-bencimidazol-6,2-diil(2S)pirrolidin-2,1-diil]}bis(2-hidroxi-2-fenilbutan-1-ona)

MS (ESI) ion positivo $(M+H)^+$.

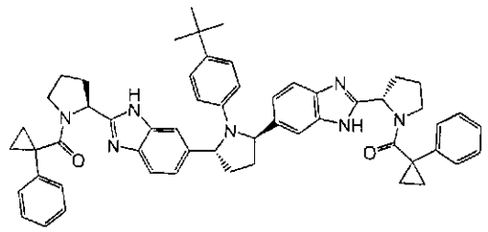


Ejemplo 296

{[(2R,5R)-1-(4-tert-butilfenil)pirrolidin-2,5-diil]bis[1H-bencimidazol-6,2-diil(2S)pirrolidin-2,1-diil]}bis{[1-(trifluorometil)ciclopropil]metanona}

MS (ESI) ion positivo 846 $(M+H)^+$.

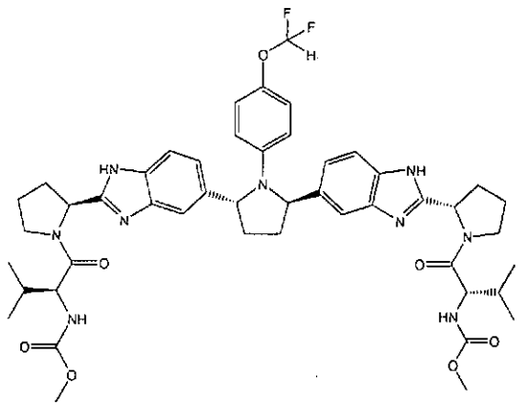
000809



Ejemplo 297

{[(2R,5R)-1-(4-tert-butilfenil)pirrolidin-2,5-diil]bis[1H-bencimidazol-6,2-diil(2S)pirrolidin-2,1-diil]}bis[(1-fenilciclopropil)metanona]

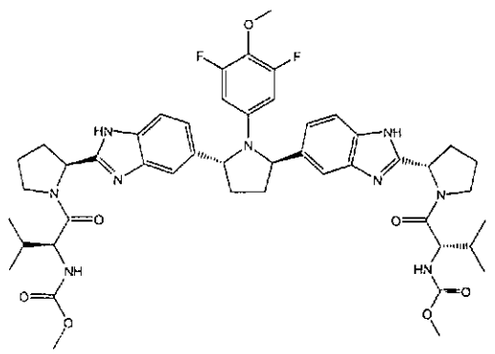
MS (ESI) ion positivo 862,5 $(M+H)^+$.



Ejemplo 298

{(2S)-1-[(2S)-2-{5-[(2R,5R)-1-[4-(difluorometoxi)fenil]-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-bencimidazol-5-il}pirrolidin-2-il]-1H-bencimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

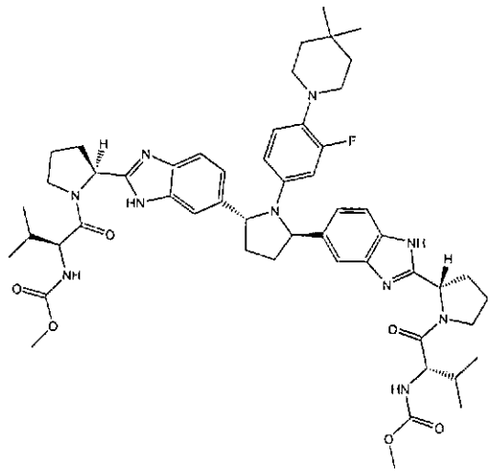
(ESI+) m/z 898,4 (M+H)+



Ejemplo 299

{(2S)-1-[(2S)-2-{5-[(2R,5R)-1-(3,5-difluoro-4-metoxifenil)-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-bencimidazol-5-il}pirrolidin-2-il]-1H-bencimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

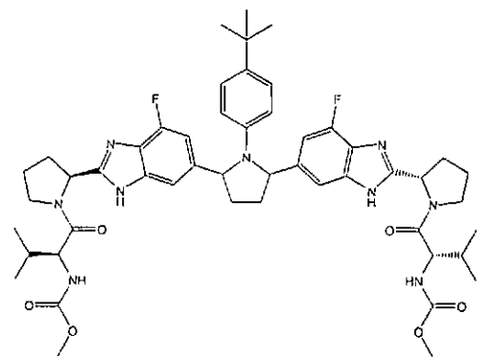
(ESI+) m/z 898,4 (M+H)+



Ejemplo 300

{(2S)-1-[(2S)-2-{5-[(2R,5R)-1-[4-(4,4-dimetilpiperidin-1-il)-3-fluorofenil]-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-bencimidazol-6-il}pirrolidin-2-il]-1H-bencimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

MS +ESI m/z (abundancia relativa) 962 (100, M+H); ^{1}H RMN (400 MHz, DMSO-d_6) δ 7,52 (d, *J* = 8,2, 1 H), 7,44 (d, *J* = 8,1, 1 H), 7,35 (d, *J* = 8,1, 3 H), 7,26 (s, 1 H), 7,14 (m, 2 H), 6,75 (s, 1 H), 6,12 (m, 2 H), 5,40 (s, 2 H), 5,19 (s, 2 H), 4,12 (t, J = 8,4, 2 H), 3,88 (s, 4 H), 3,60 (s, 6 H), 2,70 (m, 5 H), 2,24 (s, 4 H), 1,99 (m, 7 H), 1,75 (s, 2 H), 1,46 (s, 3 H), 1,39 (s, 8 H), 0,89 (m, 20 H).

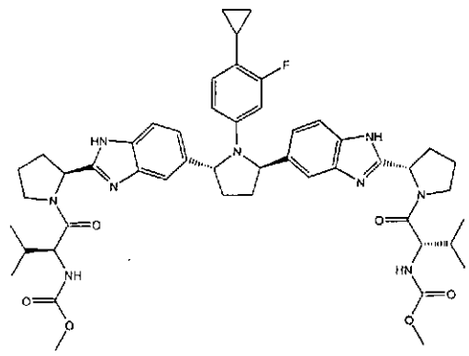


Ejemplo 301

{(2S)-1-[(2S)-2-{6-[1-(4-tert-butilfenil)-5-{4-fluoro-2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-bencimidazol-6-il}pirrolidin-2-il]-4-fluoro-1H-bencimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

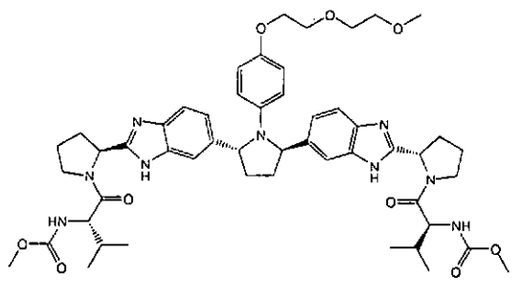
MS (ESI) *m/z* 924 $(M+H)^+$

000611



Ejemplo 302 {(2S)-1-[(2S)-2-{5-[(2R,5R)-1-(4-ciclopropil-3-fluorofenil)-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-bencimidazol-5-il}pirrolidin-2-il]-1H-bencimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

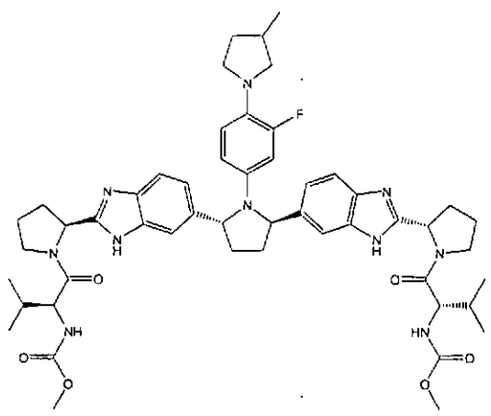
MS (ESI) *m/z* 891 $(M+H)^+$



Ejemplo 303

{(2S)-1-[(2S)-2-{6-[(2R,5R)-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-bencimidazol-6-il}-1-{4-[2-(2-metoxietoxi)etoxi]fenil}pirrolidin-2-il]-1H-bencimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

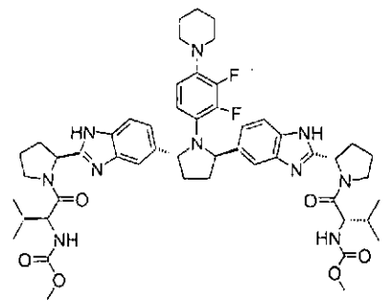
MS (ESI) *m/z* 950 $(M+H)^+$, 948 $(M-H)^+$.



Ejemplo 304

{(2S)-1-[(2S)-2-{6-[(2R,5R)-1-[3-fluoro-4-(3-metilpirrolidin-1-il)fenil]-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-bencimidazol-6-il}pirrolidin-2-il]-1H-bencimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

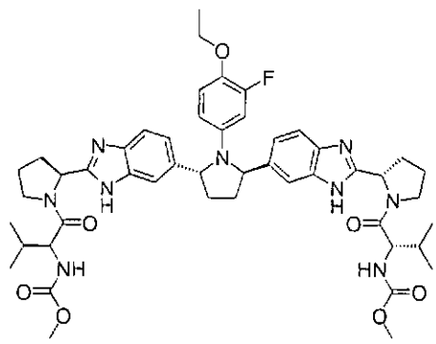
1H RMN (400 MHz, DMSO-D6) δ ppm 0,76 - 0,89 (m, 12 H) 0,95 (d, J=6,72 Hz, 3 H) 1,62 - 1,72 (m, 2 H) 1,83 - 2,06 (m, 9 H) 2,09 - 2,24 (m, 6 H) 2,52 - 2,61 (m, 2 H) 2,91 - 3,15 (m, 4 H) 3,52 (s, 6 H) 3,74 - 3,86 (m, 4 H) 4,05 (t, J=8,35 Hz, 2 H) 5,08 - 5,17 (m, 2 H) 5,26 - 5,38 (m, 2 H) 5,97 - 6,10 (m, 2 H) 6,35 - 6,45 (m, 1 H) 7,01 - 7,08 (m, 2 H) 7,19 (s, 1 H) 7,25 - 7,32 (m, 3 H) 7,36 (d, J=8,24 Hz, 1 H) 7,44 (d, J=7,92 Hz, 1 H) 12,01 (s, 2 H).



Ejemplo 305

{(2*S*)-1-[(2*S*)-2-{5-[(2*R*,5*R*)-1-[2,3-difluoro-4-(piperidin-1-il)fenil]-5-{2-[(2*S*)-1-{(2*S*)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1*H*-bencimidazol-5-il}pirrolidin-2-il]-1*H*-bencimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

ESI+ (m/z): 951,5; 1H RMN (400 MHz, DMSO-D6) δ ppm 0,74 - 0,90 (m, 12 H) 1,35 - 1,41 (m, 2 H) 1,44 - 1,51 (m, 4 H) 1,73 - 1,83 (m, 2 H) 1,86 - 2,02 (m, 6 H) 2,14 - 2,23 (m, 4 H) 2,59 - 2,72 (m, 6 H) 3,53 (s, 6 H) 3,77 - 3,84 (m, 4 H) 3,97 - 4,10 (m, 2 H) 5,06 - 5,18 (m, 2 H) 5,46 - 5,56 (m, 2 H) 6,36 - 6,47 (m, 2 H) 7,03 - 7,11 (m, 2 H) 7,23 - 7,45 (m, 6 H) 11,95 - 12,10 (m, 2 H)

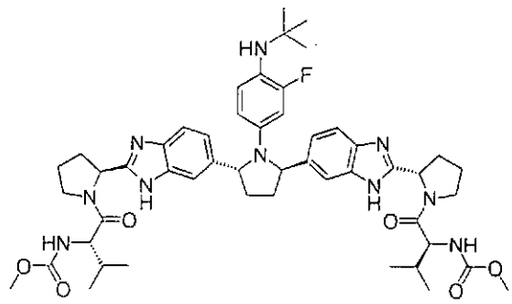


Ejemplo 306

{(2*S*)-1-[(2*S*)-2-{6-[(2*R*,5*R*)-1-(4-etoxi-3-fluorofenil)-5-{2-[(2*S*)-1-{(2*S*)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1*H*-bencimidazol-6-il}pirrolidin-2-il]-1*H*-bencimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

ESI+ (m/z): 894,4

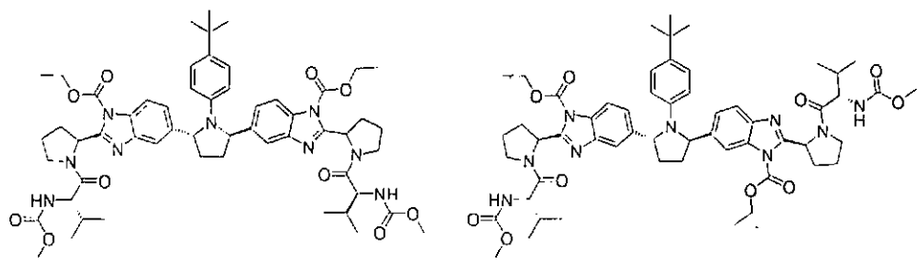
000613



Ejemplo 307

{(2*S*)-1-[(2*S*)-2-{6-[(2*R*,5*R*)-1-[4-(*tert*-butilamino)-3-fluorofenil]-5-{2-[(2*S*)-1-{(2*S*)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1*H*-bencimidazol-6-il}pirrolidin-2-il]-1*H*-bencimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

ESI+ (m/z): 922; 1H RMN (400 MHz, DMSO-D6) δ ppm 0,75 - 0,90 (m, 12 H) 0,97 (s, 9 H) 1,61 - 1,71 (m, 2 H) 1,83 - 2,04 (m, 6 H) 2,12 - 2,23 (m, 4 H) 3,52 (s, 6 H) 3,76 - 3,86 (m, 4 H) 4,01 - 4,08 (m, 2 H) 5,09 - 5,17 (m, 2 H) 5,27 - 5,37 (m, 2 H) 5,98 - 6,07 (m, 2 H) 6,56 - 6,66 (m, 1 H) 7,06 (t, J=7,92 Hz, 2 H) 7,19 (s, 1 H) 7,27 (d, J=9,00 Hz, 3 H) 7,38 (d, J=8,24 Hz, 1 H) 7,46 (d, J=8,13 Hz, 1 H) 12,00 (s, 1 H) 12,08 (s, 1 H)



Ejemplo 308

5-{(2*R*,5*R*)-1-(4-*tert*-butilfenil)-5-[1-(etoxicarbonil)-2-{(2*S*)-1-[*N*-(metoxicarbonil)-L-valil]pirrolidin-2-il}-1*H*-bencimidazol-5-il]pirrolidin-2-il}-2-{1-[*N*-(metoxicarbonil)-L-valil]pirrolidin-2-il}-1*H*-bencimidazol-1-carboxilato de etilo

y

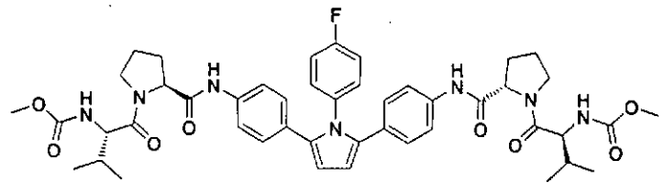
5-{(2*R*,5*R*)-1-(4-*tert*-butilfenil)-5-[1-(etoxicarbonil)-2-{(2*S*)-1-[*N*-(metoxicarbonil)-L-valil]pirrolidin-2-il}-1*H*-bencimidazol-6-il]pirrolidin-2-il}-2-{(2*S*)-1-[*N*-(metoxicarbonil)-L-valil]pirrolidin-2-il}-1*H*-bencimidazol-1-carboxilato de etilo

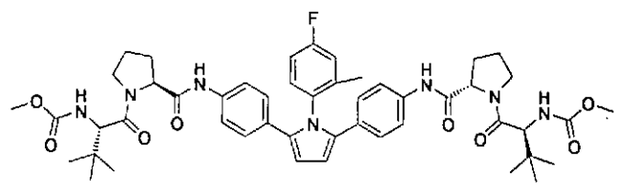
ESI+ (m/z): 1032,5; 1H RMN (400 MHz, DMSO-D6) δ ppm 0,70 - 1,04 (m, 12 H) 1,08 (s, 9 H) 1,33 - 1,46 (m, 6 H) 1,65 - 1,77 (m, 2 H) 1,81 - 2,13 (m, 8 H) 2,20 - 2,28 (m, 2 H) 2,55 - 2,62 (m, 2 H) 3,53 (d, J=4,23 Hz, 6 H) 3,80 - 3,92 (m, 4 H) 4,04 - 4,13 (m, 2 H) 4,41 - 4,59 (m, 4 H) 5,38 - 5,49 (m, 2 H) 5,66 - 5,76 (m, 2 H) 6,17 - 6,33 (m, 2 H) 6,82 - 7,00 (m, 3 H) 7,18 - 7,56 (m, 5 H) 7,75 - 7,91 (m, 2 H)

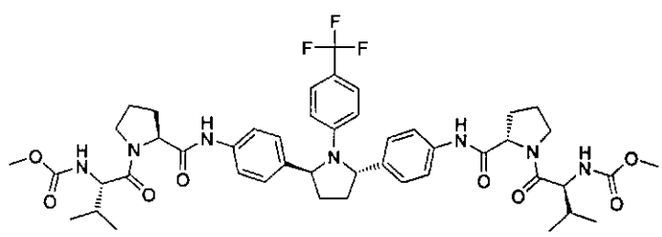
Los compuestos del título de los Ejemplos 52, 53, 54, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 74, 75, 76, 77, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 93, 94,

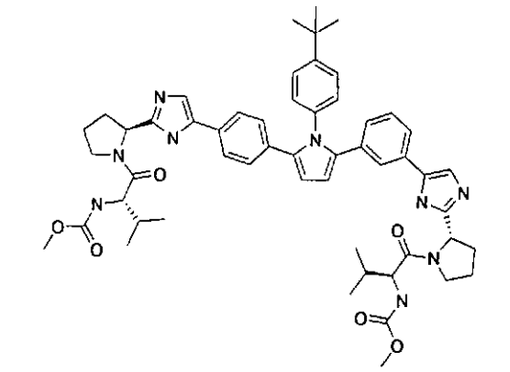
95, 96, 97, 99, 101, 102, 103, 109, 110, 111, 112, 113, 117, 121, 122, 123, 125, 126, 127, 128, 129, 130, 131, 132, 135, 136, 137, 138, 139, 140, 141, 144, 145, 146, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 159, 160, 161, 162, 163, 166, 167, 168, 169, 170, 171, 173, 176, 178, 179, 180, 181, 183, 184, 185, 186, 188, 189, 191, 192, 194, 195, 197, 198, 199, 200, 201, 202, 203, 205, 207, 208, 209, 210, 211, 212, 214, 215, 216, 217, 218, 219, 220, 221, 224, 226, 227, 228, 229, 230, 231, 233, 234, 235, 236, 237, 238, 240, 241, 242, 245, 247, 248, 250, 251, 252, 254, 256, 257, 258, 262, 263, 264, 266, 267, 268, 270, 271, 272, 273, 274, 275, 276, 277, 278, 282, 294, 295, 296, 297, 298, 299, 300, 301, 302, 305, y 306 mostraron un valor de EC_{50} inferior a aproximadamente 0,1 nM en ensayos de replicones del VHC 1b-Con1 en presencia de FBS al 5%. Los compuestos del título de los Ejemplos 51, 55, 56, 57, 70, 71, 72, 73, 78, 98, 100, 108, 114, 115, 116, 119, 120, 133, 134, 142, 143, 147, 164, 172, 174, 182, 196, 204, 206, 222, 223, 225, 239, 244, 249, 253, 259, 261, 265, 281, 287, 288, 292, 303, 304, 307, y 308 mostraron un valor de EC_{50} de entre aproximadamente 0,1 y aproximadamente 1 nM en ensayos de replicones del VHC 1b-Con1 en presencia de FBS al 5%. Los compuestos del título de los Ejemplos 92, 105, 106, 107, 118, 124, 158, 165, 175, 177, 187, 190, 193, 213, 232, 243, 246, 255, 260, 269, 279, 280, 283, 284, 285, 286, 289, 290, 291, y 293 mostraron un valor de EC_{50} de entre aproximadamente 1 y aproximadamente 100 nM en ensayos de replicones del VHC 1b-Con1 en presencia de FBS al 5%.

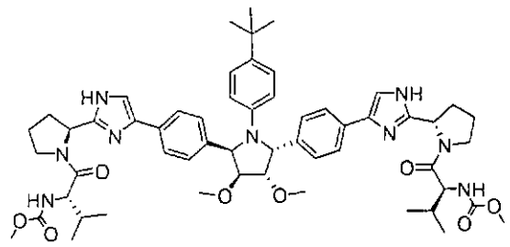
Los siguientes compuestos se prepararon de manera similar de acuerdo a los procedimientos descritos precedentemente:

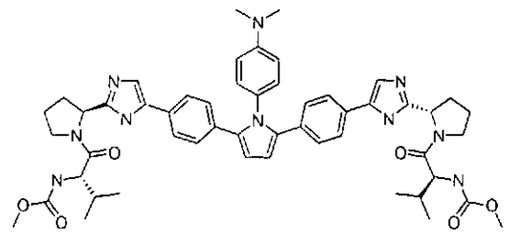












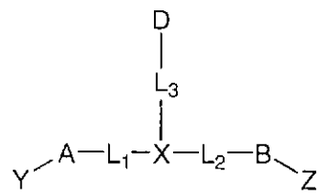
Al evaluarse utilizando ensayos de replicones del VHC 1b-Con1 en presencia de FBS al 5%, cada uno de los compuestos que se han enumerado mostró un valor de EC_{50} menor a 1 nM.

Además, las siguientes mezclas de estereoisómeros se prepararon de acuerdo a procedimientos similares a los que se han descrito, donde cada compuesto en cada mezcla de estereoisómero puede aislarse fácilmente utilizando cromatografía quiral u otros métodos adecuados según lo aprecien los especialistas en la materia y, por lo tanto, la presente invención también incluye cada compuesto en estas mezclas de estereoisómeros:

mezcla 24

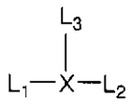
Cuando se evalúa utilizando ensayos de replicones del VHC 1b-Con1 en presencia de FBS al 5%, cada una de las mezclas precedentes (excepto la mezcla 12) mostró un valor de EC_{50} menor a 1 nM. La mezcla 12 mostró un valor de EC_{50} de entre aproximadamente 1 a 10 nM en ensayos de replicones del VHC 1b-Con1 en presencia de FBS al 5%.

De la misma manera, pueden prepararse los siguientes compuestos de fórmula I de manera similar de acuerdo con los esquemas y procedimientos que se han descrito,



I

donde A se selecciona de la Tabla 1a, B se selecciona de la Tabla 1b, D se selecciona de la Tabla 2, Y y Z se seleccionan en forma independiente entre sí de la Tabla 3, y



se selecciona de la Tabla 4, y A, B, D y X están opcionalmente sustituidos en forma independiente entre sí con uno o más R_A, y donde L_1, L_2, L_3 y R_A son como se describe precedentemente. Preferentemente, L_1, L_2 y L_3 son enlaces.

Tabla 1a. A

000630

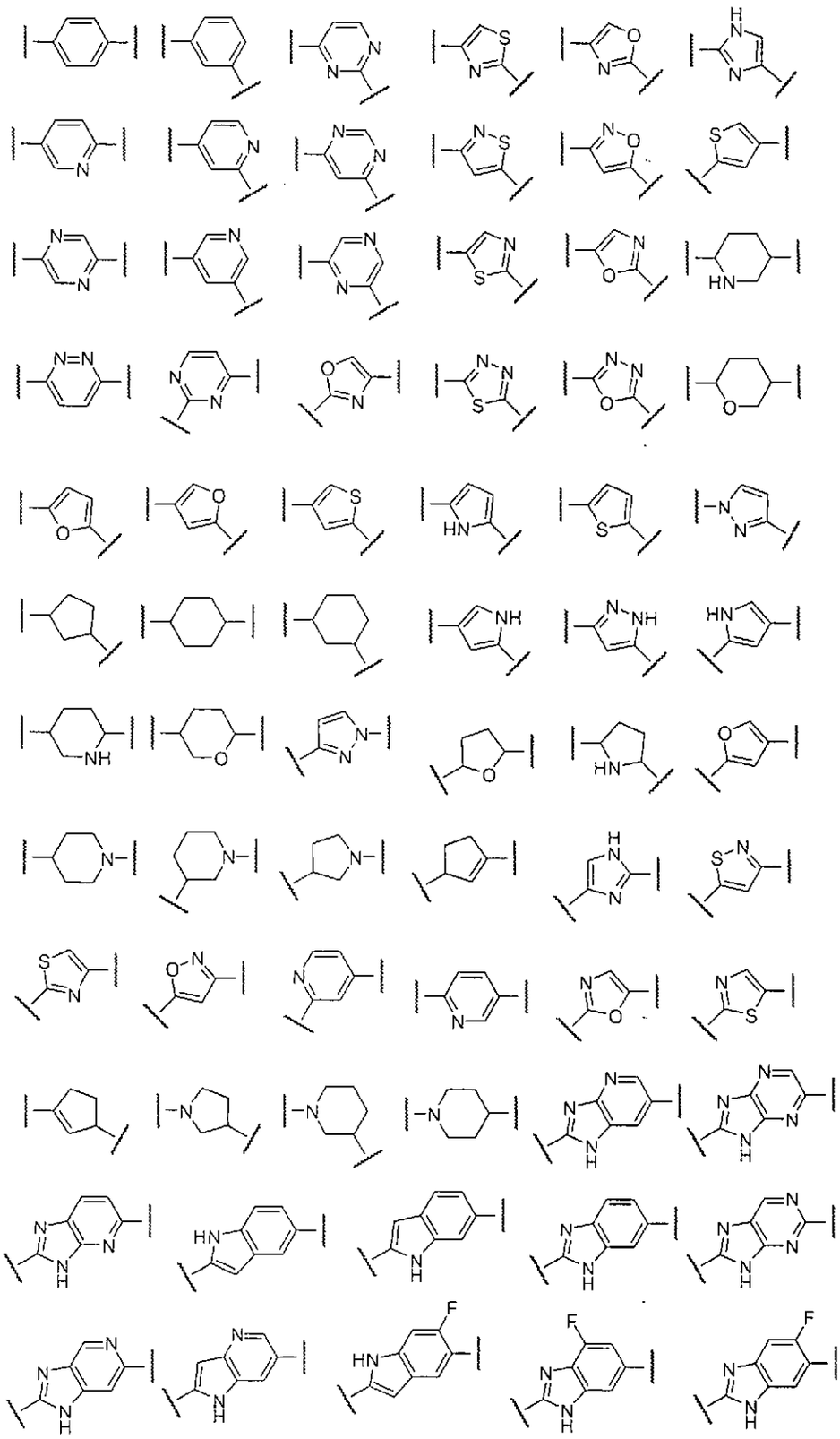


Tabla 1b. B

000631

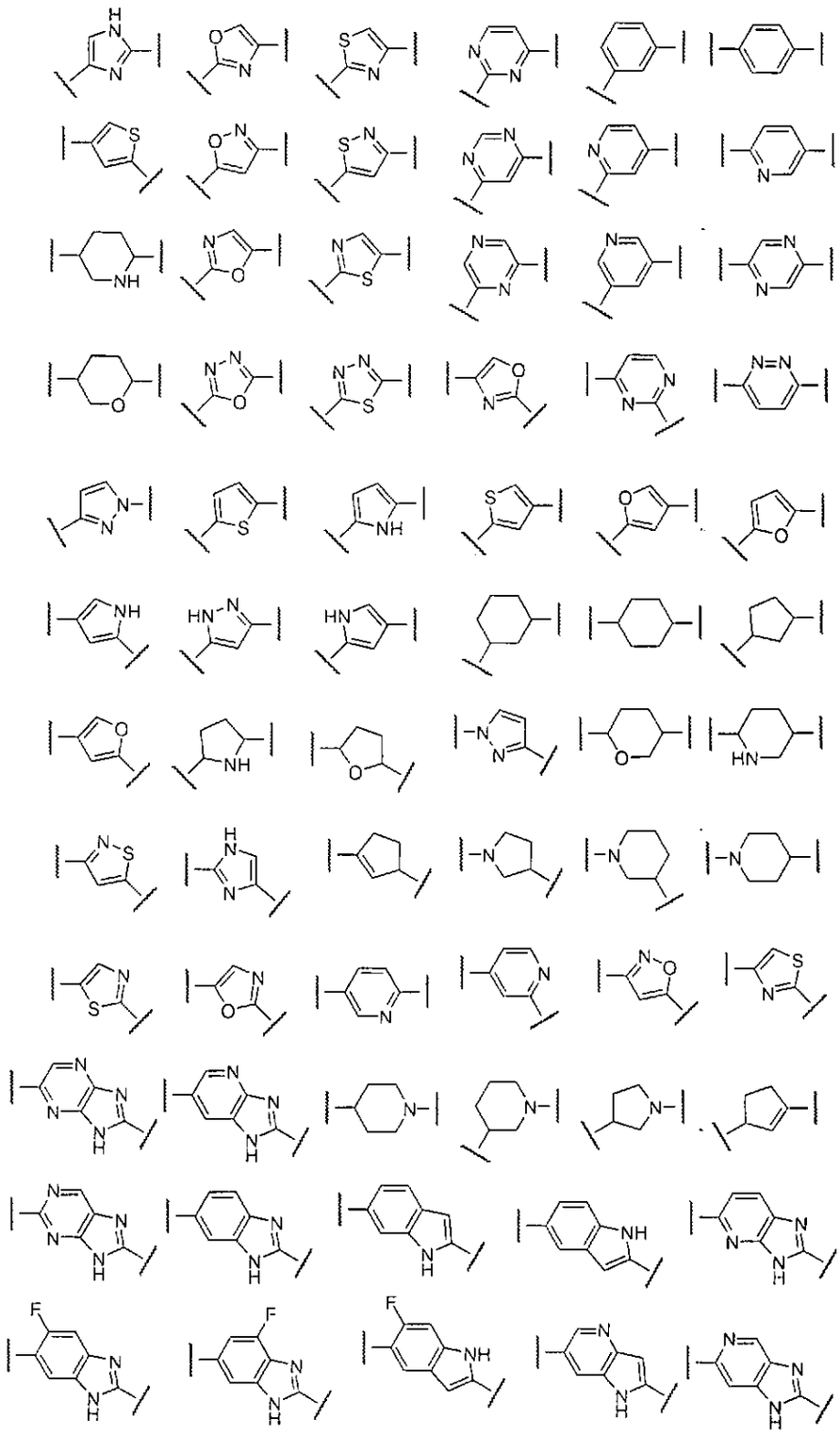
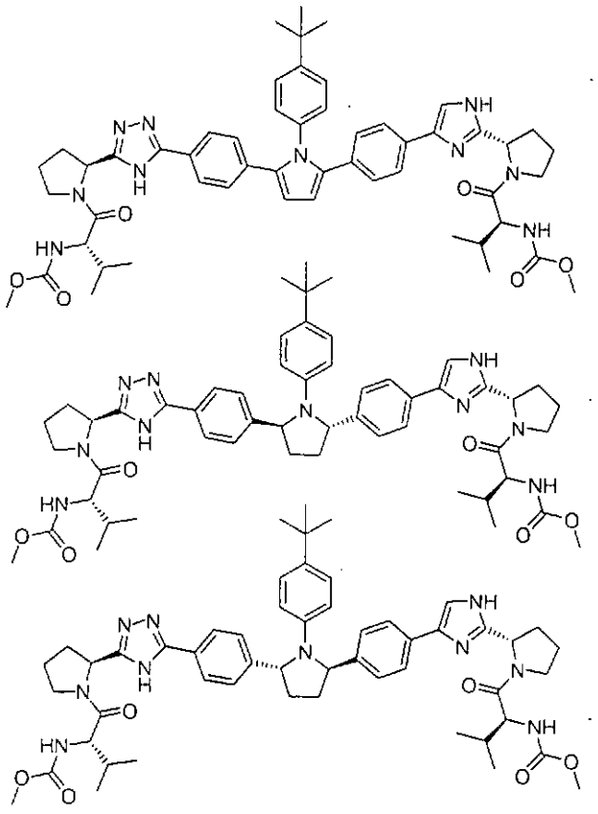


Tabla 2. D

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La actividad anti-HCV de cada compuesto se puede determinar midiendo la actividad del gen informante de luciferasa en el replicón en la presencia de FBS 5%. El gen informante de luciferasa se ubica bajo el control de traducción del IRES del poliovirus en lugar del IRES del HCV, y se usan células HuH-7 como soporte para la replicación del replicón.

Las actividades inhibidoras de los compuestos de la presente invención se pueden evaluar usando una variedad de ensayos conocidos en el arte. Por ejemplo, se pueden usar dos líneas celulares de replicón subgenómicas estables para la caracterización del compuesto en cultivo celular: una derivaba del genotipo 1a-H77 y la otra derivaba del genotipo 1b-Con1, obtenidas de la *University of Texas Medical Branch*, Galveston, TX o Apath, LLC, St. Louis, MO, respectivamente. Las construcciones del replicón pueden ser replicones subgenómicas bicistrónicas. El genotipo 1a de la construcción del replicón contiene la región codificante NS3-NS5B derivada de la cepa H77 del HCV (1a-H77). El replicón también contiene un informante de luciferasa de luciérnaga y un marcador seleccionable de neomicina fosfotransferasa (Neo). Estas dos regiones codificantes, separadas por la proteasa FMDV 2a, comprenden el primer cistrón de la construcción del replicón bicistrónico, donde el segundo cistrón que contiene a la región codificante NS3-NS5B con adición de las mutaciones de adaptación E1202G, K1691R, K2040R y S2204I. La construcción del replicón 1b-Con1 es idéntica al replicón 1a-H77, excepto que

000644

la 5' UTR, 3' UTR y la región codificante NS3-NS5B del HCV derivaba de la cepa 1b-Con1 y las mutaciones de adaptación son K1609E, K1846T y Y3005C. Además, la construcción del replicón 1b-Con1 contiene un IRES del poliovirus entre el IRES del HCV y el gen de la luciferasa. Las líneas celulares de replicón se mantuvieron en el medio de Eagle modificado por Dulbecco (DMEM) que contiene suero fetal bovino 10% (v/v) (FBS), penicilina 100 IU/ml, estreptomicina 100 mg/ml (Invitrogen) y G418 200 mg/ml (Invitrogen).

Los efectos inhibidores de los compuestos de la invención sobre la replicación del HCV se pueden determinar midiendo la actividad del gen informante de la luciferasa. Por ejemplo, las células que contienen al replicón se pueden sembrar en placas de 96 cavidades a una densidad de 5000 células por cavidad en 100 ul de DMEM que contiene FBS 5%. Al día siguiente, los compuestos se pueden diluir en dimetilsulfóxido (DMSO) para generar una solución madre 200x en una serie de ocho diluciones semilogarítmicas. Las series de dilución pueden diluir luego 100X en el medio que contiene FBS 5%. Se agrega medio con el inhibidor a las placas de cultivo celular de toda la noche que ya contenían 100 µl de DMEM con FBS 5%. En los ensayos que miden la actividad inhibidora en presencia de plasma humano, el medio de las placas de cultivo celular de toda la noche se puede reemplazar por DMEM que contiene 40% de plasma humano y FBS 5%. Las células se pueden incubar durante tres días en los incubadores de cultivo tisular después de lo cual se pueden agregar 30 µl de solución amortiguadora de lisis pasiva (Promega) a cada cavidad, y luego las placas se incuban durante 15 minutos con agitación suave para lisar las células. Se puede agregar solución de luciferina (100 µl, Promega) a cada cavidad y luego se puede medir la actividad luciferasa con un luminómetro Victor II (Perkin-Elmer). Se puede calcular el porcentaje de inhibición de la replicación del ARN del HCV para cada concentración de compuesto y el valor de EC_{50} se puede calcular usando un ajuste de curva de regresión no lineal a la ecuación logística de 4 parámetro y el software GraphPad Prism 4. Los compuestos representativos de la presente invención mostraron actividades significativamente inhibidoras contra la replicación del HCV usando los ensayos descritos previamente, o ensayos similares con replicones basados en células.

La presente invención también está dirigida a composiciones farmacéuticas que comprenden los compuestos de la invención. Una composición farmacéutica de la presente invención puede comprender uno o más compuestos de la invención, cada uno de los cuales son de la fórmula I (o I_A, I_B, I_C o I_D).

Además, la presente invención está dirigida a composiciones farmacéuticas que comprenden sales, solvatos o prodrogas farmacéuticamente aceptables de los compuestos de la invención. En un sentido no limitativo, las sales farmacéuticamente

aceptables pueden ser zwiteriones o derivados de ácidos o bases inorgánicos u orgánicos farmacéuticamente aceptables. Preferentemente, una sal farmacéuticamente aceptable retiene la eficacia biológica del ácido o de la base libre del compuesto sin una toxicidad, irritación o respuesta alérgica excesiva, tiene una relación de beneficio/riesgo razonable, es eficaz para el uso pretendido y no es indeseable biológicamente o de otra manera.

La presente invención está dirigida además a composiciones farmacéuticas que comprenden un compuesto de la invención (o una sal, solvato o prodroga del mismo) y otro agente terapéutico. A modo ilustrativo no limitativo, estos otros agentes terapéuticos se pueden seleccionar entre agentes antivirales (por ejemplo, agentes anti-HIV, agentes anti-HBV u otros agentes anti-HCV tales como inhibidores de la proteasa del HCV, inhibidores de la polimerasa del HCV, inhibidores de la helicasa del HCV, inhibidores del IRES o inhibidores de NS5A), agentes anti-bacterianos, agentes anti-fúngicos, inmunomoduladores, agentes anti-cancerosos o quimioterapéuticos, agentes anti-inflamatorios, ARN antisentido, siARN, anticuerpos o agentes para el tratamiento de cirrosis o una inflamación del hígado. Los ejemplos específicos de estos agentes terapéuticos adicionales incluyen, pero en un sentido no limitativo, ribavirina, α-interferón, β-interferón, interferón-α pegilado, interferón-lambda pegilado, ribavirina, viramidina, R-5158, nitazoxanida, amantadina, Debio-025, NIM-811, R7128, R1626, R4048, T-1106, PSI-7851, PF-00868554, ANA-598, IDX184, IDX102, IDX375, GS-9190, VCH-759, VCH-916, MK-3281, BCX-4678, MK-3281, VBY708, ANA598, GL59728, GL60667, BMS-790052, BMS-791325, BMS-650032, GS-9132, ACH-1095, AP-H005, A-831, A-689, AZD2836, telaprevir, boceprevir, ITMN-191, BI-201335, VBY-376, VX-500 (Vertex), PHX-B, ACH-1625, IDX136, IDX316, VX-813 (Vertex), SCH 900518 (Schering-Plough), TMC-435 (Tibotec), ITMN-191 (Intermune, Roche), MK-7009 (Merck), IDX-PI (Novartis), BI-201335 (Boehringer Ingelheim), R7128 (Roche), PSI-7851 (Pharmasset), MK-3281 (Merck), PF-868554 (Pfizer), IDX-184 (Novartis), IDX-375 (Pharmasset), BILB-1941 (Boehringer Ingelheim), GS-9190 (Gilead), BMS-790052 (BMS), Albuferón (Novartis), ritonavir, otro inhibidor de una citocromo P450 monooxigenasa o cualquier combinación de los mismos.

En una forma de realización, una composición farmacéutica de la presente invención comprende uno o más compuestos de la presente invención (o sales, solvatos o prodrogas de los mismos), y uno o más agentes antivirales adicionales.

En otra forma de realización, una composición farmacéutica de la presente invención comprende uno o más compuestos de la presente invención (o sales, solvatos o prodrogas de los mismos) y uno o más agentes anti-HCV adicionales. Por ejemplo, una composición farmacéutica de la presente invención puede comprender uno o más

compuestos de la presente invención que son de la fórmula I, I_A, I_B, I_C, o I_D (o una sal, solvato o prodroga de los mismos) y un agente seleccionado entre inhibidores de polimerasa del HCV (incluyendo los inhibidores de polimerasas de tipo nucleosídico o no nucleosídico), inhibidores de una proteasa del HCV, inhibidores de una helicasa del HCV, inhibidores de CD81, inhibidores de ciclofilina, inhibidores de IRES o inhibidores de NS5A.

En aún otra forma de realización, una composición farmacéutica de la presente invención comprende uno o más compuestos de la presente invención (o sales, solvatos o prodrogas de los mismos), y uno o más agentes antivirales adicionales, tales como agentes anti-HBV, anti-HIV o agentes anti-hepatitis A, anti-hepatitis D, anti-hepatitis E o anti-hepatitis G. Los ejemplos no limitativos de agentes anti-HBV incluyen adefovir, lamivudina y tenofovir. Los ejemplos no limitativos de drogas anti-HIV incluyen ritonavir, lopinavir, indinavir, nelfinavir, saquinavir, amprenavir, atazanavir, tipranavir, TMC-114, fosamprenavir, zidovudina, lamivudina, didanosina, estavudina, tenofovir, zalcitabina, abacavir, efavirenz, nevirapina, delavirdina, TMC-125, L-870812, S-1360, enfuvirtida, T-1249 u otros inhibidores de proteasas, transcriptasas inversas, integrasas o fusión del HIV. También se puede incluir cualquier otro agente antiviral deseable en una composición farmacéutica de la presente invención, como podrán apreciar los especialistas en el arte.

Una composición farmacéutica de la presente invención incluye típicamente un vehículo o excipiente farmacéuticamente aceptable. Los ejemplos no limitativos de vehículos/excipientes farmacéuticamente aceptables adecuados incluyen azúcares (por ejemplo, lactosa, glucosa o sacarosa), almidones (por ejemplo, almidón de maíz o almidón de papa), celulosa o sus derivados (por ejemplo, carboximetilcelulosa de sodio, etilcelulosa o acetato de celulosa), aceites (por ejemplo, aceite de maní, aceite de semillas de algodón, aceite de alazor, aceite de sésamo, aceite de oliva, aceite de maíz o aceite de soja), glicoles (por ejemplo, propilenglicol), agentes amortiguadores (por ejemplo, hidróxido de magnesio o hidróxido de aluminio), agar, ácido algínico, tragacanto en polvo, malta, gelatina, talco, manteca de cacao, agua libre de pirógeno, salina isotónica, solución de Ringer, soluciones amortiguadoras de etanol o fosfato. También se pueden incluir lubricantes, agentes colorantes, agentes de liberación, agentes de recubrimiento, agentes endulzantes, saborizantes o perfumantes, conservantes o antioxidantes en una composición farmacéutica de la presente invención.

Las composiciones farmacéuticas de la presente invención se pueden formular sobre la base de sus rutas de administración usando métodos bien conocidos en el arte. Por ejemplo, una preparación inyectable estéril se puede preparar como una suspensión inyectable estéril acuosa u oleaginosa usando agentes dispersión o humectantes y

agentes de suspensión adecuados. Los supositorios para una administración rectal de la droga se pueden preparar por mezclado de la droga con un excipiente no irritante adecuado, tal como manteca de cacao y polietilenglicoles, que son sólidos a las temperaturas comunes pero líquidos a la temperatura rectal y por ello se van a fundir en el recto y así liberar la droga. Las formas de dosificación sólidas para administración por vía oral pueden ser cápsulas, tabletas, píldoras, polvos o gránulos. En tales formas de dosificación sólidas, el compuesto activo se puede mezclar con al menos un diluyente inerte, tal como sacarosa, lactosa o almidón. Las formas de dosificación sólidas también pueden comprender otras sustancias además de diluyentes inertes, tales como agentes lubricantes. En el caso de cápsulas, tabletas y píldoras, las formas de dosificación pueden comprender también agentes reguladores del pH. Las tabletas y píldoras se pueden preparar además con recubrimientos entéricos. Las formas de dosificación líquidas para una administración por vía oral pueden incluir emulsiones, soluciones, suspensiones, jarabes o elixires farmacéuticamente aceptables que contienen los diluyentes inertes usados comúnmente en el arte. Las formas de dosificación líquidas también pueden comprender agentes humectantes, emulsionantes, de suspensión, endulzantes, saborizantes o perfumantes. Las composiciones farmacéuticas de la presente invención también se pueden administrar en la forma de liposomas, como se describe en la Patente de los EE.UU. Nº: 6.703.403. La formulación de drogas que es aplicable en la presente invención se describe en general en, por ejemplo, Hoover, John E., *REMINGTON'S PHARMACEUTICAL SCIENCES* (Mack Publishing Co., Easton, PA: 1975), y Lachman, L., eds., *PHARMACEUTICAL DOSAGE FORMS* (Marcel Decker, Nueva York, N.Y., 1980).

Se puede usar cualquier compuesto descrito en la presente, o una sal farmacéuticamente aceptable del mismo, para preparar las composiciones farmacéuticas de la presente invención.

La presente invención está dirigida además a métodos de uso de los compuestos de la presente invención (o sales, solvatos o prodrogas de los mismos) para inhibir la replicación del HCV. Los métodos comprenden el contacto de células infectadas con HCV con una cantidad eficaz de un compuesto de la presente invención (o una sal, solvato o prodroga del mismo), inhibiendo de esa manera la replicación del virus del HCV en las células. Según se usa en la presente, "inhibir" significa reducir significativamente, o eliminar, la actividad que se está inhibiendo (por ejemplo, la replicación viral). En muchos casos, los compuestos representativos de la presente invención pueden reducir la replicación del virus del HCV (por ejemplo, en un ensayo de replicón del HCV como se describió previamente) en al menos un 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95% o más.

Los compuestos de la presente invención pueden inhibir uno o más subtipos del HCV. Los ejemplos de subtipos del HCV que se pueden aplicar en la presente invención incluyen, pero en un sentido no limitativo, los genotipos 1, 2, 3, 4, 5 y 6 del HCV, incluyendo los genotipos 1a, 1b, 2a, 2b, 2c o 3ª del HCV. En una forma de realización, uno o más compuestos de la presente invención (o sales, solvatos o prodrogas de los mismos) se usan para inhibir la replicación del genotipo 1a del HCV. En otra forma de realización, uno o más compuestos de la presente invención (o sales, solvatos o prodrogas de los mismos) se usan para inhibir la replicación del genotipo 1b del HCV. En aún otra forma de realización, uno o más compuestos de la presente invención (o sales, solvatos o prodrogas de los mismos) se usan para inhibir la replicación de ambos genotipos 1a y 1b del HCV.

La presente invención también está dirigida a métodos de uso de los compuestos de la presente invención (o sales, solvatos o prodrogas de los mismos) para tratar una infección por HCV. Los métodos comprenden típicamente administrar una cantidad terapéuticamente eficaz de un compuesto de la presente invención (o una sal, solvato o prodroga del mismo) o una composición farmacéutica que comprende al mismo, a un paciente con HCV, reduciendo de esa manera el nivel viral del HCV en la sangre o el hígado del paciente. Según se usa en la presente, el término "tratar" se refiere a revertir, aliviar, inhibir el avance, o prevenir el trastorno o condición, o uno o más síntomas de dicho trastorno, o condición, al cual se aplica dicho término. El término "tratamiento" se refiere a la acción de tratar. En una forma de realización, los métodos comprenden administrar una cantidad terapéuticamente eficaz de dos o más compuestos de la presente invención (o sales, solvatos o prodrogas de los mismos), o una composición farmacéutica que comprende a los mismos, a un paciente con HCV, reduciendo de esa manera el nivel viral del HCV en la sangre o el hígado del paciente.

Un compuesto de la presente invención (o una sal, solvato o prodroga del mismo) se puede administrar como único agente farmacéutico activo, o en combinación con otra droga deseada, tal como otros agentes anti-HCV, agentes anti-HIV, agentes anti-HBV, agentes anti-hepatitis A, agentes anti-hepatitis D, agentes anti-hepatitis E, agentes anti-hepatitis G u otras drogas antivirales. Se puede emplear cualquiera de los compuestos que se describen en la presente, o una sal farmacéuticamente aceptable del mismo, en los métodos de la presente invención.

El compuesto de la presente invención (o una sal, solvente o prodroga del mismo) se puede administrar a un paciente en una sola dosis o en dosis divididas. Una dosificación diaria típica puede variar en un rango de, en un sentido no limitativo, entre 0,1 y 200 mg/kg de peso corporal, tal como entre 0,25 y 100 mg/kg de peso corporal. Las

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composiciones de dosis única pueden contener estas cantidades o submúltiplos de las mismas para conformar la dosis diaria. Preferentemente, cada dosificación contiene una cantidad suficiente de un compuesto de la presente invención que sea eficaz para reducir la carga viral del HCV en la sangre o el hígado del paciente. La cantidad del ingrediente activo, o de los ingredientes activos que se combinan para producir una forma de dosificación individual puede variar dependiendo del huésped tratado y del modo de administración particular. Sin embargo, se comprenderá que el nivel de dosis específico para cualquier paciente particular dependerá de diversos factores incluyendo la actividad del compuesto específico empleado, la edad, peso corporal, estado de salud general, sexo, dieta, momento de administración, ruta de administración, velocidad de excreción, combinación de drogas y la severidad de la enfermedad particular bajo terapia.

La presente invención está dirigida además a métodos de uso de las composiciones farmacéuticas de la presente invención para tratar una infección por HCV. Los métodos comprenden típicamente administrar una composición farmacéutica de la presente invención a un paciente con HCV, reduciendo de esa manera el nivel viral del HCV en la sangre o el hígado del paciente. Se puede usar cualquiera de las composiciones farmacéuticas que se describen en la presente en los métodos de la presente invención.

Además, la presente invención está dirigida al uso de los compuestos o de las sales de la presente invención en la elaboración de medicamentos para el tratamiento de una infección por HCV. Se puede usar cualquier compuesto descrito en la presente, o una sal farmacéuticamente aceptable del mismo, para elaborar los medicamentos de la presente invención.

Los compuestos de la presente invención también se pueden sustituir isotópicamente. La sustitución isotópica preferida incluye sustituciones con isótopos estables o no radioactivos, tal como deuterio, ^{13}C, ^{15}N o ^{18}O. La incorporación de un átomo pesado, tal como una sustitución de deuterio por hidrógeno, puede originar un efecto de isótopo que podría alterar la farmacocinética de la droga. En un ejemplo, se sustituye al menos un 10% molar de hidrógeno en un compuesto de la presente invención por deuterio. En otro ejemplo, se sustituye al menos un 25% molar de hidrógeno en un compuesto de la presente invención por deuterio. En un ejemplo adicional, se sustituye al menos un 50, 60, 70, 80 o 90% molar de hidrógeno en un compuesto de la presente invención por deuterio. La abundancia natural de deuterio es del 0,015% aproximadamente. La sustitución, o el enriquecimiento, con deuterio se puede lograr, en un sentido no limitativo, por intercambio de protones con deuterio o por síntesis de la molécula con materiales de partida enriquecidos o sustituidos. También se pueden usar

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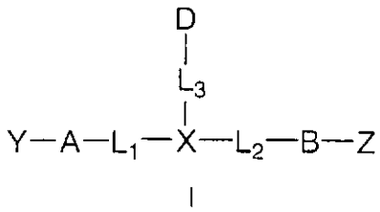
otros métodos conocidos en el arte para las sustituciones isotópicas.

Los compuestos de la presente invención también se pueden sustituir isotópicamente. La sustitución isotópica preferida incluye sustituciones con isótopos estables o no radioactivos, tal como deuterio, ^{13}C, ^{15}N o ^{18}O. La incorporación de un átomo pesado, tal como una sustitución de deuterio por hidrógeno, puede originar un efecto de isótopo que podría alterar la farmacocinética de la droga. En un ejemplo, se sustituye al menos un 10% molar de hidrógeno en un compuesto de la presente invención por deuterio. En otro ejemplo, se sustituye al menos un 25% molar de hidrógeno en un compuesto de la presente invención por deuterio. En un ejemplo adicional, se sustituye al menos un 50, 60, 70, 80 o 90% molar de hidrógeno en un compuesto de la presente invención por deuterio. La abundancia natural de deuterio es del 0,015% aproximadamente. La sustitución o el enriquecimiento con deuterio se puede lograr, en un sentido no limitativo, por intercambio de protones con deuterio o por síntesis de la molécula con materiales de partida enriquecidos o sustituidos. También se pueden usar otros métodos conocidos en el arte para las sustituciones isotópicas.

La descripción precedente de la presente invención ofrece ilustraciones y una descripción, pero no pretende ser exhaustiva ni limitar la invención a la divulgada aquí. Es posible efectuar modificaciones y variaciones a la luz de la divulgación anterior o se pueden efectuar a partir de la práctica de la invención. Por consiguiente, se hace notar que el alcance de la invención se define con las reivindicaciones y los equivalentes de las mismas.

REIVINDICACIONES:

1. Un compuesto de Fórmula I, o una sal aceptable farmacéuticamente del mismo,



en donde:

X es carbociclo de C_3-C_{12} o heterociclo de 3 a 12 miembros, y está opcionalmente sustituido con uno o más R_A;

L_1 y L_2 se seleccionan en forma independiente entre sí entre una unión; o alquileno de C_1-C_6, alquenileno de C_2-C_6 o alquinileno de C_2-C_6, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más R_L;

L_3 es una unión o $-L_S-K-L_S'-$, donde K se selecciona entre una unión, $-O-$, $-S-$, $-N(R_B)-$, $-C(O)-$, $-S(O)_2-$, $-S(O)-$, $-OS(O)-$, $-OS(O)_2-$, $-S(O)_2O-$, $-S(O)O-$, $-C(O)O-$, $-OC(O)-$, $-OC(O)O-$, $-C(O)N(R_B)-$, $-N(R_B)C(O)-$, $-N(R_B)C(O)O-$, $-OC(O)N(R_B)-$, $-N(R_B)S(O)-$, $-N(R_B)S(O)_2-$, $-S(O)N(R_B)-$, $-S(O)_2N(R_B)-$, $-C(O)N(R_B)C(O)-$, $-N(R_B)C(O)N(R_B')-$, $-N(R_B)SO_2N(R_B')-$, o $-N(R_B)S(O)N(R_B')-$;

A y B son en forma independiente entre sí carbociclo de C_3-C_{12} o heterociclo de 3 a 12 miembros, y están sustituidos en forma independiente entre sí con uno o más R_A;

D es carbociclo de C_3-C_{12} o heterociclo de 3 a 12 miembros, y está opcionalmente sustituido con uno o más R_A; o D es hidrógeno o R_A;

Y se selecciona entre $-T'-C(R_1R_2)N(R_5)-T-R_D$, $-T'-C(R_3R_4)C(R_6R_7)-T-R_D$, $-L_K-T-R_D$, o $-L_K-E$;

R_1 y R_2 son en forma independiente entre sí R_C, y R_5 es R_B; o R_1 es R_C, y R_2 y R_5, tomados junto con los átomos a los cuales están unidos, forman un heterociclo de 3 a 12 miembros que está opcionalmente sustituido con uno o más R_A;

R_3, R_4, R_6, y R_7 son en forma independiente entre sí R_C; o R_3 y R_6 son en forma independiente entre sí R_C, y R_4 y R_7, tomados junto con los átomos a los cuales están unidos, forman un carbociclo o heterociclo de 3 a 12 miembros que está opcionalmente sustituido con uno o más R_A;

Z se selecciona entre $-T'-C(R_8R_9)N(R_{12})-T-R_D$, $-T'-C(R_{10}R_{11})C(R_{13}R_{14})-T-R_D$, $-L_K-T-R_D$, o $-L_K-E$;

R_8 y R_9 son en forma independiente entre sí R_C, y R_{12} es R_B; o R_8 es R_C, y R_9 y R_{12}, tomados junto con los átomos a los cuales están unidos, forman un heterociclo de 3 a 12 miembros que está opcionalmente sustituido con uno o más R_A;

R_{10}, R_{11}, R_{13}, y R_{14} son en forma independiente entre sí R_C; o R_{10} y R_{13} son en forma independiente entre sí R_C, y R_{11} y R_{14}, tomados junto con los átomos a los cuales están unidos, forman un carbociclo o heterociclo de 3 a 12 miembros que está opcionalmente sustituido con uno o más R_A;

T y T' se seleccionan en forma independiente entre sí entre una unión, $-L_S-$, $-L_S-M-L_S'-$, o $-L_S-M-L_S'-M'-L_S''-$, donde M y M' se seleccionan en forma independiente entre sí entre una unión, $-O-$, $-S-$, $-N(R_B)-$, $-C(O)-$, $-S(O)_2-$, $-S(O)-$, $-OS(O)-$, $-OS(O)_2-$, $-S(O)_2O-$, $-S(O)O-$, $-C(O)O-$, $-OC(O)-$, $-OC(O)O-$, $-C(O)N(R_B)-$, $-N(R_B)C(O)-$, $-N(R_B)C(O)O-$, $-OC(O)N(R_B)-$, $-N(R_B)S(O)-$, $-N(R_B)S(O)_2-$, $-S(O)N(R_B)-$, $-S(O)_2N(R_B)-$, $-C(O)N(R_B)C(O)-$, $-N(R_B)C(O)N(R_B')-$, $-N(R_B)SO_2N(R_B')-$, $-N(R_B)S(O)N(R_B')-$, carbociclo de C_3-C_{12} o heterociclo de 3 a 12 miembros, y donde dicho carbociclo de C_3-C_{12} y heterociclo de 3 a 12 miembros están opcionalmente sustituidos en forma independiente entre sí en cada caso con uno o más R_A;

L_K se seleccionan en forma independiente en cada caso entre una unión , $-L_S-N(R_B)C(O)-L_S'-$ o $-L_S-C(O)N(R_B)-L_S'-$; o alquileno de C_1-C_6, alquenileno de C_2-C_6 o alquinileno de C_2-C_6, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más R_L; o carbociclo de C_3-C_{12} o heterociclo de 3 a 12 miembros, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más R_A;

E se selecciona en forma independiente en cada caso en cada caso entre carbociclo de C_3-C_{12} o heterociclo de 3 a 12 miembros, y está opcionalmente sustituido en forma independiente en cada caso con uno o más R_A;

R_D se selecciona cada uno en forma independiente en cada caso entre hidrógeno o R_A;

R_A se selecciona en forma independiente en cada caso en cada caso entre halógeno, nitro, oxo, fosfonoxi, fosfono, tioxo, ciano, o $-L_S-R_E$, donde dos R_A adyacentes, tomados junto con los átomos a los cuales están unidos y cualesquier átomos entre los átomos a los cuales están unidos, pueden formar opcionalmente carbociclo o heterociclo;

R_B y R_B' se seleccionan en forma independiente entre sí en cada caso entre

hidrógeno; o alquilo de C_1-C_6, alquenilo de C_2-C_6 o alquinilo de C_2-C_6, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano o carbociclo o heterociclo de 3 a 6 miembros; o carbociclo o heterociclo de 3 a 6 miembros; donde cada carbociclo o heterociclo de 3 a 6 miembros en R_B o R_B' está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, alquilo de C_1-C_6, alquenilo de C_2-C_6, alquinilo de C_2-C_6, haloalquilo de C_1-C_6, haloalquenilo de C_2-C_6 o haloalquinilo de C_2-C_6;

R_C se selecciona en forma independiente en cada caso en cada caso entre hidrógeno, halógeno, hidroxilo, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo o ciano; o alquilo de C_1-C_6, alquenilo de C_2-C_6 o alquinilo de C_2-C_6, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano o carbociclo o heterociclo de 3 a 6 miembros; o carbociclo o heterociclo de 3 a 6 miembros; donde cada carbociclo o heterociclo de 3 a 6 miembros en R_C está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, alquilo de C_1-C_6, alquenilo de C_2-C_6, alquinilo de C_2-C_6, haloalquilo de C_1-C_6, haloalquenilo de C_2-C_6 o haloalquinilo de C_2-C_6;

R_E se selecciona en forma independiente en cada caso entre $-O-R_S$, $-S-R_S$, $-C(O)R_S$, $-OC(O)R_S$, $-C(O)OR_S$, $-N(R_SR_S')$, $-S(O)R_S$, $-SO_2R_S$, $-C(O)N(R_SR_S')$, $-N(R_S)C(O)R_S'$, $-N(R_S)C(O)N(R_S'R_S'')$, $-N(R_S)SO_2R_S'$, $-SO_2N(R_SR_S')$, $-N(R_S)SO_2N(R_S'R_S'')$, $-N(R_S)S(O)N(R_S'R_S'')$, $-OS(O)-R_S$, $-OS(O)_2-R_S$, $-S(O)_2OR_S$, $-S(O)OR_S$, $-OC(O)OR_S$, $-N(R_S)C(O)OR_S'$, $-OC(O)N(R_SR_S')$, $-N(R_S)S(O)-R_S'$, $-S(O)N(R_SR_S')$ o $-C(O)N(R_S)C(O)-R_S'$; o alquilo de C_1-C_6, alquenilo de C_2-C_6 o alquinilo de C_2-C_6, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo o ciano; o carbociclo de C_3-C_6 o heterociclo de 3 a 6 miembros, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más

sustituyentes seleccionados entre halógeno, hidroxilo, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, alquilo de C_1-C_6, alquenilo de C_2-C_6, alquinilo de C_2-C_6, haloalquilo de C_1-C_6, haloalquenilo de C_2-C_6 o haloalquinilo de C_2-C_6;

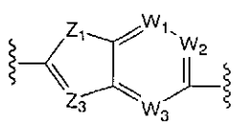
R_L se selecciona en forma independiente en cada caso en cada caso entre halógeno, nitro, oxo, fosfonoxi, fosfono, tioxo, ciano, $-O-R_S$, $-S-R_S$, $-C(O)R_S$, $-OC(O)R_S$, $-C(O)OR_S$, $-N(R_SR_S')$, $-S(O)R_S$, $-SO_2R_S$, $-C(O)N(R_SR_S')$ o $-N(R_S)C(O)R_S'$; o carbociclo de C_3-C_6 heterociclo de 3 a 6 miembros, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, alquilo de C_1-C_6, alquenilo de C_2-C_6, alquinilo de C_2-C_6, haloalquilo de C_1-C_6, haloalquenilo de C_2-C_6 o haloalquinilo de C_2-C_6;

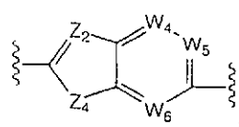
L_S, L_S' y L_S'' se seleccionan en forma independiente entre sí entre una unión; o alquileno de C_1-C_6, alquenileno de C_2-C_6 o alquinileno de C_2-C_6, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más R_L; y

R_S, R_S' y R_S'' se seleccionan en forma independiente entre sí en cada caso entre hidrógeno; alquilo de C_1-C_6, alquenilo de C_2-C_6 o alquinilo de C_2-C_6, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano o carbociclo o heterociclo de 3 a 6 miembros; o carbociclo o heterociclo de 3 a 6 miembros; donde cada carbociclo o heterociclo de 3 a 6 miembros en R_S , R_S' o R_S' está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, alquilo de C_1-C_6, alquenilo de C_2-C_6, alquinilo de C_2-C_6, haloalquilo de C_1-C_6, haloalquenilo de C_2-C_6 o haloalquinilo de C_2-C_6.

2. El compuesto o sal de la reivindicación 1, en donde:

A se selecciona entre C_5-C_6carbociclo, heterociclo de 5 a 6 miembros,

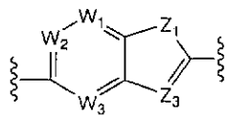
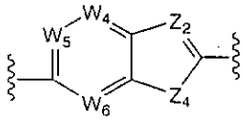


o


, y está opcionalmente sustituido con uno o más R_A;

B se selecciona entre C_5-C_6carbociclo, heterociclo de 5 a 6 miembros,

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 o  , y está opcionalmente sustituido con uno o más R_A;

D se selecciona entre carbociclo de C#5-C_6 o heterociclo de 5 a 6 miembros, y está opcionalmente sustituido con uno o más R_A; o D es hidrógeno o R_A;

Z_1 se selecciona en forma independiente en cada caso entre O, S, NH o CH_2;

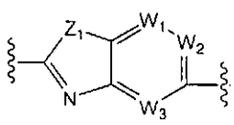
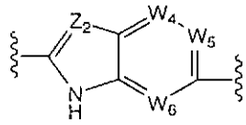
Z_2 se selecciona en forma independiente en cada caso entre N o CH;

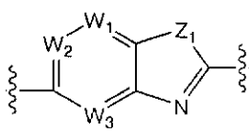
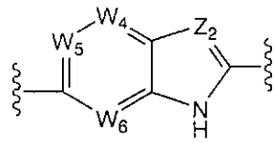
Z_3 se selecciona en forma independiente en cada caso entre N o CH;

Z_4 se selecciona en forma independiente en cada caso entre O, S, NH o CH_2; y

W_1, W_2, W_3, W_4, W_5 y W_6 se seleccionan en forma independiente entre sí en cada caso entre CH o N..

3. El compuesto o sal de la reivindicación 1, en donde:

A se selecciona entre C_5-C_6carbociclo, heterociclo de 5 a 6 miembros,  o  , y está opcionalmente sustituido con uno o más R_A;

B se selecciona entre C_5-C_6carbociclo, heterociclo de 5 a 6 miembros,  o  , y está opcionalmente sustituido con uno o más R_A;

D se selecciona entre carbociclo de C#5-C_6 o heterociclo de 5 a 6 miembros, y está opcionalmente sustituido con uno o más R_A; o D es hidrógeno o R_A;

Z_1 se selecciona en forma independiente en cada caso entre O, S, NH o CH_2;

Z_2 se selecciona en forma independiente en cada caso entre N o CH; y

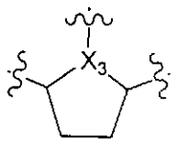
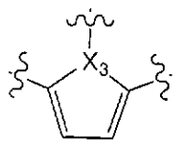
W_1, W_2, W_3, W_4, W_5 y W_6 se seleccionan en forma independiente entre sí en cada caso entre CH o N.

4. El compuesto o sal de la reivindicación 1, en donde:

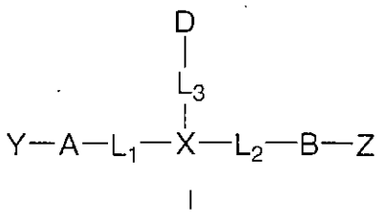
A y B son en forma independiente entre sí carbociclo de C#5-C_6 o heterociclo de 5 a 6 miembros, y están sustituidos en forma independiente entre sí con uno o más R_A;

D se selecciona entre carbociclo de C#5-C_6 o heterociclo de 5 a 6 miembros, y está opcionalmente sustituido con uno o más R_A; y

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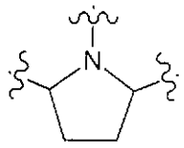
X es  o  , donde X_3 es N y está ligado directamente a $-L_3-D$, y X está opcionalmente sustituido con uno o más R_A, y dos R_A adyacentes sobre X, tomados junto con los átomos del anillo a los cuales están unidos, forman opcionalmente un carbocilo o heterociclo de 5 a 6 miembros.

5. Un compuesto de Fórmula I, o una sal aceptable farmacéuticamente del mismo,

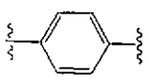


I

en donde:

X es  , donde el átomo de nitrógeno del anillo está ligado directamente a $-L_3-D$, y donde X está opcionalmente sustituido con uno o más R_A;

L_1, L_2 y L_3 son una unión;

A y B son en forma independiente entre sí  , y están sustituidos en forma independiente entre sí con uno o más R_A;

D es carbociclo de C_3-C_{12} o heterociclo de 3 a 12 miembros, y está opcionalmente sustituido con uno o más R_A;

Y es $-G-C(R_1R_2)N(R_5)-T-R_D$, $-G-C(R_3R_4)C(R_6R_7)-T-R_D$, $-N(R_B)C(O)C(R_1R_2)N(R_5)-T-R_D$, o $-N(R_B)C(O)C(R_3R_4)C(R_6R_7)-T-R_D$;

Z es $-G-C(R_8R_9)N(R_{12})-T-R_D$, $-G-C(R_{10}R_{11})C(R_{13}R_{14})-T-R_D$, $-N(R_B)C(O)C(R_8R_9)N(R_{12})-T-R_D$, o $-N(R_B)C(O)C(R_{10}R_{11})C(R_{13}R_{14})-T-R_D$;

R_1 es R_C, y R_2 y R_5, tomados junto con los átomos a los cuales están unidos, forman un heterociclo de 3 a 12 miembros que está opcionalmente sustituido con uno o más R_A;

R_3 y R_6 son en forma independiente entre sí R_C, y R_4 y R_7, tomados junto con los átomos a los cuales están unidos, forman un carbociclo o heterociclo de 3 a 12 miembros que está opcionalmente sustituido con uno o más R_A;

R_8 es R_C, y R_9 y R_{12}, tomados junto con los átomos a los cuales están unidos, forman un heterociclo de 3 a 12 miembros que está opcionalmente sustituido con uno o más R_A;

R_{10} y R_{13} son en forma independiente entre sí R_C, y R_{11} y R_{14}, tomados junto con los átomos a los cuales están unidos, forman un carbociclo o heterociclo de 3 a 12 miembros que está opcionalmente sustituido con uno o más R_A;

G es cada uno en forma independiente carbociclo de C#5-C_6 o heterociclo de 5 a 6 miembros, y es cada uno en forma independiente opcionalmente sustituido con uno o más R_A;

T se selecciona cada uno en forma independiente en cada caso entre una unión, –L_S–, –L_S–M–L_S'–, o –L_S–M–L_S'–M'–L_S''–, donde M y M' se seleccionan en forma independiente entre sí entre una unión, –O–, –S–, –N(R_B)–, –C(O)–, –S(O)$_2$–, –S(O)–, –OS(O)–, –OS(O)$_2$–, –S(O)$_2$O–, –S(O)O–, –C(O)O–, –OC(O)–, –OC(O)O–, –C(O)N(R_B)–, –N(R_B)C(O)–, –N(R_B)C(O)O–, –OC(O)N(R_B)–, –N(R_B)S(O)–, –N(R_B)S(O)$_2$–, –S(O)N(R_B)–, –S(O)$_2$N(R_B)–, –C(O)N(R_B)C(O)–, –N(R_B)C(O)N(R_B')–, –N(R_B)SO$_2$N(R_B')–, –N(R_B)S(O)N(R_B')–, carbociclo de C_3-C_{12} o heterociclo de 3 a 12 miembros, y donde dicho carbociclo de C_3-C_{12} y heterociclo de 3 a 12 miembros están opcionalmente sustituidos en forma independiente entre sí en cada caso con uno o más R_A;

R_D se selecciona cada uno en forma independiente en cada caso entre hidrógeno o R_A;

R_A se selecciona en forma independiente en cada caso en cada caso entre halógeno, nitro, oxo, fosfonoxi, fosfono, tioxo, ciano, o –L_S–R_E;

R_B y R_B' se seleccionan en forma independiente entre sí en cada caso entre hidrógeno; o alquilo de C_1-C_6, alquenilo de C_2-C_6 o alquinilo de C_2-C_6, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano o carbociclo o heterociclo de 3 a 6 miembros; o carbociclo o heterociclo de 3 a 6 miembros; donde cada carbociclo o heterociclo de 3 a 6 miembros en R_B o R_B' está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, alquilo de C_1-C_6, alquenilo de C_2-C_6, alquinilo de C_2-C_6, haloalquilo de C_1-C_6, haloalquenilo de C_2-C_6 o haloalquinilo de C_2-C_6;

R_C se selecciona en forma independiente en cada caso en cada caso entre

hidrógeno, halógeno, hidroxilo, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo o ciano; o alquilo de C_1-C_6, alquenilo de C_2-C_6 o alquinilo de C_2-C_6, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano o carbociclo o heterociclo de 3 a 6 miembros; o carbociclo o heterociclo de 3 a 6 miembros; donde cada carbociclo o heterociclo de 3 a 6 miembros en R_C está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, alquilo de C_1-C_6, alquenilo de C_2-C_6, alquinilo de C_2-C_6, haloalquilo de C_1-C_6, haloalquenilo de C_2-C_6 o haloalquinilo de C_2-C_6;

R_E se selecciona en forma independiente en cada caso entre $-O-R_S$, $-S-R_S$, $-C(O)R_S$, $-OC(O)R_S$, $-C(O)OR_S$, $-N(R_SR_S')$, $-S(O)R_S$, $-SO_2R_S$, $-C(O)N(R_SR_S')$, $-N(R_S)C(O)R_S'$, $-N(R_S)C(O)N(R_S'R_S'')$, $-N(R_S)SO_2R_S'$, $-SO_2N(R_SR_S')$, $-N(R_S)SO_2N(R_S'R_S'')$, $-N(R_S)S(O)N(R_S'R_S'')$, $-OS(O)-R_S$, $-OS(O)_2-R_S$, $-S(O)_2OR_S$, $-S(O)OR_S$, $-OC(O)OR_S$, $-N(R_S)C(O)OR_S'$, $-OC(O)N(R_SR_S')$, $-N(R_S)S(O)-R_S'$, $-S(O)N(R_SR_S')$ o $-C(O)N(R_S)C(O)-R_S'$; o alquilo de C_1-C_6, alquenilo de C_2-C_6 o alquinilo de C_2-C_6, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo o ciano; o carbociclo de C_3-C_6 o heterociclo de 3 a 6 miembros, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, alquilo de C_1-C_6, alquenilo de C_2-C_6, alquinilo de C_2-C_6, haloalquilo de C_1-C_6, haloalquenilo de C_2-C_6 o haloalquinilo de C_2-C_6;

R_L se selecciona en forma independiente en cada caso en cada caso entre halógeno, nitro, oxo, fosfonoxi, fosfono, tioxo, ciano, $-O-R_S$, $-S-R_S$, $-C(O)R_S$, $-OC(O)R_S$, $-C(O)OR_S$, $-N(R_SR_S')$, $-S(O)R_S$, $-SO_2R_S$, $-C(O)N(R_SR_S')$ o $-N(R_S)C(O)R_S'$; o carbociclo de C_3-C_6 heterociclo de 3 a 6 miembros, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, alquilo de C_1-C_6, alquenilo de C_2-C_6, alquinilo de C_2-C_6, haloalquilo de C_1-C_6,

haloalquenilo de C_2-C_6 o haloalquinilo de C_2-C_6;

L_S, L_S' y L_S'' se seleccionan en forma independiente entre sí entre una unión; o alquileno de C_1-C_6, alquenileno de C_2-C_6 o alquinileno de C_2-C_6, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más R_L; y

R_S, R_S' y R_S'' se seleccionan en forma independiente entre sí en cada caso entre hidrógeno; alquilo de C_1-C_6, alquenilo de C_2-C_6 o alquinilo de C_2-C_6, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano o carbociclo o heterociclo de 3 a 6 miembros; o carbociclo o heterociclo de 3 a 6 miembros; donde cada carbociclo o heterociclo de 3 a 6 miembros en R_S , R_S' o R_S' está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, alquilo de C_1-C_6, alquenilo de C_2-C_6, alquinilo de C_2-C_6, haloalquilo de C_1-C_6, haloalquenilo de C_2-C_6 o haloalquinilo de C_2-C_6.

6. El compuesto o sal de la reivindicación 5, en donde:

T se selecciona en forma independiente en cada caso entre $-C(O)-L_S'-M'-L_S''-$ o $-N(R_B)C(O)-L_S'-M'-L_S''-$; y

L_S' es cada uno en forma independiente alquileno de C_1-C_6, y está opcionalmente sustituido en forma independiente en cada caso con uno o más R_L.

7. El compuesto o sal de la reivindicación 5, en donde:

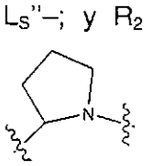
Y es $-N(R_B)C(O)C(R_1R_2)N(R_5)-T-R_D$;

Z es $-N(R_B)C(O)C(R_8R_9)N(R_{12})-T-R_D$;

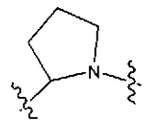
T se selecciona en forma independiente en cada caso entre $-C(O)-L_S'-M'-L_S''-$; y

D es C_5-C_6carbociclo, heterociclo de 5 a 6 miembros, o biciclos de 6 a 10 miembros, y se sustituye con uno o más R_A.

8. El compuesto o sal de la reivindicación 7, en donde T se selecciona en forma independiente en cada caso entre $-C(O)-L_S'-N(R_B)C(O)-L_S''-$ o $-C(O)-L_S'-N(R_B)C(O)O-L_S''-$; y R_2 y R_5, tomados junto con los átomos a los cuales están unidos, forman



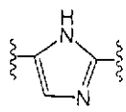
que está opcionalmente sustituido con uno o más R_A; y R_9 y R_{12}, tomados

junto con los átomos a los cuales están unidos, forman  que está opcionalmente sustituido con uno o más R_A.

9. El compuesto o sal de la reivindicación 5, en donde:

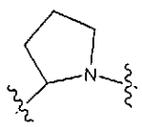
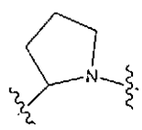
Y es $-G-C(R_1R_2)N(R_5)-T-R_D$;

Z es $-G-C(R_8R_9)N(R_{12})-T-R_D$;

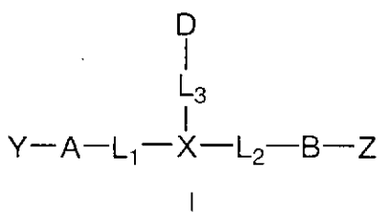
G es cada uno en forma independiente  , y es cada uno en forma independiente opcionalmente sustituido con uno o más R_A;

T se selecciona en forma independiente en cada caso entre $-C(O)-L_S'-M'-L_S''-$; y

D es C_5-C_6carbociclo, heterociclo de 5 a 6 miembros, o biciclos de 6 a 10 miembros, y se sustituye con uno o más R_A.

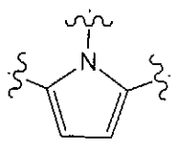
10. El compuesto o sal de la reivindicación 9, en donde T se selecciona en forma independiente en cada caso entre $-C(O)-L_S'-N(R_B)C(O)-L_S''-$ o $-C(O)-L_S'-N(R_B)C(O)O-L_S''-$; y R_2 y R_5, tomados junto con los átomos a los cuales están unidos, forman  que está opcionalmente sustituido con uno o más R_A; y R_9 y R_{12}, tomados junto con los átomos a los cuales están unidos, forman  que está opcionalmente sustituido con uno o más R_A.

11. Un compuesto de Fórmula I, o una sal aceptable farmacéuticamente del mismo,



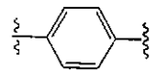
I

en donde:

X es  , donde el átomo de nitrógeno del anillo está ligado directamente a $-L_3-D$, y donde X está opcionalmente sustituido con uno o más R_A;

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L_1, L_2 y L_3 son una unión;

A y B son en forma independiente entre sí  , y están sustituidos en forma independiente entre sí con uno o más R_A;

D es carbociclo de C_3-C_{12} o heterociclo de 3 a 12 miembros, y está opcionalmente sustituido con uno o más R_A;

Y es $-G-C(R_1R_2)N(R_5)-T-R_D$, $-G-C(R_3R_4)C(R_6R_7)-T-R_D$, $-N(R_B)C(O)C(R_1R_2)N(R_5)-T-R_D$, o $-N(R_B)C(O)C(R_3R_4)C(R_6R_7)-T-R_D$;

Z es $-G-C(R_8R_9)N(R_{12})-T-R_D$, $-G-C(R_{10}R_{11})C(R_{13}R_{14})-T-R_D$, $-N(R_B)C(O)C(R_8R_9)N(R_{12})-T-R_D$, o $-N(R_B)C(O)C(R_{10}R_{11})C(R_{13}R_{14})-T-R_D$;

R_1 es R_C, y R_2 y R_5, tomados junto con los átomos a los cuales están unidos, forman un heterociclo de 3 a 12 miembros que está opcionalmente sustituido con uno o más R_A;

R_3 y R_6 son en forma independiente entre sí R_C, y R_4 y R_7, tomados junto con los átomos a los cuales están unidos, forman un carbociclo o heterociclo de 3 a 12 miembros que está opcionalmente sustituido con uno o más R_A;

R_8 es R_C, y R_9 y R_{12}, tomados junto con los átomos a los cuales están unidos, forman un heterociclo de 3 a 12 miembros que está opcionalmente sustituido con uno o más R_A;

R_{10} y R_{13} son en forma independiente entre sí R_C, y R_{11} y R_{14}, tomados junto con los átomos a los cuales están unidos, forman un carbociclo o heterociclo de 3 a 12 miembros que está opcionalmente sustituido con uno o más R_A;

G es cada uno en forma independiente carbociclo de C#5-C_6 o heterociclo de 5 a 6 miembros, y es cada uno en forma independiente opcionalmente sustituido con uno o más R_A;

T se selecciona cada uno en forma independiente en cada caso entre una unión, $-L_S-$, $-L_S-M-L_S'-$, o $-L_S-M-L_S'-M'-L_S''-$, donde M y M' se seleccionan en forma independiente entre sí entre una unión, $-O-$, $-S-$, $-N(R_B)-$, $-C(O)-$, $-S(O)_2-$, $-S(O)-$, $-OS(O)-$, $-OS(O)_2-$, $-S(O)_2O-$, $-S(O)O-$, $-C(O)O-$, $-OC(O)-$, $-OC(O)O-$, $-C(O)N(R_B)-$, $-N(R_B)C(O)-$, $-N(R_B)C(O)O-$, $-OC(O)N(R_B)-$, $-N(R_B)S(O)-$, $-N(R_B)S(O)_2-$, $-S(O)N(R_B)-$, $-S(O)_2N(R_B)-$, $-C(O)N(R_B)C(O)-$, $-N(R_B)C(O)N(R_B')-$, $-N(R_B)SO_2N(R_B')-$, $-N(R_B)S(O)N(R_B')-$, carbociclo de C_3-C_{12} o heterociclo de 3 a 12 miembros, y donde dicho carbociclo de C_3-C_{12} y heterociclo de 3 a 12 miembros están opcionalmente sustituidos en forma independiente entre sí en cada caso con uno o más R_A;

R_D se selecciona cada uno en forma independiente en cada caso entre hidrógeno

o R_A;

R_A se selecciona en forma independiente en cada caso en cada caso entre halógeno, nitro, oxo, fosfonoxi, fosfono, tioxo, ciano, o $-L_S-R_E$;

R_B y R_B' se seleccionan en forma independiente entre sí en cada caso entre hidrógeno; o alquilo de C_1-C_6, alquenilo de C_2-C_6 o alquinilo de C_2-C_6, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano o carbociclo o heterociclo de 3 a 6 miembros; o carbociclo o heterociclo de 3 a 6 miembros; donde cada carbociclo o heterociclo de 3 a 6 miembros en R_B o R_B' está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, alquilo de C_1-C_6, alquenilo de C_2-C_6, alquinilo de C_2-C_6, haloalquilo de C_1-C_6, haloalquenilo de C_2-C_6 o haloalquinilo de C_2-C_6;

R_C se selecciona en forma independiente en cada caso en cada caso entre hidrógeno, halógeno, hidroxilo, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo o ciano; o alquilo de C_1-C_6, alquenilo de C_2-C_6 o alquinilo de C_2-C_6, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano o carbociclo o heterociclo de 3 a 6 miembros; o carbociclo o heterociclo de 3 a 6 miembros; donde cada carbociclo o heterociclo de 3 a 6 miembros en R_C está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, alquilo de C_1-C_6, alquenilo de C_2-C_6, alquinilo de C_2-C_6, haloalquilo de C_1-C_6, haloalquenilo de C_2-C_6 o haloalquinilo de C_2-C_6;

R_E se selecciona en forma independiente en cada caso entre $-O-R_S$, $-S-R_S$, $-C(O)R_S$, $-OC(O)R_S$, $-C(O)OR_S$, $-N(R_SR_S')$, $-S(O)R_S$, $-SO_2R_S$, $-C(O)N(R_SR_S')$, $-N(R_S)C(O)R_S'$, $-N(R_S)C(O)N(R_S'R_S'')$, $-N(R_S)SO_2R_S'$, $-SO_2N(R_SR_S')$, $-N(R_S)SO_2N(R_S'R_S'')$, $-N(R_S)S(O)N(R_S'R_S'')$, $-OS(O)-R_S$, $-OS(O)_2-R_S$, $-S(O)_2OR_S$, $-S(O)OR_S$, $-OC(O)OR_S$, $-N(R_S)C(O)OR_S'$, $-OC(O)N(R_SR_S')$, $-N(R_S)S(O)-R_S'$, $-S(O)N(R_SR_S')$ o $-C(O)N(R_S)C(O)-R_S'$; o alquilo de C_1-C_6, alquenilo de C_2-C_6 o alquinilo de C_2-C_6, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más

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sustituyentes seleccionados entre halógeno, hidroxilo, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo o ciano; o carbociclo de C_3-C_6 o heterociclo de 3 a 6 miembros, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, alquilo de C_1-C_6, alquenilo de C_2-C_6, alquinilo de C_2-C_6, haloalquilo de C_1-C_6, haloalquenilo de C_2-C_6 o haloalquinilo de C_2-C_6;

R_L se selecciona en forma independiente en cada caso en cada caso entre halógeno, nitro, oxo, fosfonoxi, fosfono, tioxo, ciano, $-O-R_S$, $-S-R_S$, $-C(O)R_S$, $-OC(O)R_S$, $-C(O)OR_S$, $-N(R_SR_S')$, $-S(O)R_S$, $-SO_2R_S$, $-C(O)N(R_SR_S')$ o $-N(R_S)C(O)R_S'$; o carbociclo de C_3-C_6 heterociclo de 3 a 6 miembros, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, alquilo de C_1-C_6, alquenilo de C_2-C_6, alquinilo de C_2-C_6, haloalquilo de C_1-C_6, haloalquenilo de C_2-C_6 o haloalquinilo de C_2-C_6;

L_S, L_S' y L_S'' se seleccionan en forma independiente entre sí entre una unión; o alquileno de C_1-C_6, alquenileno de C_2-C_6 o alquinileno de C_2-C_6, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más R_L; y

R_S, R_S' y R_S'' se seleccionan en forma independiente entre sí en cada caso entre hidrógeno; alquilo de C_1-C_6, alquenilo de C_2-C_6 o alquinilo de C_2-C_6, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano o carbociclo o heterociclo de 3 a 6 miembros; o carbociclo o heterociclo de 3 a 6 miembros; donde cada carbociclo o heterociclo de 3 a 6 miembros en R_S , R_S' o R_S' está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxilo, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, alquilo de C_1-C_6, alquenilo de C_2-C_6, alquinilo de C_2-C_6, haloalquilo de C_1-C_6, haloalquenilo de C_2-C_6 o haloalquinilo de C_2-C_6.

12. El compuesto o sal de la reivindicación 11, en donde:

T se selecciona en forma independiente en cada caso entre $-C(O)-L_S'-M'-L_S''-$ o $-N(R_B)C(O)-L_S'-M'-L_S''-$; y

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L_S' es cada uno en forma independiente alquileno de C_1-C_6, y está opcionalmente sustituido en forma independiente en cada caso con uno o más R_L.

13. El compuesto o sal de la reivindicación 11, en donde:

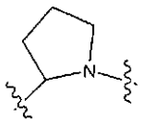
Y es $-N(R_B)C(O)C(R_1R_2)N(R_5)-T-R_D$;

Z es $-N(R_B)C(O)C(R_8R_9)N(R_{12})-T-R_D$;

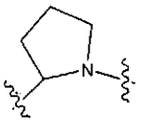
T se selecciona en forma independiente en cada caso entre $-C(O)-L_S'-M'-L_S''-$; y

D es C_5-C_6carbociclo, heterociclo de 5 a 6 miembros, o biciclos de 6 a 10 miembros, y se sustituye con uno o más R_A.

14. El compuesto o sal de la reivindicación 13, en donde T se selecciona en forma independiente en cada caso entre $-C(O)-L_S'-N(R_B)C(O)-L_S''-$ o $-C(O)-L_S'-N(R_B)C(O)O-L_S''-$; y R_2 y R_5, tomados junto con los átomos a los cuales están unidos, forman



que está opcionalmente sustituido con uno o más R_A; y R_9 y R_{12}, tomados junto con los átomos a los cuales están unidos, forman



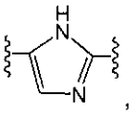
que está opcionalmente sustituido con uno o más R_A.

15. El compuesto o sal de la reivindicación 11, en donde:

Y es $-G-C(R_1R_2)N(R_5)-T-R_D$;

Z es $-G-C(R_8R_9)N(R_{12})-T-R_D$;

G se selecciona cada uno en forma independiente en cada caso

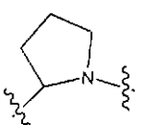


, y es cada uno en forma independiente opcionalmente sustituido con uno o más R_A;

T se selecciona en forma independiente en cada caso entre $-C(O)-L_S'-M'-L_S''-$; y

D es C_5-C_6carbociclo, heterociclo de 5 a 6 miembros, o biciclos de 6 a 10 miembros, y se sustituye con uno o más R_A.

16. El compuesto o sal de la reivindicación 15, en donde T se selecciona en forma independiente en cada caso entre $-C(O)-L_S'-N(R_B)C(O)-L_S''-$ o $-C(O)-L_S'-N(R_B)C(O)O-L_S''-$; y R_2 y R_5, tomados junto con los átomos a los cuales están unidos, forman



que está opcionalmente sustituido con uno o más R_A; y R_9 y R_{12}, tomados

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
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(71)Solicitante(s) **ABBOTT LABORATORIES**

(72) Inventor(es) **VER ANEXO # 1**

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(30) Prioridad	(31)	**No. Prioridad**	32)	**Fecha**	(33)	**País**
		61/186.291		**11/06/2009**		**US**
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(71)Solicitante(s) ABBOTT LABORATORIES

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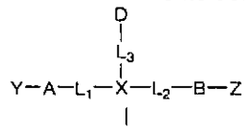
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(54) Titulo: **COMPUESTOS ANTIVIRALES**

Reivindicación(es):

1. Un compuesto de Fórmula I, o una sal aceptable farmacéuticamente del mismo,



en donde:
X es carbociclo de C_3-C_{12} o heterociclo de 3 a 12 miembros, y está opcionalmente sustituido con uno o más R_A;
L_1 y L_2 se seleccionan en forma independiente entre sí entre una unión; o alquileno de C_1-C_6, alquenileno de C_2-C_6 o alquinileno de C_2-C_6, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más R_L;
L_3 es una unión o $-L_S-K-L_S'-$, donde K se selecciona entre una unión, $-O-$, $-S-$, $-N(R_B)-$, $-C(O)-$, $-S(O)_2-$, $-S(O)-$, $-OS(O)-$, $-OS(O)_2-$, $-S(O)_2O-$, $-S(O)O-$, $-C(O)O-$, $-OC(O)-$, $-OC(O)O-$, $-C(O)N(R_B)-$, $-N(R_B)C(O)-$, $-N(R_B)C(O)O-$, $-OC(O)N(R_B)-$, $-N(R_B)S(O)-$, $-N(R_B)S(O)_2-$, $-S(O)N(R_B)-$, $-S(O)_2N(R_B)-$, $-C(O)N(R_B)C(O)-$, $-N(R_B)C(O)N(R_B')-$, $-N(R_B)SO_2N(R_B')-$, o $-N(R_B)S(O)N(R_B')-$;
A y B son en forma independiente entre si carbociclo de C_3-C_{12} o heterociclo de 3 a 12 miembros, y están sustituidos en forma independiente entre sí con uno o más R_A;
D es carbociclo de C_3-C_{12} o heterociclo de 3 a 12 miembros, y está opcionalmente sustituido con uno o más R_A; o D es hidrógeno o R_A;
Y se selecciona entre $-T'-C(R_1R_2)N(R_5)-T-R_D$, $-T'-C(R_3R_4)C(R_6R_7)-T-R_D$, $-L_K-T-R_D$, o $-L_K-E$;
R_1 y R_2 son en forma independiente entre sí R_C, y R_5 es R_B; o R_1 es R_C, y R_2 y R_5, tomados junto con los átomos a los cuales están unidos, forman un heterociclo de 3 a 12 miembros que está opcionalmente sustituido con uno o más R_A;
R_3, R_4, R_6, y R_7 son en forma independiente entre sí R_C; o R_3 y R_6 son en forma independiente entre sí R_C, y R_4 y R_7, tomados junto con los átomos a los cuales están unidos, forman un carbociclo o heterociclo de 3 a 12 miembros que está opcionalmente sustituido con uno o más R_A;
Z se selecciona entre $-T'-C(R_8R_9)N(R_{12})-T-R_D$, $-T'-C(R_{10}R_{11})C(R_{13}R_{14})-T-R_D$, $-L_K-T-R_D$, o $-L_K-E$;
R_8 y R_9 son en forma independiente entre sí R_C, y R_{12} es R_B; o R_8 es R_C, y R_9 y R_{12}, tomados junto con los átomos a los cuales están unidos, forman un heterociclo de 3 a 12 miembros que está opcionalmente sustituido con uno o más R_A;
R_{10}, R_{11}, R_{13}, y R_{14} son en forma independiente entre sí R_C; o R_{10} y R_{13} son en forma independiente entre sí R_C, y R_{11} y R_{14}, tomados junto con los átomos a los cuales están unidos, forman un carbociclo o heterociclo de 3 a 12 miembros que está opcionalmente sustituido con uno o más R_A;
T y T' se seleccionan en forma independiente entre sí entre una unión, $-L_S-$, $-L_S-M-L_S'-$, o $-L_S-M-L_S'-M'-L_S''-$, donde M y M' se seleccionan en forma independiente entre sí entre una unión, $-O-$, $-S-$, $-N(R_B)-$, $-C(O)-$, $-S(O)_2-$, $-S(O)-$, $-OS(O)-$, $-OS(O)_2-$, $-S(O)_2O-$, $-S(O)O-$, $-C(O)O-$, $-OC(O)-$, $-OC(O)O-$, $-C(O)N(R_B)-$, $-N(R_B)C(O)-$, $-N(R_B)C(O)O-$, $-OC(O)N(R_B)-$, $-N(R_B)S(O)-$, $-N(R_B)S(O)_2-$, $-S(O)N(R_B)-$, $-S(O)_2N(R_B)-$, $-C(O)N(R_B)C(O)-$, $-N(R_B)C(O)N(R_B')-$, $-N(R_B)SO_2N(R_B')-$, $-N(R_B)S(O)N(R_B')-$, carbociclo de C_3-C_{12} o heterociclo de 3 a 12 miembros, y donde dicho carbociclo de C_3-C_{12} y heterociclo de 3 a 12 miembros están opcionalmente sustituidos en forma independiente entre sí en cada caso con uno o más R_A;
L_K se seleccionan en forma independiente en cada caso entre una unión , $-L_S-N(R_B)C(O)-L_S'-$ o $-L_S-C(O)N(R_B)-L_S'-$; o alquileno de C_1-C_6, alquenileno de C_2-C_6 o alquinileno de C_2-C_6, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más R_L; o carbociclo de C_3-C_{12} o heterociclo de 3 a 12 miembros, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más R_A;
E se selecciona en forma independiente en cada caso en cada caso entre carbociclo de C_3-C_{12} o heterociclo de 3 a 12 miembros, y está opcionalmente sustituido en forma independiente en cada caso con uno o más R_A;
R_D se selecciona cada uno en forma independiente en cada caso entre hidrógeno o R_A;
R_A se selecciona en forma independiente en cada caso en cada caso entre halógeno, nitro, oxo, fosfonoxi, fosfono, tioxo, ciano, o $-L_S-R_E$, donde dos R_A adyacentes, tomados junto con los átomos a los cuales están unidos y cualesquier átomos entre los átomos a los cuales están unidos, pueden formar opcionalmente carbociclo o heterociclo;
R_B y R_B' se seleccionan en forma independiente entre sí en cada caso entre hidrógeno; o alquilo de C_1-C_6, alquenilo de C_2-C_6 o alquinilo de C_2-C_6, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre ...

000871

PATENT COOPERATION TREATY PCT/US2010/038077

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92*bis*.1 and Administrative Instructions, Section 422)

To:

MUELLER, Lisa V.
Polsinelli Shughart PC
161 N. Clark Street, Suite 4200
Chicago, Illinois 60601
ETATS-UNIS D'AMERIQUE

Date of mailing *(day/month/year)*
01 February 2011 (01.02.2011)

Applicant's or agent's file reference
10046WOO1

IMPORTANT NOTIFICATION

International application No.
PCT/US2010/038077

International filing date *(day/month/year)*
10 June 2010 (10.06.2010)

1. The following indications appeared on record concerning:

☐ the applicant ☐ the inventor ☐ the agent ☐ the common representative

Name and Address	State of Nationality	State of Residence
	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	State of Nationality	State of Residence
CASPI, Daniel, D. 807 Davis Unit 912 Evanston, IL 60201 United States of America	US	US
	Telephone No.	
	Facsimile No.	
	E-mail address ☐ Notifications by e-mail authorized	

3. Further observations, if necessary:
The person identified in Box 2 has been added to the record as inventor for all designated States and applicant for US only.

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	Authorized officer Campin Helene
Facsimile No. +41 22 338 70 80	e-mail pt11.pct@wipo.int Telephone No. +41 22 338 74 11

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Name and Address

State of Nationality

State of Residence

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

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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:
The person identified in Box 2 has been added to the record as inventor for all designated States and applicant for US only.

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:

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Industria y Comercio
SUPERINTENDENCIA

Prosperidad para todos

Bogotá D.C.,
2020

Doctor(a)
MARGARITA CASTELLANOS ABONDANO
Apoderado(a) y/o Representante de
Abbott Laboratories

REFERENCIA	Radicación No.	11 038996
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	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	14208

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.

2. La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante, conforme a lo establecido por el artículo 26 literal k) de la Decisión 486 de la Comisión de la Comunidad Andina. Cuando se trate de documentos otorgados en el extranjero, estos deberán legalizarse de conformidad con lo dispuesto por los artículos 259 y 260 del Código de Procedimiento Civil. Cuando se trate de las declaraciones a que hace referencia la Regla 4.17 ii) del Tratado de Cooperación en Materia de Patentes PCT., el alcance de las tales declaraciones se determinará según indiquen claramente una cesión de derechos del inventor al solicitante o su causante, de conformidad con lo dispuesto en el numeral 5.2.15 del Capítulo Quinto, Título X de la Circular Única de Superintendencia de Industria y Comercio.

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se consideraró abandonada y perderá su prelación.

Continua en la página siguiente...