SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 13-116472- -00000-0000
Fecha: 2013-05-09 16:23:16 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 58

Industria y Co
SUPERINTEND
República de Co
Ministerio de Comercio, Industri

Delegatura de Propiedad Industrial
División de Nuevas Creaciones

SOLICITUD DE

PATENTE DE INVENCION
PCT ENTRADA EN FASE NACIONAL

21. EXPEDIENTE No. _____

54. TITULO: **COMPUESTOS ANTIVIRALES**

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

71. SOLICITANTE: **ABBVIE INC.**

DOMICILIO: **1 North Waukegan Road, North Chicago, IL 60064, ESTADOS UNIDOS**

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

22. BOGOTA, D.C., 09 MAYO 2013

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

radicación

No. 13-116472- -00000-0000

Fecha: 2013-05-09 16:23:16 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 58

DIRECCION DE NUEVAS CREACIONES
SOLICITUD FASE NACIONAL - PCT

1	(12) TIPO DE SOLICITUD	X Patente de Invención X Capítulo I	____ Patente de Modelo de Utilidad ____ Capítulo II
2	DATOS SOLICITUD INTERNACIONAL PCT (86)		
	Solicitud Internacional No.	PCT/US2011/056045	Fecha 12/10/2011
	Publicación Internacional No.	WO/2012/051361 A1	Fecha 19/04/2012
3	(54) TITULO DE LA INVENCION (200 caracteres o espacios máximos)		
	COMPUESTOS ANTIVIRALES		
4	CLASIFICACION INTERNACIONAL (51) CIP		
	C07D 403/14		
5	(71) SOLICITANTE(S)	____ Esta persona también es inventor	Para datos adicionales utilizar hoja de información adicional

APELLIDOS O RAZON SOCIAL	NOMBRE	IDENTIFICACION	TIPO
ABBVIE INC.			

6	DATOS DEL SOLICITANTE		
	DIRECCION	1 North Waukegan Road	No. TELEFONO
	CIUDAD	North Chicago	E-MAIL
	DEPARTAMENTO/ESTADO	IL 60064	NACIONALIDAD O
	PAIS DE RESIDENCIA	ESTADOS UNIDOS	LUGAR DE CONSTITUCION ESTADOS UNIDOS
7	(72) INVENTOR(ES)		Para datos adicionales utilizar hoja de información adicional

	APELLIDOS	NOMBRES	NACIONALIDAD
1.	DEGOEY	DAVID A.	ESTADOUNIDENSE
2.	KATI	WARREN M.	ESTADOUNIDENSE
3.	HUTCHINS	CHARLES W.	ESTADOUNIDENSE
4.	DONNER	PAMELA L.	ESTADOUNIDENSE
5.	KRUEGER	ALLAN C.	ESTADOUNIDENSE
6.	RANDOLPH	JOHN T.	ESTADOUNIDENSE
7.	MOTTER	CHRISTOPHER E.	ESTADOUNIDENSE

DIRECCION DE CORREO ELECTRONICO:

8	DATOS INVENTOR(ES)			
	PAIS RESIDENCIA	DEPARTAMENTO/ESTADO	CIUDAD	DIRECCION
1.	ESTADOS UNIDOS	Wisconsin 53168	Salem	8649 226th Avenue
2.	ESTADOS UNIDOS	Illinois 60031	Gurnee	152 Knob Hill Lane
3.	ESTADOS UNIDOS	Illinois 60048	Green Oaks	31005 Prairie Ridge Road
4.	ESTADOS UNIDOS	Illinois 60060	Mundelien	1901 McRae Lane
5.	ESTADOS UNIDOS	Illinois 60031	Gurnee	7260 Presidential Drive
6.	ESTADOS UNIDOS	Illinois 60048	Libertyville	304 Broadway Avenue
7.	ESTADOS UNIDOS	Wisconsin 53154	Oak Creek	10135 South Warwick Drive

OTRO(S) SOLICITANTE(S) Y/U OTRO(S) INVENTOR(ES)

____ Los demás solicitantes y/o demás inventores se indican en una hoja a continuación

9	(74) ____ REPRESENTANTE	X APODERADO	
APELLIDOS	NOMBRES	IDENTIFICACION	
CASTELLANOS ABONDANO	MARGARITA	C.C. 39.779.654	T.P. 70.819

DIRECCION	Calle 94A No. 7A-09	No. TELEFOI	7560770
CIUDAD	BOGOTA	E-MAIL	info@castellanosyco.co
PAIS	COLOMBIA	No. DE PROTOCOLO EN LA OFICINA	

10 **(30) DECLARACIONES DE PRIORIDAD** X SI ____ NO

	(33) PAIS DE ORIGEN	CODIGO PAIS	(31) NUMERO	(32) FECHA (AAA/MM/DD)
1.	ESTADOS UNIDOS	US	12/903.822	13/10/2010
2.	ESTADOS UNIDOS	US	12/964.027	09/12/2010
3.	ESTADOS UNIDOS	US	61/446.800	25/02/2011
4.	ESTADOS UNIDOS	US	13/100.827	04/05/2011
5.				

11 **DECLARACION SOBRE USO DE RECURSOS GENETICOS O BIOLOGICOS**

Declaro que el objeto de la presente solicitud de patente fue obtenido a partir de recursos genéticos o biológicos de los que cualquiera de los paises miembros de la Comunidad Andina es país de origen.

____ SI X NO

NOTA: En caso afirmativo deberá anexar copia del contrato de acceso de recursos genéticos o productos derivados, o certificado o número de registro expedido por la Autoridad competente.

12 **DECLARACION SOBRE USO DE CONOCIMIENTOS TRADICIONALES**

Declaro que el objeto de la presente solicitud de patente fue obtenido a partir de conocimientos tradicionales de comunidades indígenas, afroamericanas o locales de países miembros de la Comunidad Andina.

____ SI X NO

NOTA: En caso afirmativo deberá anexar la licencia o autorización de uso de conocimiento tradicional, o certificado, o número de registro expedido por la Autoridad competente.

13 **REDUCCION DE TASAS**

Declaro que carezco de medios económicos para presentar la solicitud de patente

____ SI X NO

NOTA: En caso de ser persona natural y carecer de medios económicos, y por lo tanto, aplique la reducción de tasas a que se refiere la resolución vigente en tarifas, debe firmar la presente solicitud bajo la gravedad de juramento.

Micro, pequeñas y medianas empresas	Universidades públicas o privadas	Entidades sin animo de lucro
____ Copia simple de la declaración de renta del año inmediatamente anterior, o en su defecto prueba documental idónea.	____ Copia acto de reconocimiento institucional emitido por el Ministerio de Educación. Acreditación Colciencias.	____ Copia de registro vigente en Cámara de Comercio.
____ Documento de constancia de cumplimiento con lo establecido en la ley 905 de 2004.		____ Hoja de información complementaria.
		____ Otros, especificar.

14 **AUTORIZACION DE NOTIFICACION EN LINEA** ____ SI X NO

Manifiesto que he leído y entendido perfectamente los términos y condiciones de uso de medios electrónicos para las notificaciones en linea a través de Internet de los actos administrativos proferidos por la Superintendencia de Industria y Comercio que deber ser notificados personalmente y, en consecuencia, autorizo el servicio de notificación a través de internet.

14 **COMPROBANTE DE PAGO O PAGO ELECTRONICO** N° 13-004245013-004252 **Fecha:** Mayo 6 /13

15 **FIRMA DEL SOLICITANTE, DEL APODERADO O DEL REPRESENTANTE LEGAL**

Junto a cada firma, indicar el nombre del firmante y su calidad (si tal calidad no es obvia al leer el petitorio)

09 MAYO 2013

MARGARITA CASTELLANOS ABONDANO - APODERADO

16 **ORDEN Y RELACION DE DOCUMENTOS QUE ACOMPAÑAN LA SOLICITUD**

Documentación Técnica
Solicitud Internacional en Castellano

1. X Descripción N° de folios: 581
2. X Reivindicaciones N° de reivindicaciones: 22
3. ____ Dibujos y/o figuras N° de folios:
4. X Resumen
5. ____ Certificado de depósito de material biológico si fuera el caso.
6. ____ Listado de secuencias de nucleótidos y/o aminoácios en forma digital si fuera el caso.
7. ____ Arte final 12 x 12
8. X Anexo formato digital.

CDR QUE CONTIENE:
* TEXTO DE LA PUBLICACION INTERNACIONAL, CORRESPONDIENTE A LA SOLICITUD No. PCT/US2011/056045
** TEXTO EN ESPAÑOL (DESCRIP., REIV., Y RESUMEN)

Documentación Jurídica

9. X Poderes, si fuera el caso.
10. ____ Documento que legalmente pruebe la cesión del inventor al solicitante o a su causante.
11. ____ Copia del contrato de acceso de recursos genéticos o productos derivados, certificado o número de registro, si fuera el caso.
12. ____ Copia de la licencia o autorización de Conocimientos Tradicionales, certificado o número de registro, si fuera el caso.
13. ____ Documento que acredita la existencia y representación legal, cuando el solicitante es persona jurídica.
14. X Comprobante de pago de la tasa de presentación de la solicitud.
15. ____ Comprobante de pago por reivindicación de prioridad
16. ____ Comprobante de pago de la tasa por concepto de excedente de palabras en la publicación.
17. X Comprobante de pago por reivindicación adicional a 10.

Industria y Comercio
SUPERINTENDENCIA

HOJA DE INFORMACION COMPLEMENTARIA PCT

1	(12) TIPO DE SOLICITUD	NUMERO DE RADICACION
X	Patente de Invención	FECHA DE PRESENTACION
___	Patente de Modelo de Utilidad	

4 (71) SOLICITANTE(S)

	APELLIDOS O RAZON SOCIAL	NOMBRE	IDENTIFICACION	TIPO
2.				
3.				
4.				

5 DATOS DEL SOLICITANTE

	PAIS DE RESIDENCIA	DEPARTAMENTO/ESTADO	CIUDAD	DIRECCION
2.				
3.				
4.				

	TELEFONO	FAX	E-MAIL	NACIONALIDAD
2.				
3.				
4.				

6 (72) INVENTOR(ES)

	APELLIDOS	NOMBRE	NACIONALIDAD
8.	**NELSON**	**LISSA T.**	**ESTADOUNIDENSE**
9.	**PATEL**	**SACHIN V.**	**ESTADOUNIDENSE**
10.	**MATULENKO**	**MARK A.**	**ESTADOUNIDENSE**
11.	**KEDDY**	**RYAN G.**	**ESTADOUNIDENSE**
12.	**JINKERSON**	**TAMMIE K.**	**ESTADOUNIDENSE**
13.	**GAO**	**YI**	**ESTADOUNIDENSE**
14.	**LIU**	**DACHUN**	**CHINA**
15.	**PRATT**	**JOHN K.**	**ESTADOUNIDENSE**

7 DATOS INVENTOR(ES)

	DIRECCION	CIUDAD	DEPARTAMENTO/ESTADO	PAIS RESIDENCIA
8.	**640 Broadview Avenue**	**Highland Park**	**Illinois 60035**	**ESTADOS UNIDOS**
9.	**1259 S. Meadow Road**	**Round Lake**	**Illinois 60073**	**ESTADOS UNIDOS**
10.	**1875 Countryside Drive**	**Libertyville**	**Illinois 60048**	**ESTADOS UNIDOS**
11.	**10046 West Hendee Road**	**Beach Park**	**Illinois 60087**	**ESTADOS UNIDOS**
12.	**11129 10th Avenue**	**Pleasant Prairie**	**Wisconsin 53158**	**ESTADOS UNIDOS**
13.	**210 East Baltusrol Drive**	**Vernon Hills**	**Illinois 60061**	**ESTADOS UNIDOS**
14.	**1276 Georgetown Way**	**Vernon Hills**	**Illinois 60061**	**ESTADOS UNIDOS**
15.	**8210 61st Avenue**	**Kenosha**	**Wisconsin 53142**	**ESTADOS UNIDOS**

9 (30) DECLARACIONES DE PRIORIDAD

	(33) PAIS DE ORIGEN	CODIGO PAIS	(31) NUMERO	(32) FECHA (AAA/MM/DD)
4.				
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Industria y Comercio
SUPERINTENDENCIA

HOJA DE INFORMACION COMPLEMENTARIA PCT

1	(12) TIPO DE SOLICITUD	NUMERO DE RADICACION
X	Patente de Invención	FECHA DE PRESENTACION
____	Patente de Modelo de Utilidad	

4 (71) SOLICITANTE(S)

	APELLIDOS O RAZON SOCIAL	NOMBRE	IDENTIFICACION	TIPO
2.				
3.				
4.				

5 DATOS DEL SOLICITANTE

	PAIS DE RESIDENCIA	DEPARTAMENTO/ESTADO	CIUDAD	DIRECCION
2.				
3.				
4.				

	TELEFONO	FAX	E-MAIL	NACIONALIDAD
2.				
3.				
4.				

6 (72) INVENTOR(ES)

	APELLIDOS	NOMBRE	NACIONALIDAD
16	**ROCKWAY**	**TODD W.**	**ESTADOUNIDENSE**
17	**MARING**	**CLARENCE J.**	**ESTADOUNIDENSE**
18	**HUTCHINSON**	**DOUGLAS K.**	**ESTADOUNIDENSE**
19	**FLENTGE**	**CHARLES A.**	**ESTADOUNIDENSE**
20	**WAGNER**	**ROLF**	**ESTADOUNIDENSE**
21	**TUFANO**	**MICHAEL D.**	**ESTADOUNIDENSE**
22	**BETEBENNER**	**DAVID A.**	**ESTADOUNIDENSE**
23	**SARRIS**	**KATHY**	**ESTADOUNIDENSE**

7 DATOS INVENTOR(ES)

	DIRECCION	CIUDAD	DEPARTAMENTO/ESTADO	PAIS RESIDENCIA
16	**34136 N. Lavender Circle**	**Grayslake**	**Illinois 60030**	**ESTADOS UNIDOS**
17	**1228 W. Borders Drive**	**Palatine**	**Illinois 60067**	**ESTADOS UNIDOS**
18	**160 Depot Street**	**Antioch**	**Illinois 60002**	**ESTADOS UNIDOS**
19	**8628 225th Avenue**	**Salem**	**Wisconsin 53168**	**ESTADOS UNIDOS**
20	**42530 Sheridan Oaks Drive**	**Antioch**	**Illinois 60002**	**ESTADOS UNIDOS**
21	**6539 North Washtenaw**	**Chicago**	**Illinois 60645**	**ESTADOS UNIDOS**
22	**32329 N. Forest Drive**	**Grayslake**	**Illinois 60030**	**ESTADOS UNIDOS**
23	**1309 Andover Drive**	**Mundelein**	**Illinois 60060**	**ESTADOS UNIDOS**

9 (30) DECLARACIONES DE PRIORIDAD

	(33) PAIS DE ORIGEN	CODIGO PAIS	(31) NUMERO	(32) FECHA (AAA/MM/DD)
4.				
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Industria y Comercio
SUPERINTENDENCIA

HOJA DE INFORMACION COMPLEMENTARIA PCT

1	(12) TIPO DE SOLICITUD	NUMERO DE RADICACION
X	Patente de Invención	FECHA DE PRESENTACION
___	Patente de Modelo de Utilidad	

4 (71) SOLICITANTE(S)

	APELLIDOS O RAZON SOCIAL	NOMBRE	IDENTIFICACION	TIPO
2.				
3.				
4.				

5 DATOS DEL SOLICITANTE

	PAIS DE RESIDENCIA	DEPARTAMENTO/ESTADO	CIUDAD	DIRECCION
2.				
3.				
4.				

	TELEFONO	FAX	E-MAIL	NACIONALIDAD
2.				
3.				
4.				

6 (72) INVENTOR(ES)

	APELLIDOS	NOMBRE	NACIONALIDAD
24	**WOLLER**	**KEVIN R.**	**ESTADOUNIDENSE**
25	**WAGAW**	**SEBLE H.**	**ESTADOUNIDENSE**
26	**CALIFANO**	**JEAN C.**	**ESTADOUNIDENSE**
27	**LI**	**WENKE**	**ESTADOUNIDENSE**
28	**CASPI**	**DANIEL D.**	**ESTADOUNIDENSE**
29	**BELLIZZI**	**MARY E.**	**ESTADOUNIDENSE**
30	**CARROLL**	**WILLIAM A.**	**ESTADOUNIDENSE**

7 DATOS INVENTOR(ES)

	DIRECCION	CIUDAD	DEPARTAMENTO/ESTADO	PAIS RESIDENCIA
24	**1072 Joy Court**	**Antioch**	**Illinois 60002**	**ESTADOS UNIDOS**
25	**2311 Ridgeway**	**Evanston**	**Illinois 60201**	**ESTADOS UNIDOS**
26	**6167 N. Bay Ridge**	**Whitefish Bay**	**Wisconsin 53217**	**ESTADOS UNIDOS**
27	**7203 Buchanan Drive**	**Gurnee**	**Illinois 60031**	**ESTADOS UNIDOS**
28	**807 Davis Street # 912**	**Evanston**	**Illinois 60201**	**ESTADOS UNIDOS**
29	**771 N. McKinley Road**	**Lake Forest**	**Illinois 60045**	**ESTADOS UNIDOS**
30	**2325 Ridgeway Avenue**	**Evanston**	**Illinois 60201**	**ESTADOS UNIDOS**

9 (30) DECLARACIONES DE PRIORIDAD

	(33) PAIS DE ORIGEN	CODIGO PAIS	(31) NUMERO	(32) FECHA (AAA/MM/DD)
4.				
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10.				

P2826
6

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

Industria y Comercio
SUPERINTENDENCIA

RECIBO DE CAJA

No. 13 - 0042450

Bogotá D.C., Mayo 06 de 2013 - 14:49:20

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	407297881	06/05/2013	8.302.400.00

*** Conceptos Pagados ***

CANT.	RENTISTICO	CONCEPTO	Vr.UNDITARIO	Vr.CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE INVENCION	500.000.00	500.000.00
				$500.000.00

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

Responsable: _____
-*****-

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 13-116472- -00000-0000
Fecha: 2013-05-09 16:23:16 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 58

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

Industria y Comercio
SUPERINTENDENCIA

RECIBO DE CAJA

No. 13 - 0042452

Bogotá D.C., Mayo 06 de 2013 - 14:49:20

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	407297881	06/05/2013	8.302.400.00

*** Conceptos Pagados ***

CANT.	RENTISTICO	CONCEPTO	Vr.UNDITARIO	Vr.CONCEPTO
12	50005-01-01 SOLICITUDES	1607 REIVINDICACION PATENTE UNITARIA ADICIONAL A LAS 10 INIC	30.000.00	360.000.00
				$360.000.00

==========

SON: **TRESCIENTOS SESENTA MIL PESOS MONEDA CORRIENTE*

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

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 13-116472- -00000-0000
Fecha: 2013-05-09 16:23:16 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 58

COLOMBIA

PODER

El (los)

AbbVie Inc.

Domiciliados en
1 North Waukegan Road, North Chicago, IL 60064, EE. UU.

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 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 Enero 8 de 2013

en North Chicago, Illinois

por AbbVie Inc.
Perry C. Siatis – Secretaria Asistente
(El notario debe suscribir el documento en la pagina siguiente)

(Se requiere legalización consular o mediante apostilla)

POWER OF ATTORNEY

I (we) the undersigned

AbbVie Inc.

Of
1 North Waukegan Road, North Chicago, IL 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 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 8th day of Jan. 2013
in North Chicago, Illinois
by Perry C. Siatis, Assistant Secretary
For AbbVie Inc.

(Notary shall execute on the other side)

(Consular legalization or apostille is required)

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

PATENT COOPERATION TREATY PCT/US2011/056045

ADVANCE E-MAIL

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92*bis*.1 and Administrative Instructions, Section 422)

To:

ZHANG, Xu
100 Abbott Park Road
Abbott Park Road, Illinois 60064
ETATS-UNIS D'AMERIQUE

Date of mailing *(day/month/year)*
31 August 2012 (31.08.2012)

Applicant's or agent's file reference
10046WOO2

IMPORTANT NOTIFICATION

International application No.
PCT/US2011/056045

International filing date *(day/month/year)*
12 October 2011 (12.10.2011)

1. The following indications appeared on record concerning:

☒ the applicant ☐ the inventor ☐ the agent ☐ the common representative

Name and Address

ABBOTT LABORATORIES
100 Abbott Park Road
Abbott Park, Illinois 60064
United States of America

State of Nationality	State of Residence
US	US

Telephone No.

Facsimile No.

E-mail address

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person ☒ the name ☒ the address ☐ the nationality ☐ the residence

Name and Address

ABBVIE INC.
1 North Waukegan Road
North Chicago, IL 60064
United States of America

State of Nationality	State of Residence
US	US

Telephone No.

Facsimile No.

E-mail address
☐ Notifications by e-mail authorized

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

☒ the receiving Office
☐ the International Searching Authority
☐ the Authority(ies) specified for supplementary search
☐ the International Preliminary Examining Authority
☒ the designated Offices concerned
☐ the elected Offices concerned
☐ other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. +41 22 338 82 70

Authorized officer

Blanc Veronique

e-mail pt09.pct@wipo.int
Telephone No. +41 22 338 74 09

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
19 April 2012 (19.04.2012)

PCT

(10) International Publication Number
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(71) Applicant *(for all designated States except US)*: **ABBOTT LABORATORIES** [US/US]; 100 Abbott Park Road, Abbott Park, Illinois 60064 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **DEGOEY, David A.** [US/US]; 8649 226th Avenue, Salem, Wisconsin 53168 (US). **KATI, Warren M.** [US/US]; 152 Knob Hill Lane, Gurnee, Illinois 60031 (US). **HUTCHINS, Charles W.** [US/US]; 31005 Prairie Ridge Road, Green Oaks, Illinois 60048 (US). **DONNER, Pamela L.** [US/US]; 1901 McRae Lane, Mundelien, Illinois 60060 (US). **KRUEGER, Allan C.** [US/US]; 7260 Presidential Drive, Gurnee, Illinois 60031 (US). **RANDOLPH, John T.** [US/US]; 304 Broadway Avenue, Libertyville, Illinois 60048 (US). **MOTTER, Christopher E.** [US/US]; 10135 South Warwick Drive, Oak Creek, Wisconsin 53154 (US). **NELSON, Lissa T.** [US/US]; 640 Broadview Avenue, Highland Park, Illinois 60035 (US). **PATEL, Sachel V.** [US/US]; 1259 S. Meadow Road, Round Lake, Illinois 60073 (US). **MATULENKO, Mark A.** [US/US]; 1875 Countryside Drive, Libertyville, Illinois 60048 (US). **KEDDY, Ryan G.** [US/US]; 10046 West Hendce Road, Beach Park, Illinois 60087 (US). **JINKERSON, Tammie K.** [US/US]; 11129 10th Avenue, Pleasant Prairie, Wisconsin 53158 (US). **GAO, Yi** [US/US]; 210 East Baltusrol Drive, Vernon Hills, Illinois 60061 (US). **LIU, Dachun** [CN/US]; 1276 Georgetown Way, Vernon Hills, Illinois 60061 (US). **PRATT, John K.** [US/US]; 8210 61st Avenue, Kenosha, Wisconsin 53142 (US). **ROCKWAY, Todd W.** [US/US]; 34136 N. Lavender Circle, Grayslake, Illinois 60030 (US). **MARING, Clarence J.** [US/US]; 1228 W. Borders Drive, Palatine, Illinois 60067 (US). **HUTCHINSON, Douglas K.** [US/US]; 160 Depot Street, Antioch, Illinois 60002 (US). **FLENTGE, Charles A.** [US/US]; 8628 225th Avenue, Salem, Wisconsin 53168 (US). **WAGNER, Rolf** [US/US]; 42530 Sheridan Oaks Drive, Antioch, Illinois 60002 (US). **TUFANO, Michael D.** [US/US]; 6539 North Washtenaw, Chicago, Illinois 60645 (US). **BETEBENNER, David A.** [US/US]; 32329 N. Forest Drive, Grayslake, Illinois 60030 (US). **SARRIS, Kathy** [US/US]; 1309 Andover Drive, Mundelein, Illinois 60060 (US). **WOLLER, Kevin R.** [US/US]; 1072 Joy Court, Antioch, Illinois 60002 (US). **WAGAW, Sebel H.** [US/US]; 2311 Ridgeway, Evanston, Illinois 60201 (US). **CALIFANO, Jean C.** [US/US]; 6167 N. Bay Ridge, Whitefish Bay, Wisconsin 53217 (US). **LI, Wenke** [US/US]; 7203 Buchanan Drive, Gurnee, Illinois 60031 (US). **CASPI, Daniel D.** [US/US]; 807 Davis Street #912, Evanston, Illinois 60201 (US). **BELLIZZI, Mary E.** [US/US]; 771 N. McKinley Road, Lake Forest, Illinois 60045 (US). **CARROLL, William A.** [US/US]; 2325 Ridgeway Avenue, Evanston, Illinois 60201 (US).

(74) Agent: **ZHANG, Xu**; 100 Abbott Park Road, Abbott Park Road, Illinois 60064 (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.

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ANTI-VIRAL COMPOUNDS

This application claims priority from U.S. Patent Application Serial No. 13/100,827 filed May 4, 2011, U.S. Provisional Application Serial No. 61/446,800 filed February 25, 2011, U.S. Patent Application Serial No. 12/964,027 filed December 9, 2010, and U.S. Patent Application Serial No. 12/903,822 filed October 13, 2010, all of which are incorporated herein by reference in their entireties.

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.

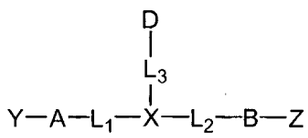
BACKGROUND

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.

The nonstructural protein NS5A is a membrane-associated phosphoprotein present in basally phosphorylated and hyperphosphorylated forms. It is a critical component of HCV replication and is believed to exert multiple functions at various stages of the viral life cycle. A full-length NS5A protein comprises three domains – namely, Domain I, Domain II, and Domain III. Domain I (residues 1 to 213) contains a zinc-binding motif and an amphipathic N-terminal helix which can promote membrane association. Domain II (residues 250 to 342) has regulatory functions, such as interactions with protein kinase PKR and PI3K, as well as NS5B, and also contains the interferon sensitivity-determining region. Domain III (residues 356 to 447) plays a role in infectious virion assembly, and can be modulated by phosphorylation within the domain. NS5A has been identified as a promising therapeutic target for treating HCV.

What is claimed is:

1. A compounds having 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 or R_F;

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 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 $-SF_5$; 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 $-O-R_S$, $-S-R_S$, $-C(O)R_S$, $-OC(O)R_S$, $-C(O)OR_S$, $-N(R_SR_S')$, $-S(O)R_S$, $-SO_2R_S$, $-C(O)N(R_SR_S')$, $-N(R_S)C(O)R_S'$, $-N(R_S)C(O)N(R_S'R_S'')$, $-N(R_S)SO_2R_S'$, $-SO_2N(R_SR_S')$, $-N(R_S)SO_2N(R_S'R_S'')$, $-N(R_S)S(O)N(R_S'R_S'')$, $-OS(O)-R_S$, $-OS(O)_2-R_S$, $-S(O)_2OR_S$, $-S(O)OR_S$, $-OC(O)OR_S$, $-N(R_S)C(O)OR_S'$, $-OC(O)N(R_SR_S')$, $-N(R_S)S(O)-R_S'$, $-S(O)N(R_SR_S')$, $-P(O)(OR_S)_2$, 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 $-N(R_SR_S')$;

R_F is independently selected at each occurrence from 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; or $-(R_X-R_Y)_Q-(R_X-R_Y')$, wherein Q is 0, 1, 2, 3 or 4, and each R_X is independently O, S or $N(R_B)$, wherein each R_Y is independently C_1-C_6alkylene, C_2-C_6alkenylene or C_2-C_6alkynylene each of which is independently optionally substituted with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl or cyano, and wherein each R_Y' is independently C_1-C_6alkyl, C_2-C_6alkenyl or C_2-

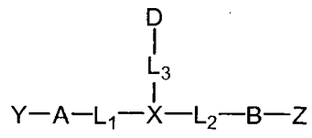
C_6alkynyl each of which is independently optionally substituted with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl or cyano;

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$$R_S$'), –S(O)$R_S$, –$SO_2R_S$, –C(O)N($R_S$$R_S$') or –N($R_S$)C(O)$R_S$'; 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; 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, –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.

2. A compounds having Formula I_E, or a pharmaceutically acceptable salt thereof,



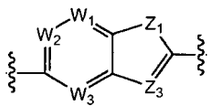
I_E

wherein:

X is 4- to 8-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 which is independently optionally substituted at each occurrence with one or more halo, hydroxy, –O–C_1-C_6alkyl, or –O–C_1-C_6haloalkyl;

L_3 is bond or C_1-C_6alkylene;

A and B are each independently phenyl, pyridinyl, thiazolyl, or  where Z_1 is independently selected at each occurrence from O, S, NH or CH_2, Z_3 is independently selected at each occurrence from N or CH, and W_1, W_2, and W_3 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.

D is C_6-C_{10}carbocycle or 5- to 12-membered heterocycle, each of which is optionally substituted with one or more R_M;

Y is –T'–$C(R_1R_2)N(R_5)$–T–R_D;

Z is –T'–$C(R_8R_9)N(R_{12})$–T–R_D;

R_1 is hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, or 3- to 6-membered carbocycle or heterocycle, wherein each said 3- to 6-membered carbocycle or heterocycle is independently optionally substituted at each occurrence with one or more substituents selected from halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, –O–C_1-C_6alkyl or –O–C_1-C_6haloalkyl;

R_2 and R_5 are each independently hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, or 3- to 6-membered carbocycle or heterocycle, wherein each said 3- to 6-membered carbocycle or heterocycle is independently optionally substituted at each occurrence with one or more substituents selected from halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, –O–C_1-C_6alkyl or –O–C_1-C_6haloalkyl; or 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_8 is hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, or 3- to 6-membered carbocycle or heterocycle, wherein each said 3- to 6-membered carbocycle or heterocycle is independently optionally substituted at each occurrence with one or more substituents selected from halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, –O–C_1-C_6alkyl or –O–C_1-C_6haloalkyl;

R_9 and R_{12} are each independently hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, or 3- to 6-membered carbocycle or heterocycle, wherein each said 3- to 6-membered carbocycle or heterocycle is independently optionally substituted at each occurrence with one or more substituents selected from halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, –O–C_1-C_6alkyl or –O–C_1-C_6haloalkyl; or 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;

T is independently selected at each occurrence from bond or –C(O)–L_S'–;

T' is independently selected at each occurrence from bond, $-C(O)N(R_B)-$, $-N(R_B)C(O)-$, or 3- to 12-membered heterocycle, wherein said 3- to 12-membered heterocycle 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 $-L_S-R_E$;

R_B and R_B' are each independently selected at each occurrence from hydrogen; or C_1-C_6alkyl which is independently optionally substituted at each occurrence with one or more substituents selected from halogen 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, C_1-C_6alkyl, C_1-C_6haloalkyl, $-O-C_1$-C_6alkyl, or $-O-C_1$-C_6haloalkyl;

R_E is independently selected at each occurrence from $-O-R_S$, $-S-R_S$, $-C(O)R_S$, $-OC(O)R_S$, $-C(O)OR_S$, $-N(R_SR_S')$, $-S(O)R_S$, $-SO_2R_S$, $-C(O)N(R_SR_S')$, $-N(R_S)C(O)R_S'$, $-N(R_S)C(O)N(R_S'R_S'')$, $-N(R_S)SO_2R_S'$, $-SO_2N(R_SR_S')$, $-N(R_S)SO_2N(R_S'R_S'')$, $-N(R_S)S(O)N(R_S'R_S'')$, $-OS(O)-R_S$, $-OS(O)_2-R_S$, $-S(O)_2OR_S$, $-S(O)OR_S$, $-OC(O)OR_S$, $-N(R_S)C(O)OR_S'$, $-OC(O)N(R_SR_S')$, $-N(R_S)S(O)-R_S'$, $-S(O)N(R_SR_S')$, $-C(O)N(R_S)C(O)-R_S'$, or $=C(R_SR_S')$; 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_{12}carbocycle or 3- to 12-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_{12}carbocycle or 3- to 12-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 is independently selected at each occurrence from bond; or C_1-C_6alkylene, C_2-C_6alkenylene or C_2-C_6alkynylene, each independently optionally substituted with halogen;

L_S' is 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;

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_6haloalkyl, or 3- to 12-membered carbocycle or heterocycle; or 3- to 12-membered carbocycle or heterocycle; wherein each 3- to 12-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;

R_M is independently selected at each occurrence from:

halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, cyano, SF_5, –N($R_S$$R_S$'), –O–$R_S$, –OC(O)$R_S$, –OC(O)O$R_S$, –OC(O)N($R_S$$R_S$'), –C(O)$R_S$, –C(O)O$R_S$, –C(O)N($R_S$$R_S$'), –N($R_S$)C(O)$R_S$', –N($R_S$)C(O)O$R_S$', –N($R_S$)$SO_2$$R_S$', –S(O)$R_S$, –$SO_2$$R_S$, –S(O)N($R_S$$R_S$'), –S$R_S$, –Si($R_S$)$_3$, or –P(O)(O$R_S$)$_2$;

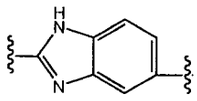
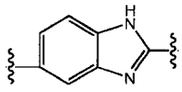
C_1-C_6alkyl, C_2-C_6alkenyl or C_2-C_6alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, –N($R_S$$R_S$'), –O–$R_S$, –OC(O)$R_S$, –OC(O)O$R_S$, –OC(O)N($R_S$$R_S$'), –C(O)$R_S$, –C(O)O$R_S$, –C(O)N($R_S$$R_S$'), –N($R_S$)C(O)$R_S$', –N($R_S$)C(O)O$R_S$', –N($R_S$)$SO_2$$R_S$', –S(O)$R_S$, –$SO_2$$R_S$, –S(O)N($R_S$$R_S$'), –S$R_S$, or –P(O)(O$R_S$)$_2$; or

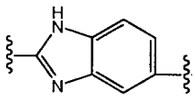
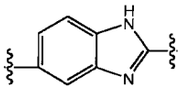
G_2, wherein G_2 is a C_3-C_{12}carbocycle or 3- to 12-membered heterocycle, each of which is independently optionally substituted at each occurrence with one or more R_{G2}, and each R_{G2} is independently selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, 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, –O–R_S, –C(O)OR_S, –C(O)R_S, –N($R_S$$R_S$'), or –$L_4$–$G_3$;

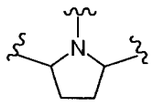
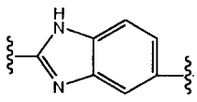
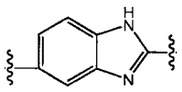
L_4 is a bond, C_1-C_6alkylene, C_2-C_6alkenylene, C_2-C_6alkynylene, –O–, –S–, –N(R_B)–, –C(O)–, –S(O)$_2$–, –S(O)–, –C(O)O–, –OC(O)–, –OC(O)O–, –C(O)N(R_B)–, –N(R_B)C(O)–, –N(R_B)C(O)O–, –OC(O)N(R_B)–, –N(R_B)S(O)–, –N(R_B)S(O)$_2$–, –S(O)N(R_B)–, –S(O)$_2$N(R_B)–, –N(R_B)C(O)N(R_B')–, –N(R_B)SO_2N(R_B')–, or –N(R_B)S(O)N(R_B')–;

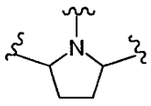
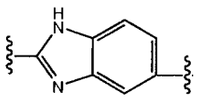
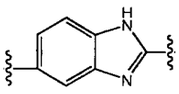
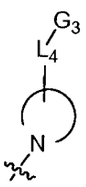
G_3 is a C_3-C_{12}carbocycle or 3- to 12-membered heterocycle, and is optionally substituted with one or more R_{G3}; and

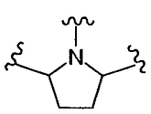
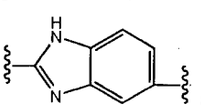
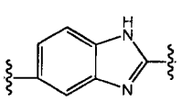
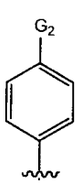
R_{G3} is each independently, at each occurrence, halogen, $-C_1$-C_6alkyl, $-C(O)C_1$-C_6alkyl, $-C_1$-C_6haloalkyl, $-O-C_1$-C_6alkyl, $-O-C_1$-C_6haloalkyl, C_3-C_6carbocycle, or 3- to 6-membered heterocycle.

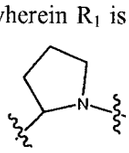
3. The compound or salt according to claim 2, wherein A is  and is optionally substituted with one or more R_A, and B is  and is optionally substituted with one or more R_A, and D is C_6-C_{10}aryl or 5- to 10-membered heteroaryl and is substituted with one or more R_M.

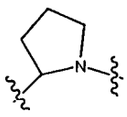
4. The compound or salt according to claim 2, wherein A is  and is optionally substituted with one or more R_A, and B is  and is optionally substituted with one or more R_A, and D is phenyl or pyridyl and is substituted by one or more R_M, wherein at least one R_M is G_2 which is substituted with L_4–G_3 and optionally substituted with one or more R_{G2}.

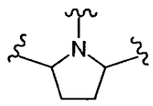
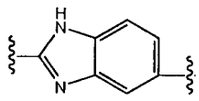
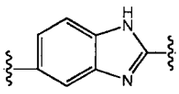
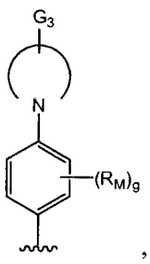
5. The compound or salt according to claim 2, wherein X is  and is optionally substituted with one or more R_A, A is  and is optionally substituted with one or more R_A, and B is  and is optionally substituted with one or more R_A, and D is phenyl or pyridyl and is substituted by one or more R_M, and wherein at least one R_M is  which is a monocyclic 4-8 membered nitrogen-containing heterocycle optionally substituted with one or more R_{G2}.

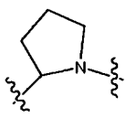
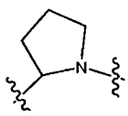
6. The compound or salt according to claim 2, wherein X is  and is optionally substituted with one or more R_A, A is  and is optionally substituted with one or more R_A, and B is  and is optionally substituted with one or more R_A, and D is phenyl or pyridyl and is substituted by one or more R_M, and at least one R_M is  , wherein  is a monocyclic 4-8 membered nitrogen-containing heterocycle optionally substituted with one or more R_{G2}.

7. The compound or salt according to claim 2, wherein X is  and is optionally substituted with one or more R_A, A is  and is optionally substituted with one or more R_A, and B is  and is optionally substituted with one or more R_A, and D is  and is optionally substituted by one or more additional R_M.

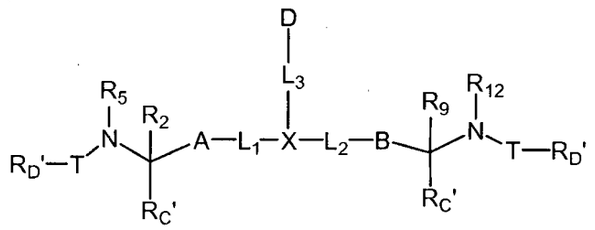
8. The compound or salt according to claim 7, wherein R_1 is hydrogen, and R_2 and R_5 taken together with the atoms to which they are attached form  which is substituted with 0, 1, 2, 3, or 4 R_A, wherein R_8 is hydrogen, and R_9 and R_{12} taken together with the atoms to which

they are attached form  which is substituted with 0, 1, 2, 3, or 4 R_A, and wherein each T' is bond.

9. The compound or salt according to claim 2, wherein X is  and is optionally substituted with one or more R_A, A is  and is optionally substituted with one or more R_A, and B is  and is optionally substituted with one or more R_A, and D is  , wherein G_3 is phenyl optionally substituted with one or two R_{G3}; g is 0, 1, or 2; R_M is each independently fluoro, chloro, methyl, methoxy, trifluoromethyl, or trifluoromethoxy; and  is a monocyclic 4-8 membered nitrogen-containing heterocycle optionally substituted with one or more R_{G2}.

10. The compound or salt according to claim 9, wherein R_1 is hydrogen, and R_2 and R_5 taken together with the atoms to which they are attached form  which is substituted with 0, 1, 2, 3, or 4 R_A, wherein R_8 is hydrogen, and R_9 and R_{12} taken together with the atoms to which they are attached form  which is substituted with 0, 1, 2, 3, or 4 R_A, and wherein each T' is bond.

11. A compounds having Formula I_B, or a pharmaceutically acceptable salt thereof,



I_B

wherein:

R_C' is each independently selected from R_C;

R_D' is each independently selected from R_D;

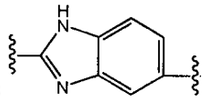
R_2 and R_5, taken together with the atoms to which they are attached, form a 3- to 12-membered heterocycle which is optionally substituted with one or more R_A;

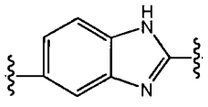
R_9 and R_{12}, taken together with the atoms to which they are attached, form a 3- to 12-membered heterocycle which is optionally substituted with one or more R_A;

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

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 is  and is optionally substituted with one or more R_A;

B is  and is optionally substituted with one or more R_A;

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;

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, 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_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$'), –P(O)($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 $-N(R_SR_S')$;

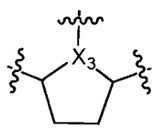
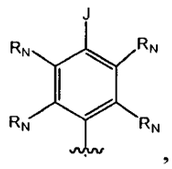
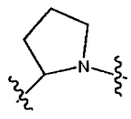
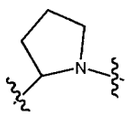
R_F is independently selected at each occurrence from C_1-C_{10}alkyl, C_2-C_{10}alkenyl or C_2-C_{10}alkynyl, each of which contains 0, 1, 2, 3, 4 or 5 heteroatoms selected from O, S or N and is optionally substituted with one or more R_L; or $-(R_X-R_Y)_Q-(R_X-R_Y')$, wherein Q is 0, 1, 2, 3 or 4, and each R_X is independently O, S or $N(R_B)$, wherein each R_Y is independently C_1-C_6alkylene, C_2-C_6alkenylene or C_2-C_6alkynylene each of which is independently optionally substituted with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl or cyano, and wherein each R_Y' is independently C_1-C_6alkyl, C_2-C_6alkenyl or C_2-C_6alkynyl each of which is independently optionally substituted with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl or cyano;

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 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; 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, –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.

12. The compound or salt according to claim 11, wherein X is  and is optionally substituted with one or more R_A or R_F, and X_3 is N and is directly linked to –L_3–D, wherein L_1, L_2 and L_3 are bond, wherein D is  , and each R_N is independently R_D, wherein J is C_3-C_6carbocycle or 3- to 6-membered heterocycle and is substituted with a C_3-C_6carbocycle or 3- to 6-membered heterocycle which is independently 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, C_2-C_6haloalkynyl, C(O)OR_S or –N($R_S$$R_S$'), and J is optionally substituted with one or more R_A, wherein 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, wherein 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, wherein -T-R_D' is –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', and wherein L_Y' is each independently L_S'.

13. A process of making a compound of the invention, comprising a step described in one of the Schemes, General Procedures or Examples described herein.

14. An intermediate described in one of Schemes, General Procedures or Examples described herein.

15. methyl {(2*S*,3*R*)-1-[(2*S*)-2-{5-[(2*R*,5*R*)-1-{3,5-difluoro-4-[4-(4-fluorophenyl)piperidin-1-yl]phenyl}-5-(6-fluoro-2-{(2*S*)-1-[*N*-(methoxycarbonyl)-*O*-methyl-L-threonyl]pyrrolidin-2-yl}-1*H*-benzimidazol-5-yl)pyrrolidin-2-yl]-6-fluoro-1*H*-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methoxy-1-oxobutan-2-yl}carbamate, or a pharmaceutically acceptable salt thereof.

16. A pharmaceutical composition comprising the compound of claim 15 or said salt.

17. methyl {(2*S*)-1-[(2*S*)-2-{5-[(2*R*,5*R*)-1-[3,5-difluoro-4-(4-phenylpiperidin-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, or a pharmaceutically acceptable salt thereof.

18. A pharmaceutical composition comprising the compound of claim 17 or said salt.

19. methyl {(2*S*,3*R*)-1-[(2*S*)-2-{5-[(2*R*,5*R*)-1-{4-[4-(2,6-difluorophenyl)piperazin-1-yl]-3,5-difluorophenyl}-5-(6-fluoro-2-{(2*S*)-1-[*N*-(methoxycarbonyl)-*O*-methyl-L-threonyl]pyrrolidin-2-yl}-1*H*-benzimidazol-5-yl)pyrrolidin-2-yl]-6-fluoro-1*H*-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methoxy-1-oxobutan-2-yl}carbamate, or a pharmaceutically acceptable salt thereof.

20. A pharmaceutical composition comprising the compound of claim 19 or said salt.

21. methyl {(2*S*)-1-[(2*S*)-2-{5-[(2*R*,5*R*)-1-(4-*tert*-butylphenyl)-5-{5-fluoro-2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1*H*-benzimidazol-6-yl}pyrrolidin-2-yl]-6-fluoro-1*H*-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate, or a pharmaceutically acceptable salt thereof.

22. A pharmaceutical composition comprising the compound of claim 21 or said salt.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2011/056045

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D403/14 C07D401/14 C07D417/14 A61K31/4184 A61K31/4439
A61K31/454 A61K31/506 A61K31/496 A61K31/4178 A61P31/14
ADD.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2008/144380 A1 (SQUIBB BRISTOL MYERS CO [US]; BACHAND CAROL [CA]; BELEMA MAKONEN [US];) 27 November 2008 (2008-11-27)	1,13,14
A	see compounds of claim 1 and e.g. examples 30, 31, 33, 34, 36 and 37 as inhibitors of HCV replication -----	11
X,P	WO 2010/144646 A2 (ABBOTT LAB [US]; DEGOEY DAVID A [US]; KATI WARREN M [US]; HUTCHINS CHA) 16 December 2010 (2010-12-16) see the claims, the examples and the pharmacological acitivity as inhibitors of HCV replication -----	1-22

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
5 March 2012	02/04/2012

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

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

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2011/056045

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1, 11, 13, 14(all partially)

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2011/056045

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2008144380 A1	27-11-2008	CN 101754966 A	23-06-2010
		EP 2146984 A1	27-01-2010
		JP 2010527373 A	12-08-2010
		US 2008311075 A1	18-12-2008
		WO 2008144380 A1	27-11-2008
WO 2010144646 A2	16-12-2010	AR 077060 A1	27-07-2011
		AU 2010258769 A1	16-12-2010
		CA 2737601 A1	16-12-2010
		CN 102333772 A	25-01-2012
		DO P2011000087 A	30-04-2011
		EA 201170401 A1	31-10-2011
		EC SP110937 A	31-05-2011
		EP 2337781 A2	29-06-2011
		EP 2368890 A1	28-09-2011
		PE 06792011 A1	20-10-2011
		SG 171708 A1	28-07-2011
		TW 201102063 A	16-01-2011
		US 2010317568 A1	16-12-2010
		UY 32699 A	31-12-2010
		WO 2010144646 A2	16-12-2010

International Application No. PCT/ US2011/ 056045

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1, 11, 13, 14(all partially)

   Claims 1, 13 and 14 (all of them partly), i.e. compounds of formula I wherein X is a carbocycle and process for preparation

   ---

2. claims: 2-10, 12, 15-22(completely); 1, 11, 13, 14(partially)

   Claims 2 to 10, 13 and 14 (all partly), i.e. the compounds of formula I wherein X is a heterocycle and process for preparation

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COMPUESTOS ANTIVIRALES

Esta Solicitud invoca la prioridad de la Solicitud de la Patente de los EE.UU. N° Acta: 13/100.827, presentada el 4 de mayo, 2011, la Solicitud Provisional de Patente de los EE.UU. N° Acta: 61/446.800, presentada el 25 de febrero, 2011, la Solicitud de Patente de los EE.UU. N° Acta: 12/964.027, presentada el 9 de diciembre, 2010, y la Solicitud de Patente de los EE.UU. N° Acta: 12/903.822, presentada el 13 de octubre, 2010, cuya divulgación pompleta se incorpora a la presente a modo de referencia.

CAMPO DE LA INVENCIÓN

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 proteína no estructural NS5A es una fosfoproteína asociada a membrana presente en las formas basalmente fosforiladas e hiperfosforiladas. Es un componente crítico de la replicación del HCV y se cree que ejerce múltiples funciones en diversas etapas del ciclo de vida viral. Una proteína NS5A de longitud completa comprende tres dominios, a saber, el Dominio I, el Dominio II y el Dominio III. El Dominio I (residuos 1 a 213) contiene un motivo de unión a zinc y una hélice anfipática N-terminal que puede

promover la asociación a membrana. El Dominio II (residuos 250 a 342) tiene funciones reguladoras, tales como interacciones con las proteína quinasas PKR y PI3K, así como NS5B, y también contiene a la región determinante de sensibilidad al interferón. El Dominio III (residuos 356 a 447) cumple un rol en el ensamblaje del virión infeccioso, y puede ser modulado por fosforilación dentro del dominio. La NS5A ha sido identificada como un blanco terapéutico promisorio para el tratamiento del HCV.

RESUMEN

La presente invención está dirigida a compuestos de las fórmulas I, IA, IB, IC, ID, IE, IF y IG 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.

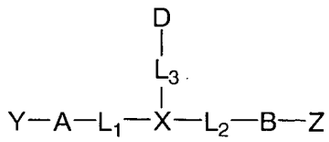
La presente invención también está dirigida a composiciones que comprenden los compuestos o las sales de la presente invención. Las composiciones también pueden incluir agentes terapéuticos adicionales, tales como inhibidores de helicasa del HCV, inhibidores de polimerasa del HCV, inhibidores de proteasa 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

REIVINDICACIONES

1. Un compuesto CARACTERIZADO PORQUE es de Fórmula I, o una sal aceptable farmacéuticamente del mismo,



I

donde:

X es C3-C12carbociclo o heterociclo de entre 3 y 12 miembros, y está opcionalmente sustituido con uno o más RA o RF;

L1 y L2 se seleccionan en forma independiente entre sí entre un enlace; o C1-C6alquileno, C2-C6alquenileno o C2-C6alquinileno, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más RL;

L3 es un enlace o –LS–K–LS'–, donde K se selecciona entre un enlace, –O–, –S–, –N(RB)–, –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(RB)–, –N(RB)C(O)–, –N(RB)C(O)O–, –OC(O)N(RB)–, –N(RB)S(O)–, –N(RB)S(O)2–, –S(O)N(RB)–, –S(O)2N(RB)–, –C(O)N(RB)C(O)–, –N(RB)C(O)N(RB')–, –N(RB)SO2N(RB')–, o –N(RB)S(O)N(RB')–;

A y B son en forma independiente entre sí C3-C12carbociclo o heterociclo de entre 3 y 12 miembros, y están opcionalmente sustituidos en forma independiente entre sí con uno o más RA;

D es C3-C12carbociclo o heterociclo de entre 3 y 12 miembros, y está opcionalmente sustituido con uno o más RA; o D es C3-C12carbociclo o heterociclo de entre 3 y 12 miembros que está sustituido con J y opcionalmente sustituido con uno o más RA, donde J es C3-C12carbociclo o

heterociclo de entre 3 y 12 miembros y está opcionalmente sustituido con uno o más RA, o J es –SF5; o D es hidrógeno o RA;

Y se selecciona entre –T'–C(R1R2)N(R5)–T–RD, –T'–C(R3R4)C(R6R7)–T–RD, –LK–T–RD, o –LK–E;

R1 y R2 son en forma independiente entre sí RC, y R5 es RB; o R1 es RC, y R2 y R5, tomados junto con los átomos a los cuales están unidos, forman un heterociclo de entre 3 y 12 miembros que está opcionalmente sustituido con uno o más RA;

R3, R4, R6, y R7 son en forma independiente entre sí RC; o R3 y R6 son en forma independiente entre sí RC, y R4 y R7, tomados junto con los átomos a los cuales están unidos, forman un carbociclo o heterociclo de entre 3 y 12 miembros que está opcionalmente sustituido con uno o más RA;

Z se selecciona entre –T'–C(R8R9)N(R12)–T–RD, –T'–C(R10R11)C(R13R14)–T–RD, –LK–T–RD, o –LK–E;

R8 y R9 son en forma independiente entre sí RC, y R12 es RB; o R8 es RC, y R9 y R12, tomados junto con los átomos a los cuales están unidos, forman un heterociclo de entre 3 y 12 miembros que está opcionalmente sustituido con uno o más RA;

R10, R11, R13, y R14 son en forma independiente entre sí RC; o R10 y R13 son en forma independiente entre sí RC, y R11 y R14, tomados junto con los átomos a los cuales están unidos, forman un carbociclo o heterociclo de entre 3 y 12 miembros que está opcionalmente sustituido con uno o más RA;

T y T' se seleccionan en forma independiente entre sí en cada caso entre un enlace, –LS–, –LS–M–LS'–, o –LS–M–LS'–M'–LS''–, donde M y M' se seleccionan en forma independiente entre sí en cada caso entre un enlace, –O–, –S–, –N(RB)–, –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(RB)–, –N(RB)C(O)–, –

N(RB)C(O)O–, –OC(O)N(RB)–, –N(RB)S(O)–, –N(RB)S(O)2–, –S(O)N(RB)–, –S(O)2N(RB)–, –C(O)N(RB)C(O)–, –N(RB)C(O)N(RB')–, –N(RB)SO2N(RB')–, –N(RB)S(O)N(RB')–, C3-C12carbociclo o heterociclo de entre 3 y 12 miembros, y donde dicho C3-C12carbociclo y heterociclo de entre 3 y 12 miembros están opcionalmente sustituidos en forma independiente entre sí en cada caso con uno o más RA;

LK se selecciona en forma independiente en cada caso entre un enlace, –LS–N(RB)C(O)–LS'– o –LS–C(O)N(RB)–LS'–; o C1-C6alquileno, C2-C6alquenileno o C2-C6alquinileno, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más RL; o C3-C12carbociclo o heterociclo de entre 3 y 12 miembros, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más RA;

E se selecciona en forma independiente en cada caso entre C3-C12carbociclo o heterociclo de entre 3 y 12 miembros, y está opcionalmente sustituido en forma independiente en cada caso con uno o más RA;

RD se selecciona en forma independiente en cada caso entre hidrógeno o RA;

RA se selecciona en forma independiente en cada caso entre halógeno, nitro, oxo, fosfonoxi, fosfono, tioxo, ciano, o –LS–RE, donde dos RA adyacentes, tomados junto con los átomos a los cuales están unidos y cualquier otro átomo entre los átomos a los cuales están unidos, pueden formar opcionalmente carbociclo o heterociclo;

RB y RB' se seleccionan en forma independiente entre sí en cada caso entre hidrógeno; o C1-C6alquilo, C2-C6alquenilo o C2-C6alquinilo, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano o carbociclo o

heterociclo de entre 3 y 6 miembros; o carbociclo o heterociclo de entre 3 y 6 miembros; donde cada carbociclo o heterociclo de entre 3 y 6 miembros en RB o RB' está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C1-C6alquilo, C2-C6alquenilo, C2-C6alquinilo, C1-C6haloalquilo, C2-C6haloalquenilo o C2-C6haloalquinilo;

RC se selecciona en forma independiente en cada caso entre hidrógeno, halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo o ciano; o C1-C6alquilo, C2-C6alquenilo o C2-C6alquinilo, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano o carbociclo o heterociclo de entre 3 y 6 miembros; o carbociclo o heterociclo de entre 3 y 6 miembros; donde cada carbociclo o heterociclo de entre 3 y 6 miembros en RC está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C1-C6alquilo, C2-C6alquenilo, C2-C6alquinilo, C1-C6haloalquilo, C2-C6haloalquenilo o C2-C6haloalquinilo;

RE se selecciona en forma independiente en cada caso entre –O–RS, –S–RS, –C(O)RS, –OC(O)RS, –C(O)ORS, –N(RSRS'), –S(O)RS, –SO2RS, –C(O)N(RSRS'), –N(RS)C(O)RS', –N(RS)C(O)N(RS'RS''), –N(RS)SO2RS', –SO2N(RSRS'), –N(RS)SO2N(RS'RS''), –N(RS)S(O)N(RS'RS''), –OS(O)–RS, –OS(O)2–RS, –S(O)2ORS, –S(O)ORS, –OC(O)ORS, –N(RS)C(O)ORS', –OC(O)N(RSRS'), –N(RS)S(O)–RS', –S(O)N(RSRS'), –P(O)(ORS)2, o –C(O)N(RS)C(O)–RS'; o C1-C6alquilo, C2-C6alquenilo o C2-C6alquinilo, cada

uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo o ciano; o C3-C6carbociclo o heterociclo de entre 3 y 6 miembros, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C1-C6alquilo, C2-C6alquenilo, C2-C6alquinilo, C1-C6haloalquilo, C2-C6haloalquenilo, C2-C6haloalquinilo, C(O)ORS, o –N(RSRS');

RF se selecciona en forma independiente en cada caso entre C1-C10alquilo, C2-C10alquenilo o C2-C10alquinilo, cada uno de los cuales contiene 0, 1, 2, 3, 4 o 5 herteroátomos seleccionados entre O, S o N y está opcionalmente sustituido con uno o más RL; o –(RX–RY)Q–(RX–RY'), donde Q es 0, 1, 2, 3 o 4, y cada RX es en forma independiente O, S o N(RB), donde cada RY es en forma independiente C1-C6alquileno, C2-C6alquenileno o C2-C6alquinileno cada uno de los cuales está opcionalmente sustituido en forma independiente con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo o ciano, y donde cada RY' es en forma independiente C1-C6alquilo, C2-C6alquenilo o C2-C6alquinilo cada uno de los cuales está opcionalmente sustituido en forma independiente con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo o ciano;

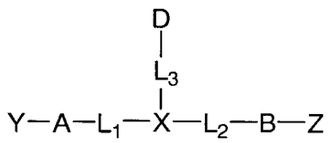
RL se selecciona en forma independiente en cada caso entre halógeno, nitro, oxo, fosfonoxi, fosfono, tioxo, ciano, –O–RS, –S–RS, –C(O)RS, –OC(O)RS, –C(O)ORS, –N(RSRS'), –S(O)RS, –SO2RS, –C(O)N(RSRS') o –N(RS)C(O)RS'; o C3-C6carbociclo o heterociclo de entre 3 y 6 miembros, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con

uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C1-C6alquilo, C2-C6alquenilo, C2-C6alquinilo, C1-C6haloalquilo, C2-C6haloalquenilo o C2-C6haloalquinilo; donde dos RL adyacentes, tomados junto con los átomos a los cuales están unidos y cualquier otro átomo entre los átomos a los cuales están unidos, pueden formar opcionalmente carbociclo o heterociclo;

LS, LS' y LS'' se seleccionan en forma independiente entre sí en cada caso entre un enlace; o C1-C6alquileno, C2-C6alquenileno o C2-C6alquinileno, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más RL; y

RS, RS' y RS'' se seleccionan en forma independiente entre sí en cada caso entre hidrógeno; C1-C6alquilo, C2-C6alquenilo o C2-C6alquinilo, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, –O–C1-C6alquilo, –O–C1-C6alquilen–O–C1-C6alquilo, o carbociclo o heterociclo de entre 3 y 6 miembros; o carbociclo o heterociclo de entre 3 y 6 miembros; donde cada carbociclo o heterociclo de entre 3 y 6 miembros en RS , RS' o RS' está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C1-C6alquilo, C2-C6alquenilo, C2-C6alquinilo, C1-C6haloalquilo, C2-C6haloalquenilo o C2-C6haloalquinilo.

2. Un compuesto CARACTERIZADO PORQUE es de Fórmula IE, o una sal aceptable farmacéuticamente del mismo,



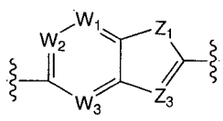
IE

donde:

X es heterociclo de entre 4 y 8 miembros, y está opcionalmente sustituido con uno o más RA;

L1 y L2 se seleccionan en forma independiente entre sí entre un enlace o C1-C6alquileno que está opcionalmente sustituido en forma independiente en cada caso con uno o más halo, hidroxi, –O–C1-C6alquilo, o –O–C1-C6haloalquilo;

L3 es un enlace o C1-C6alquileno;

A y B son en forma independiente entre sí fenilo, piridinilo, tiazolilo, o  donde Z1 se selecciona en forma independiente en cada caso entre O, S, NH o CH2, Z3 se selecciona en forma independiente en cada caso entre N o CH, y W1, W2, y W3 se seleccionan en forma independiente entre sí en cada caso entre CH o N; A y B están opcionalmente sustituidos en forma independiente entre sí con uno o más RA.

D es C6-C10carbociclo o heterociclo de entre 5 y 12 miembros, cada uno de los cuales está opcionalmente sustituido con uno o más RM;

Y es –T'–C(R1R2)N(R5)–T–RD;

Z es –T'–C(R8R9)N(R12)–T–RD;

R1 es hidrógeno, C1-C6alquilo, C1-C6haloalquilo, o carbociclo o heterociclo de entre 3 y 6 miembros, donde cada carbociclo o heterociclo de entre 3 y 6 miembros está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, C1-C6alquilo, C1-

C6haloalquilo, –O–C1-C6alquilo o –O–C1-C6haloalquilo;

R2 y R5 son en forma independiente entre sí hidrógeno, C1-C6alquilo, C1-C6haloalquilo, o carbociclo o heterociclo de entre 3 y 6 miembros, donde cada carbociclo o heterociclo de entre 3 y 6 miembros está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, C1-C6alquilo, C1-C6haloalquilo, –O–C1-C6alquilo o –O–C1-C6haloalquilo; o R2 y R5, tomados junto con los átomos a los cuales están unidos, forman un heterociclo de entre 3 y 12 miembros que está opcionalmente sustituido con uno o más RA;

R8 es hidrógeno, C1-C6alquilo, C1-C6haloalquilo, o carbociclo o heterociclo de entre 3 y 6 miembros, donde cada carbociclo o heterociclo de entre 3 y 6 miembros está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, C1-C6alquilo, C1-C6haloalquilo, –O–C1-C6alquilo o –O–C1-C6haloalquilo;

R9 y R12 son en forma independiente entre sí hidrógeno, C1-C6alquilo, C1-C6haloalquilo, o carbociclo o heterociclo de entre 3 y 6 miembros, donde cada carbociclo o heterociclo de entre 3 y 6 miembros está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, C1-C6alquilo, C1-C6haloalquilo, –O–C1-C6alquilo o –O–C1-C6haloalquilo; o R9 y R12, tomados junto con los átomos a los cuales están unidos, forman un heterociclo de entre 3 y 12 miembros que está opcionalmente sustituido con uno o más RA;

T se selecciona en forma independiente en cada caso entre un enlace o –C(O)–LS'–;

T' se selecciona en forma independiente en cada caso entre un enlace, –C(O)N(RB)–, –N(RB)C(O)–, o heterociclo de entre 3 y 12 miembros, donde dicho heterociclo de entre 3 y 12 miembros está opcionalmente sustituido en

forma independiente en cada caso con uno o más RA;

RD se selecciona en forma independiente en cada caso entre hidrógeno o RA;

RA se selecciona en forma independiente en cada caso entre halógeno, nitro, oxo, fosfonoxi, fosfono, tioxo, ciano, o –LS–RE;

RB y RB' se seleccionan en forma independiente entre sí en cada caso entre hidrógeno; o C1-C6alquilo que está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno o carbociclo o heterociclo de entre 3 y 6 miembros; o carbociclo o heterociclo de entre 3 y 6 miembros; donde cada carbociclo o heterociclo de entre 3 y 6 miembros en RB o RB' está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, C1-C6alquilo, C1-C6haloalquilo, –O–C1-C6alquilo, o –O–C1-C6haloalquilo;

RE se selecciona en forma independiente en cada caso entre –O–RS, –S–RS, –C(O)RS, –OC(O)RS, –C(O)ORS, –N(RSRS'), –S(O)RS, –SO2RS, –C(O)N(RSRS'), –N(RS)C(O)RS', –N(RS)C(O)N(RS'RS''), –N(RS)SO2RS', –SO2N(RSRS'), –N(RS)SO2N(RS'RS''), –N(RS)S(O)N(RS'RS''), –OS(O)–RS, –OS(O)2–RS, –S(O)2ORS, –S(O)ORS, –OC(O)ORS, –N(RS)C(O)ORS', –OC(O)N(RSRS'), –N(RS)S(O)–RS', –S(O)N(RSRS'), –C(O)N(RS)C(O)–RS', o =C(RSRS'); o C1-C6alquilo, C2-C6alquenilo o C2-C6alquinilo, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo o ciano; o C3-C12carbociclo o heterociclo de entre 3 y 12 miembros, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C1-C6alquilo, C2-

C6alquenilo, C2-C6alquinilo, C1-C6haloalquilo, C2-C6haloalquenilo o C2-C6haloalquinilo;

RL se selecciona en forma independiente en cada caso entre halógeno, nitro, oxo, fosfonoxi, fosfono, tioxo, ciano, –O–RS, –S–RS, –C(O)RS, –OC(O)RS, –C(O)ORS, –N(RSRS'), –S(O)RS, –SO2RS, –C(O)N(RSRS'), o –N(RS)C(O)RS'; o C3-C12carbociclo o heterociclo de entre 3 y 12 miembros, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C1-C6alquilo, C2-C6alquenilo, C2-C6alquinilo, C1-C6haloalquilo, C2-C6haloalquenilo o C2-C6haloalquinilo;

LS se selecciona en forma independiente en cada caso entre un enlace; o C1-C6alquileno, C2-C6alquenileno o C2-C6alquinileno, cada opcionalmente sustituido en forma independiente con halógeno;

LS' se selecciona en forma independiente en cada caso entre un enlace; o C1-C6alquileno, C2-C6alquenileno o C2-C6alquinileno, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más RL;

RS, RS' y RS'' se seleccionan en forma independiente entre sí en cada caso entre hidrógeno; C1-C6alquilo, C2-C6alquenilo o C2-C6alquinilo, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, –O–C1-C6alquilo, –O–C1-C6haloalquilo, o carbociclo o heterociclo de entre 3 y 12 miembros; o carbociclo o heterociclo de entre 3 y 12 miembros; donde cada carbociclo o heterociclo de entre 3 y 12 miembros en RS , RS' o RS'' está opcionalmente sustituido en forma independiente en cada caso con uno o más

sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C1-C6alquilo, C2-C6alquenilo, C2-C6alquinilo, C1-C6haloalquilo, C2-C6haloalquenilo o C2-C6haloalquinilo;

RM se selecciona en forma independiente en cada caso entre:

halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, ciano, SF5, –N(RSRS'), –O–RS, –OC(O)RS, –OC(O)ORS, –OC(O)N(RSRS'), –C(O)RS, –C(O)ORS, –C(O)N(RSRS'), –N(RS)C(O)RS', –N(RS)C(O)ORS', –N(RS)SO2RS', –S(O)RS, –SO2RS, –S(O)N(RSRS'), –SRS, –Si(RS)3, o –P(O)(ORS)2;

C1-C6alquilo, C2-C6alquenilo o C2-C6alquinilo, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, –N(RSRS'), –O–RS, –OC(O)RS, –OC(O)ORS, –OC(O)N(RSRS'), –C(O)RS, –C(O)ORS, –C(O)N(RSRS'), –N(RS)C(O)RS', –N(RS)C(O)ORS', –N(RS)SO2RS', –S(O)RS, –SO2RS, –S(O)N(RSRS'), –SRS, o –P(O)(ORS)2; o

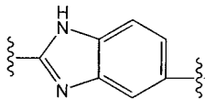
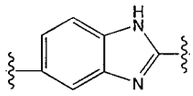
G2, donde G2 es un C3-C12carbociclo o heterociclo de entre 3 y 12 miembros, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más RG2, y cada RG2 se selecciona en forma independiente entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C1-C6alquilo, C2-C6alquenilo, C2-C6alquinilo, C1-C6haloalquilo, C2-C6haloalquenilo, C2-C6haloalquinilo, –O–RS, –C(O)ORS, –C(O)RS, –N(RSRS'), o –L4–G3;

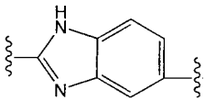
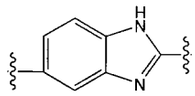
L4 es una unión, C1-C6alquileno, C2-C6alquenileno, C2-C6alquinileno, –O–, –S–, –N(RB)–, –C(O)–, –S(O)2–, –S(O)–, –C(O)O–, –OC(O)–, –OC(O)O–, –

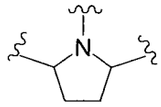
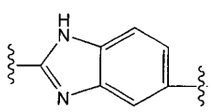
C(O)N(RB)–, –N(RB)C(O)–, –N(RB)C(O)O–, –OC(O)N(RB)–, –N(RB)S(O)–, –N(RB)S(O)2–, –S(O)N(RB)–, –S(O)2N(RB)–, –N(RB)C(O)N(RB')–, –N(RB)SO2N(RB')–, o –N(RB)S(O)N(RB')–;

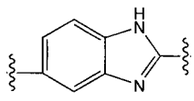
G3 es un C3-C12carbociclo o heterociclo de entre 3 y 12 miembros, y está opcionalmente sustituido con uno o más RG3; y

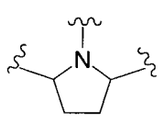
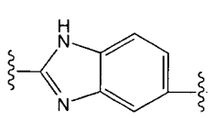
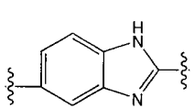
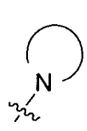
RG3 es cada en forma independiente, en cada caso, halógeno, –C1-C6alquilo, –C(O)C1-C6alquilo, –C1-C6haloalquilo, –O–C1-C6alquilo, –O–C1-C6haloalquilo, C3-C6carbociclo, o heterociclo de entre 3 y 6 miembros.

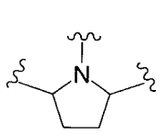
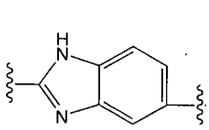
3. El compuesto o sal de acuerdo con la reivindicación 2, CARACTERIZADO PORQUE A es  y está opcionalmente sustituido con uno o más RA, y B es  y está opcionalmente sustituido con uno o más RA, y D es C6-C10arilo o heteroarilo de entre 5 y 10 miembros y está sustituido con uno o más RM.

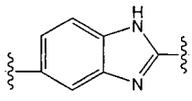
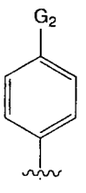
4. El compuesto o sal de acuerdo con la reivindicación 2, CARACTERIZADO PORQUE A es  y está opcionalmente sustituido con uno o más RA, y B es  y está opcionalmente sustituido con uno o más RA, y D es fenilo o piridilo y está sustituido con uno o más RM, donde al menos un RM es G2 que está sustituido con L4–G3 y opcionalmente sustituido con uno o más RG2.

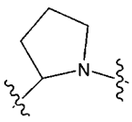
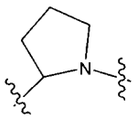
5. El compuesto o sal de acuerdo con la reivindicación 2, CARACTERIZADO PORQUE X es  y está opcionalmente sustituido con uno o más RA, A es  y está opcionalmente sustituido con uno o más RA, y B es

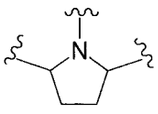
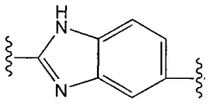
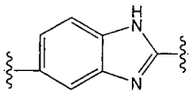
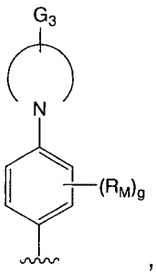
 y está opcionalmente sustituido con uno o más RA, y D es fenilo o piridilo y está sustituido con uno o más RM, y donde al menos un RM es  que es un heterociclo monocíclico que contiene nitrógeno de entre 4 y 8 miembros opcionalmente sustituido con uno o más RG2.

6. El compuesto o sal de acuerdo con la reivindicación 2, CARACTERIZADO PORQUE X es  y está opcionalmente sustituido con uno o más RA, A es  y está opcionalmente sustituido con uno o más RA, y B es  y está opcionalmente sustituido con uno o más RA, y D es fenilo o piridilo y está sustituido con uno o más RM, y al menos un RM es  , donde  es un heterociclo monocíclico que contiene nitrógeno de entre 4 y 8 miembros opcionalmente sustituido con uno o más RG2.

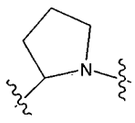
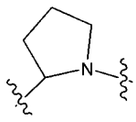
7. El compuesto o sal de acuerdo con la reivindicación 2, CARACTERIZADO PORQUE X es  y está opcionalmente sustituido con uno o más RA, A es  y está opcionalmente sustituido con uno o más RA, y B es

 y está opcionalmente sustituido con uno o más RA, y D es  y está opcionalmente sustituido con uno o más RM adicionales.

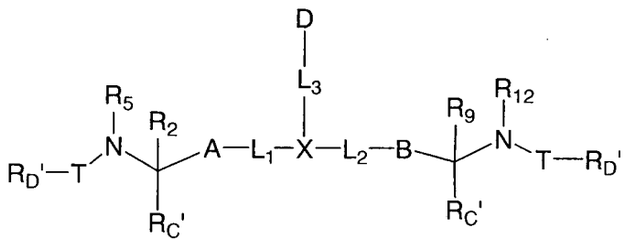
8. El compuesto o sal de acuerdo con la reivindicación 7, CARACTERIZADO PORQUE R1 es hidrógeno, y R2 y R5 tomados junto con los átomos a los cuales están unidos forman  que está sustituido con 0, 1, 2, 3, o 4 RA, donde R8 es hidrógeno, y R9 y R12 tomados junto con los átomos a los cuales están unidos forman  que está sustituido con 0, 1, 2, 3, o 4 RA, y donde cada T' es un enlace.

9. El compuesto o sal de acuerdo con la reivindicación 2, CARACTERIZADO PORQUE X es  y está opcionalmente sustituido con uno o más RA, A es  y está opcionalmente sustituido con uno o más RA, y B es  y está opcionalmente sustituido con uno o más RA, y D es  , donde G3 es fenilo opcionalmente sustituido con uno o dos RG3; g es 0, 1, o 2; RM es en forma independiente en cada caso fluoro, cloro, metilo, metoxi, trifluorometilo, o trifluorometoxi; y  es un heterociclo monocíclico que contiene nitrógeno de entre 4

y 8 miembros opcionalmente sustituido con uno o más RG2.

10. El compuesto o sal de acuerdo con la reivindicación 9, CARACTERIZADO PORQUE R1 es hidrógeno, y R2 y R5 tomados junto con los átomos a los cuales están unidos forman  que está sustituido con 0, 1, 2, 3, o 4 RA, donde R8 es hidrógeno, y R9 y R12 tomados junto con los átomos a los cuales están unidos forman  que está sustituido con 0, 1, 2, 3, o 4 RA, y donde cada T' es un enlace.

11. Un compuesto CARACTERIZADO PORQUE es de Fórmula IB, o una sal aceptable farmacéuticamente del mismo,



IB

donde:

RC' se selecciona en forma independiente entre RC;

RD' se selecciona en forma independiente entre RD;

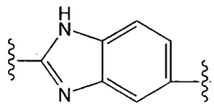
R2 y R5, tomados junto con los átomos a los cuales están unidos, forman un heterociclo de entre 3 y 12 miembros que está opcionalmente sustituido con uno o más RA;

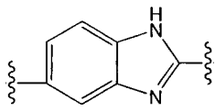
R9 y R12, tomados junto con los átomos a los cuales están unidos, forman un heterociclo de entre 3 y 12 miembros que está opcionalmente sustituido con uno o más RA;

X es C3-C12carbociclo o heterociclo de entre 3 y 12 miembros, y está opcionalmente sustituido con uno o más RA o RF;

L1 y L2 se seleccionan en forma independiente entre sí entre un enlace; o C1-C6alquileno, C2-C6alquenileno o C2-C6alquinileno, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más RL;

L3 es un enlace o –LS–K–LS'–, donde K se selecciona entre un enlace, –O–, –S–, –N(RB)–, –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(RB)–, –N(RB)C(O)–, –N(RB)C(O)O–, –OC(O)N(RB)–, –N(RB)S(O)–, –N(RB)S(O)2–, –S(O)N(RB)–, –S(O)2N(RB)–, –C(O)N(RB)C(O)–, –N(RB)C(O)N(RB')–, –N(RB)SO2N(RB')–, o –N(RB)S(O)N(RB')–;

A es  y está opcionalmente sustituido con uno o más RA;

B es  y está opcionalmente sustituido con uno o más RA;

D es C3-C12carbociclo o heterociclo de entre 3 y 12 miembros que está sustituido con J y opcionalmente sustituido con uno o más RA, donde J es C3-C12carbociclo o heterociclo de entre 3 y 12 miembros y está opcionalmente sustituido con uno o más RA;

T se selecciona en forma independiente en cada caso entre un enlace, –LS–, –LS–M–LS'–, o –LS–M–LS'–M'–LS''–, donde M y M' se seleccionan en forma independiente entre sí en cada caso entre un enlace, –O–, –S–, –N(RB)–, –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(RB)–, –N(RB)C(O)–, –N(RB)C(O)O–, –OC(O)N(RB)–, –N(RB)S(O)–, –N(RB)S(O)2–, –S(O)N(RB)–, –S(O)2N(RB)–, –C(O)N(RB)C(O)–, –N(RB)C(O)N(RB')–, –N(RB)SO2N(RB')–, –N(RB)S(O)N(RB')–, C3-C12carbociclo o heterociclo de entre 3 y 12 miembros,

y donde dicho C3-C12carbociclo y heterociclo de entre 3 y 12 miembros están opcionalmente sustituidos en forma independiente entre sí en cada caso con uno o más RA;

RD se selecciona en forma independiente en cada caso entre hidrógeno o RA;

RA se selecciona en forma independiente en cada caso entre halógeno, nitro, oxo, fosfonoxi, fosfono, tioxo, ciano, o –LS–RE, donde dos RA adyacentes, tomados junto con los átomos a los cuales están unidos y cualquier otro átomo entre los átomos a los cuales están unidos, pueden formar opcionalmente carbociclo o heterociclo;

RB y RB' se seleccionan en forma independiente entre sí en cada caso entre hidrógeno; o C1-C6alquilo, C2-C6alquenilo o C2-C6alquinilo, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano o carbociclo o heterociclo de entre 3 y 6 miembros; o carbociclo o heterociclo de entre 3 y 6 miembros; donde cada carbociclo o heterociclo de entre 3 y 6 miembros en RB o RB' está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C1-C6alquilo, C2-C6alquenilo, C2-C6alquinilo, C1-C6haloalquilo, C2-C6haloalquenilo o C2-C6haloalquinilo;

RC se selecciona en forma independiente en cada caso entre hidrógeno, halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo o ciano; o C1-C6alquilo, C2-C6alquenilo o C2-C6alquinilo, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano o

carbociclo o heterociclo de entre 3 y 6 miembros; o carbociclo o heterociclo de entre 3 y 6 miembros; donde cada carbociclo o heterociclo de entre 3 y 6 miembros en RC está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C1-C6alquilo, C2-C6alquenilo, C2-C6alquinilo, C1-C6haloalquilo, C2-C6haloalquenilo o C2-C6haloalquinilo;

RE se selecciona en forma independiente en cada caso entre –O–RS, –S–RS, –C(O)RS, –OC(O)RS, –C(O)ORS, –N(RSRS'), –S(O)RS, –SO2RS, –C(O)N(RSRS'), –N(RS)C(O)RS', –N(RS)C(O)N(RS'RS''), –N(RS)SO2RS', –SO2N(RSRS'), –N(RS)SO2N(RS'RS''), –N(RS)S(O)N(RS'RS''), –OS(O)–RS, –OS(O)2–RS, –S(O)2ORS, –S(O)ORS, –OC(O)ORS, –N(RS)C(O)ORS', –OC(O)N(RSRS'), –N(RS)S(O)–RS', –S(O)N(RSRS'), –P(O)(ORS)2, o –C(O)N(RS)C(O)–RS'; o C1-C6alquilo, C2-C6alquenilo o C2-C6alquinilo, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo o ciano; o C3-C6carbociclo o heterociclo de entre 3 y 6 miembros, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C1-C6alquilo, C2-C6alquenilo, C2-C6alquinilo, C1-C6haloalquilo, C2-C6haloalquenilo, C2-C6haloalquinilo, C(O)ORS, o –N(RSRS');

RF se selecciona en forma independiente en cada caso entre C1-C10alquilo, C2-C10alquenilo o C2-C10alquinilo, cada uno de los cuales contiene 0, 1, 2, 3, 4 o 5 herteroátomos seleccionados entre O, S o N y está opcionalmente sustituido con uno o más RL; o –(RX–RY)Q–(RX–RY'), donde Q es 0, 1, 2, 3 o 4, y cada

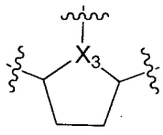
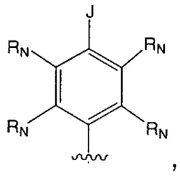
RX es en forma independiente O, S o N(RB), donde cada RY es en forma independiente C1-C6alquileno, C2-C6alquenileno o C2-C6alquinileno cada uno de los cuales está opcionalmente sustituido en forma independiente con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo o ciano, y donde cada RY' es en forma independiente C1-C6alquilo, C2-C6alquenilo o C2-C6alquinilo cada uno de los cuales está opcionalmente sustituido en forma independiente con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo o ciano;

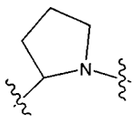
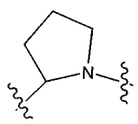
RL se selecciona en forma independiente en cada caso entre halógeno, nitro, oxo, fosfonoxi, fosfono, tioxo, ciano, –O–RS, –S–RS, –C(O)RS, –OC(O)RS, –C(O)ORS, –N(RSRS'), –S(O)RS, –SO2RS, –C(O)N(RSRS') o –N(RS)C(O)RS'; o C3-C6carbociclo o heterociclo de entre 3 y 6 miembros, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C1-C6alquilo, C2-C6alquenilo, C2-C6alquinilo, C1-C6haloalquilo, C2-C6haloalquenilo o C2-C6haloalquinilo; donde dos RL adyacentes, tomados junto con los átomos a los cuales están unidos y cualquier otro átomo entre los átomos a los cuales están unidos, pueden formar opcionalmente carbociclo o heterociclo;

LS, LS' y LS'' se seleccionan en forma independiente entre sí en cada caso entre un enlace; o C1-C6alquileno, C2-C6alquenileno o C2-C6alquinileno, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más RL; y

RS, RS' y RS'' se seleccionan en forma independiente entre sí en cada caso entre hidrógeno; C1-C6alquilo, C2-C6alquenilo o C2-C6alquinilo, cada uno de los

cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, –O–C1-C6alquilo, –O–C1-C6alquilen–O–C1-C6alquilo, o carbociclo o heterociclo de entre 3 y 6 miembros; o carbociclo o heterociclo de entre 3 y 6 miembros; donde cada carbociclo o heterociclo de entre 3 y 6 miembros en RS , RS' o RS' está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C1-C6alquilo, C2-C6alquenilo, C2-C6alquinilo, C1-C6haloalquilo, C2-C6haloalquenilo o C2-C6haloalquinilo.

12. El compuesto o sal de acuerdo con la reivindicación 11, CARACTERIZADO PORQUE X es  y está opcionalmente sustituido con uno o más RA o RF, y X3 es N y está directamente unido a –L3–D, donde L1, L2 y L3 son un enlace, donde D es  , y cada RN es en forma independiente RD, donde J es C3-C6carbociclo o heterociclo de entre 3 y 6 miembros y está sustituido con un C3-C6carbociclo o heterociclo de entre 3 y 6 miembros que está opcionalmente sustituido en forma independiente con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C1-C6alquilo, C2-C6alquenilo, C2-C6alquinilo, C1-C6haloalquilo, C2-C6haloalquenilo, C2-C6haloalquinilo, C(O)ORS o –N(RSRS'), y J está opcionalmente sustituido con uno o más RA, donde R2 y R5, tomados junto con los átomos a los cuales están unidos, forman

 que está opcionalmente sustituido con uno o más RA, donde R9 y R12, tomados junto con los átomos a los cuales están unidos, forman  que está opcionalmente sustituido con uno o más RA, donde -T-RD' es –C(O)–LY'–RD', –C(O)O–LY'–RD', –C(O)–LY'–N(RB)C(O)–LS''–RD', –C(O)–LY'–N(RB)C(O)O–LS''–RD', –N(RB)C(O)–LY'–N(RB)C(O)–LS''–RD', –N(RB)C(O)–LY'—N(RB)C(O)O–LS''–RD', o –N(RB)C(O)–LY'—N(RB)–LS''–RD', y donde LY' es en forma independiente en cada caso LS'.

13. Un proceso para preparar un compuesto de la invención, CARACTERIZADO PORQUE comprende un paso descrito en uno de los Esquemas, Procedimientos Generales o Ejemplos descritos en la presente.

14. Un intermediario CARACTERIZADO PORQUE se describe en uno de los Esquemas, Procedimientos Generales o Ejemplos descritos en la presente.

15. El compuesto CARACTERIZADO PORQUE es {(2S,3R)-1-[(2S)-2-{5-[(2R,5R)-1-{3,5-difluoro-4-[4-(4-fluorofenil)piperidin-1-il]fenil}-5-(6-fluoro-2-{(2S)-1-[N-(metoxicarbonil)-O-metil-L-treonil]pirrolidin-2-il}-1H-benzimidazol-5-il)pirrolidin-2-il]-6-fluoro-1H-benzimidazol-2-il}pirrolidin-1-il]-3-metoxi-1-oxobutan-2-il}carbamato de metilo, o una sal aceptable farmacéuticamente del mismo.

16. Una composición farmacéutica CARACTERIZADA PORQUE comprende el compuesto de la reivindicación 15 o dicha sal.17. El compuesto CARACTERIZADO PORQUE es {(2S)-1-[(2S)-2-{5-[(2R,5R)-1-[3,5-difluoro-4-(4-fenilpiperidin-1-il)fenil]-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-benzimidazol-5-il}pirrolidin-2-il]-1H-benzimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo, o una sal aceptable farmacéuticamente del mismo.

18. Una composición farmacéutica CARACTERIZADA PORQUE comprende el

compuesto de la reivindicación 17 o dicha sal.19. El compuesto CARACTERIZADO PORQUE es {(2S,3R)-1-[(2S)-2-{5-[(2R,5R)-1-{4-[4-(2,6-difluorofenil)piperazin-1-il]-3,5-difluorofenil}-5-(6-fluoro-2-{(2S)-1-[N-(metoxicarbonil)-O-metil-L-treonil]pirrolidin-2-il}-1H-benzimidazol-5-il)pirrolidin-2-il]-6-fluoro-1H-benzimidazol-2-il}pirrolidin-1-il]-3-metoxi-1-oxobutan-2-il}carbamato de metilo, o una sal aceptable farmacéuticamente del mismo.

20. Una composición farmacéutica CARACTERIZADA PORQUE comprende el compuesto de la reivindicación 19 o dicha sal.21. El compuesto CARACTERIZADO PORQUE es {(2S)-1-[(2S)-2-{5-[(2R,5R)-1-(4-tert-butilfenil)-5-{5-fluoro-2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-benzimidazol-6-il}pirrolidin-2-il]-6-fluoro-1H-benzimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo, o una sal aceptable farmacéuticamente del mismo.

22. Una composición farmacéutica CARACTERIZADA PORQUE comprende el compuesto de la reivindicación 21 o dicha sal.

COMPUESTOS ANTIVIRALES

RESUMEN

Compuestos eficaces para inhibir la replicación del virus de la hepatitis C ("HCV"); procesos de elaboración de tales compuestos, composiciones que los comprenden y métodos de uso de los mismos para tratar una infección por HCV.

Industria y Comercio
SUPERINTENDENCIA

PLANILLA DE RADICACIÓN - DIGITALIZACIÓN DIARIA
RELACIÓN DE ANEXOS

Dependencia:	Fecha: 2013/ ____/ ____/ AAAA MM DD	Recorrido:
2020		

Tipo de Radicación: Entrada: ☒ Salida: ☐ Traslado: ☐ Convenio: ☐

Radicador: | Planilla:

ID	*No. Radicación*	*Consecutivo*	*Item*
1	13-116472-0		
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
13			
14			
15			
16			
17			

Item	*Unidad de Conservación*
1	Bolsa
2	Caja
3	Libro
4	Sobre
5	Tomo
6	**Otro**
Item	***Soporte Documental***
7	CD
8	Disquete
9	DVD
10	Folleto
11	Foto
12	Periódico
13	Plano
14	Publicación Periódica
15	USB
10	**Otro**

Observaciones:

Folio 56 Sobre manila con CD

Pathy

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
TARJETA ARCHIVO PROPIETARIOS

PATENTE DE INVENCION ____ PCT __X__ MODELO DE UTILIDAD ____ DISEÑO INDUSTRIAL ___

(21) Nº de solicitud:
(22) Fecha de solicitud:
(51) Clasificación Internacional :

(71)Solicitante(s) **ABBVIE INC.**

(72) Inventor(es) **DEGOEY, David A.; KATI, Warren M.; HUTCHINS, Charles W.; DONNER, Pamela L.; KRUEGER Allan C.; RANDOLPH John T.; MOTTER, Christopher E.; NELSON, Lissa T.; PATEL, Sachin V.; MATULENKO, Mark A.; KEDDY, Ryan G.; JINKERSON, Tammie K.; GAO, Yi; LIU, Dachun; PRATT, John K.; ROCKWAY, Tood, W.; MARING, Clarence J.; HUTCHINSON, Douglas K.; FLENTGE, Charles A.; WAGNER, Rolf; TUFANO, Michael D.; BETEBENNER, David A.; SARRIS, Kathy; WOLLER, Kevin R.; WAGAW, Seble H.; CALIFANO, Jean C.; LI, Wenke; CASPI, Daniel D.; BELLIZZI, Mary E.; CARROLL, William A.**

(74) Apoderado: **DRA. MARGARITA CASTELLANOS ABONDANO**

(30) Prioridad	(31)	No. Prioridad	32)	Fecha	(33)	País
		12/903.822		13/10/2010		US
		12/964.027		09/12/2010		US
		61/446.800		25/02/2011		US
		13/100.827		04/05/2011		US

(85) Fecha inicio fase nacional:
(86) Datos relativos a la presentación de la solicitud PCT
Fecha de presentación de la solicitud: **12/10/2011**
No. de solicitud **PCT/US2011/056045**

(87) Publicación internacional
Fecha: **19/04/2012**
Nº publicación: **WO 2012/051361 A1**

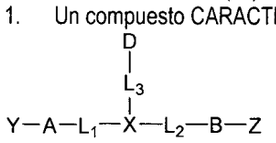
(54) Titulo: **COMPUESTOS ANTIVIRALES**

Industria y Comercio SUPERINTENDENCIA	**EXTRACTO PARA PUBLICACIÓN** ___ Patente de Invención ___ Patente modelo de utilidad _X_ PCT

(21) No. De solicitud	(51) int. Cl:
(22) Fecha de solicitud	(71) Solicitante (s) **ABBVIE INC.**
(30) Prioridad (31) No.Prioridad **12/903.822, 12/964.027, 61/446.800, 13/100.827** (32) Fecha **13/10/2010, 09/12/2010, 25/02/2011, 04/05/2011** (33) País **US, US, US, US**	(72) Interventor (es) **DEGOEY, David A.** **KATI, Warren M.** **HUTCHINS, Charles W.** **DONNER, Pamela L.** **KRUEGER, Allan C.** **Y otros** (74) Apoderado (s) **DRA. MARGARITA CASTELLANOS ABONDANO**
(54) Titulo **COMPUESTOS ANTIVIRALES**	
Las casillas identificadas con 85, 86 y 87 sólo aplican para PCT	
(85) Fecha límite inicio Fase Nacional (86) Datos relativos a la presentación de la solicitud PCT Fecha de presentación de la solicitud **12/10/2011** No. de solicitud **PCT/US2011/056045**	(87) Publicación internacional Fecha **19/04/2012** No. Publicación **WO2012/051361 A1**

Resumen reivindicación (es):

1. Un compuesto CARACTERIZADO PORQUE es de Fórmula I, o una sal aceptable farmacéuticamente del mismo,



I

donde:

X es C3-C12carbociclo o heterociclo de entre 3 y 12 miembros, y está opcionalmente sustituido con uno o más RA o RF;

L1 y L2 se seleccionan en forma independiente entre sí entre un enlace; o C1-C6alquileno, C2-C6alquenileno o C2-C6alquinileno, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más RL;

L3 es un enlace o –LS–K–LS'–, donde K se selecciona entre un enlace, –O–, –S–, –N(RB)–, –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(RB)–, –N(RB)C(O)–, –N(RB)C(O)O–, –OC(O)N(RB)–, –N(RB)S(O)–, –N(RB)S(O)2–, –S(O)N(RB)–, –S(O)2N(RB)–, –C(O)N(RB)C(O)–, –N(RB)C(O)N(RB')–, –N(RB)SO2N(RB')–, o –N(RB)S(O)N(RB')–;

A y B son en forma independiente entre sí C3-C12carbociclo o heterociclo de entre 3 y 12 miembros, y están opcionalmente sustituidos en forma independiente entre sí con uno o más RA;

D es C3-C12carbociclo o heterociclo de entre 3 y 12 miembros, y está opcionalmente sustituido con uno o más RA; o D es C3-C12carbociclo o heterociclo de entre 3 y 12 miembros que está sustituido con J y opcionalmente sustituido con uno o más RA, donde J es C3-C12carbociclo o heterociclo de entre 3 y 12 miembros y está opcionalmente sustituido con uno o más RA, o J es –SF5; o D es hidrógeno o RA;

Y se selecciona entre –T'–C(R1R2)N(R5)–T–RD, –T'–C(R3R4)C(R6R7)–T–RD, –LK–T–RD, o –LK–E;

R1 y R2 son en forma independiente entre sí RC, y R5 es RB; o R1 es RC, y R2 y R5, tomados junto con los átomos a los cuales están unidos, forman un heterociclo de entre 3 y 12 miembros que está opcionalmente sustituido con uno o más RA;

R3, R4, R6, y R7 son en forma independiente entre sí RC; o R3 y R6 son en forma independiente entre sí RC, y R4 y R7, tomados junto con los átomos a los cuales están unidos, forman un carbociclo o heterociclo de entre 3 y 12 miembros que está opcionalmente sustituido con uno o más RA;

Z se selecciona entre –T'–C(R8R9)N(R12)–T–RD, –T'–C(R10R11)C(R13R14)–T–RD, –LK–T–RD, o –LK–E;

R8 y R9 son en forma independiente entre sí RC, y R12 es RB; o R8 es RC, y R9 y R12, tomados junto con los átomos a los cuales están unidos, forman un heterociclo de entre 3 y 12 miembros que está opcionalmente sustituido con uno o más RA;

R10, R11, R13, y R14 son en forma independiente entre sí RC; o R10 y R13 son en forma independiente entre sí RC, y R11 y R14, tomados junto con los átomos a los cuales están unidos, forman un carbociclo o heterociclo de entre 3 y 12 miembros...

Industria y Comercio SUPERINTENDENCIA	LISTA DE CHEQUEO ADMISIÓN A TRÁMITE – NUEVAS CREACIONES

PATENTE DE INVENCIÓN _____ **MODELO DE UTILIDAD** _____ **Art 33 Decisión 486/00**

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

Completa _____ Incompleta _____

PATENTE DE INVENCIÓN PCT X **MODELO DE UTILIDAD PCT** ___ **Art.33 Decisión 486/00, Circular Única**

X Indicación que se solicita una PCT
X Copia de la solicitud en español, tal como fue presentada inicialmente (capítulo 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 _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
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(71) Applicant *(for all designated States except US)*: **ABBOTT LABORATORIES** [US/US]; 100 Abbott Park Road, Abbott Park, Illinois 60064 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **DEGOEY, David A.** [US/US]; 8649 226th Avenue, Salem, Wisconsin 53168 (US). **KATI, Warren M.** [US/US]; 152 Knob Hill Lane, Gurnee, Illinois 60031 (US). **HUTCHINS, Charles W.** [US/US]; 31005 Prairie Ridge Road, Green Oaks, Illinois 60048 (US). **DONNER, Pamela L.** [US/US]; 1901 McRae Lane, Mundelien, Illinois 60060 (US). **KRUEGER, Allan C.** [US/US]; 7260 Presidential Drive, Gurnee, Illinois 60031 (US). **RANDOLPH, John T.** [US/US]; 304 Broadway Avenue, Libertyville, Illinois 60048 (US). **MOTTER, Christopher E.** [US/US]; 10135 South Warwick Drive, Oak Creek, Wisconsin 53154 (US). **NELSON, Lissa T.** [US/US]; 640 Broadview Avenue, Highland Park, Illinois 60035 (US). **PATEL, Sachel V.** [US/US]; 1259 S. Meadow Road, Round Lake, Illinois 60073 (US). **MATULENKO, Mark A.** [US/US]; 1875 Countryside Drive, Libertyville, Illinois 60048 (US). **KEDDY, Ryan G.** [US/US]; 10046 West Hendee Road, Beach Park, Illinois 60087 (US). **JINKERSON, Tammie K.** [US/US]; 11129 10th Avenue, Pleasant Prairie, Wisconsin 53158 (US). **GAO, Yi** [US/US]; 210 East Baltusrol Drive, Vernon Hills, Illinois 60061 (US). **LIU, Dachun** [CN/US]; 1276 Georgetown Way, Vernon Hills, Illinois 60061 (US). **PRATT, John K.** [US/US]; 8210 61st Avenue, Kenosha, Wisconsin 53142 (US). **ROCKWAY, Todd W.** [US/US]; 34136 N. Lavender Circle, Grayslake, Illinois 60030 (US). **MARING, Clarence J.** [US/US]; 1228 W. Borders Drive, Palatine, Illinois 60067 (US). **HUTCHINSON, Douglas K.** [US/US]; 160 Depot Street, Antioch, Illinois 60002 (US). **FLENTGE, Charles A.** [US/US]; 8628 225th Avenue, Salem, Wisconsin 53168 (US). **WAGNER, Rolf** [US/US]; 42530 Sheridan Oaks Drive, Antioch, Illinois 60002 (US). **TUFANO, Michael D.** [US/US]; 6539 North Washtenaw, Chicago, Illinois 60645 (US). **BETEBENNER, David A.** [US/US]; 32329 N. Forest Drive, Grayslake, Illinois 60030 (US). **SARRIS, Kathy** [US/US]; 1309 Andover Drive, Mundelein, Illinois 60060 (US). **WOLLER, Kevin R.** [US/US]; 1072 Joy Court, Antioch, Illinois 60002 (US). **WAGAW, Sebel H.** [US/US]; 2311 Ridgeway, Evanston, Illinois 60201 (US). **CALIFANO, Jean C.** [US/US]; 6167 N. Bay Ridge, Whitefish Bay, Wisconsin 53217 (US). **LI, Wenke** [US/US]; 7203 Buchanan Drive, Gurnee, Illinois 60031 (US). **CASPI, Daniel D.** [US/US]; 807 Davis Street #912, Evanston, Illinois 60201 (US). **BELLIZZI, Mary E.** [US/US]; 771 N. McKinley Road, Lake Forest, Illinois 60045 (US). **CARROLL, William A.** [US/US]; 2325 Ridgeway Avenue, Evanston, Illinois 60201 (US).

(74) Agent: **ZHANG, Xu**; 100 Abbott Park Road, Abbott Park Road, Illinois 60064 (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.

ANTI-VIRAL COMPOUNDS

This application claims priority from U.S. Patent Application Serial No. 13/100,827 filed May 4, 2011, U.S. Provisional Application Serial No. 61/446,800 filed February 25, 2011, U.S. Patent Application Serial No. 12/964,027 filed December 9, 2010, and U.S. Patent Application Serial No. 12/903,822 filed October 13, 2010, all of which are incorporated herein by reference in their entireties.

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.

The nonstructural protein NS5A is a membrane-associated phosphoprotein present in basally phosphorylated and hyperphosphorylated forms. It is a critical component of HCV replication and is believed to exert multiple functions at various stages of the viral life cycle. A full-length NS5A protein comprises three domains – namely, Domain I, Domain II, and Domain III. Domain I (residues 1 to 213) contains a zinc-binding motif and an amphipathic N-terminal helix which can promote membrane association. Domain II (residues 250 to 342) has regulatory functions, such as interactions with protein kinase PKR and PI3K, as well as NS5B, and also contains the interferon sensitivity-determining region. Domain III (residues 356 to 447) plays a role in infectious virion assembly, and can be modulated by phosphorylation within the domain. NS5A has been identified as a promising therapeutic target for treating HCV.

SUMMARY

The present invention features compounds of Formulae I, I_A, I_B, I_C, I_D, I_E, I_F and I_G 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.

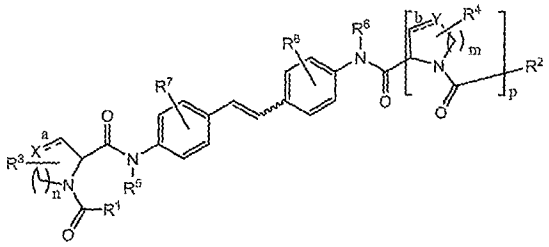
Furthermore, the present invention features processes of making the compounds or salts of the invention.

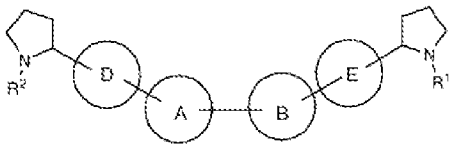
Other features, objects, and advantages of the present invention are apparent in the detailed description that follows. It should be understood, however, that the detailed description, while indicating preferred embodiments of the invention, are given by way of illustration only, not limitation. Various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

DETAILED DESCRIPTION

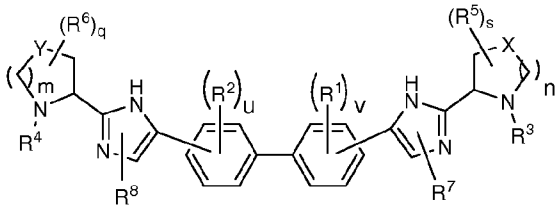
Tellinghuisen *et al.*, NATURE 435:374-379 (2005), describes a crystal structure of the NS5A protein in which two NS5A monomers are packed as a dimer via contacts near the N-terminal ends of the molecules. WO2006093867 postulates the use of the crystal structure of the NS5A protein in conjunction of computer modeling to design or select NS5A inhibitors.

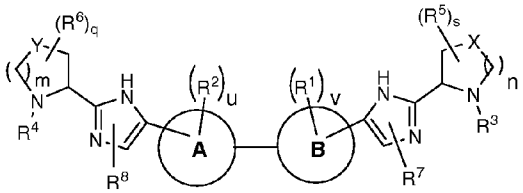
To improve interactions with the NS5A protein, many NS5A inhibitors have been designed to have dimeric or dimer-like structures. For instance, WO2006133326 (BMS) describes compounds

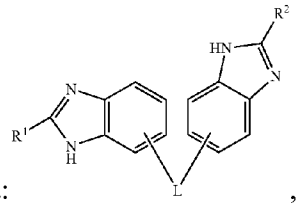
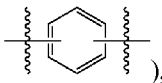
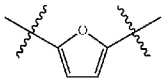
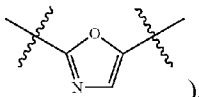
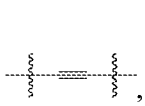
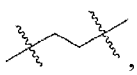
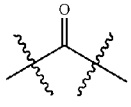
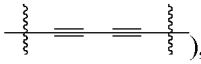
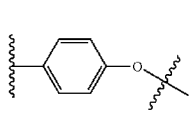
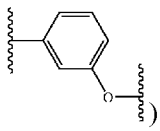
with the formula:  ; WO2008144380 (BMS)

depicts compounds with the formula:  ;

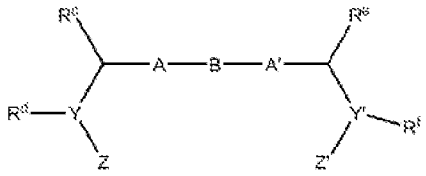
WO2008021927(BMS) shows compounds with the formula:

 ; WO2008021927 (BMS) describes compounds

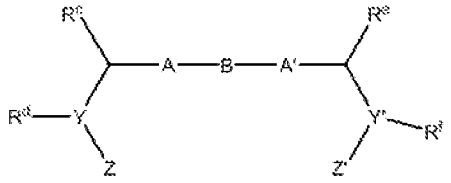
with the formula:  ; and US20100068176 (BMS)

shows compounds with the formula:  , wherein L is selected from aryls (e.g., ), heteroaryls (e.g.,  or ), aliphatic groups (e.g.,  ,  ,  or ), or a combination thereof (e.g.,  or ).

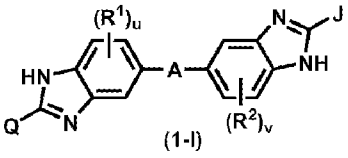
Certain modifications to the above formulae have also been provided. For instance,



WO2010065681 (Presidio) discloses the formula: , wherein B is Q or Q-Q, and each Q is independently selected from cycloalkyl, cycloalkenyl, heterocycle, aryl or heteroaryl, with the proviso that only one Q is a six member aromatic ring when B is Q-Q and with the proviso that if B is Q-Q , any Q is that is polycyclic is connected to the remainder of the molecule through only one cycle of the polycycle; WO2010096777 (Presidio) describes a similar formula:

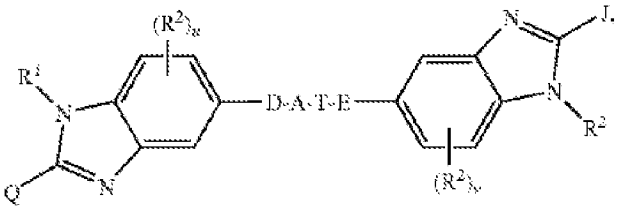


, wherein B is W-W or W-X''-W, and wherein each W is optionally substituted aryl or heteroaryl, and X'' is selected from -O-, -S(O)$_k$, -N(R^N)- and –CR'$_2$-; WO2010091413 (Enanta) and US20100266543 (Enanta) show the formula:



(1-I)

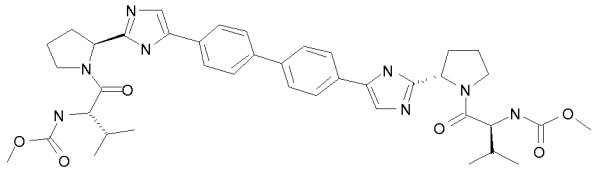
, wherein A is substituted aryl, heteroaryl, heterocyclic, C_3-C_8cycloalkyl or C_3-C_8cycloalkenyl and is optionally substituted with selected substituents; and US20100221215 (Enanta) depicts the formula:



, wherein A is selected from aryl, heteroaryl, heterocyclic, C_3-C_8cycloalkyl or C_3-C_8cycloalkenyl, each optionally substituted, D is absent or an optionally substituted aliphatic group, T is absent or an optionally substituted linear aliphatic group containing zero to eight carbons, E is absent or independently selected from optionally substituted aryl and optionally substituted heteroaryl, and wherein one or two of D, E, and T are absent.

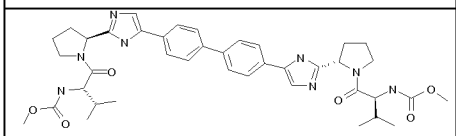
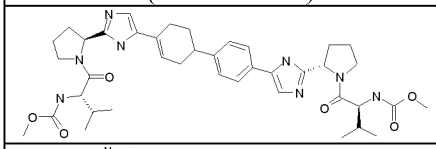
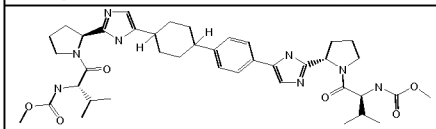
Tables 1-4 compare the antiviral activities of different NS5A compounds. As demonstrated by these tables, several compounds that are generically covered by WO2010065681 (Presidio) WO2010096777 (Presidio), WO2010096462 (Enanta), US20100266543 (Enanta), WO2010096462

(Enanta) and US20100266543 (Enanta) appear to have comparable or worse anti-HCV activities than the corresponding compounds described in the BMS applications. WO2010065681 (Presidio) WO2010096777 (Presidio), WO2010096462 (Enanta), US20100266543 (Enanta), WO2010096462 (Enanta) and US20100266543 (Enanta) also fail to identify any advantage of these compounds over those described in the BMS applications.



(BMS-790052) employs a biphenyl linker between the imidazole moieties. See WO2008021927(BMS). The EC_{50} values of BMS-790052 against different HCV genotypes were shown by Nettles *et al.*, "BMS-790052 is a First-in-class Potent Hepatitis C Virus (HCV) NS5A Inhibitor for Patients with Chronic HCV Infection: Results from a Proof-of-concept Study", 59th Annual Meeting of the American Association for the Study of Liver Diseases (Oct 31-Nov 1 2008, San Francisco, CA; www.natap.org/2008/AASLD/AASLD_06.htm). Specifically, Nettles *et al.*, observed that the EC_{50} values of BMS-790052 against HCV genotypes 1a 1b, 3a, 4a and 5a were 0.05, 0.009, 0.127, 0.012, and 0.033 nM, respectively. See also Gao *et al.*, NATURE 465:96–100 (2010). The compounds in Table 1 use different linkers between the imidazole moieties. Table 1 depicts the EC_{50} values of these compounds when tested using respective replicon assays in the presence of 5% (v/v) fetal bovine serum (FBS). As compared to BMS-790052, the replacement of the biphenyl linker with other linkers can significantly reduce the compounds' activities against various HCV genotypes.

Table 1. Biphenyl linker versus other linkers

	EC_{50} (nM)							
	1a	**1b**	**2a**	**2b**	**3a**	**4a**	**5a**	**6a**
 (BMS-790052)	see Nettles *et al.*, *supra*							
	0.12	0.03	16	0.09	1.5	0.03	0.05	0.5
 (isomer 1, in which the cyclohexanyl moiety has a different cis/trans configuration than isomer 2)	0.71	0.06	9.0	0.4	2.3	0.04	0.08	0.5

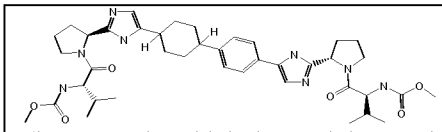
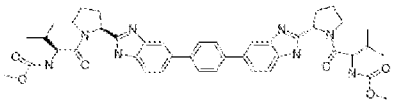
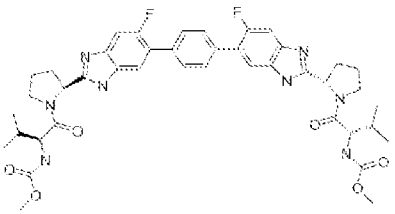
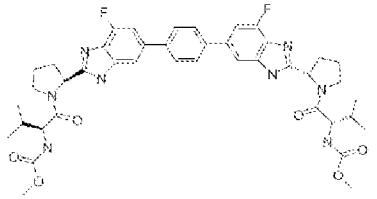
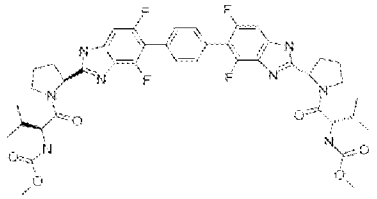
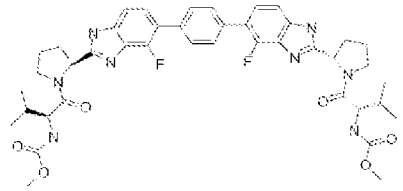
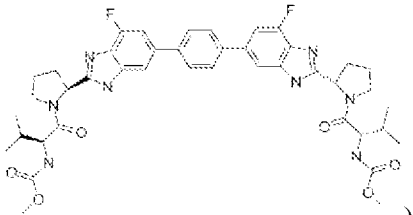
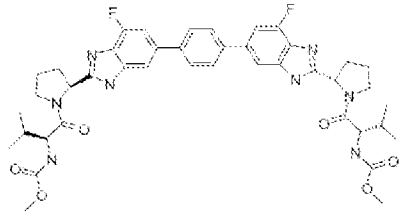
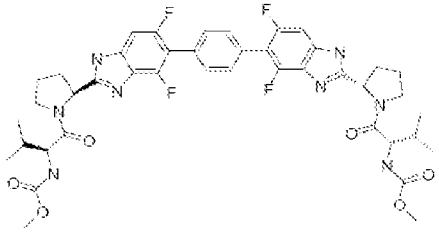
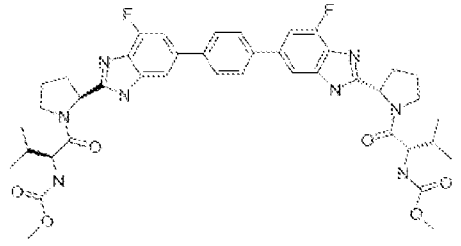
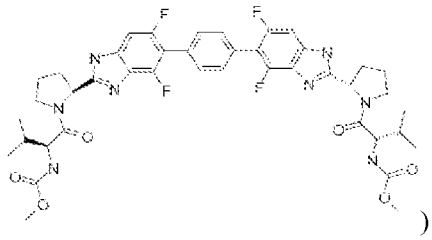
 (isomer 2, in which the cyclohexanyl moiety has a different cis/trans configuration than isomer 1)	>10	8.5	>100	>10	>10	4.0	>10	>10

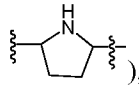
Table 2 compares compounds containing unsubstituted benzimidazole to those containing halo-substituted benzimidazole. Anti-viral activities were assessed using wild-type replicons (e.g., 1b WT or 1a WT) as well as replicons containing specific NS5A mutations (e.g., 1b L28T, 1b Y93H, 1a L31V, 1a Y93C, 1a M28V, or 1a Q30E) in the absence of FBS. As compared to the reference compound which contains unsubstituted benzimidazole, compounds containing substituted benzimidazole generally exhibited comparable or worse activities against many of these HCV viruses.

Table 2. Unsubstituted benzimidazole versus halo-substituted benzimidazole

	EC_{50} (nM)							
	1b WT	**1b L28T**	**1b Y93H**	**1a WT**	**1a L31V**	**1a Y93C**	**1a M28V**	**1a Q30E**
 (reference compound)	0.01	2.7	0.9	0.09	36	40	1.0	40
	0.003	1.8	0.5	0.14	109	26	2.4	119
	0.004	4.3	2.4	0.26	5.5	34	1.8	59
	0.005	>10	5.7	0.28	33	103	11.6	306

	0.007	>10	3.6	0.1	80	141	5.8	52

The present invention surprisingly discovered that compounds with halo-substituted benzimidazole (e.g., ) can have better activity against certain HCV variants containing NS5A mutations (e.g., 1a L31V). Similar testing also showed that  and  , as compared to the reference compound in Table 2, exhibited significantly improved activity against the HCV 1a variant containing the NS5A mutation M28T. These improvements have not been described or suggested in any of the above-mentioned BMS, Presidio or Enanta applications. Accordingly, the present invention features methods of using the compounds containing halo-substituted benzimidazole (e.g.,  or ) to treat HCV variants (e.g., 1a M28T or 1a L31V). These methods comprise administering an effective amount of such a compound to a patient infected with such a HCV variant (e.g., 1a M28T or 1a L31V).

It was also found that when the phenyl linker between the benzimidazole moieties was replaced with a pyrrolidinyl link (e.g., ), the process chemistry to introduce halo substitutions to the benzimidazole moieties became extremely difficult. The above-mentioned BMS, Presidio and Enanta applications do not provide any enable disclosure that would allow halo

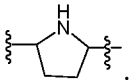
substitutions on the benzimidazole moieties in a compound in which the phenyl linker is replaced with  . Scheme XXIV and various Example of the present application (e.g., Examples 2.16, 3.35-3.41, 3.46-3.53, 4.26-4.31, 4.37-4.40, 4.42-4.46, and 4.51-4.57) provide an enabling disclosure that allows such substitutions in compounds with substituted pyrrolidinyl linkers.

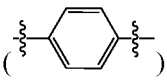
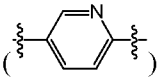
Table 3 compares compounds with different linkers between the benzimidazole moieties. Anti-viral activities were determined using 1a and 1b replicon assays. "HP" refers to human plasma. The compound containing the pyrrolidinyl linker showed significantly worse anti-HCV activities than those containing the pyridinyl linker. As compared to the phenyl linker () used in US20100068176 (BMS), the pyridinyl linker () or like 6-membered aromatic linkers are expected to provide similar or comparable anti-HCV activities.

Table 3. Non-aromatic heterocyclic linker versus aromatic heterocyclic linker

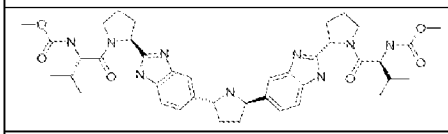
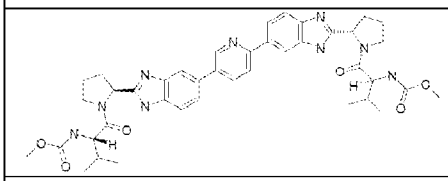
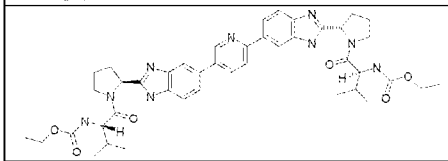
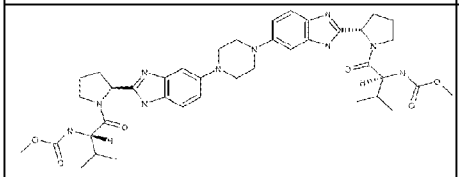
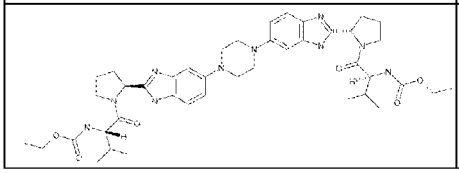
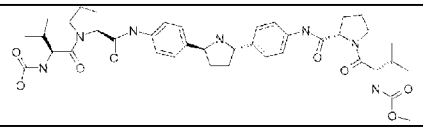
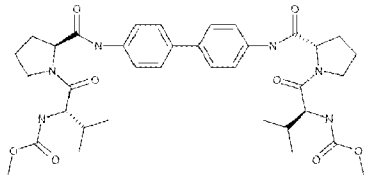
	EC_{50} (nM, in the presence of 5% FBS)		**EC_{50} (nM, in the presence of 5% FBS and 40% HP)**	
	1a	**1b**	**1a**	**1b**
	> 250	> 250	2500 - 8000	> 4500
	< 0.32	< 0.32	< 3.2	< 3.2
	6.8	2.9	83	190
	1.7	1.7	< 3.2	6
	82	73	166	548

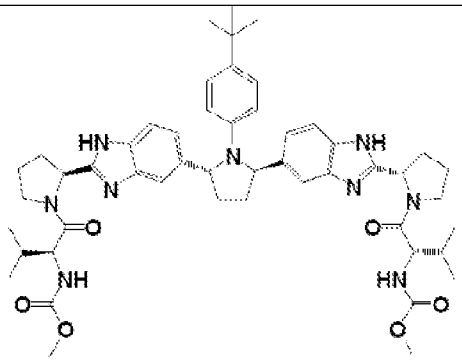
Table 4 further shows that when the phenyl linker is replaced with a pyrrolidinyl linker, the compound's activity against HCV can be significantly reduced. The compound in Table 4 contains a pyrrolidinyl linker and has EC_{50} values of over 200 nM. In comparison, BMS-790052, which contains a biphenyl linker, has EC_{50} values of no more than 0.2 nM. see Nettles *et al.*, *supra*. Therefore, Tables 3 and 4 clearly demonstrate that the use of an unsubstituted pyrrolidinyl linker in a dimeric or dimer-like NS5A inhibitor can lead to poor anti-HCV activities.

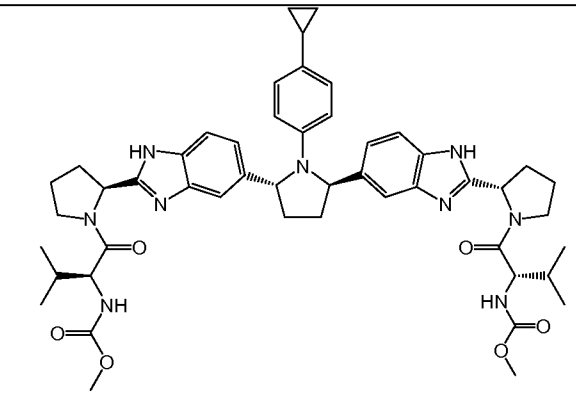
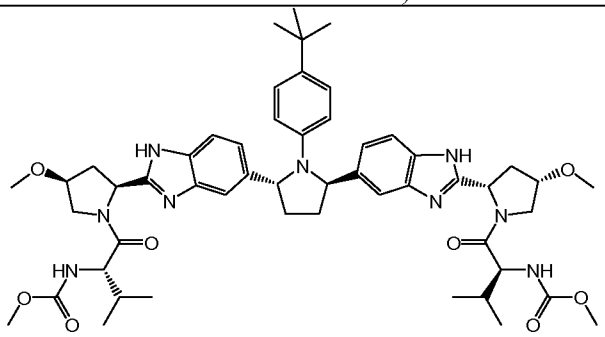
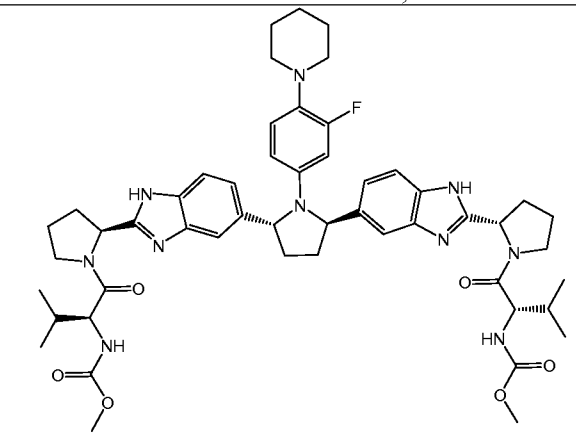
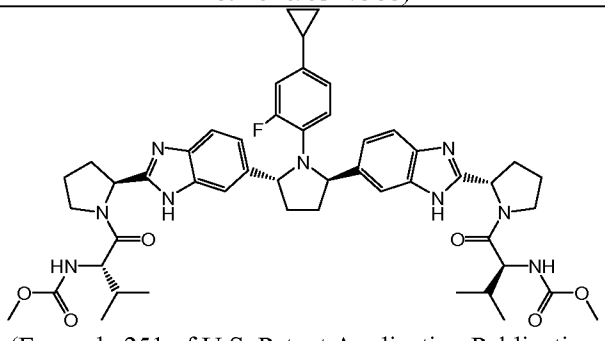
Table 4. Non-aromatic heterocyclic linker versus aromatic heterocyclic linker

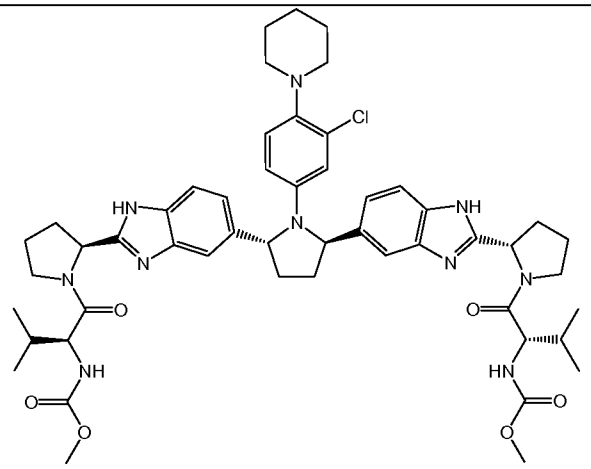
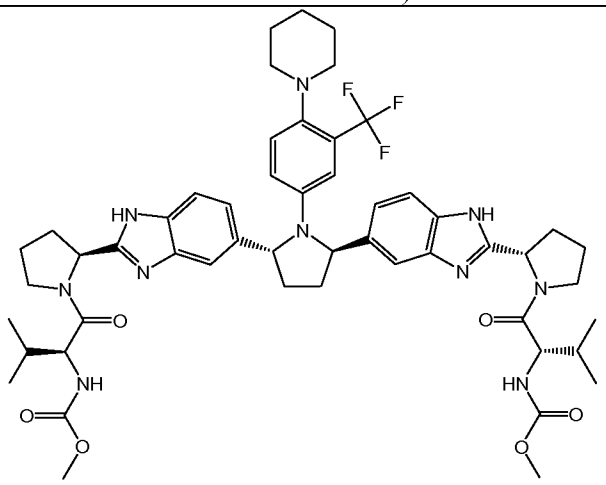
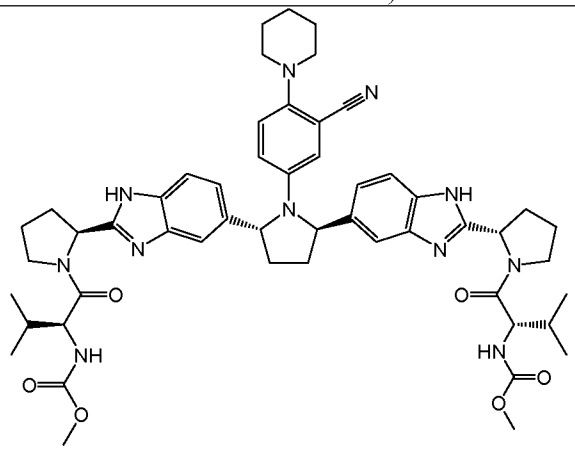
	EC_{50} (nM, in the presence of 5% FBS)		EC_{50} (nM, in the presence of 5% FBS and 40% HP)	
	1a	**1b**	**1a**	**1b**
	290	320	1200	2400
	> 1000	10	> 10000	60

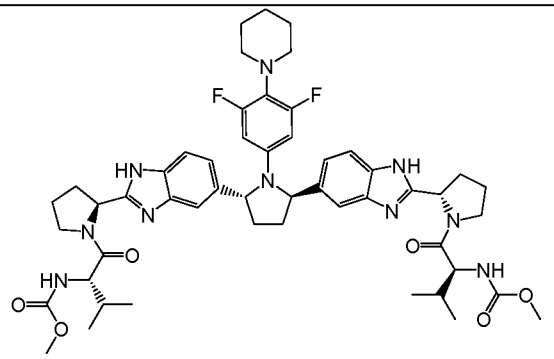
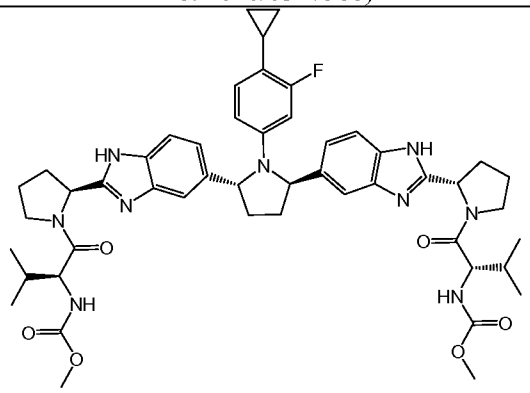
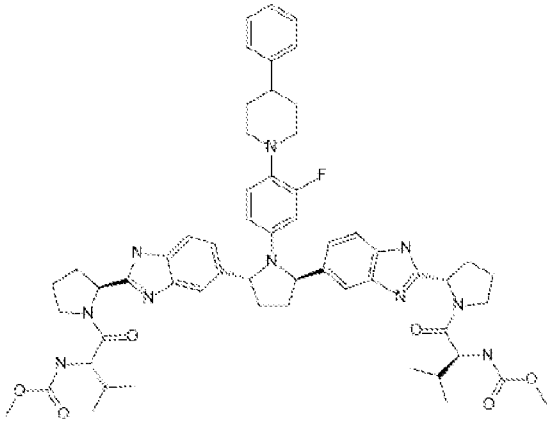
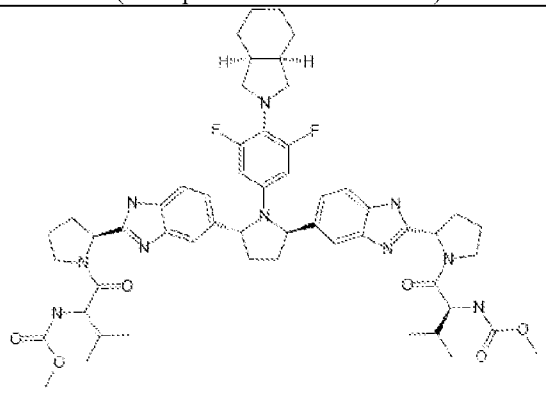
It was unexpectedly discovered that when the nitrogen atom in the pyrrolidinyl linker is substituted with carbocycle or heterocycle, the anti-viral activities of the compound can be drastically improved. Table 5 shows the anti-HCV activities of compounds in which the pyrrolidinyl linker is substituted with substituted carbocycle or heterocycle.

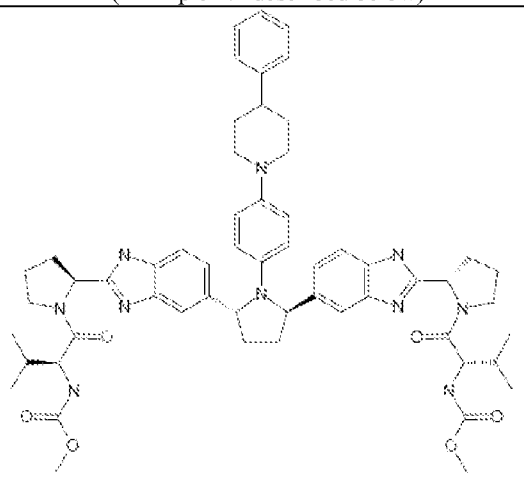
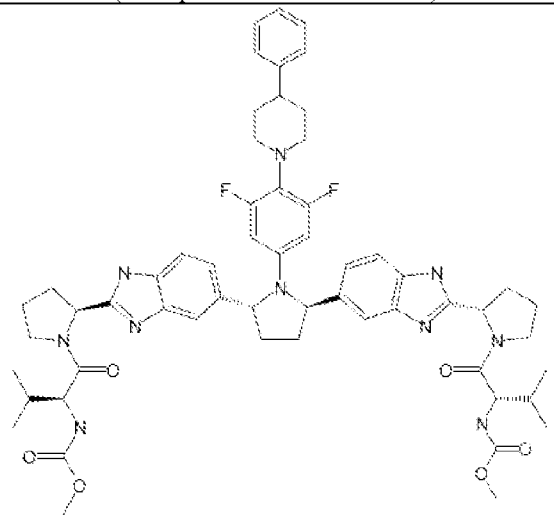
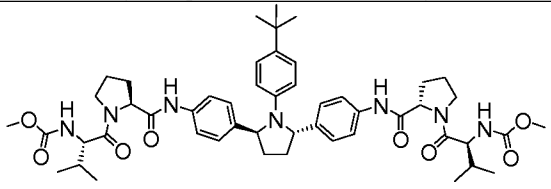
Table 5. Substituted pyrrolidinyl linker

	EC_{50} (nM, in the presence of 40% HP)		EC_{50} (nM, in the absence of HP)			
	1a	**1b**	**2a**	**2b**	**3a**	**4a**
 (Example 109 of U.S. Patent Application Publication No. 2010/0317568)	0.1	0.3	0.2	≤ 0.05	≤ 0.05	≤ 0.05

 (Example 163 of U.S. Patent Application Publication No. 2010/0317568)	0.1	0.3	≤ 0.05	≤ 0.05	≤ 0.05	≤ 0.05
 (Example 236 of U.S. Patent Application Publication No. 2010/0317568)	0.3	0.8				
 (Example 245 of U.S. Patent Application Publication No. 2010/0317568)	0.2	0.4	≤ 0.05	≤ 0.05	≤ 0.05	≤ 0.05
 (Example 251 of U.S. Patent Application Publication No. 2010/0317568)	0.1	0.2	≤ 0.05	≤ 0.05	≤ 0.05	≤ 0.05

 (Example 256 of U.S. Patent Application Publication No. 2010/0317568)	0.2	0.2	≤ 0.05	≤ 0.05	≤ 0.05	≤ 0.05
 (Example 257 of U.S. Patent Application Publication No. 2010/0317568)	0.6	0.3	0.5	≤ 0.05	≤ 0.05	≤ 0.05
 (Example 258 of U.S. Patent Application Publication No. 2010/0317568)	0.4	0.5	0.07	≤ 0.05	≤ 0.05	≤ 0.05

 (Example 271 of U.S. Patent Application Publication No. 2010/0317568)	0.1	0.2	≤ 0.05	≤ 0.05	≤ 0.05	≤ 0.05
 (Example 302 of U.S. Patent Application Publication No. 2010/0317568)	0.1	0.1	≤ 0.05	≤ 0.05	≤ 0.05	≤ 0.05
 (Example 3.20 described below)	0.5	0.6	≤ 0.05	≤ 0.05	≤ 0.05	≤ 0.05
	0.1	0.2				

(Example 4.3 described below)						
 (Example 4.25 described below)	1.5	1.5	0.5	0.5	0.5	0.2
 (Example 5.1 described below)	0.1	0.2	≤ 0.05	≤ 0.05	≤ 0.05	≤ 0.05
 (Example 37 of U.S. Patent Application Publication No. 2010/0317568)	0.2	0.1	≤ 0.05	≤ 0.05	≤ 0.05	≤ 0.05

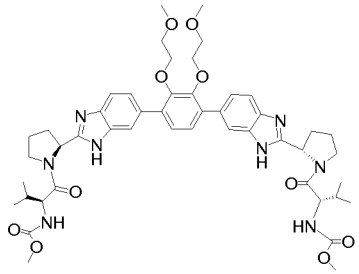
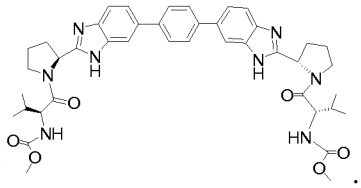
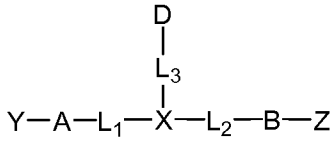
It is noted that the anti-HCV activity of  has not been shown to be better than that of  .

Table 5 also demonstrates that additional halo substitution(s) on the carbocycle/heterocycle substituents on the pyrrolidinyl linker can significantly improve the compounds' anti-HCV activities (e.g., compare Example 4.25 to Example 3.20 or Example 5.1).

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 or R_F;

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 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 $-SF_5$; 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 $-O-R_S$, $-S-R_S$, $-C(O)R_S$, $-OC(O)R_S$, $-C(O)OR_S$, $-N(R_SR_S')$, $-S(O)R_S$, $-SO_2R_S$, $-C(O)N(R_SR_S')$, $-N(R_S)C(O)R_S'$, $-N(R_S)C(O)N(R_S'R_S'')$, $-N(R_S)SO_2R_S'$, $-SO_2N(R_SR_S')$, $-N(R_S)SO_2N(R_S'R_S'')$, $-N(R_S)S(O)N(R_S'R_S'')$, $-OS(O)-R_S$, $-OS(O)_2-R_S$, $-S(O)_2OR_S$, $-S(O)OR_S$, $-OC(O)OR_S$, $-N(R_S)C(O)OR_S'$, $-OC(O)N(R_SR_S')$, $-N(R_S)S(O)-R_S'$, $-S(O)N(R_SR_S')$, $-P(O)(OR_S)_2$, 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 $-N(R_SR_S')$;

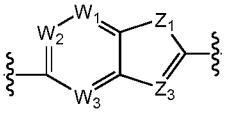
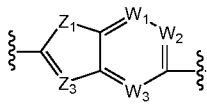
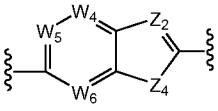
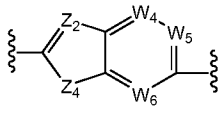
R_F is independently selected at each occurrence from C_1-C_{10}alkyl, C_2-C_{10}alkenyl or C_2-C_{10}alkynyl, each of which contains 0, 1, 2, 3, 4 or 5 heteroatoms selected from O, S or N and is independently optionally substituted with one or more R_L; or $-(R_X-R_Y)_Q-(R_X-R_Y')$, wherein Q is 0, 1, 2, 3 or 4, and each R_X is independently O, S or $N(R_B)$, wherein each R_Y is independently C_1-C_6alkylene, C_2-C_6alkenylene or C_2-C_6alkynylene each of which is independently optionally substituted with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl or cyano, and wherein each R_Y' is independently C_1-C_6alkyl, C_2-C_6alkenyl or C_2-C_6alkynyl each of which is independently optionally substituted with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl or cyano;

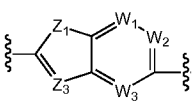
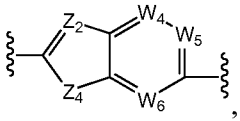
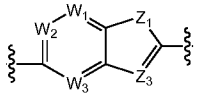
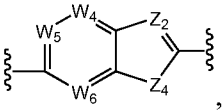
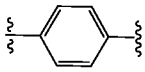
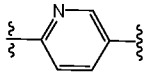
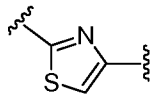
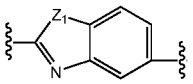
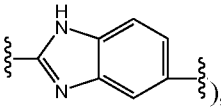
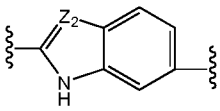
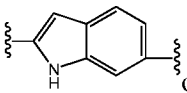
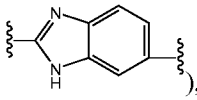
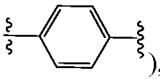
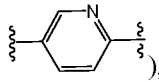
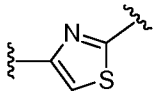
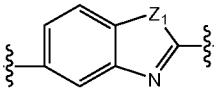
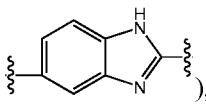
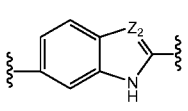
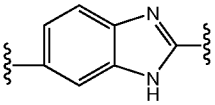
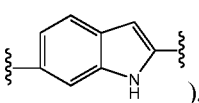
R_L is independently selected at each occurrence from halogen, nitro, oxo, phosphonoxy, phosphono, thioxo, cyano, $-O-R_S$, $-S-R_S$, $-C(O)R_S$, $-OC(O)R_S$, $-C(O)OR_S$, $-N(R_SR_S')$, $-S(O)R_S$, $-SO_2R_S$, $-C(O)N(R_SR_S')$ or $-N(R_S)C(O)R_S'$; or C_3-C_6carbocycle or 3- to 6-membered heterocycle, 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; 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;

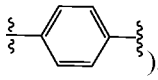
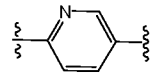
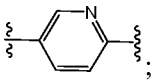
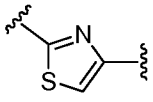
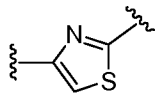
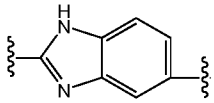
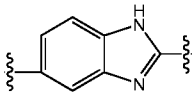
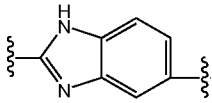
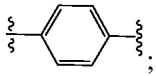
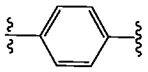
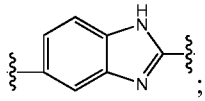
L_S, L_S' and L_S'' are each independently selected at each occurrence from bond; or C_1-C_6alkylene, C_2-C_6alkenylene or C_2-C_6alkynylene, each of which is independently optionally substituted at each occurrence with one or more R_L; and

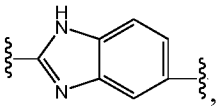
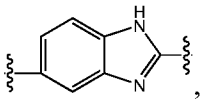
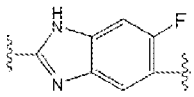
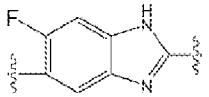
R_S, R_S' and R_S'' are each independently selected at each occurrence from hydrogen; C_1-C_6alkyl, C_2-C_6alkenyl or C_2-C_6alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, $-O-C_1$-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.

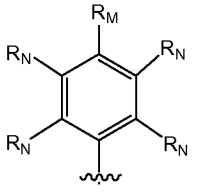
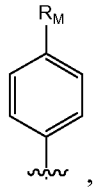
A and B preferably are independently selected from C_5-C_6carbocycle (e.g., phenyl), 5- to 6-membered heterocycle (e.g., pyridinyl or thiazolyl), or 8- to 12-membered bicycles such as  ,  ,  or  , where Z_1 is independently selected at each occurrence from O, S, NH or CH_2, Z_2 is independently selected 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.

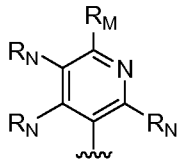
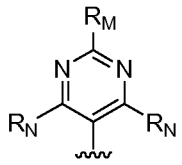
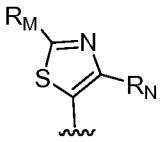
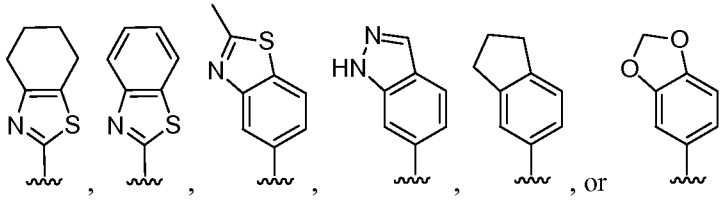
More preferably, A is selected from C_5-C_6carbocycle, 5- to 6-membered heterocycle,  or  , and is optionally substituted with one or more R_A; B is selected from C_5-C_6carbocycle, 5- to 6-membered heterocycle,  or  , and is optionally substituted with one or more R_A; where Z_1, Z_2, Z_3, Z_4, W_1, 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.

Also preferably, A is  , B is  , and A and B are substituted with one or more halogen, such as F or Cl. It was surprisingly discovered that when A and/or B were halo-substituted benzimidazole (e.g., A is  and B is ), the compounds of Formula I (as well as compounds of Formula I_A, I_B, I_C, I_D, I_E, I_F or I_G described below, and compounds of each embodiment described thereunder) unexpectedly showed significantly improved pharmacokinetic properties, as compared to compounds with unsubstituted benzimidazole. The improvements in pharmacokinetics can be observed, for instance, as a greater total plasma level exposure, measured as the area under the curve (AUC) over a 24 hour period following oral dosing in mouse (for examples see infra). It was also surprisingly discovered that these compounds with halo-substituted benzimidazole unexpectedly displayed improved inhibitory activity against certain HCV genotype 1a variants (e.g., variants containing NS5A mutations L31M, Y93H, or Y93N). Accordingly, the present invention contemplates methods of using such compounds to treat HCV genotype 1a variant infection (e.g., L31M, Y93H, or Y93N 1a variant infection). These methods comprise administering such a compound to a patient having HCV genotype 1a variant (e.g., L31M, Y93H, or Y93N 1a variant). The present invention also contemplates the use of such compounds for the manufacture of a medicament for the treatment of genotype 1a variant infection (e.g., L31M, Y93H, or Y93N 1a variant infection).

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.

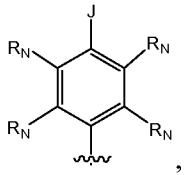
Preferably, R_M is halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, cyano; or C_1-C_6alkyl, C_2-C_6alkenyl or C_2-C_6alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto,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

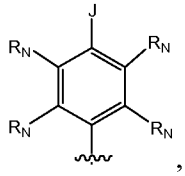
Also preferably, R_M is halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, or cyano; or R_M is $-L_S-R_E$, wherein L_S is a bond or C_1-C_6alkylene, and R_E is $-N(R_SR_S')$, $-O-R_S$, $-C(O)R_S$, $-C(O)OR_S$, $-C(O)N(R_SR_S')$, $-N(R_S)C(O)R_S'$, $-N(R_S)C(O)OR_S'$, $-N(R_S)SO_2R_S'$, $-SO_2R_S$, $-SR_S$, 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_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-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).

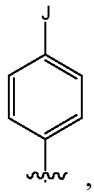
More preferably, D is C_5-C_6carbocycle, 5- to 6-membered heterocycle or 6- to 12-membered bicycle and is substituted with J and optionally substituted with one or more R_A, wherein J is C_3-C_6carbocycle, 3- to 6-membered heterocycle or 6- to 12-membered bicycle and is optionally substituted with one or more R_A. Preferably, J is substituted with a C_3-C_6carbocycle or 3- to 6-membered heterocycle, wherein said C_3-C_6carbocycle or 3- to 6-membered heterocycle is independently 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, C_2-C_6haloalkynyl, C(O)OR_S or –N(R_SR_S'), and J can also be optionally substituted with one or more R_A. Also preferably, D is C_5-C_6carbocycle or 5- to 6-membered heterocycle and is substituted with J and 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, and preferably, J is at least substituted with a C_3-C_6carbocycle or 3- to 6-membered heterocycle which is independently 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, C_2-C_6haloalkynyl, C(O)OR_S or –N(R_SR_S'). Also preferably, D is C_5-C_6carbocycle or 5- to 6-membered heterocycle and is substituted with J and optionally substituted with one or more R_A, and J is 6- to 12-membered bicycle (e.g., a 7- to 12-membered fused, bridged or spiro bicycle comprising a nitrogen ring atom through which J is covalently attached to D) and is optionally substituted with one or more R_A. More preferably, D is phenyl and is substituted with J and optionally substituted with one or more R_A, and J is C_3-C_6carbocycle, 3- to 6-membered heterocycle or 6- to 12-membered bicycle and is optionally substituted with one or more R_A, and preferably J is at least substituted with a C_3-C_6carbocycle or 3- to 6-membered heterocycle which is independently 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, C_2-C_6haloalkynyl, C(O)OR_S or –



$N(R_SR_S')$. Highly preferably, D is , wherein each R_N is independently selected from R_D and preferably is hydrogen or halogen, and J is C_3-C_6carbocycle, 3- to 6-membered heterocycle or 6- to 12-membered bicycle and is optionally substituted with one or more R_A, and preferably J is at least substituted with a C_3-C_6carbocycle or 3- to 6-membered heterocycle which is independently 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, C_2-C_6haloalkynyl, $C(O)OR_S$ or –$N(R_SR_S')$. Also preferably, D is

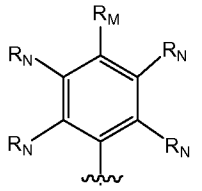
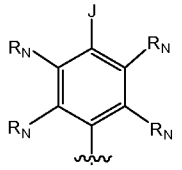
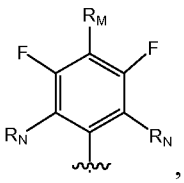
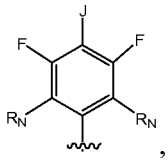
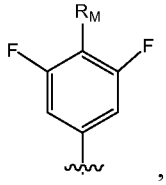
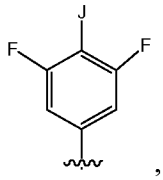
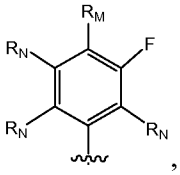
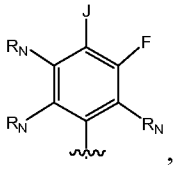
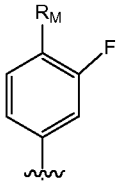
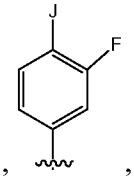
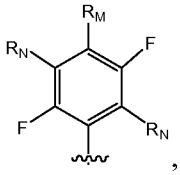
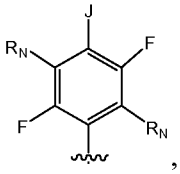
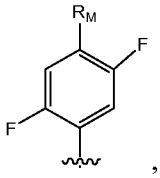
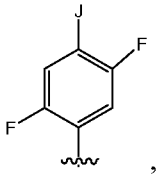


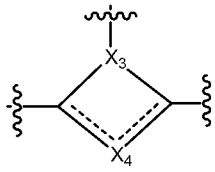
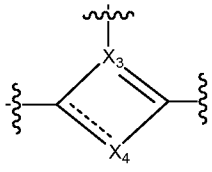
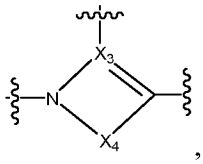
, wherein each R_N is independently selected from R_D and preferably is hydrogen or halogen, and J is C_3-C_6carbocycle or 3- to 6-membered heterocycle and is substituted with a C_3-C_6carbocycle or 3- to 6-membered heterocycle which is independently optionally substituted with one or more substituents 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, C_2-C_6haloalkynyl, $C(O)OR_S$ or –$N(R_SR_S')$, and J can also be optionally substituted with one or more R_A. Also preferably, D is



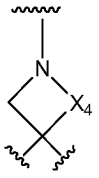
, and J is C_3-C_6carbocycle or 3- to 6-membered heterocycle and is optionally substituted with one or more R_A, and preferably J is at least substituted with a C_3-C_6carbocycle or 3- to 6-membered heterocycle which is independently optionally substituted with one or more substituents selected from 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, C_2-C_6haloalkynyl, $C(O)OR_S$ or –$N(R_SR_S')$.

It was surprisingly discovered that when D contains a halo-substituted carbocycle or heterocycle (e.g., a halo-substituted 5-6 membered carbocycle or heterocycle directly linked to X), the compound of Formula I (as well as compounds of Formula I_A, I_B, I_C, I_D, I_E, I_F or I_G described below, and compounds of each embodiment described thereunder) can exhibit significantly improved inhibitory activity against HCV genotypes 2a, 2b, 3a or 4a and/or improved pharmacokinetic properties. Therefore, the present invention contemplates methods of using such compounds to treat HCV genotype 2a, 2b, 3a or 4a infection. These methods comprise administering such a compound to

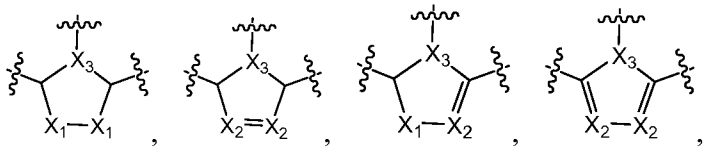
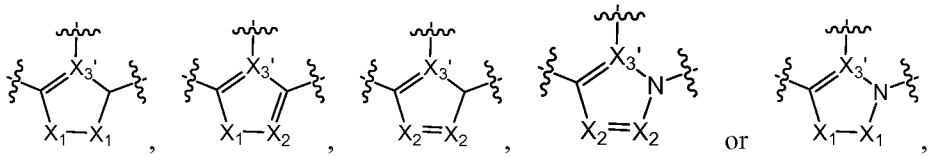
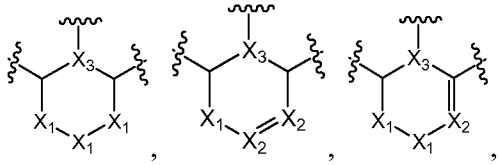
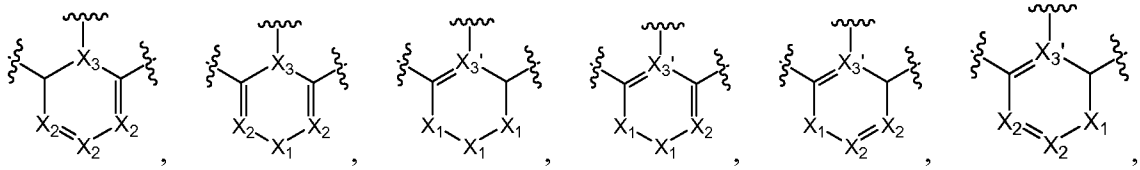
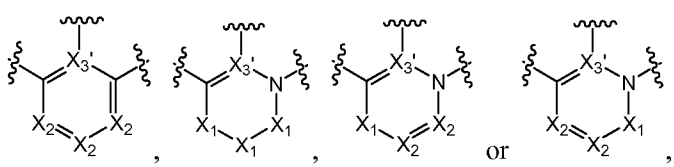
a patient having HCV genotype 2a, 2b, 3a or 4a. The present invention also contemplates the use of such compounds for the manufacture of a medicament for the treatment of HCV genotypes 2a, 2b, 3a or 4a. Suitable D for this purpose can be, for instance,  or  as described above, wherein at least one R_N is halo such as fluorine. Specific examples of suitable D include, but are not limited to,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  and , wherein R_N, R_M and J are as described above.

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 or R_F. X can also be C_5-C_6carbocycle or 5- to 6-membered heterocycle which is optionally substituted with one or more R_A or R_F, 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 or R_F, 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

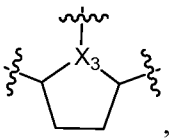
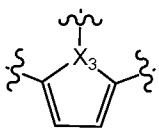
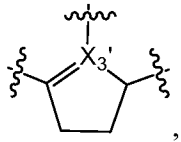
optionally contains one or two heteroatoms selected from O, S or N, and X is optionally substituted with one or more R_A or R_F, and two adjacent R_A on X, taken together with the ring atoms to which they are attached, optionally form a 5- to 6-membered carbocycle or heterocycle. Moreover, X can be



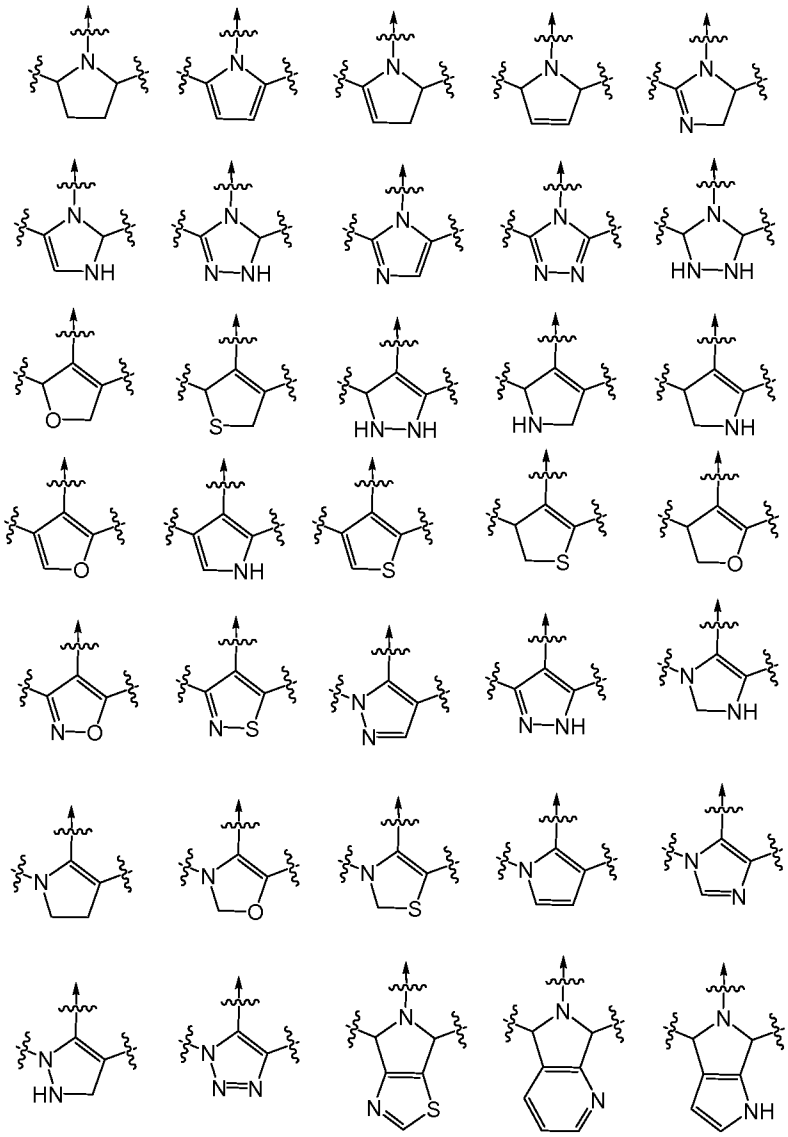
wherein N is directly linked to L_3–D, X_4 is C_2-C_4alkylene, C_2-C_4alkenylene or C_2-C_4alkynylene each of which optionally contains one or two heteroatoms selected from O, S or N, and X is optionally substituted with one or more R_A or R_F, and two adjacent R_A on X, taken together with the ring atoms to which they are attached, optionally form a 5- to 6-membered carbocycle or heterocycle.

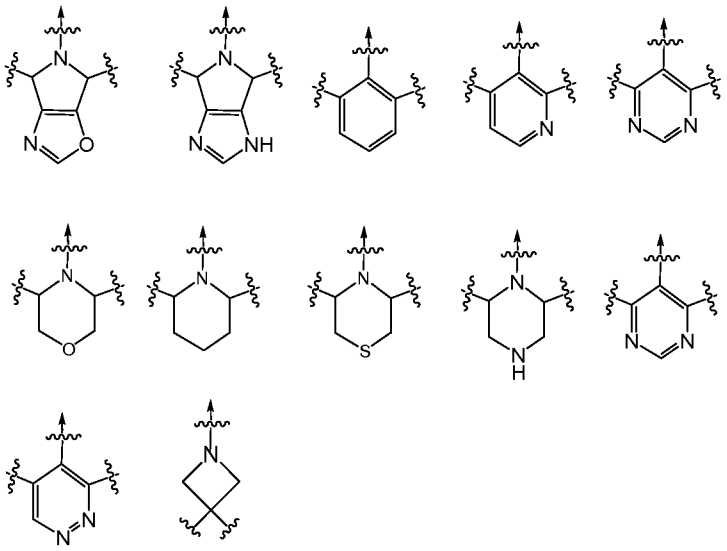
For instance, X can be  ,  , or , wherein X_1 is independently selected at each occurrence from CH_2, O, S or NH, X_2 is independently selected at each occurrence from CH or N, X_3 is N and is directly linked to –L_3–D, and X_3' is C and is directly linked to –L_3–D; and X is optionally substituted with one or more R_A or R_F, 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 or R_F, 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 or R_F, 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.

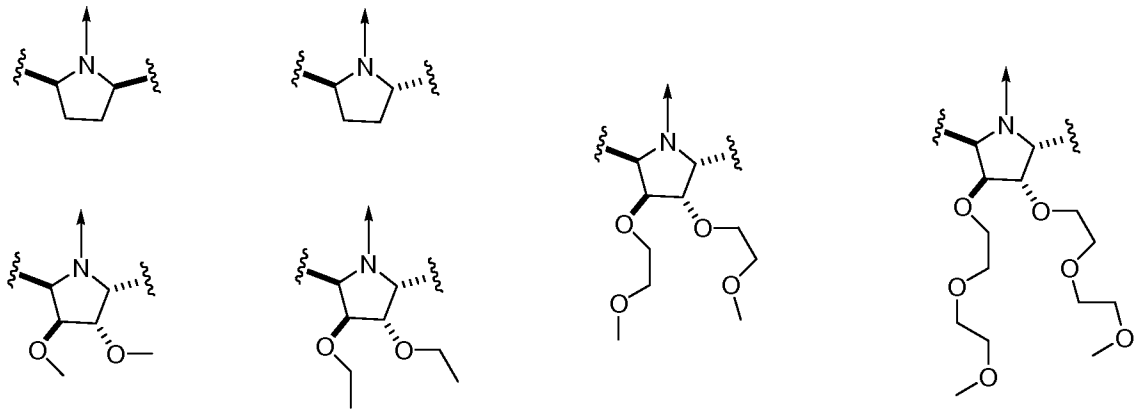
Non-limiting examples of X include:





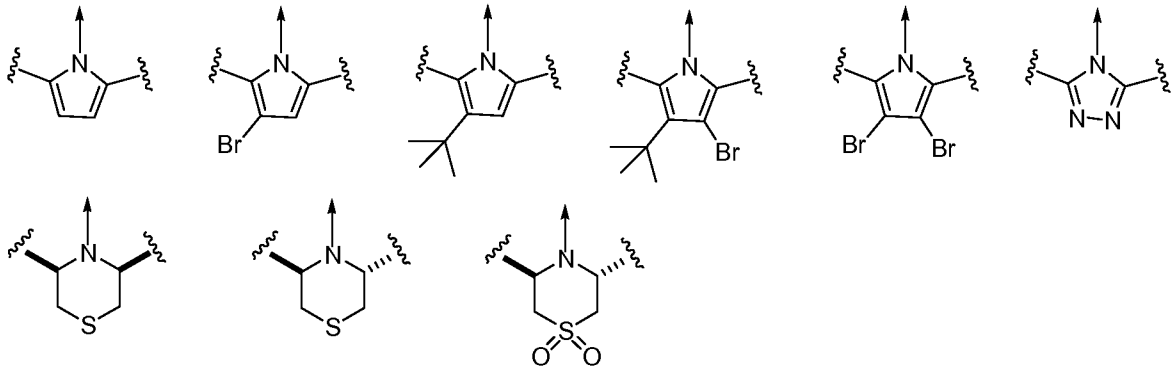
wherein "→" indicates the covalent attachment to $-L_3-D$. Each X can be optionally substituted with one or more R_A or R_F, and two adjacent R_A on X, taken together with the ring atoms to which they are attached, optionally form a 5- to 6-membered carbocycle or heterocycle.

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

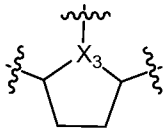
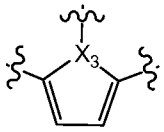


As shown, the relative stereochemistry at the 2- and 5-positions of the above pyrrolidine ring may be either cis or trans. The stereochemistries of optional substituents R_A at the 3- or 4-positions of the pyrrolidine may vary relative to any substituent at any other position on the pyrrolidine ring. 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 or R_F:

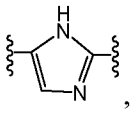
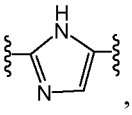
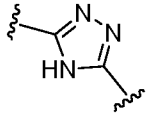
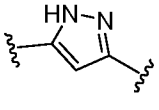
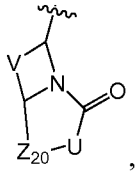
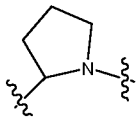
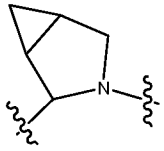
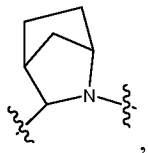
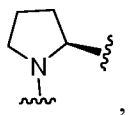
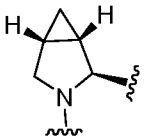
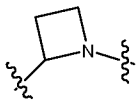
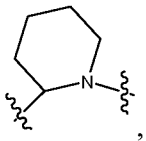
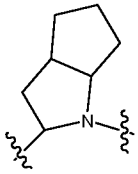
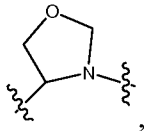
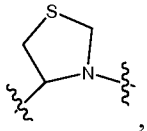
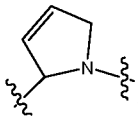
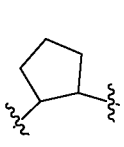
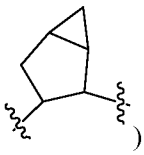


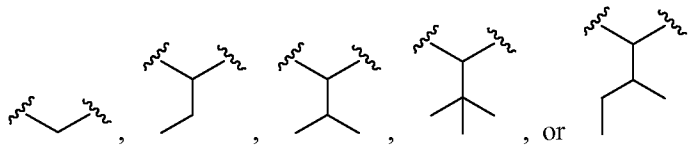
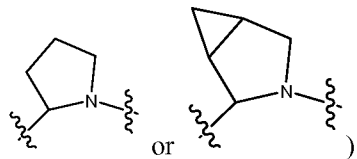
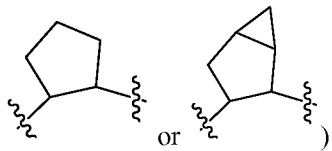
As shown, the relative stereochemistry at the 3- and 5-positions of the thiomorpholine ring may be either cis or trans. Depending on the particular substituents attached to the thiomorpholine, the stereochemistry at any carbon may be either (R) or (S).

Also preferably, 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 or R_F. Preferably, R_F is 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 independently optionally substituted with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl or cyano. Also preferably, R_F is 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 independently optionally substituted with one or more R_L. Also preferably, R_F is $-(R_X-R_Y)_Q-(R_X-R_Y')$, wherein Q is 0, 1, 2, 3 or 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 independently optionally substituted with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl or cyano; and each R_Y' is independently C_1-C_6alkyl, C_2-C_6alkenyl or C_2-C_6alkynyl each of which is independently optionally substituted with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl or cyano. Preferably, each R_X is O. More preferably, X is optionally substituted with one or more R_A or R_F, each R_F 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 independently optionally substituted with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl or cyano. Also preferably, X is optionally substituted with one or more R_A or R_F, each R_F is independently selected from $-(O-C_1-C_6\text{alkylene})_Q-(O-C_1-C_6\text{alkyl})$, wherein Q preferably is 0, 1, 2 or 3.

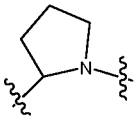
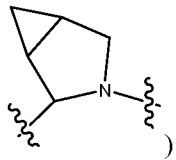
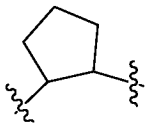
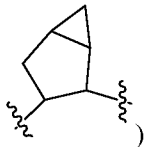
L_1 and L_2 are preferably independently bond or C_1-C_6alkylene, L_3 is preferably selected from bond, C_1-C_6alkylene or –C(O)–, and L_1, L_2, and L_3 are each independently optionally substituted with one or more R_L. More preferably, L_1, L_2 and L_3 are each independently bond or C_1-C_6alkylene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

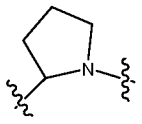
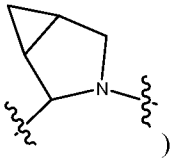
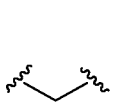
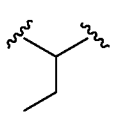
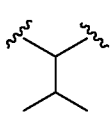
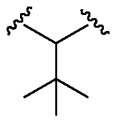
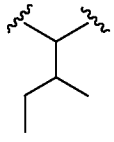
CH_2– or –CH_2CH_2–), and are each independently optionally substituted with one or more R_L. Highly preferably, L_1, L_2 and L_3 are bond.

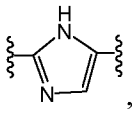
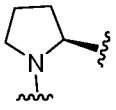
Y is preferably selected from –L_S–$C(R_1R_2)N(R_5)$–T–R_D, –L_S–$C(R_3R_4)C(R_6R_7)$–T–R_D, –G–$C(R_1R_2)N(R_5)$–T–R_D, –G–$C(R_3R_4)C(R_6R_7)$–T–R_D, –$N(R_B)C(O)C(R_1R_2)N(R_5)$–T–$R_D$, –$N(R_B)C(O)C(R_3R_4)C(R_6R_7)$–T–$R_D$, –$C(O)N(R_B)C(R_1R_2)N(R_5)$–T–$R_D$, –$C(O)N(R_B)C(R_3R_4)C(R_6R_7)$–T–$R_D$, –$N(R_B)C(O)$–$L_S$–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 independently 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  ,  ,  ,  ,  , 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)).

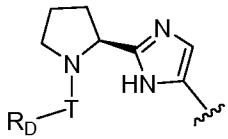
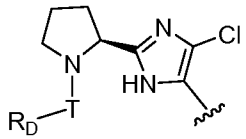
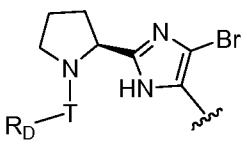
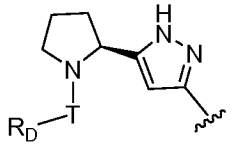
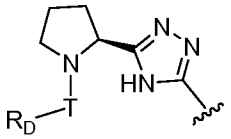
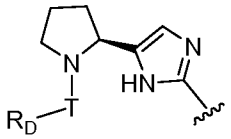
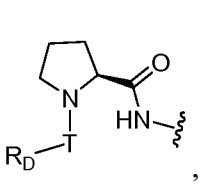
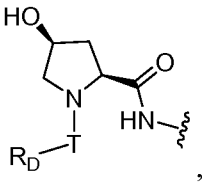
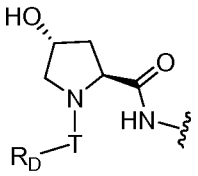
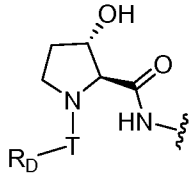
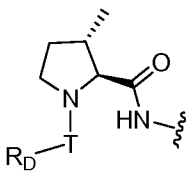
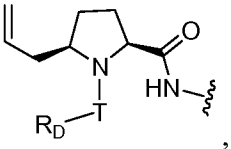
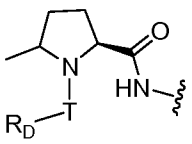
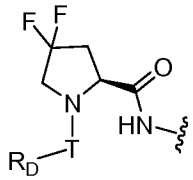
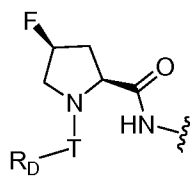
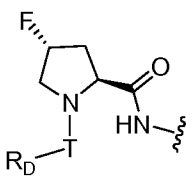
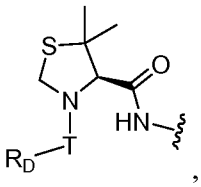
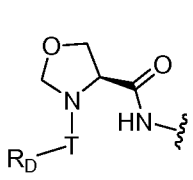
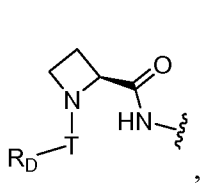
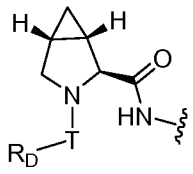
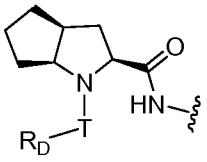
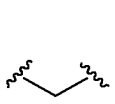
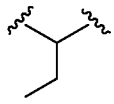
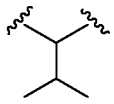
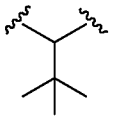
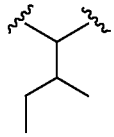
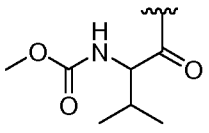
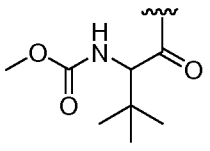
Y can also be selected from –M–C(R_1R_2)N(R_5)–C(O)–L_Y'–M'–R_D, –M–C(R_1R_2)N(R_5)–L_Y'–M'–R_D, –L_S–C(R_1R_2)N(R_5)–C(O)–L_Y'–M'–R_D, –L_S–C(R_1R_2)N(R_5)–L_Y'–M'–R_D, –M–C(R_3R_4)C(R_6R_7)–C(O)–L_Y'–M'–R_D, –M–C(R_3R_4)C(R_6R_7)–L_Y'–M'–R_D, –L_S–C(R_3R_4)C(R_6R_7)–C(O)–L_Y'–M'–R_D, or –L_S–C(R_3R_4)C(R_6R_7)–L_Y'–M'–R_D, 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,  , 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_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) 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.,  or) which is optionally substituted with one or more R_A.

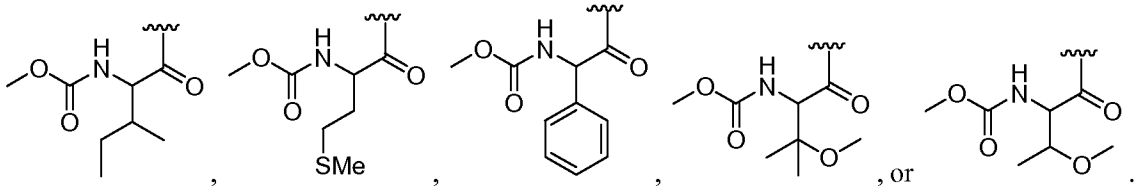
Also preferably, Y is selected from –N(R_B)CO–C(R_1R_2)N(R_5)–C(O)–L_Y'–N(R_B)C(O)O–R_D, –N(R_B)CO–C(R_1R_2)N(R_5)–C(O)–L_Y'–N(R_B)C(O)–R_D, –N(R_B)CO–C(R_1R_2)N(R_5)–C(O)–L_Y'–N(R_B)S(O)$_2$–R_D, –N(R_B)CO–C(R_1R_2)N(R_5)–C(O)–L_Y'–N(R_BR_B')–R_D, –N(R_B)CO–C(R_1R_2)N(R_5)–C(O)–L_Y'–O–R_D, –N(R_B)CO–C(R_1R_2)N(R_5)–C(O)–L_Y'–R_D, –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 or 3- to 6-membered heterocycle which is independently 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,  ,  ,  ,  , or  (stereochemistry at a carbon within the group L_Y can be either (R) or (S)), L_Y is independently optionally substituted with one or more R_L (e.g., one or more phenyl or methoxy), G

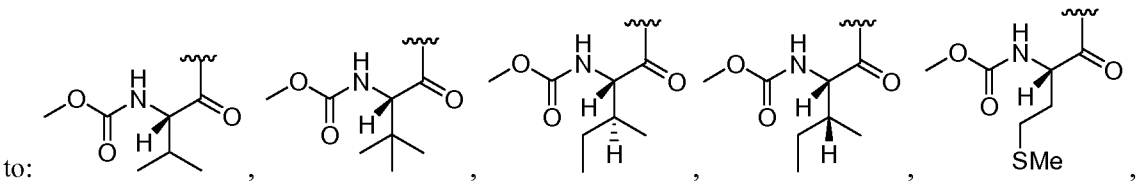
preferably is  , R_B'' is hydrogen; $-C(R_1R_2)N(R_5)-$ is  ; L_S is a bond; and R_E is methoxy.

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 independently 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:  ,  ,

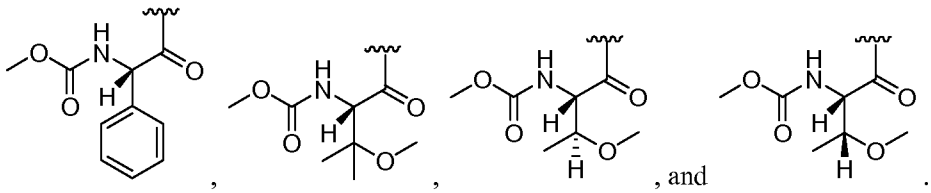


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T-R_D may also include certain stereochemical configurations; thus T-R_D includes, but is not limited to:

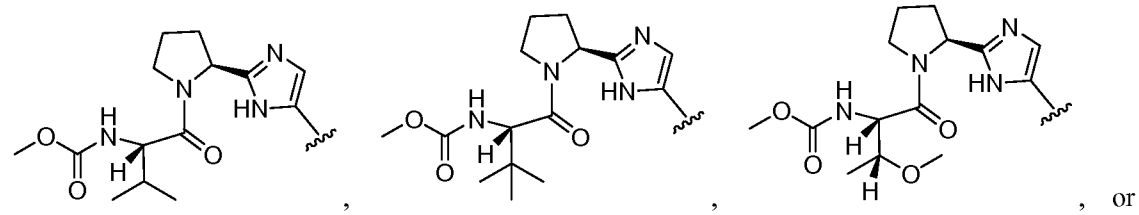


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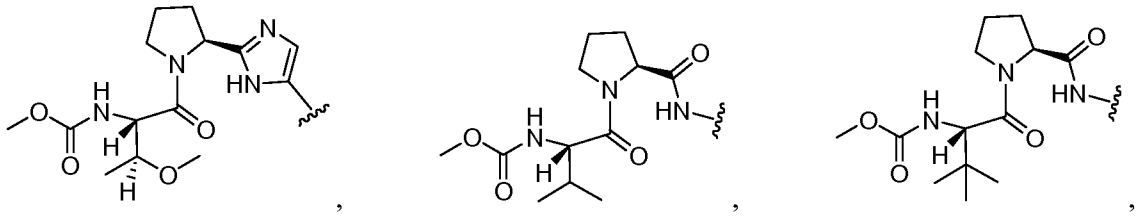


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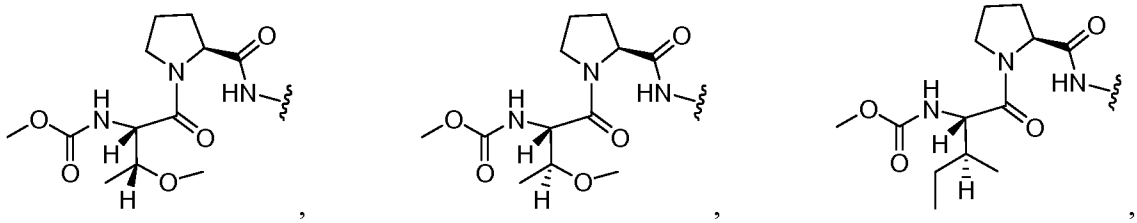
Non-limiting examples of preferred Y also include:



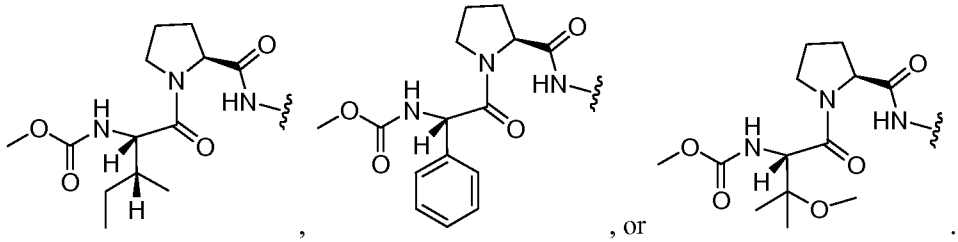
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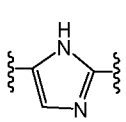
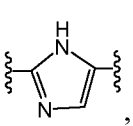
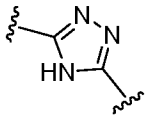
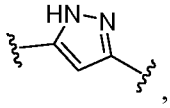


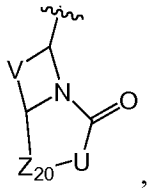
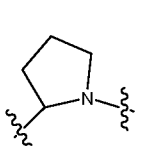
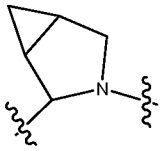
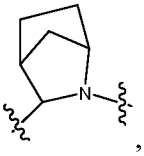
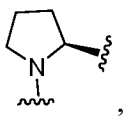
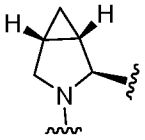
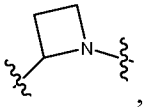
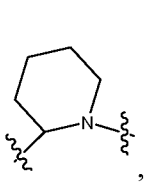
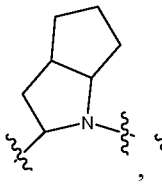
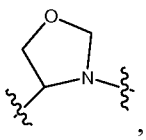
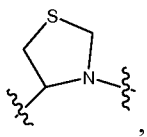
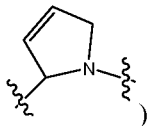
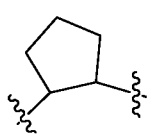
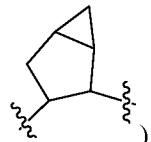
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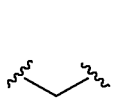
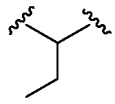
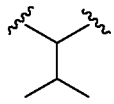
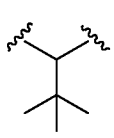
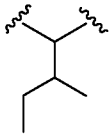
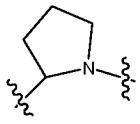
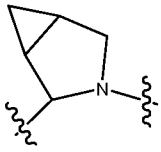
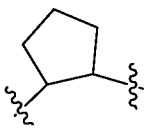
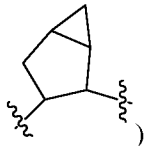
, , or .

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

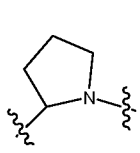
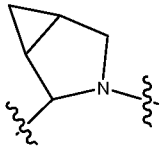
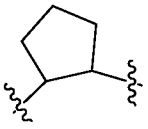
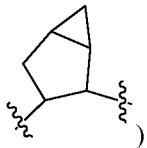
$N(R_B)C(O)C(R_{10}R_{11})C(R_{13}R_{14})–T–R_D$, $–C(O)N(R_B)C(R_8R_9)N(R_{12})–T–R_D$, $–C(O)N(R_B)C(R_{10}R_{11})C(R_{13}R_{14})–T–R_D$, $–N(R_B)C(O)–L_S–E$, or $–C(O)N(R_B)–L_S–E$. G is C_5-C_6carbocycle or 5- to 6-membered heterocycle, such as  ,  ,  or  , and is optionally substituted with one or more R_A (e.g., one or more chloro or bromo).

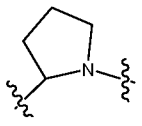
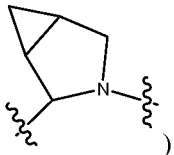
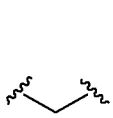
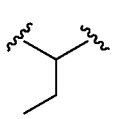
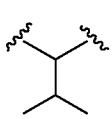
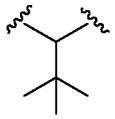
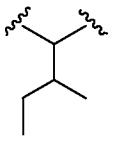
E preferably is a 8- to 12-membered bicycle (such as  , wherein U is independently selected at each occurrence from -(CH_2)- or -(NH)-; and V and Z_{20} are each independently selected from C_1-C_4alkylene, C_2-C_4alkenylene or C_2-C_4alkynylene, in which at least one carbon atom is independently optionally replaced with O, S or N), and is independently 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)).

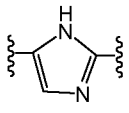
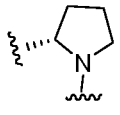
Z can also be selected from $–M–C(R_8R_9)N(R_{12})–C(O)–L_Y'–M'–R_D$, $–M–C(R_8R_9)N(R_{12})–L_Y'–M'–R_D$, $–L_S–C(R_8R_9)N(R_{12})–C(O)–L_Y'–M'–R_D$, $–L_S–C(R_8R_9)N(R_{12})–L_Y'–M'–R_D$, $–M–C(R_{10}R_{11})C(R_{13}R_{14})–C(O)–L_Y'–M'–R_D$, $–M–C(R_{10}R_{11})C(R_{13}R_{14})–L_Y'–M'–R_D$, $–L_S–$

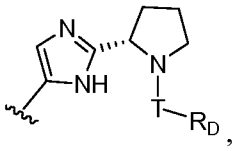
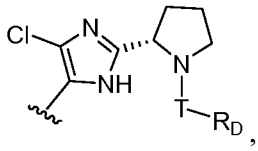
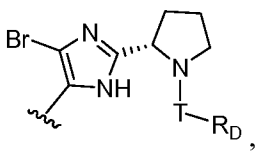
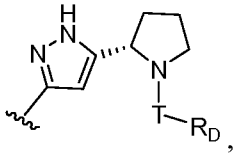
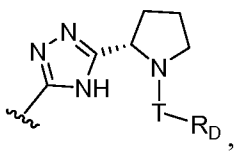
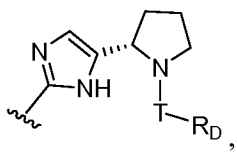
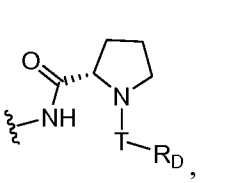
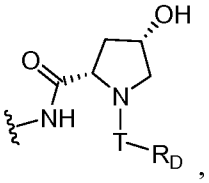
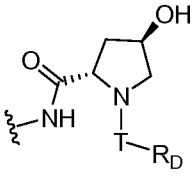
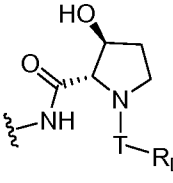
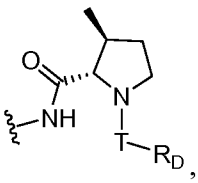
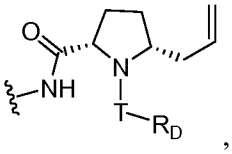
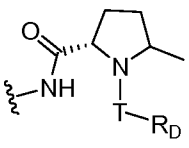
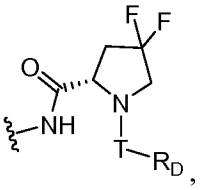
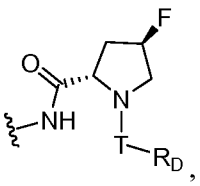
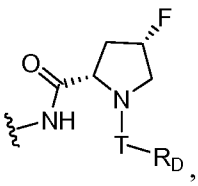
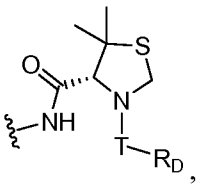
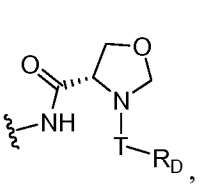
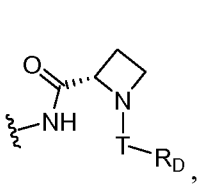
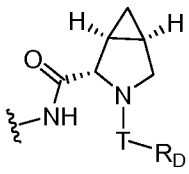
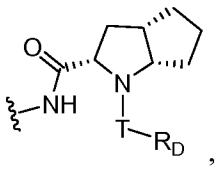
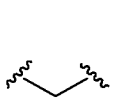
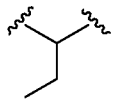
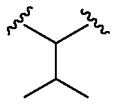
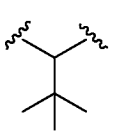
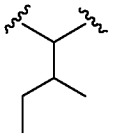
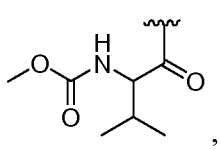
$C(R_{10}R_{11})C(R_{13}R_{14})$–$C(O)$–$L_Y$'–M'–$R_D$, or –$L_S$–$C(R_{10}R_{11})C(R_{13}R_{14})$–$L_Y$'–M'–$R_D$, wherein M preferably is bond, –$C(O)N(R_B)$– or –$N(R_B)C(O)$–, M' preferably is bond, –$C(O)N(R_B)$–, –$N(R_B)C(O)$–, –$N(R_B)C(O)O$–, $N(R_B)C(O)N(R_B')$–, –$N(R_B)S(O)$– or –$N(R_B)S(O)_2$–, and L_Y' preferably is C_1-C_6alkylene which is independently 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.

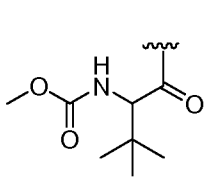
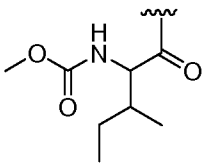
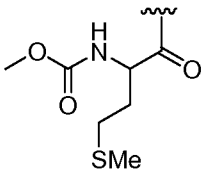
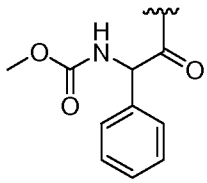
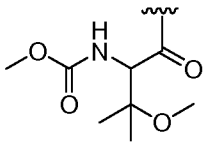
Also preferably, Z is selected from –$N(R_B)CO$–$C(R_8R_9)N(R_{12})$–$C(O)$–L_Y'–$N(R_B)C(O)O$–R_D, –$N(R_B)CO$–$C(R_8R_9)N(R_{12})$–$C(O)$–L_Y'–$N(R_B)C(O)$–R_D, –$N(R_B)CO$–$C(R_8R_9)N(R_{12})$–$C(O)$–L_Y'–$N(R_B)S(O)_2$–R_D, –$N(R_B)CO$–$C(R_8R_9)N(R_{12})$–$C(O)$–L_Y'–$N(R_BR_B')$–R_D, –$N(R_B)CO$–$C(R_8R_9)N(R_{12})$–$C(O)$–L_Y'–O–R_D,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

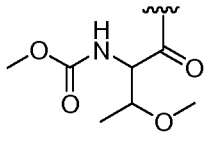
R_D, $-L_S-C(R_{10}R_{11})C(R_{13}R_{14})-C(O)-L_Y'-N(R_B)S(O)_2-R_D$, $-L_S-C(R_{10}R_{11})C(R_{13}R_{14})-C(O)-L_Y'-N(R_BR_B')-R_D$, $-L_S-C(R_{10}R_{11})C(R_{13}R_{14})-C(O)-L_Y'-O-R_D$, $-L_S-C(R_{10}R_{11})C(R_{13}R_{14})-C(O)-L_Y'-R_D$, or $-L_S-C(R_{10}R_{11})C(R_{13}R_{14})-R_D$, wherein L_Y' preferably is C_1-C_6alkylene which is independently 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.

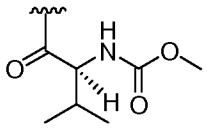
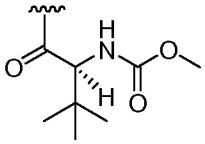
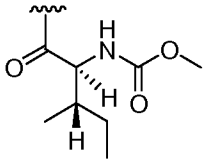
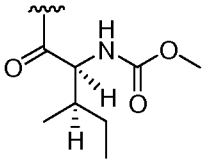
Highly preferably, Z is selected from $-N(R_B'')CO-C(R_8R_9)N(R_{12})-C(O)-L_Y-N(R_B'')C(O)-L_S-R_E$ or $-C(R_8R_9)N(R_{12})-C(O)-L_Y-N(R_B'')C(O)-L_S-R_E$, or Z is $-G-C(R_8R_9)N(R_{12})-C(O)-L_Y-N(R_B'')C(O)-L_S-R_E$, wherein L_Y is C_1-C_6alkylene optionally substituted with one or more R_L, and R_B'' 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 or 3- to 6-membered heterocycle which is independently 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,  ,  ,  ,  , or  (stereochemistry at a carbon within the group L_Y can be either (R) or (S)); L_Y is independently optionally substituted with one or more R_L (e.g., one or more phenyl or methoxy); G

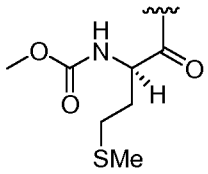
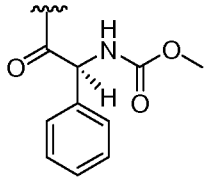
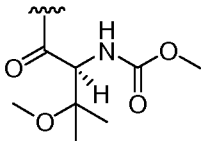
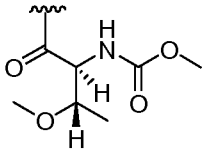
preferably is  ; R_B'' is hydrogen; $-C(R_8R_9)N(R_{12})-$ is  ; L_S is a bond; and R_E is methoxy.

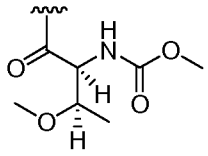
Non-limiting examples of preferred Z include:  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , or  , wherein T and R_D are as defined herein. T, for example, can be $-L_S-M-L_S'-M'-L_S''-$ where L_S is a bond; M is C(O); L_S' is C_1-C_6alkylene such as, but not limited to,  ,  ,  ,  , or  , where L_S' is independently 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

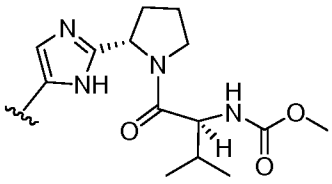

. $T\text{-}R_D$ may also include certain stereochemical configurations; thus $T\text{-}R_D$ includes, but is not limited to:

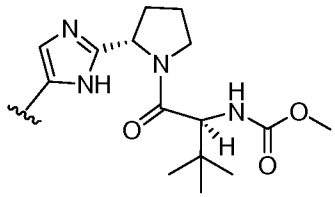
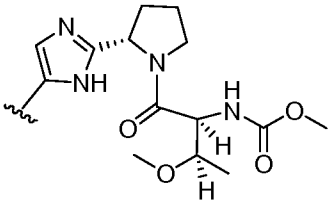
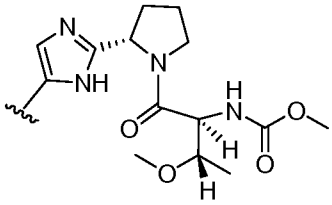




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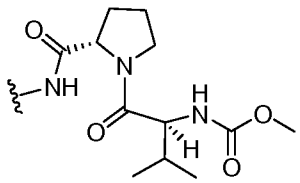
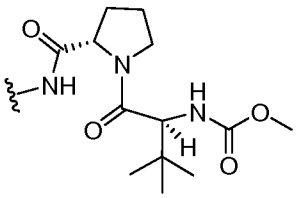
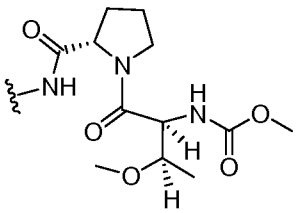




, and

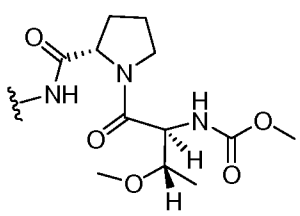
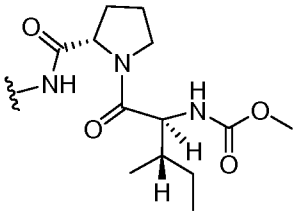
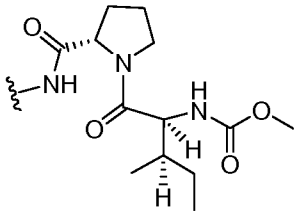
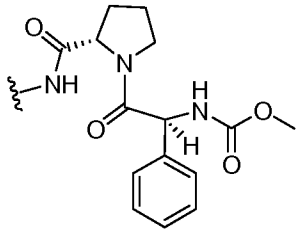
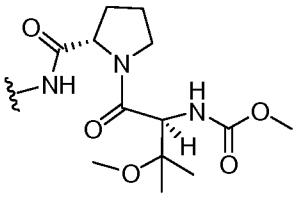

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Non-limiting examples of preferred Z also include:

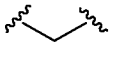

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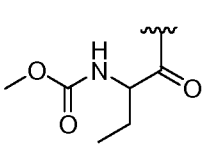
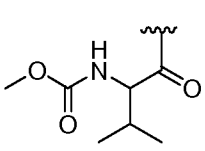
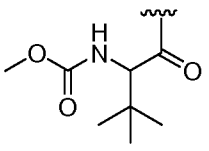
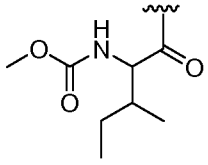
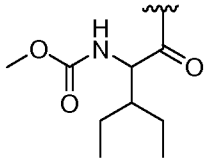
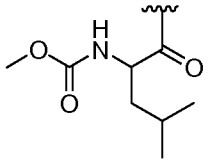
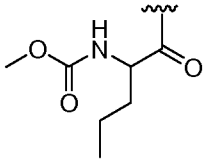
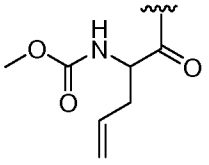
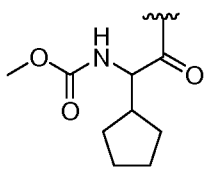
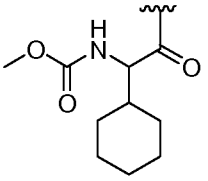
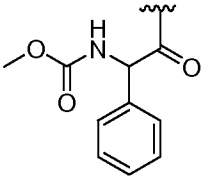
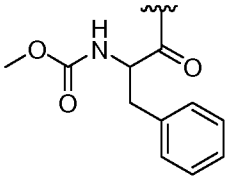
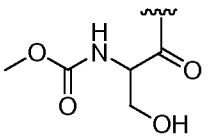



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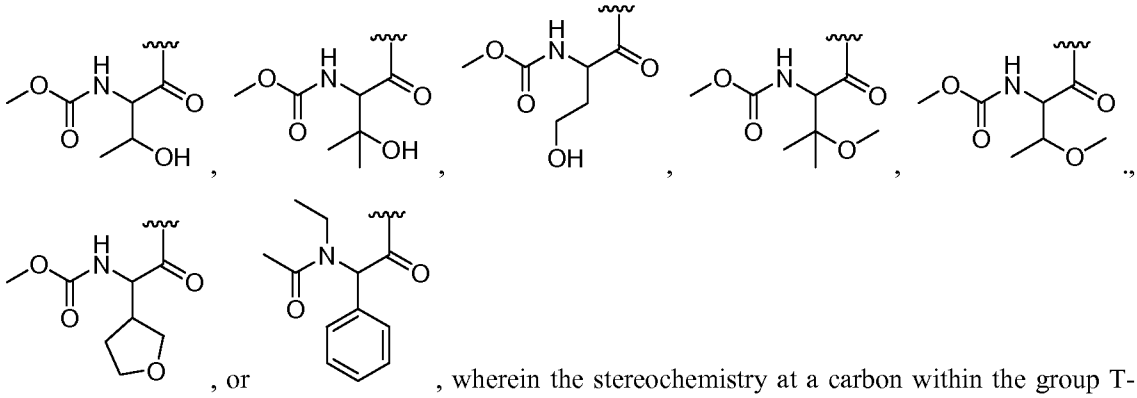



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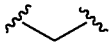
T can be, without limitation, independently selected at each occurrence from –C(O)–L_S'–, –C(O)O–L_S'–, –C(O)–L_S'–N(R_B)C(O)–L_S''–, –C(O)–L_S'–N(R_B)C(O)O–L_S''–, –N(R_B)C(O)–L_S'–N(R_B)C(O)–L_S''–, –N(R_B)C(O)–L_S'—N(R_B)C(O)O–L_S''–, or –N(R_B)C(O)–L_S'—N(R_B)–L_S''–. Preferably, T is independently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

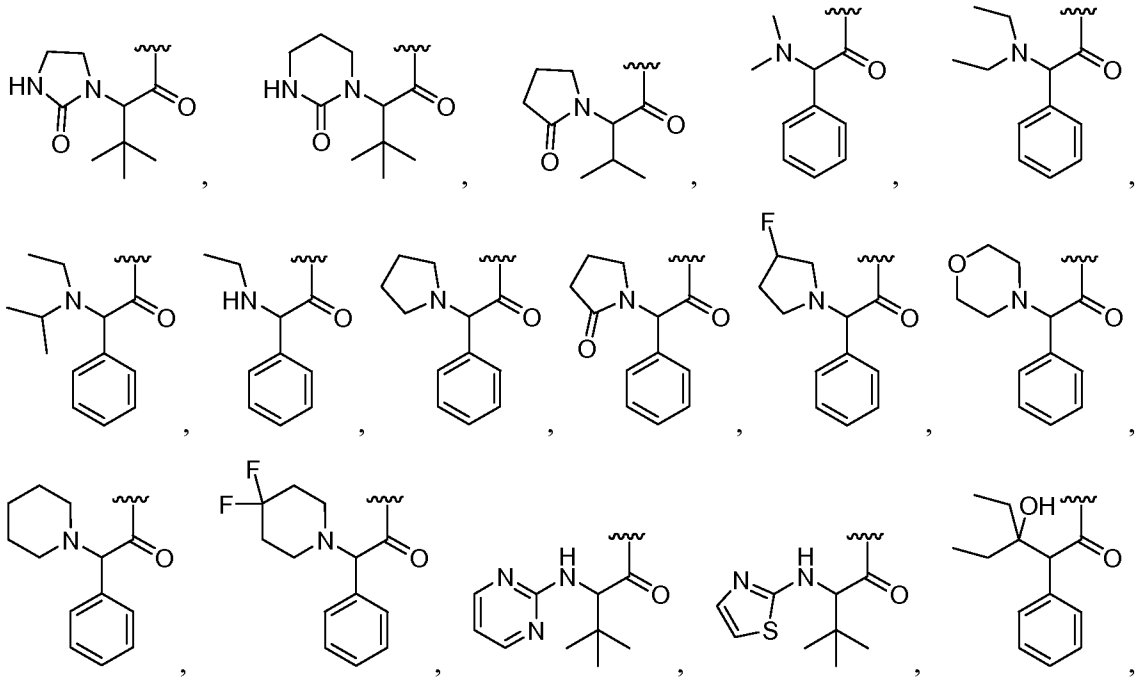
T can also be, for example, –L_S–M–L_S'–M'–L_S''– where L_S is a bond; M is C(O); L_S' is C_1-C_6alkylene (e.g., ), where L_S' is independently optionally substituted with R_T; the optional R_T is a substituent selected from –C_1-C_6alkyl, –C_2-C_6alkenyl, –C_1-C_6alkyl–OH, –C_1-C_6alkyl–O–C_1-C_6alkyl, 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).

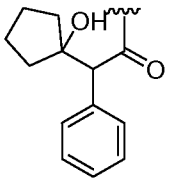
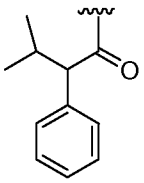
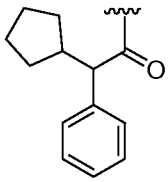
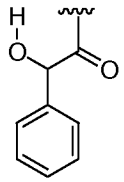
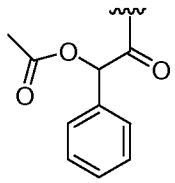
T-R_D can be, without limitation,

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, 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 independently 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:



, , , , 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 R_T, R_B, R_S, R_S', L_S and L_S' are as defined above.

For Formula I as well as Formulae I_A, I_B, I_C, I_D, I_E, I_F or I_G 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.

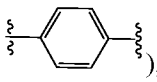
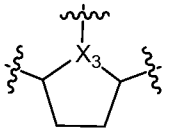
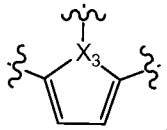
More preferably, R_A is halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, cyano; or C_1-C_6alkyl, C_2-C_6alkenyl or C_2-C_6alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy,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

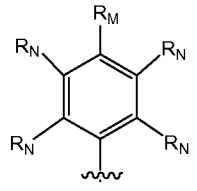
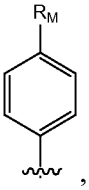
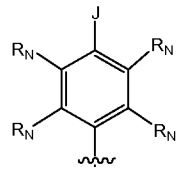
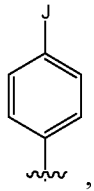
Highly preferably, R_A is halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, cyano; or C_1-C_6alkyl, C_2-C_6alkenyl or C_2-C_6alkynyl, each of which

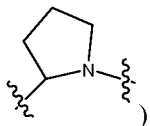
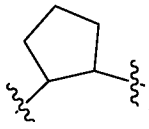
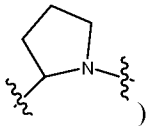
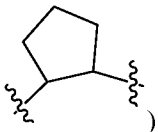
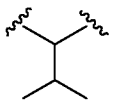
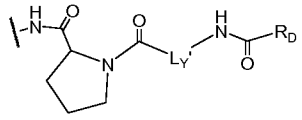
is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl or cyano.

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.

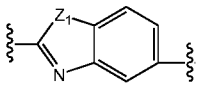
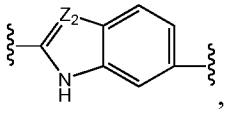
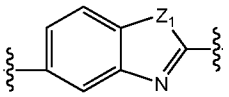
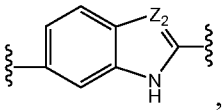
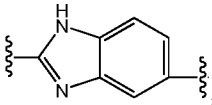
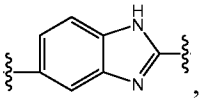
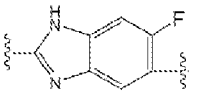
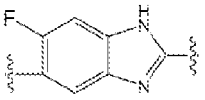
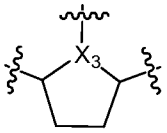
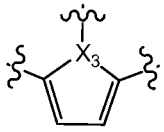
A and B can be the same or different. Likewise, L_1 and L_2, or Y and Z, or Y–A– and Z–B–, or –A–L_1– and –B–L_2–, can be the same or different. In some instances, Y–A–L_1– is identical to Z–B–L_2–. In some other instances, Y–A–L_1– is different from Z–B–L_2–.

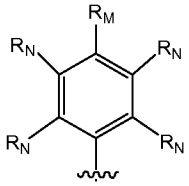
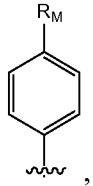
In one embodiment, A and B are each independently 5- or 6-membered carbocycle or heterocycle (e.g., phenyl such as ), and are each independently optionally substituted with one or more R_A. X is 5- or 6-membered carbocycle or heterocycle or 6- to 12-membered bicycle (e.g.,  or  , wherein X_3 is N and 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, or is substituted with J and optionally substituted with one or more R_A, wherein J is C_3-C_6carbocycle, 3- to 6-membered heterocycle or 6- to 12-membered bicycle and is optionally substituted with one or more R_A. Preferably, J is substituted with a C_3-C_6carbocycle or 3- to 6-membered heterocycle which is independently 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, C_2-C_6haloalkynyl, C(O)OR_S or –N($R_S$$R_S$'), and J can also be optionally substituted with one or more R_A.

Preferably, D is  or  , wherein R_M and R_N are as defined above. Also preferably, D is  or  , wherein J 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_1$$R_2$)N($R_5$)–T–$R_D$, or –N($R_B$)C(O)C($R_3$$R_4$)C($R_6$$R_7$)–T–$R_D$, and Z is –N($R_B$)C(O)C($R_8$$R_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,

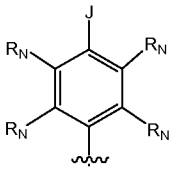
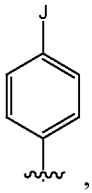
taken together with the atoms to which they are attached, form a 5- to 6-membered heterocyclic ring (e.g., ) which is optionally substituted with one or more R_A; R_3 and R_6 are each independently R_C, and R_4 and R_7, taken together with the atoms to which they are attached, form a 5- to 6-membered 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- or ) 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-

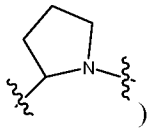
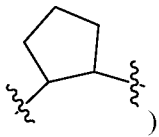
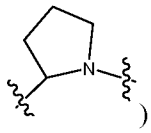
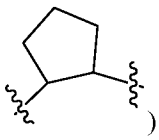
membered carbocycle or heterocycle, said 3- to 6-membered carbocycle or heterocycle being optionally substituted with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6haloalkyl, C_2-C_6haloalkenyl or C_2-C_6haloalkynyl.

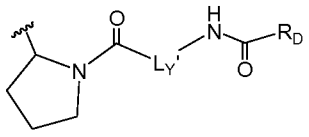
In another embodiment, A is  or  , and is optionally substituted with one or more R_A; B is  or  , and is optionally substituted with one or more R_A. Z_1 is independently selected at each occurrence from O, S, NH or CH_2; and Z_2 is independently selected at each occurrence from N or CH. Preferably, A is  , B is  , and A and B are substituted with one or more halogen, such as F or Cl. When A and/or B are halo-substituted benzimidazole (e.g., A is  and B is ), the compounds of this embodiment can have significantly improved pharmacokinetic properties as well as improved inhibitory activity against certain HCV genotype 1a mutants, as compared to the same compounds but with unsubstituted benzimidazole. 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, or is substituted with J and optionally substituted with one or more R_A, wherein J is C_3-C_6carbocycle, 3- to 6-membered heterocycle or 6- to 12-membered bicycle and is optionally substituted with one or more R_A. Preferably, J is substituted with a C_3-C_6carbocycle or 3- to 6-membered heterocycle which is independently 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, C_2-C_6haloalkynyl, C(O)OR_S or $-N(R_SR_S')$, and J can also be optionally substituted with one or more R_A. Preferably, D is

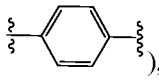
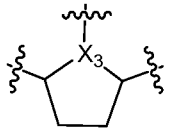
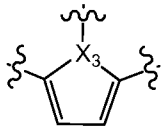



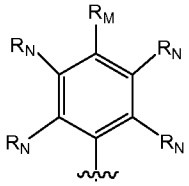
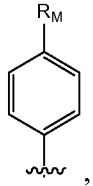
or , wherein R_M and R_N are as defined above. Also preferably, D is

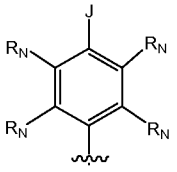
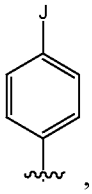
or , wherein J and R_N are as defined above. L_1 and L_2 are each independently bond or C_1-C_6alkylene, and L_3 is bond, C_1-C_6alkylene or -C(O)-, and L_1, L_2, and L_3 are each independently optionally substituted with one or more R_L. Preferably, L_1, L_2, and L_3 are bond. Y is $-L_S-C(R_1R_2)N(R_5)-T-R_D$ 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.

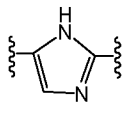
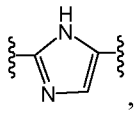
In still yet another embodiment, A and B are each independently 5- or 6-membered carbocycle or heterocycle (e.g., A and B are each independently phenyl, such as ), and are each independently optionally substituted with one or more R_A. X is 5- or 6-membered carbocycle or heterocycle or 6- to 12-membered 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, or is substituted with J and optionally substituted with one or more R_A, wherein J is C_3-C_6carbocycle, 3- to 6-membered heterocycle or 6- to 12-membered bicycle and is optionally substituted with one or more R_A. Preferably, J is substituted with a C_3-C_6carbocycle or 3- to 6-membered heterocycle which is independently 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, C_2-C_6haloalkynyl, C(O)OR_S or –N(R_SR_S'), and J can also be optionally substituted with one or more R_A. Preferably, D is

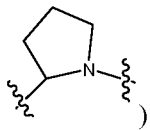
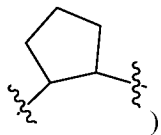
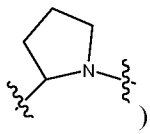
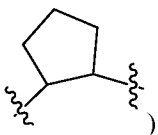



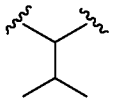
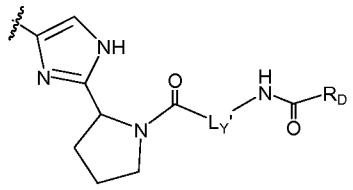
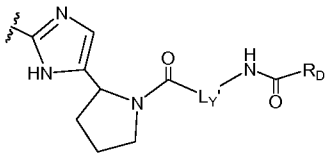
or , wherein R_M and R_N are as defined above. Also preferably, D is

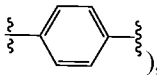
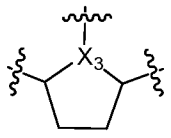
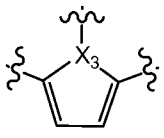



or , wherein J and R_N are as defined above. L_1 and L_2 are each independently bond or C_1-C_6alkylene, and L_3 is bond, C_1-C_6alkylene or -C(O)-, and L_1, L_2, and L_3 are each independently optionally substituted with one or more R_L. Preferably, L_1, L_2, and L_3 are bond. Y is –G–$C(R_1R_2)N(R_5)$–T–R_D 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,

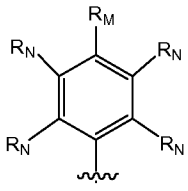



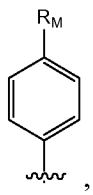
such as or , and is independently optionally substituted with one or more R_A. R_1 is R_C, and R_2 and R_5, taken together with the atoms to which they are attached, form a 5- to 6-membered heterocyclic ring (e.g., ) which is optionally substituted with one or more R_A; R_3 and R_6 are each independently 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., $-CH_2-$ or ) 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.

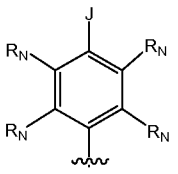
In yet another embodiment, A and B are each independently 5- or 6-membered carbocycle or heterocycle (e.g., A and B are each independently phenyl, such as ), and are each independently optionally substituted with one or more R_A. X is 5- or 6-membered carbocycle or heterocycle or 6- to 12-membered bicycle (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, or is substituted with J

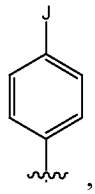
and optionally substituted with one or more R_A, wherein J is C_3-C_6carbocycle, 3- to 6-membered heterocycle or 6- to 12-membered bicycle and is optionally substituted with one or more R_A. Preferably, J is substituted with a C_3-C_6carbocycle or 3- to 6-membered heterocycle which is independently optionally 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, C_2-C_6haloalkynyl, $C(O)OR_S$ or $-N(R_SR_S')$, and J can also be optionally substituted with one or more R_A. Preferably, D is

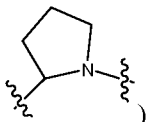


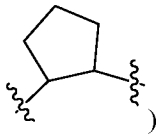
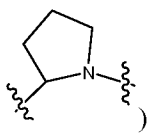
or


, wherein R_M and R_N are as defined above. Also preferably, D is

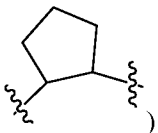
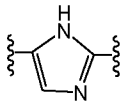
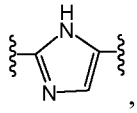
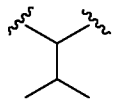
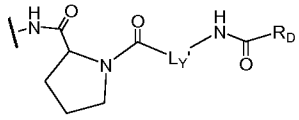
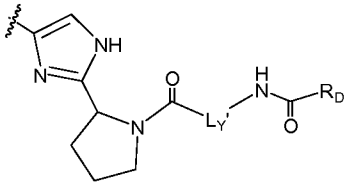
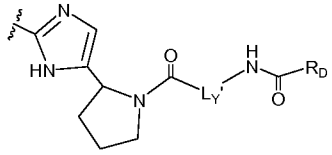
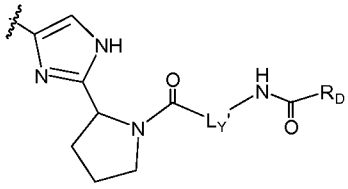
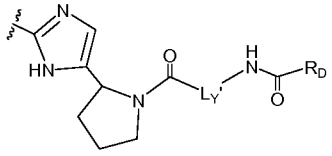
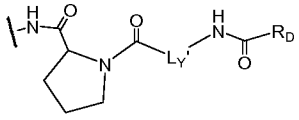


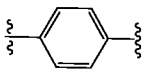
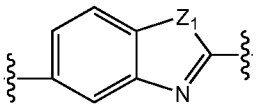
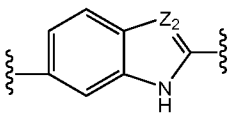
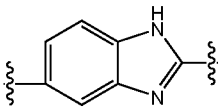
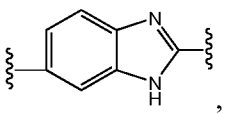
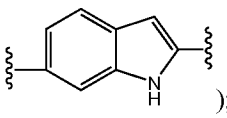
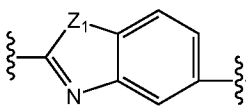
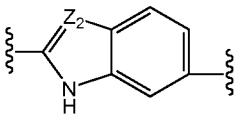
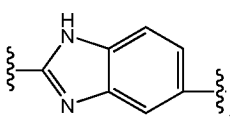
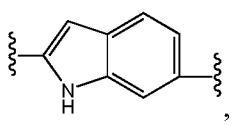
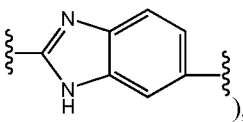
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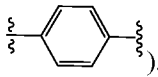
, wherein J and R_N are as defined above. L_1 and L_2 are each independently bond or C_1-C_6alkylene, and L_3 is bond, C_1-C_6alkylene or -C(O)-, and L_1, L_2, and L_3 are each independently optionally substituted with one or more R_L. Preferably, L_1, L_2, and L_3 are bond. Y is $-N(R_B)C(O)C(R_1R_2)N(R_5)–T–R_D$ 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., 

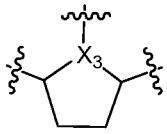
) which is optionally substituted with one or more R_A; R_3 and R_6 are each independently R_C, and R_4 and R_7, taken together with the atoms to which they are attached, form a 5- to 6-membered carbocyclic or heterocyclic ring (e.g., ) which is optionally substituted with one or more R_A. R_8 is R_C, 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., 

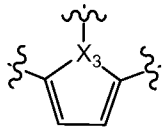
) which is optionally substituted with one or more R_A; and R_{10} and R_{13} are each independently R_C, and R_{11} and R_{14}, taken together with the atoms to which they are attached, form a 5- to 6-membered carbocyclic or

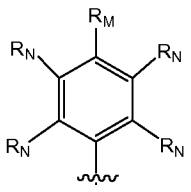
heterocyclic ring (e.g., ) which is optionally substituted with one or more R_A. G is independently C_5-C_6carbocycle or 5- to 6-membered heterocycle, such as  or  , and is independently optionally substituted with one or more R_A. T is preferably independently selected at each occurrence from –C(O)–L_Y'–N(R_B)C(O)–L_S''– 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- or ) 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.

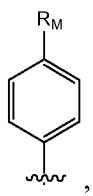
In still another embodiment, A is 5- or 6-membered carbocycle or heterocycle (e.g., phenyl such as ), and B is  or  (e.g.,  ,  , or ); or A is  or  (e.g.,  ,  , or ), and B

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.

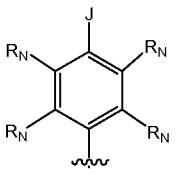
X is 5- or 6-membered carbocycle or heterocycle or 6- to 12-membered bicycle (e.g., 

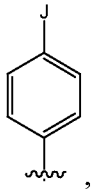
or  , wherein X_3 is N and is directly linked to $-L_3-D$) and is optionally substituted with one or more R_A. Specific examples of X are described hereinabove. D is C_5-C_6carbocycle or 5- to 6-membered heterocycle (e.g., phenyl), and is optionally substituted with one or more R_A, or is substituted with J and optionally substituted with one or more R_A, wherein J is C_3-C_6carbocycle, 3- to 6-membered heterocycle or 6- to 12-membered bicycle and is optionally substituted with one or more R_A. Preferably, J is substituted with a C_3-C_6carbocycle or 3- to 6-membered heterocycle which is independently 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, C_2-C_6haloalkynyl, $C(O)OR_S$ or $-N(R_SR_S')$, and J can also be optionally substituted with one or more R_A. Preferably, D is

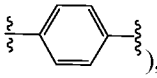


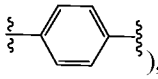
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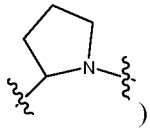
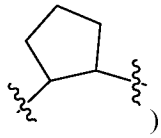
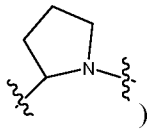
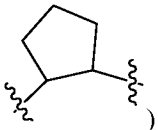
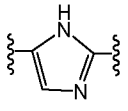
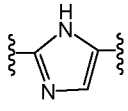
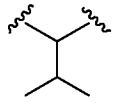
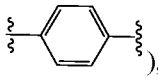
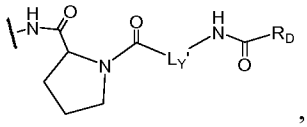
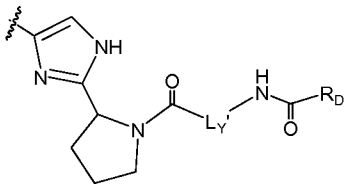
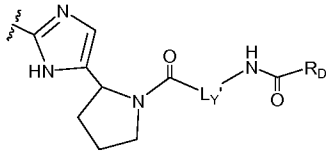
, wherein R_M and R_N are as defined above. Also preferably, D is

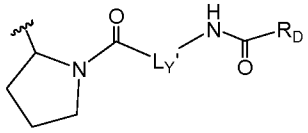


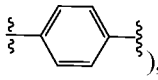
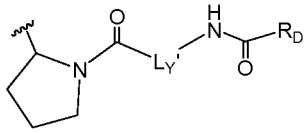
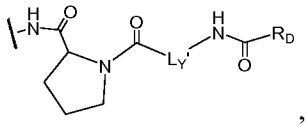
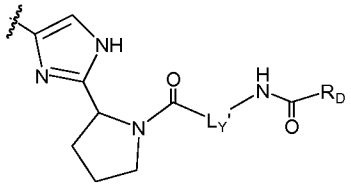
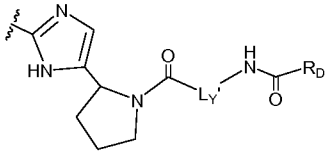
or 

, wherein J 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., $-CH_2-$ or ) 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 carbocycle or heterocycle (e.g., phenyl such as ), Y is  as described above, and Z is  ,  or  as described above.

The present invention also features compounds of Formulae I, I_A, I_B, I_C and I_D as described herein (including each embodiment described hereunder) and pharmaceutically acceptable salts thereof, wherein:

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 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_{15}carbocycle or 3- to 15-membered heterocycle (e.g., a 3- to 6-membered monocycle, a 6- to 12-membered fused, bridged or spiro bicycle, a 10- to 15-memberd tricycle containing fused, bridged or spiro rings, or a 13- to 15-membered carbocycle or heterocycle) and is optionally substituted with one or more R_A, or J is $-SF_5$; or D is hydrogen or R_A;

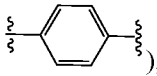
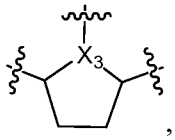
R_A is independently selected at each occurrence from halogen, nitro, oxo, phosphonoxy, phosphono, thioxo, cyano, or $-L_B-R_E$; wherein two adjacent R_A, taken together with the atoms to which they are attached and any atoms between the atoms to which they are attached, can optionally form carbocycle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

L_B is independently selected at each occurrence from L_S; or C_1-C_{10}alkylene, C_2-C_{10}alkenylene or C_2-C_{10}alkynylene, each of which optionally has 1, 2, 3, 4 or 5 carbon atoms independently replaced with O, S or N(R_B), and each of said C_1-C_{10}alkylene, C_2-C_{10}alkenylene or C_2-C_{10}alkynylene being independently optionally substituted with one or more R_L;

R_E is independently selected at each occurrence from $-O-R_S$, $-S-R_S$, $-C(O)R_S$, $-OC(O)R_S$, $-C(O)OR_S$, $-N(R_SR_S')$, $-S(O)R_S$, $-SO_2R_S$, $-C(O)N(R_SR_S')$, $-N(R_S)C(O)R_S'$, $-$

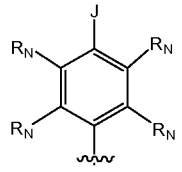
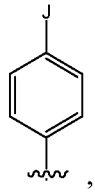
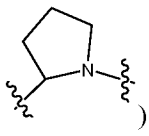
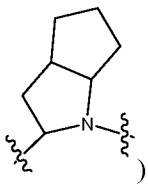
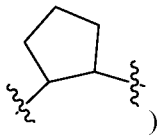
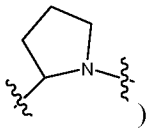
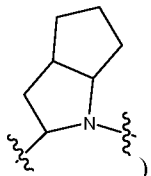
$N(R_S)C(O)N(R_S'R_S'')$, $-N(R_S)SO_2R_S'$, $-SO_2N(R_SR_S')$, $-N(R_S)SO_2N(R_S'R_S'')$, $-N(R_S)S(O)N(R_S'R_S'')$, $-OS(O)-R_S$, $-OS(O)_2-R_S$, $-S(O)_2OR_S$, $-S(O)OR_S$, $-OC(O)OR_S$, $-N(R_S)C(O)OR_S'$, $-OC(O)N(R_SR_S')$, $-N(R_S)S(O)-R_S'$, $-S(O)N(R_SR_S')$, $-P(O)(OR_S)_2$, $=C(R_SR_S')$, 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, cyano, C_3-C_{12}carbocycle or 3- to 12-membered heterocycle; or C_3-C_{12}carbocycle or 3- to 12-membered heterocycle (e.g., 7- to 12-membered carbocycle or 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, trimethylsilyl, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6haloalkyl, C_2-C_6haloalkenyl, C_2-C_6haloalkynyl, $-O-R_S$, $-S-R_S$, $-C(O)R_S$, $-C(O)OR_S$, or $-N(R_SR_S')$.

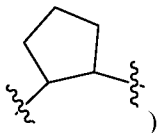
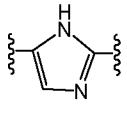
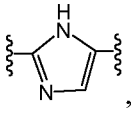
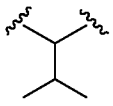
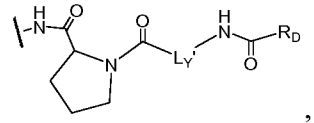
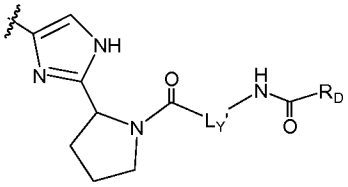
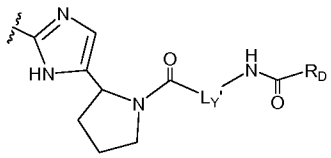
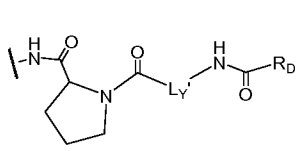
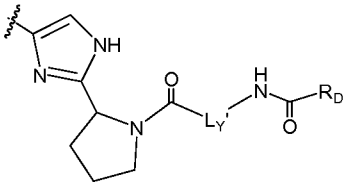
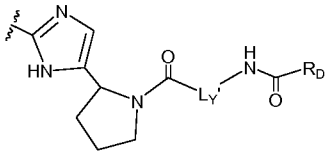
R_L is independently selected at each occurrence from halogen, nitro, oxo, phosphonoxy, phosphono, thioxo, cyano, $-O-R_S$, $-S-R_S$, $-C(O)R_S$, $-OC(O)R_S$, $-C(O)OR_S$, $-N(R_SR_S')$, $-S(O)R_S$, $-SO_2R_S$, $-C(O)N(R_SR_S')$ or $-N(R_S)C(O)R_S'$; or C_3-C_{12}carbocycle or 3- to 12-membered heterocycle (e.g., 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; 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.

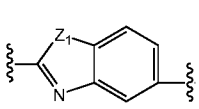
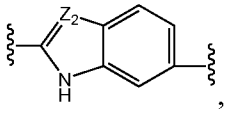
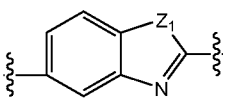
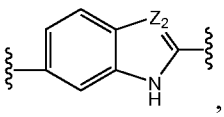
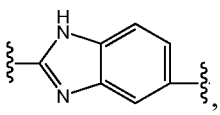
In one embodiment, A and B are each independently 5- or 6-membered carbocycle or heterocycle (preferably, A and B are each independently phenyl such as ), and are each independently optionally substituted with one or more R_A (preferably, A and B are each independently substituted with at least one halo such as F). X is 5- or 6-membered carbocycle or heterocycle or 6- to 12-membered bicycle (preferably, X is 

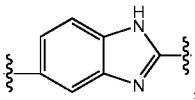
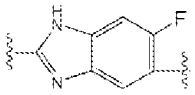
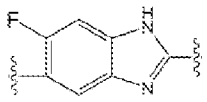
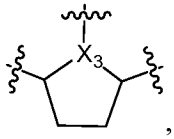
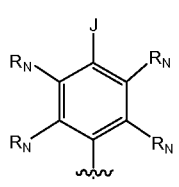
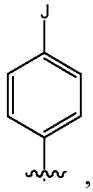
, wherein X_3 is N and is directly linked to $-L_3-D$), and is optionally substituted with one or more R_A. D is a C_5-C_6carbocycle or 5- to 6-membered heterocycle (e.g., phenyl), and is substituted with J and optionally substituted with one or more R_A. J is C_3-C_6carbocycle, 3- to 6-membered heterocycle, 6- to 12-membered bicycle, 10- to 15-membered tricycle, or 13- to 15-membered carbocycle/heterocycle, and J is optionally substituted with one or more R_A. Preferably, J is substituted with a C_3-C_6carbocycle, 3- to 6-membered heterocycle, 6- to 12-

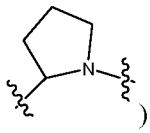
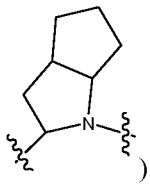
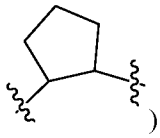
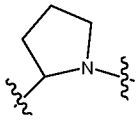
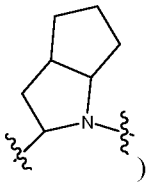
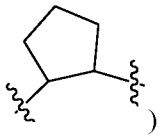
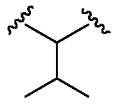
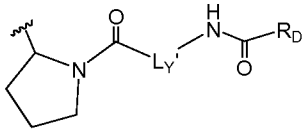
membered bicycle or 7- to 12-membered carbocycle/heterocycle, which is independently optionally substituted with one or more substituents selected from (1) halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6haloalkyl, C_2-C_6haloalkenyl, C_2-C_6haloalkynyl, –C(O)OR_S or –N($R_S$$R_S$'), or (2) trimethylsilyl, –O–R_S, –S–R_S, –C(O)R_S; and J can also be optionally substituted with one or more R_A.

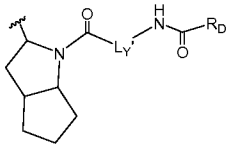
Preferably, D is  or  , wherein J is as defined above, and each R_N is independently selected from R_D and preferably is hydrogen or halo such as F. L_1 and L_2 are each independently bond or C_1-C_6alkylene, and L_3 is bond, C_1-C_6alkylene or -C(O)-, and L_1, L_2, and L_3 are each independently optionally 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, –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. 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., ) or 6- to 12-membered bicycle (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., ) or 6- to 12-membered bicycle 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., ) or 6- to 12-membered bicycle (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., ) or 6- to 12-membered bicycle 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., $-CH_2-$ or ) 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  ,  or  as described above, and Z is  ,  or  as described above.

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. Preferably, A and B are each independently substituted with at least one halo such as F. Also preferably, A is  ,

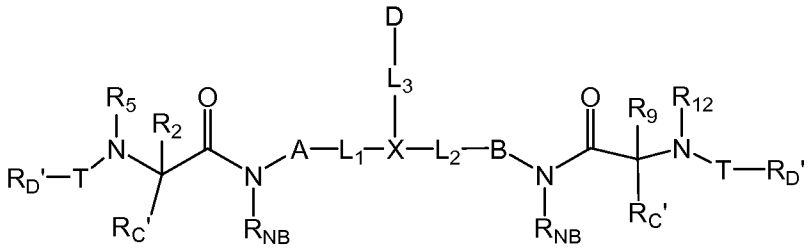
B is  , and A and B are substituted with one or more halogen, such as F or Cl. When A and/or B are halo-substituted benzimidazole (e.g., A is  and B is ), the compounds of this embodiment can have significantly improved pharmacokinetic properties as well as improved inhibitory activity against certain HCV genotype 1a mutants, as compared to the same compounds but with unsubstituted benzimidazole. X is 5- or 6-membered carbocycle or heterocycle or 6- to 12-membered bicycle (preferably, X is  , wherein X_3 is N and is directly linked to $-L_3-D$), and is optionally substituted with one or more R_A. D is a C_5-C_6carbocycle or 5- to 6-membered heterocycle (e.g., phenyl), and is substituted with J and optionally substituted with one or more R_A. J is C_3-C_6carbocycle, 3- to 6-membered heterocycle, 6- to 12-membered bicycle, 10- to 15-membered tricycle or 13- to 15-membered carbocycle/heterocycle, and J is optionally substituted with one or more R_A. Preferably, J is substituted with a C_3-C_6carbocycle, 3- to 6-membered heterocycle, 6- to 12-membered bicycle or 7- to 12-membered carbocycle/heterocycle, which is independently optionally substituted with one or more substituents selected from (1) 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 $-N(R_SR_S')$, or (2) trimethylsilyl, $-O-R_S$, $-S-R_S$, or $-C(O)R_S$; and J can also be optionally substituted with one or more R_A. Preferably, D is  or  , wherein J is as defined above, and each R_N is independently selected from R_D and preferably is hydrogen or halo such as F. 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 $-L_S-C(R_3R_4)C(R_6R_7)-T-R_D$. 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., ) or 6- to 12-membered bicycle (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., ) or 6- to 12-membered bicycle 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., ) or 6- to 12-membered bicycle (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., ) or 6- to 12-membered bicycle 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- or ) 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 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 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;

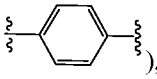
R_C' is each independently selected from R_C;

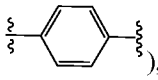
R_D' is each independently selected from R_D;

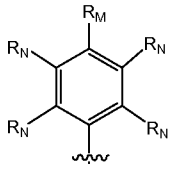
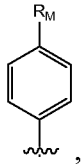
R_2 and R_5, taken together with the atoms to which they are attached, form a 3- to 12-membered heterocycle which is optionally substituted with one or more R_A;

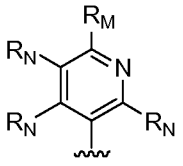
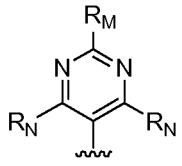
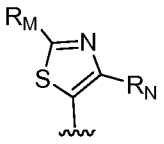
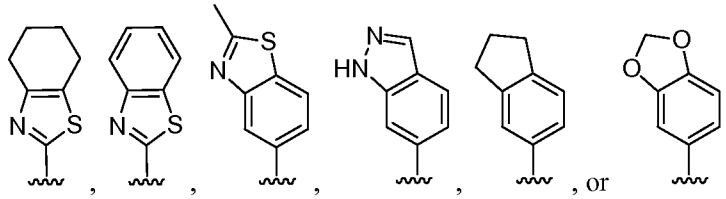
R_9 and R_{12}, taken together with the atoms to which they are attached, form a 3- to 12-membered heterocycle which is optionally substituted with one or more R_A;

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, 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.

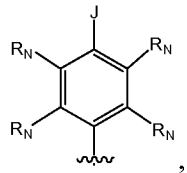
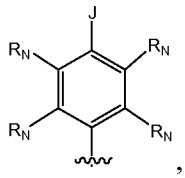
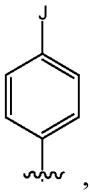
Preferably, R_M is halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, cyano; or C_1-C_6alkyl, C_2-C_6alkenyl or C_2-C_6alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto,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

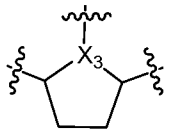
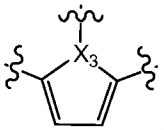
cyano; or C_3-C_6carbocycle or 3- to 6-membered heterocycle, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, C_1-C_6alkyl, C_2-C_6alkenyl, 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 independently 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 $-O-R_S$, $-C(O)OR_S$, –

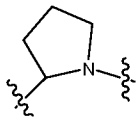
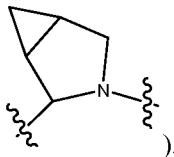
$N(R_S)C(O)OR_S$', or $-P(O)(OR_S)_2$. For example R_M is $-C_1$-C_6alkylene–O–R_S (e.g., $-C(CH_3)_2-CH_2-OMe$); $-C_1$-C_6alkylene–$C(O)OR_S$ (e.g., $-C(CH_3)_2-C(O)OMe$); $-C_1$-C_6alkylene–$N(R_S)C(O)OR_S$' (e.g., $-C(CH_3)_2-CH_2-NHC(O)OCH_3$); or $-C_1$-C_6alkylene–$P(O)(OR_S)_2$ (e.g., $-CH_2-P(O)(OEt)_2$). 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 $-N(R_SR_S')$. 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-C_6alkyl which is independently optionally substituted with one or more substituents selected from halogen, hydroxy, mercapto, amino or carboxy (e.g., tert-butyl, CF_3).

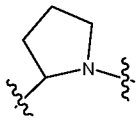
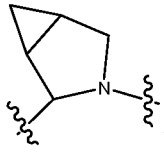
More preferably, D is C_5-C_6carbocycle, 5- to 6-membered heterocycle or 6- to 12-membered bicycle and is substituted with J and optionally substituted with one or more R_A, wherein J is C_3-C_6carbocycle, 3- to 6-membered heterocycle or 6- to 12-membered bicycle and is optionally substituted with one or more R_A. Preferably, J is substituted with a C_3-C_6carbocycle or 3- to 6-membered heterocycle, wherein said C_3-C_6carbocycle or 3- to 6-membered heterocycle is independently 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, C_2-C_6haloalkynyl, $C(O)OR_S$ or $-N(R_SR_S')$, and J can also be optionally substituted with one or more R_A. Also preferably, D is C_5-C_6carbocycle or 5- to 6-membered heterocycle and is substituted with J and 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, and preferably, J is at least substituted with a C_3-C_6carbocycle or 3- to 6-membered heterocycle which is independently 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, C_2-C_6haloalkynyl, $C(O)OR_S$ or $-N(R_SR_S')$. Also preferably, D is C_5-C_6carbocycle or 5- to 6-membered heterocycle and is substituted with J and optionally substituted with one or more R_A, and J is 6- to 12-membered bicycle (e.g., a 7- to 12-membered fused, bridged or spiro bicycle comprising a nitrogen ring atom through which J is covalently attached to D) and is optionally substituted with one or more R_A. More preferably, D is phenyl and is substituted with J and optionally substituted with one or more R_A, and J is C_3-C_6carbocycle, 3- to 6-membered heterocycle or 6- to 12-membered bicycle and is optionally substituted with one or more R_A, and preferably J is at

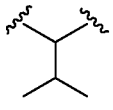
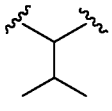
least substituted with a C_3-C_6carbocycle or 3- to 6-membered heterocycle which is independently optionally substituted with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6haloalkyl, C_2-C_6haloalkenyl, C_2-C_6haloalkynyl, $C(O)OR_S$ or $-N(R_SR_S')$. Highly preferably, D is  , wherein each R_N is independently selected from R_D and preferably is hydrogen or halogen, and J is C_3-C_6carbocycle, 3- to 6-membered heterocycle or 6- to 12-membered bicycle and is optionally substituted with one or more R_A, and preferably J is at least substituted with a C_3-C_6carbocycle or 3- to 6-membered heterocycle which is independently 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, C_2-C_6haloalkynyl, $C(O)OR_S$ or $-N(R_SR_S')$. Also preferably, D is  , wherein each R_N is independently selected from R_D and preferably is hydrogen or halogen, and J is C_3-C_6carbocycle or 3- to 6-membered heterocycle and is substituted with a C_3-C_6carbocycle or 3- to 6-membered heterocycle which is independently 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, C_2-C_6haloalkynyl, $C(O)OR_S$ or $-N(R_SR_S')$, and J can also be optionally substituted with one or more R_A. Also preferably, 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, and preferably J is at least substituted with a C_3-C_6carbocycle or 3- to 6-membered heterocycle which is independently 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, C_2-C_6haloalkynyl, $C(O)OR_S$ or $-N(R_SR_S')$.

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 or R_F. 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- or ) 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- or ) 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.

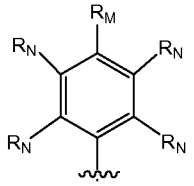
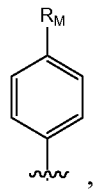
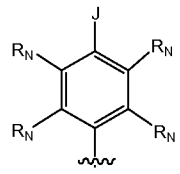
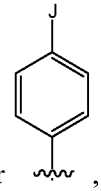
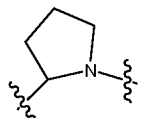
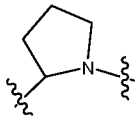
More preferably, R_A is halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, cyano; or C_1-C_6alkyl, C_2-C_6alkenyl or C_2-C_6alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy,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

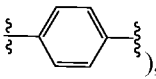
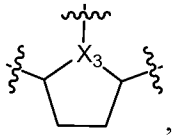
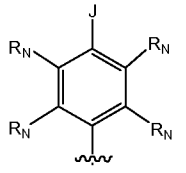
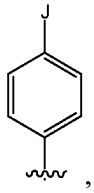
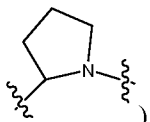
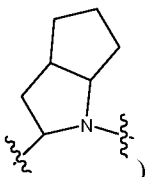
Highly preferably, R_A is halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, cyano; or C_1-C_6alkyl, C_2-C_6alkenyl or C_2-C_6alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy,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

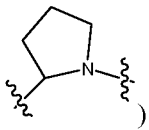
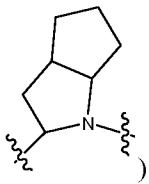
L_S, L_S' and L_S'' preferably are each independently selected at each occurrence from bond; or C_1-C_6alkylene, C_2-C_6alkenylene or C_2-C_6alkynylene.

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

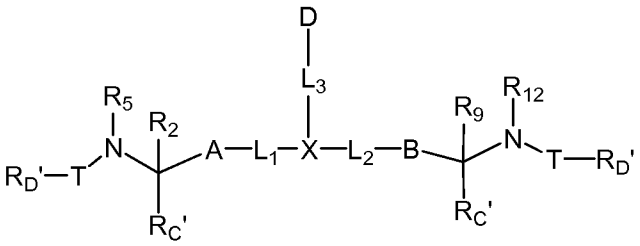
In one embodiment of this aspect, A and B are each independently phenyl, and are each independently optionally substituted with one or more R_A; D is phenyl, and is optionally substituted with one or more R_A, or is substituted with J and optionally substituted with one or more R_A, wherein J is C_3-C_6carbocycle, 3- to 6-membered heterocycle or 6- to 12-membered bicycle and is optionally substituted with one or more R_A. Preferably, J is substituted with a C_3-C_6carbocycle or 3- to 6-membered heterocycle which is independently 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, C_2-C_6haloalkynyl, C(O)OR_S or –N($R_S R_S$'), and J can also be optionally substituted with one or more R_A.

Preferably, D is  or  , wherein R_M and R_N are as defined above. Also preferably, D is  or  , wherein J 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'. Preferably, 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; 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.

In another embodiment of this aspect, A and B are each independently phenyl (e.g., ), and are each independently optionally substituted with one or more R_A (preferably, A and B are each independently substituted with at least one halo such as F). X is  , wherein X_3 is N and is directly linked to $-L_3-D$, and X is optionally substituted with one or more R_A or R_F. D is phenyl, and is substituted with J and optionally substituted with one or more R_A. J is C_3-C_6carbocycle, 3- to 6-membered heterocycle, 6- to 12-membered bicycle, 10- to 15-membered tricycle or 13- to 15-membered carbocycle/heterocycle, and J is optionally substituted with one or more R_A. Preferably, J is substituted with a C_3-C_6carbocycle, 3- to 6-membered heterocycle, 6- to 12-membered bicycle or 7- to 12-membered carbocycle/heterocycle, which is independently optionally substituted with one or more substituents selected from (1) 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 $-N(R_SR_S')$, or (2) trimethylsilyl, $-O-R_S$, $-S-R_S$ or $-C(O)R_S$; and J can also be optionally substituted with one or more R_A. Preferably, D is  or  , wherein J is as defined above, and each R_N is independently selected from R_D and preferably is hydrogen or halo such as F. 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 $-C(O)-L_Y'-N(R_B)S(O)_2-L_S''-R_D'$. 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., ) or 6- to 12-membered bicycle (e.g., ) 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 a 5- to 6-membered heterocyclic

ring (e.g., ) or 6- to 12-membered bicycle (e.g., ) which is optionally substituted with one or more R_A.

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



I_B

wherein:

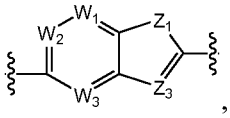
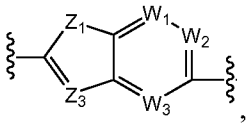
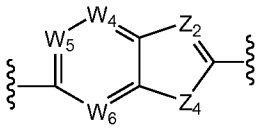
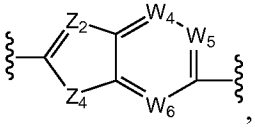
R_C' is each independently selected from R_C;

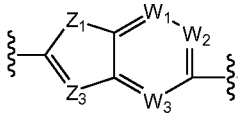
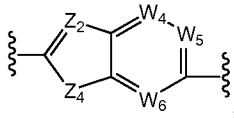
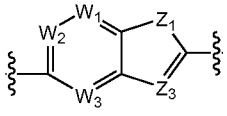
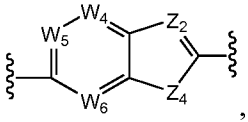
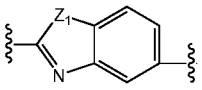
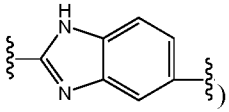
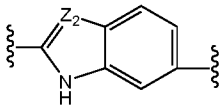
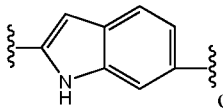
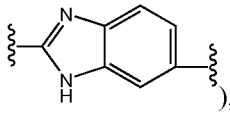
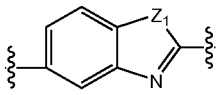
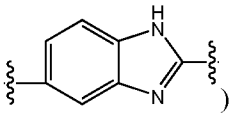
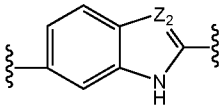
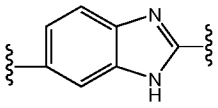
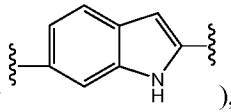
R_D' is each independently selected from R_D;

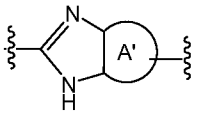
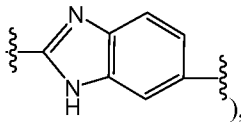
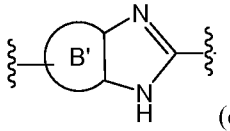
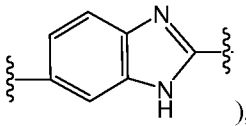
R_2 and R_5, taken together with the atoms to which they are attached, form a 3- to 12-membered heterocycle which is optionally substituted with one or more R_A;

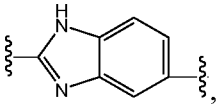
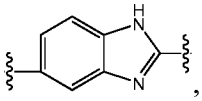
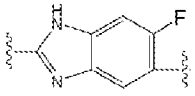
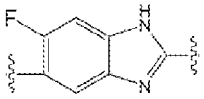
R_9 and R_{12}, taken together with the atoms to which they are attached, form a 3- to 12-membered heterocycle which is optionally substituted with one or more R_A;

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.

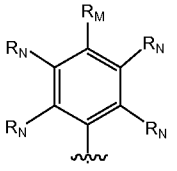
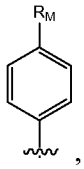
In this aspect, A and B preferably are independently selected from 8- to 12-membered bicycles such as  ,  ,  or  , where Z_1 is independently selected at each occurrence from O, S, NH or CH_2, Z_2 is independently selected at each occurrence from N or CH, Z_3 is independently selected at each occurrence 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.

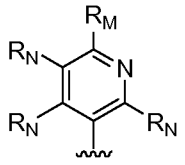
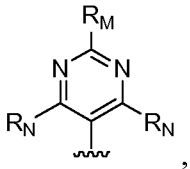
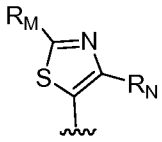
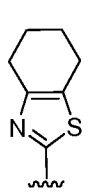
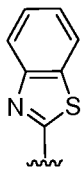
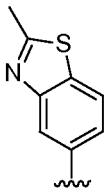
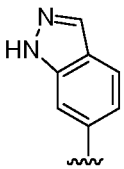
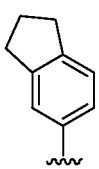
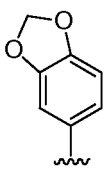
More preferably, A is selected from  or  , and is optionally substituted with one or more R_A; B is selected from  or  , and is optionally substituted with one or more R_A, where Z_1, Z_2, Z_3, Z_4, W_1, W_2, W_3, W_4, W_5, W_6 are as defined above. Preferably, Z_3 is N and Z_4 is NH. For instance, A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

More preferably, A is  , B is  , and A and B are substituted with one or more halogen, such as F or Cl. When A and/or B are halo-substituted benzimidazole (e.g., A is  and B is ), the compounds of Formula I_B can have significantly improved pharmacokinetic properties as well as improved inhibitory activity against

certain HCV genotype 1a mutants, as compared to the same compounds but with unsubstituted benzimidazole.

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

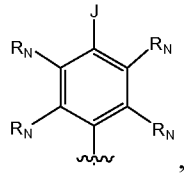
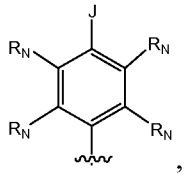
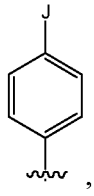
Preferably, R_M is halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, cyano; or C_1-C_6alkyl, C_2-C_6alkenyl or C_2-C_6alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto,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

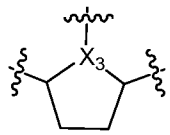
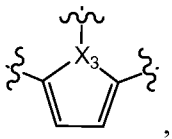
optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6haloalkyl, C_2-C_6haloalkenyl or C_2-C_6haloalkynyl. More preferably, 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_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-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).

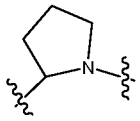
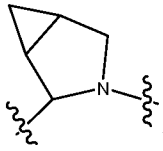
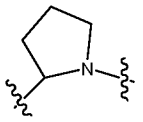
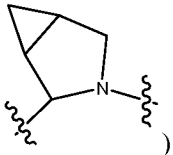
More preferably, D is C_5-C_6carbocycle, 5- to 6-membered heterocycle or 6- to 12-membered bicycle and is substituted with J and optionally substituted with one or more R_A, wherein J is C_3-C_6carbocycle, 3- to 6-membered heterocycle or 6- to 12-membered bicycle and is optionally substituted with one or more R_A. Preferably, J is substituted with a C_3-C_6carbocycle or 3- to 6-membered heterocycle, wherein said C_3-C_6carbocycle or 3- to 6-membered heterocycle is independently 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, C_2-C_6haloalkynyl, C(O)OR_S or –N(R_SR_S'), and J can also be optionally substituted with one or more R_A. Also preferably, D is C_5-C_6carbocycle or 5- to 6-membered heterocycle and is substituted with J and 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, and preferably, J is at least substituted with a C_3-C_6carbocycle or 3- to 6-membered heterocycle which is independently 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, C_2-C_6haloalkynyl, C(O)OR_S or –N(R_SR_S'). Also preferably, D is C_5-C_6carbocycle or 5- to 6-membered heterocycle and is substituted with J and optionally substituted with one or more R_A, and J is 6- to 12-membered bicycle (e.g., a 7- to 12-membered fused, bridged or spiro bicycle comprising a nitrogen ring atom through which J is covalently attached to D) and is optionally substituted with one or more R_A. More preferably, D is phenyl and is substituted with J and optionally substituted with one or more R_A, and J is C_3-C_6carbocycle, 3- to 6-membered heterocycle or 6- to 12-membered bicycle and is optionally substituted with one or more R_A, and preferably J is at least substituted with a C_3-C_6carbocycle or 3- to 6-membered heterocycle which is independently

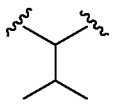
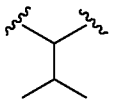
optionally substituted with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6haloalkyl, C_2-C_6haloalkenyl, C_2-C_6haloalkynyl, $C(O)OR_S$ or $-N(R_SR_S')$. Highly preferably, D is  , wherein each R_N is independently selected from R_D and preferably is hydrogen or halogen, and J is C_3-C_6carbocycle, 3- to 6-membered heterocycle or 6- to 12-membered bicycle and is optionally substituted with one or more R_A, and preferably J is at least substituted with a C_3-C_6carbocycle or 3- to 6-membered heterocycle which is independently 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, C_2-C_6haloalkynyl, $C(O)OR_S$ or $-N(R_SR_S')$. Also preferably, D is  , wherein each R_N is independently selected from R_D and preferably is hydrogen or halogen, and J is C_3-C_6carbocycle or 3- to 6-membered heterocycle and is substituted with a C_3-C_6carbocycle or 3- to 6-membered heterocycle which is independently 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, C_2-C_6haloalkynyl, $C(O)OR_S$ or $-N(R_SR_S')$, and J can also be optionally substituted with one or more R_A. Also preferably, 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, and preferably J is at least substituted with a C_3-C_6carbocycle or 3- to 6-membered heterocycle which is independently 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, C_2-C_6haloalkynyl, $C(O)OR_S$ or $-N(R_SR_S')$.

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 or R_F. 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'–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- or ) 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- or ) 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.

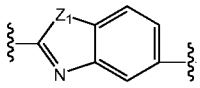
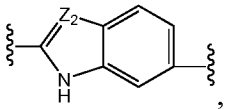
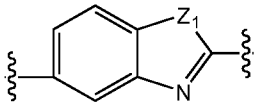
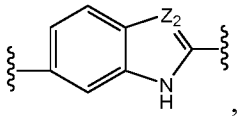
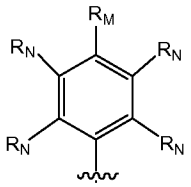
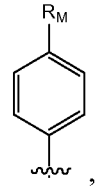
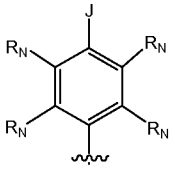
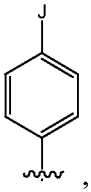
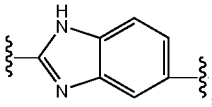
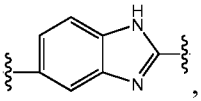
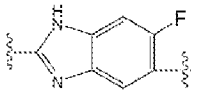
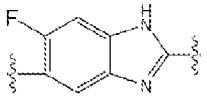
R_A preferably is halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, cyano; or C_1-C_6alkyl, C_2-C_6alkenyl or C_2-C_6alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto,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

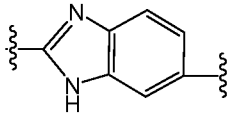
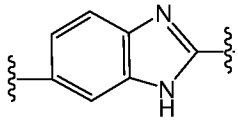
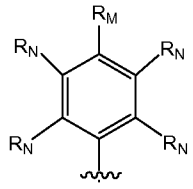
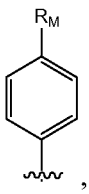
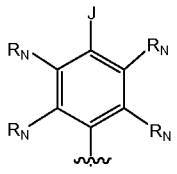
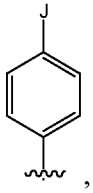
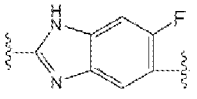
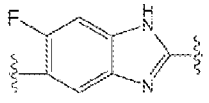
Highly preferably, R_A is halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, cyano; or C_1-C_6alkyl, C_2-C_6alkenyl or C_2-C_6alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy,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

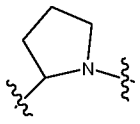
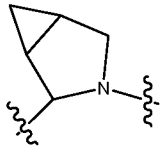
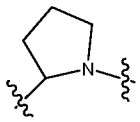
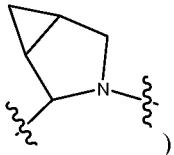
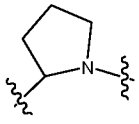
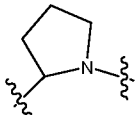
L_S, L_S' and L_S'' preferably are each independently selected at each occurrence from bond; or C_1-C_6alkylene, C_2-C_6alkenylene or C_2-C_6alkynylene.

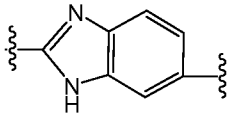
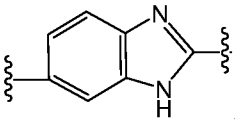
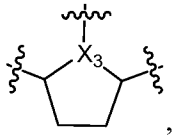
A and B can be the same or different. Likewise, L_1 and L_2 can be the same or different.

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, or is substituted with J and optionally substituted with one or more R_A, wherein J is C_3-C_6carbocycle, 3- to 6-membered heterocycle or 6- to 12-membered bicycle and is optionally substituted with one or more R_A. Preferably, J is substituted with a C_3-C_6carbocycle or 3- to 6-membered heterocycle which is independently 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, C_2-C_6haloalkynyl, $C(O)OR_S$ or $-N(R_SR_S')$, and J can also be optionally substituted with one or more R_A. Preferably, D is  or  , wherein R_M and R_N are as defined above. Also preferably, D is  or  , wherein J 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. Preferably, A is  , B is  , and A and B are substituted with one or more halogen, such as F or Cl. When A and/or B are halo-substituted benzimidazole (e.g., A is  and B is ), the compounds of this embodiment can have significantly improved pharmacokinetic properties as well as improved inhibitory activity against certain HCV genotype 1a mutants, as compared to the same compounds but with unsubstituted benzimidazole. 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. $-T\text{-}R_D'$ 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-

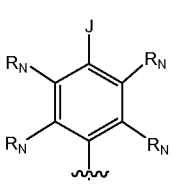
C_6alkylene (e.g., -CH_2-) and optionally substituted with one or more substituents selected from R_L, and L_S'' preferably is bond. –T-R_D' can also be, without limitation, selected from –C(O)–L_Y'–L_S''–R_D', –C(O)–L_Y'–O–L_S''–R_D', –C(O)–L_Y'–N(R_B)–L_S''–R_D', or –C(O)–L_Y'–N(R_B)S(O)$_2$–L_S''–R_D'.

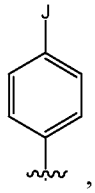
In another embodiment of this aspect, A is  and optionally substituted with one or more R_A (e.g., halogen); B is  , and is optionally substituted with one or more R_A (e.g., halogen); and D is C_5-C_6carbocycle or 5- to 6-membered heterocycle (e.g., phenyl), and is optionally substituted with one or more R_A, or is substituted with J and optionally substituted with one or more R_A, wherein J is C_3-C_6carbocycle, 3- to 6-membered heterocycle or 6- to 12-membered bicycle and is optionally substituted with one or more R_A. Preferably, J is substituted with a C_3-C_6carbocycle or 3- to 6-membered heterocycle which is independently 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, C_2-C_6haloalkynyl, C(O)OR_S or –N($R_S$$R_S$'), and J can also be optionally substituted with one or more R_A. Preferably, D is  or  , wherein R_M and R_N are as defined above. Also preferably, D is  or  , wherein J and R_N are as defined above. When A and/or B are halo-substituted benzimidazole (e.g., A is  and B is ), the compounds of this embodiment can have significantly improved pharmacokinetic properties as well as improved inhibitory activity against certain HCV genotype 1a mutants, as compared to the same compounds but with unsubstituted benzimidazole. 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'. 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. More preferably, 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; 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.

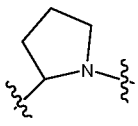
In still another embodiment of this aspect, A is  and optionally substituted with one or more R_A (preferably, A is substituted with at least one halogen such as F); B is  , and is optionally substituted with one or more R_A (preferably, B is substituted with at least one halogen such as F). X is  , wherein X_3 is N and is directly linked to –L_3–D, and X is optionally substituted with one or more R_A or R_F. D is phenyl, and is substituted with J and optionally substituted with one or more R_A. J is C_3-C_6carbocycle, 3- to 6-membered heterocycle, 6- to 12-membered bicycle, 10- to 15-membered tricycle or 13- to 15-membered carbocycle/heterocycle, and J is optionally substituted with one or more R_A. Preferably, J is substituted with a C_3-C_6carbocycle, 3- to 6-membered heterocycle, 6- to 12-membered bicycle or 7- to

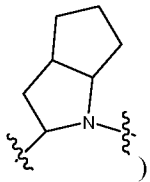
12-membered carbocycle/heterocycle, which is independently optionally substituted with one or more substituents selected from (1) halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6haloalkyl, C_2-C_6haloalkenyl, C_2-C_6haloalkynyl, –C(O)OR_S or –N(R_SR_S'), or (2) trimethylsilyl, –O–R_S, –S–R_S or –C(O)R_S; and J can also be optionally substituted with one or more R_A. Preferably, D is



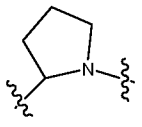
or


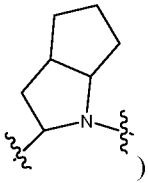
, wherein J is as defined above, and each R_N is independently selected from R_D and preferably is hydrogen or halo such as F. L_1 and L_2 are each independently bond or C_1-C_6alkylene, and L_3 is bond, C_1-C_6alkylene or -C(O)-, and L_1, L_2, and L_3 are each independently optionally substituted with 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'. 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.,



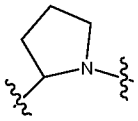
or


) 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.,

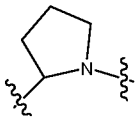


or


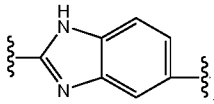
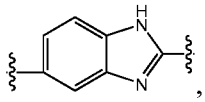
) which is optionally substituted with one or more R_A. More preferably, R_2 and R_5, taken together with the atoms to which they are attached, form

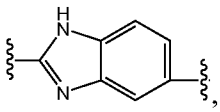
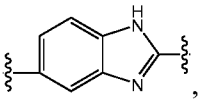


which is optionally substituted with one or more R_A; R_9 and R_{12}, taken together with the atoms to which they are attached, form



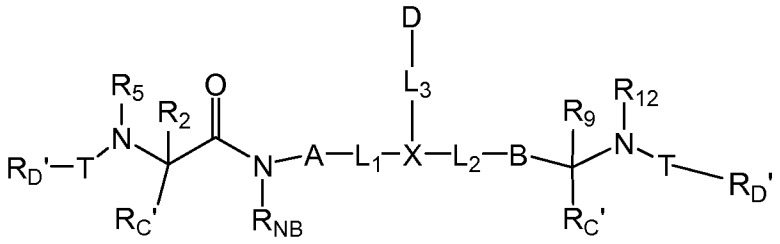
which is optionally substituted with one or more R_A.

The present invention unexpectedly found that a compound according to this aspect of the invention (preferably a compound of Formula I_B or a pharmaceutically acceptable salt thereof, wherein A is  , B is  , and A and B are independently optionally substituted with one or more R_A such as one or more halo) showed significantly improved activities against different HCV genotypes and variants. For instance, when tested against HCV replicons of different genotypes in stable cell lines (in the presence of 5% FBS), and as compared to Example 37 of U.S. Patent Application Publication No. 2010/0317568, the EC_{50} values of the compounds of Examples 3.48, 3.52, 4.38, and 5.1 were at least about 6-fold less than that of Example 37 against genotype 1a, at least about 3-fold less against genotype 3a, at least about 50-fold less against genotype 6a, and significantly less against genotype 2a. In addition, when tested against HCV genotype 1a replicons containing certain NS5A mutations in transient transfection assays, and as compared to Example 37 of U.S. Patent Application Publication No. 2010/0317568, the EC_{50} values of the compounds of Examples 3.48, 3.52, 4.38, and 5.1 were at least about 130-fold less than that of Example 37 against the L31V variant, at least about 7,500 fold less against the M28T variant, at least about 80-fold less against the M28V variant, at least about 500-fold less against the Q30E variant, at least about 300-fold less against the Q30R variant, at least about 800-fold less against the Y93C variant, at least about 1,500-fold less against the Y93H variant, and significantly less against the Q30H variant. Likewise, when tested against HCV genotype 1b replicons containing certain NS5A mutations in transient transfection assays, and as compared to Example 37 of U.S. Patent Application Publication No. 2010/0317568, the EC_{50} value of the compound of Example 5.1 was at least about 10-fold less than that of Example 37 against the Y93H variant.

Accordingly, the present invention features methods of treating different HCV genotype or variant infection. The methods comprise administering a compound of Formula I_B, or a pharmaceutically acceptable salt thereof, to a patient infected with HCV genotype 1a, 1b, 2a, 2b, 3a, 4a, 5a or 6a, or infected with one of the variants described above. Preferably, A is  , B is  , and A and B are independently optionally substituted with one or more R_A such as one or more halo. Other compounds described in this aspect of the invention or any embodiment thereunder, as well as the title compounds in the Examples described below, may also be used. In one embodiment, the patient being treated is infected with HCV genotype 1, such as 1a. In another embodiment, the patient being treated is infected with HCV genotype 2, such as 2a. In still another embodiment, the patient being treated is infected with HCV genotype 3, such as 3a. In another embodiment, the patient being treated is infected with HCV genotype 4, such as 4a. In a

further embodiment, the patient being treated is infected with HCV genotype 5, such as 5a. In yet another embodiment, the patient being treated is infected with HCV genotype 6, such as 6a.

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;

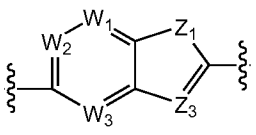
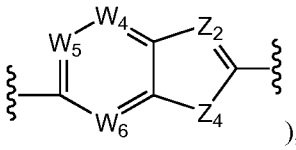
R_C' is each independently selected from R_C;

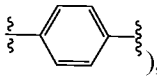
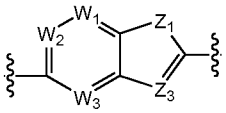
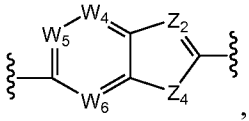
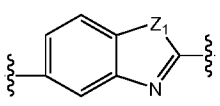
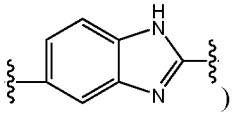
R_D' is each independently selected from R_D;

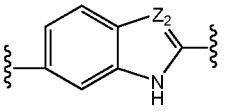
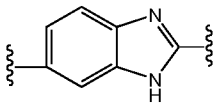
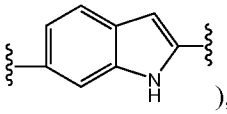
R_2 and R_5, taken together with the atoms to which they are attached, form a 3- to 12-membered heterocycle which is optionally substituted with one or more R_A;

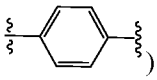
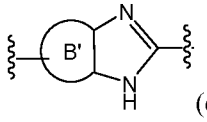
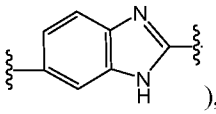
R_9 and R_{12}, taken together with the atoms to which they are attached, form a 3- to 12-membered heterocycle which is optionally substituted with one or more R_A;

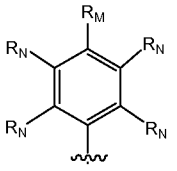
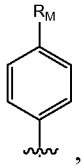
A, B, D, X, L_1, L_2, L_3, T, R_A, R_B, R_C, and R_D are as described above in Formula I.

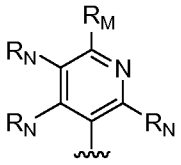
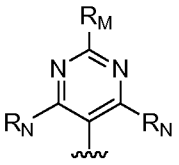
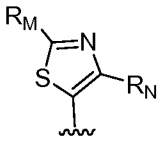
In this aspect, A preferably is C_5-C_6carbocycle or 5- to 6-membered heterocycle, and is optionally substituted with one or more R_A; and B preferably is 8- to 12-membered bicycle (such as  or ), and is optionally substituted with one or more R_A. Z_1 is O, S, NH or CH_2; Z_2 is N or CH; Z_3 is N or 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.

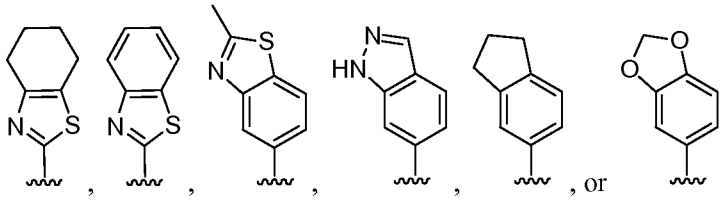
More preferably, A is phenyl (e.g., ), and is optionally substituted with one or more R_A; and B is  or  , and is optionally substituted with one or more R_A, where Z_1, Z_2, Z_3, Z_4, W_1, W_2, W_3, W_4, W_5, W_6 are as defined above. Preferably, Z_3 is N and Z_4 is NH. For instance, B can be  (e.g.,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

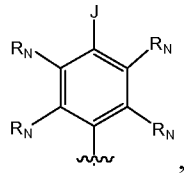
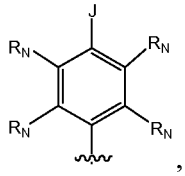
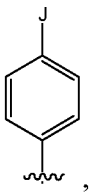
is  , and is optionally substituted with one or more R_M.

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.

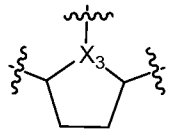
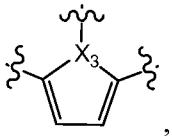
Also preferably, R_M is halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, or cyano; or R_M is $-L_S-R_E$, wherein L_S is a bond or C_1-C_6alkylene, and R_E is $-N(R_SR_S')$, $-O-R_S$, $-C(O)R_S$, $-C(O)OR_S$, $-C(O)N(R_SR_S')$, $-N(R_S)C(O)R_S'$, $-N(R_S)C(O)OR_S'$, $-N(R_S)SO_2R_S'$, $-SO_2R_S$, $-SR_S$, 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 $C_3\text{-}C_6carbocycle$ 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 $-N(R_SR_S')$. 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).

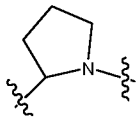
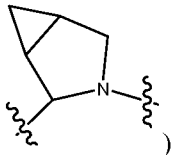
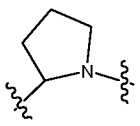
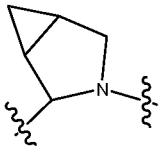
More preferably, D is $C_5\text{-}C_6carbocycle$, 5- to 6-membered heterocycle or 6- to 12-membered bicycle and is substituted with J and optionally substituted with one or more R_A, wherein J is $C_3\text{-}C_6carbocycle$, 3- to 6-membered heterocycle or 6- to 12-membered bicycle and is optionally substituted with one or more R_A. Preferably, J is substituted with a $C_3\text{-}C_6carbocycle$ or 3- to 6-membered heterocycle, wherein said $C_3\text{-}C_6carbocycle$ or 3- to 6-membered heterocycle is independently optionally substituted 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 $-N(R_SR_S')$, and J can also be optionally substituted with one or more R_A. Also preferably, D is $C_5\text{-}C_6carbocycle$ or 5- to 6-membered heterocycle and is substituted with J and optionally substituted with one or more R_A, and J is $C_3\text{-}C_6carbocycle$ or 3- to 6-membered heterocycle and is optionally substituted with one or more R_A, and preferably, J is at least substituted with a $C_3\text{-}C_6carbocycle$ or 3- to 6-membered heterocycle which is independently optionally substituted with one or more

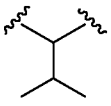
substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6haloalkyl, C_2-C_6haloalkenyl, C_2-C_6haloalkynyl, C(O)OR_S or –N(R_SR_S'). Also preferably, D is C_5-C_6carbocycle or 5- to 6-membered heterocycle and is substituted with J and optionally substituted with one or more R_A, and J is 6- to 12-membered bicycle (e.g., a 7- to 12-membered fused, bridged or spiro bicycle comprising a nitrogen ring atom through which J is covalently attached to D) and is optionally substituted with one or more R_A. More preferably, D is phenyl and is substituted with J and optionally substituted with one or more R_A, and J is C_3-C_6carbocycle, 3- to 6-membered heterocycle or 6- to 12-membered bicycle and is optionally substituted with one or more R_A, and preferably J is at least substituted with a C_3-C_6carbocycle or 3- to 6-membered heterocycle which is independently 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, C_2-C_6haloalkynyl, C(O)OR_S or –N(R_SR_S'). Highly preferably, D is  , wherein each R_N is independently selected from R_D and preferably is hydrogen or halogen, and J is C_3-C_6carbocycle, 3- to 6-membered heterocycle or 6- to 12-membered bicycle and is optionally substituted with one or more R_A, and preferably J is at least substituted with a C_3-C_6carbocycle or 3- to 6-membered heterocycle which is independently 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, C_2-C_6haloalkynyl, C(O)OR_S or –N(R_SR_S'). Also preferably, D is  , wherein each R_N is independently selected from R_D and preferably is hydrogen or halogen, and J is C_3-C_6carbocycle or 3- to 6-membered heterocycle and is substituted with a C_3-C_6carbocycle or 3- to 6-membered heterocycle which is independently 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, C_2-C_6haloalkynyl, C(O)OR_S or –N(R_SR_S'), and J can also be optionally substituted with one or more R_A. Also preferably, D is  ,

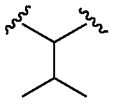
and J is C_3-C_6carbocycle or 3- to 6-membered heterocycle and is optionally substituted with one or more R_A, and preferably J is at least substituted with a C_3-C_6carbocycle or 3- to 6-membered heterocycle which is independently optionally substituted with one or more substituents selected from halogen, 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, C_2-C_6haloalkynyl, $C(O)OR_S$ or $-N(R_SR_S')$.

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 or R_F. 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. 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., $-CH_2-$ or ) 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- or ) and optionally substituted with one or more substituents selected from R_L.

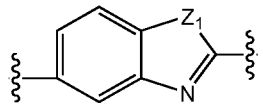
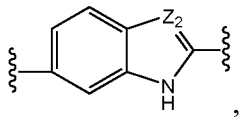
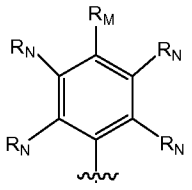
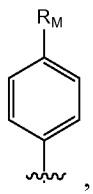
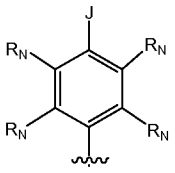
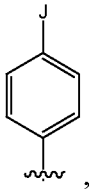
R_{NB} and R_C' are preferably hydrogen, and R_D' preferably is independently selected at each occurrence from R_E. More preferably, R_D' is independently selected at each occurrence from C_1-C_6alkyl, C_2-C_6alkenyl or C_2-C_6alkynyl, each of which is independently optionally substituted at each occurrence 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.

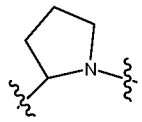
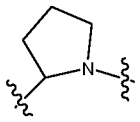
R_A preferably is halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, cyano; or C_1-C_6alkyl, C_2-C_6alkenyl or C_2-C_6alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, 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_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$$R_S$'), –$L_A$–N($R_S$)$SO_2$N($R_S$'$R_S$''), –$L_A$–N($R_S$)S(O)N($R_S$'$R_S$''), –$L_A$–OS(O)–$R_S$, –$L_A$–$OS(O)_2$–$R_S$, –$L_A$–$S(O)_2OR_S$, –$L_A$–S(O)O$R_S$, –$L_A$–OC(O)O$R_S$, –$L_A$–N($R_S$)C(O)O$R_S$', –$L_A$–OC(O)N($R_S$$R_S$'), –$L_A$–N($R_S$)S(O)–$R_S$', –$L_A$–S(O)N($R_S$$R_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.

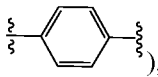
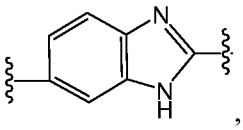
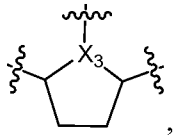
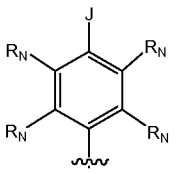
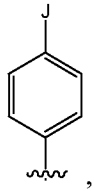
More preferably, R_A is halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, cyano; or C_1-C_6alkyl, C_2-C_6alkenyl or C_2-C_6alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy,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

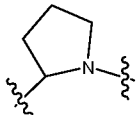
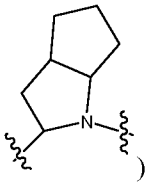
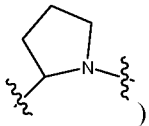
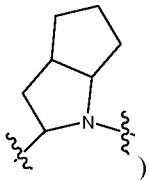
Highly preferably, R_A is halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, cyano; or C_1-C_6alkyl, C_2-C_6alkenyl or C_2-C_6alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy,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

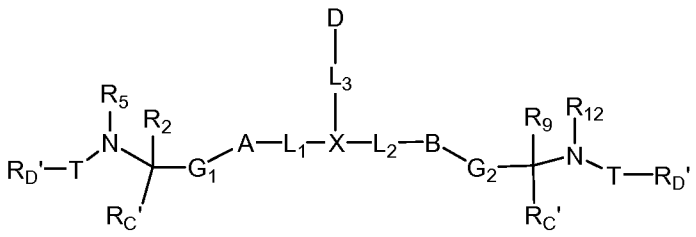
In one embodiment of this aspect, A is phenyl, and is optionally substituted with one or more R_A; and B is  or  , and is optionally substituted with one or more R_A, wherein Z_1 is O, S, NH or CH_2; and Z_2 is N or CH. D is C_5-C_6carbocycle or 5- to 6-membered heterocycle (e.g., phenyl), and is optionally substituted with one or more R_A, or is substituted with J and optionally substituted with one or more R_A, wherein J is C_3-C_6carbocycle, 3- to 6-membered heterocycle or 6- to 12-membered bicycle and is optionally substituted with one or more R_A. Preferably, J is substituted with a C_3-C_6carbocycle or 3- to 6-membered heterocycle which is independently 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, C_2-C_6haloalkynyl, $C(O)OR_S$ or $-N(R_SR_S')$, and J can also be optionally substituted with one or more R_A. Preferably, D is  or  , wherein R_M and R_N are as defined above. Also preferably, D is  or  , wherein J 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 $-C(O)-L_Y'-N(R_B)S(O)_2-L_S''-R_D'$. Preferably, 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; 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.

In another embodiment of this aspect, A is phenyl (e.g., ), and is optionally substituted with one or more R_A (preferably, A is substituted with at least one halogen such as F); and B is  , and is optionally substituted with one or more R_A (preferably, B is substituted with at least one halogen such as F). X is  , wherein X_3 is N and is directly linked to $-L_3-D$, and X is optionally substituted with one or more R_A or R_F. D is phenyl, and is substituted with J and optionally substituted with one or more R_A. J is C_3-C_6carbocycle, 3- to 6-membered heterocycle, 6- to 12-membered bicycle, 10- to 15-membered tricycle or 13- to 15-membered carbocycle/heterocycle, and J is optionally substituted with one or more R_A. Preferably, J is substituted with a C_3-C_6carbocycle, 3- to 6-membered heterocycle, 6- to 12-membered bicycle or 7- to 12-membered carbocycle/heterocycle, which is independently optionally substituted with one or more substituents selected from (1) 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 $-N(R_SR_S')$, or (2) trimethylsilyl, $-O-R_S$, $-S-R_S$ or $-C(O)R_S$; and J can also be optionally substituted with one or more R_A. Preferably, D is  or  , wherein J is as defined above, and each R_N is independently selected from R_D and preferably is hydrogen or halo such as F. 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'. Preferably, 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., ) or 6- to 12-membered bicycle (e.g., ) 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 5- to 6-membered heterocyclic ring (e.g., ) or 6- to 12-membered bicycle (e.g., ) which is optionally substituted with one or more R_A.

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;

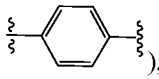
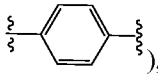
R_D' is each independently selected from R_D;

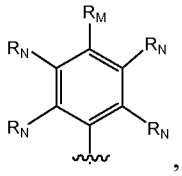
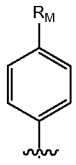
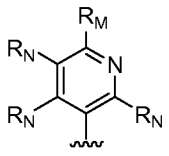
R_2 and R_5, taken together with the atoms to which they are attached, form a 3- to 12-membered heterocycle which is optionally substituted with one or more R_A;

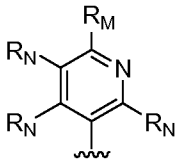
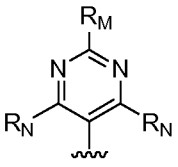
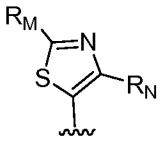
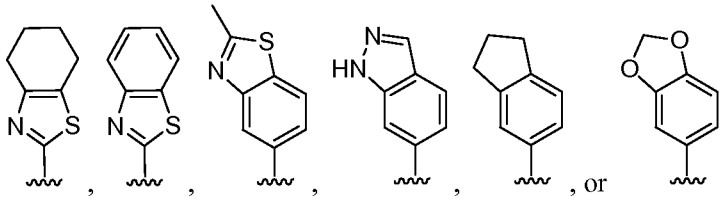
R_9 and R_{12}, taken together with the atoms to which they are attached, form a 3- to 12-membered heterocycle which is optionally substituted with one or more R_A;

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.

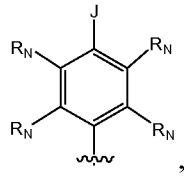
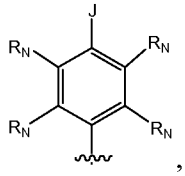
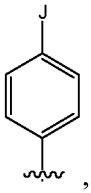
D is also preferably pyridinyl, pyrimidinyl, or thiazolyl, optionally substituted with one or more R_A. More preferably D is pyridinyl, pyrimidinyl, or thiazolyl, and is substituted with one or more R_M. Highly preferably, D is  ,  , or  , wherein R_M is as defined above, and each R_N is independently 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.

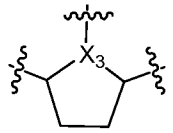
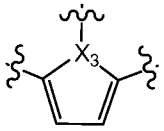
Also preferably, R_M is halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, or cyano; or R_M is $-L_S-R_E$, wherein L_S is a bond or C_1-C_6alkylene, and R_E is $-N(R_SR_S')$, $-O-R_S$, $-C(O)R_S$, $-C(O)OR_S$, $-C(O)N(R_SR_S')$, $-N(R_S)C(O)R_S'$, $-N(R_S)C(O)OR_S'$, $-N(R_S)SO_2R_S'$, $-SO_2R_S$, $-SR_S$, 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_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-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).

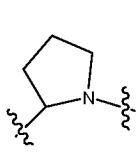
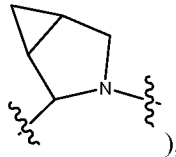
More preferably, D is C_5-C_6carbocycle, 5- to 6-membered heterocycle or 6- to 12-membered bicycle and is substituted with J and optionally substituted with one or more R_A, wherein J is C_3-C_6carbocycle, 3- to 6-membered heterocycle or 6- to 12-membered bicycle and is optionally substituted with one or more R_A. Preferably, J is substituted with a C_3-C_6carbocycle or 3- to 6-membered heterocycle, wherein said C_3-C_6carbocycle or 3- to 6-membered heterocycle is independently 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, C_2-C_6haloalkynyl, C(O)OR_S or –N(R_SR_S'), and J can also be optionally substituted with one or more R_A. Also preferably, D is C_5-C_6carbocycle or 5- to 6-membered heterocycle and is substituted with J and 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, and preferably, J is at least substituted with a C_3-C_6carbocycle or 3- to 6-membered heterocycle which is independently 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, C_2-C_6haloalkynyl, C(O)OR_S or –N(R_SR_S'). Also preferably, D is C_5-C_6carbocycle or 5- to 6-membered heterocycle and is substituted with J and optionally substituted with one or more R_A, and J is 6- to 12-membered bicycle (e.g., a 7- to 12-membered fused, bridged or spiro bicycle

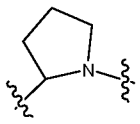
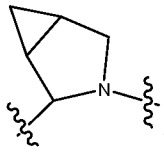
comprising a nitrogen ring atom through which J is covalently attached to D) and is optionally substituted with one or more R_A. More preferably, D is phenyl and is substituted with J and optionally substituted with one or more R_A, and J is C_3-C_6carbocycle, 3- to 6-membered heterocycle or 6- to 12-membered bicycle and is optionally substituted with one or more R_A, and preferably J is at least substituted with a C_3-C_6carbocycle or 3- to 6-membered heterocycle which is independently 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, C_2-C_6haloalkynyl, $C(O)OR_S$ or $-N(R_SR_S')$. Highly preferably, D is  , wherein each R_N is independently selected from R_D and preferably is hydrogen or halogen, and J is C_3-C_6carbocycle, 3- to 6-membered heterocycle or 6- to 12-membered bicycle and is optionally substituted with one or more R_A, and preferably J is at least substituted with a C_3-C_6carbocycle or 3- to 6-membered heterocycle which is independently 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, C_2-C_6haloalkynyl, $C(O)OR_S$ or $-N(R_SR_S')$. Also preferably, D is  , wherein each R_N is independently selected from R_D and preferably is hydrogen or halogen, and J is C_3-C_6carbocycle or 3- to 6-membered heterocycle and is substituted with a C_3-C_6carbocycle or 3- to 6-membered heterocycle which is independently 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, C_2-C_6haloalkynyl, $C(O)OR_S$ or $-N(R_SR_S')$, and J can also be optionally substituted with one or more R_A. Also preferably, 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, and preferably J is at least substituted with a C_3-C_6carbocycle or 3- to 6-membered heterocycle which is independently optionally substituted with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl,

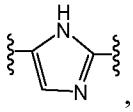
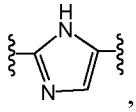
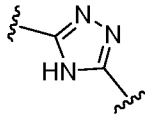
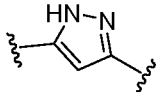
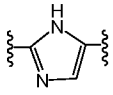
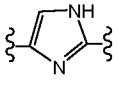
cyano, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6haloalkyl, C_2-C_6haloalkenyl, C_2-C_6haloalkynyl, $C(O)OR_S$ or $-N(R_SR_S')$.

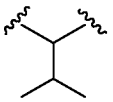
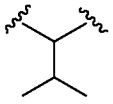
X preferably is C_5-C_6carbocycle, 5- to 6-membered heterocycle, or 6- to 12-membered bicycles (e.g.,  or  , wherein X_3 is N and is directly linked to $-L_3-D$), and is optionally substituted with one or more R_A or R_F. Non-limiting examples of X are described hereinabove.

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- or ) 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- or ) 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$–S(O)O$R_S$, –$L_A$–OC(O)O$R_S$, –$L_A$–N($R_S$)C(O)O$R_S$', –$L_A$–

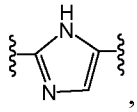
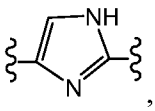
$OC(O)N(R_SR_S')$, $-L_A-N(R_S)S(O)-R_S'$, $-L_A-S(O)N(R_SR_S')$ or $-L_A-C(O)N(R_S)C(O)-R_S'$, wherein L_A is bond, C_1-C_6alkylene, C_2-C_6alkenylene or C_2-C_6alkynylene.

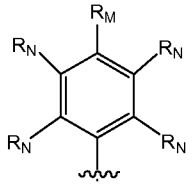
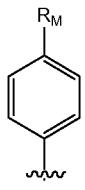
More preferably, R_A is halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, cyano; or C_1-C_6alkyl, C_2-C_6alkenyl or C_2-C_6alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy,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

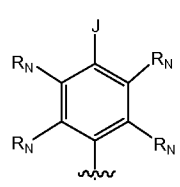
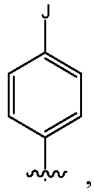
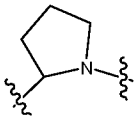
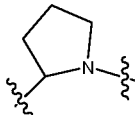
Highly preferably, R_A is halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, cyano; or C_1-C_6alkyl, C_2-C_6alkenyl or C_2-C_6alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy,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

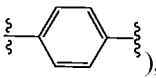
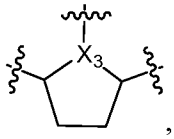
L_S, L_S' and L_S'' preferably are each independently selected at each occurrence from bond; or C_1-C_6alkylene, C_2-C_6alkenylene or C_2-C_6alkynylene.

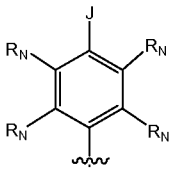
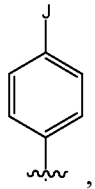
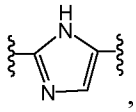
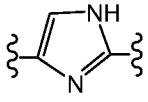
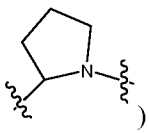
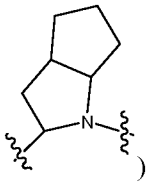
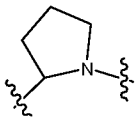
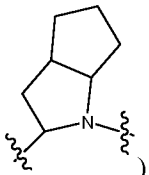
A and B can be the same or different. Likewise, L_1 and L_2 can be the same or different.

In one embodiment of this aspect, A and B are each independently phenyl, and are each independently optionally substituted with one or more R_A; D is phenyl, and is independently optionally substituted with one or more R_A, or is substituted with J and optionally substituted with one or more R_A, wherein J is C_3-C_6carbocycle, 3- to 6-membered heterocycle or 6- to 12-membered bicycle and is optionally substituted with one or more R_A. Preferably, J is substituted with a C_3-C_6carbocycle or 3- to 6-membered heterocycle which is independently 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, C_2-C_6haloalkynyl, $C(O)OR_S$ or $-N(R_SR_S')$, and J can also be 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).

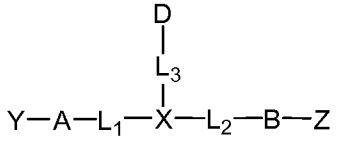
Preferably, D is  or  , wherein R_M and R_N are as defined above. Also

preferably, D is  or  , wherein J 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'. Preferably, 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; 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.

In another embodiment of this aspect, A and B are each independently phenyl (e.g., ), and are each independently optionally substituted with one or more R_A (preferably, A and B are each independently substituted with at least one halogen such as F). X is  , wherein X_3 is N and is directly linked to –L_3–D, and X is optionally substituted with one or more R_A or R_F. D is phenyl, and is substituted with J and optionally substituted with one or more R_A. J is C_3-C_6carbocycle, 3- to 6-membered heterocycle, 6- to 12-membered bicycle, 10- to 15-membered tricycle or 13- to 15-membered carbocycle/heterocycle, and J is optionally substituted with one or more R_A. Preferably, J is substituted with a C_3-C_6carbocycle, 3- to 6-membered heterocycle, 6- to 12-membered bicycle or 7- to 12-membered carbocycle/heterocycle, which is independently optionally substituted with one or more substituents selected from (1) 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$'), or (2) trimethylsilyl, –O–R_S, –S–R_S or –C(O)R_S; and J can also be optionally substituted with one or more

R_A. Preferably, D is  or  , wherein J is as defined above, and each R_N is independently selected from R_D and preferably is hydrogen or halo such as F. 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). 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'. Preferably, 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., ) or 6- to 12-membered bicycle (e.g., ) 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 5- to 6-membered heterocyclic ring (e.g., ) or 6- to 12-membered bicycle (e.g., ) which is optionally substituted with one or more R_A.

In another aspect, the present invention features compounds having Formula I_E and pharmaceutically acceptable salts thereof,



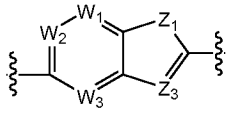
I_E

wherein:

X is 4- to 8-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 which is independently optionally substituted at each occurrence with one or more halo, hydroxy, –O–C_1-C_6alkyl, or –O–C_1-C_6haloalkyl;

L_3 is bond or C_1-C_6alkylene;

A and B are each independently phenyl, pyridinyl, thiazolyl, or  where Z_1 is independently selected at each occurrence from O, S, NH or CH_2, Z_3 is independently selected at each occurrence from N or CH, and W_1, W_2, and W_3 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.

D is C_6-C_{10}carbocycle or 5- to 12-membered heterocycle, each of which is optionally substituted with one or more R_M;

Y is –T'–C(R_1R_2)N(R_5)–T–R_D;

Z is –T'–C(R_8R_9)N(R_{12})–T–R_D;

R_1 is hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, or 3- to 6-membered carbocycle or heterocycle, wherein each said 3- to 6-membered carbocycle or heterocycle is independently optionally substituted at each occurrence with one or more substituents selected from halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, –O–C_1-C_6alkyl or –O–C_1-C_6haloalkyl;

R_2 and R_5 are each independently hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, or 3- to 6-membered carbocycle or heterocycle, wherein each said 3- to 6-membered carbocycle or heterocycle is independently optionally substituted at each occurrence with one or more substituents selected from halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, –O–C_1-C_6alkyl or –O–C_1-C_6haloalkyl; or 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 (e.g., 1, 2, 3, or 4 R_A);

R_8 is hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, or 3- to 6-membered carbocycle or heterocycle, wherein each said 3- to 6-membered carbocycle or heterocycle is independently optionally substituted at each occurrence with one or more substituents selected from halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, –O–C_1-C_6alkyl or –O–C_1-C_6haloalkyl;

R_9 and R_{12} are each independently hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, or 3- to 6-membered carbocycle or heterocycle, wherein each said 3- to 6-membered carbocycle or heterocycle is independently optionally substituted at each occurrence with one or more substituents selected from halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, –O–C_1-C_6alkyl or –O–C_1-

C_6haloalkyl; or 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 (e.g., 1, 2, 3, or 4 R_A);

T is independently selected at each occurrence from bond or $–C(O)–L_S'–$;

T' is independently selected at each occurrence from bond, $–C(O)N(R_B)–$, $–N(R_B)C(O)–$, or 3- to 12-membered heterocycle, wherein said 3- to 12-membered heterocycle 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 $–L_S–R_E$;

R_B and R_B' are each independently selected at each occurrence from hydrogen; or C_1-C_6alkyl which is independently optionally substituted at each occurrence with one or more substituents selected from halogen 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, C_1-C_6alkyl, C_1-C_6haloalkyl, $–O–C_1$-C_6alkyl, or $–O–C_1$-C_6haloalkyl;

R_E is independently selected at each occurrence from $–O–R_S$, $–S–R_S$, $–C(O)R_S$, $–OC(O)R_S$, $–C(O)OR_S$, $–N(R_SR_S')$, $–S(O)R_S$, $–SO_2R_S$, $–C(O)N(R_SR_S')$, $–N(R_S)C(O)R_S'$, $–N(R_S)C(O)N(R_S'R_S'')$, $–N(R_S)SO_2R_S'$, $–SO_2N(R_SR_S')$, $–N(R_S)SO_2N(R_S'R_S'')$, $–N(R_S)S(O)N(R_S'R_S'')$, $–OS(O)–R_S$, $–OS(O)_2–R_S$, $–S(O)_2OR_S$, $–S(O)OR_S$, $–OC(O)OR_S$, $–N(R_S)C(O)OR_S'$, $–OC(O)N(R_SR_S')$, $–N(R_S)S(O)–R_S'$, $–S(O)N(R_SR_S')$, $–C(O)N(R_S)C(O)–R_S'$, or $=C(R_SR_S')$; 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_{12}carbocycle or 3- to 12-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_{12}carbocycle or 3- to 12-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 is independently selected at each occurrence from bond; or C_1-C_6alkylene, C_2-C_6alkenylene or C_2-C_6alkynylene, each independently optionally substituted with halogen;

L_S' is 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;

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_6haloalkyl, or 3- to 12-membered carbocycle or heterocycle; or 3- to 12-membered carbocycle or heterocycle; wherein each 3- to 12-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;

R_M is independently selected at each occurrence from:

halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, cyano, SF_5, –N($R_S$$R_S$'), –O–$R_S$, –OC(O)$R_S$, –OC(O)O$R_S$, –OC(O)N($R_S$$R_S$'), –C(O)$R_S$, –C(O)O$R_S$, –C(O)N($R_S$$R_S$'), –N($R_S$)C(O)$R_S$', –N($R_S$)C(O)O$R_S$', –N($R_S$)$SO_2$$R_S$', –S(O)$R_S$, –$SO_2$$R_S$, –S(O)N($R_S$$R_S$'), –S$R_S$, –Si($R_S$)$_3$, or –P(O)(O$R_S$)$_2$;

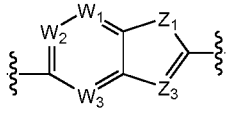
C_1-C_6alkyl, C_2-C_6alkenyl or C_2-C_6alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, –N($R_S$$R_S$'), –O–$R_S$, –OC(O)$R_S$, –OC(O)O$R_S$, –OC(O)N($R_S$$R_S$'), –C(O)$R_S$, –C(O)O$R_S$, –C(O)N($R_S$$R_S$'), –N($R_S$)C(O)$R_S$', –N($R_S$)C(O)O$R_S$', –N($R_S$)$SO_2$$R_S$', –S(O)$R_S$, –$SO_2$$R_S$, –S(O)N($R_S$$R_S$'), –S$R_S$, or –P(O)(O$R_S$)$_2$; or

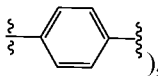
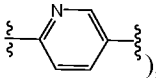
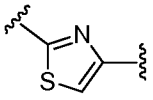
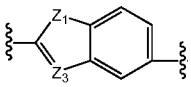
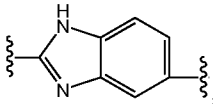
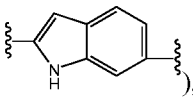
G_2, wherein G_2 is a C_3-C_{12}carbocycle or 3- to 12-membered heterocycle, each of which is independently optionally substituted at each occurrence with one or more R_{G2}, and each R_{G2} is independently selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, 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, –O–R_S, –C(O)OR_S, –C(O)R_S, –N($R_S$$R_S$'), or –$L_4$–$G_3$;

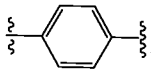
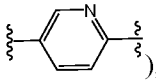
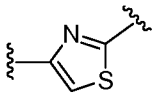
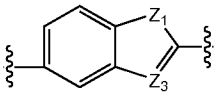
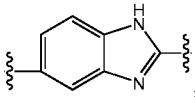
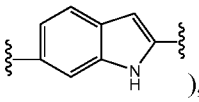
L_4 is a bond, C_1-C_6alkylene, C_2-C_6alkenylene, C_2-C_6alkynylene, –O–, –S–, –N(R_B)–, –C(O)–, –$S(O)_2$–, –S(O)–, –C(O)O–, –OC(O)–, –OC(O)O–, –C(O)N(R_B)–, –N(R_B)C(O)–, –N(R_B)C(O)O–, –OC(O)N(R_B)–, –N(R_B)S(O)–, –N(R_B)$S(O)_2$–, –S(O)N(R_B)–, –$S(O)_2$N(R_B)–, –N(R_B)C(O)N(R_B')–, –N(R_B)SO_2N(R_B')–, or –N(R_B)S(O)N(R_B')–;

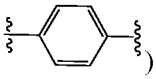
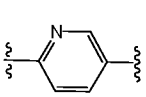
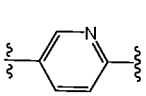
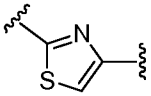
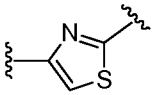
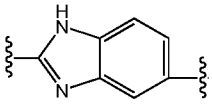
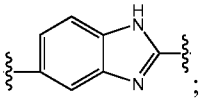
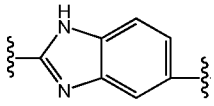
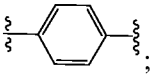
G_3 is a C_3-C_{12}carbocycle or 3- to 12-membered heterocycle, and is optionally substituted with one or more R_{G3}; and

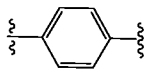
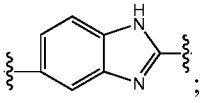
R_{G3} is each independently, at each occurrence, halogen, –C_1-C_6alkyl, –C(O)C_1-C_6alkyl, –C_1-C_6haloalkyl, –O–C_1-C_6alkyl, –O–C_1-C_6haloalkyl, C_3-C_6carbocycle, or 3- to 6-membered heterocycle.

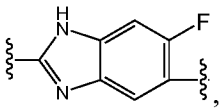
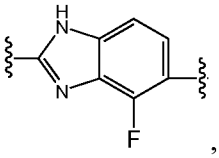
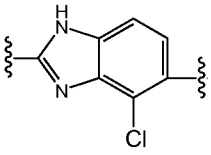
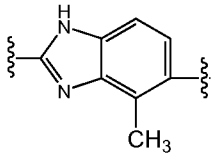
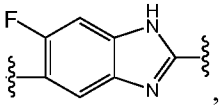
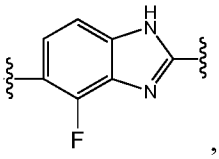
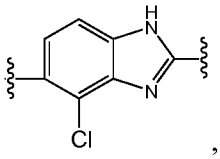
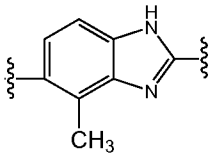
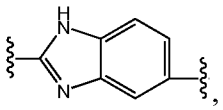
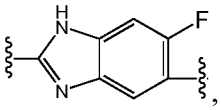
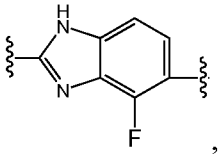
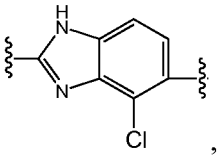
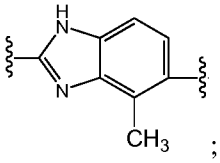
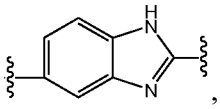
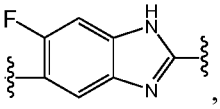
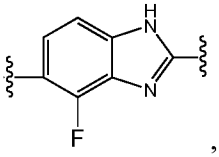
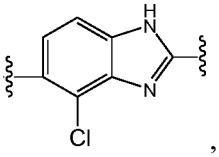
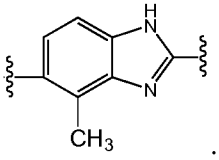
As described hereinabove for compounds of Formula I_E A and B are each phenyl, pyridinyl, thiazolyl, or  where Z_1 is independently selected at each occurrence from O, S, NH or CH_2, Z_3 is independently selected at each occurrence from N or CH, and W_1, W_2, and W_3 are each independently selected at each occurrence from CH or N; A and B are each independently optionally substituted with one or more R_A.

Preferably, A is selected from phenyl (e.g., ), pyridinyl (e.g., ), thiazolyl (e.g., ), or  (e.g.,  , ), and is optionally substituted with one or more R_A.

Preferably, B is selected from phenyl (e.g., ), pyridinyl (e.g., ), thiazolyl (e.g., ), or  (e.g.,  , ), and is optionally substituted with one or more R_A.

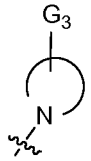
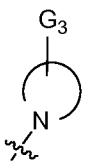
Highly preferably, both A and B are phenyl (e.g., both A and B are ); or A is  and B is  ; or A is  and B is  ; or A is  and B is  ; or A is  and B is  ; or A

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

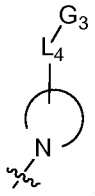
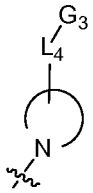
In certain embodiments of this aspect of the invention, A and B are substituted by one or more R_A, wherein each R_A is independently selected from halogen (e.g., fluoro, chloro), L_S–R_E (where L_S is bond and R_E is –C_1-C_6alkyl (e.g., methyl), –O–R_S (e.g., –O–C_1-C_6alkyl, –OCH_3), or –C_1-C_6alkyl optionally substituted with one or more halogen (e.g., –CF_3)), or L_S–R_E (where L_S is C_1-C_6alkylene and R_E is –O–R_S (e.g., –C_1-C_6alkyl–O–C_1-C_6alkyl, –CH_2OCH_3)). For example, in certain embodiments A is  ,  ,  , or  and B is as defined hereinabove. In certain other embodiments B is  ,  ,  , or  and A is as defined hereinabove. In still other embodiments A is  ,  ,  ,  , or  ; and B is  ,  ,  ,  , or  .

As described hereinabove for compounds of Formula I_E D is C_6-C_{10}carbocycle or 3- to 12-membered heterocycle optionally substituted by one or more R_M. Preferably, D is C_6-C_{10}aryl (e.g., phenyl, naphthyl, indanyl), or 5- to 10-membered heteroaryl (pyridinyl, thiazolyl, 4,5,6,7-tetrahydrobenzo[d]thiazolyl, benzo[d]thiazolyl, indazolyl, benzo[d][1,3]dioxol-5-yl), and D is substituted with one or more R_M. For example, in certain embodiments D is preferably phenyl substituted by one or more R_M, wherein each R_M is independently halogen (e.g., fluoro, chloro, bromo); C_1-C_6alkyl (e.g., tert-butyl); C_1-C_6alkyl substituted with one or more halogen (e.g., CF_3); –O–

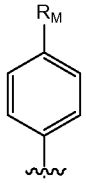
R_S such as –O–C_1-C_6alkyl (e.g., –O–CH_2CH_3); or –O–C_1-C_6alkyl substituted at each occurrence with one or more halogen (e.g., –O–CF_3, –O–CH_2CHF_2) or –O–C_1-C_6alkyl (e.g., –O–$CH_2CH_2OCH_3$); –O–R_S (e.g., –O–C_1-C_6alkyl, such as –O–CH_2) substituted with 3- to 12-membered heterocycle (e.g., 3-ethyloxetan-3-yl, 1,3-dioxolan-4-yl); –O–R_S where R_S is an optionally substituted 3- to 12-membered carbocycle or heterocycle (e.g., cyclopentyl, cyclohexyl, phenyl, 1,3-dioxan-5-yl); –N(R_S)C(O)R_S' wherein R_S and R_S' are each independently C_1-C_6alkyl (e.g., –N(t-Bu)C(O)Me); SF_5; –SO_2R_S wherein R_S is C_1-C_6alkyl (e.g., –SO_2Me); or C_3-C_{12}carbocycle (e.g., cyclopropyl, cyclohexyl, phenyl).

In certain embodiments of this aspect of the invention, D is preferably phenyl or pyridyl and is substituted by one or more R_M where one R_M is G_2. In certain embodiments where D is phenyl or pyridyl, D is substituted by G_2, G_2 is 3- to 12-membered heterocycle (e.g., pyridinyl, piperidinyl, pyrrolidinyl, azetidinyl, oxazolyl) and is optionally substituted with one or more halogen (e.g., fluoro, chloro), hydroxy, oxo, cyano, C_1-C_6alkyl (e.g., methyl), C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6haloalkyl (e.g., CF_3), C_2-C_6haloalkenyl, C_2-C_6haloalkynyl, –O–C_1-C_6alkyl (e.g., –O–CH_3), –C(O)OR_S (e.g., –C(O)OCH_3), –C(O)R_S (e.g., –C(O)CH_3), or –N(R_SR_S'); and D is further optionally substituted by one or more R_M where R_M is halogen (e.g., fluoro, chloro), C_1-C_6alkyl (e.g., methyl), C_1-C_6haloalkyl (e.g., CF_3), or –O–C_1-C_6alkyl (e.g., –O–CH_3). In certain other embodiments D is phenyl or pyridyl and G_2 is, for example, a monocyclic 3-8 membered carbocycle or monocyclic 4-8 membered heterocycle substituted with L_4–G_3 and optionally substituted with one or more R_{G2} wherein L_4, G_3 and R_{G2} are as defined herein. L_4, for example is a bond, a C_1-C_6 alkylene (e.g., –CH_2–, –CH_2CH_2–, –$CH_2CH_2CH_2$–, etc.), –O–, or –$S(O)_2$–. G_3 is for example a C_3-C_{12}carbocycle optionally substituted with one or more R_{G3}. R_{G2} and R_{G3} are each independently at each occurrence halogen, –C(O)C_1-C_6alkyl, –C_1-C_6alkyl, –C_1-C_6haloalkyl, –O–C_1-C_6alkyl, or –O–C_1-C_6haloalkyl. In certain embodiments G_2 is  , wherein  is a monocyclic 4-8 membered nitrogen-containing heterocycle (e.g., azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl) attached to the parent molecular moiety through a nitrogen atom and substituted with one or two L_4–G_3 and optionally substituted with one or more R_{G2}. Thus, in certain embodiments where L_4 is a bond G_2 is  , where  is optionally substituted with R_{G2} and G_3 is optionally substituted with R_{G3}. Thus,  can be, for example, 3-phenylazetidin-

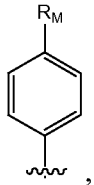
1-yl, 3-phenylpyrrolidin-1-yl, 4-phenylpiperazin-1-yl, 4-phenylpiperidin-1-yl, 4-phenyl-3,6-dihydropyridin-1(2H)-yl, 4,4-diphenylpiperidin-1-yl, 4-acetyl-4-phenylpiperidin-1-yl, 4-(4-methoxyphenyl)piperidin-1-yl, 4-(4-fluorophenyl)piperidin-1-yl, or 3-phenylpiperidin-1-yl, and wherein D can be further optionally substituted with one or more R_M (e.g., fluoro, chloro, methyl, methoxy).

In certain other embodiments of this aspect of the invention, L_4 is a C_1-C_6 alkylene, –O–, or –$S(O)_2$–, and G_2 is  , where  is as defined above and is optionally substituted with R_{G2} and G_3 is as defined above and is optionally substituted with R_{G3}. Thus,  can be, for example, 4-tosylpiperazin-1-yl, 4-phenoxypiperidin-1-yl, 3-phenoxypyrrolidin-1-yl, 4-benzylpiperidin-1-yl, 4-phenethylpiperidin-1-yl, or 3-phenylpropyl)piperidin-1-yl.

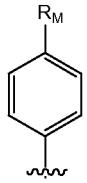
In certain other embodiments of this aspect of the invention, D is phenyl or pyridyl, D is substituted by G_2 and G_2 is a spiro, bridged, or fused bicyclic carbocycle or heterocycle optionally substituted with L_4–G_3 and one or more R_{G2}, wherein D is optionally substituted with one or more R_M and R_M, L_4, G_3, and R_{G2} are as defined herein. In certain embodiments G_2 is  , wherein  is a spiro, bridged, or fused bicyclic nitrogen-containing heterocycle (e.g., 3-azabicyclo[3.2.0]hept-3-yl, 2-azabicyclo[2.2.2]oct-2-yl, 6-azaspiro[2.5]oct-6-yl, octahydro-2H-isoindol-2-yl, 3-azaspiro[5.5]undec-3-yl, 1,3-dihydro-2H-isoindol-2-yl, 1,4-dioxa-8-azaspiro[4.5]dec-8-yl) attached to the parent molecular moiety through a nitrogen atom and optionally substituted with G_3 and one or more R_{G2}. Thus, G_2 is 3-azabicyclo[3.2.0]hept-3-yl, 2-azabicyclo[2.2.2]oct-2-yl, 6-azaspiro[2.5]oct-6-yl, octahydro-2H-isoindol-2-yl, 3-azaspiro[5.5]undec-3-yl, 1,3-dihydro-2H-isoindol-2-yl, or 1,4-dioxa-8-azaspiro[4.5]dec-8-yl; L_4 is a bond and D is optionally substituted with one or more R_M (e.g., fluoro, chloro, methyl, methoxy).



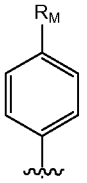
In certain embodiments of this aspect of the invention, D is wherein R_M is as defined above in connection with Formula I_E, and D is optionally substituted by one or more additional R_M.



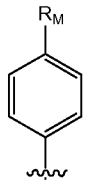
For instance, where D is , R_M can be fluoro, chloro, tert-butyl, –O–CH_2CH_3, –O–CF_3, –O–CH_2CHF_2, –O–$CH_2CH_2OCH_3$, –O–CH_2–(3-ethyloxetan-3-yl), –O–CH_2–(1,3-dioxolan-4-yl), –O–cyclopentyl, –O–cyclohexyl, –O–phenyl, –O–(1,3-dioxan-5-yl), cyclopropyl, cyclohexyl, phenyl, SF_5, –SO_2Me, or –N(t-Bu)C(O)Me and D can be optionally substituted by one or more additional R_M selected from the group consisting of halogen (e.g., fluoro, chloro) and C_1-C_6alkyl (e.g., methyl).



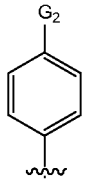
In certain embodiments, D is wherein R_M is fluoro, chloro, tert-butyl, –O–CH_2CH_3, –O–CF_3, –O–CH_2CHF_2, –O–$CH_2CH_2OCH_3$, SF_5, –SO_2Me, or –N(t-Bu)C(O)Me and D is optionally substituted by one or more additional R_M selected from the group consisting of halogen (e.g., fluoro, chloro) and C_1-C_6alkyl (e.g., methyl).



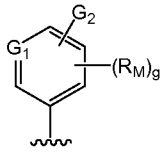
In certain embodiments, D is wherein R_M is cyclopropyl, cyclohexyl, or phenyl and D is optionally substituted by one or more additional R_M selected from the group consisting of halogen (e.g., fluoro, chloro) and C_1-C_6alkyl (e.g., methyl).

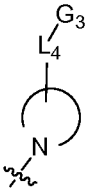
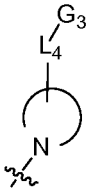


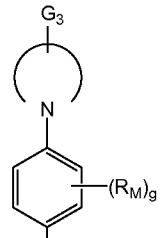
In certain embodiments, D is wherein R_M is –O–CH_2–(3-ethyloxetan-3-yl), –O–CH_2–(1,3-dioxolan-4-yl), –O–cyclopentyl, –O–cyclohexyl, –O–phenyl, or –O–(1,3-dioxan-5-yl) and D is optionally substituted by one or more additional R_M selected from the group consisting of halogen (e.g., fluoro, chloro) and C_1-C_6alkyl (e.g., methyl).

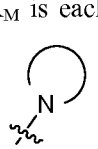


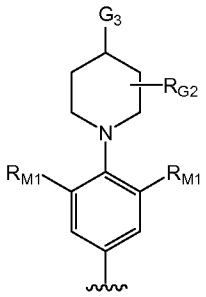
In certain embodiments, D is wherein G_2 is pyridinyl (e.g., pyridin-2-yl), piperidin-1-yl, 4,4-dimethylpiperidin-1-yl, 4,4-difluoropiperidin-1-yl, 2,6-dimethylpiperidin-1-yl, 4-(propan-2-yl)piperidin-1-yl, 4-fluoropiperidin-1-yl, 3,5-dimethylpiperidin-1-yl, 4-(trifluoromethyl)piperidin-1-yl, 4-methylpiperidin-1-yl, 4-tert-butylpiperidin-1-yl, 2-oxopiperidin-1-yl, 3,3-dimethylazetidin-1-yl, or oxazolyl (e.g., 1,3-oxazol-2-yl) and D is optionally substituted by one or more additional R_M selected from the group consisting of halogen (e.g., fluoro, chloro) and C_1-C_6alkyl (e.g., methyl).



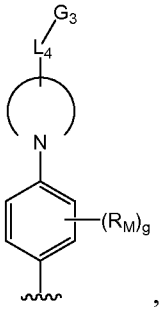
In another embodiment of this aspect of the invention, D is wherein G_1 is N, C–H, or C–R_M; G_2 is  , wherein  is a monocyclic 4-8 membered nitrogen-containing heterocycle (e.g., azetidinyl, pyrrolidinyl, piperidinyl) attached to the parent molecular moiety through a nitrogen atom and substituted by L_4–G_3 and optionally substituted with one or more R_{G2}; L_4 is a bond, C_1-C_6 alkylene, –O–, or –$S(O)_2$–; G_3 is aryl (e.g., phenyl), cycloalkyl (e.g., cyclohexyl), or heterocycle (e.g., thienyl) wherein each G_3 is optionally substituted with one or more R_{G3}; R_{G2} and R_{G3} at each occurrence are each independently halogen, –C(O)C_1-C_6alkyl, –C_1-C_6alkyl, –C_1-C_6haloalkyl, –O–C_1-C_6alkyl, or –O–C_1-C_6haloalkyl; g is 0, 1, 2, or 3; and R_M is as defined above in connection with

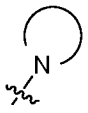


Formula I_E. In one group of compounds according to this embodiment, D is , wherein G_3 is phenyl optionally substituted with one or two R_{G3}; g is 0, 1, or 2; R_M is each independently fluoro, chloro, methyl, methoxy, trifluoromethyl, or trifluoromethoxy; and  and R_{G3} are as

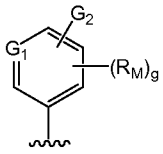


defined above. In a further subgroup of compounds of this embodiment, D is wherein G_3 is phenyl optionally substituted with one or two R_{G3}; R_{M1} is each independently hydrogen, fluoro, chloro, or methyl; and R_{G2} is an optional substituent as described herein. In another group of



compounds according to this embodiment, D is , wherein L_4 is C_1-C_6 alkylene, –O–, or –$S(O)_2$–; G_3 is phenyl optionally substituted with one or two R_{G3}; g is 0, 1, or 2; R_M is each independently fluoro, chloro, methyl, methoxy, trifluoromethyl, or trifluoromethoxy; and 

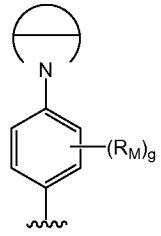
and R_{G3} are as defined above.

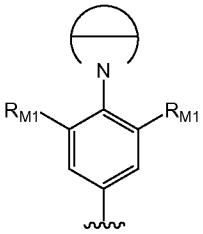
In yet another embodiment of this aspect of the invention, D is 

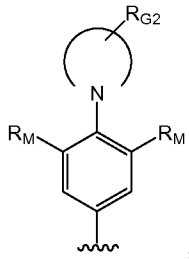
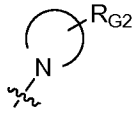
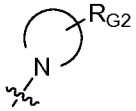
wherein G_1 is N, C–H, or C–R_M; G_2 is 

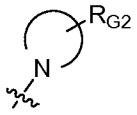
, wherein 

is a spiro, bridged, or fused bicyclic nitrogen-containing heterocycle (e.g., 3-azabicyclo[3.2.0]hept-3-yl, 2-azabicyclo[2.2.2]oct-2-yl, 6-azaspiro[2.5]oct-6-yl, octahydro-2H-isoindol-2-yl, 3-azaspiro[5.5]undec-3-yl, 1,3-dihydro-2H-isoindol-2-yl, 1,4-dioxa-8-azaspiro[4.5]dec-8-yl) attached to the parent molecular moiety through a nitrogen atom and optionally substituted with L_4–G_3 and one or more R_{G2}; L_4 is a bond, C_1-C_6 alkylene, –O–, or –$S(O)_2$–; G_3 is aryl (e.g., phenyl), cycloalkyl (e.g., cyclohexyl), or heterocycle (e.g., thienyl) wherein each G_3 is optionally substituted with one or more R_{G3}; R_{G2} and R_{G3} at each occurrence are each independently halogen, –C(O)C_1-C_6alkyl, –C_1-C_6alkyl, –C_1-C_6haloalkyl, –O–C_1-C_6alkyl, or –O–C_1-C_6haloalkyl; g is 0, 1, 2, or 3; and R_M is as defined above in connection with

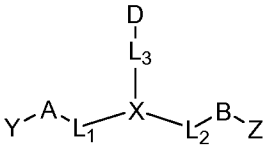


Formula I_E. In one group of compounds according to this embodiment, D is wherein g is 0, 1, or 2; R_M is each independently fluoro, chloro, methyl, methoxy, trifluoromethyl, or trifluoromethoxy; and  is as defined above. In a further subgroup of compounds D is  wherein R_{M1} is each independently hydrogen, fluoro, chloro, or methyl, and  is as defined above (e.g., 3-azabicyclo[3.2.0]hept-3-yl, octahydro-2H-isoindol-2-yl, 2-azabicyclo[2.2.2]oct-2-yl, 6-azaspiro[2.5]oct-6-yl, 3-azaspiro[5.5]undec-3-yl, 1,3-dihydro-2H-isoindol-2-yl, 1,4-dioxa-8-azaspiro[4.5]dec-8-yl).

In still another embodiment of this aspect of the invention, D is  , wherein  is a monocyclic 4-8 membered nitrogen-containing heterocycle (e.g., azetidinyl, pyrrolidinyl, piperidinyl) substituted with one or more R_{G2}, wherein R_{G2} at each occurrence is each independently halogen, $–C(O)C_1$-C_6alkyl, $–C_1$-C_6alkyl, $–C_1$-C_6haloalkyl, $–O–C_1$-C_6alkyl, or $–O–C_1$-C_6haloalkyl; and R_M is each independently halogen, $–C_1$-C_6alkyl, $–C_1$-C_6haloalkyl, $–O–C_1$-C_6alkyl, or $–O–C_1$-C_6haloalkyl. In one group of compounds according to this embodiment,  is azetidinyl, pyrrolidinyl, or piperidinyl substituted with one or two R_{G2}, wherein R_{G2} at each occurrence is each independently methyl, ethyl, isopropyl, tert-butyl, fluoro, chloro, or trifluoromethyl; and R_M is

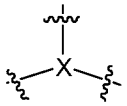
each independently fluoro, chloro, or methyl. For example  is 4,4-dimethylpiperidin-1-yl, 4,4-difluoropiperidin-1-yl, 2,6-dimethylpiperidin-1-yl, 4-(propan-2-yl)piperidin-1-yl, 4-fluoropiperidin-1-yl, 3,5-dimethylpiperidin-1-yl, 4-(trifluoromethyl)piperidin-1-yl, 4-methylpiperidin-1-yl, 4-tert-butylpiperidin-1-yl, 2-oxopiperidin-1-yl, or 3,3-dimethylazetidin-1-yl.

For compounds of Formula I_E



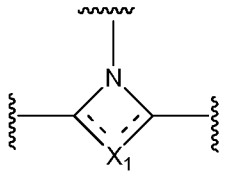
I_E

attachment of X to the remainder of the molecule can be conveniently depicted by the abbreviated structural Formula X', wherein the groups attached to X maintain the same relative spatial orientation as drawn in Formula I_E It is understood that in subsequent depictions of the variable group X, the substituents of X will retain the same relative positions and orientation as in Formula I_E and Formula X'.

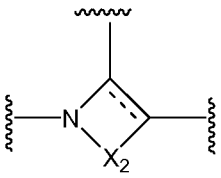


X'

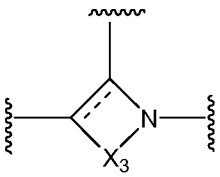
Compounds of Formula I_E include those where the variable X is selected from the group consisting of X-1, X-2, X-3, and X-4 wherein X-1, X-2, X-3, and X-4 retain the same orientation as structure X' relative to the remainder of the molecule; wherein the presence of === in X-1, X-2, and X-3 represents single or double bonds, X_1 is C_1-C_2alkylene or C_2alkenylene, X_2 and X_3 are each C_1-C_2alkylene or C_2alkenylene, and X_4 is C_1-C_2 alkylene.



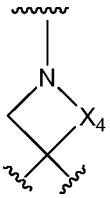
X-1



X-2

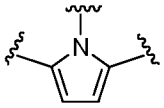


X-3

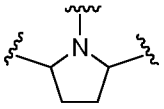


X-4

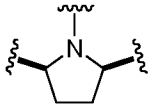
In accordance with the foregoing description, in certain embodiments of this aspect of the invention, X is pyrrolyl and is attached to the remainder of the molecule as shown in Formula

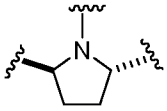


X_A: X_A . In certain embodiments, X is pyrrolidinyl and is attached to the remainder of the



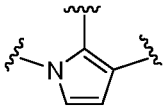
molecule as shown in Formula X_B: X_B . Embodiments according to Formula X_B may exist

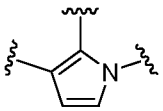




in cis (X_{B1}) or trans (X_{B2}) forms: X_{B1} X_{B2} . Chiral carbon atoms in X_B, X_{B1}, and X_{B2} may have either the (R) or (S) absolute stereochemistry.

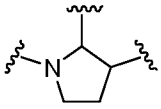
In yet another embodiment of this aspect of the invention, X is pyrrolyl and is attached to the

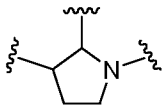




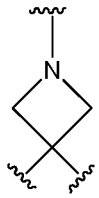
remainder of the molecule as shown in Formulae X_{C1} or X_{C2}: X_{C1} X_{C2} .

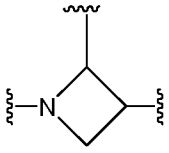
In certain embodiments, X is pyrrolidinyl and is attached to the remainder of the molecule as shown





in Formulae X_{D1} or X_{D2}: X_{D1} X_{D2} . Embodiments according to Formulae X_{D1} or X_{D2} may exist in cis or trans forms and chiral carbon atoms in X_{D1} and X_{D2} may have either the (R) or (S) absolute stereochemistry. In certain embodiments, X is azetidinyl and is attached to the remainder of the molecule as shown in Formulae X_{E1} or X_{E2}:



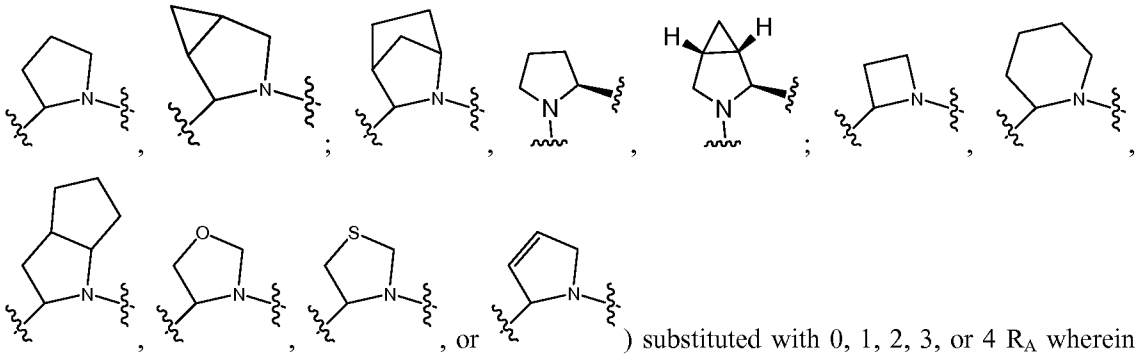
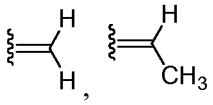
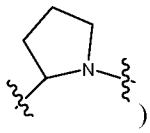
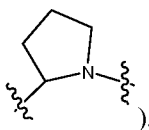


X_{E1} X_{E2} . Chiral carbon atoms in X_{E1} and X_{E2} may independently have either the (R) or (S) absolute stereochemistry.

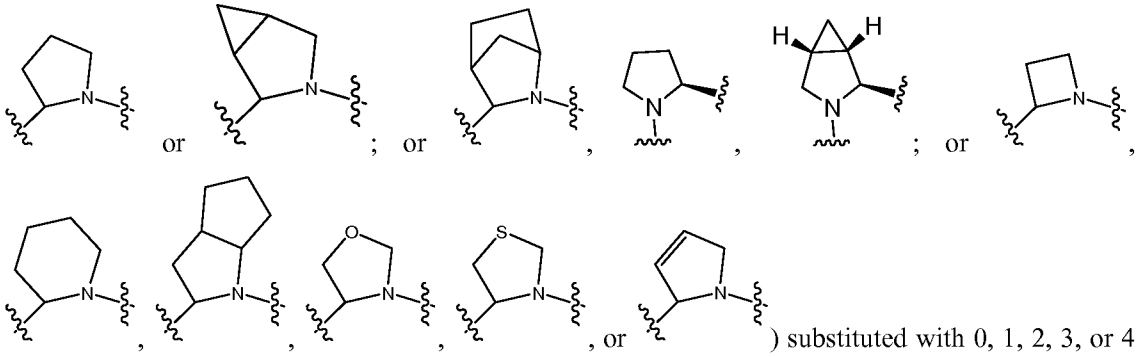
In certain preferred embodiments of this aspect of the invention, X is X_A, X_B, X_{B1}, X_{B2}, X_{C1}, or X_{C2} and L_1, L_2, and L_3 are each a bond. In certain other embodiments, X is X_{D1}, X_{D2}, X_{E1}, or X_{E2} and L_1, L_2, and L_3 are each a bond. In another embodiment, X is X_{E1} and L_1 and L_2 are each methylene (i.e. $-CH_2-$), and L_3 is a bond.

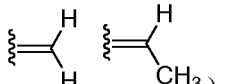
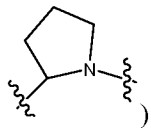
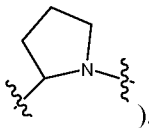
In compounds of Formula I_E, Y is–T'–$C(R_1R_2)N(R_5)$–T–R_D and Z is –T'–$C(R_8R_9)N(R_{12})$–T–R_D; wherein T', R_1, R_2, R_5, R_8, R_9, R_{12}, T, and R_D are as defined herein.

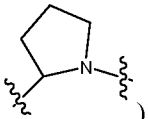
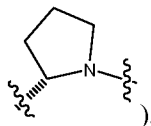
Preferably R_1, R_2, R_5, R_8, R_9, and R_{12} are each independently hydrogen; C_1-C_6alkyl; or 3- to 6-membered carbocycle or heterocycle, wherein each 3- to 6-membered carbocycle or heterocycle is independently optionally substituted at each occurrence with one or more substituents selected from halogen or C_1-C_6alkyl; wherein R_2 and R_5, taken together with the atoms to which they are attached, optionally form a 3- to 12-membered heterocycle which is substituted with 0, 1, 2, 3, or 4 R_A, and R_9 and R_{12} taken together with the atoms to which they are attached, optionally form a 3- to 12-membered heterocycle which is substituted with 0, 1, 2, 3, or 4 R_A wherein R_A is as defined herein.

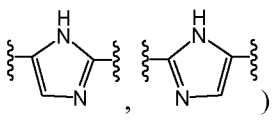
In certain embodiments of this aspect of the invention, R_1 is hydrogen and R_2 and R_5, taken together with the atoms to which they are attached form a 3- to 12-membered heterocycle (e.g., ) substituted with 0, 1, 2, 3, or 4 R_A wherein R_A is halogen (e.g., fluoro, chloro); cyano; L_S–R_E where L_S is a single bond and R_E is C_1-C_6alkyl (e.g., methyl, ethyl), –O–C_1-C_6alkyl (e.g., methoxy), or –O–C_1-C_6haloalkyl (e.g., trifluoromethoxy); or L_S–R_E where L_S is a double bond and R_E is $=C(R_SR_S')$ (e.g., ). In a preferred embodiment R_2 and R_5, taken together with the atoms to which they are attached form a pyrrolidine ring (i.e., ) substituted with 0 or 1 R_A wherein R_A is fluoro, methoxy, methyl, ethyl, or cyano. In another preferred embodiment R_2 and R_5, taken together with the atoms to which they are attached form a pyrrolidine ring (i.e., ).

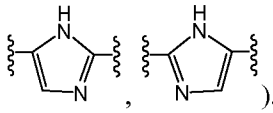
In certain other embodiments of this aspect of the invention, R_8 is hydrogen and R_9 and R_{12}, taken together with the atoms to which they are attached form a 3- to 12-membered heterocycle (e.g.,

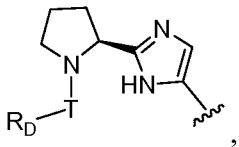
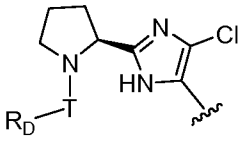
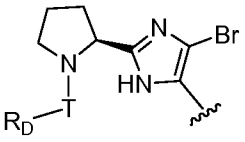
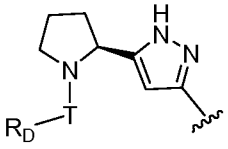
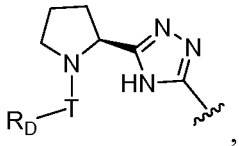
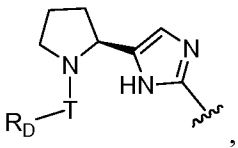
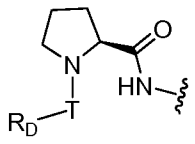
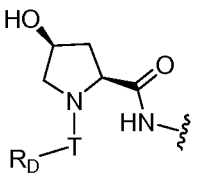
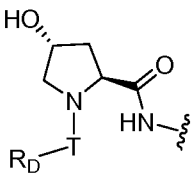
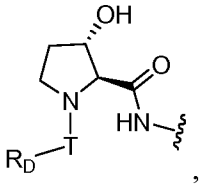
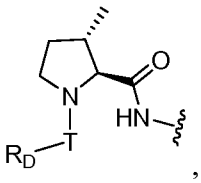
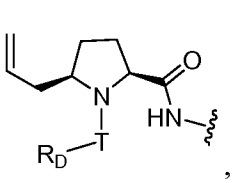
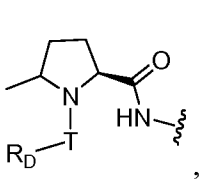
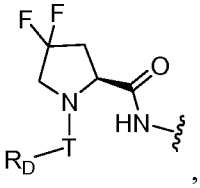
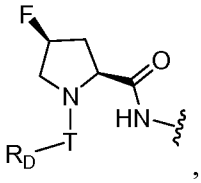
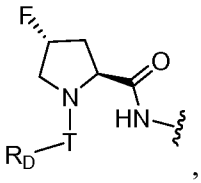
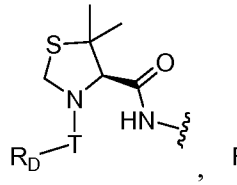
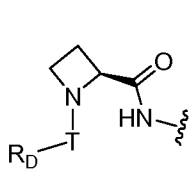
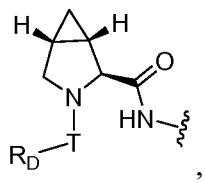
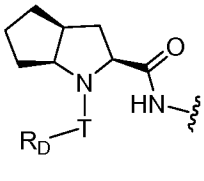
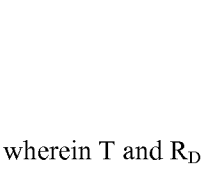
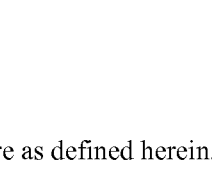
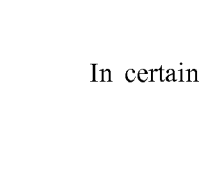


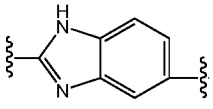
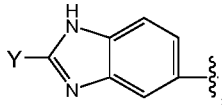
) substituted with 0, 1, 2, 3, or 4 R_A wherein R_A is halogen (e.g., fluoro, chloro); cyano; L_S–R_E where L_S is a single bond and R_E is C_1-C_6alkyl (e.g., methyl, ethyl), –O–C_1-C_6alkyl (e.g., methoxy), or –O–C_1-C_6haloalkyl (e.g., trifluoromethoxy); or L_S–R_E where L_S is a double bond and R_E is =C($R_S$$R_S$') (e.g., ). In a preferred embodiment, R_9 and R_{12}, taken together with the atoms to which they are attached form a pyrrolidine ring (i.e., ) substituted with 0 or 1 R_A wherein R_A is fluoro, methoxy, methyl, ethyl, or cyano. In another preferred embodiment R_9 and R_{12}, taken together with the atoms to which they are attached form a pyrrolidine ring (i.e., ).

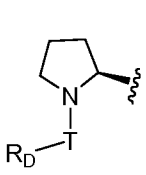
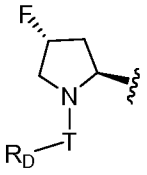
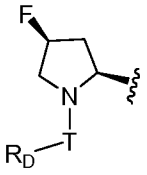
As used herein, a chiral carbon in any rings formed by joining R_2 and R_5 or R_9 and R_{12} may possess either (R) or (S) stereochemistry. A pyrrolidine ring (i.e., ) formed from either R_2 and R_5 or R_9 and R_{12} preferably possesses the (S) stereochemistry (i.e., ).

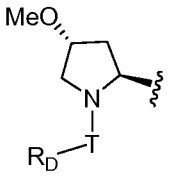
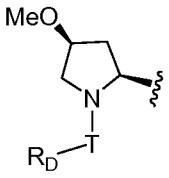
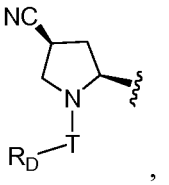
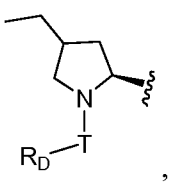
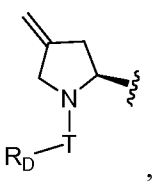
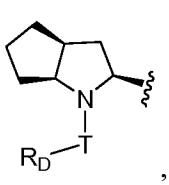
In this aspect of the invention, T' is independently selected at each occurrence from a bond,–C(O)N(R_B)–, –N(R_B)C(O)–, or 3- to 12-membered heterocycle, and wherein said 3- to 12-membered heterocycle is each independently optionally substituted at each occurrence with one or more R_A, and R_A and R_B are as described herein. In particular, where T' is –C(O)N(R_B)–, R_B can be hydrogen (i.e., T' is –C(O)N(H)–). In certain embodiments, T' is imidazolyl (i.e., ) optionally substituted at each occurrence with one or more R_A wherein R_A is halogen (e.g., fluoro, chloro), C_1-

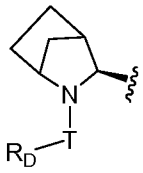
C_6alkyl (e.g., methyl, ethyl), or C_1-C_6haloalkyl (e.g., trifluoromethyl). In certain embodiments, T' is imidazolyl (i.e., ).

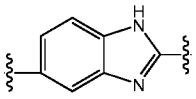
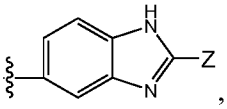
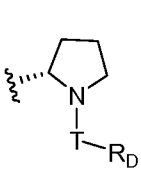
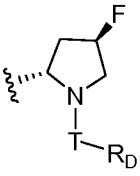
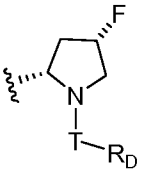
This aspect of the invention contemplates particular combinations of A with Y and B with Z. Non-limiting examples of preferred Y when A is C_5-C_6carbocycle (e.g., phenyl) or 5- to 6-membered heterocycle (e.g., pyridinyl or thiazolyl) and preferred Z when B is C_5-C_6carbocycle (e.g., phenyl) or 5- to 6-membered heterocycle (e.g., pyridinyl or thiazolyl) include:  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , , ,  , or , wherein T and R_D are as defined herein.

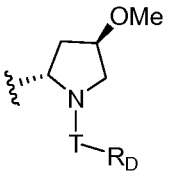
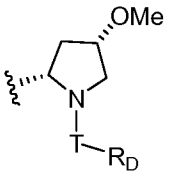
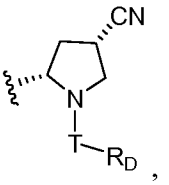
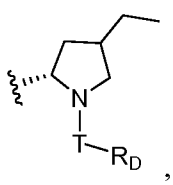
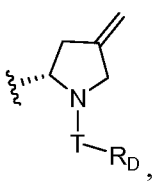
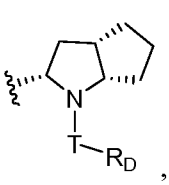
In certain embodiments of this aspect of the invention, A is  optionally substituted with one or more R_A as described herein, or Y–A is  , and non-limiting

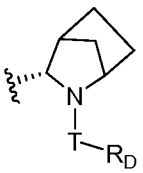
examples of preferred Y, where T' is a bond, include:  ,  ,  ,

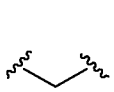
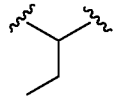
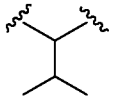
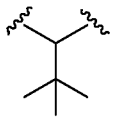
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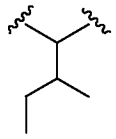
 wherein T and R_D are as defined herein.

In certain embodiments of this aspect of the invention, B is  optionally substituted with one or more R_A as described herein, or B–Z is  , and non-limiting examples of preferred Z, where T' is a bond, include:  ,  ,  ,

 ,  ,  ,  ,  ,  ,

 wherein T and R_D are as defined herein.

T at each occurrence is independently a bond or –C(O)–L_S'–, wherein L_S' is as defined herein. L_S' includes, but is not limited to,  ,  ,  ,  , or

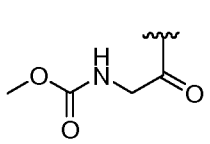
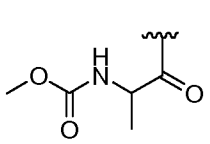
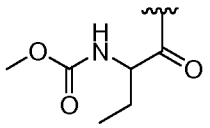
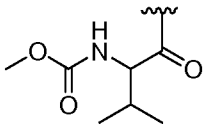
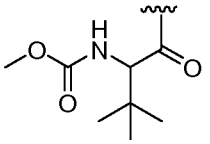
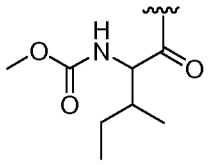
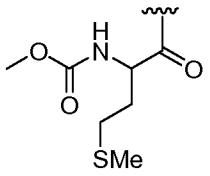


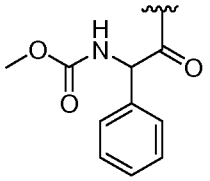
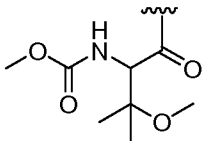
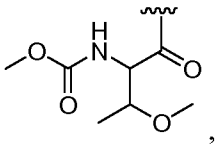
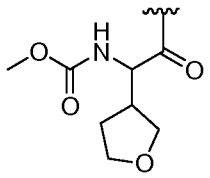
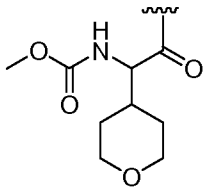
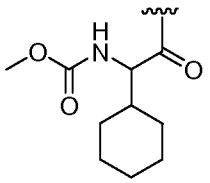
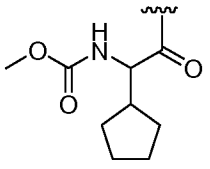
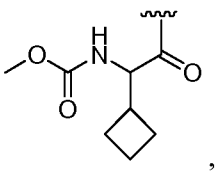
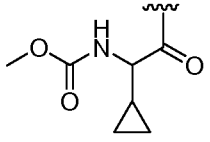
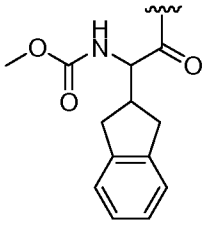
, where L_S' is optionally substituted with one or more R_L; and R_L is a substituent such as, but not limited to carbocycle (e.g., cyclohexyl, cyclopentyl, cyclobutyl, cyclopropyl, phenyl), methoxy, or heterocycle (e.g., tetrahydrofuranyl, tetrahydropyranyl).

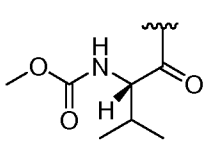
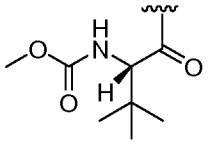
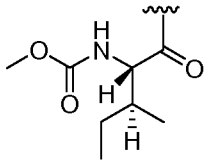
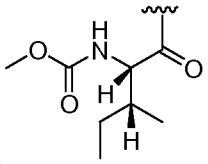
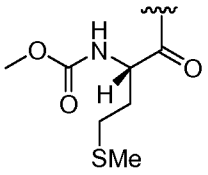
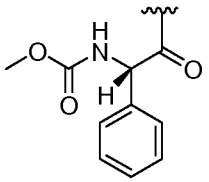
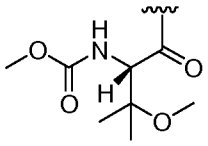
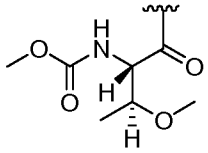
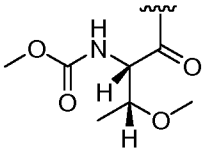
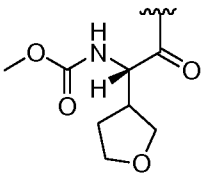
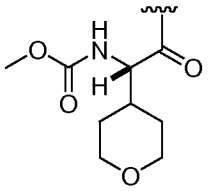
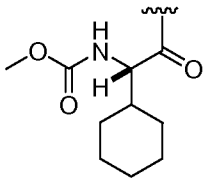
R_D is hydrogen or R_A wherein R_A is as defined herein. Thus R_D includes, but is not limited to, R_A wherein R_A is L_S-R_E, and L_S and R_E are as defined herein. Thus R_D includes, but is not limited to, L_S-R_E wherein L_S is a bond and R_E is–$N(R_SR_S')$, $–N(R_S)C(O)R_S'$, $–N(R_S)C(O)N(R_S'R_S'')$, $–N(R_S)SO_2R_S'$, —$N(R_S)SO_2N(R_S'R_S'')$, $–N(R_S)S(O)N(R_S'R_S'')$, $–N(R_S)C(O)OR_S'$, or $–N(R_S)S(O)–R_S'$; 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 substituents selected from halogen, hydroxy, cyano, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, or C_1-C_6haloalkyl.

In one embodiment of this aspect of the invention, R_D is L_S-R_E wherein L_S is a bond and R_E is $–N(R_S)C(O)OR_S'$ or 3- to 12-membered heterocycle (e.g., pyrrolidine, piperidine, azepanyl) wherein R_S and R_S' are as defined herein. For example R_D is preferably L_S-R_E wherein L_S is a bond and R_E is –N(H)C(O)OMe.

Thus according to the foregoing description T-R_D includes, but is not limited to:

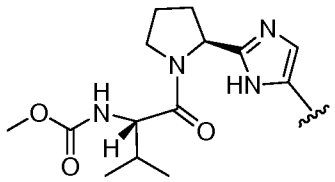
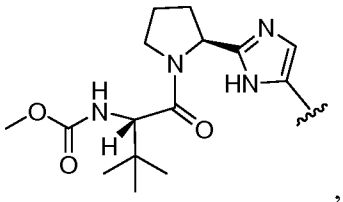
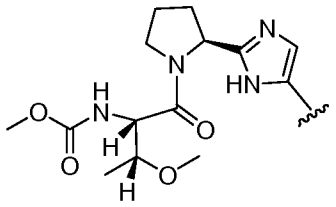

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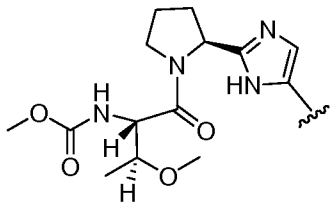
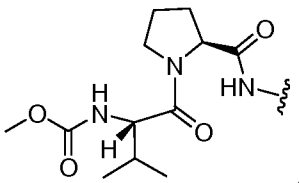
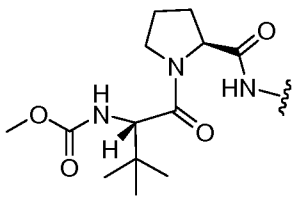
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. T-R_D may also include particular stereochemical

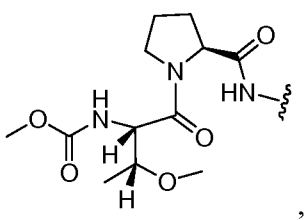
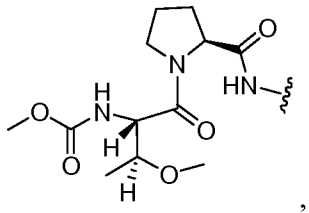
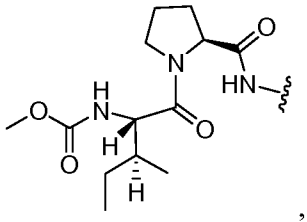
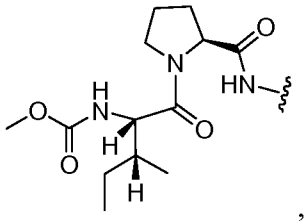
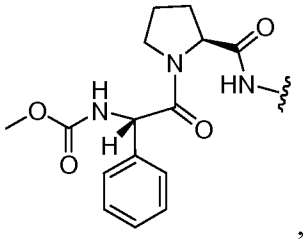
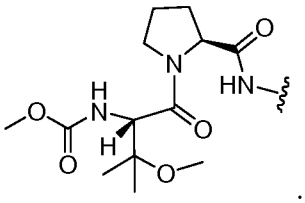
configurations; thus T-R_D includes, but is not limited to:  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,

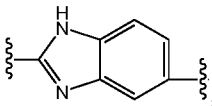
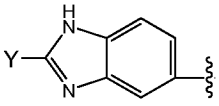
etc.

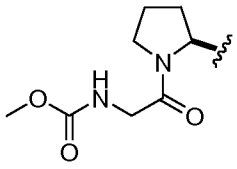
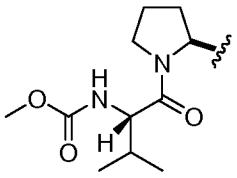
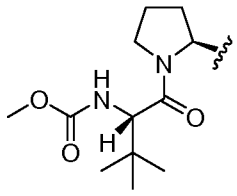
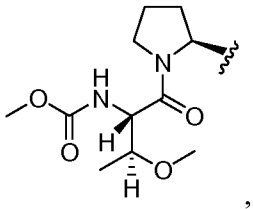
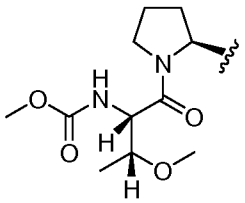
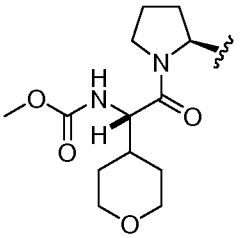
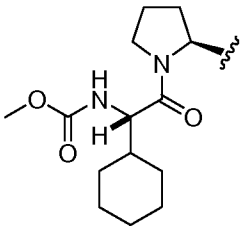
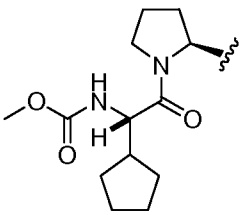
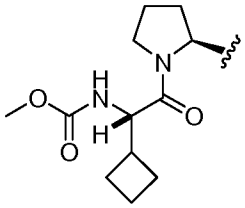
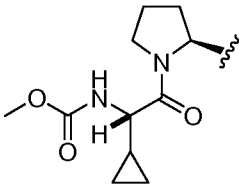
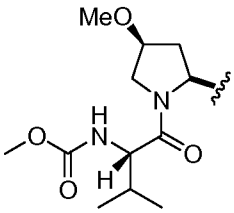
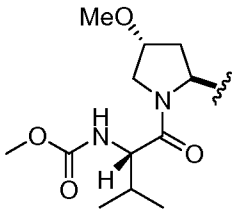
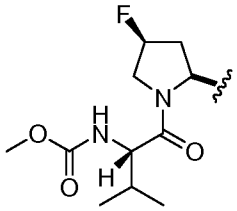
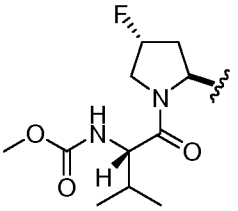
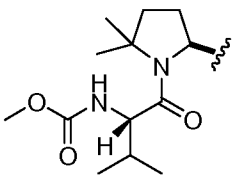
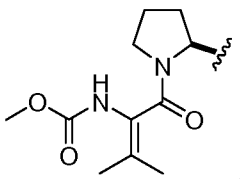
According to this aspect of the invention, non-limiting examples of preferred Y when A is C_5-C_6carbocycle (e.g., phenyl) or 5- to 6-membered heterocycle (e.g., pyridinyl or thiazolyl) and preferred Z when B is C_5-C_6carbocycle (e.g., phenyl) or 5- to 6-membered heterocycle (e.g., pyridinyl or thiazolyl) include:

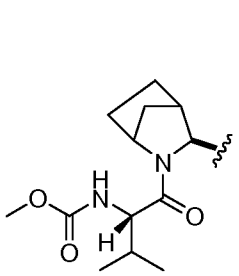
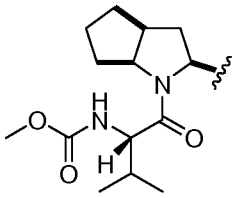
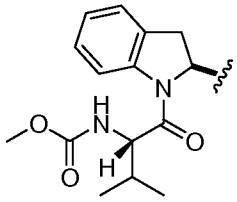
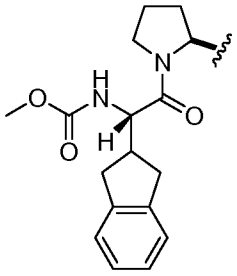
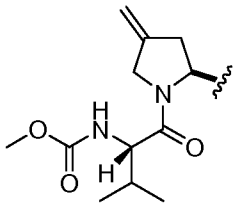
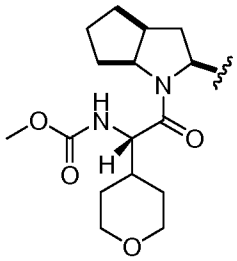
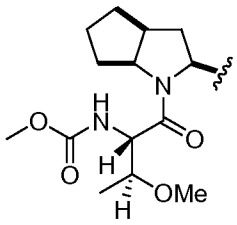
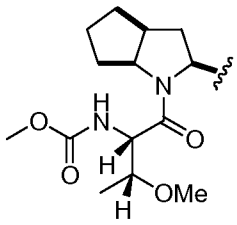
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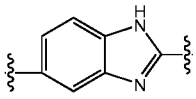
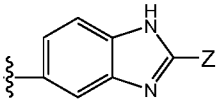
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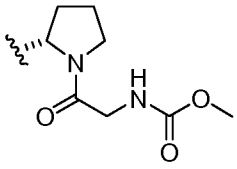
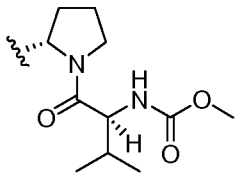
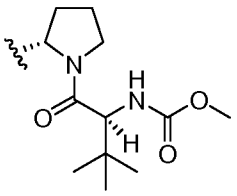
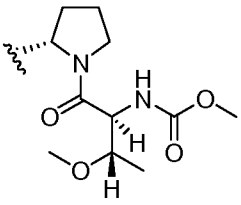
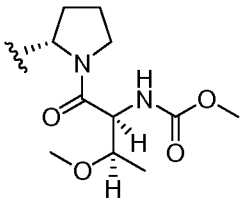
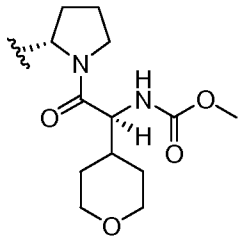
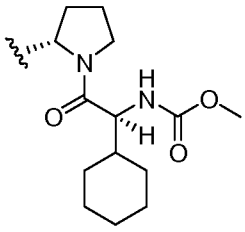
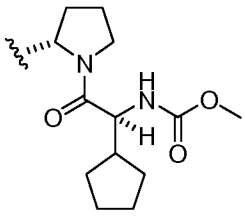
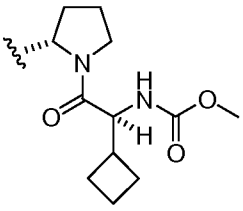
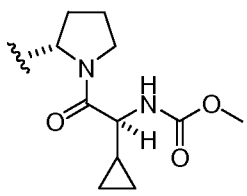
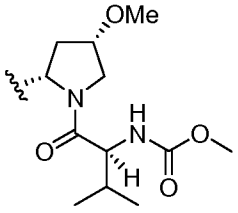
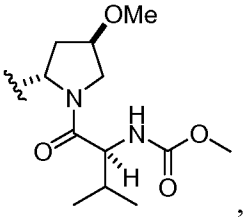
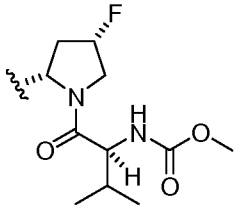

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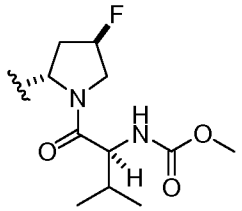
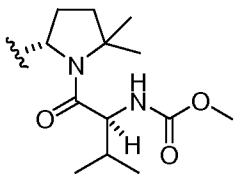
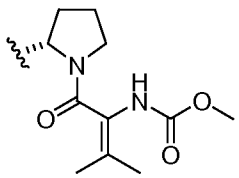
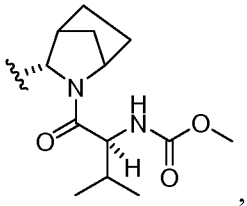
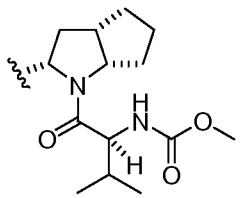
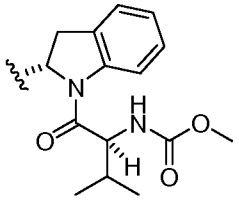
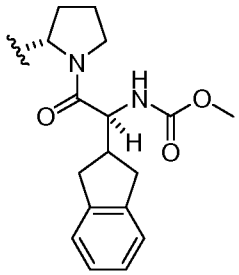
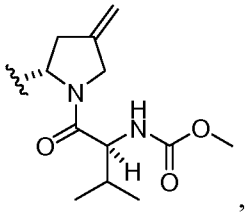
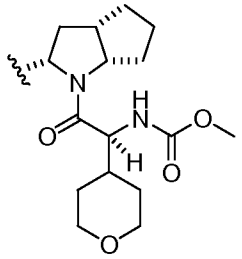
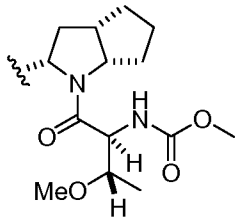
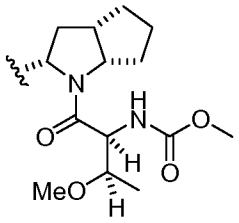
Non-limiting examples of preferred Y when A is  , optionally substituted with one or more R_A as described herein, and Y–A is  include:

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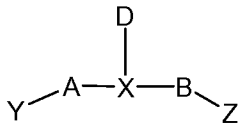

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Non-limiting examples of preferred Z where B is  optionally substituted with one or more R_A as described herein, and B–Z is  include:


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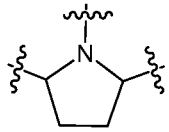
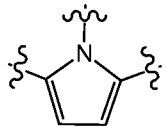

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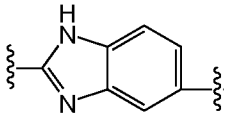
In still another aspect, the present invention features compounds of Formula I_F and pharmaceutically acceptable salts thereof:

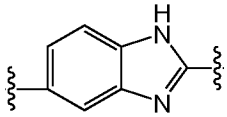
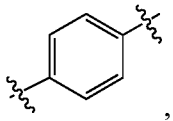


I_F

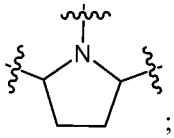
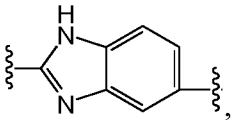
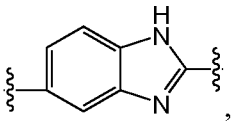
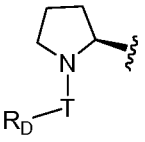
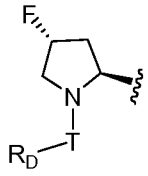
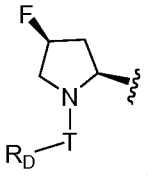
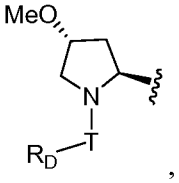
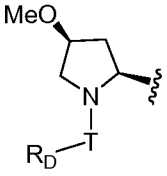
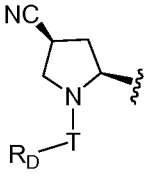
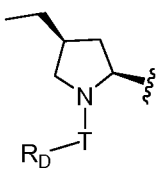
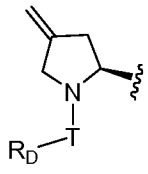
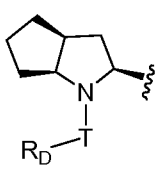
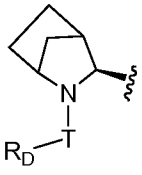
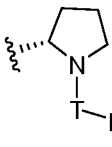
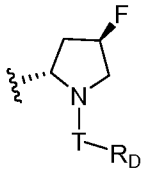
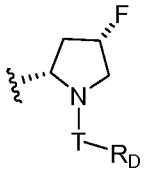
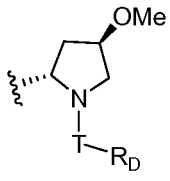
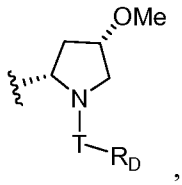
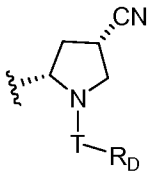
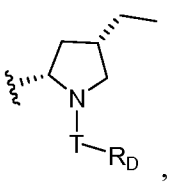
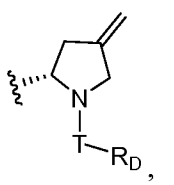
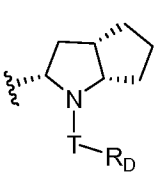
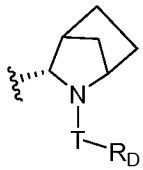
wherein:

X is  or  , wherein X is optionally substituted with one or more R_A

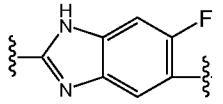
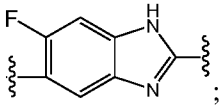
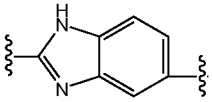
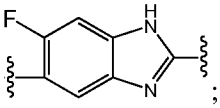
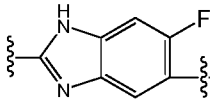
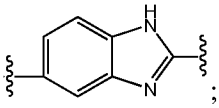
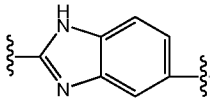
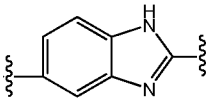
A is  , wherein A is optionally substituted with one or more R_A;

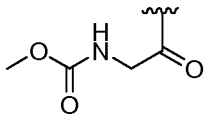
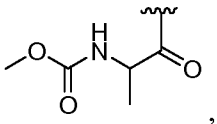
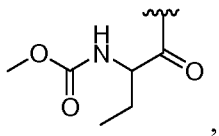
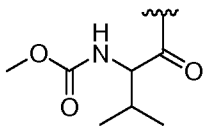
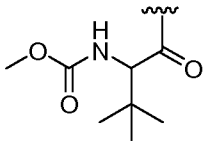
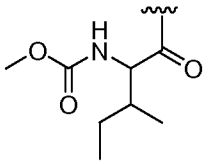
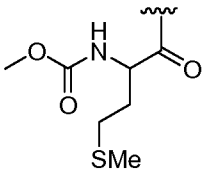
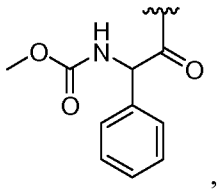
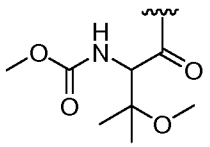
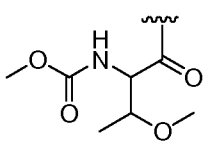
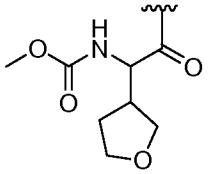
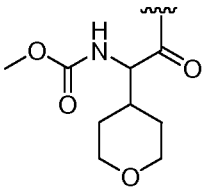
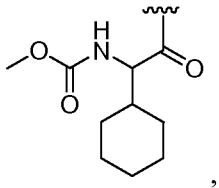
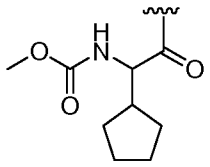
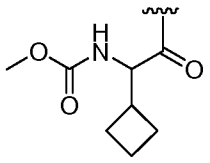
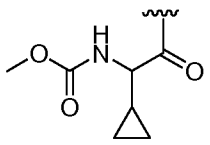
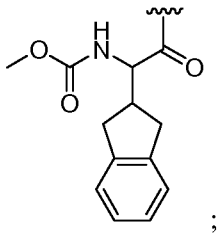
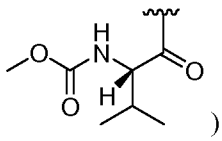
B is  or  , wherein B is optionally substituted with one or more R_A; and

Y, Z, R_A, and D are as described hereinabove (e.g., Y, Z, R_A, and D as described for Formula I, I_A, I_B, I_C, I_D, or I_E, preferably as described for Formula I_E).

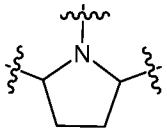
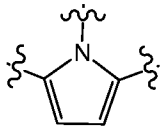
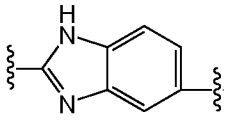
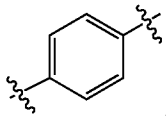
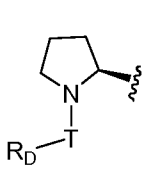
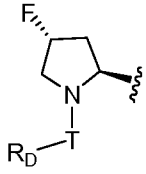
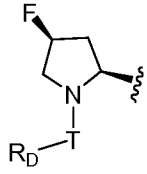
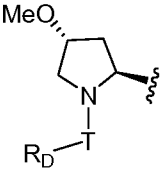
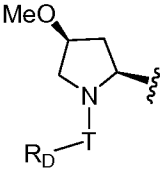
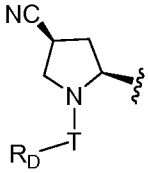
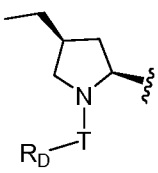
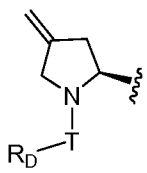
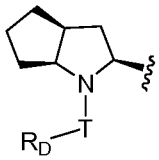
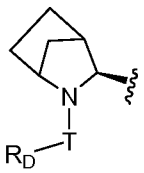
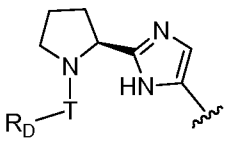
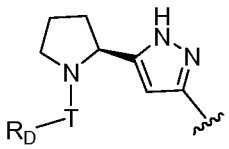
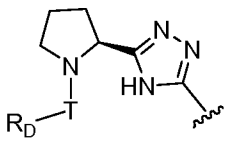
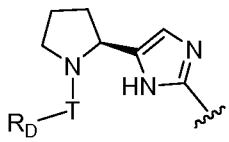
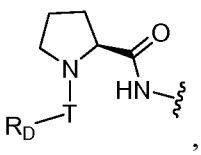
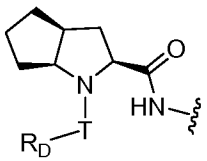
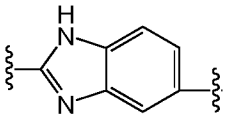
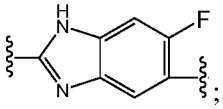
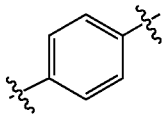
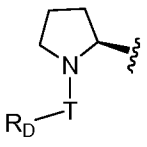
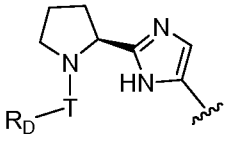
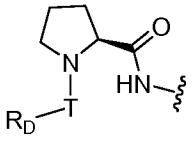
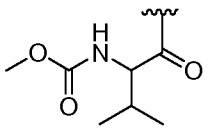
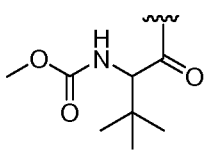
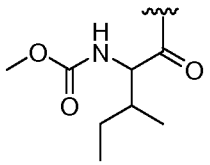
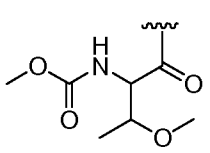
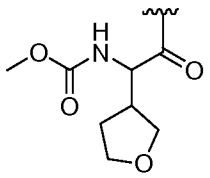
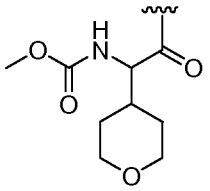
In one embodiment of this aspect of the invention, X is  ; A is  , wherein A is optionally substituted with one or more R_A; B is  , wherein B is optionally substituted with one or more R_A; Y is  ,  ,  ,  ,  ,  ,  ,  ,  ,  , or  ; Z is ,  ,  ,  ,  ,  ,  ,  ,  , or  ; and D, R_A, T and R_D are as defined hereinabove (e.g., as described for Formula I, I_A, I_B, I_C, I_D or I_E, preferably as described for Formula I_E).

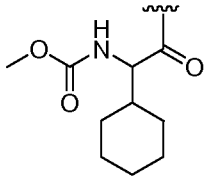
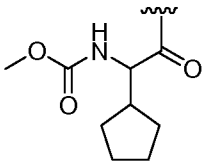
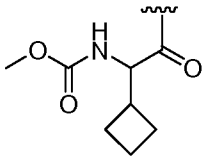
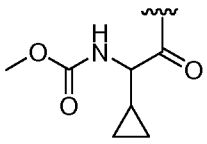
In another embodiment according to this aspect of the invention, A or B are optionally substituted with one or more substituents selected from: R_A wherein R_A is each independently halogen (e.g., fluoro, chloro); L_S–R_E where L_S is a single bond, and R_E is –C_1-C_6alkyl (e.g., methyl), –O–R_S (e.g., –O–C_1-C_6alkyl, –OCH_3), or –C_1-C_6alkyl optionally substituted with one or more halogen (e.g., –CF_3); or L_S–R_E where L_S is a C_1-C_6alkylene and R_E is –O–R_S (e.g., –C_1-C_6alkyl–O–C_1-C_6alkyl, –CH_2OCH_3). This embodiment includes compounds where A and B are both substituted by one R_A; compounds where A and B are both substituted by zero R_A; compounds where A is substituted by one

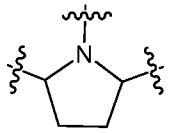
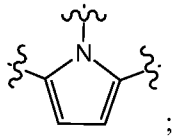
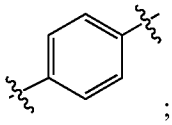
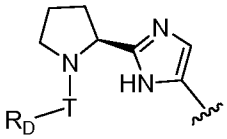
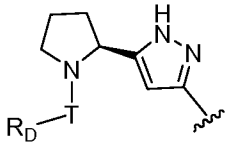
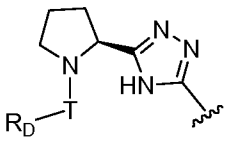
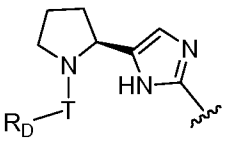
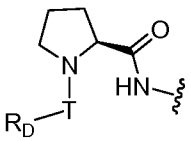
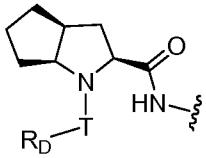
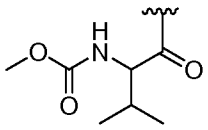
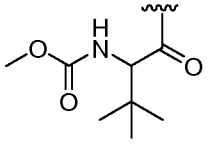
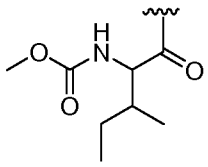
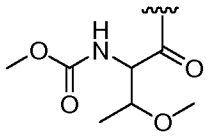
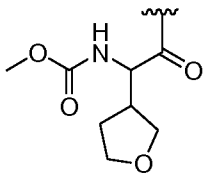
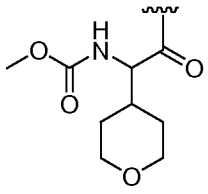
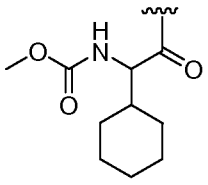
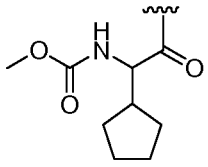
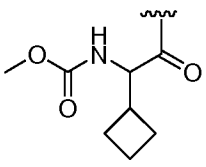
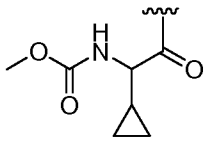
R_A and B is substituted by zero R_A; and compounds where A is substituted by zero R_A and B is substituted by one R_A. Preferably, A is  and B is  ; or A is  and B is  ; or A is  and B is  ; or A is  and B is  .

In a further embodiment of this aspect of the invention, T–R_D is independently selected at each occurrence from the group consisting of  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , and  ; wherein compounds having (S) stereochemistry (e.g., ) are preferred and wherein D is as defined hereinabove.

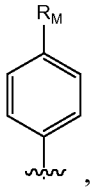
In another embodiment, this aspect of the invention features compound of Formula I_F and pharmaceutically acceptable salts thereof, wherein:

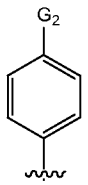
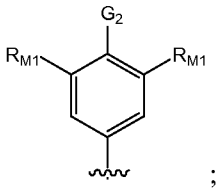
X is  or  ; A is  , wherein A is optionally substituted with one or more R_A; B is  , wherein B is optionally substituted with one or more R_A; Y is  ,  ,  ,  ,  ,  ,  ,  ,  , or  ; Z is  ,  ,  ,  ,  , or  ; and D, R_A, T and R_D are as defined hereinabove. A particular subgroup according to this embodiment includes compounds where A is  or  ; B is  ; Y is  ; Z is  or  ; $T–R_D$ is each independently  ,  ,  ,  ,  ,  ,

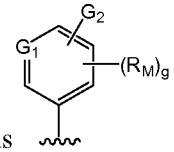
 ,  ,  , or  ; and D is as defined hereinabove.

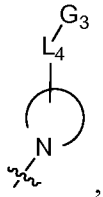
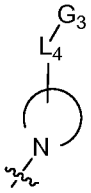
In yet another embodiment, this aspect of the invention features compounds of Formula I_F and pharmaceutically acceptable salts thereof, wherein: X is  or  ; A and B are each  ; Y and Z are each independently  ,  ,  ,  ,  , or  ; and D, T and R_D are as defined hereinabove. A particular subgroup according to this embodiment includes compounds where T–R_D is each independently selected from  ,  ,  ,  ,  ,  ,  ,  ,  ,  ; and D is as defined hereinabove.

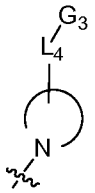
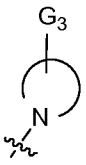
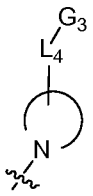
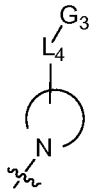
According to each of the foregoing embodiments and description of this aspect of the invention of Formula I_F are groups and subgroups of compounds having particular values for D. Included in each of the foregoing embodiments are groups and subgroups of compounds with the following particular values for D:

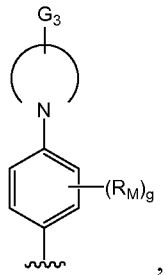
In certain groups of compounds according to Formula I_F and the foregoing embodiments and description of this aspect of the invention, D is  , where R_M is fluoro, chloro, tert-butyl, –O–CH_2CH_3, –O–CF_3, –O–CH_2CHF_2, –O–$CH_2CH_2OCH_3$, –O–CH_2–(3-ethyloxetan-3-yl), –O–CH_2–(1,3-dioxolan-4-yl), –O–cyclopentyl, –O–cyclohexyl, –O–phenyl, –O–(1,3-dioxan-5-yl), cyclopropyl, cyclohexyl, phenyl, SF_5, –SO_2Me, or –N(t-Bu)C(O)Me and D is optionally substituted by one or more additional R_M, selected from the group consisting of halogen (e.g., fluoro, chloro) or C_1-C_6alkyl (e.g., methyl).

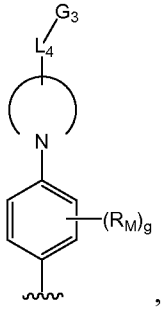
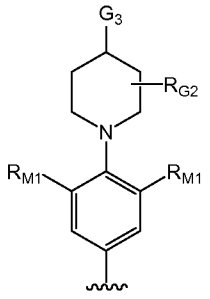
In other groups of compounds according Formula I_F and the foregoing embodiments and description of this aspect of the invention, D is  wherein G_2 is pyridinyl (e.g., pyridin-2-yl), piperidin-1-yl, 4,4-dimethylpiperidin-1-yl, 4,4-difluoropiperidin-1-yl, 2,6-dimethylpiperidin-1-yl, 4-(propan-2-yl)piperidin-1-yl, 4-fluoropiperidin-1-yl, 3,5-dimethylpiperidin-1-yl, 4-(trifluoromethyl)piperidin-1-yl, 4-methylpiperidin-1-yl, 4-tert-butylpiperidin-1-yl, 2-oxopiperidin-1-yl, 3,3-dimethylazetidin-1-yl, or oxazolyl (e.g., 1,3-oxazol-2-yl) and D is optionally substituted by one or more additional R_M selected from the group consisting of halogen (e.g., fluoro, chloro), or C_1-C_6alkyl (e.g., methyl). In particular according to these groups are compounds where D is  ; G_2 is piperidin-1-yl, 4,4-dimethylpiperidin-1-yl, 4,4-difluoropiperidin-1-yl, 2,6-dimethylpiperidin-1-yl, 4-(propan-2-yl)piperidin-1-yl, 4-fluoropiperidin-1-yl, 3,5-dimethylpiperidin-1-yl, 4-(trifluoromethyl)piperidin-1-yl, 4-methylpiperidin-1-yl, 4-tert-butylpiperidin-1-yl, 2-oxopiperidin-1-yl, or 3,3-dimethylazetidin-1-yl; and R_{M1} is each independently hydrogen, fluoro, chloro, or methyl.

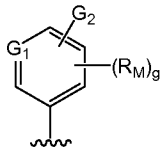
In other groups of compounds according Formula I_F and the foregoing embodiments and description of this aspect of the invention, D is  wherein G_1 is N, C–H, or C–R_M; G_2 is

, wherein , R_M, and g are as defined hereinabove. In particular according to these groups, R_M is each independently fluoro, chloro, methyl, methoxy, trifluoromethyl, or trifluoromethoxy; g is 0, 1, or 2; and  is as defined hereinabove. In further subgroups L_4 is a bond; G_2 is  ; R_M is each independently fluoro, chloro, methyl, methoxy, trifluoromethyl, or trifluoromethoxy; and g is 0, 1, or 2. In particular subgroups,  is 3-phenylazetidin-1-yl, 3-phenylpyrrolidin-1-yl, 4-phenylpiperazin-1-yl, 4-phenylpiperidin-1-yl, 4-phenyl-3,6-dihydropyridin-1(2H)-yl, 4,4-diphenylpiperidin-1-yl, 4-acetyl-4-phenylpiperidin-1-yl, 4-(4-methoxyphenyl)piperidin-1-yl, 4-(4-fluorophenyl)piperidin-1-yl, or 3-phenylpiperidin-1-yl; R_M is each independently fluoro, chloro, methyl, methoxy, trifluoromethyl, or trifluoromethoxy; and g is 0, 1, or 2. In other subgroups L_4 is C_1-C_6 alkylene, –O–, or –$S(O)_2$–; G_2 is  ; R_M is each independently fluoro, chloro, methyl, methoxy, trifluoromethyl, or trifluoromethoxy; and g is 0, 1, or 2. In particular subgroups,  is 4-tosylpiperazin-1-yl, 4-phenoxypiperidin-1-yl, 3-phenoxypyrrolidin-1-yl, 4-benzylpiperidin-1-yl, 4-phenethylpiperidin-1-yl, or 3-phenylpropyl)piperidin-1-yl; R_M is each independently fluoro, chloro, methyl, methoxy, trifluoromethyl, or trifluoromethoxy; and g is 0, 1, or

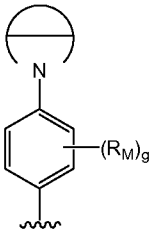


2. In further subgroups of compounds D is , wherein G_3 is phenyl optionally substituted with one or two R_{G3}; g is 0, 1, or 2; R_M is each independently fluoro, chloro, methyl, methoxy, trifluoromethyl, or trifluoromethoxy; and  and R_{G3} are as defined above. In other groups of compounds D is  , wherein L_4 is C_1-C_6 alkylene, –O–, or –$S(O)_2$–; G_3 is phenyl optionally substituted with one or two R_{G3}; g is 0, 1, or 2; R_M is each independently fluoro, chloro, methyl, methoxy, trifluoromethyl, or trifluoromethoxy; and  and R_{G3} are as defined above. In further subgroups of compounds D is  wherein G_3 is phenyl optionally substituted with one or two R_{G3} as defined hereinabove; R_{M1} is each independently hydrogen, fluoro, chloro, or methyl; and R_{G2} is an optional substituent, as described above, selected from the group consisting of –C(O)C_1-C_6alkyl, –C_1-C_6alkyl, –C_1-C_6haloalkyl, –O–C_1-C_6alkyl, and –O–C_1-C_6haloalkyl.

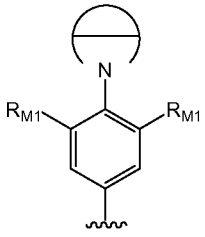
In other groups of compounds according Formula I_F and the foregoing embodiments and description of this aspect of the invention, D is  wherein G_1 is N, C–H, or C–R_M; G_2 is




, wherein , R_M, and g are as defined hereinabove. In particular according to these subgroups, R_M is each independently fluoro, chloro, methyl, methoxy, trifluoromethyl, or trifluoromethoxy; g is 0, 1, or 2; and  is 3-azabicyclo[3.2.0]hept-3-yl, 2-azabicyclo[2.2.2]oct-2-yl, 6-azaspiro[2.5]oct-6-yl, octahydro-2H-isoindol-2-yl, 3-azaspiro[5.5]undec-3-yl, 1,3-dihydro-2H-isoindol-2-yl, or 1,4-dioxa-8-azaspiro[4.5]dec-8-yl. In further subgroups of compounds D is

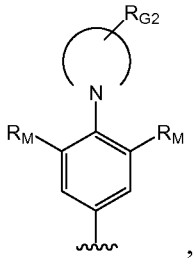


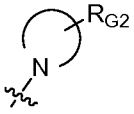
wherein g is 0, 1, or 2; R_M is each independently fluoro, chloro, methyl, methoxy, trifluoromethyl, or trifluoromethoxy; and  is as defined above. In further subgroups of compounds D is

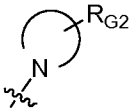
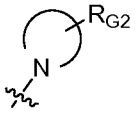


wherein R_{M1} is each independently hydrogen, fluoro, chloro, or methyl and  is as defined above (e.g., 3-azabicyclo[3.2.0]hept-3-yl, octahydro-2H-isoindol-2-yl, 2-azabicyclo[2.2.2]oct-2-yl, 6-azaspiro[2.5]oct-6-yl, 3-azaspiro[5.5]undec-3-yl, 1,3-dihydro-2H-isoindol-2-yl, 1,4-dioxa-8-azaspiro[4.5]dec-8-yl).

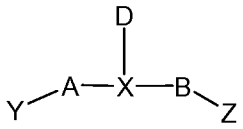
In other groups of compounds according Formula I_F and the foregoing embodiments and description of this aspect of the invention, D is



, wherein  is a monocyclic 4-8 membered nitrogen-containing heterocycle (e.g., azetidinyl, pyrrolidinyl, piperidinyl) substituted with one or more R_{G2}, wherein R_{G2} at each occurrence is each independently halogen, $–C(O)C_1$-C_6alkyl, $–C_1$-C_6alkyl, $–C_1$-C_6haloalkyl, $–O–C_1$-C_6alkyl, or $–O–C_1$-C_6haloalkyl; and R_M is each

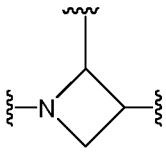
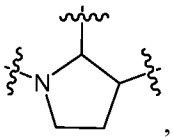
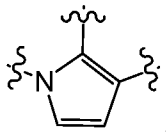
independently halogen, –C_1-C_6alkyl, –C_1-C_6haloalkyl, –O–C_1-C_6alkyl, or –O–C_1-C_6haloalkyl. In each group of compounds according to the foregoing embodiments  is azetidinyl, pyrrolidinyl, or piperidinyl substituted with one or two R_{G2}, wherein R_{G2} at each occurrence is each methyl, ethyl, isopropyl, tert-butyl, fluoro, chloro, or trifluoromethyl; and R_M is each independently fluoro, chloro, or methyl. For example  is 4,4-dimethylpiperidin-1-yl, 4,4-difluoropiperidin-1-yl, 2,6-dimethylpiperidin-1-yl, 4-(propan-2-yl)piperidin-1-yl, 4-fluoropiperidin-1-yl, 3,5-dimethylpiperidin-1-yl, 4-(trifluoromethyl)piperidin-1-yl, 4-methylpiperidin-1-yl, 4-tert-butylpiperidin-1-yl, 2-oxopiperidin-1-yl, or 3,3-dimethylazetidin-1-yl.

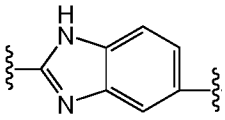
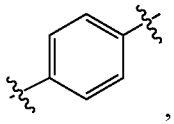
In still another aspect, the present invention features compounds of Formula I_G and pharmaceutically acceptable salts thereof,

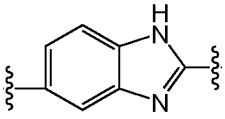
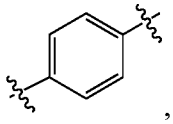


I_G

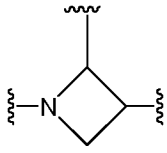
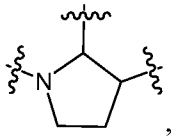
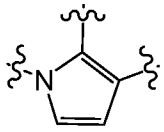
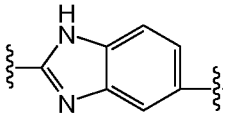
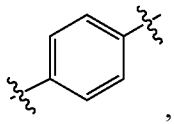
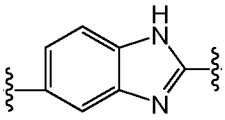
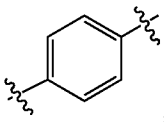
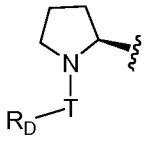
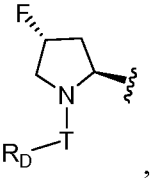
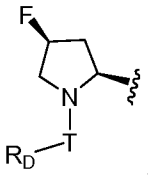
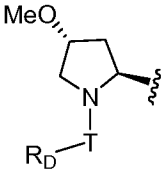
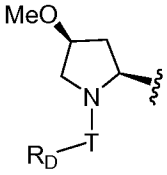
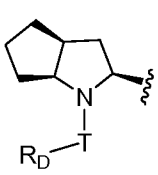
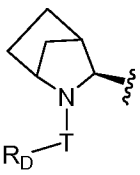
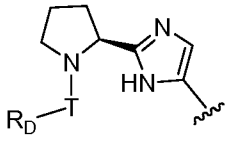
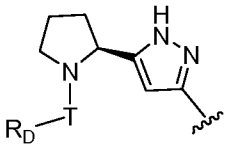
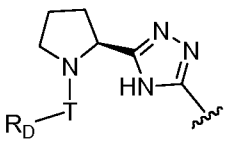
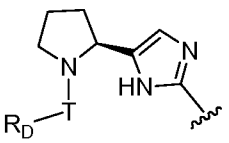
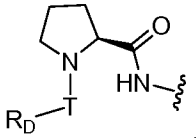
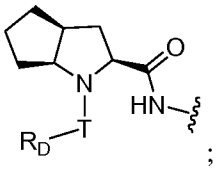
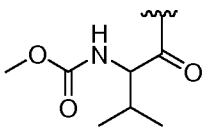
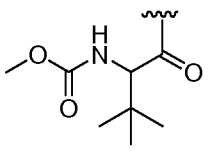
wherein:

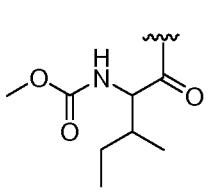
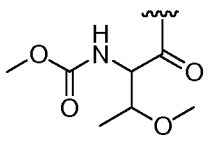
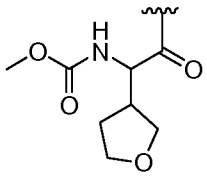
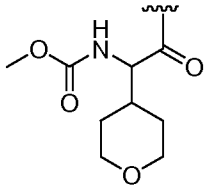
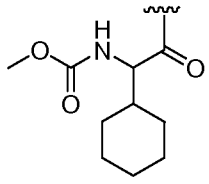
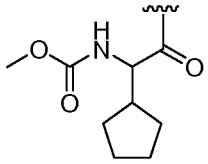
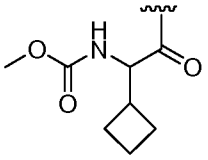
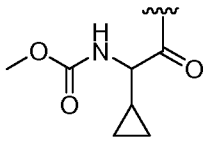
X is  ,  , or  , wherein X is optionally substituted with one or more R_A

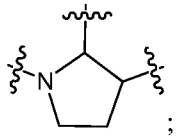
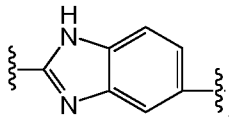
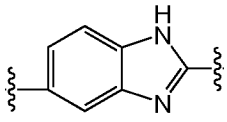
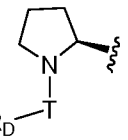
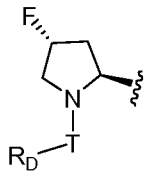
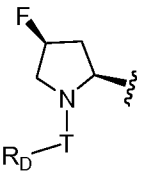
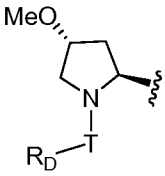
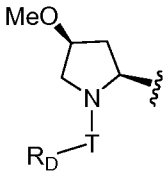
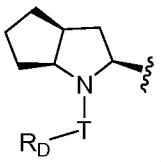
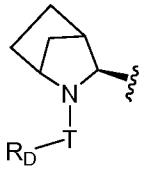
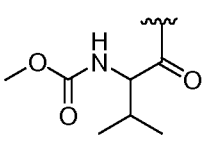
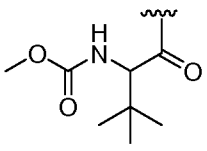
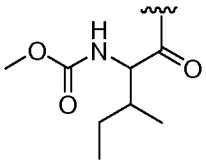
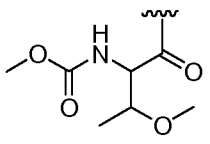
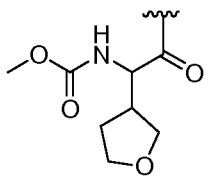
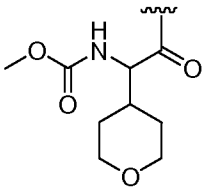
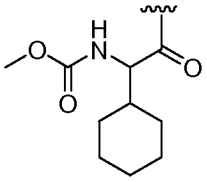
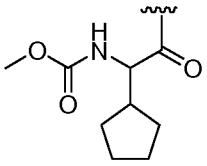
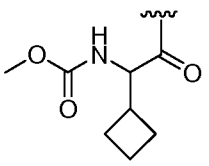
A is  or  , wherein A is optionally substituted with one or more R_A;

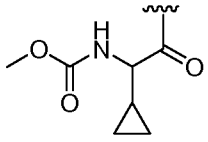
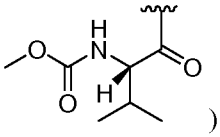
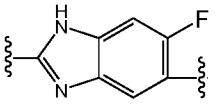
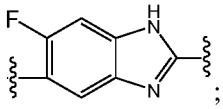
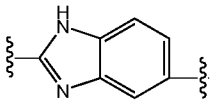
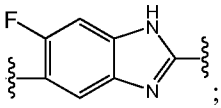
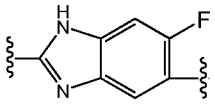
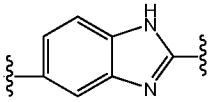
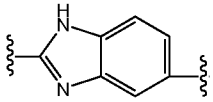
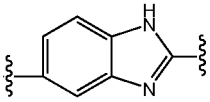
B is  or  , wherein B is optionally substituted with one or more R_A; and

Y, Z, R_A, and D are as described hereinabove (e.g., as described for Formula I, I_A, I_B, I_C, I_D, I_E or I_F, preferably as described for Formula I_E).

In one embodiment, this aspect of the invention features compounds of Formula I_G and pharmaceutically acceptable salts thereof, wherein: X is  ,  , or  ; A is  or  , wherein A is optionally substituted with one R_A; B is  or  , wherein B is optionally substituted with one R_A; R_A is halogen (e.g., fluoro, chloro); L_S–R_E where L_S is a single bond and R_E is –C_1-C_6alkyl (e.g., methyl), –O–R_S (e.g., –O–C_1-C_6alkyl, –OCH_3), or –C_1-C_6alkyl optionally substituted with one or more halogen (e.g., –CF_3); or L_S–R_E where L_S is a C_1-C_6alkylene and R_E is –O–R_S (e.g., –C_1-C_6alkyl–O–C_1-C_6alkyl, –CH_2OCH_3); Y and Z are each independently  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , or  ; T–R_D is each independently  ,  ,

 ,  ,  ,  ,  ,  ,  , or  ; and D is as defined hereinabove.

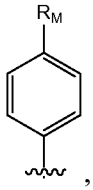
In another embodiment, this aspect of the invention features compounds of Formula I_G and pharmaceutically acceptable salts thereof, wherein X is  ; A is  , wherein A is optionally substituted with one R_A; B is  , wherein B is optionally substituted with one R_A; R_A is halogen (e.g., fluoro, chloro); L_S–R_E where L_S is a single bond and R_E is –C_1-C_6alkyl (e.g., methyl), –O–R_S (e.g., –O–C_1-C_6alkyl, –OCH_3), or –C_1-C_6alkyl optionally substituted with one or more halogen (e.g., –CF_3); or L_S–R_E where L_S is a C_1-C_6alkylene and R_E is –O–R_S (e.g., –C_1-C_6alkyl–O–C_1-C_6alkyl, –CH_2OCH_3); Y and Z are each independently  ,  ,  ,  ,  ,  , or  , T–R_D is each independently  ,  ,  ,  ,  ,  ,  ,  ,  , or

 , wherein compounds having (S) stereochemistry (e.g., ) are particularly contemplated; and D is as defined hereinabove. This subgroup includes compounds where A and B are both substituted by one R_A; compounds where A and B are both substituted by zero R_A; compounds where A is substituted by one R_A and B is substituted by zero R_A; and compounds where A is substituted by zero R_A and B is substituted by one R_A. In particular, according to this subgroup are included compounds where A is  and B is  ; or A is  and B is  ; or A is  and B is  ; or A is  and B is  .

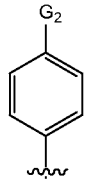
According to each of the foregoing embodiments and description of this aspect of the invention of Formula I_G are groups and subgroups of compounds having particular values for D. Included in each of the foregoing embodiments are groups and subgroups of compounds with the following particular values for D:

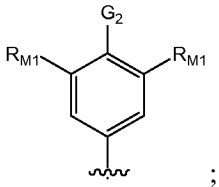
Groups of compounds according to this aspect of the invention include compounds where D is C_6-C_{10}aryl (e.g., phenyl, naphthyl, indanyl), or 5- to 10-membered heteroaryl (pyridinyl, thiazolyl, 4,5,6,7-tetrahydrobenzo[d]thiazolyl, benzo[d]thiazolyl, indazolyl, benzo[d][1,3]dioxol-5-yl), and D is substituted with one or more R_M. Particular subgroups according to this aspect and these embodiments include compounds wherein R_M is halogen (e.g., fluoro, chloro, bromo); C_1-C_6alkyl (e.g., tert-butyl); C_1-C_6alkyl substituted with one or more halogen (e.g., CF_3); –O–C_1-C_6alkyl (e.g., –O–CH_2CH_3); –O–C_1-C_6alkyl substituted at each occurrence with one or more halogen (e.g., –O–CF_3, –O–CH_2CHF_2) or –O–C_1-C_6alkyl (–O–$CH_2CH_2OCH_3$); –O–C_1-C_6alkyl (e.g., –O–CH_2) substituted with an optionally substituted 3- to 12-membered heterocycle (e.g., 3-ethyloxetan-3-yl, 1,3-dioxolan-4-yl); –O–R_S where R_S is an optionally substituted 3- to 12-membered carbocycle or heterocycle (e.g., cyclopentyl, cyclohexyl, phenyl, 1,3-dioxan-5-yl); –N(R_S)C(O)R_S' wherein R_S and R_S' are each independently C_1-C_6alkyl (e.g., –N(t-Bu)C(O)Me); SF_5; –SO_2R_S wherein R_S is C_1-C_6alkyl (e.g., –SO_2Me); or C_3-C_{12}carbocycle (e.g., cyclopropyl, cyclohexyl, phenyl). Other subgroups according to this embodiment include compounds wherein D is phenyl substituted by G_2 and optionally substituted by one or more R_M, wherein G_2 is a 3- to 12-membered heterocycle (e.g., pyridinyl, piperidinyl, pyrrolidinyl, azetidinyl, oxazolyl) wherein the heterocycle is optionally substituted with one or more substituents selected from halogen, hydroxy, oxo, cyano, C_1-C_6alkyl (e.g., methyl), C_2-C_6alkenyl, C_2-

C_6alkynyl, C_1-C_6haloalkyl (e.g., CF_3), C_2-C_6haloalkenyl, C_2-C_6haloalkynyl, –O–C_1-C_6alkyl (e.g., –O–CH_3), –C(O)OR_S (e.g., –C(O)OCH_3), –C(O)R_S (e.g., –C(O)CH_3), –N(R_SR_S'), or L_4–G_3; R_M is halogen (e.g., fluoro, chloro), alkyl (e.g., methyl), haloalkyl (e.g., CF_3), or –O–C_1-C_6alkyl (e.g., –O–CH_3); and L_4, G_3, R_S, and R_S' are as defined hereinabove.

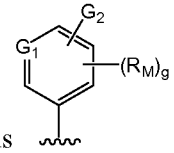
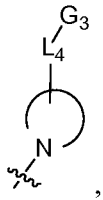
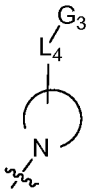
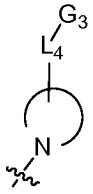
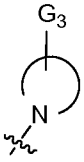
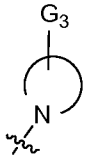
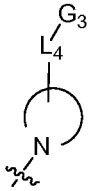
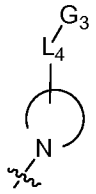
In certain groups of compounds according to Formula I_G and the foregoing embodiments and description of this aspect of the invention, D is 

, where R_M is fluoro, chloro, tert-butyl, –O–CH_2CH_3, –O–CF_3, –O–CH_2CHF_2, –O–$CH_2CH_2OCH_3$, –O–CH_2–(3-ethyloxetan-3-yl), –O–CH_2–(1,3-dioxolan-4-yl), –O–cyclopentyl, –O–cyclohexyl, –O–phenyl, –O–(1,3-dioxan-5-yl), cyclopropyl, cyclohexyl, phenyl, SF_5, –SO_2Me, or –N(t-Bu)C(O)Me and D is optionally substituted by one or more additional R_M, selected from the group consisting of halogen (e.g., fluoro, chloro) or C_1-C_6alkyl (e.g., methyl).

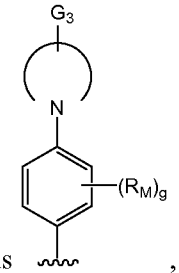
In other groups of compounds according Formula I_G and the foregoing embodiments and description of this aspect of the invention, D is 

wherein G_2 is pyridinyl (e.g., pyridin-2-yl), piperidin-1-yl, 4,4-dimethylpiperidin-1-yl, 4,4-difluoropiperidin-1-yl, 2,6-dimethylpiperidin-1-yl, 4-(propan-2-yl)piperidin-1-yl, 4-fluoropiperidin-1-yl, 3,5-dimethylpiperidin-1-yl, 4-(trifluoromethyl)piperidin-1-yl, 4-methylpiperidin-1-yl, 4-tert-butylpiperidin-1-yl, 2-oxopiperidin-1-yl, 3,3-dimethylazetidin-1-yl, or oxazolyl (e.g., 1,3-oxazol-2-yl) and D is optionally substituted by one or more additional R_M selected from the group consisting of halogen (e.g., fluoro, chloro), or C_1-C_6alkyl (e.g., methyl). In particular according to these groups are compounds where D is 

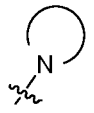
; G_2 is piperidin-1-yl, 4,4-dimethylpiperidin-1-yl, 4,4-difluoropiperidin-1-yl, 2,6-dimethylpiperidin-1-yl, 4-(propan-2-yl)piperidin-1-yl, 4-fluoropiperidin-1-yl, 3,5-dimethylpiperidin-1-yl, 4-(trifluoromethyl)piperidin-1-yl, 4-methylpiperidin-1-yl, 4-tert-butylpiperidin-1-yl, 2-oxopiperidin-1-yl, or 3,3-dimethylazetidin-1-yl; and R_{M1} is each independently hydrogen, fluoro, chloro, or methyl.

In other groups of compounds according Formula I_G and the foregoing embodiments and description of this aspect of the invention, D is  wherein G_1 is N, C–H, or C–R_M; G_2 is  , wherein  , R_M, and g are as defined hereinabove. In particular according to these groups, R_M is each independently fluoro, chloro, methyl, methoxy, trifluoromethyl, or trifluoromethoxy; g is 0, 1, or 2; and  is as defined hereinabove. In further subgroups L_4 is a bond; G_2 is  ; R_M is each independently fluoro, chloro, methyl, methoxy, trifluoromethyl, or trifluoromethoxy; and g is 0, 1, or 2. In particular subgroups,  is 3-phenylazetidin-1-yl, 3-phenylpyrrolidin-1-yl, 4-phenylpiperazin-1-yl, 4-phenylpiperidin-1-yl, 4-phenyl-3,6-dihydropyridin-1(2H)-yl, 4,4-diphenylpiperidin-1-yl, 4-acetyl-4-phenylpiperidin-1-yl, 4-(4-methoxyphenyl)piperidin-1-yl, 4-(4-fluorophenyl)piperidin-1-yl, or 3-phenylpiperidin-1-yl; R_M is each independently fluoro, chloro, methyl, methoxy, trifluoromethyl, or trifluoromethoxy; and g is 0, 1, or 2. In other subgroups L_4 is C_1-C_6 alkylene, –O–, or –$S(O)_2$–; G_2 is  ; R_M is each independently fluoro, chloro, methyl, methoxy, trifluoromethyl, or trifluoromethoxy; and g is 0, 1, or 2. In particular subgroups,  is 4-tosylpiperazin-1-yl, 4-phenoxypiperidin-1-yl, 3-phenoxypyrrolidin-1-yl, 4-

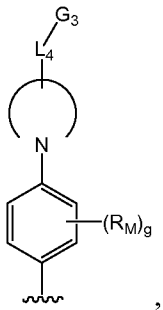
benzylpiperidin-1-yl, 4-phenethylpiperidin-1-yl, or 3-phenylpropyl)piperidin-1-yl; R_M is each independently fluoro, chloro, methyl, methoxy, trifluoromethyl, or trifluoromethoxy; and g is 0, 1, or



2. In further subgroups of compounds D is , wherein G_3 is phenyl optionally substituted with one or two R_{G3}; g is 0, 1, or 2; R_M is each independently fluoro, chloro, methyl, methoxy,



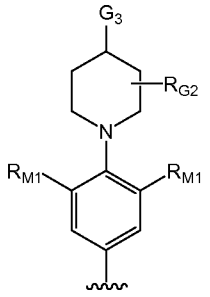
trifluoromethyl, or trifluoromethoxy; and and R_{G3} are as defined above. In other groups of



compounds D is , wherein L_4 is C_1-C_6 alkylene, –O–, or –$S(O)_2$–; G_3 is phenyl optionally substituted with one or two R_{G3}; g is 0, 1, or 2; R_M is each independently fluoro, chloro, methyl,

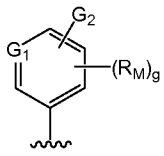


methoxy, trifluoromethyl, or trifluoromethoxy; and and R_{G3} are as defined above. In further



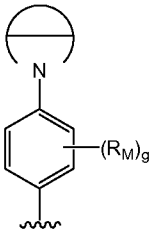
subgroups of compounds D is wherein G_3 is phenyl optionally substituted with one or two R_{G3} as defined hereinabove; R_{M1} is each independently hydrogen, fluoro, chloro, or methyl; and R_{G2} is an optional substituent, as described above, selected from the group consisting of –C(O)C_1-C_6alkyl, –C_1-C_6alkyl, –C_1-C_6haloalkyl, –O–C_1-C_6alkyl, and –O–C_1-C_6haloalkyl.

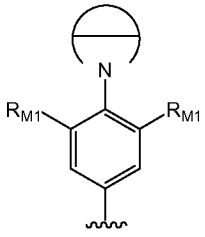
In other groups of compounds according Formula I_G and the foregoing embodiments and



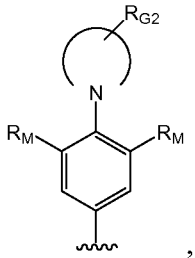
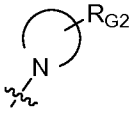
description of this aspect of the invention, D is wherein G_1 is N, C–H, or C–R_M; G_2 is

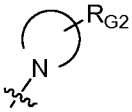
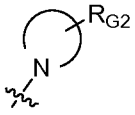

, wherein 
, R_M, and g are as defined hereinabove. In particular according to these subgroups, R_M is each independently fluoro, chloro, methyl, methoxy, trifluoromethyl, or trifluoromethoxy; g is 0, 1, or 2; and 
is 3-azabicyclo[3.2.0]hept-3-yl, 2-azabicyclo[2.2.2]oct-2-yl, 6-azaspiro[2.5]oct-6-yl, octahydro-2H-isoindol-2-yl, 3-azaspiro[5.5]undec-3-yl, 1,3-dihydro-2H-isoindol-2-yl, or 1,4-dioxa-8-azaspiro[4.5]dec-8-yl. In further subgroups of compounds D is


wherein g is 0, 1, or 2; R_M is each independently fluoro, chloro, methyl, methoxy, trifluoromethyl, or trifluoromethoxy; and 
is as defined above. In further subgroups of compounds D is


wherein R_{M1} is each independently hydrogen, fluoro, chloro, or methyl and 
is as defined above (e.g., 3-azabicyclo[3.2.0]hept-3-yl, octahydro-2H-isoindol-2-yl, 2-azabicyclo[2.2.2]oct-2-yl, 6-azaspiro[2.5]oct-6-yl, 3-azaspiro[5.5]undec-3-yl, 1,3-dihydro-2H-isoindol-2-yl, 1,4-dioxa-8-azaspiro[4.5]dec-8-yl).

In other groups of compounds according Formula I_G and the foregoing embodiments and description of this aspect of the invention, D is


, wherein 
is a monocyclic 4-8 membered nitrogen-containing heterocycle (e.g., azetidinyl, pyrrolidinyl, piperidinyl) substituted with one or more R_{G2}, wherein R_{G2} at each occurrence is each independently halogen, $–C(O)C_1$-C_6alkyl, $–C_1$-C_6alkyl, $–C_1$-C_6haloalkyl, $–O–C_1$-C_6alkyl, or $–O–C_1$-C_6haloalkyl; and R_M is each

independently halogen, –C_1-C_6alkyl, –C_1-C_6haloalkyl, –O–C_1-C_6alkyl, or –O–C_1-C_6haloalkyl. In each group of compounds according to the foregoing embodiments  is azetidinyl, pyrrolidinyl, or piperidinyl substituted with one or two R_{G2}, wherein R_{G2} at each occurrence is each methyl, ethyl, isopropyl, tert-butyl, fluoro, chloro, or trifluoromethyl; and R_M is each independently fluoro, chloro, or methyl. For example  is 4,4-dimethylpiperidin-1-yl, 4,4-difluoropiperidin-1-yl, 2,6-dimethylpiperidin-1-yl, 4-(propan-2-yl)piperidin-1-yl, 4-fluoropiperidin-1-yl, 3,5-dimethylpiperidin-1-yl, 4-(trifluoromethyl)piperidin-1-yl, 4-methylpiperidin-1-yl, 4-tert-butylpiperidin-1-yl, 2-oxopiperidin-1-yl, or 3,3-dimethylazetidin-1-yl.

The present invention also features compounds of Formulae I_E, I_F and I_G as described herein (including each embodiment described hereunder) and pharmaceutically acceptable salts thereof, 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_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$$R_S$'), –$P(O)(OR_S)_2$, =C($R_S$$R_S$'), or –C(O)N($R_S$)C(O)–$R_S$'; or C_1-C_6alkyl, C_2-C_6alkenyl or C_2-C_6alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl or cyano; or C_3-C_{12}carbocycle or 3- to 12-membered heterocycle, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, trimethylsilyl, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6haloalkyl, C_2-C_6haloalkenyl, C_2-C_6haloalkynyl, –O–R_S, –S–R_S, –C(O)R_S, –C(O)OR_S, or –N($R_S$$R_S$').

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.

Where a moiety is substituted with oxo or thioxo, it means that the moiety contains a carbon atom covalently bonded to at least two hydrogens (e.g., CH_2), and the two hydrogen radicals are substituted with oxo or thioxo to form C=O or C=S, respectively.

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.

A heterocycle or carbocycle may be further substituted. Unless specified, the term "substituted" refers to substitution by independent replacement of one, two, or three or more of the hydrogen atoms with substituents including, but not limited to, -F, -Cl, -Br, -I, hydroxy, protected hydroxy, $-NO_2$, $-N_3$, -CN, $-NH_2$, protected amino, oxo, thioxo, -NH-C_1-C_{12}-alkyl, -NH-C_2-C_8-alkenyl, -NH-C_2-C_8-alkynyl, -NH-C_3-C_{12}-cycloalkyl, -NH-aryl, -NH-heteroaryl, -NH-heterocycloalkyl, -dialkylamino, -diarylamino, -diheteroarylamino, -O-C_1-C_{12}-alkyl, -O-C_2-C_8-alkenyl, -O-C_2-C_8-alkynyl, -O-C_3-C_{12}-cycloalkyl, -O-aryl, -O-heteroaryl, -O-heterocycloalkyl, -C(O)-C_1-C_{12}-alkyl, -C(O)-C_2-C_8-alkenyl, -C(O)-C_2-C_8-alkynyl, -C(O)-C_3-C_{12}-cycloalkyl, -C(O)-aryl, -C(O)-heteroaryl, -C(O)-heterocycloalkyl, $-CONH_2$, -CONH-C_1-C_{12}-alkyl, -CONH-C_2-C_8-alkenyl, -CONH-C_2-C_8-alkynyl, -CONH-C_3-C_{12}-cycloalkyl, -CONH-aryl, -CONH-heteroaryl, -CONH-heterocycloalkyl, -OCO_2-C_1-C_{12}-alkyl, -OCO_2-C_2-C_8-alkenyl, -OCO_2-C_2-C_8-alkynyl, -OCO_2-C_3-C_{12}-cycloalkyl, -OCO_2-aryl, -OCO_2-heteroaryl, -OCO_2-heterocycloalkyl, $-OCONH_2$, -OCONH-C_1-C_{12}-alkyl, -OCONH-C_2-C_8-alkenyl, -OCONH-C_2-C_8-alkynyl, -OCONH-C_3-C_{12}-cycloalkyl, -OCONH-aryl, -OCONH-heteroaryl, -OCONH-heterocycloalkyl, -NHC(O)-C_1-C_{12}-alkyl, -NHC(O)-C_2-C_8-alkenyl, -NHC(O)-C_2-C_8-alkynyl, -NHC(O)-C_3-C_{12}-cycloalkyl, -NHC(O)-aryl, -NHC(O)-heteroaryl, -NHC(O)-heterocycloalkyl, -$NHCO_2$-C_1-C_{12}-alkyl, -$NHCO_2$-C_2-C_8-alkenyl, -$NHCO_2$-C_2-C_8-alkynynl, -$NHCO_2$-C_3-C_{12}-cycloalkyl, -$NHCO_2$-aryl, -$NHCO_2$-heteroaryl, -$NHCO_2$-heterocycloalkyl, $-NHC(O)NH_2$, -NHC(O)NH-C_1-C_{12}-alkyl, -NHC(O)NH-C_2-C_8-alkenyl, -NHC(O)NH-C_2-C_8-alkynyl, -NHC(O)NH-C_3-C_{12}-cycloalkyl, -NHC(O)NH-aryl, -NHC(O)NH-heteroaryl, -NHC(O)NH-heterocycloalkyl, $NHC(S)NH_2$, -NHC(S)NH-C_1-C_{12}-alkyl, -NHC(S)NH-C_2-C_8-alkenyl, -NHC(S)NH-C_2-C_8-alkynyl, -NHC(S)NH-C_3-C_{12}-cycloalkyl, -NHC(S)NH-aryl, -NHC(S)NH-heteroaryl, -NHC(S)NH-heterocycloalkyl, $-NHC(NH)NH_2$, -NHC(NH)NH-C_1-C_{12}-alkyl, -NHC(NH)NH-C_2-C_8-alkenyl, -NHC(NH)NH-C_2-C_8-alkynyl, -NHC(NH)NH-C_3-C_{12}-cycloalkyl, -NHC(NH)NH-aryl, -NHC(NH)NH-heteroaryl, -NHC(NH)NH-heterocycloalkyl, -NHC(NH)-C_1-C_{12}-alkyl, -NHC(NH)-C_2-C_8-alkenyl, -NHC(NH)-C_2-C_8-alkynyl, -NHC(NH)-C_3-C_{12}-cycloalkyl, -NHC(NH)-aryl, -NHC(NH)-heteroaryl, -NHC(NH)-heterocycloalkyl, -C(NH)NH-C_1-C_{12}-alkyl, -C(NH)NH-C_2-C_8-alkenyl, -C(NH)NH-C_2-C_8-alkynyl, -C(NH)NH-C_3-C_{12}-cycloalkyl, -C(NH)NH-aryl, -C(NH)NH-heteroaryl, -C(NH)NH-heterocycloalkyl, -S(O)-C_1-C_{12}-alkyl, -S(O)-C_2-C_8-alkenyl, -S(O)-C_2-C_8-alkynyl, -S(O)-C_3-C_{12}-cycloalkyl, -S(O)-aryl, -S(O)-heteroaryl, -S(O)-heterocycloalkyl, $-SO_2NH_2$, -SO_2NH-C_1-C_{12}-alkyl, -SO_2NH-C_2-C_8-alkenyl, -SO_2NH-C_2-C_8-alkynyl, -SO_2NH-C_3-C_{12}-cycloalkyl, -SO_2NH-aryl, -SO_2NH-heteroaryl, -SO_2NH-heterocycloalkyl, -$NHSO_2$-C_1-C_{12}-alkyl, -$NHSO_2$-C_2-C_8-alkenyl, -$NHSO_2$-C_2-C_8-alkynyl, -$NHSO_2$-C_3-C_{12}-cycloalkyl, -$NHSO_2$-aryl, -$NHSO_2$-heteroaryl, -$NHSO_2$-heterocycloalkyl, -

CH_2NH_2, $-CH_2SO_2CH_3$, -aryl, -arylalkyl, -heteroaryl, -heteroarylalkyl, -heterocycloalkyl, $-C_3-C_{12}$-cycloalkyl, polyalkoxyalkyl, polyalkoxy, -methoxymethoxy, -methoxyethoxy, -SH, $-S-C_1-C_{12}$-alkyl, $-S-C_2-C_8$-alkenyl, $-S-C_2-C_8$-alkynyl, $-S-C_3-C_{12}$-cycloalkyl, -S-aryl, -heteroaryl, -S-heterocycloalkyl, or methylthiomethyl. It is understood that the aryls, heteroaryls, alkyls, and the like can be further substituted.

An "aliphatic" group is a non-aromatic moiety comprised of any combination of carbon atoms, hydrogen atoms, halogen atoms, oxygen, nitrogen or other atoms, and optionally contains one or more units of unsaturation, e.g., double and/or triple bonds. Examples of aliphatic groups are functional groups, such as, O, OH, NH, NH_2, C(O), $S(O)_2$, C(O)O, C(O)NH, OC(O)O, OC(O)NH, $OC(O)NH_2$, $S(O)_2NH$, $S(O)_2NH_2$, $NHC(O)NH_2$, NHC(O)C(O)NH, $NHS(O)_2NH$, $NHS(O)_2NH_2$, $C(O)NHS(O)_2$, $C(O)NHS(O)_2NH$ or $C(O)NHS(O)2NH_2$, and the like, groups comprising one or more functional groups, non-aromatic hydrocarbons (optionally substituted), and groups wherein one or more carbons of a non-aromatic hydrocarbon (optionally substituted) is replaced by a functional group. Carbon atoms of an aliphatic group can be optionally oxo-substituted. An aliphatic group may be straight chained, branched or cyclic and preferably contains between about 1 and about 24 carbon atoms, more typically between about 1 and about 12 carbon atoms. In addition to aliphatic hydrocarbon groups, as used herein, aliphatic groups expressly include, for example, alkoxyalkyls, polyalkoxyalkyls, such as polyalkylene glycols, polyamines, and polyimines, for example. Aliphatic groups may be optionally substituted. A linear aliphatic group is a non-cyclic aliphatic group. It is to be understood that when a linear aliphatic group is said to "contain" or "include" or "comprise" one or more specified functional groups, the linear aliphatic group can be selected from one or more of the specified functional groups or a combination thereof, or a group wherein one or more carbons of a non-aromatic hydrocarbon (optionally substituted) is replaced by a specified functional group. An exemplary linear aliphatic group is an alkyl, alkenyl or alkynyl, each optionally substituted, which is interrupted or terminated by a functional group.

------ 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, carboxy or phosphate 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, or phosphate esters of 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.

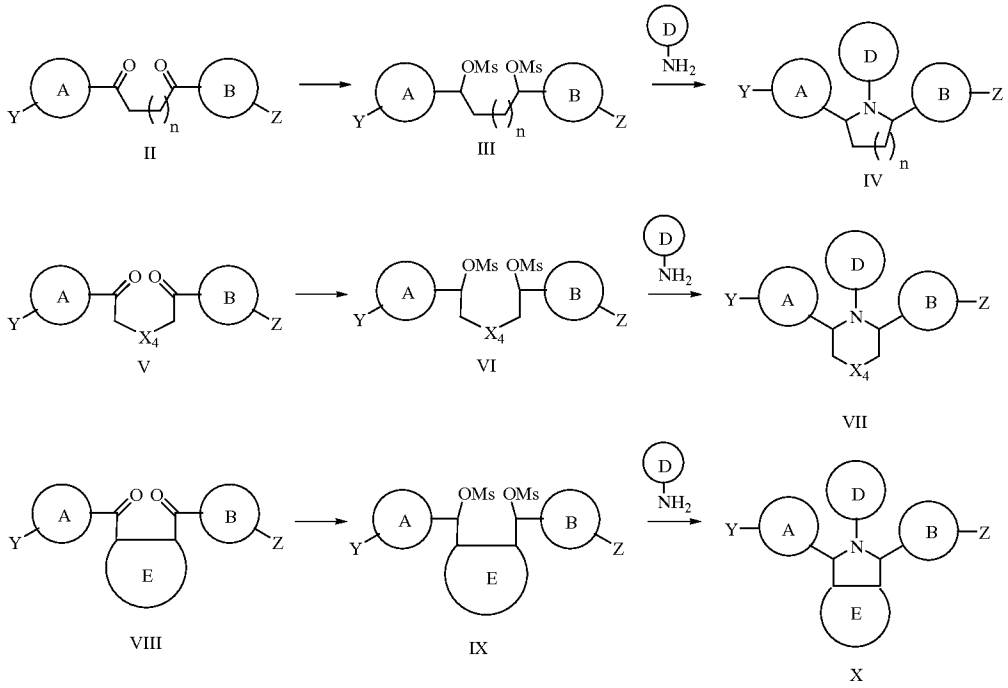
The term "N-protecting group" or "N-protected" refers to those groups capable of protecting an amino group against undesirable reactions. Commonly used N-protecting groups are described in Greene and Wuts, PROTECTING GROUPS IN CHEMICAL SYNTHESIS (3rd ed., John Wiley & Sons, NY (1999). Non-limiting examples 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).

Abbreviations which have been used in the descriptions of the Schemes, Intermediates and Examples that follow are: Ac for acetyl; APCI for atmospheric pressure chemical ionization; aq or

aq. for aqueous; atm for atmosphere; Boc for *t*-butoxycarbonyl; Bu for butyl; *t*-Bu or *tert*-butyl for *tertiary*-butyl; Cbz for benzyloxycarbonyl; dba for dibenzylidineacetone; DCI for desorption chemical ionization; DDQ for 2,3-dichloro-5,6-dicyano-*p*-benzoquinone; DEPBT for 3-(diethoxyphosphoryloxy)-1, 2, 3-benzotriazin-4(3*H*)-one; DIBAL for diisobutylaluminum hydride; DMA for *N*,*N*-dimethylacetamide; DME for 1,2-dimethoxyethane; DMF for *N*,*N*-dimethylformamide; DMSO for dimethyl sulfoxide; DMPU for 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone; dppf for 1,1′-bis(diphenylphosphino)ferrocene; EDC, EDAC or EDCI for *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride; e.e. for enantiomeric excess; ELSD for evaporative light scattering detector; ESI for electrospray ionization; Et for ethyl; Et_3N for triethylamine; EtOAc for ethyl acetate; EtOH for ethanol; Et_2O for diethyl ether; eq or equiv for equivalents; Fmoc for 9-fluorenylmethoxycarbonyl; HATU for *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium hexafluorophosphate; HOBt for 1-hydroxybenzotriazole; HPLC for high performance liquid chromatography; HOBt for 1-hydroxybenzotriazole; LCMS for liquid chromatography/mass spectrometry; mCPBA for *m*-chloroperoxybenzoic acid; Me for methyl; MeOH for methanol; OAc for acetate; Ms for methanesulfonyl; OTF for triflate or trifluoromethanesulfonate; PDC for pyridinium dichromate; *i*-Pr for isopropyl; Ph for phenyl; PPh_3 for triphenylphosphine; psi or psig for pounds per square inch (gas); PTFE for polytetrafluoroethylene; PXPd for $[(t\text{-}Bu)_2PCl]_2PdCl_2$, PyBOP for (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate; SEM for 2-(trimethylsilyl)ethoxymethyl; T3P for propane phosphonic acid anhydride; Tf for trifluorosulfonyl; TFA for trifluoroacetic acid; THF for tetrahydrofuran; TLC for thin layer chromatography; Troc for 2,2,2-trichloroethoxycarbonyl; v/v for volume/volume; wt% for weight percent; w/v for weight/volume; w/w for weight/weight; XantPhos for 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene;

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.

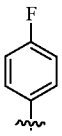
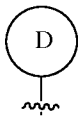


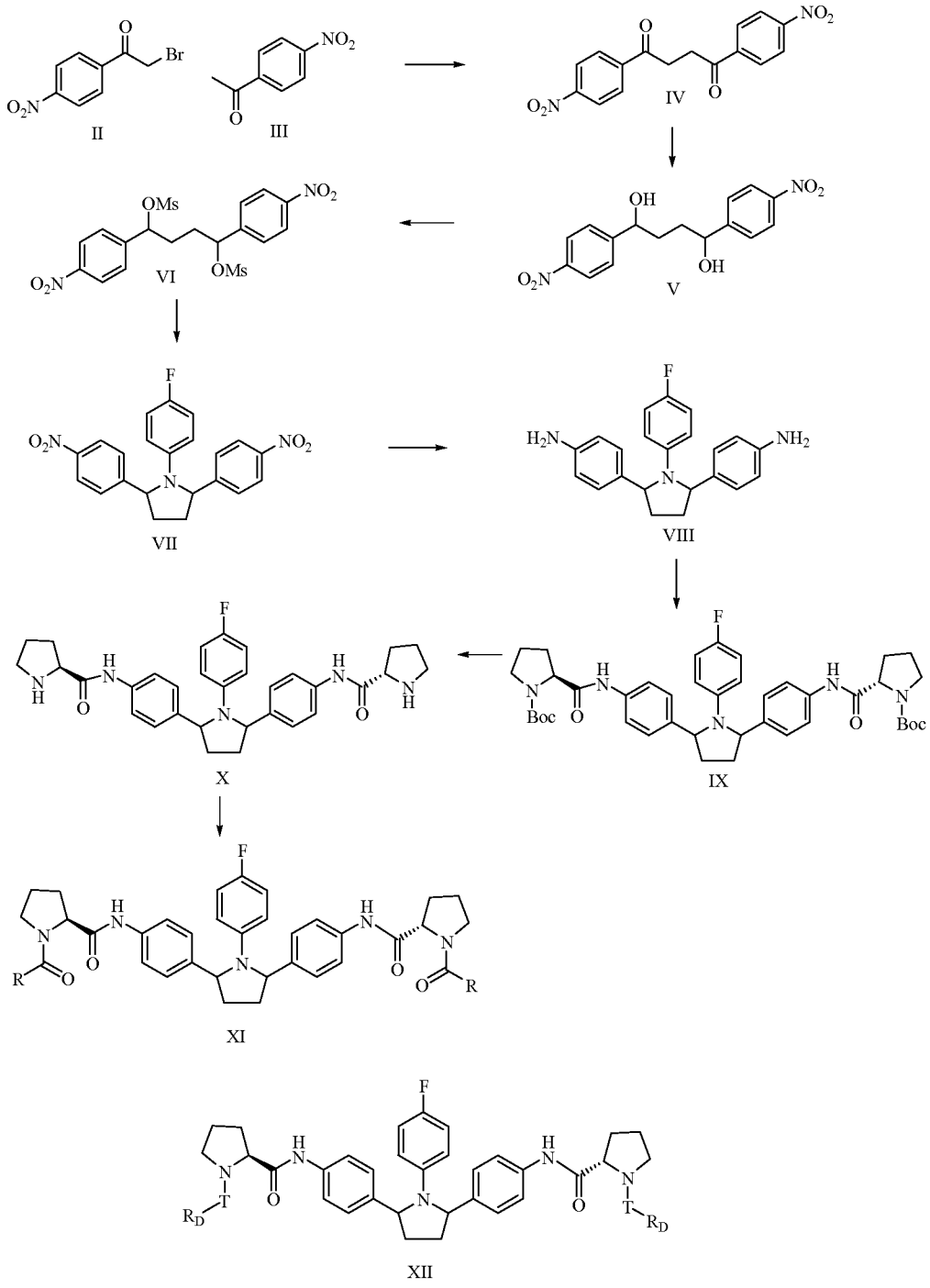
Scheme I

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 $Ti(OiPr)_4$. For example reaction of II (1 equivalent) with III (1.5 equivalents) in the presence of $ZnCl_2$ (2 equivalents), diethylamine (1.5 equivalents) and *tert*-butanol (1.5 equivalents) in a solvent such as benzene at around room temperature can provide the diketones IV. 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 diketones IV (1 equivalent) can be reduced by NaBH4 (3 equivalents) in solvents such as tetrahydrofuran with heating to about 50 °C. The diketones IV (1 equivalent) can be enantioselectively reduced upon addition to a mixture made from *N*,*N*-diethylaniline borane (about 2 equivalents), trimethylborate (about 0.2 equivalents) and either (*S*) or (*R*) α,α-diphenyl-2-pyrrolidinemethanol (about 0.17 equivalents) in a solvent such as THF at temperatures ranging from about 10 °C to about 30 °C (Synthesis 2507-2510 (2003)). The resultant racemic, enantiomerically enriched, or meso 1,4-diols V may be reacted with methanesulfonyl chloride or methanesulfonic anhydride to provide the dimesylate Formula VI. For example, diols V (1 equivalent) can be reacted with methanesulfonic anhydride (about 2.5 equivalents) in the presence of a base such as diisopropylethylamine (about 4 equivalents) in a solvent such as tetrahydrofuran or 2-methyltetrahydrofuran at temperatures starting from about -15 °C to -25 °C and increasing to about room temperature. 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. The dimesylate VI (1 equivalent) (or in the alternative the ditriflate, ditosylate, or dihalide) may be reacted with between 1 to 20 equiv of an amine D-NH_2, such as, for example, a substituted aniline in solvents such as tetrahydrofuran or 2-methyltetrahydrofuran with or without a co-solvent such as DMF, at about room temperature to about 100 °C, to give the pyrrolidines such as Formula VII. Where fewer equivalents of amine D-NH_2 are employed (i.e., 1-2 equivalents), a base such as diisopropylethylamine can be added to promote the reaction. In certain cases, the amine can be used in a large excess (i.e., as reaction solvent). For example, the reaction of a dimesylate (1 equivalent) with excess aniline (about 6.5 equivalents) can be conducted by heating to 65 °C in 2-methyltetrahydrofuran until completion of the reaction. Numerous substituted anilines can be reacted with the dimesylate Formula VI, including, but not limited to, 3-fluoro-4-(piperidin-1-yl)aniline, 3,5-difluoro-4-(piperidin-1-yl)aniline, 3,5-difluoro-4-(4-phenylpiperidin-1-yl)aniline, 3-difluoro-4-(4-phenylpiperidin-1-yl)aniline, 4-(4-phenylpiperidin-1-yl)aniline, 4-cyclopropylaniline, 4-cyclopropyl-2-fluoroaniline, 4-cyclopropyl-3,5-difluoroaniline, 4-cyclohexyl-3-fluoroaniline, biphenyl-4-amine, 4-(pyridin-2-yl)aniline, 3,5-dichloro-4-(piperidin-1-yl)aniline, 4-(4,4-dimethylpiperidin-1-yl)-3,5-difluoroaniline, 4-(4,4-fluoropiperidin-1-yl)-3,5-difluoroaniline, 3-methyl-4-(piperidin-1-yl)aniline, 2,5-difluoro-4-(piperidin-1-yl)aniline, 4-(3,5-dimethylpiperidin-1-yl)-3,5-difluoroaniline, 4-(2,6-dimethylpiperidin-1-yl)-3,5-difluoroaniline,

2,3,5-trifluoro-4-(piperidin-1-yl)aniline, 3,5-difluoro-4-(4-isopropylpiperidin-1-yl)aniline, 3,5-difluoro-4-(4-methylpiperidin-1-yl)aniline, 3,5-difluoro-4-(4-(trifluoromethyl)piperidin-1-yl)aniline, 4-(4-*tert*-butylpiperidin-1-yl)-3,5-difluoroaniline, 3,5-difluoro-4-(6-azaspiro[2.5]octan-6-yl)aniline, 4-(2-azabicyclo[2.2.2]octan-2-yl)-3,5-difluoroaniline, 4-(3,3-dimethylazetidin-1-yl)-3,5-difluoroaniline, 4-*tert*-butylaniline, 4-ethoxyaniline, 4-phenoxyaniline, 1-(4-aminophenyl)piperidin-2-one, 4-(cyclopentyloxy)-3-fluoroaniline, 3-chloro-4-(trifluoromethoxy)aniline, 2,5-difluoro-4-(trifluoromethyl)aniline, 4-(2,2-difluoroethoxy)aniline, 4-chloroaniline, 4-(2-methoxyethoxy)aniline, 4-(oxazol-2-yl)aniline, 4-(2-fluoropyridin-4-yl)aniline, 3,4-difluoroaniline, 4-chloro-3-fluoroaniline, 3-fluoro-4-(methylsulfonyl)aniline, 4-(3-azabicyclo[3.2.0]heptan-3-yl)-3,5-difluoroaniline, 4-((3-ethyloxetan-3-yl)methoxy)aniline, 4-cyclopropyl-3,5-difluoroaniline, 4-(1,3-dioxan-5-yloxy)aniline, 3,5-difluoro-4-(octahydroisoindol-2-yl)aniline, 4-((1,3-dioxolan-4-yl)methoxy)aniline, 4-((3-ethyloxetan-3-yl)methoxy)-3,5-difluoroaniline, 4-(pentafluorosulfanyl)aniline, *N*1-*tert*-butyl-2-fluorobenzene-1,4-diamine, heteroaryl amines, alkyl amines, cycloalkyl amines, substituted benzylamines, allylamine, or anilines that are listed in or can be made using General Procedures 1, 1.1, or 1.2. 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. For example compounds VII (1 equivalent) can be reduced to VIII by reaction with iron powder (about 6 equivalents) and ammonium chloride in a 1:1 mix of THF and ethanol with heating to about 60-80 °C. 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. For example reduction of VII to VIII can be effected by exposure to 30 psig hydrogen gas in the presence of Raney-nickel Grace 2800 in a solvent such as tetrahydrofuran with shaking. 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, T3P or DEPBT, in a solvent such as THF, DMF, dichloromethane, ethyl acetate, or DMSO, with or without the addition of an amine base such as *N*-methylmorpholine, Hunig's base, pyridine, 2,6-lutidine, or triethylamine, to give Formula IX. For example, reaction of VIII (1 equivalent) with 1-(*tert*-butoxycarbonyl)pyrrolidine-2-carboxylic acid (2.5 equivalents) and HATU (2.5 equivalents) in the presence of diisopropylethylamine (3 equivalents) in DMSO at about room temperature can provide the product 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. For example, reaction of IX (1 equivalent) with TFA:CH_2Cl_2 (1:1) at room temperature can provide compounds X. Compounds XI may be prepared by coupling of Formula X with an acid of choice using the standard peptide coupling reagents and conditions described above. For example, X(1 equivalent) can be reacted with acids (2 equivalents) such as, but

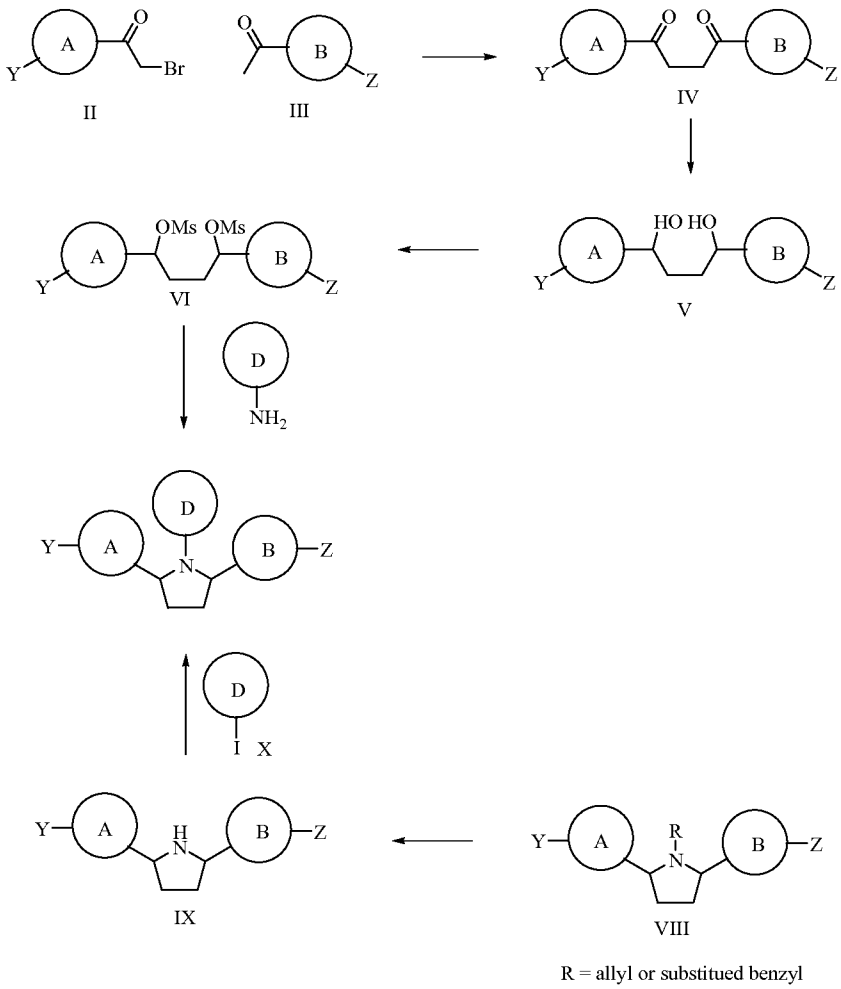
not limited to, 2-(methoxycarbonylamino)-3-methylbutanoic acid, 2-(methoxycarbonylamino)-3,3-dimethylbutanoic acid, 2-cyclohexyl-2-(methoxycarbonylamino)acetic acid, 2-(methoxycarbonylamino)-2-(tetrahydro-2*H*-pyran-4-yl)acetic acid, or acids listed under General Procedure 19. Alternately, diamine VIII may be reacted directly with an appropriately *N*-substituted proline in the presence of a peptide coupling reagent such as EDAC/HOBT, PyBOP, HATU, T3P, or DEPBT, in a solvent such as THF, DMF, dichloromethane, or DMSO, with or without the addition of an amine base such as *N*-methylmorpholine, Hunig's base, pyridine, 2,6-lutidine, or triethylamine, to directly give compounds XI. For example, VIII (1 equivalent) can be reacted directly with 1-(2-(methoxycarbonylamino)-3-methylbutanoyl)pyrrolidine-2-carboxylic acid (about 2 equivalents) and T3P (about 2.8 equivalents) in the presence of diisopropylethylamine (about 5.5 equivalents) in a solvent such as ethyl acetate at temperatures from about 0 °C to about room temperature to provide XI. The foregoing sequence illustrates the synthesis of particular compounds of the invention XI having a substituted proline group at Y and Z (i.e., R_2 and R_5 taken together with the atoms to which they are attached, and R_9 and R_{12} taken together with the atoms to which they are attached, each form a 5-membered heterocycle). It is understood that analogous synthetic procedures can be used to make compounds of the invention where Y, Z, R_2, R_5, R_9, and R_{12} are other than that shown and described in Scheme II.  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). Likewise, compounds of Formula XII can be prepared from compounds of Formula X or directly from compounds of Formula VIII.



Scheme II

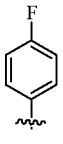
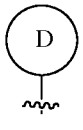
As yet another non-limiting example, the compounds of the present invention can be prepared starting from compounds of Formula II and Formula III as shown in Scheme III, where A, B, D, Y, and Z are as described above, using conditions similar to those described above for the preparation of IV in Scheme II. Similarly, the resulting 1,4-diketone IV may be reduced to the 1,4-diols V using the

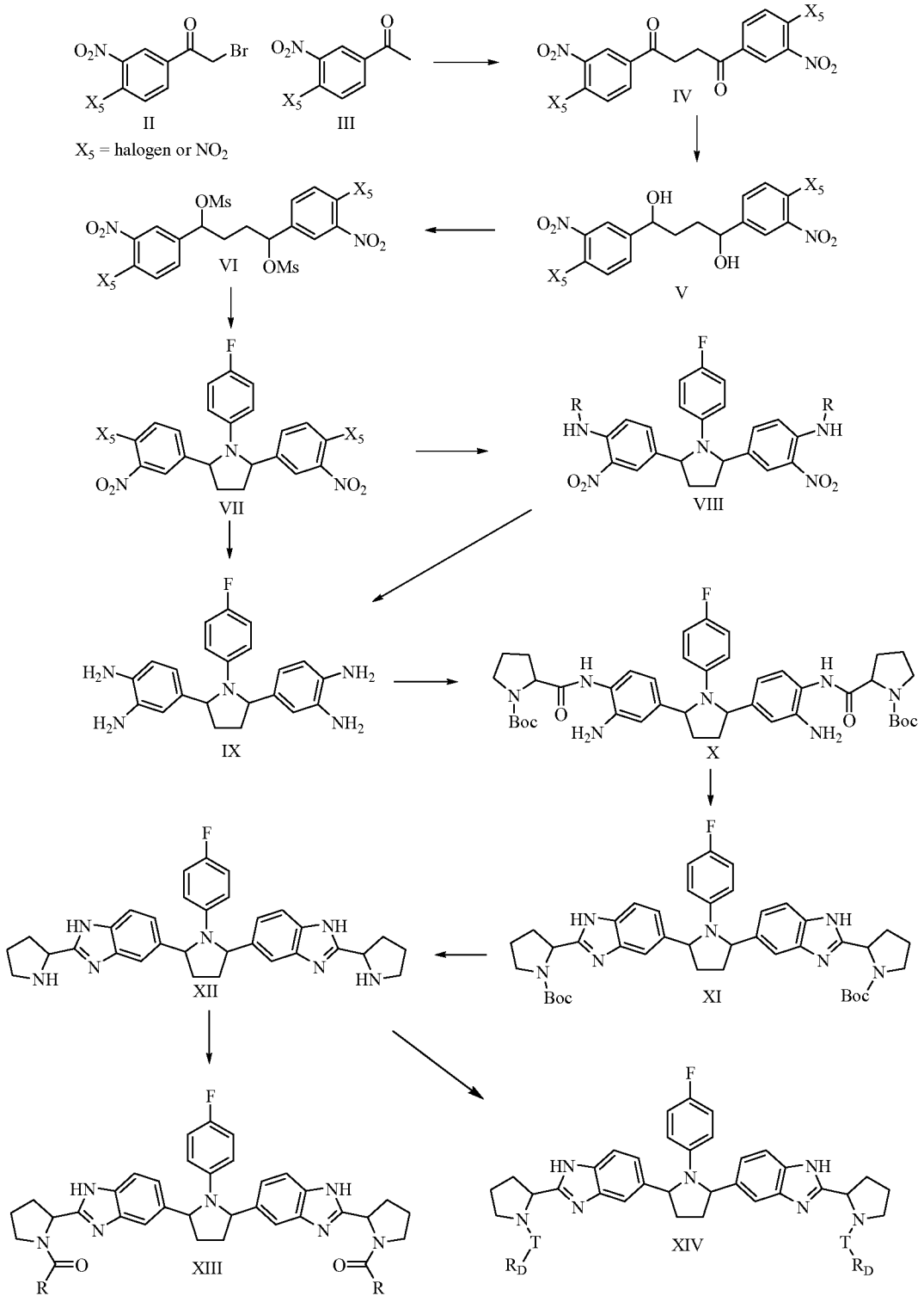
methods described above for Scheme II. The resultant racemic, enantiomerically enriched, or meso 1,4-diols V may be converted to the dimesylate VI or alternatively to a ditriflate, ditosylate, or dihalide by the methods described above. The dimesylate VI, ditriflate, ditosylate, or dihalide may be reacted 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

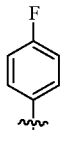
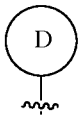
As a further non-limiting example, the compounds of XIII can be prepared starting from compounds of Formula II and Formula III as shown in Scheme IV, where X_5 in Formula II and Formula III represents a halogen (e.g., Cl, Br, or F) or a nitro group. Additionally, each phenyl ring can be substituted with X_{13}, wherein X_{13} is X_5, H, alkyl, haloalkyl, alkoxy, or haloalkoxy. 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 in Scheme II. As described for Intermediate 20D, the chiral reduction may proceed with lower stereoselectivity with an additional substituent X_{13} on the phenyl ring. The resultant racemic, enantiomerically enriched, or meso 1,4-diols V may be reacted with methansulfonyl chloride or methanesulfonic anhydride 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,

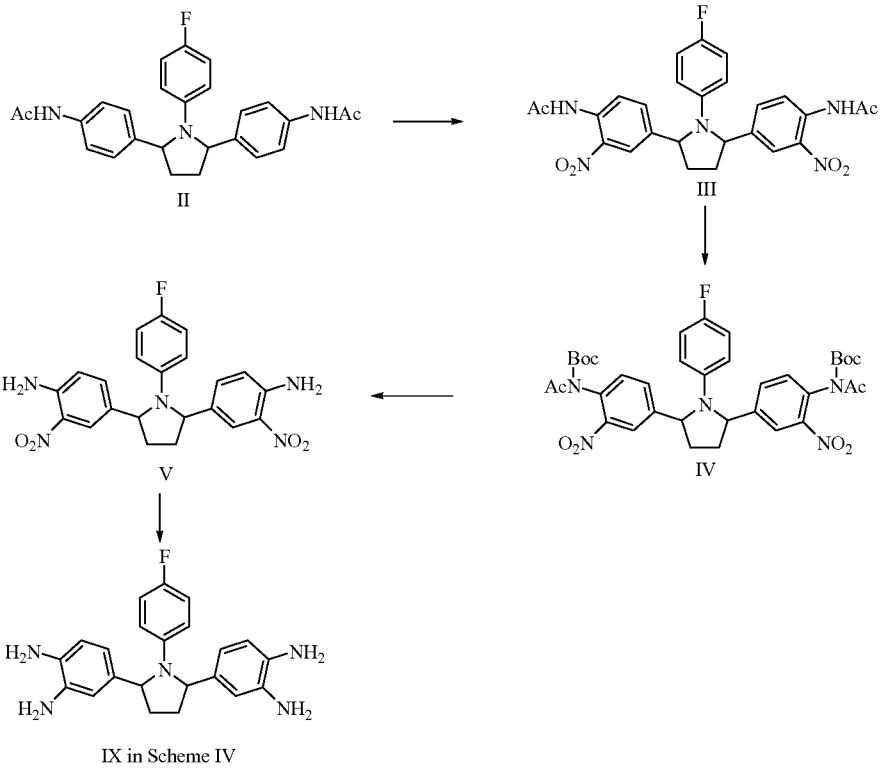
analogously to Scheme II, with an amine D–NH_2 including but not limited to those amines described or referred to in Scheme II to give VII. When X_5 in Formula VII is nitro, the nitro groups may be reduced to the tetraamino product IX using Fe in the presence of NH_4Cl, HCl, or acetic acid, or with a 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, T3P, or DEPBT, in a solvent such as THF, DMF, dichloromethane, or DMSO, with or without the addition of an amine base, such as N-methylmorpholine, Hunig's base, pyridine, 2,6-lutidine, or triethylamine, to give X as a mixture of the amide products. Although formula X depicts reaction taking place on a specific NH_2 group, the reaction may take place at either NH_2. 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. 2008, 16, 6965-6975. 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 to give XIII.  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. Compounds of Formula XIV can be similarly prepared from compounds of Formula XII. When subjected to synthetic processes in Scheme IV, enantiomerically enriched diols V may produce mixtures containing varying amounts of stereoisomeric cis and trans pyrrolidines VII. The stereoisomeric pyrrolidines may be separated according to standard chromatography techniques. Alternatively, such separations may be carried out at a later stage in the synthetic process including the steps of Schemes XIII and XIV, or after the final step.



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

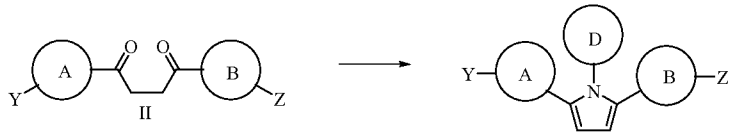
chloride or acetic anhydride to give compound II (Scheme V). Nitration of compound II to provide III may be accomplished using known methods, such as treatment with nitric acid or potassium nitrate in the presence of an acid such as sulfuric acid or treatment with NO_2BF_4. Removal of the acetamide protecting 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 to provide V. The nitro groups in V may be reduced to amino groups using the methods described above for Scheme IV to provide IX.  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.



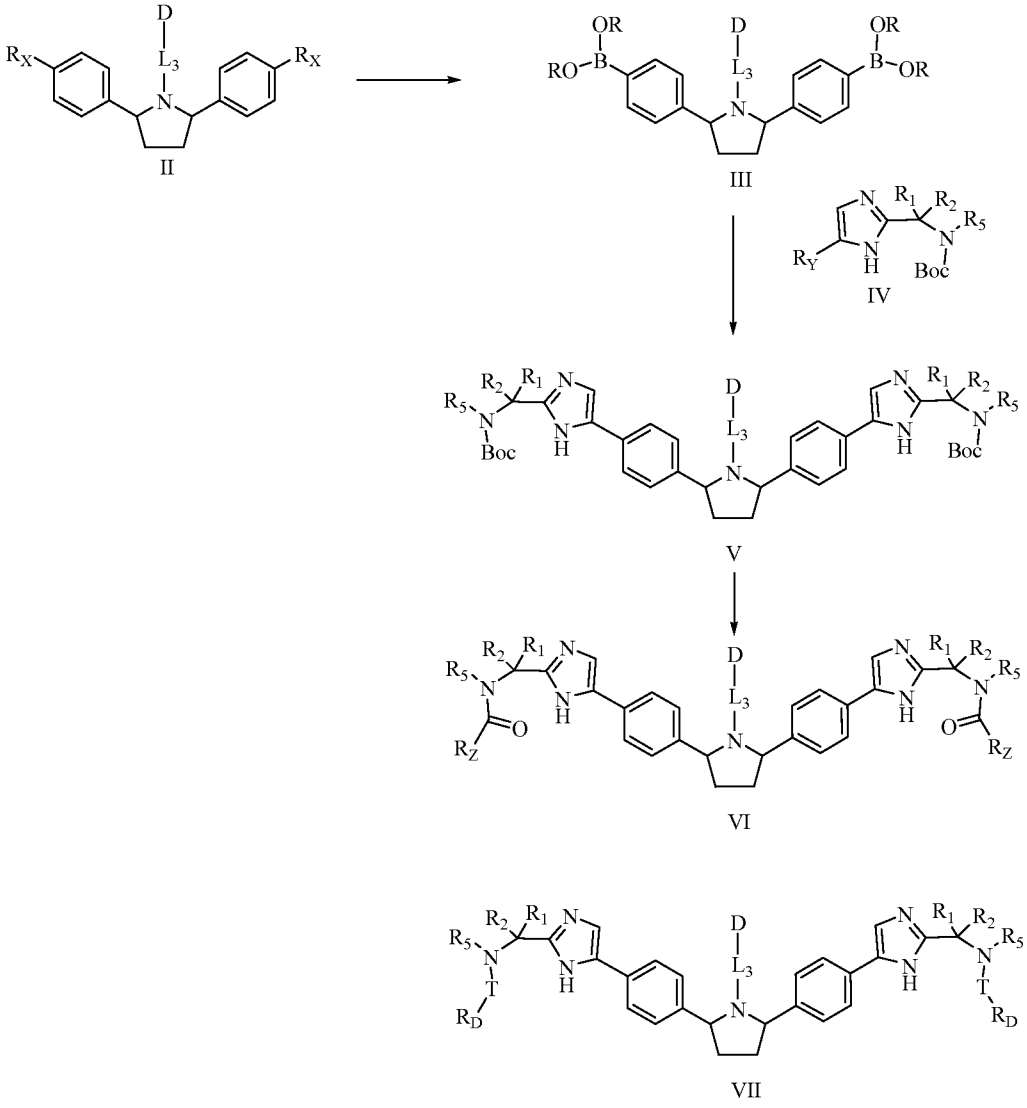
Scheme VI

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, using the chemistry analogous to that of Scheme II to prepare VII (in Scheme II); for example, by starting with 1-(4-bromophenyl)ethanone and 2-bromo-1-(4-bromophenyl)ethanone. 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, (e.g., a cyclic pinacolate ester) 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,

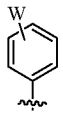
cesium carbonate, or cesium fluoride; and solvent such as, for example, toluene, ethanol, water, or tetrahydrofuran, or mixtures thereof heated in the temperature range from about 40 to about 130°C.

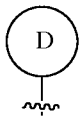
Removal of the Boc protecting groups from V may be accomplished by treatment with an acid, such as TFA, HCl, or formic acid. Certain compounds of the present invention such as VI may be prepared by coupling the resulting amino compounds with an acid of choice using the standard peptide coupling reagents, such as EDAC/HOBT, PyBOP, HATU, or DEPBT, in a solvent such as THF, DMF, dichloromethane, or DMSO, with or without the addition of an amine base such as *N*-methymorpholine, 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. Alternatively, the functionality of T-R_D can similarly be introduced following removal of the Boc protecting groups in V give compounds of Formula VII.



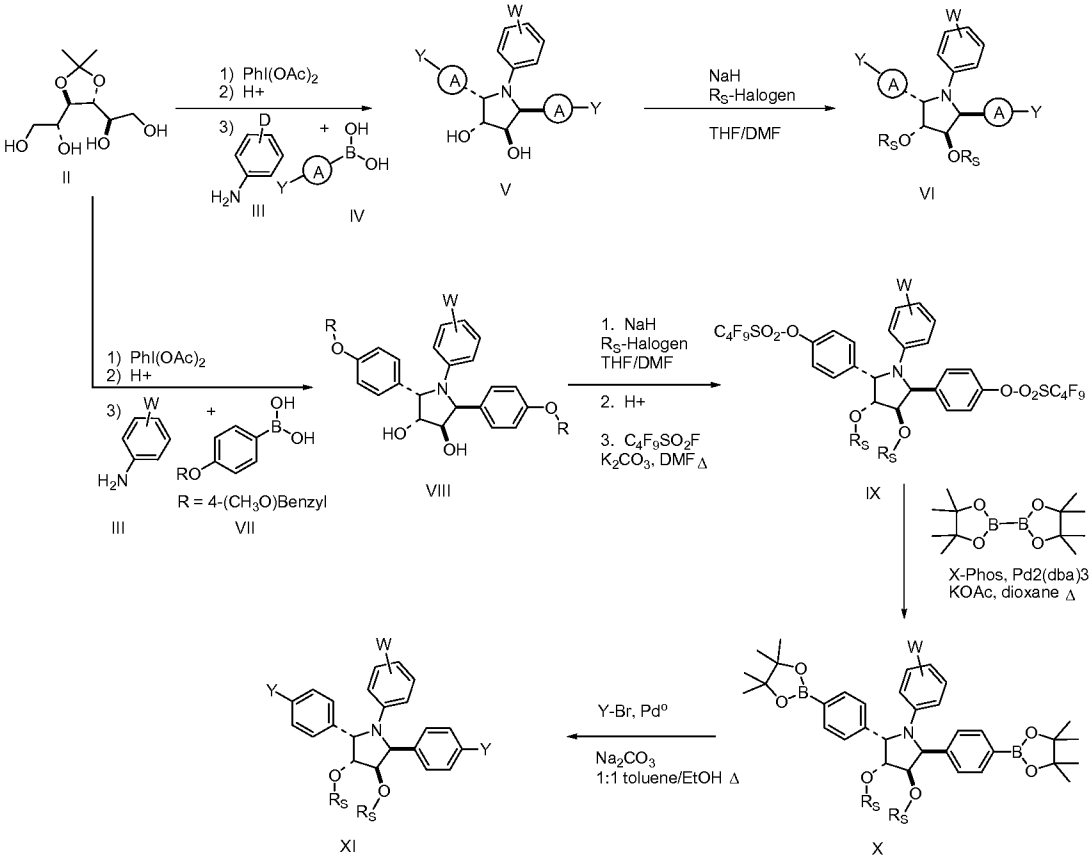
Scheme VII

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. 

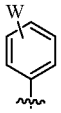
in each Formula within Scheme VIII can be replaced with 

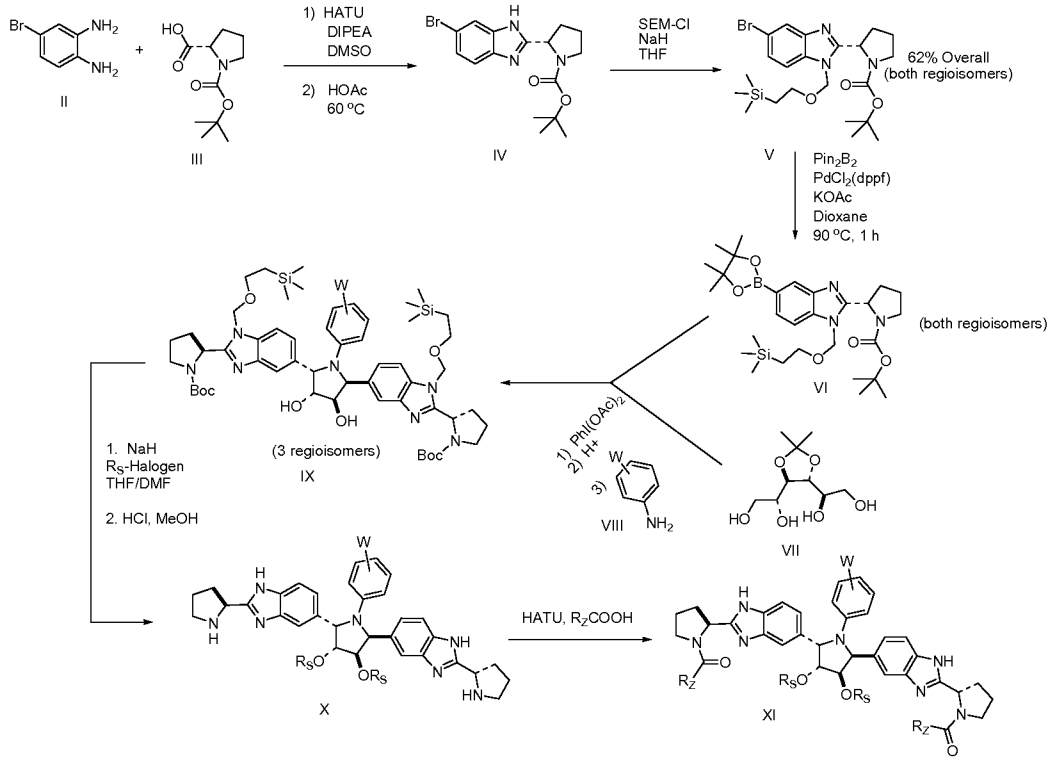
where D is defined above, and such compounds can be readily prepared according to the process described in Scheme VIII.



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,

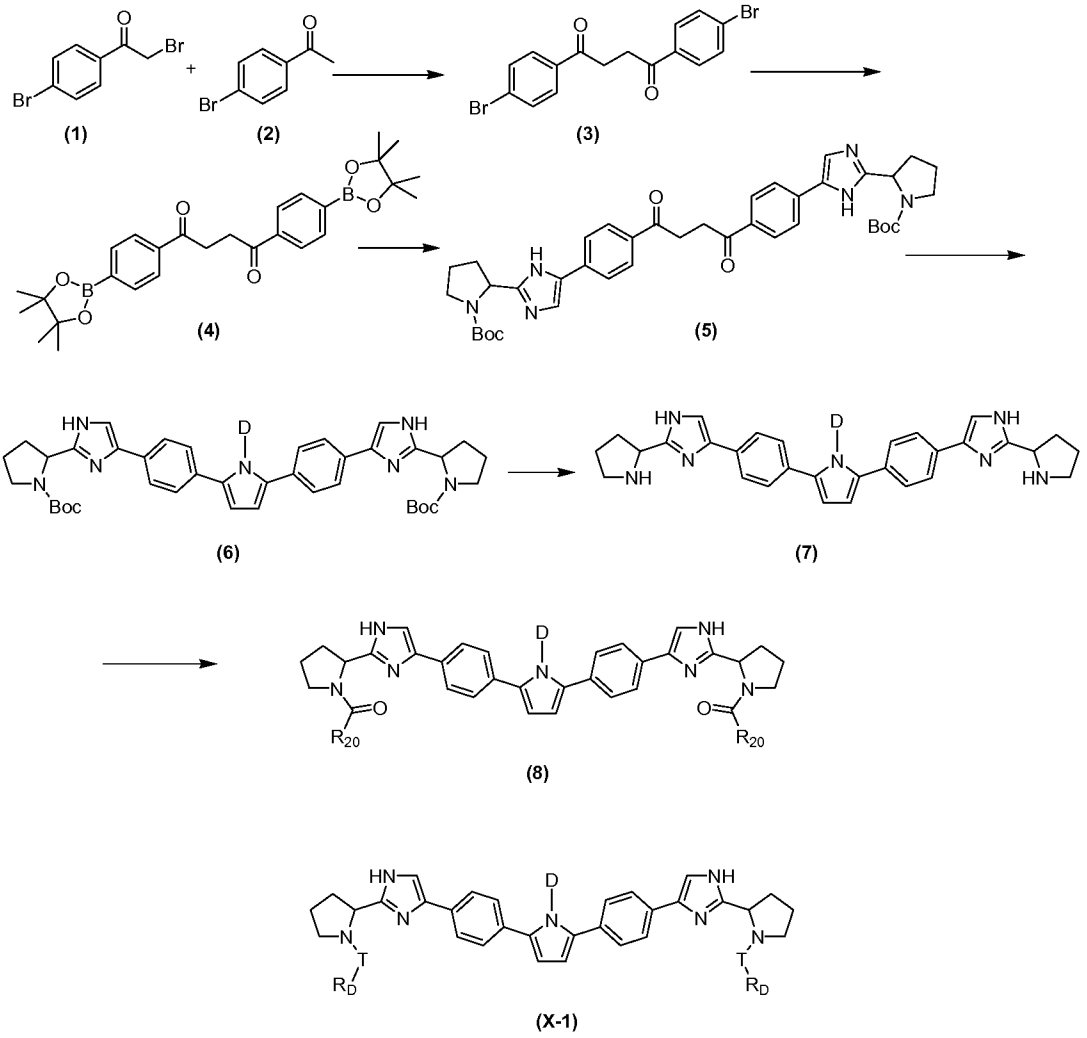
followed by acid hydrolysis of the pyrrolidine and benzimidazole protecting groups, preferably by treatment with mineral acid, such as hydrochloric acid in an alcoholic solvent such as methanol. The carboxylic acid R_Z-COOH is activated towards coupling using reagents such as isobutylchloroformate, DCC, 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

Certain 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

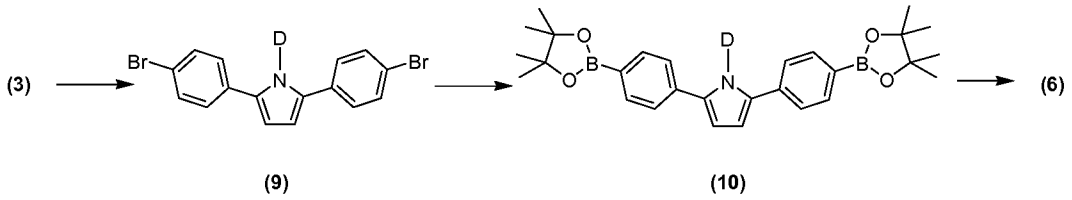
the intermediate (5) by Suzuki reaction using, in analogous fashion, the Suzuki conditions described in Scheme VII. The intermediate (5) can be converted to (6) by reaction with an amine D–NH_2 under the analogous conditions described in Scheme VI. For example, reaction of (5) with D–NH_2 in the presence 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. Alternatively, the functionality of T-R_D can be similarly introduced to compounds of Formula (7) to give compounds of Formula (X-1).



Scheme X

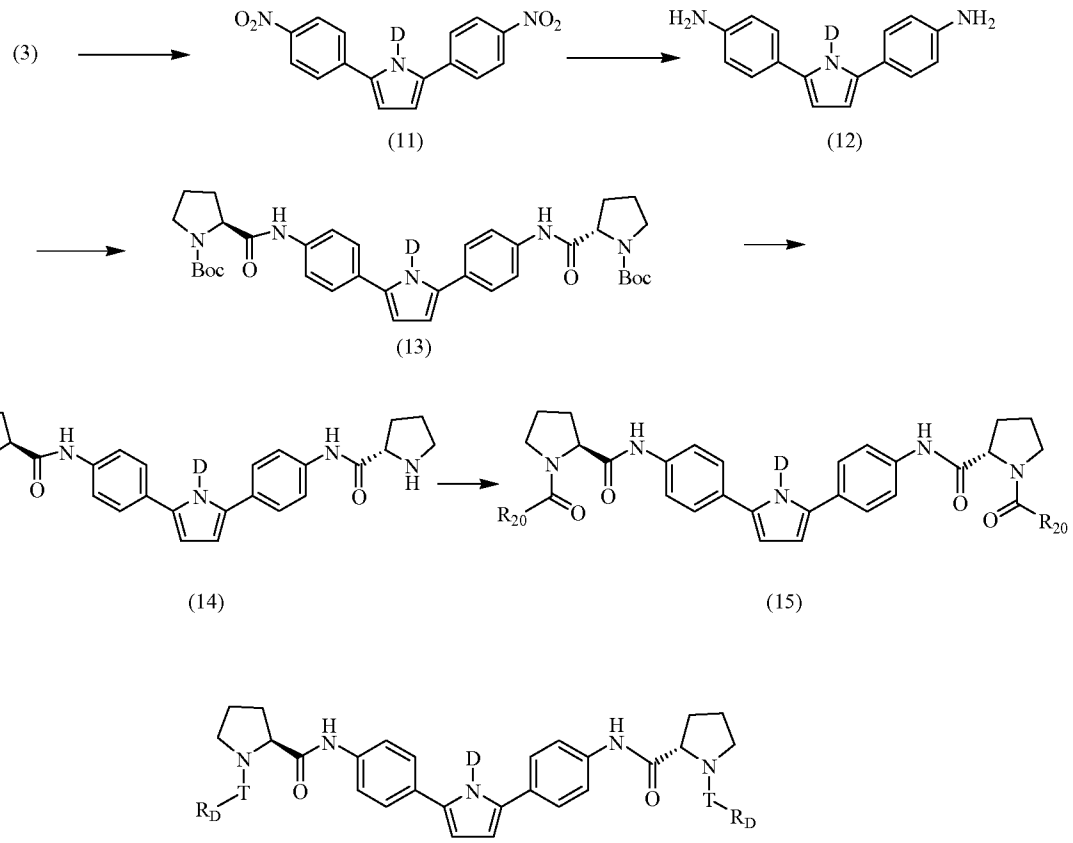
The intermediates (6) can also be prepared using the route depicted in Scheme XI. The intermediate (3) can be reacted with an amine D–NH_2 using, in analogous fashion, the conditions described in Schemes VI and X to provide intermediates (9), which can be converted to (10) using,

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.



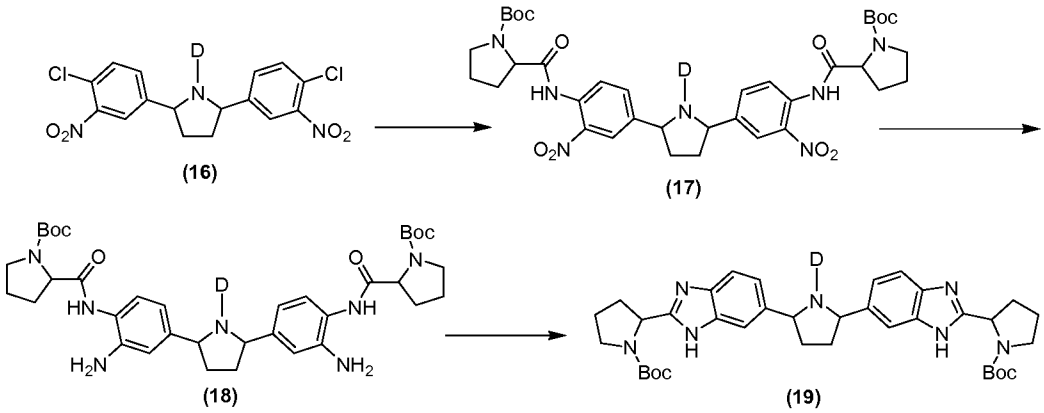
Scheme XI

As still another non-limiting example, the 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 as shown in Scheme XII. A 1,4-diketone compound (3) may be reacted with an amine D-NH_2, under acid catalyzed conditions, such as acetic acid, TFA, formic acid or HCl, to give the compounds (11). For example, a diketone (3) (1 equivalent) can be reacted with an aniline (1.2 equivalents) and TFA (2 equivalents) in a solvent such as toluene with heating to between around 80 and 120 °C to provide the compounds (11). Alternatively, a diketone (3) can be reacted with an aniline (about 10 equivalents) with heating in acetic acid to around about 70 °C to provide the compounds (11). Amines that can be reacted according to the foregoing description include but are not limited to, those amines described or referred to in Scheme II as suitable for reacting with intermediate (5). Compounds of formula (11) can be converted to compounds of formula (12) by reduction with iron in the presence of ammonium chloride. For example, reaction of compounds (11) (1 equivalent) with iron powder (about 6 equivalents) in the presence of ammonium chloride (about 3 equivalents) in a mixed solvent of ethanol:THF:water (1:1:0.25) at reflux can provide compounds (12). The conversion of (11) to (12) may also be effected by other methods described above in Scheme II to convert VII to VIII, for example by catalytic hydrogenation. Compounds (12) (1 equivalent) can be converted to compounds (13) using the peptide coupling condition described for the conversion of VIII to IX in Scheme II, for example using EDAC/HOBt (2 equivalents) and an appropriate acid in solvents such as DMF at around room temperature. Compounds (13) can be converted to compounds (14) using TFA/CH_2Cl_2 as described above for converting IX to X in Scheme II. Compounds (14) can be converted to compounds (15) using procedures analogous to those in Scheme II to convert X to XI, such as the coupling procedure to convert (12) to (13). Alternatively, the functionality of T-R_D can be similarly introduced to compounds of Formula (14) to give compounds of Formula (XII-1).



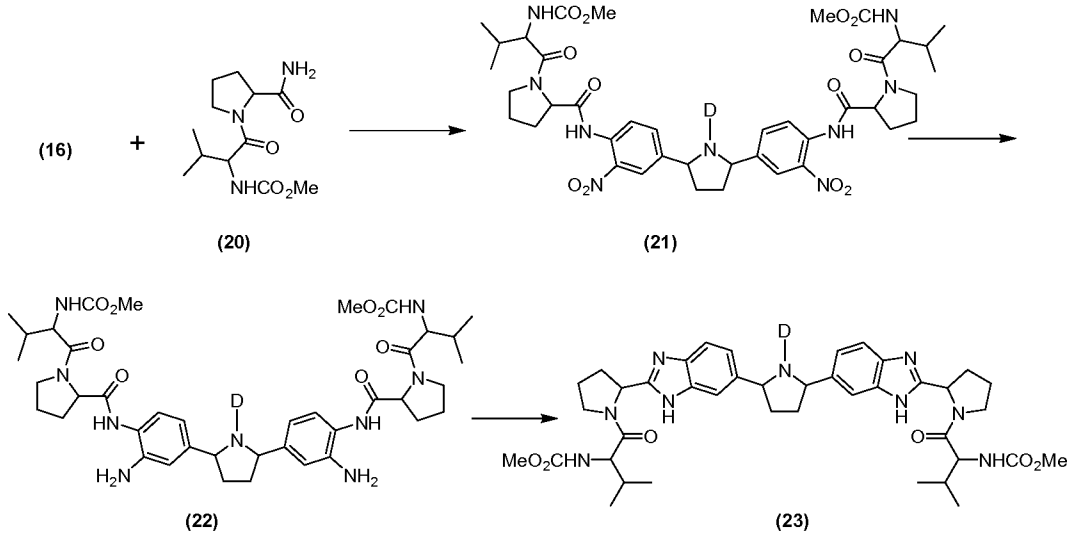
Scheme XII

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. Each phenyl ring in the above structures can be substituted with X_{13}, wherein X_{13} is H, halogen, alkyl, haloalkyl, alkoxy, or haloalkoxy. Mixtures of cis and trans stereoisomeric pyrrolidines in Scheme XIII may be separated into the cis and trans isomers using standard chromatographic techniques.



Scheme XIII

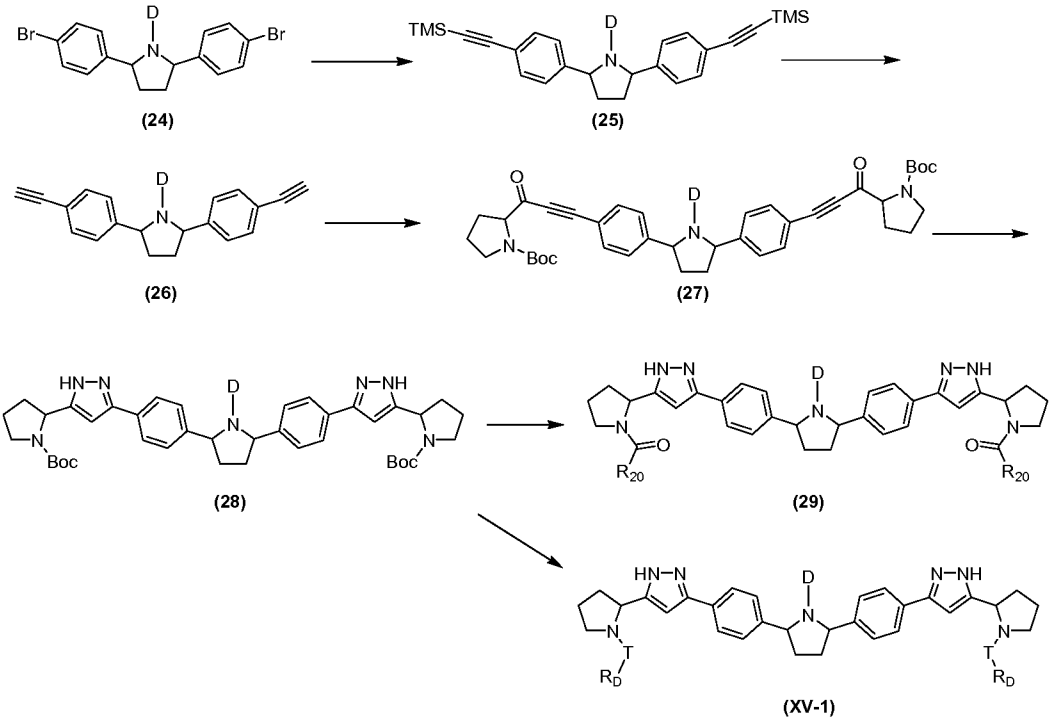
Certain compounds of the invention of general formula (23), where D is as described above, can be prepared according to the methods of Scheme XIV. Compounds (16) can be reacted with compound (20) using a Buchwald reaction as described generally in Scheme XIII to provide compounds (21). Compounds (21)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



Scheme XIV

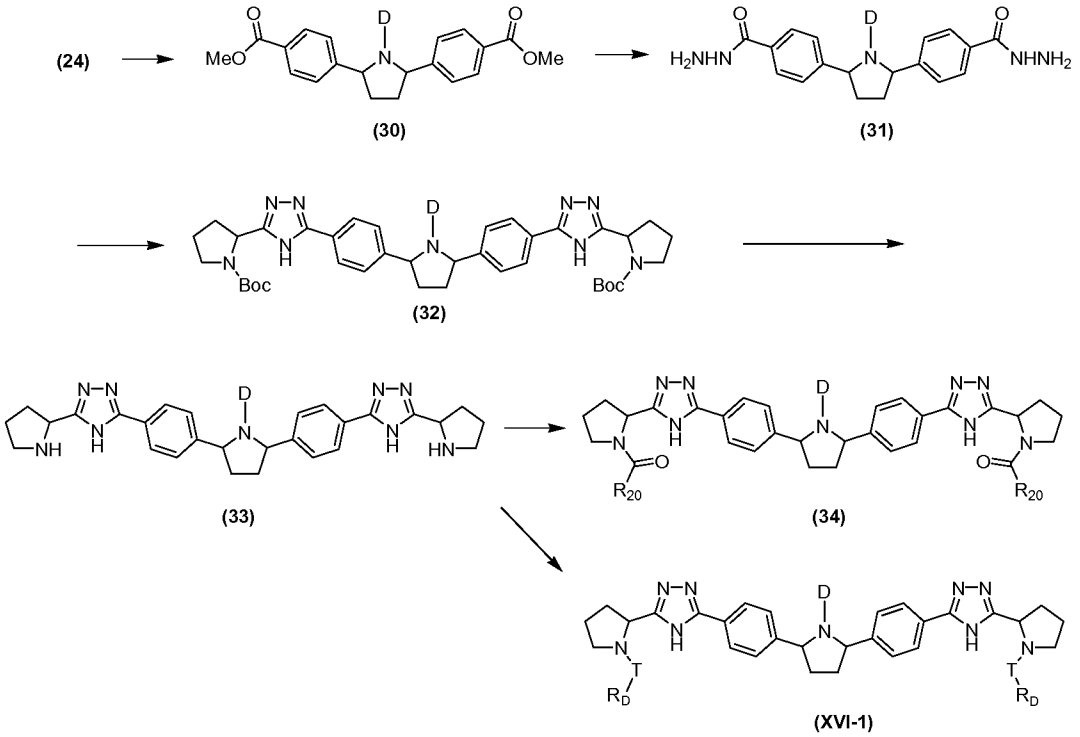
Certain compounds of the invention of general formula (29), where R_{20} is $-L_S'-M'-L_S''-R_D$ and D is as described above, can be prepared according to the methods of Scheme XV. Compounds of formula (24) can be converted to compounds of formula (25) (Sonogashira reaction) by reaction with trimethylsilylacetylene, 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. Alternatively, the functionality of T-R_D can be similarly introduced to compounds of Formula (28) to give compounds of Formula (XV-1).



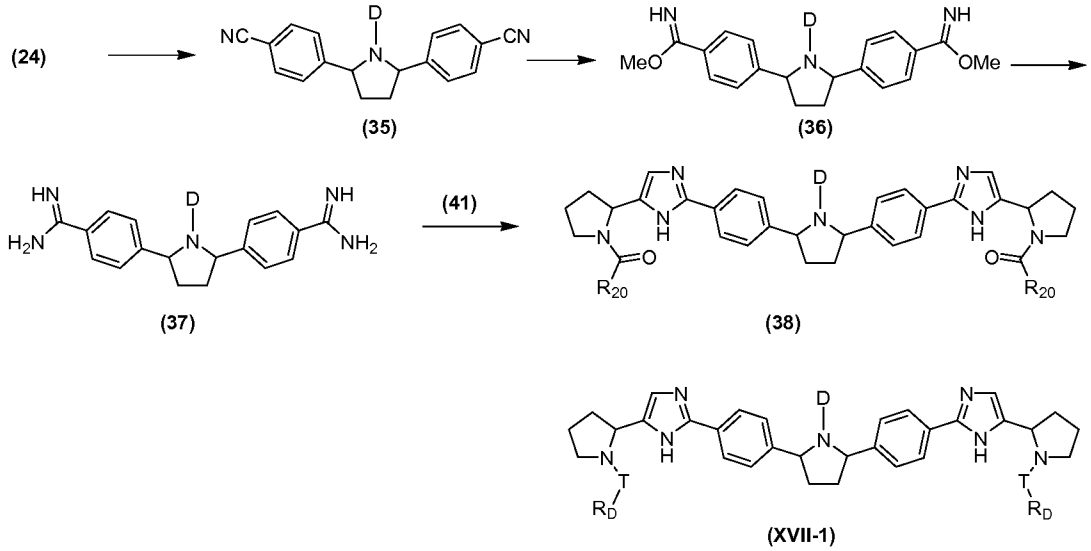
Scheme XV

Certain 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. Alternatively, the functionality of T-R_D can be similarly introduced to compounds of Formula (33) to give compounds of Formula (XVI-1).



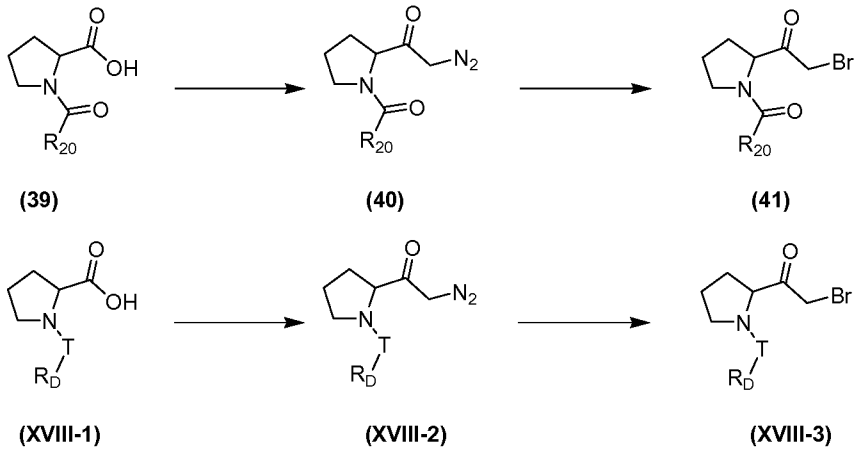
Scheme XVI

Certain 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). Alternatively, the functionality of $T-R_D$ can be similarly introduced to compounds of Formula (33) to give compounds of Formula (XVII-1).



Scheme XVII

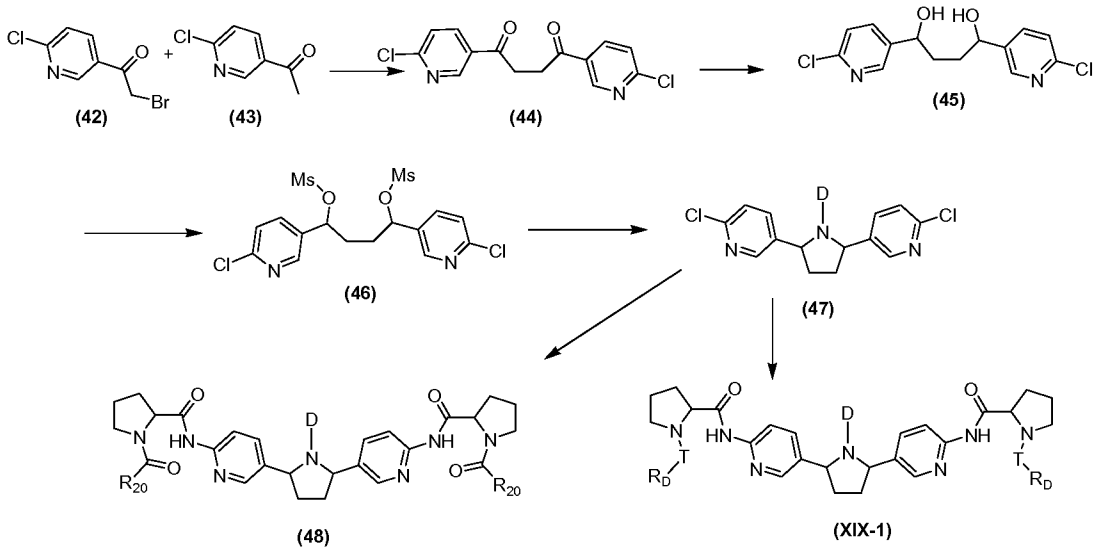
Compounds of formula (41), where R_{20} is $-L_S'-M'-L_S''-R_D$, can be prepared using the methods of Scheme XVIII. Compounds (39) can be converted to compounds (40) by sequential reaction of (39) with isobutylchloroformate in THF at 0 °C followed by diazomethane. Compounds (40) can be converted to compounds (41) by reaction with HBr in acetic acid. Similarly, compounds of formula (XVIII-1) can be converted to compounds of formula (XVIII-2) and then (XVIII-3), wherein $T-R_D$ are as defined above.



Scheme XVIII

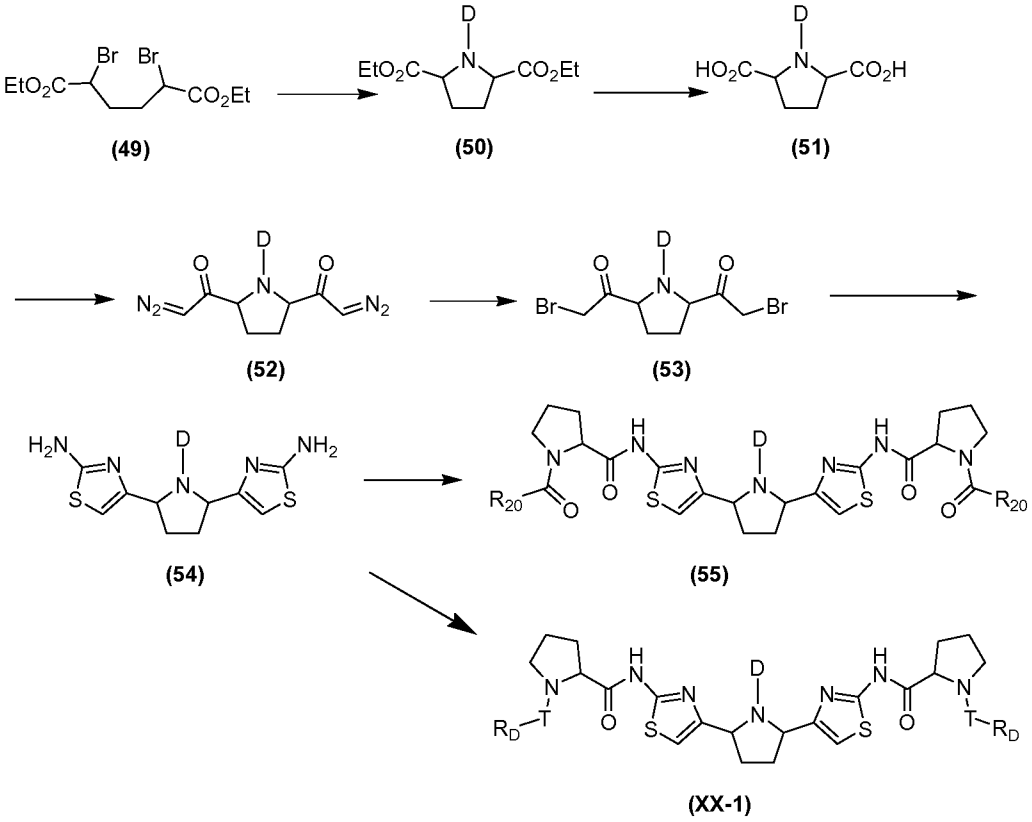
Certain compounds of the invention of general formula (48), where R_{20} is $-L_S'-M'-L_S''-R_D$ and D is as described above, can be prepared according to the methods of Scheme XIX. Compound (42) can be reacted with compound (43) using, in analogous fashion, the Lewis acid mediated conditions described 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. Alternatively, the functionality of T-R_D, wherein T and R_D are as defined above, can be similarly introduced to compounds of Formula (47) to give compounds of Formula (XIX-1).



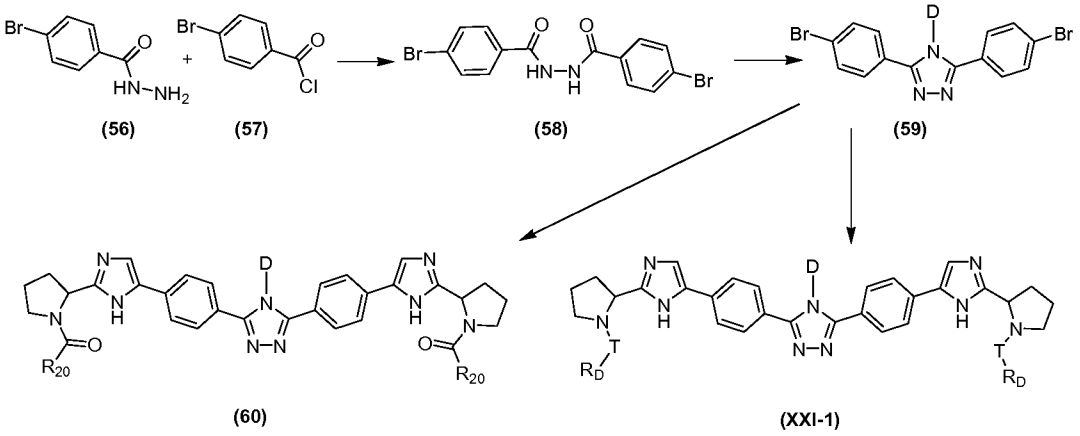
Scheme XIX

Certain 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. Similarly, the functionality of T-R_D, wherein T and R_D are as defined above, can be introduced to compounds of Formula (54) to give compounds of Formula (XX-1).



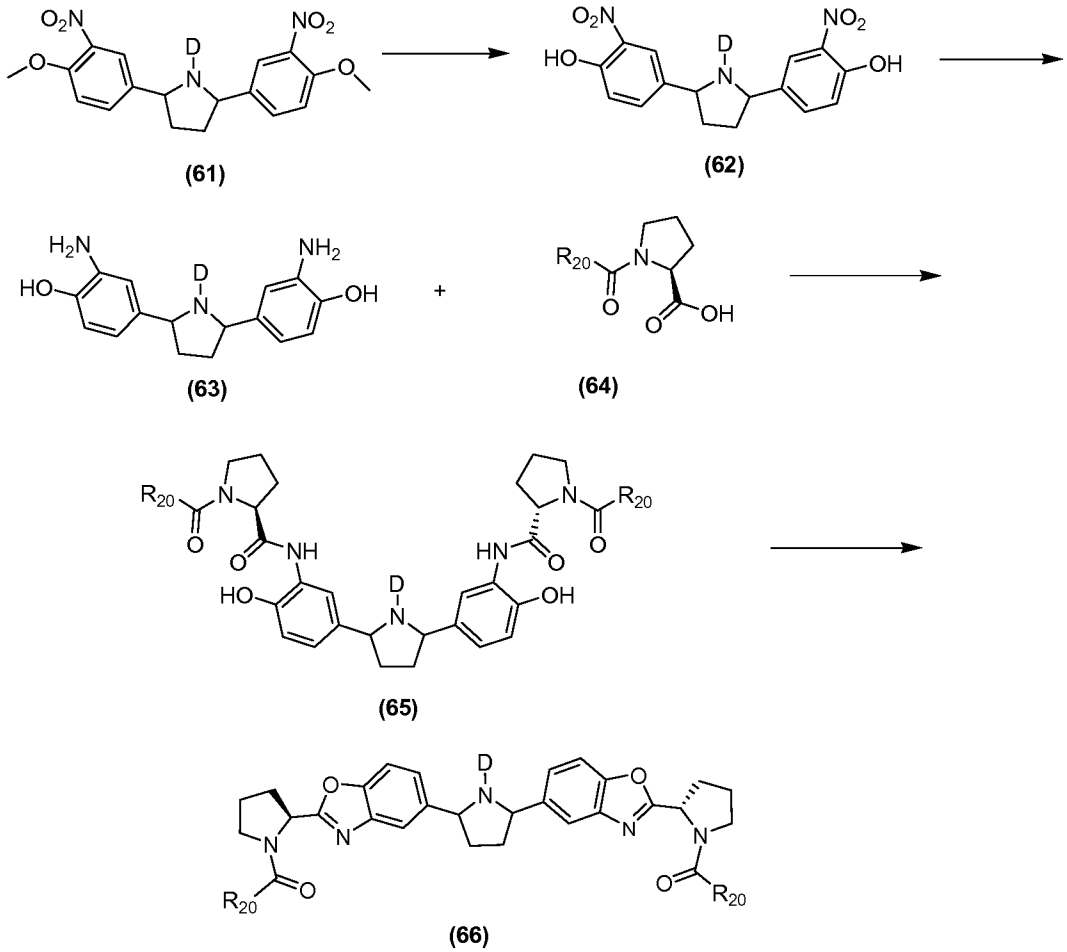
Scheme XX

Certain 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. Similarly, the functionality of T-R_D, wherein T and R_D are as defined above, can be introduced to compounds of Formula (59) to give compounds of Formula (XXI-1).



Scheme XXI

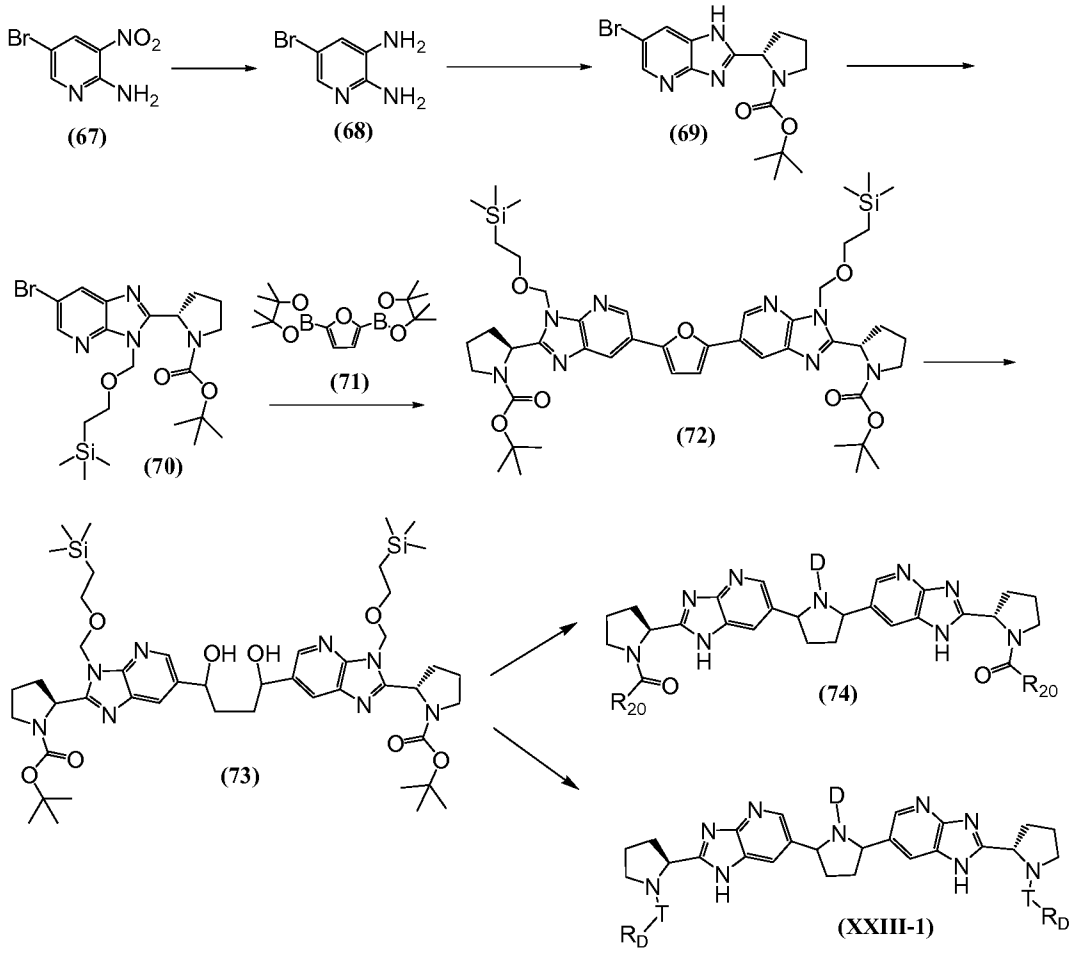
Certain compounds of the invention of general formula (66), where R_{20} is $-L_S'-M'-L_S''-R_D$ and D are as described above, can be prepared according to the methods of Scheme XXII. Compounds of general formula (61) can be reacted with borontribromide in dichloromethane at 0 °C to give compounds (62), 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

Certain 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 4 N HCl in 1,4-dioxane and then coupling with $R_{20}CO_2H$ using peptide coupling procedures

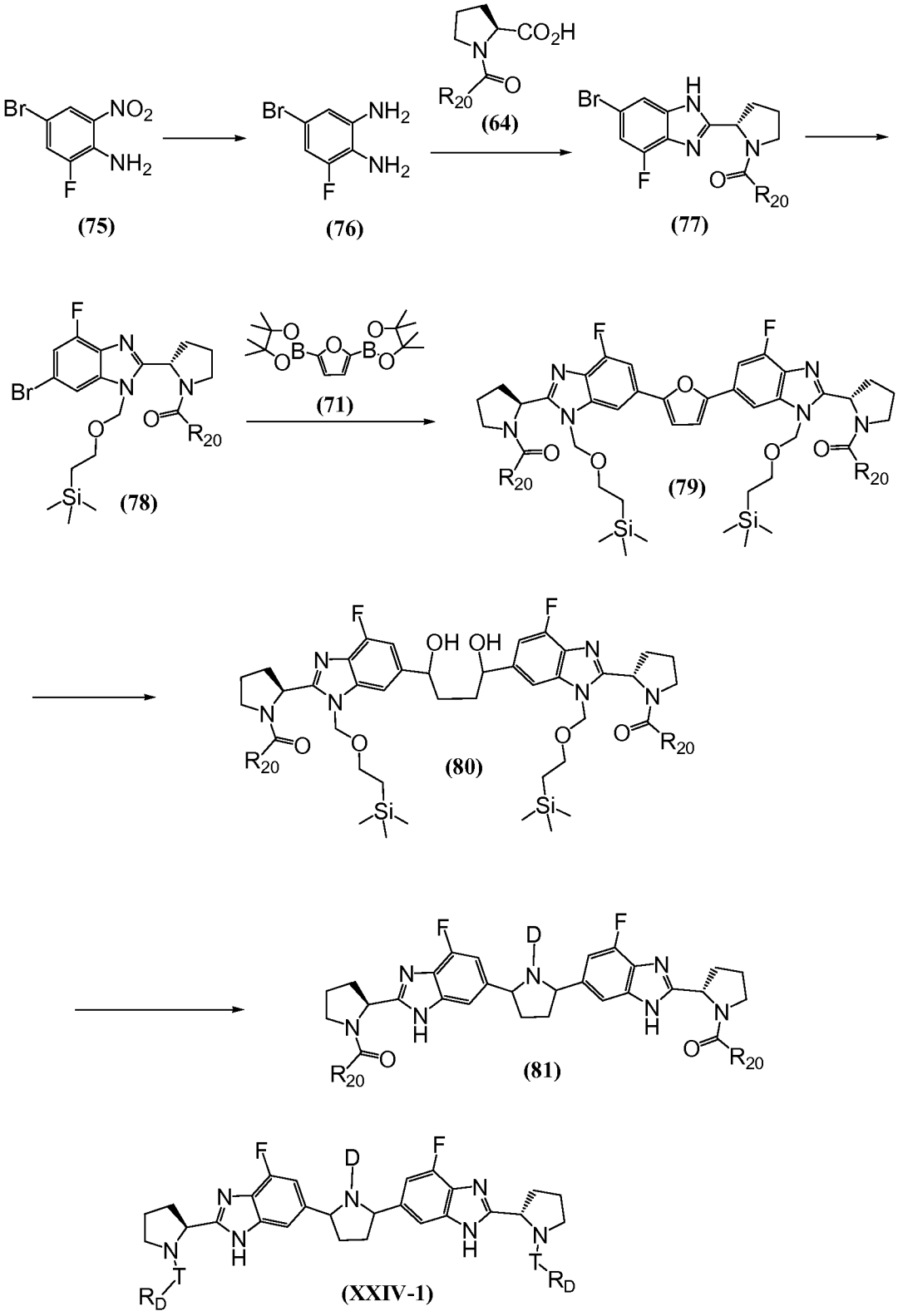
described above. Similarly, the functionality of T-R_D, wherein T and R_D are as defined above, can be introduced to compounds of Formula (73) to give compounds of Formula (XXIII-1).



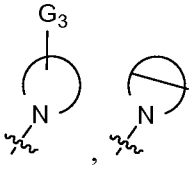
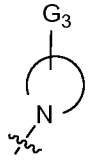
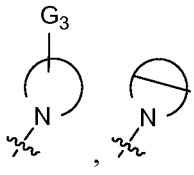
Scheme XXIII

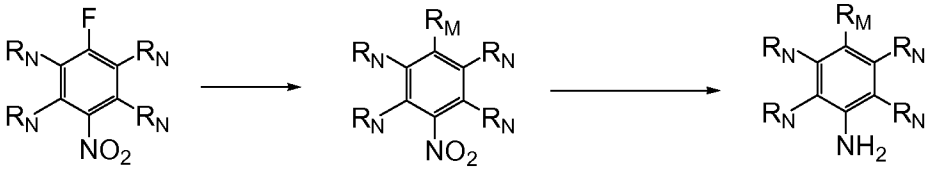
Certain compounds of the invention of general formula (81), where R_{20} is $-L_S'-M'-L_S''-R_D$ and D is as described above, can be prepared according to the methods of Scheme XXIV. Compound (75) can be converted to (76) using $SnCl_2$ in ethanol. Additionally, the phenyl ring of compound (75) can be substituted with X_{13} at any position substituted with hydrogen or fluorine, wherein X_{13} is H, alkyl, haloalkyl, alkoxy, or haloalkoxy, and those compounds carried through the subsequent sequence. 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). For convenient illustration, the SEM protecting groups on the benzimidazoles are shown attached to particular nitrogens of the benzimidazole. The actual substitution positions of the SEM groups may be at either nitrogen (i.e., (78) may be a mixture of regioisomers). In subsequent compounds (79) through (80), the positional isomerism of the SEM group results in mixtures of SEM regioisomers that may or may not be

separable. In practice the SEM regioisomers can be carried through as mixtures. Compound (78) 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 or chiral reduction conditions with (*S*) or (*R*) α,α-diphenyl-2-pyrrolidinemethanol, diethylaniline borane and trimethylborane. 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 4 N HCl in 1,4-dioxane. Similarly, the functionality of T-R_D, wherein T and R_D are as defined above, can be introduced to compounds of Formula (77) to give compounds of Formula (XXIV-1) at the end of the synthetic sequence.



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., wherein G_3 is defined above,  is a nitrogen containing heterocycle substituted with G_3, and  is a nitrogen containing bridged, bicyclic heterocycle), 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.

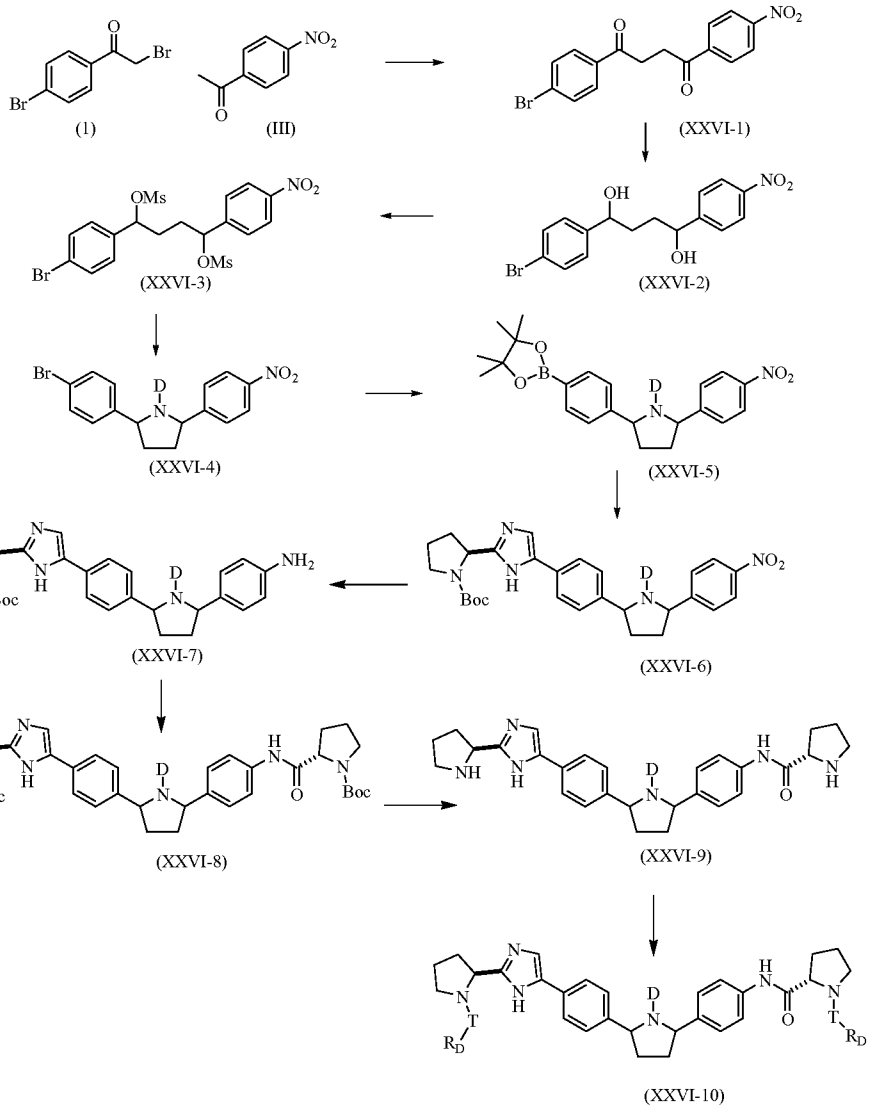


(82) **(83)** **(84)**

Scheme XXV

Certain compounds of the present invention (XXVI-10) can be prepared as shown generally in Scheme XXVI, where D, T, and R_D are as described above. Reaction of compounds (1) with compounds (III), using the conditions described generally in Scheme II for the preparation of compounds (IV), can provide diketone compounds (XXVI-1). Compounds (XXVI-1) can be converted to compounds (XXVI-2) using the general conditions of Scheme II for the conversion of (IV) to (V). Compounds (XXVI-2) can be converted to compounds (XXVI-3) using the general

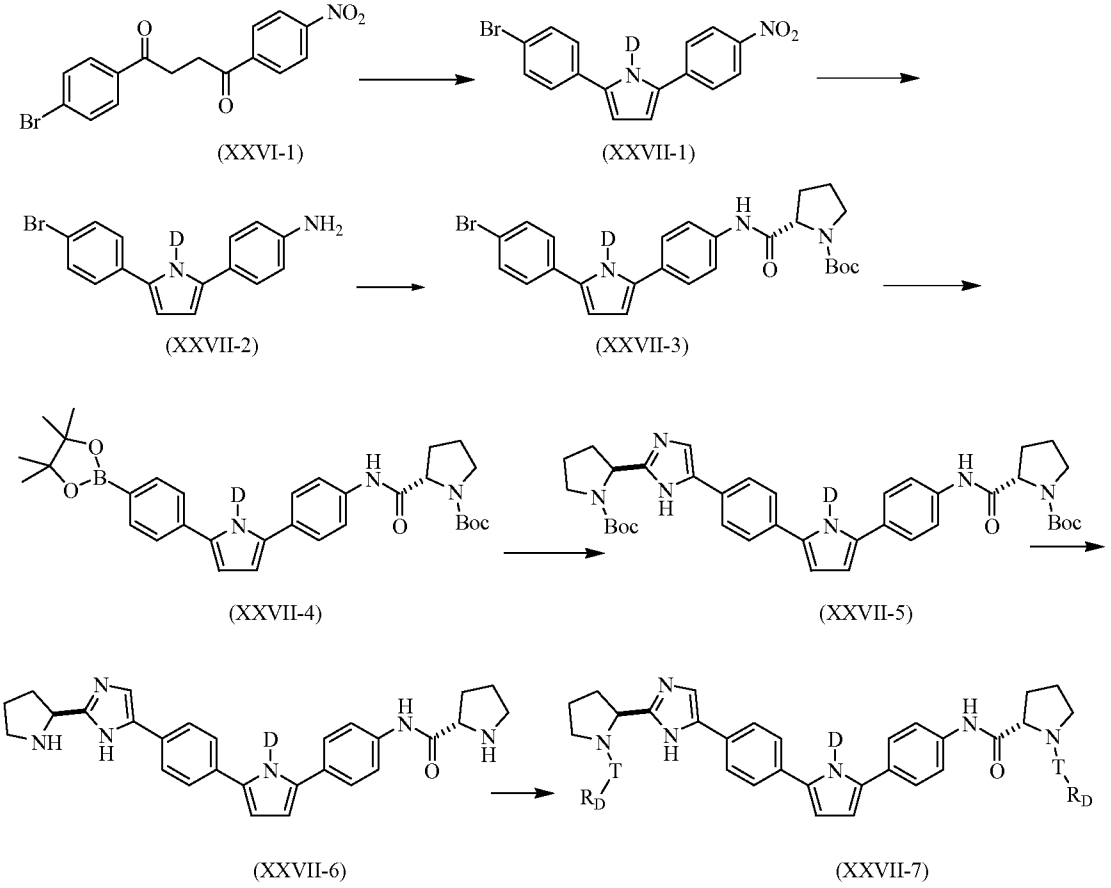
conditions of Scheme II for the conversion of (V) to (VI). Compounds (XXVI-3) can be converted to compounds (XXVI-4) using the general conditions of Scheme II for the conversion of (VI) to (VII). Compounds of formula (XXVI-4) can be converted to compounds (XXVI-5) using the general conditions of Scheme VII for the conversion of (II) to (III). Compounds (XXVI-5) can be converted to compounds (XXVI-6) using the general conditions of Scheme VII for the conversion of (III) to (IV). Compounds (XXVI-6) can be converted to compounds (XXVI-7) using the general conditions of Scheme II for the conversion of (VII) to (VIII). For example, compounds (XXVI-6) (1 equivalent) can be reduced with hydrogen gas (1 atm) in the presence of PtO_2 (about 0.2 equivalents) in a solvent such as ethanol:THF (1:1). Compounds (XXVI-7) can be converted to compounds (XXVI-8) using the methods described generally in Scheme II for conversion of (VIII) to (IX). For example, reaction of (XXVI-7) (1 equivalent) with 1-(*tert*-butoxycarbonyl)pyrrolidine-2-carboxylic acid (1.5 to 3 equivalents) and HATU (about 1.6 equivalents) in the presence of diisopropylethylamine (3 equivalents) in DMSO at about room temperature can provide the compounds (XXVI-8). Compounds (XXVI-8) can be converted to compounds (XXVI-9) using the methods described generally in Scheme II for conversion of (IX) to (X). For example, reaction of (XXVI-8) (1 equivalent) with HCl in dioxane at about room temperature can provide the compounds (XXVI-9). Compounds (XXVI-9) can be converted to compounds (XXVI-10) by reaction with an appropriate acid using the methods described generally in Scheme II for the conversion of (X) to (XI). For example, reaction of (XXVI-9) (1 equivalent) with 2-(methoxycarbonylamino)-3-methylbutanoic acid (about 2 to 3 equivalents), HATU (about 2.5 to 3.5 equivalents), and diisopropylethylamine (about 10 equivalents) in a solvent such as DMSO can provide the products (XXVI-10).



Scheme XXVI

Certain compounds of the present invention (XXVII-7) can be prepared as shown generally in Scheme XXVII, where D, T, and R_D are as described above. Compounds (XXVI-1) can be converted to compounds (XXVII-1) using the general conditions of Scheme XII for the conversion of (3) to (11). Compounds (XXVII-1) can be converted to compounds (XXVII-2) by reduction using conditions described generally above in Scheme II. For example (XXVII-1) (1 equivalent) can be reduced with iron powder (about 6 equivalents) and ammonium chloride (about 3 equivalents) in ethanol:THF:water (1:1:0.25) with heating up to the reflux temperature to provide (XXVII-2). Compounds (XXVII-2) can be converted to compounds (XXVII-3) using the conditions described above for conversion of VIII to IX in Scheme II, (12) to (13) in Scheme XII, or (XXVI-7) to (XXVI-8) in Scheme XXVI. Compounds (XXVII-3) can be converted sequentially to compounds (XXVII-4) and (XXVII-5) using the methods and conditions described generally in Scheme VII for the

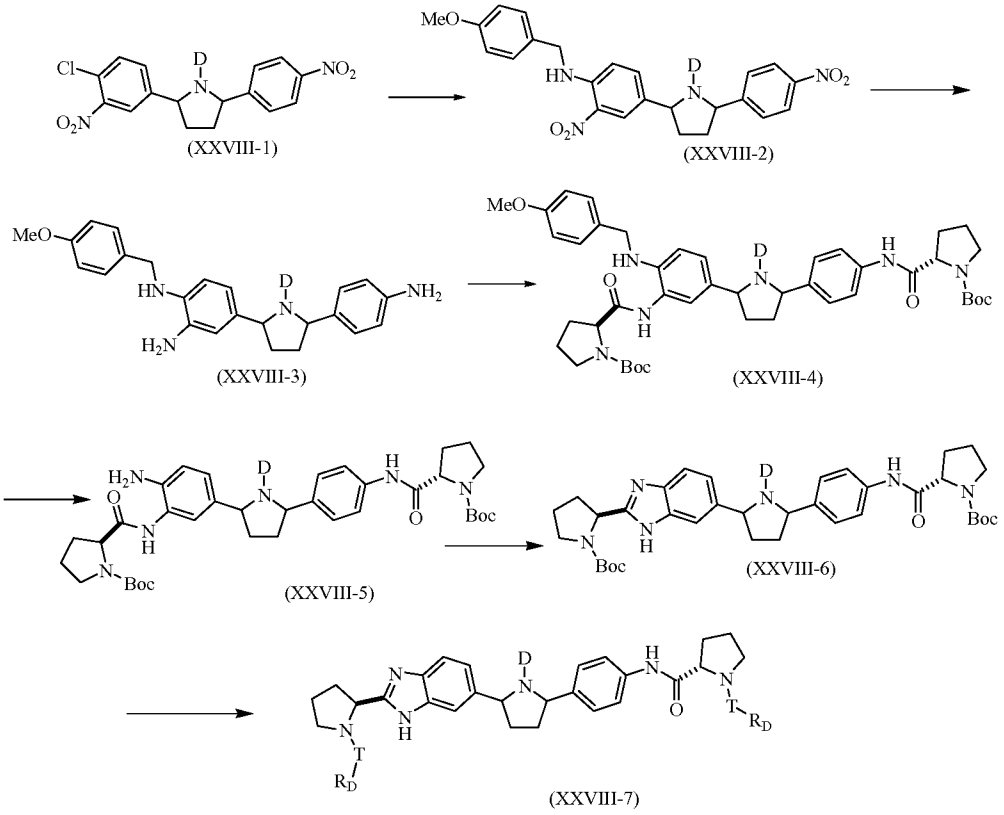
conversion of (II) to (III) to (V). Compounds (XXVII-5) can be converted sequentially to compounds (XXVII-6) and (XXVII-7) using the methods and conditions described generally above, for example using the methods to convert (IX) to (X) to (XI) in Scheme II.



Scheme XXVII

Certain compounds of the invention of general formula (XXVIII-7), where D, T, and R_D are as described above, can be prepared according to the sequence of Scheme XXVIII. Compounds (XXVIII-1) can be prepared from 2-bromo-1-(4-nitrophenyl)ethanone, 1-(4-chloro-3-nitrophenyl)ethanone, and an amine D–NH_2 according to the methods described above to prepare compounds (VII) in Scheme II, (XXVI-4) in Scheme XXVI,, and (VII) in Scheme IV. Compounds (XXVIII-1) (1 equivalent) can be converted to compounds (XXVIII-2) by reaction with neat 4-methoxybenzylamine (about 4-6 equivalents) with heating to around 140-150 °C. Compounds (XXVIII-2) can be converted to compounds (XXVIII-3) by reduction according to the conditions described generally in Scheme II to prepare compounds (VIII). For example, reaction of (XXVIII-2) (1 equivalent) with PtO_2 (about 0.4-0.5 equivalents) in a solvent such as ethanol:THF (1:1) under a hydrogen atmosphere (1-4 atm) can provide compounds (XXVIII-3). Compounds (XXVIII-3) can be converted to compounds (XXVIII-4) according to the conditions described generally in Scheme II to

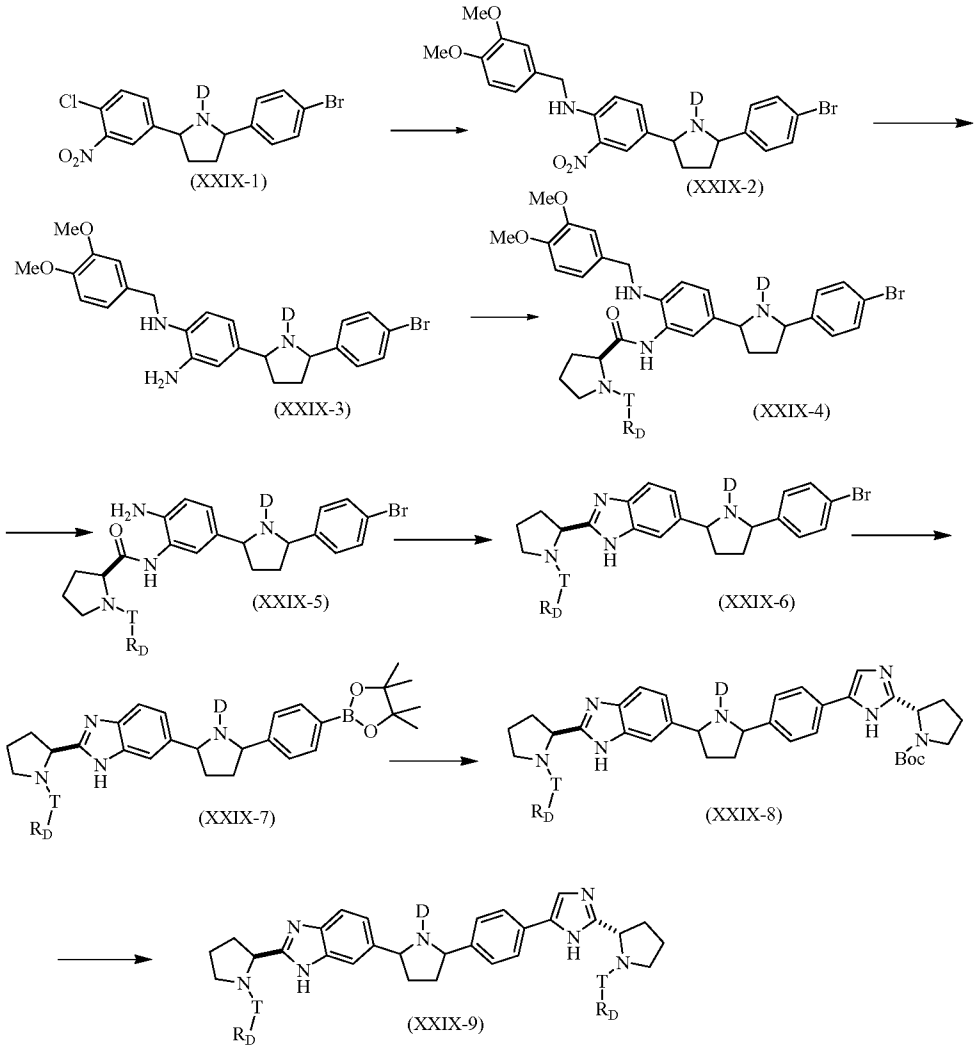
prepare compounds (IX). For example, reaction of (XXVIII-3) (1 equivalent) with 1-(*tert*-butoxycarbonyl)pyrrolidine-2-carboxylic acid (about 2-3 equivalents), HATU (about 2-3 equivalents), and diisopropylethylamine (about 3 equivalents) in a solvent such as DMSO at room temperature can provide compounds (XXVIII-4). Compounds (XXVIII-4) (1 equivalent) can be converted to compounds (XXVIII-5) by reaction with DDQ (about 1.2 equivalents) in a solvent mixture of CH_2Cl_2:water (20:1) at room temperature. Compounds (XXVIII-5) can be converted to compounds (XXVIII-6) according to the general methods described in Scheme IV to prepare compounds (XI) (e.g., heating in acetic acid to around 60-70 °C). Compounds (XXVIII-6) can further be converted to compounds (XXVIII-7) by using the standard deprotection and coupling methods referred to in Scheme IV to prepare compounds (XIII) or (XIV).



Scheme XXVIII

Certain compounds of the invention (XXIX-9) where D, T, and R_D are as described above, can be prepared according to the sequence of Scheme XXIX. Compounds (XXIX-1) can be prepared from 2-bromo-1-(4-bromophenyl)ethanone, 1-(4-chloro-3-nitrophenyl)ethanone, and an amine D–NH_2 according to the methods described above to prepare compounds (VII) in Scheme II, (XXVI-4) in Scheme XXVI, and (VII) in Scheme IV. Compounds (XXIX-1) (1 equivalent) can be converted to compounds (XXIX-2) by reaction with neat 3,4-dimethoxybenzylamine (about 10 equivalents) with heating up to around 140-150 °C. Compounds (XXIX-2) can be converted to compounds (XXIX-3)

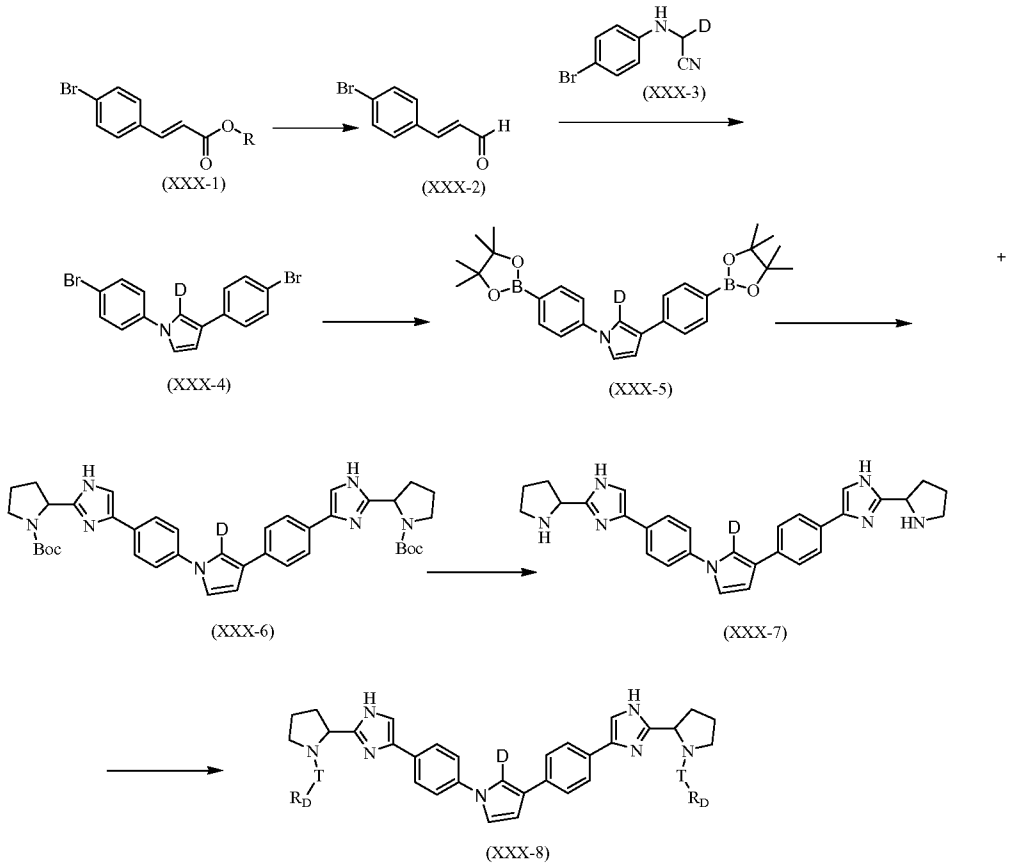
by reduction according to the conditions described generally in Scheme II to prepare compounds (VIII). For example, reaction of (XXIX-2) (1 equivalent) with PtO_2 (about 0.1 equivalent) in a solvent such as ethanol:THF:EtOAc (1:1) under a hydrogen atmosphere (e.g., 1 atm) can provide compounds (XXIX-3). Compounds (XXIX-3) can be converted to compounds (XXIX-4) according to the conditions described generally in Scheme II to prepare compounds (IX). For example, reaction of (XXIX-3) (1 equivalent) with a substituted proline like (*S*)-1-((*S*)-2-(methoxycarbonylamino)-3-methylbutanoyl)pyrrolidine-2-carboxylic acid (about 1.2-1.5 equivalents), HOBt (about 1.2-1.5 equivalents), EDAC (about 1.2-1.5 equivalents), and *N*-methylmorpholine (about 5-6 equivalents) in a solvent such as DMF at room temperature can provide compounds (XXIX-4). Compounds (XXIX-4) can be deprotected to compounds (XXIX-5) by reaction with excess TFA in solvents such as methylene chloride at about room temperature. Compounds (XXIX-5) can be converted to compounds (XXIX-6) according to the general methods described in Scheme IV to prepare compounds (XI) (e.g., heating in acetic acid to around 60-80 °C). Compounds (XXIX-6) can be converted to compounds (XXIX-7) according to the general conditions of Scheme VII to prepare compounds (III). For example, reaction of (XXIX-6) (1 equivalent) with $PdCl_2$(dppf) (about 0.1 equivalent), potassium acetate (about 3-5 equivalents), and bis(pinacolato)diboron (about 3 equivalents) in a solvent such as toluene with heating to 80-100 °C can provide compounds (XXIX-7). Compounds (XXIX-7) can be converted to compounds (XXIX-8) according to the general conditions of Scheme VII to prepare compounds (V). For example, reaction of compounds (XXIX-7) (1 equivalent) with Intermediate 1D (about 2 equivalents), 1M sodium carbonate (about 3 equivalents), and $PdCl_2$(dppf) (about 0.1 equivalent) in a solvent such as toluene at around 80-100 °C can provide compounds (XXIX-8). Compounds (XXIX-8) can further be converted to compounds (XXIX-9) by using the standard deprotection (e.g., HCl/dioxane) and coupling methods (e.g., carboxylic acid, HOBt, EDAC, and *N*-methylmorpholine) referred to in Scheme IV to prepare compounds (XIV).



Scheme XXIX

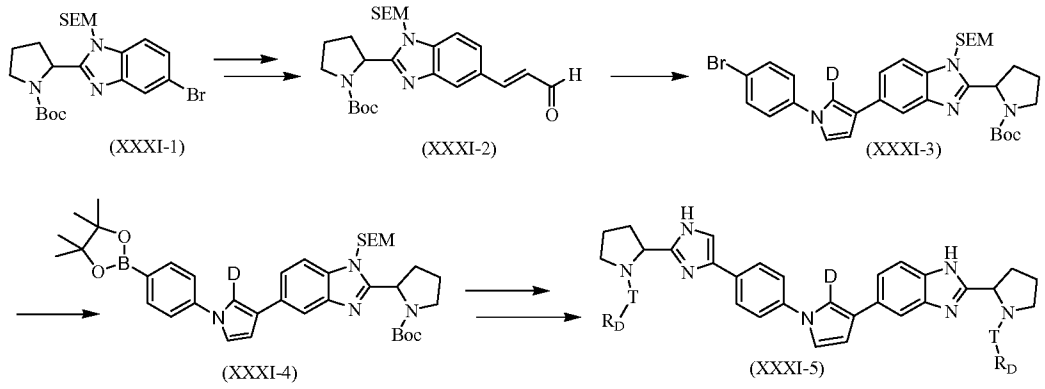
Certain compounds of the present invention (XXX-8) can be prepared as shown in Scheme XXX. An ester (XXX-1) can be reacted with a suitable reducing agent such as DIBAL-H, in a solvent such as THF, dichloromethane, or diethyl ether, to the corresponding alcohol then oxidized to the aldehyde (XXX-2) by employing a suitable oxidizing agent such as PDC in a solvent such as dichloromethane, THF or diethyl ether. A pyrrole of formula (XXX-4) can be prepared by reacting (XXX-3) (available from an aniline, an aldehyde and KCN using the Strecker reaction) together with aldehyde (XXX-2) with a base such as potassium hydroxide in a solvent such as ethanol (*Synlett*, **2003**, pp1427-1430). The bromine atoms in the pyrrole compounds (XXX-4) can be converted to a bis-borane compound (XXX-5) by utilization of palladium catalysis as described above in Scheme VII. The pyrrole compounds (XXX-5) can be reacted with bromoimidazoles like Intermediate 1D using Suzuki reaction conditions to give the phenylimidazole (XXX-6). A variety of reaction conditions are well known to those of skill in the art to be effective in mediating the Suzuki reaction.

In particular, the reaction to produce (XXX-6) can be performed with $Pd(dppf)Cl_2$ catalyst and potassium carbonate in a mixture of toluene and water and with heating to about 100 °C. Removal of the Boc protecting groups to give (XXX-7) can be accomplished by treatment with an acid, such as TFA, HCl, or formic acid. Certain compounds of the present invention (XXX-8), wherein T, R_D, and D are as described above, may be prepared by coupling of (XXX-7) with an acid of choice using the standard peptide coupling reagents and conditions described above.



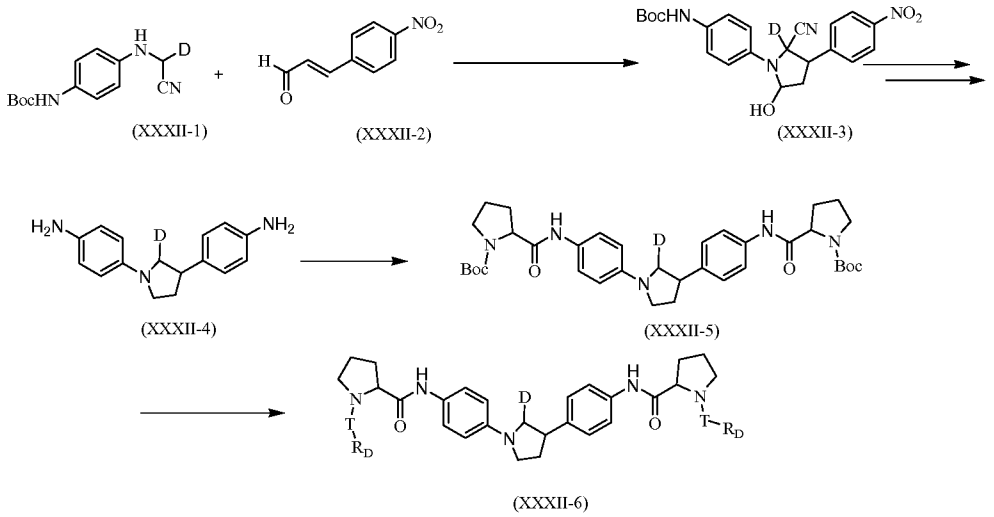
Scheme XXX

The present invention also contemplate Schemes XXXI-XXXIII to make a compound of the invention. For instance, compounds of the invention (XXXI-5) may be prepared using the sequence of steps outlined generally in Scheme XXXI. This sequence parallels that of Scheme XXX. A compound (XXXI-1) may be converted to a compound (XXXI-2) by sequential Heck reaction with ethylacrylate followed by reduction to an aldehyde (XXXI-2). An aldehyde like (XXXI-2) may be reacted with a compound (XXX-3) analogously to the conditions of Scheme XXX to provide compounds (XXXI-3). Compounds (XXXI-3) in turn may be converted to boronate compounds (XXXI-4) using the condition described above generally in Scheme VII. Compounds (XXXI-4) may be converted to compounds (XXXI-5) over several steps including Suzuki reaction, deprotection and coupling as described generally in the foregoing Schemes.



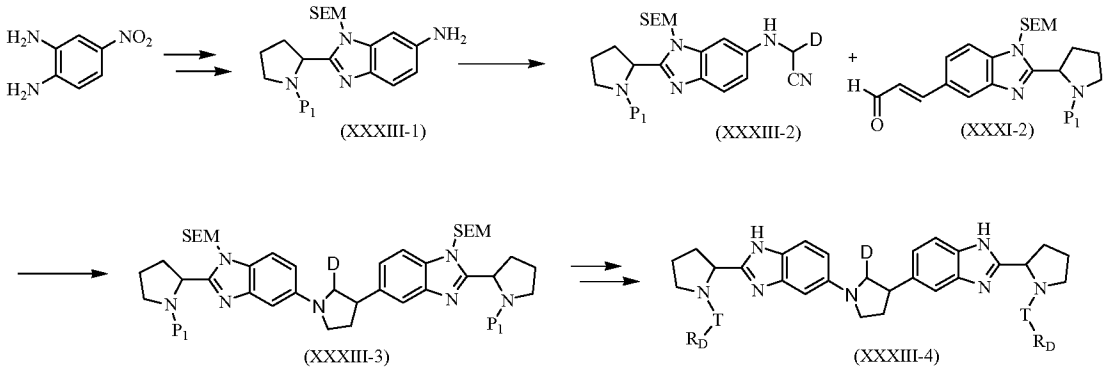
Scheme XXXI

As described in Meyer et al. *Synthesis*, **2005**, pp. 945-956 and Meyer et al *Synlett*, **2003**, pp1427-1430, substituted α-aminonitriles can be reacted with α,β-unsaturated carbonyl compounds to provide substituted hydroxy-cyano pyrrolidines. In analogous fashion, a compound (XXXII-1) may be reacted with an α,β-unsaturated aldehyde (XXXII-2) to give a pyrrolidine (XXXII-3). The hydroxy and cyano groups of compounds such as (XXXII-3) may be reduced off using reagents such as $NaBH_3CN$ or $NaBH_3CN$ with $FeSO_4$ as described in *Synthesis*, **2005**, pp. 945-956. The nitro group of compounds such as (XXXII-3) may be reduced using standard conditions such as catalytic hydrogenation or reduction with iron powder and ammonium chloride. Typical nitro reduction conditions are described elsewhere herein. The Boc group of compounds such as (XXXII-3) may be removed using standard conditions such as with TFA/CH_2Cl_2 or HCl in dioxane. Compounds such as (XXXII-4) may be reacted with an appropriate *N*-protected proline acid under standard conditions as described elsewhere herein to give compounds (XXXII-5). Compounds such as (XXXII-5) may be deprotected and coupled with an acid of choice as described herein to give compounds (XXXII-6) wherein T, R_D, and D are as described herein.



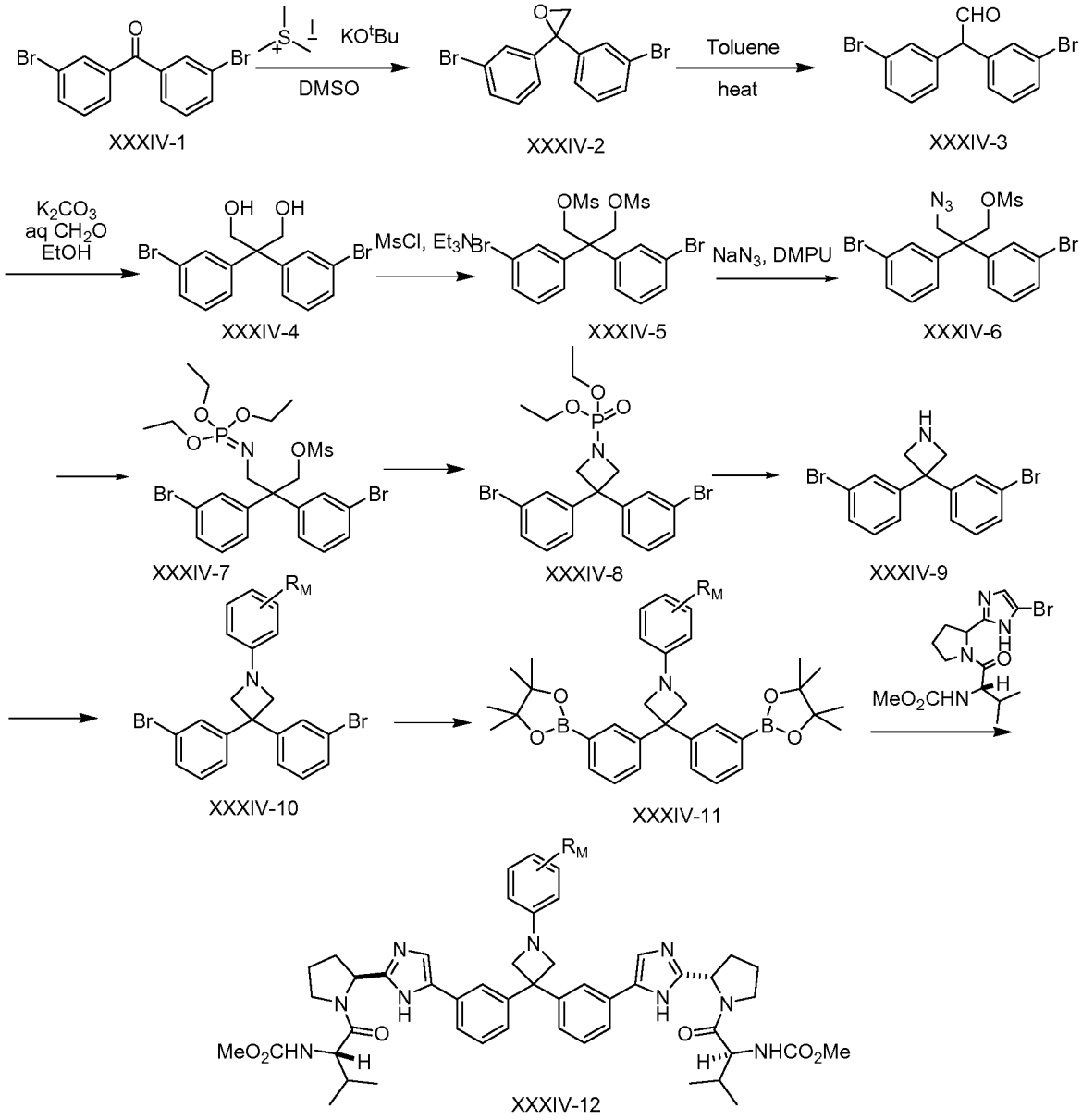
Scheme XXXII

Further compounds of the invention may be prepared as generally outlined in Scheme XXXIII. Compounds such as (XXXIII-1) may be prepared from 4-nitro-o-phenylenediamine by acylation with a protected proline acid (see *Tetrahedron* **2003**, pp 2701-2712), cyclization (see *Tet. Lett.* **2003**, 5807-5810), SEM protection, and nitro reduction. Compounds such as (XXXIII-1) may be converted to the Strecker product (XXXIII-2) by reaction with an aldehyde D–CHO and KCN in analogy with the process referred to in Scheme XXX. Compounds such as (XXXIII-2) may be condensed with compounds such as (XXXI-2) followed by reduction to give compounds such as (XXXIII-3) (see for example Meyer et al. *Synthesis*, **2005**, pp. 945-956 and Meyer et al *Synlett*, **2003**, pp1427-1430). Compounds such as (XXXIII-3) may be deprotected using standard conditions for removal of Boc and SEM groups (see General Procedure 23) and the resultant amino compound reacted with an appropriate acid under conventional amide bond forming conditions to give compounds (XXXIII-4) wherein T, R_D, and D are as described herein.



Scheme XXXIII

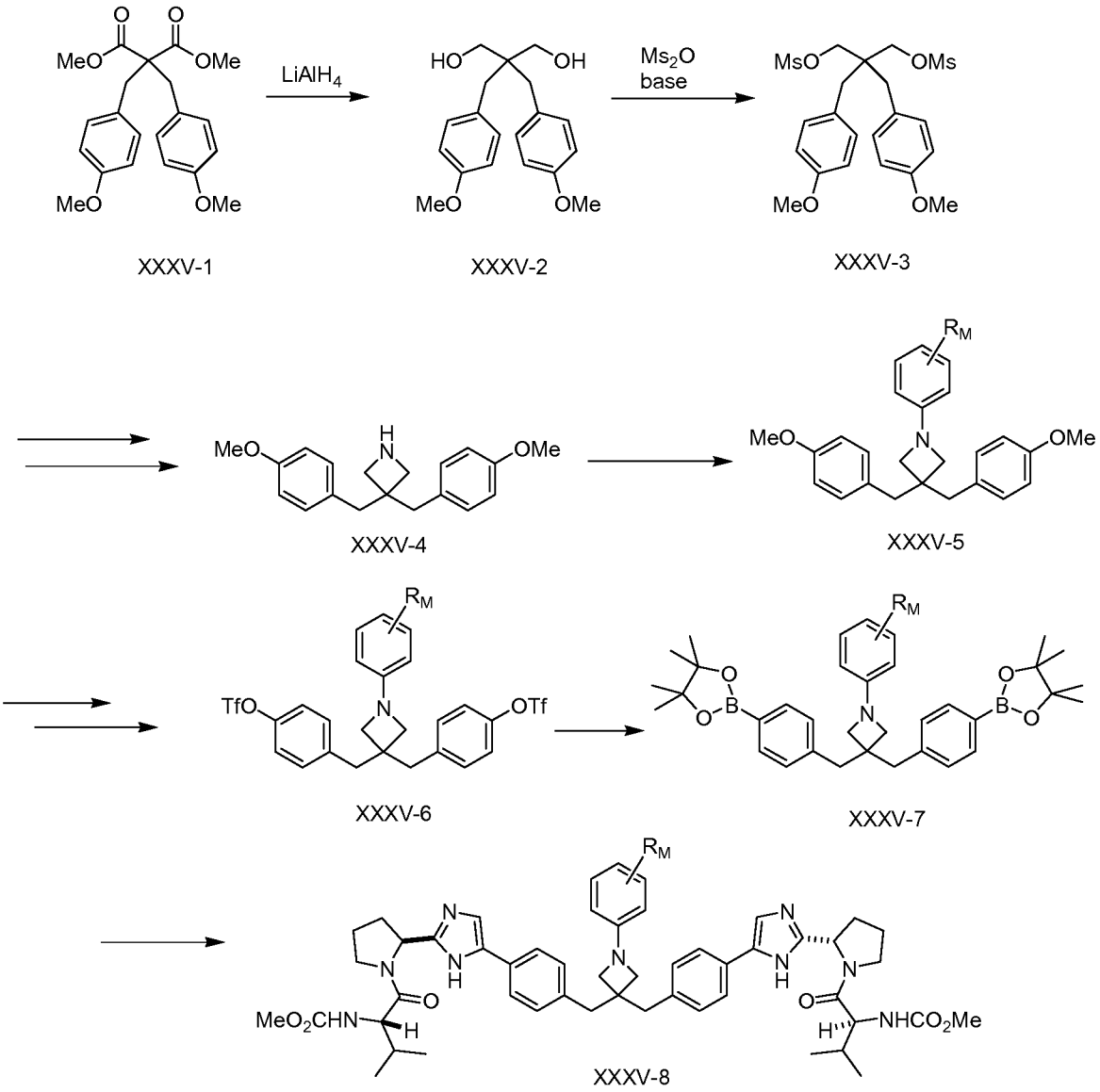
Certains compounds of the invention may also be prepared using the methods shown generally in Scheme XXXIV. The ketone XXXIV-1 (Reference: US20090076076; p19, [0146]) can be homologated in two steps to the aldehyde XXXIV-3. In the first step, the ketone can be reacted with dimethylsulfonium methylide in dimethylsulfoxide to produce the epoxide XXXIV-2. The epoxide can be rearranged to the aldehyde by treatment with an acid such p-toluenesulfonic acid with heating in toluene at temperatures between around 80-110 °C (References: J. Am. Chem. Soc. (1965) 1353, 1358; J. Org. Chem. (1972) 4075, 4076, 4077; Bioorg. Med. Chem. Lett. (2009) 5684, 5686). The aldehyde XXXIV-3 can be converted to the diol XXXIV-4 with potassium carbonate and formaldehyde in ethanol as described generally in J. Am. Chem. Soc, 1951, 73, p5171 and US5095153, Example 3a. The diol can be converted to the bismesylate XXXIV-5 by reaction with excess methanesulfonyl chloride and triethylamine in dichloromethane at 0 °C to room temperature. The bismesylate can be converted to the azide XXXIV-6 by reaction with sodium azide (about 1 equivalent) in DMPU and heating up to around 110 °C. The azide can be converted to the phosphorimidate XXXIV-7 by reaction with freshly distilled triethylphosphite (about 1 equivalent) in anhydrous toluene/tetrahydrofuran at room temperature. The phosphorimidate can be converted to the azetidine-phosphonate XXXIV-8 by heating in o-xylene up to around 150 °C. The azetidine-phosphonate can be converted to the azetidine XXXIV-9 by reaction with trifluoroacetic acid in dichloromethane at room temperature. The azetidine can be reacted with an appropriate aryl halide (e.g., iodide) using the Buchwald reaction to generate an N-arylazetidine XXXIV-10. Appropriate conditions include reaction with an aryliodide (about 2 equivalent), $Pd_2(dba)_3$ (about 0.025 equivalent), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (Xantphos; about 0.1 equivalents) and sodium tert-butoxide (about 1.2 equivalent) with heating in a solvent such as dioxane to 80-100 °C, optionally with microwave irradiation. The bisbromide may be converted to the bisboronate XXXIV-11 by reaction with bis(pinacolato)diborane, potassium acetate, and $PdCl_2(dppf)$ in a solvent such as DME, dioxane, or DMSO with heating up to around 85 °C. The bisboronate can be converted to compounds of the invention XXXIV-12 by reaction with an appropriate halide (i.e. Suzuki reaction) such as methyl (S)-1-((S)-2-(5-bromo-1H-imidazol-2-yl)pyrrolidin-1-yl)-3-methyl-1-oxobutan-2ylcarbamate.



Scheme XXXIV

Certain compounds of the invention may also be prepared using the methods shown generally in Scheme XXXV. Compounds such as XXXV-1 can be prepared using known methods by alkylation of a malonate ester with a benzyl halide. Compound XXXV-1 can be converted to compound XXXV-2 by reduction with lithium aluminum hydride. Compound XXXV-2 can be converted to compound XXXV-3 by reaction with Ms_2O and a base such as diisopropylethylamine. Compound XXXV-3 may be converted to compound XXXV-4 using methods analogs to those to convert XXXIV-5 to XXXIV-9 (see Scheme XXXIV). Similarly compound XXXV-4 may be converted to compound XXXV-5 using a Buchwald reaction analogous to that of Scheme XXXIV.

Compounds XXXV-5, in turn, may be converted to XXXV-6 by demethylation (e.g. with BBr_3) and triflate formation with Tf_2O. Compounds XXXV-6 may be converted to compounds XXXV-7 by analogy with the conversion of XXXIV-10 to XXXIV-11. Finally, compounds XXXV-7 may be converted to compounds XXXV-8 using the Suzuki coupling of Scheme XXXIV.



In the foregoing Schemes (Schemes I-XXXV) , 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 regiochemsitry (e.g., meta) would provide a final product with a different regiochemistry. For example, replacement of a para-

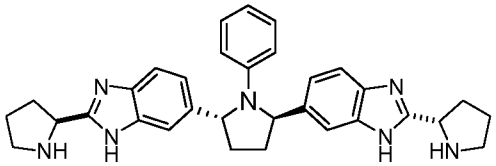
substituted starting material or intermediate in the foregoing Schemes with a meta substituted starting material or intermediate would lead to a meta-substituted product.

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 Intermediates, General Procedures, and Examples, as appreciated by those skilled in the art. It should be understood that the above-described embodiments and schemes and the following Intermediates, General Procedures, and 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 ACD Name version 12 (ACD Name v12). Other compounds were named using ChemDraw version 9.0 (v9), unless otherwise indicated as being named using ACD Name v12. Both naming programs may provide a chemical name that depends on the tautomeric structure chosen for naming. Structures may be shown or named as any chemically distinct tautomer.

For example, the tautomeric structure:

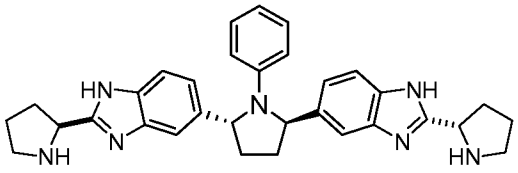


is given the following names:

(*S*)-6,6'-((2*R*,5*R*)-1-phenylpyrrolidine-2,5-diyl)bis(2-((*S*)-pyrrolidin-2-yl)-1*H*-benzo[*d*]imidazole) (Chemdraw v9);

6,6'-[(2*R*,5*R*)-1-phenylpyrrolidine-2,5-diyl]bis{2-[(2*S*)-pyrrolidin-2-yl]-1*H*-benzimidazole} (ACD Name v12).

The tautomeric structure:

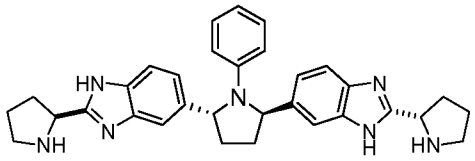


is given the following names:

(*S*)-5,5'-((2*R*,5*R*)-1-phenylpyrrolidine-2,5-diyl)bis(2-((*S*)-pyrrolidin-2-yl)-1*H*-benzo[*d*]imidazole) (Chemdraw v9);

5,5'-[(2*R*,5*R*)-1-phenylpyrrolidine-2,5-diyl]bis{2-[(2*S*)-pyrrolidin-2-yl]-1*H*-benzimidazole} (ACD Name v12).

The tautomeric structure:



is given the following names:

(*S*)-5,5'-((2*R*,5*R*)-1-phenylpyrrolidine-2,5-diyl)bis(2-((*S*)-pyrrolidin-2-yl)-1*H*-benzo[*d*]imidazole) (Chemdraw v9);

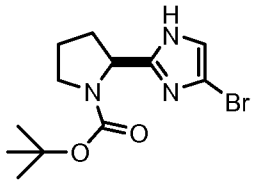
5-[(2*R*,5*R*)-1-phenyl-5-{2-[(2*S*)-pyrrolidin-2-yl]-1*H*-benzimidazol-6-yl}pyrrolidin-2-yl]-2-[(2*S*)-pyrrolidin-2-yl]-1*H*-benzimidazole (ACD Name v12).

Certain compounds in the Examples below can be purified using reverse-phase HPLC. Purification can be conducted using either a C18 or C8 reverse-phase column. Compounds can be 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 can be 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). Compounds can also be purified by prep-TLC.

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.

Synthesis of Intermediates



Intermediate 1

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

Intermediate 1A

(*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 was 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 a 20-minute 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 a 20-minute period, and then the reaction mixture was stirred at -78 °C for 30 minutes. Triethylamine (32.6 mL, 234 mmol) was added dropwise via syringe over a 5-minute period and the thick white mixture was stirred in an ice-water bath for 30 minutes. The reaction was quenched with 10% (w/v) aq. citric acid (30 mL). The mixture was partitioned in a separatory funnel between Et_2O (550 mL) and 10% (w/v) aq citric acid. The layers were separated, and the organic phase was washed with water and brine. The organic phase was dried over anhydrous Na_2SO_4, filtered, and concentrated to afford a yellow oil (9.4 g), which was used directly in the next reaction.

Intermediate 1B

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

The product from Intermediate 1A (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 minutes. The reaction was stirred at room temperature overnight. The reaction was concentrated under reduced pressure, diluted with 50 mL of water, and then extracted with ethyl acetate. The organic layer was washed with brine, dried (Na_2SO_4) and concentrated to a tan solid. The 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. ^{1}HNMR (400 MHz, DMSO-d_6) δ ppm 1.14/1.40 (s, 9H), 1.81-2.12 (m, 4H), 3.32-3.33 (m, 1H), 3.35-3.50 (m, 1H), 4.72-4.81 (m, 1H), 6.84 (s, 1 H), 11.68 (s, 1 H).

Intermediate 1C

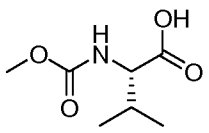
(*S*)-*tert*-butyl 2-(4,5-dibromo-1*H*-imidazol-2-yl)pyrrolidine-1-carboxylate

N-Bromosuccinimide (108 mmol) was added to a cold (0 °C) solution of the product from Intermediate 1B (12.05 g, 50.8 mmol) in dichloromethane (200 mL). The mixture was stirred in ice bath for 2 hours and then concentrated, dissolved in ethyl acetate (250 mL), washed with water (3×150 mL) and brine (1×100 mL), dried ($MgSO_4$), and concentrated to very dark residue. The residue was mixed with and concentrated from dichloromethane/hexanes (1:1) to get brown solid (~19 g). The solid was triturated with ether (~100 mL) and filtered to isolate a tan solid (13.23 g, 65% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.49 (s, 9 H), 1.86 - 2.17 (m, 3 H), 2.80 - 2.95 (m, 1 H), 3.30 - 3.44 (m, 2 H), 4.85 (dd, *J*=7.54, 2.55 Hz, 1 H), 10.82 (s, 1 H); MS (DCI+) *m/z* 394/396/398 $(M+H)^+$.

Intermediate 1D

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

The product from Intermediate 1C (6.25 g, 15.82 mmol) was dissolved in dioxane (200 mL) and water (200 mL) in a 1 L round bottom flask equipped with a condenser and glass stopper. A solution of sodium sulfite (22.38 g, 174 mmol) in water (200 mL) was added, and the mixture was heated at reflux for 16 hours. The reaction mixture was cooled to room temperature, and dioxane and some water were removed by rotary evaporation. The residue was extracted with dichloromethane. The combined organic phases were washed 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). The foam was dissolved in dichloromethane (2 mL), hexanes (2 mL) were added, and the resultant solution was applied to a 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). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.48 (s, 9 H), 1.83 - 2.33 (m, 3 H), 2.79 - 3.02 (m, 1 H), 3.37 (dd, *J*=7.10, 5.37 Hz, 2 H), 4.88 (dd, *J*=7.59, 2.49 Hz, 1 H), 6.92 (s, 1 H), 10.70 (br s, 1 H); MS (ESI+) *m/z* 316/318 $(M+H)^+$.

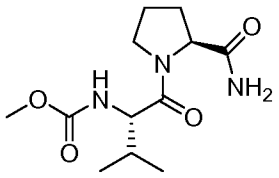


Intermediate 2

(*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 2 *N* aqueous sodium hydroxide solution (803 mL, 1606 mmol) followed by the dropwise addition of methyl chloroformate (75 mL, 973 mmol) over 1 hour which caused warming of the

solution to occur. After the addition, the mixture was heated at 60 °C for 22 hours, then cooled and extracted with dichloromethane (400 mL). The resultant aqueous layer was cooled in an ice bath, and then 12 *N* hydrochloric acid was added dropwise until the pH was 2. The resultant mixture was stirred at 0 °C for 2 hours, and then the resultant solid was collected by vacuum filtration, and dried in a vacuum oven to provide 80g (94%) of the title compound as a colorless solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 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).



Intermediate 3

methyl (*S*)-1-((*S*)-2-carbamoylpyrrolidin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamate

Intermediate 3A

(*S*)-pyrrolidine-2-carboxamide hydrochloride salt

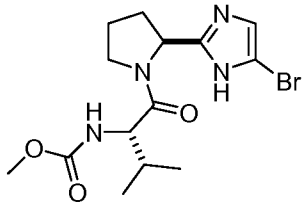
To (*S*)-*tert*-butyl 2-carbamoylpyrrolidine-1-carboxylate (29.8 g, 139 mmol) was added a solution of 4 *N* HCl in dioxane (209 mL, 836 mmol), and the resultant mixture was stirred at room temperature for 18 hours. The mixture was then concentrated and triturated with diethyl ether then vacuum filtered and dried under vacuum to provide 21.6 g (104%) of the title product as a colorless solid.

Intermediate 3B

methyl (*S*)-1-((*S*)-2-carbamoylpyrrolidin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamate

Intermediate 3A (21.6 g, 144 mmol), Intermediate 2 (29.1 g, 166 mmol), 1*H*-benzo[*d*][1,2,3]triazol-1-ol hydrate (27.6 g, 180 mmol), N^1-((ethylimino)methylene)-N^3,N^3-dimethylpropane-1,3-diamine hydrochloride (34.6 g, 180 mmol) and 4-methylmorpholine (63.5 mL, 578 mmol) were dissolved in dichloromethane (960 mL) and stirred at room temperature for 18 hours. The resultant solution was then concentrated to a residue, water was then added and the solution extracted with a 25% isopropanol in chloroform solution (2×2000 mL). The organic layer was washed with brine, and then the organic extract was 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 compound as a colorless solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 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).



Intermediate 4

methyl (*S*)-1-((*S*)-2-(5-bromo-1*H*-imidazol-2-yl)pyrrolidin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamate

Intermediate 4A

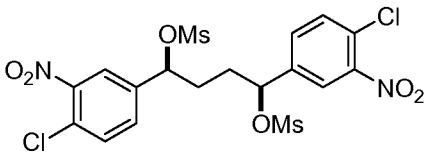
(*S*)-5-bromo-2-(pyrrolidin-2-yl)-1*H*-imidazole hydrochloride

A mixture of Intermediate 1D (5.0g, 15.8 mmol) in 4 *M* HCl/Dioxane (40 mL) was allowed to stir for one hour. The mixture was concentrated to afford 3.99 g (100%) of the title compound. MS (ESI) *m/z* 217 $(M+H)^+$.

Intermediate 4B

methyl (*S*)-1-((*S*)-2-(5-bromo-1*H*-imidazol-2-yl)pyrrolidin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamate

A mixture of Intermediate 4A (3.99g, 15.8 mmol), Intermediate 2 (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. The mixture was diluted with H_2O and extracted with EtOAc (3×300 mL). The organic was washed with H_2O and brine. The organic phase 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 $(M+H)^+$.



Intermediate 5

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

Intermediate 5A

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 hours, the mixture was then filtered and resulting solids washed with EtOAc. The organic solution was then concentrated, H_2O and 10% aq. $NaHCO_3$ were added, and the mixture was washed with EtOAc (2×300 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. The residue was dissolved in EtOAc (100 mL) and hexanes were slowly added until the mixture was cloudy. After standing for a few hours, 2-bromo-1-(4-chloro-3-nitrophenyl)ethanone (9.81 g, 70%) was collected as an off white colored solid product. ^{1}H NMR (500 MHz, DMSO-d_6) 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. The mixture was 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 gave 2-bromo-1-(4-chloro-3-nitrophenyl)ethanone as yellow needles.

Intermediate 5B

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) followed by diethylamine (8.35 mL, 81 mmol) and *tert*-butanol (7.73 mL, 81 mmol). The resultant heterogeneous solution was stirred at room temperature for approximately 2 hours. Afterwards Intermediate 5A (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 was stirred at room temperature for 42 hours. The reaction was then quenched with 5% aqueous sulfuric acid (500 mL) and stirred vigorously to induce solid formation. The resultant solid was collected by vacuum filtration, 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. The solid was then collected and dried overnight in a vacuum oven to provide 16.6 g (78%) of the title compound. ^{1}H NMR (400 MHz,

DMSO-d_6) 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).

Intermediate 5C

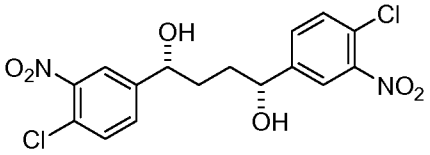
(1*S*,4*S*)-1,4-bis(4-chloro-3-nitrophenyl)butane-1,4-diol

(*R*)-(+)-α,α-Diphenyl-2-pyrrolidinemethanol (1.08g, 4.28mmol) was dissolved in 70 mL of THF at ambient temperature in a dry flask under nitrogen and trimethyl borate (650 uL, 5.54 mmol) was added dropwise. The resulting solution was stirred for 1 hour. 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 minutes, this solution was transferred to an addition funnel and added dropwise to 1,4-bis(4-chloro-3-nitrophenyl)butane-1,4-dione (Intermediate 5B) (10.0g, 25.2 mmol) suspended in 200 mL of THF and cooled to ~ 10 °C. Bubbling was observed. After the addition, the mixture was stirred at ambient temperature for 4 hours. The mixture was cooled in an ice bath and 30 mL or methanol was added dropwise until bubbling stopped, then the mixture was allowed to stir at ambient temperature for 30 minutes. The mixture was filtered to get rid of a trace of insoluble unreacted starting material. The filtrate was concentrated, poured into 1 *M* HCl and extracted into ethyl acetate, dried over sodium sulfate, and concentrated to give the title compound (9.9 g, 99%) as a yellow waxy solid. Chiral HPLC e.e. >99.9% (*RR* diol was undetectable). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 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).

Intermediate 5D

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

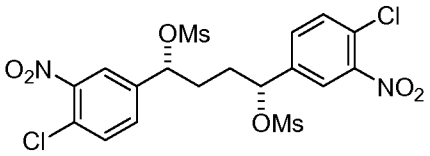
In a 1 L round-bottomed flask containing Intermediate 5C (20.0 g, 49.9 mmol) was added 310 mL of dichloromethane with stirring and cooling in an ice bath. To the slurry was added triethylamine (20.84 mL, 150 mmol) and after 10 minutes stirring in the ice bath, a solution of methanesulfonyl chloride (8.5 mL, 110 mmol) in dichloromethane (10 mL) was added dropwise to the reaction. After complete addition, the flask was removed from the ice bath and stirred at room temperature for 3 hours. To the reaction was added water (400 mL) with vigorous stirring for 20 minutes. The solid was collected by filtration and washed thoroughly with water dichloromethane and diethyl ether. The solid was dried overnight in a vacuum drying oven at 60 °C to provide a white solid (20.49 g, 73.7% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.81 - 1.91 (m, 2 H) 2.06 (m, 2 H) 3.18 (s, 6 H) 5.73 - 5.84 (m, 2 H) 7.71 - 7.77 (m, 2 H) 7.80 - 7.85 (m, 2 H) 8.13 (d, *J*=1.74 Hz, 2 H).



Intermediate 5.1

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

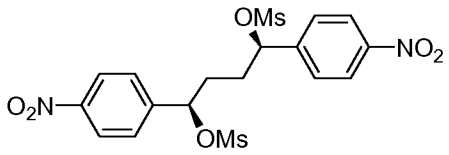
(1*R*,4*R*)-1,4-bis(4-chloro-3-nitrophenyl)butane-1,4-diol can be prepared using (*S*)-(-)-α,α-diphenyl-2-pyrrolidinemethanol and the method of Intermediate 5C.



Intermediate 5.2

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

(1*R*,4*R*)-1,4-bis(4-chloro-3-nitrophenyl)butane-1,4-diol can be transformed to (1*R*,4*R*)-1,4-bis(4-chloro-3-nitrophenyl)butane-1,4-diyl dimethanesulfonate as described under Intermediate 5D.



Intermediate 6

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

Intermediate 6A

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 minutes 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 (3×50 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 g, 61% yield).

Intermediate 6B

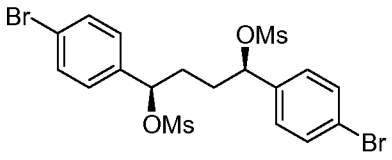
(1*R*,4*R*)-1,4-bis(4-nitrophenyl)butane-1,4-diol

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 hour. 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 minutes (caution: vigorous H_2 evolution), while the internal temperature was maintained at 16-19 °C. After 15 minutes, the H_2 evolution had ceased. To a separate vessel was added the product from Example 6A (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 minutes. 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 hours. After reaction completion, the mixture was cooled to 5 °C and methanol (16.7 g, 521 mmol) was added dropwise over 5-10 minutes, maintaining an internal temperature <20 °C (note: vigorous H_2 evolution). After the exotherm had ceased (ca. 10 minutes), 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 separated. The organic phase was then washed successively with 1 *M* HCl (2×120 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 minutes. The slurry was then allowed to mix at 23 °C for 30 minutes 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 hours 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).

Intermediate 6C

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

The product from Intermediate 6B (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 minutes, maintaining the internal temperature between -15 °C and -25 °C. After mixing for 5 minutes 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 is used directly without purification or isolation.



Intermediate 7

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

Intermediate 7A

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 hours. 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 hours). The reaction mixture was 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, and then dichloromethane, successively. The product was dried under vacuum to give the title compound as a white solid (11.15 g, 39.1% yield).

Intermediate 7B

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

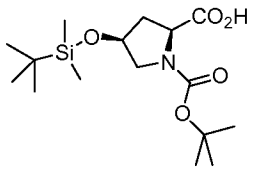
To (*S*)-(-)-α,α-diphenyl-2-pyrrolidinemethanol (3.81 g, 15.04 mmol) was added THF (140 mL) at 23 °C. The thin slurry was treated with trimethyl borate (2.189 mL, 19.63 mmol) to form a clear solution. After stirring for 1.5 hours, the solution was cooled to 10-15 °C, and *N*,*N*-diethylaniline borane (33.1 mL, 186 mmol) was added over 5-10 minutes via a syringe. A slight exotherm and H_2 evolution were observed. To a separate vessel was charged Intermediate 7A (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 minutes and then the temperature was maintained at 23 °C for 3 hours. 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 hour in order to ensure complete quenching. The hazy solution was diluted with EtOAc (500 mL) and 1 *M* HCl (220 mL). The phases were separated, and the organic phase was washed successively with 1 *M* HCl (2×220 mL), H_2O (110 mL), and 25% aq. NaCl (110 mL). The organic layer was concentrated in vacuo; then the residue was dissolved in EtOAc, filtered,

concentrated and crystallized from EtOAc/hexane to provide the title compound (16.92 g; 100% ee; 47% isolated yield).

Intermediate 7C

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

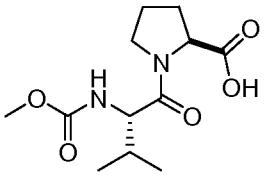
To Intermediate 7B (0.60 g, 1.500 mmol) in anhydrous CH_2Cl_2 (15 mL) at 0 °C was added Et_3N (0.627 mL, 4.50 mmol), and the resulting mixture was stirred at 0 °C for 10 minutes until a homogenous solution was obtained. To the cooled solution was added methanesulfonyl chloride (0.292 mL, 3.75 mmol) dropwise, and the resulting mixture was stirred at 0 °C for 1.5 hours 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.



Intermediate 8

(2*S*,4*S*)-1-(*tert*-butoxycarbonyl)-4-(*tert*-butyldimethylsilyloxy)pyrrolidine-2-carboxylic acid

(2*S*,4*S*)-1-(*tert*-Butoxycarbonyl)-4-hydroxypyrrolidine-2-carboxylic acid (5.31 g, 22.96 mmol) and imidazole (7.82 g, 115 mmol) were combined in dichloromethane (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.



Intermediate 9

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

Intermediate 2 (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 minutes to give a clear solution. EDC hydrochloride (172 g, 899 mmol) was charged and mixed for 20 minutes. 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 minutes. The resulting suspension was mixed at room temperature for 1.5 hours. The reaction mixture was cooled to 15 °C and 1500 mL of 6.7% $NaHCO_3$

charged in 1.5 hours, followed by the addition of 1200 mL of water over 60 minutes. The mixture was stirred at room temperature for 30 minutes, an then it was filtered and washed with water/DMF mixture (1:2, 250 mL) and then with water (1500 mL). The wet cake was dried at 55 ºC for 24 hours to give 282 g of product (*S*)-benzyl 1-((*S*)-2-(methoxycarbonylamino)-3-methylbutanoyl)pyrrolidine-2-carboxylate as a white solid (90%).

(*S*)-Benzyl 1-((*S*)-2-(methoxycarbonylamino)-3-methylbutanoyl)pyrrolidine-2-carboxylate (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 (120 mL) was added, and the solution was stirred until solids formed. After an addition 2–3 hours, additional heptane (240 mL) was added drop-wise, the slurry was stirred for approximately 1 hour, then filtered. The solids were dried to afford the title compound (*S*)-1-((*S*)-2-(methoxycarbonylamino)-3-methylbutanoyl)pyrrolidine-2-carboxylic acid.

Intermediate 10

4-Cyclohexyl-3-fluoroaniline hydrochloride

Intermediate 10A

3-Fluoro-4-iodoaniline

To a suspension of 3-fluoroaniline (1.0 mL, 1.16 g, 10.39 mmol) and solid sodium bicarbonate (1.75 g, 20.79 mmol) in 1:1 methanol-dichloromethane (20 mL) at 0 ºC was added a solution of benzyl trimethylammonium dichloroiodate (3.62 g, 10.39 mmol) in dichloromethane (15 mL) over 30 minutes. The mixture was then allowed to warm to room temperature for 1 hour. The mixture was quenched by addition of water and the organic layer was extracted with water (2×). Drying (Na_2SO_4) and concentration in vacuo afforded an oil, which was chromatographed over a 100 g silica gel cartridge, eluting with 10-100% ethyl acetate in hexanes. These procedures afforded the title compound (2.20 g, 89%) as a pink solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.41 (dd, J = 8.3, 7.3 Hz, 1 H), 6.42 (dd, J = 9.9, 2.5 Hz, 1 H), 6.27 (dd, J = 8.5, 2.5 Hz, 1 H), 3.81 (s, 2 H); MS +ESI *m/z* (rel abundance) 238 (100, M+H).

Intermediate 10B

4-(Cyclohexen-1-yl)-3-fluoroaniline

The procedure to prepare the title compound is described in General Procedure 1.2A.

Intermediate 10C

4-Cyclohexyl-3-fluoroaniline hydrochloride

A solution of 4-(cyclohexen-1-yl)-3-fluoroaniline (General Procedure 1.2A) (1.16 g, 6.07 mmol) in ethanol (30 mL) was treated with 10% palladium on carbon (300 mg) followed by hydrogenation at one atmosphere for 18 hours. The mixture was filtered through diatomaceous earth and concentrated to about one quarter volume and treated with a solution of hydrogen chloride in dioxane (4 *N*, 10 mL). The mixture was then partially concentrated in vacuo to about one quarter volume and diluted with ether (*ca.* 100 mL) and the solids were collected by filtration. After drying in a vacuum oven at 50 °C for 3 hours, these procedures afforded the title compound (1.13 g, 81%) as a light grey solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.35 (t, J = 8.1 Hz, 1 H), 7.03 (d, J = 9.4 Hz, 2 H), 2.76 (dd, J = 15.6, 6.9 Hz, 1 H), 1.74 (m, 5 H), 1.40 (m, 4 H), 1.21 (m, 1 H). MS (DCI+) *m/z* (rel abundance) 194 (100, M+H), 211 (67, M+NH_4).

Intermediate 11A

N-(4-bromo-5-fluoro-2-nitrophenyl)-2,2,2-trifluoroacetamide

To a flask containing trifluoroacetic anhydride (10.0 mL, 70.5 mmol) at 0 °C was added 4-bromo-3-fluoroaniline (2.0,g, 10.5 mmol) and stirring was continued for 30 minutes (Charifson, P.S.; et al. J. Med. Chem. 2008, 51, 5243-5263). Potassium nitrate (1.3 g, 12.6 mmol) was added and the solution was allowed to warm to 25 °C. The solution was concentrated, the residue dissolved in EtOAc and washed with 10% $NaHCO_3$, brine, dried (Na_2SO_4), and filtered. The filtrate was concentrated to give the title compound (3.5 g, 10.5 mmol, 100%).

Intermediate 11B

4-bromo-5-fluoro-2-nitroaniline

To *N*-(4-bromo-5-fluoro-2-nitrophenyl)-2,2,2-trifluoroacetamide (3.5 g, 10.5 mmol) was added CH_3OH (30mL) followed by 1.0 *M* K_2CO_3 (10.5mL, 10.5 mmol), and the solution was stirred for 30 minutes (Charifson, P.S.; et al. J. Med. Chem. 2008, 51, 5243-5263). The solution was diluted with H_2O and stirred for 1 hour. The resulting orange solid was collected by filtration and dried in a vacuum oven to give the title compound (2.1,g, 8.8 mmol, 84%).

Intermediate 11C

4-bromo-5-fluorobenzene-1,2-diamine

To a solution of 4-bromo-5-fluoro-2-nitroaniline (1.0 g, 4.3 mmol) in THF (9.0mL), EtOH (9.0 mL) and H_2O (3 mL) was added iron powder (1.2 g, 21.3 mmol) and ammonium chloride (0.34 g, 6.4 mmol), and the mixture was heated at 95 °C for 4 hours. The cooled mixture was diluted with EtOH, filtered through diatomaceous earth until no further color came through the filter, and concentrated. The residue was dissolved in EtOAc, washed with H_2O, brine, dried (Na_2SO_4), filtered

and concentrated. Hexane was added and the resulting solid collected by filtration to give the title compound (710 mg, 3.5 mmol, 81%).

Intermediate 12

4-bromo-3-chlorobenzene-1,2-diamine

Intermediate 12A

4-bromo-3-chloro-2-nitroaniline

3-Chloro-2-nitroaniline (5.00 g, 29.0 mmol) was dissolved in glacial acetic Acid (258 mL). *N*-Bromosuccinimide (5.06 g, 28.4 mmol) was added and the resulting mixture was refluxed for 1 hour. The reaction was cooled to room temperature and poured into water to give a precipitate that was filtered, rinsed with water and dried to constant weight to give the title compound (4.78 g, 67%). ^{1}H NMR (400 MHz, $CDCL_3$) δ ppm 7.46 (d, J = 9.0, 1H), 6.64 (d, J = 9.0, 1H), 4.74 (s, 2H).

Intermediate 12B

4-bromo-3-chlorobenzene-1,2-diamine

4-Bromo-3-chloro-2-nitroaniline (4.78 g, 19.01 mmol) was dissolved in ethanol (112 mL). Tin (II) chloride (14.42 g, 76 mmol) was added, and the resulting mixture was stirred at reflux for 12 hours. The mixture was cooled to room temperature, poured into water, and adjusted to pH 5 with saturated sodium bicarbonate solution. The resulting solid was filtered and rinsed well with ethyl acetate. The filtrate was washed with water and brine, 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% EtOAc in hexane to give the title compound (3.32 g, 79%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 6.94 (d, 1H), 6.51 (d, J = 7.0, 1H), 3.87 (br s, 2H), 3.46 (br s, 2H).

Intermediate 13

4-bromo-3-methylbenzene-1,2-diamine

Intermediate 13A

N-(3-bromo-2-methyl-6-nitrophenyl)-2,2,2-trifluoroacetamide

To a solution of 3-bromo-2-methylaniline (1.0 g, 5.37 mmol) in CH_2Cl_2 (4.0 mL) at 0 °C was added trifluoroacetic anhydride (2.0 mL, 14.2 mmol). The mixture was stirred at 0 °C for 30 minutes, and solid potassium nitrate (0.679 g, 6.72 mmol) was added. The cooling bath was removed, and the mixture was stirred at room temperature overnight. LCMS showed a single product formed. The mixture was concentrated in vacuo, and the residue was partitioned between water and CH_2Cl_2 (2×).

The organic layers were combined and dried over Na_2SO_4. The drying agent was filtered off and the crude product was purified by crystallization from aq EtOH to give the title compound (1.3 g, 74%).

Intermediate 13B

3-bromo-2-methyl-6-nitroaniline

A solution of *N*-(3-bromo-2-methyl-6-nitrophenyl)-2,2,2-trifluoroacetamide (1.3 g, 3.97 mmol) in CH_3OH (30 mL) was treated with potassium carbonate (1.099 g, 7.95 mmol), and the mixture was stirred at 50 °C overnight. The mixture was cooled to room temperature and poured into water, 1*N* aq HCl was added to adjust to pH 6, and the mixture was extracted with CH_2Cl_2 (3×). The combined extracts were dried over Na_2SO_4, and the drying agent was filtered off and solvent was removed in vacuo to give the title compound as a yellow solid (0.57 g, 62%).

Intermediate 13C

4-bromo-3-methylbenzene-1,2-diamine

To a solution of 3-bromo-2-methyl-6-nitroaniline (0.45 g, 1.95 mmol) in EtOH (6 mL) was added tin(II) chloride (1.48 g, 7.8 mmol), and the resulting solution was stirred at 70 °C for 4 hours. The mixture was cooled to room temperature and poured into water, and 1 *N* aq. NaOH was added to adjust to pH>7. The resulting mixture was extracted with CH_2Cl_2 (2×), and the combined extracts were dried over Na_2SO_4. The drying agent was filtered off and solvent was removed in vacuo to give the title compound as an oil (0.34 g, 88%).

Intermediate 14

5-bromo-3-fluorobenzene-1,2-diamine

To a solution of 4-bromo-2-fluoro-6-nitroaniline (0.5 g, 2.1 mmol) in THF (4.6 mL), EtOH (4.6 mL) and H_2O (1.5 mL) was added iron powder (0.6 g, 10.6 mmol) and ammonium chloride (0.17 g, 3.2 mmol). The resulting mixture was stirred at 95 °C for 22 hours. The mixture was cooled to room temperature and filtered through diatomaceous earth. The solid was washed with EtOH until no further color came through the filter. The filtrate was concentrated and the residue was dissolved in EtOAc, washed with H_2O and brine, dried over Na_2SO_4, filtered and concentrated to give the title compound (0.43 g, 99%) as a brown, waxy solid.

Intermediate 15

4-bromo-3-fluorobenzene-1,2-diamine

Intermediate 15A

3-fluoro-2-nitroaniline

To a pressure tube was added 1,3-difluoro-2-nitrobenzene (2.8 mL, 26.4 mmol) and 7 *N* NH_3 in CH_3OH (10 mL, 70 mmol). The tube was sealed and the mixture was stirred at room temperature for 5 days. The solution was diluted with H_2O, extracted with CH_2Cl_2, and the combined extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated to give an oil. The oil was triturated with hexane and the resulting orange solid was collected by filtration to give the title compound (2.1 g, 51%).

Intermediate 15B

4-bromo-3-fluoro-2-nitroaniline

To a solution of 3-fluoro-2-nitroaniline (2.1 g, 13.4 mmol) in DMF (30 mL) at 0 °C was added a solution of *N*-bromosuccinimide (2.4 g, 13.4 mmol) in DMF (20 mL). The resulting solution was stirred at 0 °C for 30 minutes and then warmed to room temperature over 1 hour. The solution was diluted with EtOAc, washed with H_2O and brine, dried over $MgSO_4$, filtered and concentrated to give the title compound (3.1 g, 97%).

Intermediate 15C

4-bromo-3-fluorobenzene-1,2-diamine

To a solution of 4-bromo-3-fluoro-2-nitroaniline (3.0 g, 12.8 mmol) in THF (30 mL) was added EtOH (30 mL) and H_2O (10 mL) followed by iron powder (3.6 g, 63.8 mmol) and ammonium chloride (1.0 g, 19.2 mmol). The resulting mixture was stirred at 80 °C for 16 hours. The mixture was cooled to room temperature and filtered through diatomaceous earth. The solid was washed with EtOH until no further color came through the filter. The filtrate was concentrated in vacuo and the crude product was purified by column chromatography on silica gel using a solvent gradient of 0-40% EtOAc in hexane to give the title compound (2.2 g, 84%).

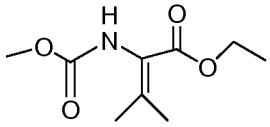
Intermediate 16

4-cyclopropyl-2-fluoroaniline

4-Cyclopropyl-2-fluoro-1-nitrobenzene (prepared as described in General Procedure 1.2C) (2.2 g, 12.14mmol) was dissolved in 7 mL of an ethanol:THF:water 3:3:1 (v/v) mixture. To this was added ammonium chloride (1.02 g, 19.07 mmol) followed by iron powder (3.50 g, 62.7mmol). The resulting mixture was heated in a 90 °C oil bath under a nitrogen atmosphere with rapid stirring for one hour. The reaction mixture was vacuum filtered through a sand and diatomaceous earth plug. The filtrate was concentrated in vacuo and the residue partitioned between dichloromethane and water. The organic phase was washed with brine, dried ($MgSO_4$) and concentrated in vacuo to provide an orange oil (1.90 g).

Intermediate 17

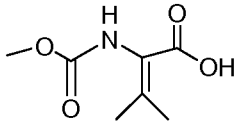
2-(methoxycarbonylamino)-3-methylbut-2-enoic acid



Intermediate 17A

ethyl 2-(methoxycarbonylamino)-3-methylbut-2-enoate

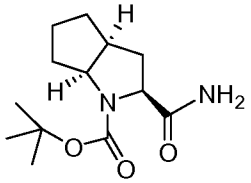
A benzene solution (90 mL) of ethyl-3-methyl-2-oxobutanoate (4.03 g, 28.0 mmol), methyl carbamate (2.098g, 28.0 mmol) and pyridine 4-methylbenzenesulfonate (0.70 g, 2.80 mmol) was heated to reflux in a round bottom flask equipped with a Dean-Stark trap and reflux condenser. After 44hours of heating the mixture was cooled and then partitioned between ethyl acetate (50mL) and brine (50 mL). The organic phase was washed with brine (2×50 mL) then dried ($MgSO_4$) and concentrated in vacuo. The crude product was purified by chromatography on silica gel (ethyl acetate-hexanes) to provide the title compound as an off white crystalline solid (1.487 g, 26%).



Intermediate 17B

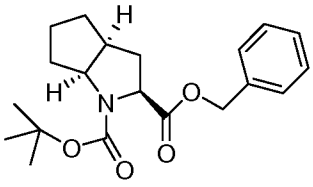
2-(methoxycarbonylamino)-3-methylbut-2-enoic acid

The product from Intermediate 17A (0.373 g, 1.85 mmol) was dissolved in 2 mL of a 1:1(v/v) ethanol:water mixture at room temperature. To this was added lithium hydroxide (0.095 g, 3.99 mmol) in one portion. After stirring overnight, the reaction mixture was partitioned between ethyl acetate (25 mL) and 1 *N* HCl (5 mL) to which was added solid NaCl. The aqueous phase was extracted with ethyl acetate one time and the combined organics washed with brine (3×5 mL) then dried ($MgSO_4$) and concentrated to give the title compound (0.289 g, 90%) as an off white solid sufficiently pure for use as isolated.



Intermediate 18

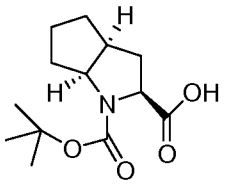
(2*S*,3a*S*,6a*S*)-*tert*-butyl 2-carbamoylhexahydrocyclopenta[b]pyrrole-1(2H)-carboxylate



Intermediate 18A

(2*S*,3a*S*,6ba*S*)-2-benzyl 1-*tert*-butyl hexahydrocyclopenta[b]pyrrole-1,2(2H)-dicarboxylate

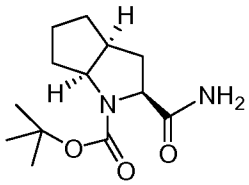
To a suspension of (2*S*,3a*S*,6a*S*)-benzyl octahydrocyclopenta[*b*]pyrrole-2-carboxylate hydrochloride (2.0 g, 7.10 mmol) in dichloromethane (36 mL) at room temperature was added di-*tert*-butyl dicarbonate (1.7 0g, 7.81 mmol) followed by triethylamine (2.18 mL, 15.62 mmol). The solution rapidly becomes homogeneous along with vigorous gas evolution which quickly subsides. After two hours, the mixture was diluted with dichloromethane, washed with brine (3×60 mL), dried ($MgSO_4$) and concentrated. The crude product was purified by chromatography on silica gel (ethyl acetate–hexanes) to give the title compound (2.58 g, quantitative) as a clear oil.



Intermediate 18B

(2*S*,3a*S*,6a*S*)-1-(*tert*-butoxycarbonyl)octahydrocyclopenta[b]pyrrole-2-carboxylic acid

The product from Intermediate 18A (2.45 g, 7.1mmol) was dissolved in methanol (35 mL) at room temperature. To this was added Pearlman's catalyst (0.153 g) followed by vacuum degassing (3×) and hydrogen addition (balloon). After one hour, the reaction mixture was vacuum filtered through diatomaceous earth and the filtrate concentrated to give a clear thick oil (1.89 g, quantitative) which was sufficiently pure for use as isolated.



Intermediate 18C

(2*S*,3a*S*,6a*S*)-*tert*-butyl 2-carbamoylhexahydrocyclopenta[b]pyrrole-1(2H)-carboxylate

The product from Intermediate 18B (1.81 g, 7.1 mmol) was dissolved in THF (40 mL) at room temperature under nitrogen. To this was added *N*-methyl morpholine (1.0 mL, 9.09 mmol) and the resulting solution was cooled to -15 °C. To the cold solution was added isobutylchloroformate

(1.03 mL, 7.81 mmol) dropwise via syringe. A white precipitate forms at once. On completion of the addition, the mixture was allowed to stir in the cold for twenty minutes. Ammonia gas was then introduced by bubbling through the mixture for two minutes with additional cooling. On completion of the addition, the reaction was allowed to warm to ice bath temperature and stir for one half hour and then warmed to room temperature. After fifteen minutes at room temperature, the mixture was poured into brine (450 mL) and extracted with dichloromethane (6×50 mL). The combined extracts were dried ($MgSO_4$) and concentrated. The crude product was purified by chromatography on silica gel (ethyl acetate–hexanes) to give the title compound (1.68 g, 93%) as a sticky white foam.

Intermediate 19

(*S*,*E*)-*tert*-butyl 2-(5-(3-oxoprop-1-enyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-benzo[*d*]imidazol-2-yl)pyrrolidine-1-carboxylate

Intermediate 19A

(*S*,*E*)-*tert*-butyl 2-(5-(3-ethoxy-3-oxoprop-1-enyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-benzo[*d*]imidazol-2-yl)pyrrolidine-1-carboxylate

To (*S*)-*tert*-butyl 2-(5-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-benzo[*d*]imidazol-2-yl)pyrrolidine-1-carboxylate (2.973 g, 5.99 mmol), ethyl acrylate (0.714 mL, 6.59 mmol), tri-*tert*-butylphosphonium tetrafluoroborate (0.104 g, 0.359 mmol), *N*,*N*-dicyclohexylmethylamine (1.461 mL, 6.89 mmol), and tris(dibenzylideneacetone)dipalladium(0) (0.164 g, 0.18 mmol) dissolved in THF (18 mL) had nitrogen bubbled through the solution for 15 minutes to remove the oxygen, and then the mixture heated at 60 °C for 2 hours. After cooling to room temperature the solution was filtered through diatomaceous earth and washed with EtOAc. The filtrated was then concentrated to a residue, and then the residue was dissolved in dichloromethane and extracted with water. The organic layer was then dried and concentrated. The residue was purified by chromatography (silica gel, hexanes in ethyl acetate) which afforded 2.56 g, (83%) of the title compound. MS (ESI) *m/z* 516 $(M+H)^+$.

Intermediate 19B

(*S*,*E*)-*tert*-butyl 2-(5-(3-hydroxyprop-1-enyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-benzo[*d*]imidazol-2-yl)pyrrolidine-1-carboxylate

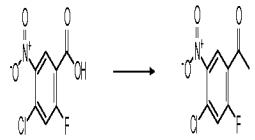
Intermediate 19A (2.56 g, 4.97 mmol) was dissolved in THF (17 mL), and the mixture was cooled to -78 °C in a dry ice acetone bath. Then a solution of diisobutylaluminium hydride (1.0 *N* in THF, 22.75 mL, 24.75 mmol) was added dropwise. The resultant mixture was allowed to slowly warm to room temperature overnight, and then was quenched with a 1 *N* aqueous sodium hydroxide solution. The mixture was then added to ethyl acetate and extracted with an aqueous solution of

Rochelle's salt (sodium, potassium tartrate). The organic layers were combined and dried, and then concentrated. The residue was purified by chromatography (silica gel, hexanes in ethyl acetate) which afforded 0.93 g, (40%) of the title compound. MS (ESI) *m/z* 474 $(M+H)^+$.

Intermediate 19C

(*S*,*E*)-*tert*-butyl 2-(5-(3-oxoprop-1-enyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-benzo[*d*]imidazol-2-yl)pyrrolidine-1-carboxylate

The product of Intermediate 19B (0.93 g, 1.96 mmol) was dissolved in dichloromethane (7.5 mL) and pyridinium dichromate (1.11 g, 2.95 mmol) was added, and the resultant mixture was stirred at room temperature overnight. The solution had hexanes added to it, and then it was filtered through diatomaceous earth. The filtrate was then concentrated to a residue which was then dissolved in dichloromethane and extracted with water. The organic layer was then dried, concentrated and the residue purified by chromatography (silica gel, hexanes in ethyl acetate) which afforded 0.3 g, (32%) of the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.65 (d, J=7.8 Hz, 1H), 8.05 (m, 1H), 7.82 (d, J=15.8 Hz, 1H), 7.70 (m, 2H), 6.87 (dd, J=15.8, 7.8 Hz, 1H), 5.70 (s, 2H), 5.14 (m, 1H), 3.57 (m, 2H), 3.42 (m, 1H), 2.40 (m, 5H), 1.30 (s, 4H), 0.95 (s, 5H), 0.80 (m, 2H), -0.10 (s, 9H); MS (ESI) *m/z* 472 $(M+H)^+$.



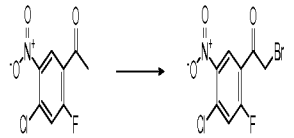
Intermediate 20A

1-(4-chloro-2-fluoro-5-nitrophenyl)ethanone

To a solution of 4-chloro-2-fluoro-5-nitrobenzoic acid (16.0 g, 72.9 mmol) in anhydrous CH_2Cl_2 (400 mL) was added oxalyl chloride (9.57 mL, 109 mmol) and DMF (2 drops), and the resulting mixture was stirred at room temperature until gas evolution ceased. The mixture was concentrated and dried in vacuo. In a separate, heat-dried reaction flask a mixture of $ZnBr_2$ (24.6 g , 109 mmol) in anhydrous THF (300 mL) at -78°C was added a solution of CH_3MgBr (29.1 mL, 3.0 *M* in Et_2O, 87 mmol) dropwise. The resulting mixture was stirred at -78 °C for 15 minutes, and then the reaction mixture was allowed to warm to room temperature and stirred for 30 minutes. The mixture was cooled to -78 °C and a solution of the acid chloride in anhydrous THF (100 mL) was added dropwise, followed by $Pd(PPh_3)_4$ (1.68 g, 1.46 mmol). The resulting mixture was allowed to stir at -78 °C for 10 minutes, and was then allowed to warm to ambient temperature and stirred for an additional 16 hours. The mixture was quenched by adding aq. 1 *M* HCl, diluted with H_2O (100 mL), and extracted with CH_2Cl_2 (3×300 mL). The combined organic extracts were dried ($MgSO_4$), filtered

and concentrated. The crude product was purified by column chromatography (silica gel, 5% EtOAc in hexanes) to afford the title compound (11.79 g, 74%).

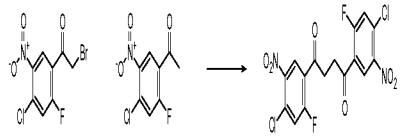
Intermediate 20A may also be prepared by reacting the intermediate acid chloride with dimethylmalonate, $MgCl_2$, and triethylamine in methylene chloride, followed by acidic hydrolysis and decarboxylation.



Intermediate 20B

2-bromo-1-(4-chloro-2-fluoro-5-nitrophenyl)ethanone

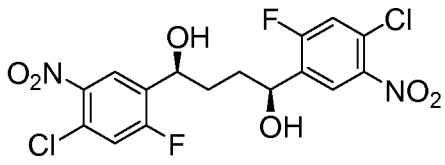
The product of Intermediate 20A (3.0 g, 13.79 mmol) dissolved in THF (100 mL) was treated with pyridinium bromide perbromide (4.63 g, 14.48 mmol) portionwise over several minutes. The resulting mixture was stirred at ambient temperature for 2 hours and then filtered. The filtered solids were rinsed with EtOAc, and the filtrate was concentrated in vacuo. The crude product was purified by column chromatography (silica gel, 20% EtOAc in hexanes) to afford the title compound (3.8 g, 93%).



Intermediate 20C

1,4-bis(4-chloro-2-fluoro-5-nitrophenyl)butane-1,4-dione

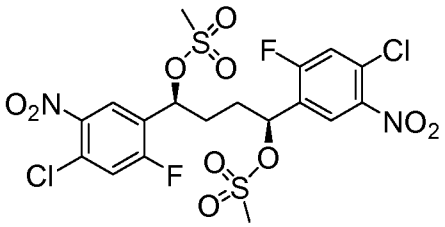
Intermediate 20A (4.92 g, 22.62 mmol) and Intermediate 20B (4.47 g, 15.08 mmol) were processed using the method described in Intermediate 5B to afford the title compound (4.74 g, 73%).



Intermediate 20D

(1S,4S)-1,4-bis(4-chloro-2-fluoro-5-nitrophenyl)butane-1,4-diol

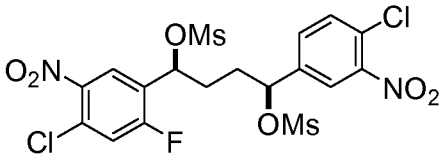
The product of Intermediate 20C (1.0 g, 2.309 mmol) was processed using the method described in Intermediate 5C to afford the title compound (0.96 g, 95%). In the chiral reduction to form Intermediate 20D, the reaction proceeds with lower stereoselectivity than in the case of Intermediate 5C.



Intermediate 20E

(1S,4S)-1,4-bis(4-chloro-2-fluoro-5-nitrophenyl)butane-1,4-diyl dimethanesulfonate

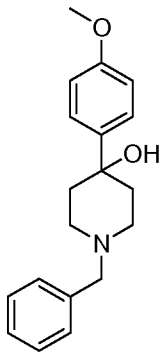
To a solution of Intermediate 20D (0.95 g, 2.17 mmol) in anhydrous CH_2Cl_2 (20 mL) at 0 °C was added methanesulfonyl chloride (0.42 mL, 5.43 mmol), followed by the dropwise addition of triethylamine (0.91 mL, 6.52 mmol). The resulting mixture was stirred at room temperature for 90 minutes, and was then concentrated in vacuo. Hexanes were added, and the resulting solids were collected by filtration, washed with H_2O, and dried in vacuo to provide the title compound (1.29 g, 100%).



Intermediate 21

(1S,4S)-1-(4-chloro-2-fluoro-5-nitrophenyl)-4-(4-chloro-3-nitrophenyl)butane-1,4-diyl dimethanesulfonate

Intermediate 21 can be made from Intermediate 20B and 1-(4-chloro-3-nitrophenyl)ethanone (commercially available from Aldrich) following the general methods to prepare Intermediate 20E.

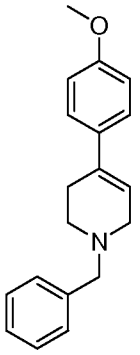


Intermediate 22A

1-benzyl-4-(4-methoxyphenyl)piperidin-4-ol

(4-Methoxyphenyl)magnesium bromide (0.5 *M* in THF, 90 mL, 45.0 mmol) was added slowly (~25 minutes) via cannula to a cold (0 °C) solution of 1-benzylpiperidin-4-one (5.4 mL, 30.2

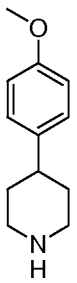
mmol) in THF (60 mL). The reaction was stirred at 0 ºC under nitrogen for 2 hours. The reaction was quenched with saturated aqueous NH_4Cl then diluted with ether. The organic fraction was washed with saturated aqueous NH_4Cl (2×) brine (1×) and concentrated. Purification using flash chromatography (5 – 100% EtOAc/hexane) provided 4.02 g (44%) of the titled compound. MS (DCI) *m/z* 298 $(M+H)^+$.



Intermediate 22B

1-benzyl-4-(4-methoxyphenyl)-1,2,3,6-tetrahydropyridine

6 *M* HCl (100 mL, aqueous) was added to a solution of 1-benzyl-4-(4-methoxyphenyl)piperidin-4-ol (12.31 g, 41.36 mmol) in dioxane (50 mL), and the reaction was heated to strong reflux (110 ºC). After 2 hours, the reaction was not complete. The heat was turned off and the reaction was left to stir at ambient temperature for 2 days. The reaction had progressed but was not complete so it was heated to 110 ºC. After 1 hour, the reaction was cooled and the volume was reduced by approximately one third. The solution was then cooled in an ice bath and neutralized with NaOH pellets. The thick suspension was filtered. The precipitate was rinsed with water and then dried under vacuum at 70ºC to afford 6.2 g (47%) of the titled compound. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 2.74 - 2.62 (m, 1H), 3.30 - 3.06 (m, 2H), 3.50 (d, J = 18.5, 1H), 3.67 - 3.56 (m, 1H), 3.82 (s, 3H), 4.03 - 3.90 (m, 1H), 4.21 (dd, J = 5.7, 13.0, 1H), 4.34 (dd, J = 5.1, 13.0, 1H), 5.88 (s, 1H), 6.88 (d, J = 8.7, 2H), 7.32 (d, J = 8.7, 2H), 7.51 - 7.43 (m, 3H), 7.71 (dd, J = 2.7, 6.3, 2H), 12.85 (s, 1H); MS (ESI) *m/z* 280 $(M+H)^+$; MS (DCI) *m/z* 280 $(M+H)^+$.

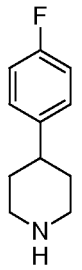


Intermediate 22C

4-(4-methoxyphenyl)piperidine

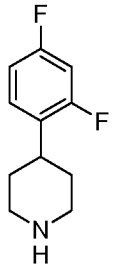
The product from Intermediate 22B (6.2 g) in trifluoroethanol (60 mL) was added to 20% Pd(OH)2-C, wet (1.240 g, 8.83 mmol) in a 250 mL stainless steel pressure bottle. The mixture was shaken under 30 psi of hydrogen at 50 °C for 23 hours. The mixture was filtered through a PTFE membrane, concentrated and dried under vacuum to afford 4.33 g of the desired product as the HCl salt. (HCl salt) ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 2.03 (d, J = 13.1, 2H), 2.28 - 2.11 (m, 2H), 2.72 (t, J = 10.2, 1H), 3.08 - 2.91 (m, 2H), 3.62 (d, J = 8.3, 2H), 3.79 (s, 3H), 6.86 (d, J = 8.3, 2H), 7.16 (d, J = 8.5, 2H), 9.65 (d, J = 83.1, 2H); MS (DCI) *m/z* 192 $(M+H)^+$.

Intermediates 23, 24, and 25 can be prepared using the methodology used to prepare Intermediate 22C



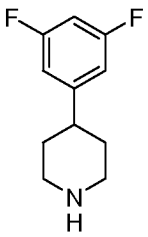
Intermediate 23

4-(4-fluorophenyl)piperidine



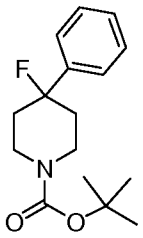
Intermediate 24

4-(2,4-difluorophenyl)piperidine



Intermediate 25

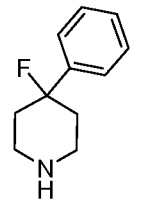
4-(3,5-difluorophenyl)piperidine



Intermediate 26A

tert-butyl 4-fluoro-4-phenylpiperidine-1-carboxylate

A solution of diethylaminosulfur trifluoride (4 mL, 32.7 mmol) in dichloromethane (10 mL) was added to a cold (-78 °C; dry ice/acetone bath) solution of *tert*-butyl 4-hydroxy-4-phenylpiperidine-1-carboxylate (8.05 g, 29.0 mmol) in dichloromethane (100 mL) under nitrogen. The reaction was stirred at -78 °C for ~ 1 hour. The reaction was removed from the bath and warmed to ambient temperature then stirred another 30 minutes. The reaction was quenched with saturated aqueous $NaHCO_3$ (100 mL). The organic fraction was washed with brine (~50 mL). Then 3-chloroperoxybenzoic acid (1.0995 g, 6.37 mmol) was added to the reaction and stirred at ambient temperature for 30 minutes. This step was quenched with saturated aqueous $NaHCO_3$ (100 mL). The organic fraction was washed with saturated aqueous $NaHCO_3$ (1×100 mL), water (1×100 mL), and brine (1×100 mL), dried ($MgSO_4$), tested for peroxide (3 - 10 ppm) and concentrated to light yellow oil. The oil was dried under vacuum to afford 8.27 g (100%) of the titled compound. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 1.42 (d, J = 5.7, 9H), 1.96 - 1.85 (m, 3.5H), 2.03 (ddd, J = 5.2, 13.3, 17.8, 1.5H), 3.06 (s, 2H), 3.98 (d, J = 12.0, 2H), 7.33 (d, J = 7.1, 1H), 7.46 - 7.36 (m, 4H); MS (DCI) *m/z* 280 ($M+H^+$, 60%), 297 ($M+NH_4^+$, 100%).

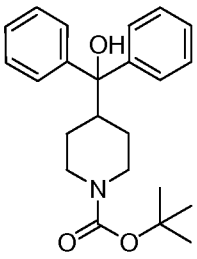


Intermediate 26B

4-fluoro-4-phenylpiperidine

Hydrochloric acid (4 *M* in dioxane, 20 mL, 80 mmol) was added to a solution of *tert*-butyl 4-fluoro-4-phenylpiperidine-1-carboxylate (8.27 g, 29.6 mmol) in dioxane (10 mL). The reaction was stirred at ambient temperature for 4 hours. The reaction was concentrated to an oil. Ether was added, and the resulting solid was sonicated and then stirred vigorously overnight to provide a tan solid. The

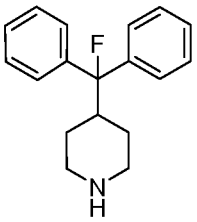
solid was filtered, rinsed with ether and dried under vacuum at 60 °C for 3 hours to provide 5.56 g (87%) of the titled product. MS (DCI) *m/z* 180 $(M+H)^+$.



Intermediate 27A

tert-butyl 4-(hydroxydiphenylmethyl)piperidine-1-carboxylate

A solution of di-*tert*-butyl dicarbonate (8.43 mL, 36.7 mmol) in dichloromethane (15 mL) was added to a solution of diphenyl(piperidin-4-yl)methanol (8.0721 g, 30.2 mmol) in dichloromethane (100 mL); triethylamine (5.1 mL, 36.6 mmol) was added and the reaction was stirred at ambient temperature for 2 hours. The reaction was diluted with dichloromethane and then washed with saturated aqueous NaHCO3 (2×), water (1×), and brine (1×), dried (MgSO4) and concentrated to afford 11.63 g (105%) of the titled compound. MS (ESI) *m/z* 367 $(M+H)^+$, 366 $(M-H)^+$.



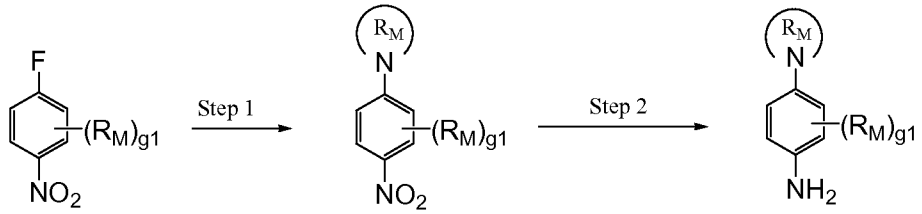
Intermediate 27B

4-(fluorodiphenylmethyl)piperidine

The title compound was prepared from *tert*-butyl 4-(hydroxydiphenylmethyl)piperidine-1-carboxylate using the general methods of Intermediates 26A and 26B. 3.37 g (100%) as HCl salt, MS (DCI) *m/z* 270 $(M+H)^+$.

General Procedures

General Procedure 1. Synthesis of 4-aminosubstituted anilines



Intermediate anilines having an amino group para to the aniline can be made using a two-step procedure. Fluoronitrobenzenes, fluoronitropyridines, or fluoronitropyrimidines can be reacted in Step 1 with an appropriate amine  , where  represents any amine group that can be present in R_M and attached through nitrogen, in the presence of dibasic potassium phosphate (equivalents) or potassium carbonate in a solvent such as DMSO optionally with heating and optional microwave irradiation. Step 2 can be accomplished by standard nitro reduction conditions such as catalytic hydrogenation using palladium on carbon or Raney-nickel. Alternatively, the reduction can be effected with iron/ammonium chloride in THF/methanol/water as solvent. Where the group  is an optionally substituted cyclic amine (e.g., piperidine, pyrrolidine), the optionally substituted cyclic amines can be accessed as described herein or using generally known methodologies. See for example the methods shown in Patel et al. *J Medicinal Chemistry* **49**(25) 7450 (2006).

Illustration of General Procedure 1: General Procedure 1A

Step 1

1-(2,6-difluoro-4-nitrophenyl)-4-phenylpiperidine

In a 100 mL round-bottom flask was mixed 3,4,5-trifluoronitrobenzene (1.751 mL, 15 mmol) and potassium phosphate, dibasic (5.23 g, 30.0 mmol) in DMSO (15.00 mL) to give a yellow suspension. 4-Phenylpiperidine (2.419 g, 15.00 mmol) was added portion-wise as a solid over 10 minutes to produce a deeper yellow suspension and a mild exotherm. The mixture was stirred for 1 hour and partitioned between EtOAc and water. The EtOAc layer was washed 2× by 50 mL each with water and brine, dried (Na_2SO_4), filtered and concentrated to give the title compound as a yellow solid (4.53 g, 95% yield).

Step 2

3,5-difluoro-4-(4-phenylpiperidin-1-yl)aniline

In a 500 mL round-bottom flask was added 1-(2,6-difluoro-4-nitrophenyl)-4-phenylpiperidine (4.53 g, 14.23 mmol), iron (3.97 g, 71.2 mmol), and ammonium chloride (1.142 g, 21.35 mmol) in a

solvent mixture of EtOH (60 mL)/THF (60 mL)/water (20 mL). The mixture was refluxed for 3 hours with vigorous stirring, cooled, filtered through diatomaceous earth and the filtrate was concentrated. The residue was partitioned between ethyl acetate and water. The organic layer was washed with brine, dried (Na_2SO_4), filtered and evaporated to give the title compound as yellow solid (3.93 g, 96% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.63 - 1.81 (m, 4 H) 2.54 - 2.64 (m, 1 H) 2.95 - 3.03 (m, 2 H) 3.09 (t, *J*=10.57 Hz, 2 H) 5.42 (s, 2 H) 6.10 - 6.21 (m, 2 H) 7.15 - 7.22 (m, 1 H) 7.25 - 7.34 (m, 4 H); MS (ESI+) *m/z* 289 $(M+H)^+$.

Illustration of General Procedure 1: General Procedure 1B

Step 1

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 hours. The cooled solution was concentrated in vacuo and the residue partitioned between CH_2Cl_2 and 1 *M* NaOH. The organic layer was dried (Na_2SO_4), filtered and solvent removed in vacuo to give title compound (9.52 g, 78%). MS (ESI) *m/z* 194 $(M+H)^+$.

Step 2

6-(pyrrolidin-1-yl)pyridin-3-amine

5-Nitro-2-(pyrrolidin-1-yl)pyridine (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%) (9.52 g, 162 mmol). The mixture was stirred for 2 hours 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%). ^{1}H NMR (400 MHz, DMSO-d_6) 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 $(M+H)^+$.

Illustration of General Procedure 1, step 2: General Procedure 1C

4-(3,5-dimethylpiperidin-1-yl)-3,5-difluoroaniline

1-(2,6-Difluoro-4-nitrophenyl)-3,5-dimethylpiperidine (14.01 g, 51.8 mmol) and THF (240 mL) were added to Raney-nickel 2800, water slurry (14.01 g, 239 mmol) in a 500 mL stainless steel pressure bottle. The mixture was stirred for 8 hours at 30 psi and room temperature. The mixture was filtered through a nylon membrane and concentrated to give the title compound.

Illustration of General Procedure 1, step 2: General Procedure 1D

3-methyl-4-(piperidin-1-yl)aniline

To a solution of 1-(2-methyl-4-nitrophenyl)piperidine (6.75 g, 30.6 mmol) in ethyl acetate (50 mL) was added 10% palladium on carbon (0.033 g, 0.306 mmol) and the mixture hydrogenated (hydrogen balloon) at room temperature for 20 hours. The mixture was then filtered through diatomaceous earth and washed with ethyl acetate; the filtrate was then concentrated to afford 5.5 g (94%) of the title compound. MS (ESI) *m/z* 191 $(M+H)^+$.

Illustration of General Procedure 1, step 1: General Procedure 1E

1-(4-nitrophenyl)-4-phenylpiperidine

An oven-dried 20 mL microwave tube was charged with 4-fluoronitrobenzene (0.752 mL, 7.02 mmol), 4-phenylpiperidine (1.166 g, 7.02 mmol), and potassium carbonate (0.970 g, 7.02 mmol) under nitrogen, anhydrous DMSO (7 mL) was added, the tube was sealed with an aluminum crimp cap, and heated in a microwave reactor (Personal Chemistry, 300 W, 2.4 bar) at 190 °C for 10 minutes. TLC (SiO_2, 5% EtOAc/hexanes) showed complete reaction. The reaction was poured into water (50 mL), stirred for 5 minutes, and vacuum filtered in a Büchner funnel. The collected yellow solids were washed with water (2×10 mL) and Et_2O (5 mL), and the bright yellow solid was dried *in vacuo* to provide the title compound (1.712 g, 6.06 mmol, 86%). ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.73 - 1.90 (m, 2 H), 2.00 (d, *J*=13.34 Hz, 2 H), 2.73 - 2.86 (m, 1 H), 3.02 - 3.17 (m, 2 H), 4.10 (d, *J*=13.23 Hz, 2 H), 6.87 (d, *J*=9.43 Hz, 2 H), 7.23 (t, *J*=7.75 Hz, 3 H), 7.33 (t, *J*=7.43 Hz, 2 H), 8.14 (d, *J*=9.33 Hz, 2 H); MS (ESI+) *m/z* 283 $(M+H)^+$.

The following amines can be made using methods shown in the foregoing General Procedure 1:

4-(4,4-dimethylpiperidin-1-yl)-3,5-difluoroaniline;

4-(2-azabicyclo[2.2.2]octan-2-yl)-3,5-difluoroaniline;

3,5-difluoro-4-(4-isopropylpiperidin-1-yl)aniline;

3,5-difluoro-4-(4-(trifluoromethyl)piperidin-1-yl)aniline;

4-(4-*tert*-butylpiperidin-1-yl)-3,5-difluoroaniline;

3,5-difluoro-4-(6-azaspiro[2.5]octan-6-yl)aniline;

4-(3,3-dimethylazetidin-1-yl)-3,5-difluoroaniline;

4-(4,4-difluoropiperidin-1-yl)-3,5-difluoroaniline;

3,5-difluoro-4-(4-fluoropiperidin-1-yl)aniline;

3,5-difluoro-4-(piperidin-1-yl)aniline;

2,3,5,6-tetrafluoro-4-(piperidin-1-yl)aniline;

3-methyl-4-(piperidin-1-yl)aniline;

3,5-difluoro-4-((3a*R*,7a*S*)-1*H*-isoindol-2(3*H*,3a*H*,4*H*,5*H*,6*H*,7*H*,7a*H*)-yl)aniline;

N^1-*tert*-butyl-2-fluorobenzene-1,4-diamine;

3,5-difluoro-4-(4-methylpiperidin-1-yl)aniline;

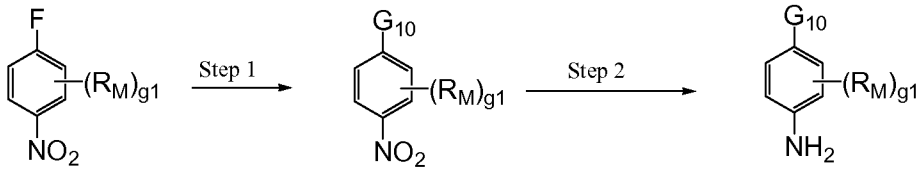
3,5-dichloro-4-(piperidin-1-yl)aniline;
2,5-difluoro-4-(piperidin-1-yl)aniline;
4-((2*R*,6*S*)-2,6-dimethylpiperidin-1-yl)-3,5-difluoroaniline;
2,3,5-trifluoro-4-(piperidin-1-yl)aniline;
4-((1*R*,5*S*)-3-azabicyclo[3.2.0]heptan-3-yl)-3,5-difluoroaniline;
3-fluoro-4-(piperidin-1-yl)aniline;
3,5-difluoro-4-(3-azaspiro[5.5]undecan-3-yl)aniline;
3,5-difluoro-4-(isoindolin-2-yl)aniline;
3,5-difluoro-4-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)aniline;
4-(4-phenyl-5,6-dihydropyridin-1(2*H*)-yl)aniline;
3-fluoro-4-(4-phenylpiperidin-1-yl)aniline;
4-(4,4-diphenylpiperidin-1-yl)-3,5-difluoroaniline;
4-(4-phenylpiperidin-1-yl)aniline;
1-(1-(4-amino-2,6-difluorophenyl)-4-phenylpiperidin-4-yl)ethanone;
3,5-difluoro-4-(4-(3-phenylpropyl)piperidin-1-yl)aniline;
3,5-difluoro-4-(8-azaspiro[4.5]decan-8-yl)aniline;
3,5-difluoro-4-(3-phenylpiperidin-1-yl)aniline;
3,5-difluoro-4-(3-phenylpyrrolidin-1-yl)aniline;
3,5-difluoro-4-(4-(4-(trifluoromethyl)phenyl)piperazin-1-yl)aniline;
3,5-difluoro-4-(4-phenylpiperazin-1-yl)aniline;
4-(4-(2,6-difluorophenyl)piperazin-1-yl)-3,5-difluoroaniline;
3,5-difluoro-4-(4-(pyrimidin-2-yl)piperazin-1-yl)aniline;
3,5-difluoro-4-(2-phenylmorpholino)aniline;
(S)-3,5-difluoro-4-(2-phenylmorpholino)aniline
3,5-difluoro-4-(2-phenylpiperidin-1-yl)aniline;
4-((2S,6R)-2,6-dimethylmorpholino)-3,5-difluoroaniline;
4-(4-cyclohexylpiperidin-1-yl)-3,5-difluoroaniline;
4-(4-benzylpiperidin-1-yl)-3,5-difluoroaniline;
3,5-difluoro-4-(4-(4-methoxyphenyl)piperidin-1-yl)aniline;
3,5-difluoro-4-(4-(4-fluorophenyl)piperidin-1-yl)aniline;
4-(4-(3,4-difluorophenyl)piperidin-1-yl)-3,5-difluoroaniline;
4-(4-(3,5-difluorophenyl)piperidin-1-yl)-3,5-difluoroaniline;
3,5-difluoro-4-(4-fluoro-4-phenylpiperidin-1-yl)aniline;
3,5-difluoro-4-(4-(fluorodiphenylmethyl)piperidin-1-yl)aniline;
4-(4-fluoro-4-phenylpiperidin-1-yl)aniline;
3,5-difluoro-4-(4-(pyridin-2-yl)piperidin-1-yl)aniline;

3,5-difluoro-4-(4-(naphthalen-2-yl)piperidin-1-yl)aniline;

3,5-difluoro-4-(4-(naphthalen-1-yl)piperidin-1-yl)aniline; and

3,5-difluoro-4-(4-(4-(trimethylsilyl)phenyl)piperidin-1-yl)aniline.

General Procedure 1.1. 4-Alkoxy-substituted aniline



Intermediate anilines having an alkoxy substituent para to the aniline may be prepared through a two-step procedure wherein G_{10} is $-OR_S$ (e.g., –O–t-butyl, –O–isopropyl, –O–CH_2–(3-ethyloxetan-3-yl), –O–CH_2–(1,3-dioxolan-4-yl), –O–cyclopentyl, –O–cyclohexyl, –O–(1,3-dioxan-5-yl)). In Step 1, fluoronitrobenzenes can be reacted with an appropriate alcohol and base (e.g., Cs_2CO_3, potassium *tert*-butoxide) in DMSO or like solvent with heating to between 50-100 °C. Step 2 can be accomplished by standard nitro reduction conditions such as catalytic hydrogenation using palladium on carbon or Raney nickel as described elsewhere herein. Alternatively, the reduction can be effected with iron/ammonium chloride in THF/methanol/water as solvent.

Illustration of General Procedure 1.1: General Procedure 1.1A

Step 1

3-ethyl-3-((4-nitrophenoxy)methyl)oxetane

To a solution of 4-fluoronitrobenzene (3.76 mL, 35.4 mmol) in DMSO (35 mL) at room temperature was added cesium carbonate (7.09 mL, 89.0 mmol) followed by 3-ethyl-3-oxetanemethanol (4.48 mL, 42.5 mmol). The mixture was heated to 70 °C for 2 hours. After cooling water was added and the resulting precipitate was filtered, washed with water, and dried in a vacuum oven to provide the title compound (8.28 g, 98% yield).

Step 2

4-((3-ethyloxetan-3-yl)methoxy)aniline

To a solution of 3-ethyl-3-((4-nitrophenoxy)methyl)oxetane (8.28 g, 34.9 mmol) in a 3:3:1 mixture of THF:EtOH:water (140 mL) at room temperature was added ammonium chloride (2.80 g, 52.3 mmol) followed by iron powder (9.74 g, 174 mmol). The mixture was heated to 90 °C for 1 hour, then it was filtered hot through diatomaceous earth with a THF wash to complete the transfer. The filtrate was concentrated under reduced pressure, and the residue was taken up in ethyl acetate then washed with brine, dried (Na_2SO_4), and concentrated to provide the title compound (7.12 g, 98% yield) without further purification.

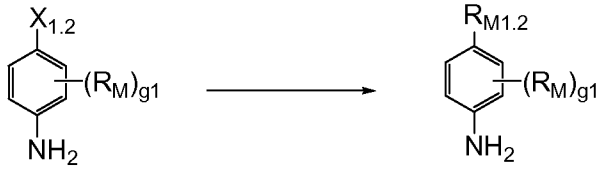
The following amines can be made using methods shown in the foregoing General Procedure 1:

4-((3-ethyloxetan-3-yl)methoxy)-3,5-difluoroaniline;

4-((1,3-dioxolan-4-yl)methoxy)aniline;

4-(1,3-dioxan-5-yloxy)aniline.

General Procedure 1.2. Aniline formation through Suzuki-type reaction



Certain intermediate anilines can be made from a bromide, iodide, or triflate (i.e., $X_{1.2}$ = Br, I, or OTf) through a Suzuki, Stille, or other similar transition metal-mediated carbon-carbon bond forming reaction to form products where $R_{M1..2}$ is cycloalkyl, aryl, heteroaryl, or cycloalkenyl. Above is an illustration of the process conducted on an aniline, however the process can be done also using other functionality which can be converted to an aniline (e.g., a nitro group).

Illustration of General Procedure 1.2. General Procedure 1.2A.

4-(cyclohexen-1-yl)-3-fluoroaniline

In a pressure tube, a solution of 3-fluoro-4-iodoaniline (2.29 g, 9.66 mmol) and potassium carbonate (1.74 g, 12.58 mmol) in 4:1 dimethoxyethane-water (33 mL) was degassed by nitrogen sparge for 40 minutes, followed by addition of 1-cyclohexenyl boronic acid pinacol ester (2.7 mL, 2.61 g, 12.56 mmol). Then 1,1'-bis(diphenylphosphino)ferrocene palladium (II) chloride dichloromethane complex (237 mg, 0.29 mmol) was added followed by degassing for another 5 minutes. The pressure tube was sealed and warmed at 100 °C for 18 hours. 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 with 3-(mercaptopropyl) silica gel for 1 hour. Concentration in vacuo afforded a brown oil, which was chromatographed over a 340 g silica gel cartridge, eluting with 10-100% ethyl acetate in hexanes. These procedures afforded the title compound (1.16 g, 63%) as a light brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.00 (m, 1 H), 6.37 (m, 2 H), 5.84 (s, 1 H), 3.71 (br s, 2 H), 2.32 (m, 2 H), 2.17 (m, 2 H), 1.73 (m, 2 H), 1.65 (m, 2 H); MS (+DCI) *m/z* (rel abundance) 192 (100, M+H).

Illustration of General Procedure 1.2. General Procedure 1.2B.

4-cyclopropyl-3,5-difluoroaniline

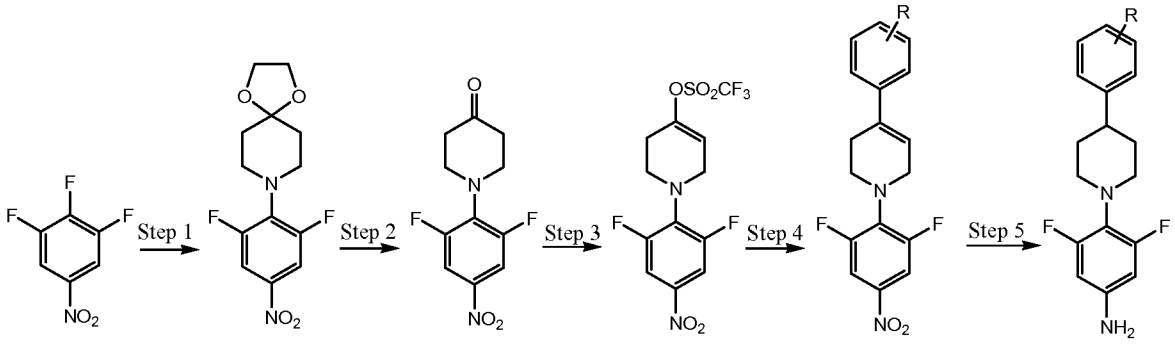
To a pressure tube was added 4-bromo-3,5-difluoroaniline (1.0g, 4.8 mmol), cesium carbonate (4.7g, 14.4 mmol), toluene (10mL) and water (1mL). The solution was de-gassed with N_2 gas for 30 minutes, followed by the addition of cyclopropyltrifluoro-borate, potassium salt (0.8g, 5.3 mmol), di(1-adamantyl)-*n*-butylphosphine hydroiodide (0.07g, 0.14 mmol) and palladium(II) acetate (0.02g, 0.096 mmol). De-gassing was continued for 5 minutes, the tube was sealed and heated at 100 °C for 18hours. The cooled solution was diluted with EtOAc, washed with H_2O and brine, dried (Na_2SO_4), and filtered. The filtrate was treated with 3-mercaptopropyl silica gel for 1 hour. The mixture was filtered and concentrated to give crude product which was purified by flash chromatography (0-30% EtOAc/hexane) to give the title compound (0.67 g, 4.0 mmol, 82%).

Illustration of General Procedure 1.2. General Procedure 1.2C.

4-cyclopropyl-2-fluoro-1-nitrobenzene

A solution of 4-bromo-2-fluoronitrobenzene (0.5g, 2.27mmol), cyclopropylboronic acid (0.293g, 3.41mmol), tribasic potassium phosphate (0.965g, 4.55mmol), tricyclohexylphosphonium tetrafluoroborate (0.021g, 0.057mmol) and palladium (II) acetate (6.12mg 0.027mmol) in 11 mL of a toluene–water mixture 10:1 (v/v) was nitrogen purged-vacuum degassed three times. The reaction mixture was then heated in an oil bath at 85°C for four hours. The reaction mixture was partitioned with ethyl acetate and the organic phase water washed then dried (Na_2SO_4) and concentrated. The reaction mixture was partitioned between ethyl acetate and water. The organic phase was washed with water, dried (Na_2SO_4) and concentrated. The crude product was purified by chromatography on silica gel (ethyl acetate–hexane) to provide the title compound (0.382g, 88%) as a yellow oil.

General Procedure 1.3



Certain intermediate anilines can be made using the general sequence outlined above and illustrated below. The sequence consists of reaction of a fluoronitrobenzene with a cyclic amine moiety (Step 1); conversion to a vinylic coupling partner (Steps 2 and 3); coupling of the vinylic coupling partner with another suitable partner (Step 4); and reduction of the nitro group and olefin (Step 5). Alternatively, this route may be adapted to prepare anilines wherein the olefin remains

intact through selective reduction of the nitro group. Carbon-carbon bond forming reactions that may be suitable for Step 4 include, for example, the Suzuki reaction, the Stille reaction, or the Negishi reaction.

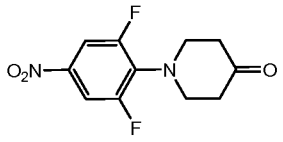
Illustration of General Procedure 1.3: General Procedure 1.3A

Step 1

8-(2,6-difluoro-4-nitrophenyl)-1,4-dioxa-8-azaspiro[4.5]decane

A mixture of 1,2,3-trifluoro-5-nitrobenzene (4.0 mL, 34.3 mmol), 1,4-dioxa-8-azaspiro[4.5]decane (6.59 mL, 51.4 mmol) and potassium carbonate (5.68 g, 41.1 mmol) in DMSO (35 mL) was heated at 100 °C for 3 hours and then cooled to room temperature. The mixture was partitioned between water and EtOAc, 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 0-20% EtOAc in hexanes to give a yellow oil.

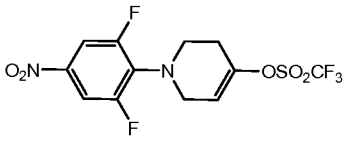
Step 2



1-(2,6-difluoro-4-nitrophenyl)piperidin-4-one

The crude 8-(2,6-difluoro-4-nitrophenyl)-1,4-dioxa-8-azaspiro[4.5]decane from the preceding procedure was dissolved in 4:1 acetone:water (100 mL). Concentrated HCl (5 mL) was added, and the resulting mixture was stirred at 50 °C for 8 hours and then cooled to room temperature. The mixture was concentrated in vacuo to approximately 20 mL, which was carefully added to concentrated aq. $NaHCO_3$ (100 mL) and extracted with EtOAc (2 x 100 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated in vacuo. The crude product was triturated with Et_2O and hexanes to give a bright-yellow solid that was collected and dried to provide the title compound (7.13 g, 81%).

Step 3

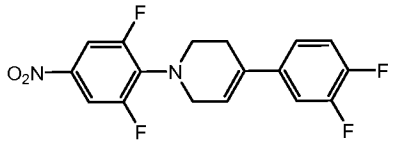


1-(2,6-difluoro-4-nitrophenyl)-1,2,3,6-tetrahydropyridin-4-yl trifluoromethanesulfonate

To a solution of 1-(2,6-difluoro-4-nitrophenyl)piperidin-4-one (5.0 g, 19.52 mmol) in anhydrous THF (50 mL) at -78 °C under a dry N_2 atmosphere was added a 1 *M* THF solution of lithium bis(triethylsilyl)amide (29.3 ml, 29.3 mmol) in THF dropwise over 10 minutes. The resulting deep red solution was stirred at -78 °C for 5 minutes and 1,1,1-trifluoro-*N*-phenyl-*N*-

(trifluoromethylsulfonyl)methanesulfonamide (7.67 g, 21.47 mmol) was added. The resulting mixture was stirred at - 78 °C for 1 hour, and then the mixture was allowed to warm to room temperature. The mixture was diluted with EtOAc (100 mL) and washed with 1 *N* aq. NaOH (50 mL) and water (50 mL), and dried over Na_2SO_4. The drying agent was filtered off, and the solvent was removed in vacuo to give a crude product that was purified by column chromatography on silica gel using a solvent gradient of 0-40% EtOAc in hexanes. The title compound was obtained as a yellow oil that crystallized in vacuo (6.12 g, 81%).

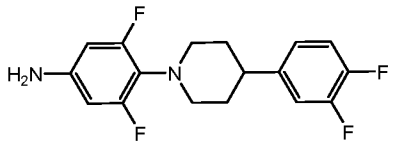
Step 4 (Suzuki reaction)



1-(2,6-difluoro-4-nitrophenyl)-4-(3,4-difluorophenyl)-1,2,3,6-tetrahydropyridine

A mixture of 1-(2,6-difluoro-4-nitrophenyl)-1,2,3,6-tetrahydropyridin-4-yl trifluoromethanesulfonate (1.18 g, 3.04 mmol), 2-(3,4-difluorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.02 g, 4.25 mmol), lithium chloride (0.387 g, 9.12 mmol) and a 2.0 *M* aq. solution of sodium carbonate (4.56 mL, 9.12 mmol) in anhydrous DME (15 mL) was vigorously stirred while bubbling with N_2 gas for 20 minutes. Tetrakis(triphenylphosphine)palladium(0) (0.176 g, 0.152 mmol) was added, and the resulting mixture was degassed for 5 minutes more. The reaction flask was equipped with a condenser and placed in 100 °C oil bath. The dark mixture was stirred at 100 °C under a dry N_2 atmosphere for 16 hours, and was then cooled to room temperature and partitioned between water (50 mL) and EtOAc (2×50 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo, and the crude product was purified by column chromatography on silica gel using a solvent gradient of 0-40% EtOAc in hexanes to provide a yellow oil that solidified on standing. The solid was triturated with Et_2O and hexanes, filtered and dried to provide the title compound (0.67 g, 63%).

Step 5



(4-(4-(3,4-difluorophenyl)piperidin-1-yl)-3,5-difluoroaniline

To a solution of 1-(2,6-difluoro-4-nitrophenyl)-4-(3,4-difluorophenyl)-1,2,3,6-tetrahydropyridine (0.67 g, 1.90 mmol) in THF (20 mL) was added 10% Pd on carbon (50 mg). The reaction flask was flushed with N_2 gas, and the resulting mixture was vigorously stirred under 1 atm

H_2 gas for 24 hours. The mixture was filtered through diatomaceous earth and concentrated in vacuo to give the title compound as a solid (0.62 g, 100%).

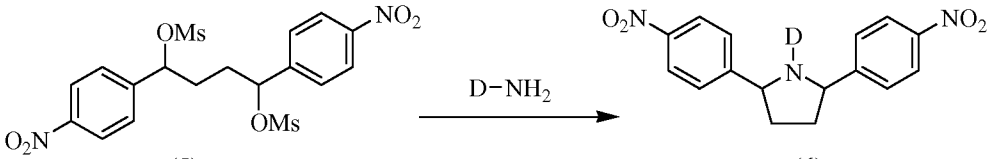
The following amines can be made using methods shown in the foregoing General Procedure 1.3:

3,5-difluoro-4-(4-(4-fluorophenyl)piperidin-1-yl)aniline;

3,5-difluoro-4-(4-(3-(trimethylsilyl)phenyl)piperidin-1-yl)aniline; and

3,5-difluoro-4-(4-(5-methylthiophen-2-yl)piperidin-1-yl)aniline.

General Procedure 2. Pyrrolidine formation from amine and dimesylate (5)



(5) (6)

A dimesylate (5) (1 equivalent), as a single stereoisomer or mixture of isomers, may be reacted with between 1 to 20 equivalents of an amine,.D-NH_2, either neat, or in solvents such as tetrahydrofuran or 2-methyltetrahydrofuran with or without a co-solvent such as DMF, at about room temperature to about 100 °C, to give the pyrrolidines such as Formula (6). Where fewer equivalents of amine, D-NH_2, are employed (i.e., 1-2 equivalents), a base such as diisopropylethylamine can be added to promote the reaction. For example, the reaction of a dimesylate (1 equivalent) with excess of an aniline, D-NH_2, (about 5-10 equivalents) can be conducted by heating from 50 to 65 °C in 2-methyltetrahydrofuran or DMF until completion of the reaction. Or the dimesylate (1 equivalent) can be reacted neat with excess of an aniline, D-NH_2, (about 15-20 equivalents) at room temperature or with heating to around 65 °C. The reaction can be partitioned between an organic solvent (e.g., ethyl acetate) and dilute aqueous HCl, followed by separation of the organic layer, optional washing of the organic with water, drying the organic layer with a drying agent (e.g., $MgSO_4$, Na_2SO_4), filtration and evaporation of solvent. The product can be purified by column chromatography over silica gel, eluting with standard solvents such as mixtures of ethyl acetate and hexane; or alternatively the product can be purified by trituration or recrystallization.

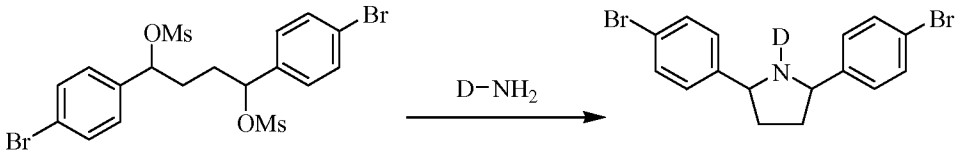
Illustration of General Procedure 2: General Procedure 2A

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

To the crude product solution of Intermediate 6C (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 hours. 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 CH_3OH (46 mL) for 3 hours, filtered, and the wet solid was washed with additional CH_3OH (18 mL). The solid was dried at 45 °C in a vacuum oven for 16 hours to provide the title compound (3.08 g).

General Procedure 3. Pyrrolidine formation from amine and bisbromophenyldimesylate



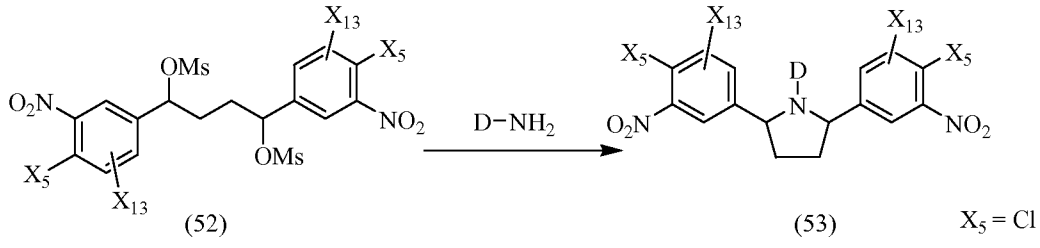
General Procedure 3 can be conducted using conditions substantially similar to the conditions of General Procedure 2.

Illustration of General Procedure 3: General Procedure 3A

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

Intermediate 7C 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 4 hours, and then it was partitioned between 1 *N* 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.

General Procedure 4. Pyrrolidine formation from amine and dimesylate (52)



(52) (53) X_5 = Cl

General Procedure 4 can be conducted using conditions substantially similar to the conditions of General Procedure 2. For example, a dimesylate (52) (1 equivalent), as a single stereoisomer or mixture of isomers, may be reacted with between 1 to 20 equivalents of an amine D-NH_2 either neat, or in solvents or mixtures of solvents including ethanol, acetonitrile, methylene chloride,

tetrahydrofuran , 2-methyltetrahydrofuran, DMF, or DMA, at about room temperature to about 100 °C, to give the pyrrolidines such as Formula (53). Alternatively, a dimesylate (52) (1 equivalent) can be reacted with an amine D–NH_2 (1-4 equivalents) in the presence of a base like diisopropylethylamine (3-10 equivalents) in solvents or mixtures of solvents including methylene chloride, tetrahydrofuran, 2-methyltetrahydrofuran, DMF, or DMA at temperatures from around room temperature to about 70 °C. Where fewer equivalents of amine D-NH_2 are employed (i.e., 1-2 equivalents), greater amounts of a base (about 8-10 equivalents) such as diisopropylethylamine may be added to promote the reaction. For less reactive amines (e.g., 2,5-difluoro-4-(trifluoromethyl)aniline, 2-fluoropyridin-4-amine), a reaction time of several days may be required. The reaction can be partitioned between an organic solvent (e.g., ethyl acetate) and water or dilute aqueous HCl, followed by separation of the organic layer, optional washing of the organic with water and/or brine, drying the organic layer with a drying agent (e.g., $MgSO_4$, Na_2SO_4), filtration and evaporation of solvent. The product (53) can be purified by column chromatography over silica gel, eluting with standard solvents such as mixtures of ethyl acetate and hexane or methylene chloride in hexane. The methylene chloride/hexane system can be used to remove residual amine in cases where the reaction is quenched in water instead of aqueous HCl. In such cases a second chromatography using an ethyl acetate/hexane system may be necessary to separate cis from trans pyrrolidine products. Or alternatively, the product can be purified by trituration or recrystallization.

Illustration of General Procedure 4: General Procedure 4A

(2*R*,5*R*)-2,5-bis(4-chloro-3-nitrophenyl)-1-(4-cyclohexylphenyl)pyrrolidine

To Intermediate 5D (4.99 mmol) in dimethylformamide (8 mL) was added 4-cyclohexylaniline (5.24 g, 29.9 mmol), and the solution was heated at 65 °C for 2 hours. The reaction mixture was then poured into 1 *M* HCl and extracted into dichloromethane. The organic phase was concentrated and purified with a CombiFlash® 80g silica column eluting with 0-20% ethyl acetate in hexanes to give 1.38 g (51%) of the title compound.

Illustration of General Procedure 4: General Procedure 4B

1-(4-((2*R*,5*R*)-2,5-bis(4-chloro-3-nitrophenyl)pyrrolidin-1-yl)-2,6-difluorophenyl)-4-phenylpiperidine

A 250 mL flask was charged with 3,5-difluoro-4-(4-phenylpiperidin-1-yl)aniline (3.1 g, 10.76 mmol), Intermediate 5D (5.0 g, 8.97 mmol), DMF (15 mL) and diisopropylethylamine (15.7 mL, 90 mmol). The resulting slurry was placed in a 60 °C oil bath and heated under N_2 for 18 hours. The amber solution was cooled, diluted with 300 mL of ethyl acetate, washed 2×100 mL water, 2×100 mL with 1 *N* HCl, brine, dried (Na_2SO_4), filtered and concentrated. The crude material was flash chromatographed on a 330 g silica cartridge eluting with 50-80% dichloromethane in hexane to remove unreacted aniline. The column fractions containing the product were combined and

concentrated to give an orange solid that was dissolved in 20 mL of hot ethyl acetate, treated with 15 mL hexane, and allowed to stir at ambient temperature overnight producing a precipitate (cis pyrrolidine) that was removed by filtration. The filtrate was concentrated and chromatographed again on a 330 g silica cartridge eluting with 40-70% methylene chloride in hexane to give 1-(4-((2*R*,5*R*)-2,5-bis(4-chloro-3-nitrophenyl)pyrrolidin-1-yl)-2,6-difluorophenyl)-4-phenylpiperidine as an orange foam (2.26 g, 36%). MS (ESI+) *m/z* 653 $(M+H)^+$.

Illustration of General Procedure 4: General Procedure 4C

1-(4-((2*R*,5*R*)-2,5-bis(4-chloro-3-nitrophenyl)pyrrolidin-1-yl)-2-fluorophenyl)-4-phenylpiperidine

Intermediate 5D (6.0 g, 10.76 mmol), 3-fluoro-4-(4-phenylpiperidin-1-yl)aniline (4.37 g, 16.15 mmol), and diisopropylethylamine (15.04 mL, 86 mmol) were combined in *N*,*N*-dimethylacetamide (15 mL) and heated at 60 °C for 3 hours. The solution was diluted with water, extracted into dichloromethane and washed with brine. The organics were concentrated and purified by chromatography, eluting with 30-100% dichloromethane in hexanes to give 5.05 g (74%) of a yellow solid.

Illustration of General Procedure 4: General Procedure 4D

(2*R*,5*R*)-2,5-bis(4-chloro-3-nitrophenyl)-1-(4-ethoxyphenyl)pyrrolidine

Intermediate 5D (2.5805 g, 4.63 mmol) and 4-ethoxyaniline (2.4 mL, 18.60 mmol) were combined in DMF (30 mL) and stirred at room temperature overnight. The reaction was diluted with EtOAc/ether and washed with water (2×), brine (1×) and concentrated. The residue was purified by silica gel chromatography (hexane/EtOAc) to provide 1.8 g of the title compound (77%).

Illustration of General Procedure 4: General Procedure 4E

1-(4-((2*R*,5*R*)-2,5-bis(4-chloro-2-fluoro-5-nitrophenyl)pyrrolidin-1-yl)-2,6-difluorophenyl)piperidine

To a solution of (1*S*,4*S*)-1,4-bis(4-chloro-2-fluoro-5-nitrophenyl)butane-1,4-diyl dimethanesulfonate (500 mg, 0.843 mmol) in CH_3CN (4.5 ml) was added 3,5-difluoro-4-(piperidin-1-yl)aniline (358 mg, 1.685 mmol) and Hunig's base (0.736 mL, 4.21 mmol). The suspension was heated at 75 °C for 24 hours. Solvent was removed by rotary evaporation and the residue was dissolved in EtOAc, washed with 1 *N* HCl, H_2O, brine, dried ($MgSO_4$), filtered and concentrated. The crude product was chromatographed on an ISCO 24g silica gel cartridge eluting with 20-70% CH_2Cl_2/hexane to provide the title compound with some of the corresponding cis-pyrrolidine isomer.

The following substituted pyrrolidines can be made using the foregoing general methods:

1-(4-((2*R*,5*R*)-2,5-bis(4-chloro-3-nitrophenyl)pyrrolidin-1-yl)-2,6-difluorophenyl)-4,4-dimethylpiperidine;

2-(4-((2*R*,5*R*)-2,5-bis(4-chloro-3-nitrophenyl)pyrrolidin-1-yl)-2,6-difluorophenyl)-2-azabicyclo[2.2.2]octane;

1-(4-((2*R*,5*R*)-2,5-bis(4-chloro-3-nitrophenyl)pyrrolidin-1-yl)-2,6-difluorophenyl)-4-isopropylpiperidine;

1-(4-((2*R*,5*R*)-2,5-bis(4-chloro-3-nitrophenyl)pyrrolidin-1-yl)-2,6-difluorophenyl)-4-(trifluoromethyl)piperidine;

1-(4-((2*R*,5*R*)-2,5-bis(4-chloro-3-nitrophenyl)pyrrolidin-1-yl)-2,6-difluorophenyl)-4-*tert*-butylpiperidine;

6-(4-((2*R*,5*R*)-2,5-bis(4-chloro-3-nitrophenyl)pyrrolidin-1-yl)-2,6-difluorophenyl)-6-azaspiro[2.5]octane;

1-(4-((2*R*,5*R*)-2,5-bis(4-chloro-3-nitrophenyl)pyrrolidin-1-yl)-2,6-difluorophenyl)-4,4-dimethylpiperidine;

(2*R*,5*R*)-2,5-bis(4-chloro-3-nitrophenyl)-1-(4-(3,3-dimethylazetidin-1-yl)-3,5-difluorophenyl)pyrrolidine;

(2*R*,5*R*)-2,5-bis(4-chloro-3-nitrophenyl)-1-(4-phenoxyphenyl)pyrrolidine;

1-(4-((2*R*,5*R*)-2,5-bis(4-chloro-3-nitrophenyl)pyrrolidin-1-yl)phenyl)pyridin-2(1*H*)-one;

(2*R*,5*R*)-2,5-bis(4-chloro-3-nitrophenyl)-1-(2,5-difluoro-4-(trifluoromethyl)phenyl)pyrrolidine;

2-(4-((2*R*,5*R*)-2,5-bis(4-chloro-3-nitrophenyl)pyrrolidin-1-yl)phenyl)oxazole;

4-((2*R*,5*R*)-2,5-bis(4-chloro-3-nitrophenyl)pyrrolidin-1-yl)-2-fluoropyridine;

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

1-(4-((2*R*,5*R*)-2,5-bis(4-chloro-3-nitrophenyl)pyrrolidin-1-yl)-2,6-difluorophenyl)-4,4-difluoropiperidine;

1-(4-((2*R*,5*R*)-2,5-bis(4-chloro-3-nitrophenyl)pyrrolidin-1-yl)-2,6-difluorophenyl)-4-fluoropiperidine;

1-(4-((2*R*,5*R*)-2,5-bis(4-chloro-3-nitrophenyl)pyrrolidin-1-yl)-2,6-difluorophenyl)piperidine;

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

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

(2*R*,5*R*)-2,5-bis(4-chloro-3-nitrophenyl)-1-(4-cyclopropyl-3,5-difluorophenyl)pyrrolidine;

(2*R*,5*R*)-2,5-bis(4-chloro-3-nitrophenyl)-1-(4-cyclohexyl-3-fluorophenyl)pyrrolidine;

(2*R*,5*R*)-2,5-bis(4-chloro-3-nitrophenyl)-1-(3,4-difluorophenyl)pyrrolidine;

(2*R*,5*R*)-2,5-bis(4-chloro-3-nitrophenyl)-1-(4-(2,2-difluoroethoxy)phenyl)pyrrolidine;

1-(4-((2*R*,5*R*)-2,5-bis(4-chloro-3-nitrophenyl)pyrrolidin-1-yl)-2,6-difluorophenyl)-3,5-dimethylpiperidine;

(2*R*,5*R*)-2,5-bis(4-chloro-3-nitrophenyl)-1-[4-(pentafluoro-λ^6-sulfanyl)phenyl]pyrrolidine (ACD Name v12);

2-(4-((2*R*,5*R*)-2,5-bis(4-chloro-3-nitrophenyl)pyrrolidin-1-yl)phenyl)pyridine;
(2*R*,5*R*)-2,5-bis(4-chloro-3-nitrophenyl)-1-(3-chloro-4-(trifluoromethoxy)phenyl)pyrrolidine;
(2*R*,5*R*)-2,5-bis(4-chloro-3-nitrophenyl)-1-(4-(2-methoxyethoxy)-3-methylphenyl)pyrrolidine;
(2*R*,5*R*)-2,5-bis(4-chloro-3-nitrophenyl)-1-(4-chlorophenyl)pyrrolidine;
(2*R*,5*R*)-2,5-bis(4-chloro-3-nitrophenyl)-1-(4-((3-ethyloxetan-3-yl)methoxy)phenyl)pyrrolidine;
(2*R*,5*R*)-1-(biphenyl-4-yl)-2,5-bis(4-chloro-3-nitrophenyl)pyrrolidine;
(2*R*,5*R*)-1-(4-(1,3-dioxan-5-yloxy)phenyl)-2,5-bis(4-chloro-3-nitrophenyl)pyrrolidine;
(2*R*,5*R*)-1-(4-((1,3-dioxolan-4-yl)methoxy)phenyl)-2,5-bis(4-chloro-3-nitrophenyl)pyrrolidine;
(2*R*,5*R*)-2,5-bis(4-chloro-3-nitrophenyl)-1-(4-((3-ethyloxetan-3-yl)methoxy)-3,5-difluorophenyl)pyrrolidine;
1-(4-((2*R*,5*R*)-2,5-bis(4-chloro-3-nitrophenyl)pyrrolidin-1-yl)-2,3,5,6-tetrafluorophenyl)piperidine;
1-(4-((2*R*,5*R*)-2,5-bis(4-chloro-3-nitrophenyl)pyrrolidin-1-yl)-2-methylphenyl)piperidine;
(3a*R*,7a*S*)-2-(4-((2*R*,5*R*)-2,5-bis(4-chloro-3-nitrophenyl)pyrrolidin-1-yl)-2,6-difluorophenyl)octahydro-1*H*-isoindole;
4-((2*R*,5*R*)-2,5-bis(4-chloro-3-nitrophenyl)pyrrolidin-1-yl)-*N*-*tert*-butyl-2-fluoroaniline;
1-(4-((2*R*,5*R*)-2,5-bis(4-chloro-3-nitrophenyl)pyrrolidin-1-yl)-2,6-difluorophenyl)-4-methylpiperidine;
(2*R*,5*R*)-2,5-bis(4-chloro-3-nitrophenyl)-1-(4-(cyclopentyloxy)-3-fluorophenyl)pyrrolidine;
(2*R*,5*R*)-2,5-bis(4-chloro-3-nitrophenyl)-1-(3-fluoro-4-(methylthio)phenyl)pyrrolidine
1-(4-((2*R*,5*R*)-2,5-bis(4-chloro-3-nitrophenyl)pyrrolidin-1-yl)-2,6-dichlorophenyl)piperidine;
1-(4-((2*R*,5*R*)-2,5-bis(4-chloro-3-nitrophenyl)pyrrolidin-1-yl)-2,5-difluorophenyl)piperidine;
(2*R*,6*S*)-1-(4-((2*R*,5*R*)-2,5-bis(4-chloro-3-nitrophenyl)pyrrolidin-1-yl)-2,6-difluorophenyl)-2,6-dimethylpiperidine;
1-(4-((2*R*,5*R*)-2,5-bis(4-chloro-3-nitrophenyl)pyrrolidin-1-yl)-2,3,6-trifluorophenyl)piperidine;
(2*R*,5*R*)-2,5-bis(4-chloro-3-nitrophenyl)-1-(4-cyclopropylphenyl)pyrrolidine;
(1*R*,5*S*)-3-(4-((2*R*,5*R*)-2,5-bis(4-chloro-3-nitrophenyl)pyrrolidin-1-yl)-2,6-difluorophenyl)-3-azabicyclo[3.2.0]heptane;
(2*R*,5*R*)-2,5-bis(4-chloro-3-nitrophenyl)-1-(4-cyclopropyl-2-fluorophenyl)pyrrolidine;
1-(4-((2*R*,5*R*)-2,5-bis(4-chloro-3-nitrophenyl)pyrrolidin-1-yl)-2-fluorophenyl)piperidine;
1-(4-((2*R*,5*R*)-2,5-bis(4-chloro-3-nitrophenyl)pyrrolidin-1-yl)phenyl)-4-phenylpiperidine;
3-(4-((2*R*,5*R*)-2,5-bis(4-chloro-3-nitrophenyl)pyrrolidin-1-yl)-2,6-difluorophenyl)-3-azaspiro[5.5]undecane;
2-(4-((2*R*,5*R*)-2,5-bis(4-chloro-3-nitrophenyl)pyrrolidin-1-yl)-2,6-difluorophenyl)isoindoline;
8-(4-((2*R*,5*R*)-2,5-bis(4-chloro-3-nitrophenyl)pyrrolidin-1-yl)-2,6-difluorophenyl)-1,4-dioxa-8-azaspiro[4.5]decane;

1-(4-((2*R*,5*R*)-2,5-bis(4-chloro-3-nitrophenyl)pyrrolidin-1-yl)-2,6-difluorophenyl)-4-phenyl-1,2,3,6-tetrahydropyridine;

1-(4-((2*R*,5*R*)-2,5-bis(4-chloro-3-nitrophenyl)pyrrolidin-1-yl)-2,6-difluorophenyl)-4,4-diphenylpiperidine;

1-(1-(4-((2*R*,5*R*)-2,5-bis(4-chloro-3-nitrophenyl)pyrrolidin-1-yl)-2,6-difluorophenyl)-4-phenylpiperidin-4-yl)ethanone;

1-(4-((2R,5R)-2,5-bis(4-chloro-2-fluoro-5-nitrophenyl)pyrrolidin-1-yl)-2,6-difluorophenyl)piperidine;

1-(4-(2,5-bis(4-chloro-2-fluoro-5-nitrophenyl)pyrrolidin-1-yl)-2,6-difluorophenyl)piperidine;

1-(4-((2R,5R)-2,5-bis(4-chloro-3-nitrophenyl)pyrrolidin-1-yl)-2,6-difluorophenyl)-4-(3-phenylpropyl)piperidine;

8-(4-((2R,5R)-2,5-bis(4-chloro-3-nitrophenyl)pyrrolidin-1-yl)-2,6-difluorophenyl)-8-azaspiro[4.5]decane;

1-(4-((2R,5R)-2,5-bis(4-chloro-3-nitrophenyl)pyrrolidin-1-yl)-2,6-difluorophenyl)-4-(naphthalen-2-yl)piperidine;

2-(1-(4-((2R,5R)-2,5-bis(4-chloro-3-nitrophenyl)pyrrolidin-1-yl)-2,6-difluorophenyl)piperidin-4-yl)pyridine;

1-(4-((2R,5R)-2,5-bis(4-chloro-3-nitrophenyl)pyrrolidin-1-yl)-2,6-difluorophenyl)-4-(4-(trimethylsilyl)phenyl)piperidine;

1-(4-((2R,5R)-2,5-bis(4-chloro-3-nitrophenyl)pyrrolidin-1-yl)-2,6-difluorophenyl)-4-(naphthalen-1-yl)piperidine;

1-(4-((2R,5R)-2,5-bis(4-chloro-2-fluoro-5-nitrophenyl)pyrrolidin-1-yl)-2,6-difluorophenyl)-4-(3-phenylpropyl)piperidine;

6-(4-((2R,5R)-2,5-bis(4-chloro-2-fluoro-5-nitrophenyl)pyrrolidin-1-yl)-2,6-difluorophenyl)-6-azaspiro[2.5]octane;

1-(4-((2R,5R)-2,5-bis(4-chloro-2-fluoro-5-nitrophenyl)pyrrolidin-1-yl)-2,6-difluorophenyl)-4-*tert*-butylpiperidine;

1-(4-((2R,5R)-2,5-bis(4-chloro-2-fluoro-5-nitrophenyl)pyrrolidin-1-yl)-2,6-difluorophenyl)-4-(naphthalen-2-yl)piperidine;

1-(4-((2R,5R)-2,5-bis(4-chloro-2-fluoro-5-nitrophenyl)pyrrolidin-1-yl)-2,6-difluorophenyl)-3,5-dimethylpiperidine;

1'-(4-((2R,5R)-2,5-bis(4-chloro-2-fluoro-5-nitrophenyl)pyrrolidin-1-yl)-2,6-difluorophenyl)-2,3-dihydrospiro[indene-1,4'-piperidine];

1-(4-((2R,5R)-2,5-bis(4-chloro-3-nitrophenyl)pyrrolidin-1-yl)-2,6-difluorophenyl)-3-phenylpiperidine;

(2R,5R)-2,5-bis(4-chloro-3-nitrophenyl)-1-(3,5-difluoro-4-(3-phenylpyrrolidin-1-yl)phenyl)pyrrolidine;

1-(4-((2R,5R)-2,5-bis(4-chloro-3-nitrophenyl)pyrrolidin-1-yl)-2,6-difluorophenyl)-4-(4-methoxyphenyl)piperidine;

1-(4-((2R,5R)-2,5-bis(4-chloro-3-nitrophenyl)pyrrolidin-1-yl)-2,6-difluorophenyl)-4-fluoro-4-phenylpiperidine;

1-(4-((2R,5R)-2,5-bis(4-chloro-3-nitrophenyl)pyrrolidin-1-yl)phenyl)-4-fluoro-4-phenylpiperidine;

1-(4-((2R,5R)-2,5-bis(4-chloro-2-fluoro-5-nitrophenyl)pyrrolidin-1-yl)-2,6-difluorophenyl)-4-(fluorodiphenylmethyl)piperidine;

1-(4-((2R,5R)-2,5-bis(4-chloro-2-fluoro-5-nitrophenyl)pyrrolidin-1-yl)-2,6-difluorophenyl)-4-phenylpiperidine;

1-(4-((2R,5R)-2,5-bis(4-chloro-3-nitrophenyl)pyrrolidin-1-yl)-2,6-difluorophenyl)-4-(4-fluorophenyl)piperidine;

1-(4-((2R,5R)-2,5-bis(4-chloro-3-nitrophenyl)pyrrolidin-1-yl)-2,6-difluorophenyl)-4-(3,4-difluorophenyl)piperidine;

1-(4-((2R,5R)-2,5-bis(4-chloro-3-nitrophenyl)pyrrolidin-1-yl)-2,6-difluorophenyl)-4-(3,5-difluorophenyl)piperidine;

1-(4-((2R,5R)-2,5-bis(4-chloro-3-nitrophenyl)pyrrolidin-1-yl)-2,6-difluorophenyl)-4-(3-(trimethylsilyl)phenyl)piperidine;

(2R,5R)-1-(4-(benzyloxy)phenyl)-2,5-bis(4-chloro-3-nitrophenyl)pyrrolidine;

1-(4-((2R,5R)-2,5-bis(4-chloro-2-fluoro-5-nitrophenyl)pyrrolidin-1-yl)-2,6-difluorophenyl)-4-(4-(trifluoromethyl)phenyl)piperazine;

1-(4-((2R,5R)-2-(4-chloro-2-fluoro-5-nitrophenyl)-5-(4-chloro-3-nitrophenyl)pyrrolidin-1-yl)-2,6-difluorophenyl)piperidine;

4-benzyl-1-(4-((2R,5R)-2,5-bis(4-chloro-2-fluoro-5-nitrophenyl)pyrrolidin-1-yl)-2,6-difluorophenyl)piperidine;

4-(4-((2R,5R)-2,5-bis(4-chloro-3-nitrophenyl)pyrrolidin-1-yl)-2,6-difluorophenyl)-2-phenylmorpholine;

1-(4-((2R,5R)-2,5-bis(4-chloro-3-nitrophenyl)pyrrolidin-1-yl)-2,6-difluorophenyl)-2-phenylpiperidine;

(2S,6R)-4-(4-((2R,5R)-2,5-bis(4-chloro-2-fluoro-5-nitrophenyl)pyrrolidin-1-yl)-2,6-difluorophenyl)-2,6-dimethylmorpholine;

3-(4-((2R,5R)-2,5-bis(4-chloro-2-fluoro-5-nitrophenyl)pyrrolidin-1-yl)-2,6-difluorophenyl)-3-azaspiro[5.5]undecane;

1-(4-((2R,5R)-2,5-bis(4-chloro-2-fluoro-5-nitrophenyl)pyrrolidin-1-yl)-2,6-difluorophenyl)-4-cyclohexylpiperidine;

(S)-4-(4-((2R,5R)-2,5-bis(4-chloro-3-nitrophenyl)pyrrolidin-1-yl)-2,6-difluorophenyl)-2-phenylmorpholine;

1-(4-((2R,5R)-2,5-bis(4-chloro-2-fluoro-5-nitrophenyl)pyrrolidin-1-yl)-2,6-difluorophenyl)-4-(2,4-difluorophenyl)piperidine;

1-(4-((2R,5R)-2,5-bis(4-chloro-2-fluoro-5-nitrophenyl)pyrrolidin-1-yl)-2,6-difluorophenyl)-4-(4-fluorophenyl)piperidine;

1-(4-((2R,5R)-2,5-bis(4-chloro-3-nitrophenyl)pyrrolidin-1-yl)-2,6-difluorophenyl)-4-phenylpiperazine;

1-(4-((2R,5R)-2,5-bis(4-chloro-3-nitrophenyl)pyrrolidin-1-yl)-2,6-difluorophenyl)-4-(4-(trifluoromethyl)phenyl)piperazine;

1-(4-((2R,5R)-2,5-bis(4-chloro-2-fluoro-5-nitrophenyl)pyrrolidin-1-yl)-2,6-difluorophenyl)-4-(2,6-difluorophenyl)piperazine;

2-(4-(4-((2R,5R)-2,5-bis(4-chloro-2-fluoro-5-nitrophenyl)pyrrolidin-1-yl)-2,6-difluorophenyl)piperazin-1-yl)pyrimidine;

5-((2S,5R)-2,5-bis(4-chloro-2-fluoro-5-nitrophenyl)pyrrolidin-1-yl)-2-(4-phenylpiperidin-1-yl)pyrimidine;

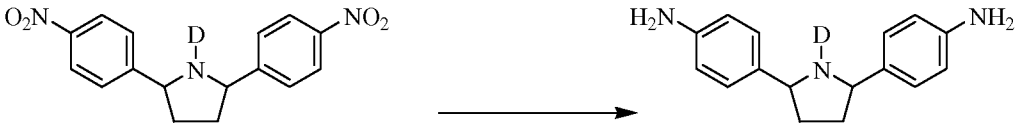
5-((2S,5R)-2,5-bis(4-chloro-2-fluoro-5-nitrophenyl)pyrrolidin-1-yl)-2-(piperidin-1-yl)pyrimidine;

1-(4-((2S,5S)-2,5-bis(4-chloro-2-fluoro-5-nitrophenyl)pyrrolidin-1-yl)-2,6-difluorophenyl)-4-(2,6-difluorophenyl)piperazine;

1-(4-((2R,5R)-2,5-bis(4-chloro-2-fluoro-5-nitrophenyl)pyrrolidin-1-yl)-2,6-difluorophenyl)-4-(5-methylthiophen-2-yl)piperidine; and

1-(4-((2R,5R)-2,5-bis(4-chloro-2-fluoro-5-nitrophenyl)pyrrolidin-1-yl)-2,6-difluorophenyl)-4-fluoro-4-phenylpiperidine.

General Procedure 5. Nitro reduction

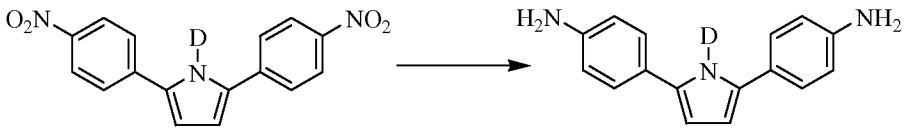


(6) (7)

Compounds (6) (1 equivalent) can be reduced to (7) by reaction with iron powder (about 6 equivalents) and ammonium chloride (about 3 equivalents) in a solvent of THF:ethanol:water (1:1:0.2) with heating to about 60-80 °C. The reaction can be worked up by cooling, filtering through diatomaceous earth, washing with ethanol and concentrating in vacuo. Alternatively, (6) (1 equivalent) can be reduced to (7) by hydrogenation (30 psi H_2) in the presence of PtO_2 (about 0.4 equivalents) in a solvent of ethanol:THF (about 1:1). The reaction can be worked up by filtration and evaporation of solvent. Alternatively, the reduction of (6) (1 equivalent) to (7) can be effected by exposure to 30 psig hydrogen gas in the presence of Raney-nickel Grace 2800 (50% by weight of reactant) in a solvent such as tetrahydrofuran with shaking. The reaction can be worked up by

filtration and evaporation of solvent. The product (7) can be purified by chromatography over silica gel using typical organic solvents including mixtures of ethyl acetate and hexane.

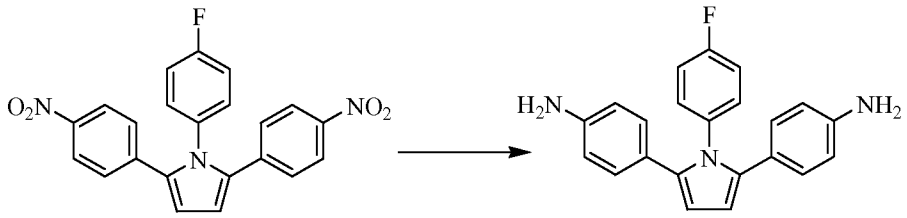
General Procedure 5.1. Nitro reduction for pyrrole



(11) (12)

Compounds (11) can be converted to (12) using the conditions described generally for General Procedure 5, particularly through the iron reduction method.

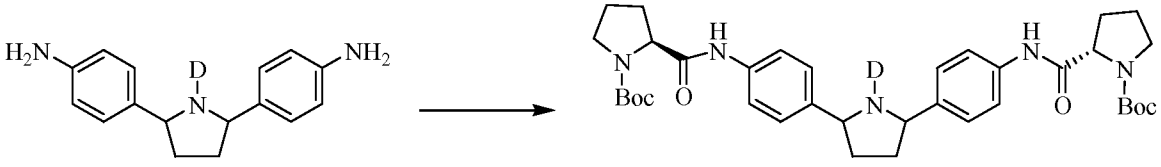
Illustration of General Procedure 5.1: General Procedure 5.1A



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

To a solution of 1-(4-fluorophenyl)-2,5-bis(4-nitrophenyl)-1*H*-pyrrole (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). The reaction mixture was refluxed for 45 minutes. The reaction mixture was slurry filtered through diatomaceous earth and washed with ethanol. The combined filtrates were 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.

General Procedure 6. Amide coupling

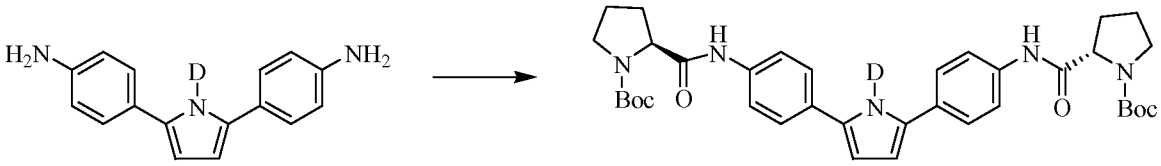


(7) (8)

Compounds (7) (1 equivalent) can be converted to compounds (8) by reaction with 1-(*tert*-butoxycarbonyl)pyrrolidine-2-carboxylic acid (about 2.5 equivalents) and HATU (about 2 to 3 equivalents) in the presence of diisopropylethylamine (3-4 equivalents) in DMSO at about room

temperature. Alternatively to using HATU, this reaction can be promoted using T3P or 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide/1-hydroxybenzotriazole. The reaction can also be conducted in solvents such as tetrahydrofuran, ethyl acetate, or DMF. The reaction can be worked up by partitioning between an organic solvent (e.g., ethyl acetate) and water or dilute aqueous HCl, followed by separation of the organic layer, optional washing of the organic with water and/or brine, drying the organic layer with a drying agent (e.g., $MgSO_4$, Na_2SO_4), filtration and evaporation of solvent. The product (8) can be purified by column chromatography over silica gel, eluting with standard organic solvents including mixtures of ethyl acetate and hexane.

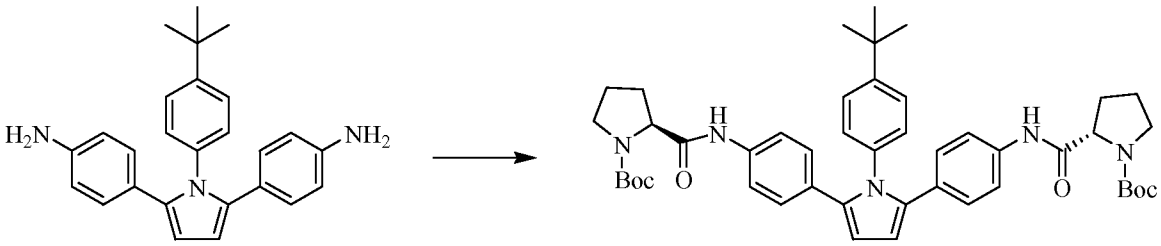
General Procedure 6.1. Amide coupling for pyrroles



(12) (13)

Aniline compounds (12) can be converted to amides (13) using the conditions described generally above in General Procedure 6.

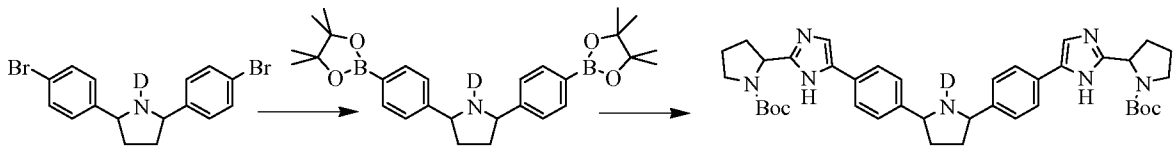
Illustration of General Procedure 6.1: General Procedure 6.1A



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

To a solution of 4,4'-(1-(4-*tert*-butylphenyl)-1*H*-pyrrole-2,5-diyl)dianiline (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. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 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).

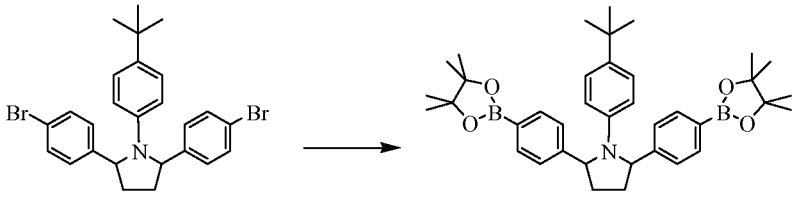
General Procedure 7. Suzuki coupling



(34.1) (35.1) (36.1)

Dibromo compounds (34.1) (1 equivalent) can be converted to diboronate compounds (35.1) by mixing with bis(pinacolato)diborane (about 2 to 4 equivalents), potassium acetate (about 4-8 equivalents), and 1,1'-bis(diphenylphosphino)ferrocene-palladium(II) chloride dichloromethane complex ($PdCl_2$(dppf)) (about 0.1 to 0.2 equivalents) in a solvent such as DME, dioxane, or DMSO, degassing the mixture and heating to about 85 °C. The reaction can be worked up by cooling to room temperature, diluting with methylene chloride, optionally washing the organics with water and/or brine, drying the organics with a drying agent (e.g., $MgSO_4$, Na_2SO_4), filtration and evaporation of solvent. Compounds (35.1) can be converted to compounds (36.1) by mixing with Intermediate 1D (about 1 to 2 equivalents), aqueous sodium carbonate solution (about 1 to 3.5 equivalents), and $PdCl_2$(dppf) (about 0.03 to 0.2 equivalents) in a solvent like dimethoxyethane or toluene:ethanol (1:1), degassing, and heating the reaction to around 80-100 °C. The reaction can be worked up by cooling to room temperature, partitioning between an organic solvent (e.g., ethyl acetate) and water, optionally washing the organics with water and/or brine, drying the organics with a drying agent (e.g., $MgSO_4$, Na_2SO_4), filtration and evaporation of solvent. Alternatively, the reaction can be worked up by concentration in vacuo, partitioning between 25% isopropylalcohol/chloroform, drying the organics (e.g., Na_2SO_4), filtration, and evaporation of the solvent. Compounds (35.1) and (36.1) can be purified by column chromatography over silica gel, eluting with standard organic solvents including mixtures of ethyl acetate and hexane; or purified by trituration or recrystallization.

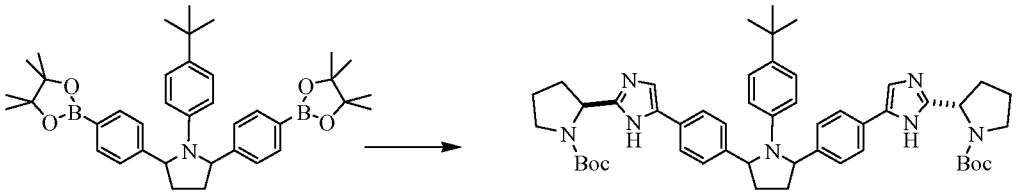
Illustration of General Procedure 7: General Procedure 7A



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

Racemic trans-2,5-bis(4-bromophenyl)-1-(4-*tert*-butylphenyl)pyrrolidine (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) were combined in dimethoxyethane (70 mL) and nitrogen gas was sparged

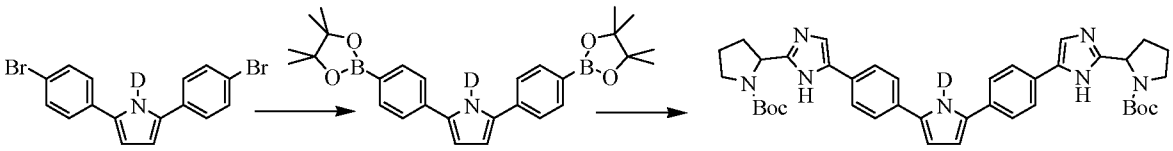
through the solution for 10 minutes. The reaction mixture was then heated at 85 °C for 1 hour. The reaction solution was cooled to room temperature, filtered through diatomaceous earth and washed with ethyl acetate (20 mL). The filtrate was dried and concentrated, and the residue was purified by column 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.



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

Racemic trans-1-(4-*tert*-butylphenyl)-2,5-bis(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)pyrrolidine (0.915 g, 1.506 mmol), Intermediate 1D (1.429 g, 4.52 mmol), and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.123 g, 0.151 mmol) were dissolved in a mixture of toluene (7 mL), ethanol (7 mL) and a 2 *N* aq. sodium bicarbonate solution (2.64 mL, 5.28 mmol). Nitrogen gas was bubbled through the solution for 10 minutes, and then the reaction mixture was heated at 100 °C for 3 hours. The reaction solution was cooled to room temperature and water (20 mL) was added. Then the reaction mixture was extracted with dichloromethane (50 mL), dried, and concentrated. The residue was 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.

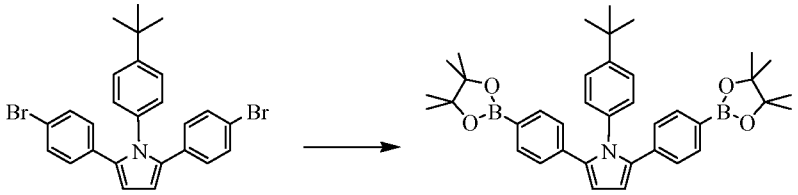
General Procedure 7.1. Suzuki coupling for pyrroles



(46) (47) (43)

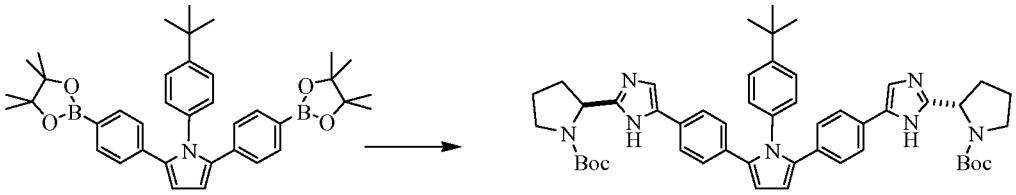
Dibromo compounds (46) can be converted sequentially to compounds (47) and (43) using the conditions described generally above in General Procedure 7.

Illustration of General Procedure 7.1: General Procedure 7.1B



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

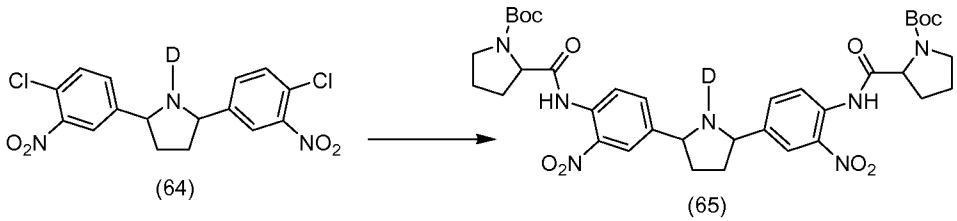
To a solution of 2,5-bis(4-bromophenyl)-1-(4-*tert*-butylphenyl)-1*H*-pyrrole (2.32 g, 4.56 mmol) in DMSO (26 mL) at room temperature were added bis(pinacolato)diborane (2.54 g, 10.02 mmol), potassium acetate (5.00 g, 36.4 mmol) and $PdCl_2$(dppf) (744 mg, 0.91 mmol). The mixture was degassed and heated to 85 °C. After 4 hours, 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).



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

A mixture of Intermediate 1D (664 mg, 2.10 mmol), 1-(4-*tert*-butylphenyl)-2,5-bis(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1*H*-pyrrole (1.48 g, 2.45 mmol), 2 *M* sodium carbonate (1400 μL, 2.80 mmol), and Pd(dppf)Cl_2 (51.2 mg, 0.070 mmol) in DME (2800 μL) was subjected to microwave irradiation at 140 °C for 20 minutes. 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 eluting with 30 to 70% ethyl acetate:hexanes to provide the title compound (140 mg; 24% yield).

General Procedure 8. Buchwald reaction

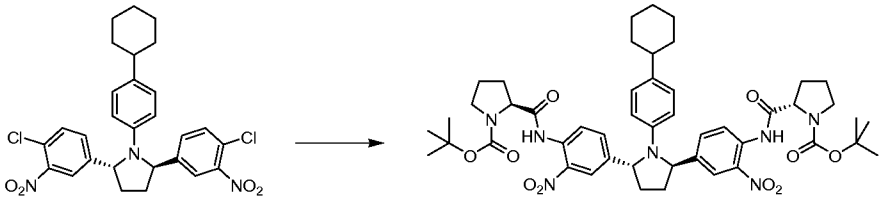


(64) (65)

Compounds (64) (1 equivalent) can be converted to compounds (65) by mixing with *tert*-butyl 2-carbamoylpyrrolidine-1-carboxylate (about 3 equivalents), cesium carbonate (about 3

equivalents), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (about 0.05 to 0.3 equivalents), and tris(dibenzylideneacetone)dipalladium(0) (about 0.05 to 0.2 equivalents) in dioxane, degassing the mixture, and heating to around 100 °C for between about 1 to 8 hours. Alternatively, the reaction can be conducted using potassium carbonate (about 3 equivalents), $Pd(OAc)_2$ (about 0.02 equivalents), and 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (about 0.04 equivalents). The reaction can be conducted in a flask with a reflux condenser under inert atmosphere or in a sealed tube. The products (65) can be purified by silica gel chromatography eluting with standard solvents including ethyl acetate and methylene chloride.

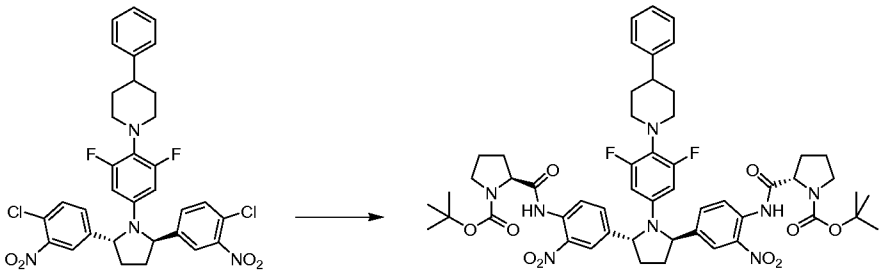
Illustration of General Procedure 8: General Procedure 8A



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

(2*R*,5*R*)-2,5-Bis(4-chloro-3-nitrophenyl)-1-(4-cyclohexylphenyl)pyrrolidine (General Procedure 4A) (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 minutes. Then the flask was capped with a reflux condenser and the solution was heated at 100 °C for 8 hours. After filtering through diatomaceous earth and concentrating, the residue was purified with a CombiFlash® 80g silica column, eluting with 0-20% ethyl acetate in dichloromethane to give 1.71 g (80%) of the title compound.

Illustration of General Procedure 8: General Procedure 8B, Example 1A



(2*S*,2'*S*)-*tert*-butyl 2,2'-(4,4'-((2*R*,5*R*)-1-(3,5-difluoro-4-(4-phenylpiperidin-1-yl)phenyl)pyrrolidine-2,5-diyl)bis(2-nitro-4,1-phenylene))bis(azanediyl)bis(oxomethylene)dipyrrolidine-1-carboxylate

To a 100 mL round-bottomed flask was added 1-(4-((2*R*,5*R*)-2,5-bis(4-chloro-3-nitrophenyl)pyrrolidin-1-yl)-2,6-difluorophenyl)-4-phenylpiperidine (2.26 g, 3.46 mmol), (*S*)-*tert*-butyl 2-carbamoylpyrrolidine-1-carboxylate (2.223 g, 10.37 mmol), cesium carbonate (3.38 g, 10.37 mmol), tris(dibenzyideneacetone)dipalladium(0) (0.190 g, 0.207 mmol) and (9,9-dimethyl-9*H*-xanthene-4,5-diyl)bis(diphenylphosphine) (0.300 g, 0.519 mmol) in dioxane (34.6 mL) to give a purple suspension. The mixture was sparged with N_2 for 20 minutes, heated under N_2 at 100 °C for 3 hours, cooled and poured into EtOAc. The EtOAc layer was washed 2×50 mL with H_2O and then with saturated NaCl. The EtOAc layer was treated simultaneously for 1 hour with 3-mercaptopropyl silica and Na_2SO_4, filtered and concentrated. Purification using chromatography on a 120 g silica cartridge eluting with 1-3 % methanol in methylene chloride gave material that was 90% pure by HPLC. A second column on a 120 g silica cartridge eluting with 15-50% EtOAc in hexane provided the title compound as an orange foam (2.6 g, 72%, 97% purity by HPLC). MS (ESI+) *m/z* 1009 $(M+H)^+$.

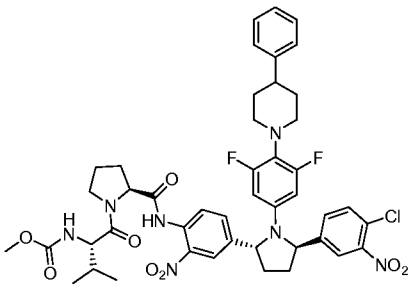
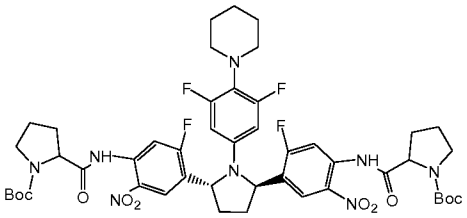


Illustration of General Procedure 8: General Procedure 8B, Example 1B (mono-displacement)

methyl (*S*)-1-((*S*)-2-(4-((2*R*,5*R*)-5-(4-chloro-3-nitrophenyl)-1-(3,5-difluoro-4-(4-phenylpiperidin-1-yl)phenyl)pyrrolidin-2-yl)-2-nitrophenylcarbamoyl)pyrrolidin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamate

1-(4-((2*R*,5*R*)-2,5-Bis(4-chloro-3-nitrophenyl)pyrrolidin-1-yl)-2,6-difluorophenyl)-4-phenylpiperidine (0.745 g, 1.14 mmol) was dissolved in dioxane (12 mL) in a tube and treated with methyl (*S*)-1-((*S*)-2-carbamoylpyrrolidin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamate (0.309 g, 1.14 mmol), cesium carbonate (0.409 g, 1.25 mmol), Xantphos (0.066 g, 0.11 mmol), and tris(dibenzylideneacetone)dipalladium(0) (0.052 g, 0.057mmol). Nitrogen was bubbled through this mixture for 15 minutes, then the tube was sealed and heated at 100 °C for 2 hours. The mixture was diluted with water, extracted into dichloromethane, concentrated, and purified by chromatography, eluting with 0-5% methanol in dichloromethane to give 0.44 g (43%) of a dark yellow solid.

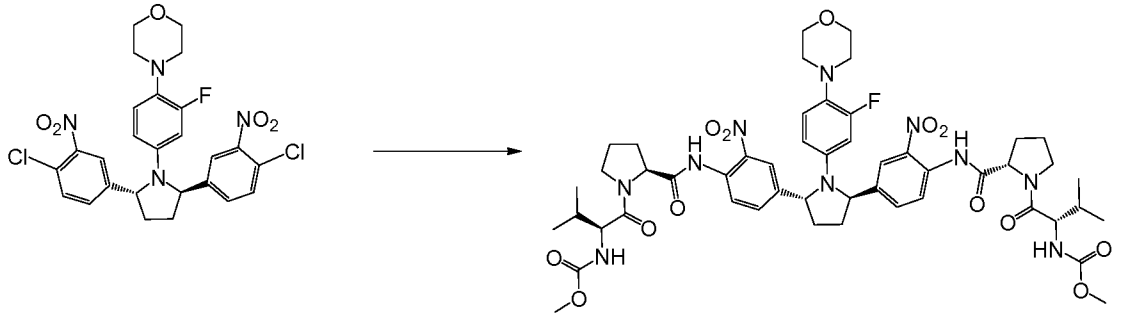
Illustration of General Procedure 8: General Procedure 8B, Example 2



tert-butyl 2,2'-(4,4'-((2*R*,5*R*)-1-(3,5-difluoro-4-(piperidin-1-yl)phenyl)pyrrolidine-2,5-diyl)bis(5-fluoro-2-nitro-4,1-phenylene))bis(azanediyl)bis(oxomethylene)dipyrrolidine-1-carboxylate

To a round bottom flask was combined 1-(4-((2*R*,5*R*)-2,5-bis(4-chloro-2-fluoro-5-nitrophenyl)pyrrolidin-1-yl)-2,6-difluorophenyl)piperidine (4.1 g, 6.68 mmol), (*S*)-*tert*-butyl 2-carbamoylpyrrolidine-1-carboxylate (4.30 g, 20.05 mmol), cesium carbonate (6.1 g, 18.72 mmol), and XantPhos (0.696 g, 1.203 mmol) followed by dioxane (30 ml) and the solution was de-gassed with N_2 gas for 30 minutes. The solution was stirred vigorously to keep the solids mixing and kept the flow rate of N_2 gas at a high rate to ensure complete de-gassing of the mixture. Tris(dibenzylideneacetone)dipalladium (0.367 g, 0.401 mmol) was added and the solution heated at 100 °C for 2 hours under N_2 gas. The solution was cooled and diluted with EtOAc, filtered through diatomaceous earth, washed with H_2O and brine, dried (Na_2SO_4), filtered, treated for 30 minutes with 3-mercaptopropyl-functionalized silica gel, filtered and concentrated to give crude product. Purification was run on an ISCO 120g silica gel cartridge eluting with 0-40% EtOAc/hexane over 30 minutes to give the title compound (4.52 g, 4.66 mmol, 69.8%).

General Procedure 8.1. Buchwald with dipeptide

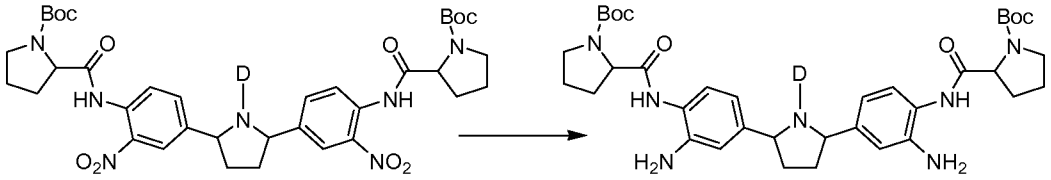


dimethyl *(2R,2'R)*-1,1'-((*2S,2'S)*-2,2'-(4,4'-((*2R,5R)*-1-(3-fluoro-4-morpholinophenyl)pyrrolidin-2,5-diyl)bis(2-nitro-4,1-phenylene))bis(azanediyl)bis(oxomethylene)bis(pyrrolidine-2,1-diyl))bis(3-methyl-1-oxobutane-2,1-diyl)dicarbamate

In a microwave tube, a suspension of 4-(4-((*2R,5R)*-2,5-bis(4-chloro-3-nitrophenyl)pyrrolidin-1-yl)-2-fluorophenyl)morpholine (1.39 g, 2.48 mmoL), Intermediate 3B (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 minutes. The mixture was treated with tris(dibenzylideneacetone)dipalladium (0) (68 mg, 0.074 mmol) followed by degassing for another 5

minutes. The microwave tube was sealed and the mixture was warmed at 100 °C for 2 hours. The mixture was cooled and diluted with ethyl acetate and extracted with water (3×) 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-d_6) 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) 6.74f6.81 (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 $(M+H)^+$.

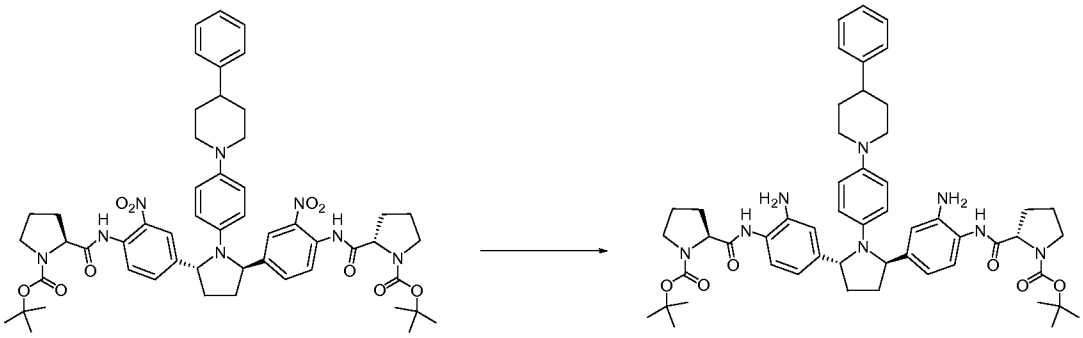
General Procedure 9. Nitro reduction



(65) (66)

Compounds (65) (1 equivalent) can be converted to compounds (66) by hydrogenation with hydrogen gas (1-4 atm) over a catalyst such as PtO_2 (about 0.2 to 0.3 equivalents) or Raney-nickel (e.g., 50% aqueous; 1 equivalent by weight) in solvents such as tetrahydrofuran, ethanol, or mixtures thereof. The reaction can be worked up by filtration through diatomaceous earth or silica gel, and the filtrate concentrated to give compounds (66). Reduction of (65) (1 equivalent) can also be effected by reaction with iron powder (about 6 equivalents) and ammonium chloride (about 3 equivalents) in a solvent of THF:ethanol:water (1:1:0.2) with heating to about 60-100 °C.

Illustration of General Procedure 9: General Procedure 9A, Example 1



(2*S*,2'*S*)-*tert*-butyl 2,2'-(4,4'-((2*R*,5*R*)-1-(4-(4-phenylpiperidin-1-yl)phenyl)pyrrolidine-2,5-diyl)bis(2-amino-4,1-phenylene))bis(azanediyl)bis(oxomethylene)dipyrrolidine-1-carboxylate

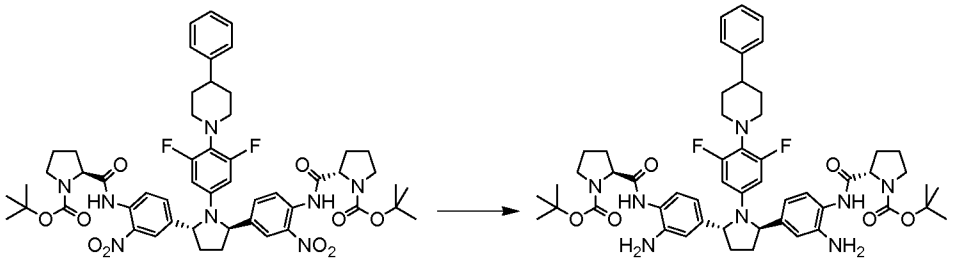
A solution of (2*S*,2'*S*)-*tert*-butyl 2,2'-(4,4'-((2*R*,5*R*)-1-(4-(4-phenylpiperidin-1-yl)phenyl)pyrrolidine-2,5-diyl)bis(2-nitro-4,1-phenylene))bis(azanediyl)bis(oxomethylene)dipyrrolidine-1-carboxylate (2.287 g, 2.350 mmol) in THF (60 mL) was added to PtO_2 (0.457 g, 2.014 mmol) in a 250 mL stainless steel pressure bottle and stirred for 4 hours at room temperature under 30 psi hydrogen pressure. The mixture was then filtered through a nylon membrane and the filtrate concentrated by rotary evaporation and dried *in vacuo* to give the title compound as a brown solid (2.02 g, 94%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.30 - 1.44 (m, 18 H), 1.53 - 1.98 (m, 11 H), 2.08 - 2.29 (m, 1 H), 2.43 - 2.60 (m, 3 H), 3.35 - 3.50 (m, 4 H), 4.16 - 4.29 (m, 2 H), 4.79 (d, *J*=35.46 Hz, 4 H), 4.97 (s, 2 H), 6.21 (d, *J*=8.89 Hz, 2 H), 6.41 (dd, *J*=20.66, 7.86 Hz, 2 H), 6.53 - 6.61 (m, 2 H), 6.66 (d, *J*=8.89 Hz, 2 H), 6.93 - 7.06 (m, 2 H), 7.17 (t, *J*=6.89 Hz, 1 H), 7.21 - 7.32 (m, 4 H), 9.18 (d, *J*=39.25 Hz, 2 H); MS (ESI+) *m/z* 913 $(M+H)^+$; MS (ESI-) *m/z* 911 $(M-H)^-$.

Illustration of General Procedure 9: General Procedure 9A, Example 2

tert-butyl 2,2'-(4,4'-((2*R*,5*R*)-1-(3,5-difluoro-4-(piperidin-1-yl)phenyl)pyrrolidine-2,5-diyl)bis(2-amino-5-fluoro-4,1-phenylene))bis(azanediyl)bis(oxomethylene)dipyrrolidine-1-carboxylate

tert-Butyl 2,2'-(4,4'-((2*R*,5*R*)-1-(3,5-difluoro-4-(piperidin-1-yl)phenyl)pyrrolidine-2,5-diyl)bis(5-fluoro-2-nitro-4,1-phenylene))bis(azanediyl)bis(oxomethylene)dipyrrolidine-1-carboxylate (4.5 g, 4.64 mmol) and THF (100 ml) were added to PtO_2 (0.900 g, 3.96 mmol) in a 250 ml stainless steel pressure bottle and stirred for 22 hours under a hydrogen atmosphere (30 psi) at room temperature. The mixture was filtered through a nylon membrane and concentrated to a yellow-orange foam.

Illustration of General Procedure 9: General Procedure 9B

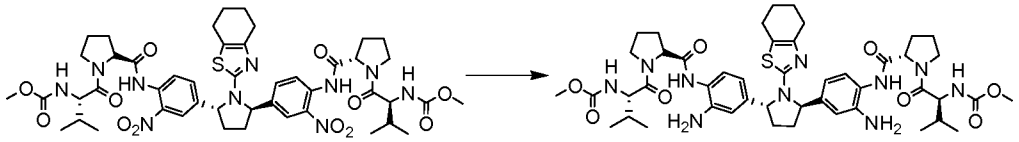


(2*S*,2'*S*)-*tert*-butyl 2,2'-(4,4'-((2*R*,5*R*)-1-(3,5-difluoro-4-(4-phenylpiperidin-1-yl)phenyl)pyrrolidine-2,5-diyl)bis(2-amino-4,1-phenylene))bis(azanediyl)bis(oxomethylene)dipyrrolidine-1-carboxylate

In a 250 mL pressure bottle were combined (2*S*,2'*S*)-*tert*-butyl 2,2'-(4,4'-((2*R*,5*R*)-1-(3,5-difluoro-4-(4-phenylpiperidin-1-yl)phenyl)pyrrolidine-2,5-diyl)bis(2-nitro-4,1-phenylene))bis(azanediyl)bis(oxomethylene)dipyrrolidine-1-carboxylate (General Procedure 8B) (2.6 g, 2.58 mmol) and Raney-nickel 2800 (45% w/w in water, 2.6 g, 44 mmol) in THF (40 mL). The

vessel was sealed and stirred under 30 psi H_2 for 5 hours. The solution was filtered through a nylon membrane and the filtrate was concentrated to afford the title compound as a tan foam (2.44 g, quantitative yield) that was used without purification. MS (ESI+) *m/z* 949 $(M+H)^+$.

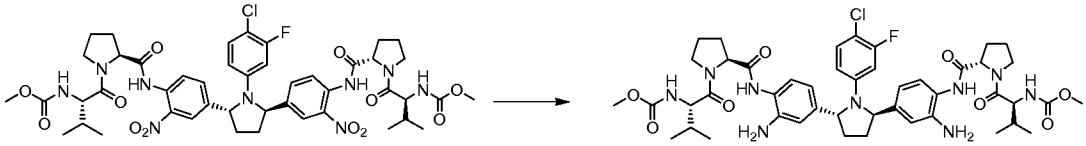
Illustration of General Procedure 9: General Procedure 9C



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 Name v12))

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 Name v12)) (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.

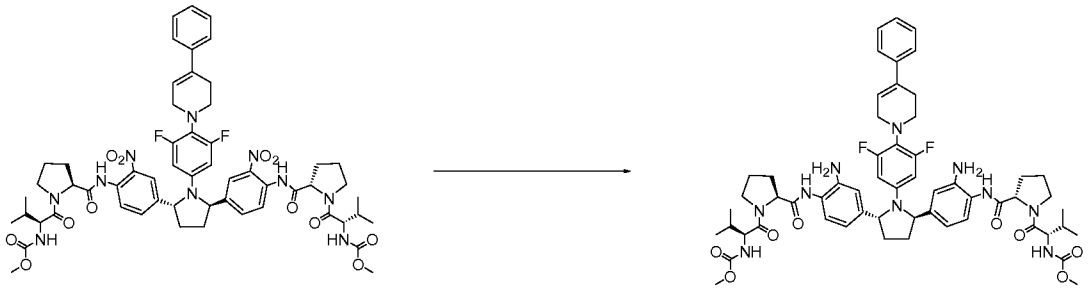
Illustration of General Procedure 9: General Procedure 9D



dimethyl (2*S*,2'*S*)-1,1'-((2*S*,2'*S*)-2,2'-(4,4'-((2*R*,5*R*)-1-(4-chloro-3-fluorophenyl)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

Dimethyl (2*S*,2'*S*)-1,1'-((2*S*,2'*S*)-2,2'-(4,4'-((2*R*,5*R*)-1-(4-chloro-3-fluorophenyl)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 (1.0g, 1.02 mmol) and tetrahydrofuran (25 mL) were added to platinum oxide (0.20 g, 0.88 mmol) in a pressure bottle and stirred at ambient temperature under hydrogen at 30 psi for 1.5 hours. The solution was filtered through a nylon membrane and concentrated to dryness to give 100% yield of a brown residue that was used without purification.

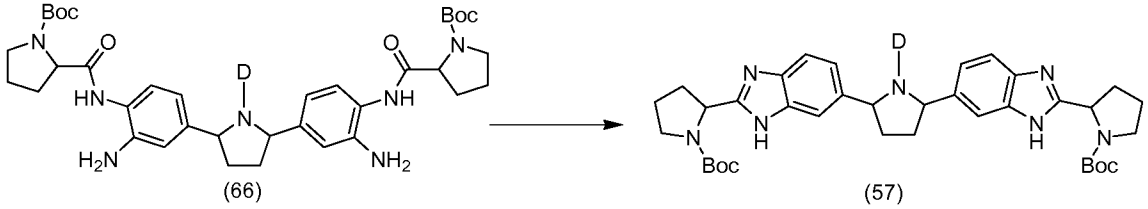
Illustration of General Procedure 9: General Procedure 9E



dimethyl (2*S*,2'*S*)-1,1'-((2*S*,2'*S*)-2,2'-(4,4'-((2*R*,5*R*)-1-(3,5-difluoro-4-(4-phenyl-5,6-dihydropyridin-1(2H)-yl)phenyl)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

Dimethyl (2*S*,2'*S*)-1,1'-((2*S*,2'*S*)-2,2'-(4,4'-((2*R*,5*R*)-1-(3,5-difluoro-4-(4-phenyl-5,6-dihydropyridin-1(2*H*)-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 (150 mg, 0.134 mmol) was dissolved in a mixture of THF (1 mL) and absolute EtOH (1 mL) under nitrogen. A solution of ammonium chloride (10.73 mg, 0.201 mmol) in water (0.333 mL), followed by iron powder (37.4 mg, 0.669 mmol) was added, and the mixture was heated under a reflux condenser in an oil bath at 90 °C. After 1 hour, the reaction mixture was cooled to room temperature, vacuum filtered through a bed of Celite 545, and washed thoroughly with EtOAc. The filtrate was concentrated by rotary evaporation to remove the organic solvents. The residue was dissolved in EtOAc (50 mL), washed with water (2×25 mL) and brine (25 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated by rotary evaporation. The residue was purified by SiO_2 flash chromatography (Alltech Extract-Clean column, 10 g bed) eluting with a step gradient of 3% to 4% methanol/CH_2Cl_2 to afford the product as a yellow solid (77 mg, 0.073 mmol, 54%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.92 (dd, *J*=13.07, 6.56 Hz, 12 H), 1.58 - 1.75 (m, 2 H), 1.83 - 2.09 (m, 8 H), 2.13 - 2.28 (m, 1 H), 3.17 (s, 2 H), 3.38 - 3.68 (m, 8 H), 3.55 (s, 6 H), 3.84 (s, 2 H), 4.05 (t, *J*=8.35 Hz, 2 H), 4.37 - 4.47 (m, 2 H), 4.93 (s, 4 H), 5.01 (d, *J*=5.10 Hz, 2 H), 5.85 - 6.00 (m, 2 H), 6.14 (s, 1 H), 6.44 (d, *J*=8.02 Hz, 2 H), 6.55 - 6.66 (m, 2 H), 7.02 (d, *J*=7.81 Hz, 2 H), 7.21 - 7.49 (m, 8 H), 9.28 (s, 2 H); MS (ESI+) *m/z* 1061 $(M+H)^+$; MS (ESI-) *m/z* 1059 $(M-H)^-$.

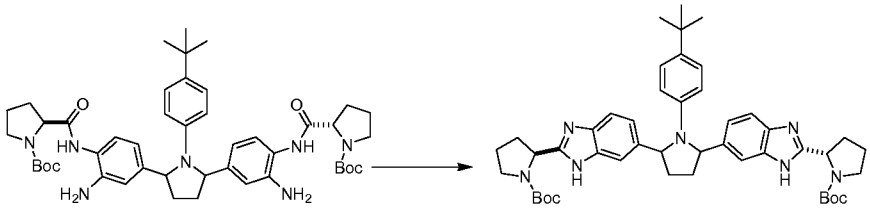
General Procedure 10. Benzimidazole formation



(66) (57)

Compounds (66) can be converted to compounds (57) by heating neat in acetic acid or with acetic acid in toluene or dioxane at 50-80 °C. The reaction can be worked up by concentrating the solution, neutralizing with aqueous sodium bicarbonate solution, extracting with an organic solvent (e.g., dichloromethane), drying the organic solvent mixture (e.g., $MgSO_4$, Na_2SO_4), filtering and concentrating in vacuo. The reaction can also be conducted in toluene as solvent with added acetic acid (about 3 to 5 equivalents) also with heating to 50-80 °C. Workup can consist of simple solvent evaporation and the removal of residual acetic acid by the addition and evaporation of toluene. Compounds (57) can be purified by chromatography over silica gel eluting with ethyl acetate/dichloromethane or methanol/dichloromethane. Although the cyclization depicted above is shown with a t-butoxycarbonyl (Boc) group attached, the reaction can also be conducted with the groups –T–R_D attached, wherein T and R_D are as defined herein.

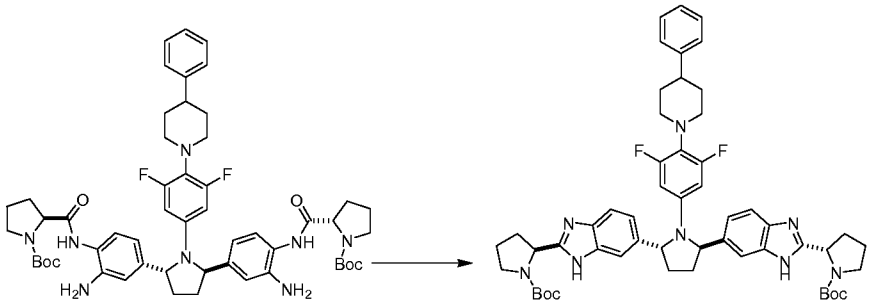
Illustration of General Procedure 10: General Procedure 10A; Example 1



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

As a mixture of trans diastereomers, (2*S*,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 (0.355 g) was dissolved in neat acetic acid (3 mL) and heated at 72 °C for 2 hours. The solution was concentrated and then poured into water where the pH was adjusted to ~7-8 with sodium bicarbonate. The product was extracted into dichloromethane, concentrated and purified by chromatography on silica gel with a 40 g column, eluting with 0-5%methanol/dichloromethane to give 0.185 g (55%) of the title compound as a light yellow solid.

Illustration of General Procedure 10: General Procedure 10A; Example 2



(2*S*,2'*S*)-*tert*-butyl 2,2'-(6,6'-((2*R*,5*R*)-1-(3,5-difluoro-4-(4-phenylpiperidin-1-yl)phenyl)pyrrolidine-2,5-diyl)bis(1*H*-benzo[*d*]imidazole-6,2-diyl))dipyrrolidine-1-carboxylate

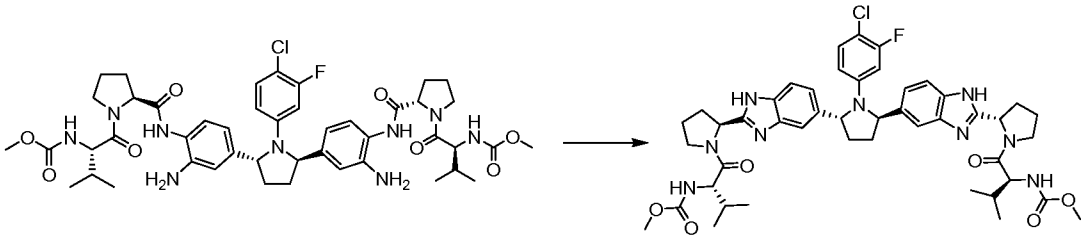
A solution of (2*S*,2'*S*)-*tert*-butyl 2,2'-(4,4'-((2*R*,5*R*)-1-(3,5-difluoro-4-(4-phenylpiperidin-1-yl)phenyl)pyrrolidine-2,5-diyl)bis(2-amino-4,1-phenylene))bis(azanediyl)bis(oxomethylene)dipyrrolidine-1-carboxylate (2.4 g, 2.57 mmol) and acetic acid (1.54 g, 25.7 mmol) in toluene (50 mL) was heated at 70 °C for 2 hours, cooled and concentrated. The residue was azeotroped 3×15 mL with toluene and dried under vacuum to give a yellow foam (2.34 g, quantitative yield) that was used without purification. MS (ESI+) *m/z* 913 $(M+H)^+$.

Illustration of General Procedure 10: General Procedure 10A; Example 3

(2*S*,2'*S*)-*tert*-butyl 2,2'-(6,6'-((2*R*,5*R*)-1-(3,5-difluoro-4-(piperidin-1-yl)phenyl)pyrrolidine-2,5-diyl)bis(5-fluoro-1*H*-benzo[d]imidazole-6,2-diyl))dipyrrolidine-1-carboxylate

To crude *tert*-butyl 2,2'-(4,4'-((2*R*,5*R*)-1-(3,5-difluoro-4-(piperidin-1-yl)phenyl)pyrrolidine-2,5-diyl)bis(2-amino-5-fluoro-4,1-phenylene))bis(azanediyl)bis(oxomethylene)dipyrrolidine-1-carboxylate (from General Procedure 9A, Example 2) was added toluene (45 ml) followed by acetic acid (2.66 ml, 46.4 mmol) and the solution was stirred at 50 °C for 16 hours. The cooled solution was concentrated , azeotroped twice with toluene, and the crude residue was purified on an ISCO 40 g silica gel cartridge eluting with 0-5% CH_3OH/CH_2Cl_2 to give the title compound (2.85 g).

Illustration of General Procedure 10: General Procedure 10B, Example 1

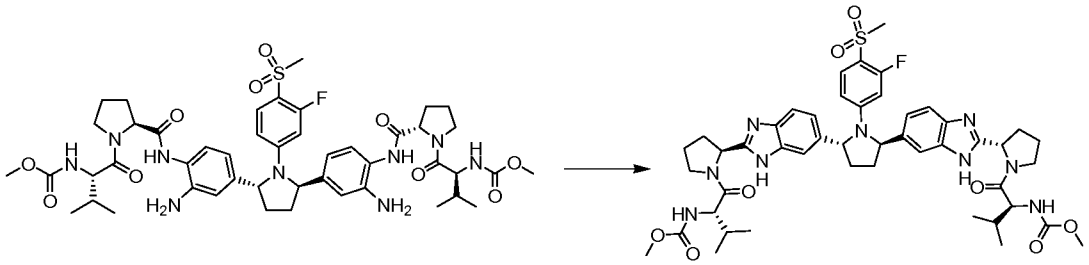


methyl {(2*S*)-1-[(2*S*)-2-{5-[(2*R*,5*R*)-1-(4-chloro-3-fluorophenyl)-5-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1*H*-benzimidazol-5-yl}pyrrolidin-2-yl]-1*H*-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate (ACD Name v12)

Dimethyl (2*S*,2'*S*)-1,1'-((2*S*,2'*S*)-2,2'-(4,4'-((2*R*,5*R*)-1-(4-chloro-3-fluorophenyl)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 (General Procedure 9D) (0.98 g, 1.01 mmol) was dissolved in toluene (12 mL) and treated with glacial acetic acid (1.16 mL, 20.2 mmol) and heated at 65 °C for 1.5 hours. The mixture was concentrated, dissolved in dichloromethane, and washed with sodium bicarbonate solution. The organic reaction mixture was concentrated and purified by chromatography, eluting with 0-6% methanol in dichloromethane to give 0.17 g (19%) of the title

compound as a dark yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.77 - 0.90 (m, 12 H) 1.66 - 1.78 (m, 2 H) 1.88 - 1.95 (m, 2 H) 1.96 - 2.06 (m, 4 H) 2.15 - 2.24 (m, 4 H) 2.54 - 2.60 (m, 2 H) 3.54 (s, 6 H) 3.79 - 3.86 (m, 4 H) 4.06 (t, J=8.46 Hz, 2 H) 5.10 - 5.18 (m, 2 H) 5.37 - 5.45 (m, 2 H) 6.16 (dd, J=9.49, 2.01 Hz, 1 H) 6.22 (dd, J=13.55, 2.06 Hz, 1 H) 7.00 - 7.11 (m, 3 H) 7.22 (s, 1 H) 7.28 (d, J=8.57 Hz, 2 H) 7.32 (s, 1 H) 7.40 (d, J=8.24 Hz, 1 H) 7.47 (d, J=8.13 Hz, 1 H) 12.07 (d, J=2.93 Hz, 2 H); MS (APCI+) *m/z* 884 $(M+H)^+$.

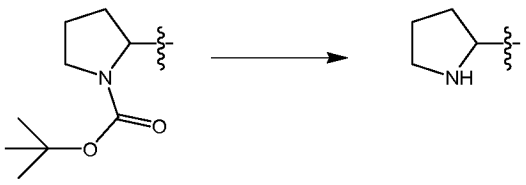
Illustration of General Procedure 10: General Procedure 10B; Example 2



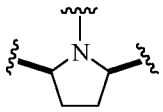
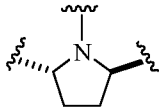
methyl {(2*S*)-1-[(2*S*)-2-{6-[(2*R*,5*R*)-1-[3-fluoro-4-(methylsulfonyl)phenyl]-5-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1*H*-benzimidazol-6-yl}pyrrolidin-2-yl]-1*H*-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate (ACD Name v12)

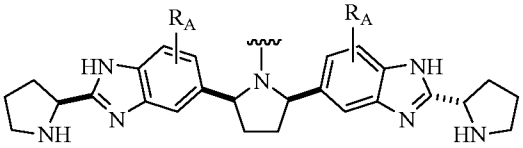
To a suspension of dimethyl (2*S*,2'*S*)-1,1'-((2*S*,2'*S*)-2,2'-(4,4'-((2*R*,5*R*)-1-(3-fluoro-4-(methylsulfonyl)phenyl)pyrrolidine-2,5-diyl)bis(2-amino-4,1-phenylene))bis(azanediyl)bis(oxomethylene)bis(pyrrolidine-2,1-diyl))bis(3-methyl-1-oxobutane-2,1-diyl)dicarbamate (0.190 g, 0.197 mmol) in toluene (2 mL) was added acetic acid (1 mL, 17.48 mmol), and the reaction mixture was stirred at 60 °C overnight. LCMS shows completion of reaction. The reaction mixture was diluted with ethyl acetate and washed with a saturated solution of $NaHCO_3$. The organic extract was separated, dried over anhydrous sodium sulfate, filtered, concentrated on a rotovap and purified by reverse phase HPLC using 5-100% acetonitrile/ water(TFA). Pure fractions were combined, neutralized with saturated solution of $NaHCO_3$, and concentrated. The residue was extracted with CH_2Cl_2. The organic extract was separated, dried over anhydrous sodium sulfate, filtered, and concentrated to supply the title compound (30 mg) as a white solid.

General Procedure 11. Procedure to Remove t-Butoxycarbonyl Protecting Groups

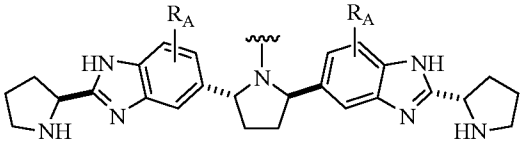


Removal of a t-butoxycarbonyl (Boc) protecting group, according to the above depiction can be effected using standard conditions such as by treatment with an acid, such as TFA, HCl, or formic acid. For example, reaction with TFA/CH_2Cl_2 or HCl in dioxane at room temperature can remove the Boc protecting group. Compounds may be used or isolated as the salt or free base.

After removal of the Boc-protecting groups and in cases where compounds have been processed through as mixtures of cis,  , and trans,  , pyrrolidines, the cis and trans diastereomers may be subject to separation using standard chromatographic methods (e.g., normal phase silica gel or reverse phase). For example, compounds of general type 11-1 and 11-2 can be separated in this manner.

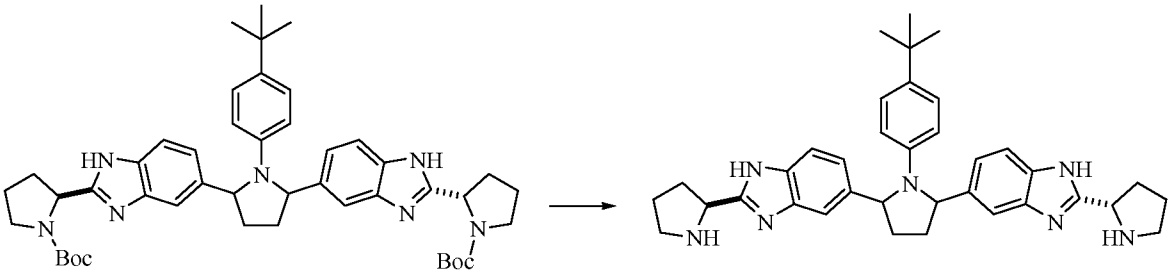


11-1



11-2

Illustration of General Procedure 11. General Procedure 11A (HCl-Dioxane), Example 1



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

(2*S*,2'*S*)-*tert*-Butyl 2,2'-(5,5'-(1-(4-*tert*-butylphenyl)pyrrolidine-2,5-diyl)bis(1*H*-benzo[*d*]imidazole-5,2-diyl))dipyrrolidine-1-carboxylate (0.204 g, 0.264 mmol) was dissolved in THF (2 mL) at room temperature and treated with 4 *M* HCl in dioxane (2 mL). After completion of the reaction, the mixture was concentrated to dryness to provide the crude title compound.

Illustration of General Procedure 11. General Procedure 11A (HCl-Dioxane), Example 2

(*S*)-6,6'-((2*R*,5*R*)-1-(3,5-difluoro-4-(4-phenylpiperidin-1-yl)phenyl)pyrrolidine-2,5-diyl)bis(2-((*S*)-pyrrolidin-2-yl)-1*H*-benzo[*d*]imidazole)

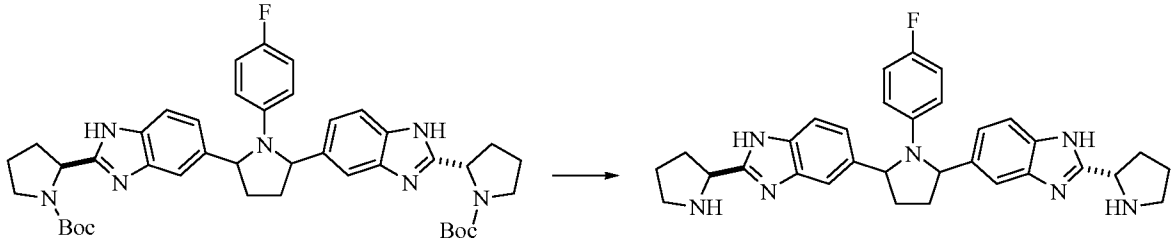
A solution of (2*S*,2'*S*)-*tert*-butyl 2,2'-(6,6'-((2*R*,5*R*)-1-(3,5-difluoro-4-(4-phenylpiperidin-1-yl)phenyl)pyrrolidine-2,5-diyl)bis(1*H*-benzo[*d*]imidazole-6,2-diyl))dipyrrolidine-1-carboxylate (2.34 g, 2.57 mmol) in dioxane (25 mL) was treated with 4 *M* hydrogen chloride in dioxane (16.06 mL, 64.3 mmol) to give a tan suspension. The mixture was sonicated for 10 minutes to break up solids into a fine suspension, stirred for 2 hours and concentrated. The residue was azeotroped 3×30 mL with toluene and dried to give the HCl salt of the title compound as a tan powder that was used without purification (assume quantitative yield, 2.57 mmol). MS (ESI+) *m/z* 713 $(M+H)^+$.

Illustration of General Procedure 11. General Procedure 11A (HCl-Dioxane), Example 3

6,6'-{(2*R*,5*R*)-1-[3,5-difluoro-4-(piperidin-1-yl)phenyl]pyrrolidine-2,5-diyl}bis{5-fluoro-2-[(2*S*)-pyrrolidin-2-yl]-1*H*-benzimidazole} (ACD Name v12)

To a solution of (2*S*,2'*S*)-*tert*-butyl 2,2'-(6,6'-((2*R*,5*R*)-1-(3,5-difluoro-4-(piperidin-1-yl)phenyl)pyrrolidine-2,5-diyl)bis(5-fluoro-1*H*-benzo[*d*]imidazole-6,2-diyl))dipyrrolidine-1-carboxylate (2.85 g, 3.26 mmol) in dioxane (10 ml) was added 4 *M* HCl/dioxane (10.0 mL, 40.0 mmol) and the solution was vigorously stirred at room temperature for 1 hour. The solution was concentrated, dissolved in minimal H_2O and applied to an ISCO 130 g C18 cartridge and eluted with 0-100% CH_3CN/(0.1% TFA/H_2O). Desired fractions were combined, made basic with 10% $NaHCO_3$ solution, and extracted with EtOAc. The combined extracts were dried ($MgSO_4$), filtered and concentrated to give the title compound (932.5 mg, 1.386 mmol, 42.5%).

Illustration of General Procedure 11. General Procedure 11B (TFA-CH_2Cl_2)



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

(2*S*,2'*S*)-*tert*-Butyl 2,2'-(5,5'-(1-(4-fluorophenyl)pyrrolidine-2,5-diyl)bis(1*H*-benzo[*d*]imidazole-5,2-diyl))dipyrrolidine-1-carboxylate (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% isopropanol/dichloromethane and washed with sodium bicarbonate solution. The resulting solids were filtered off and dried. The organic filtrate was concentrated and dried to give the more title compound. The batches of off-white solid were combined to give the titled compound (0.062 g 72% yield).

The following compounds as free base or salt can be made using General Procedure 8, General Procedure 9A (PtO_2), General Procedure 10/10A, and General Procedure 11/11A:

(*S*)-6,6'-((2*R*,5*R*)-1-(4-(pyridin-2-yl)phenyl)pyrrolidine-2,5-diyl)bis(2-((*S*)-pyrrolidin-2-yl)-1*H*-benzo[*d*]imidazole);

(*S*)-6,6'-((2*R*,5*R*)-1-(3-chloro-4-(trifluoromethoxy)phenyl)pyrrolidine-2,5-diyl)bis(2-((*S*)-pyrrolidin-2-yl)-1*H*-benzo[*d*]imidazole);

(*S*)-6,6'-((2*R*,5*R*)-1-(4-(2-methoxyethoxy)phenyl)pyrrolidine-2,5-diyl)bis(2-((*S*)-pyrrolidin-2-yl)-1*H*-benzo[*d*]imidazole);

(*S*)-6,6'-((2*R*,5*R*)-1-(4-chlorophenyl)pyrrolidine-2,5-diyl)bis(2-((*S*)-pyrrolidin-2-yl)-1*H*-benzo[*d*]imidazole);

(*S*)-6,6'-((2*R*,5*R*)-1-(3-methyl-4-(piperidin-1-yl)phenyl)pyrrolidine-2,5-diyl)bis(2-((*S*)-pyrrolidin-2-yl)-1*H*-benzo[*d*]imidazole);

(*S*)-6,6'-((2*S*,5*S*)-1-(4-cyclopropyl-3,5-difluorophenyl)pyrrolidine-2,5-diyl)bis(2-((*S*)-pyrrolidin-2-yl)-1*H*-benzo[*d*]imidazole);

(*S*)-6,6'-((2*S*,5*S*)-1-(4-cyclopropyl-2-fluorophenyl)pyrrolidine-2,5-diyl)bis(2-((*S*)-pyrrolidin-2-yl)-1*H*-benzo[*d*]imidazole);

(*S*)-6,6'-((2*R*,5*R*)-1-(3-fluoro-4-(piperidin-1-yl)phenyl)pyrrolidine-2,5-diyl)bis(2-((*S*)-pyrrolidin-2-yl)-1*H*-benzo[*d*]imidazole);

(*S*)-6,6'-((2*R*,5*R*)-1-(3,5-difluoro-4-(4-(trifluoromethyl)piperidin-1-yl)phenyl)pyrrolidine-2,5-diyl)bis(2-((*S*)-pyrrolidin-2-yl)-1*H*-benzo[*d*]imidazole);

(*S*)-6,6'-((2*R*,5*R*)-1-(4-(4-*tert*-butylpiperidin-1-yl)-3,5-difluorophenyl)pyrrolidine-2,5-diyl)bis(2-((*S*)-pyrrolidin-2-yl)-1*H*-benzo[*d*]imidazole);

(*S*)-6,6'-((2*R*,5*R*)-1-(4-(4,4-dimethylpiperidin-1-yl)-3,5-difluorophenyl)pyrrolidine-2,5-diyl)bis(2-((*S*)-pyrrolidin-2-yl)-1*H*-benzo[*d*]imidazole);

(*S*)-6,6'-((2*R*,5*R*)-1-(3,5-difluoro-4-(6-azaspiro[2.5]octan-6-yl)phenyl)pyrrolidine-2,5-diyl)bis(2-((*S*)-pyrrolidin-2-yl)-1*H*-benzo[*d*]imidazole);

(*S*)-6,6'-((2*R*,5*R*)-1-(3,5-difluoro-4-(isoindolin-2-yl)phenyl)pyrrolidine-2,5-diyl)bis(2-((*S*)-pyrrolidin-2-yl)-1*H*-benzo[*d*]imidazole);

2-(4-((2*R*,5*R*)-2,5-bis(2-((*S*)-pyrrolidin-2-yl)-1*H*-benzo[*d*]imidazol-6-yl)pyrrolidin-1-yl)-2,6-difluorophenyl)-2-azabicyclo[2.2.2]octane;

(*S*)-6,6'-((2*R*,5*R*)-1-(3,5-difluoro-4-(4-isopropylpiperidin-1-yl)phenyl)pyrrolidine-2,5-diyl)bis(2-((*S*)-pyrrolidin-2-yl)-1*H*-benzo[*d*]imidazole);

(*S*)-6,6'-((2*R*,5*R*)-1-(4-(3,3-dimethylazetidin-1-yl)-3,5-difluorophenyl)pyrrolidine-2,5-diyl)bis(2-((*S*)-pyrrolidin-2-yl)-1*H*-benzo[*d*]imidazole);

(*S*)-6,6'-((2*R*,5*R*)-1-(4-(4-phenylpiperidin-1-yl)phenyl)pyrrolidine-2,5-diyl)bis(2-((*S*)-pyrrolidin-2-yl)-1*H*-benzo[*d*]imidazole);

6,6'-{(2*R*,5*R*)-1-[3,5-difluoro-4-(piperidin-1-yl)phenyl]pyrrolidine-2,5-diyl}bis{5-fluoro-2-[(2*S*)-pyrrolidin-2-yl]-1*H*-benzimidazole} (ACD Name v12);

(S)-6,6'-((2S,5R)-1-(3,5-difluoro-4-(piperidin-1-yl)phenyl)pyrrolidine-2,5-diyl)bis(5-fluoro-2-((S)-pyrrolidin-2-yl)-1H-benzo[d]imidazole)

(S,S,S)-6,6'-((2R,5R)-1-(3,5-difluoro-4-(piperidin-1-yl)phenyl)pyrrolidine-2,5-diyl)bis(5-fluoro-2-((2S,3aS,6aS)-octahydrocyclopenta[b]pyrrol-2-yl)-1H-benzo[d]imidazole);

(S,S,S)-6,6'-((2R,5R)-1-(3,5-difluoro-4-(piperidin-1-yl)phenyl)pyrrolidine-2,5-diyl)bis(2-((2S,3aS,6aS)-octahydrocyclopenta[b]pyrrol-2-yl)-1H-benzo[d]imidazole);

(S)-6,6'-((2R,5R)-1-(4-(2,3-dihydrospiro[indene-1,4'-piperidine]-1'-yl)-3,5-difluorophenyl)pyrrolidine-2,5-diyl)bis(5-fluoro-2-((S)-pyrrolidin-2-yl)-1H-benzo[d]imidazole);

(S)-6,6'-((2R,5R)-1-(3,5-difluoro-4-(4-(4-methoxyphenyl)piperidin-1-yl)phenyl)pyrrolidine-2,5-diyl)bis(2-((S)-pyrrolidin-2-yl)-1H-benzo[d]imidazole);

(S)-6,6'-((2R,5R)-1-(3,5-difluoro-4-(4-fluoro-4-phenylpiperidin-1-yl)phenyl)pyrrolidine-2,5-diyl)bis(2-((S)-pyrrolidin-2-yl)-1H-benzo[d]imidazole);

(S)-6,6'-((2R,5R)-1-(4-(4-fluoro-4-phenylpiperidin-1-yl)phenyl)pyrrolidine-2,5-diyl)bis(2-((S)-pyrrolidin-2-yl)-1H-benzo[d]imidazole);

(S)-6,6'-((2R,5R)-1-(3,5-difluoro-4-(4-(fluorodiphenylmethyl)piperidin-1-yl)phenyl)pyrrolidine-2,5-diyl)bis(5-fluoro-2-((S)-pyrrolidin-2-yl)-1H-benzo[d]imidazole);

(S)-6,6'-((2R,5R)-1-(3,5-difluoro-4-(4-phenylpiperidin-1-yl)phenyl)pyrrolidine-2,5-diyl)bis(5-fluoro-2-((S)-pyrrolidin-2-yl)-1H-benzo[d]imidazole);

(S)-6,6'-((2R,5R)-1-(3,5-difluoro-4-(4-(4-fluorophenyl)piperidin-1-yl)phenyl)pyrrolidine-2,5-diyl)bis(2-((S)-pyrrolidin-2-yl)-1H-benzo[d]imidazole);

(S)-6,6'-((2R,5R)-1-(3,5-difluoro-4-(4-(3-(trimethylsilyl)phenyl)piperidin-1-yl)phenyl)pyrrolidine-2,5-diyl)bis(2-((S)-pyrrolidin-2-yl)-1H-benzo[d]imidazole);

(S)-6,6'-((2R,5R)-1-(4-(4-(3,4-difluorophenyl)piperidin-1-yl)-3,5-difluorophenyl)pyrrolidine-2,5-diyl)bis(2-((S)-pyrrolidin-2-yl)-1H-benzo[d]imidazole);

(S)-6,6'-((2R,5R)-1-(4-(4-(3,5-difluorophenyl)piperidin-1-yl)-3,5-difluorophenyl)pyrrolidine-2,5-diyl)bis(2-((S)-pyrrolidin-2-yl)-1H-benzo[d]imidazole);

(S)-6,6'-((2R,5R)-1-(3,5-difluoro-4-(4-(4-(trifluoromethyl)phenyl)piperazin-1-yl)phenyl)pyrrolidine-2,5-diyl)bis(5-fluoro-2-((S)-pyrrolidin-2-yl)-1H-benzo[d]imidazole);

6-((2R,5R)-1-(3,5-difluoro-4-(piperidin-1-yl)phenyl)-5-(2-((S)-pyrrolidin-2-yl)-1H-benzo[d]imidazol-6-yl)pyrrolidin-2-yl)-5-fluoro-2-((S)-pyrrolidin-2-yl)-1H-benzo[d]imidazole;

(S)-6,6'-((2R,5R)-1-(4-(4-benzylpiperidin-1-yl)-3,5-difluorophenyl)pyrrolidine-2,5-diyl)bis(5-fluoro-2-((S)-pyrrolidin-2-yl)-1H-benzo[d]imidazole);

(S)-6,6'-((2R,5R)-1-(4-(4-benzylpiperidin-1-yl)-3,5-difluorophenyl)pyrrolidine-2,5-diyl)bis(2-((S)-pyrrolidin-2-yl)-1H-benzo[d]imidazole);

(S)-6,6'-((2S,5R)-1-(3,5-difluoro-4-(4-phenylpiperidin-1-yl)phenyl)pyrrolidine-2,5-diyl)bis(2-((S)-pyrrolidin-2-yl)-1H-benzo[d]imidazole);

4-(4-((2R,5R)-2,5-bis(2-((S)-pyrrolidin-2-yl)-1H-benzo[d]imidazol-6-yl)pyrrolidin-1-yl)-2,6-difluorophenyl)-2-phenylmorpholine;

(S)-6,6'-((2R,5R)-1-(3,5-difluoro-4-(2-phenylpiperidin-1-yl)phenyl)pyrrolidine-2,5-diyl)bis(2-((S)-pyrrolidin-2-yl)-1H-benzo[d]imidazole);

(2S,6R)-4-(4-((2R,5R)-2,5-bis(5-fluoro-2-((S)-pyrrolidin-2-yl)-1H-benzo[d]imidazol-6-yl)pyrrolidin-1-yl)-2,6-difluorophenyl)-2,6-dimethylmorpholine;

(S)-6,6'-((2R,5R)-1-(3,5-difluoro-4-(3-azaspiro[5.5]undecan-3-yl)phenyl)pyrrolidine-2,5-diyl)bis(5-fluoro-2-((S)-pyrrolidin-2-yl)-1H-benzo[d]imidazole);

(S)-6,6'-((2R,5R)-1-(4-(4-cyclohexylpiperidin-1-yl)-3,5-difluorophenyl)pyrrolidine-2,5-diyl)bis(5-fluoro-2-((S)-pyrrolidin-2-yl)-1H-benzo[d]imidazole);

(S)-4-(4-((2R,5R)-2,5-bis(5-fluoro-2-((S)-pyrrolidin-2-yl)-1H-benzo[d]imidazol-6-yl)pyrrolidin-1-yl)-2,6-difluorophenyl)-2-phenylmorpholine;

(S)-6,6'-((2R,5R)-1-(3,5-difluoro-4-(4-phenylpiperazin-1-yl)phenyl)pyrrolidine-2,5-diyl)bis(2-((S)-pyrrolidin-2-yl)-1H-benzo[d]imidazole);

(S,R)-6,6'-((2R,5R)-1-(3,5-difluoro-4-(piperidin-1-yl)phenyl)pyrrolidine-2,5-diyl)bis(2-((2S,4R)-4-fluoropyrrolidin-2-yl)-1H-benzo[d]imidazole);

(S)-6,6'-((2R,5R)-1-(4-(4-(2,6-difluorophenyl)piperazin-1-yl)-3,5-difluorophenyl)pyrrolidine-2,5-diyl)bis(5-fluoro-2-((S)-pyrrolidin-2-yl)-1H-benzo[d]imidazole);

(S)-6,6'-((2R,5R)-1-(4-(4-(2,4-difluorophenyl)piperidin-1-yl)-3,5-difluorophenyl)pyrrolidine-2,5-diyl)bis(5-fluoro-2-((S)-pyrrolidin-2-yl)-1H-benzo[d]imidazole);

(S)-6,6'-((2R,5R)-1-(3,5-difluoro-4-(4-(4-fluorophenyl)piperidin-1-yl)phenyl)pyrrolidine-2,5-diyl)bis(5-fluoro-2-((S)-pyrrolidin-2-yl)-1H-benzo[d]imidazole);

(S)-6,6'-((2S,5S)-1-(4-(4-(2,6-difluorophenyl)piperazin-1-yl)-3,5-difluorophenyl)pyrrolidine-2,5-diyl)bis(5-fluoro-2-((S)-pyrrolidin-2-yl)-1H-benzo[d]imidazole);

(S)-6,6'-((2R,5R)-1-(3,5-difluoro-4-(4-(5-methylthiophen-2-yl)piperidin-1-yl)phenyl)pyrrolidine-2,5-diyl)bis(5-fluoro-2-((S)-pyrrolidin-2-yl)-1H-benzo[d]imidazole); and

(S)-6,6'-((2R,5R)-1-(3,5-difluoro-4-(4-fluoro-4-phenylpiperidin-1-yl)phenyl)pyrrolidine-2,5-diyl)bis(5-fluoro-2-((S)-pyrrolidin-2-yl)-1H-benzo[d]imidazole).

The following compounds as free base or salt can be made using General Procedure 8, General Procedure 9B (Raney-nickel), General Procedure 10/10A, and General Procedure 11/11A:

(*S*)-6,6'-((2*R*,5*R*)-1-(biphenyl-4-yl)pyrrolidine-2,5-diyl)bis(2-((*S*)-pyrrolidin-2-yl)-1*H*-benzo[*d*]imidazole);

(*S*)-6,6'-((2*R*,5*R*)-1-(4-(cyclopentyloxy)-3-fluorophenyl)pyrrolidine-2,5-diyl)bis(2-((*S*)-pyrrolidin-2-yl)-1*H*-benzo[*d*]imidazole);

(*S*)-6,6'-((2*R*,5*R*)-1-(3,5-difluoro-4-((3a*R*,7a*S*)-1*H*-isoindol-2(3*H*,3a*H*,4*H*,5*H*,6*H*,7*H*,7a*H*)-yl)phenyl)pyrrolidine-2,5-diyl)bis(2-((*S*)-pyrrolidin-2-yl)-1*H*-benzo[*d*]imidazole);

(*S*)-6,6'-((2*R*,5*R*)-1-(3,5-dichloro-4-(piperidin-1-yl)phenyl)pyrrolidine-2,5-diyl)bis(2-((*S*)-pyrrolidin-2-yl)-1*H*-benzo[*d*]imidazole);

(*S*)-6,6'-((2*R*,5*R*)-1-(2,5-difluoro-4-(piperidin-1-yl)phenyl)pyrrolidine-2,5-diyl)bis(2-((*S*)-pyrrolidin-2-yl)-1*H*-benzo[*d*]imidazole);

(*S*)-6,6'-((2*R*,5*R*)-1-(4-((2*R*,6*S*)-2,6-dimethylpiperidin-1-yl)-3,5-difluorophenyl)pyrrolidine-2,5-diyl)bis(2-((*S*)-pyrrolidin-2-yl)-1*H*-benzo[*d*]imidazole);

(*S*)-6,6'-((2*R*,5*R*)-1-(2,3,5-trifluoro-4-(piperidin-1-yl)phenyl)pyrrolidine-2,5-diyl)bis(2-((*S*)-pyrrolidin-2-yl)-1*H*-benzo[*d*]imidazole);

(*S*)-6,6'-((2*R*,5*R*)-1-(4-cyclohexyl-3-fluorophenyl)pyrrolidine-2,5-diyl)bis(2-((*S*)-pyrrolidin-2-yl)-1*H*-benzo[*d*]imidazole);

(*S*)-6,6'-((2*R*,5*R*)-1-(3,4-difluorophenyl)pyrrolidine-2,5-diyl)bis(2-((*S*)-pyrrolidin-2-yl)-1*H*-benzo[*d*]imidazole);

(*S*)-6,6'-((2*R*,5*R*)-1-(4-ethoxyphenyl)pyrrolidine-2,5-diyl)bis(2-((*S*)-pyrrolidin-2-yl)-1*H*-benzo[*d*]imidazole);

(*S*)-6,6'-((2*R*,5*R*)-1-(4-(2,2-difluoroethoxy)phenyl)pyrrolidine-2,5-diyl)bis(2-((*S*)-pyrrolidin-2-yl)-1*H*-benzo[*d*]imidazole);

(*S*)-6,6'-((2*R*,5*R*)-1-(4-(3,5-dimethylpiperidin-1-yl)-3,5-difluorophenyl)pyrrolidine-2,5-diyl)bis(2-((*S*)-pyrrolidin-2-yl)-1*H*-benzo[*d*]imidazole);

6,6'-{(2*R*,5*R*)-1-[4-(pentafluoro-λ^6-sulfanyl)phenyl]pyrrolidine-2,5-diyl}bis{2-[(2*S*)-pyrrolidin-2-yl]-1*H*-benzimidazole} (ACD Name v12);

(*S*)-6,6'-((2*S*,5*S*)-1-(4-cyclopropylphenyl)pyrrolidine-2,5-diyl)bis(2-((*S*)-pyrrolidin-2-yl)-1*H*-benzo[*d*]imidazole);

(*S*)-6,6'-((2*R*,5*R*)-1-(4-*tert*-butylphenyl)pyrrolidine-2,5-diyl)bis(2-((*S*)-pyrrolidin-2-yl)-1*H*-benzo[*d*]imidazole);

(*S*,*S*)-6,6'-((2*R*,5*R*)-1-(3,5-difluoro-4-(piperidin-1-yl)phenyl)pyrrolidine-2,5-diyl)bis(2-((2*S*,4*S*)-4-methoxypyrrolidin-2-yl)-1*H*-benzo[*d*]imidazole);

(*S*,*S*)-6,6'-((2*R*,5*R*)-1-(3,5-difluoro-4-(piperidin-1-yl)phenyl)pyrrolidine-2,5-diyl)bis(2-((2*S*,4*S*)-4-fluoropyrrolidin-2-yl)-1*H*-benzo[*d*]imidazole);

(*S*,*S*)-6,6'-((2*R*,5*R*)-1-(4-fluorophenyl)pyrrolidine-2,5-diyl)bis(2-((2*S*,4*S*)-4-fluoropyrrolidin-2-yl)-1*H*-benzo[*d*]imidazole);

(*S*,*S*)-6,6'-((2*R*,5*R*)-1-(4-fluorophenyl)pyrrolidine-2,5-diyl)bis(2-((2*S*,4*S*)-4-methoxypyrrolidin-2-yl)-1*H*-benzo[*d*]imidazole);

(*S*)-6,6'-((2*R*,5*R*)-1-(4-*tert*-butylphenyl)pyrrolidine-2,5-diyl)bis(2-((*S*)-5,5-dimethylpyrrolidin-2-yl)-1*H*-benzo[*d*]imidazole);

(*S*,*S*)-6,6'-((2*R*,5*R*)-1-(4-*tert*-butylphenyl)pyrrolidine-2,5-diyl)bis(2-((2*S*,4*S*)-4-fluoropyrrolidin-2-yl)-1*H*-benzo[*d*]imidazole);

(*S*)-6,6'-((2*R*,5*R*)-1-(3,5-difluoro-4-(piperidin-1-yl)phenyl)pyrrolidine-2,5-diyl)bis(2-((3*S*)-2-azabicyclo[2.2.1]heptan-3-yl)-1*H*-benzo[*d*]imidazole);

(*S*)-6,6'-((2*R*,5*R*)-1-(3,5-difluoro-4-(piperidin-1-yl)phenyl)pyrrolidine-2,5-diyl)bis(2-((*S*)-indolin-2-yl)-1*H*-benzo[*d*]imidazole);

(*S*,*R*)-6,6'-((2*R*,5*R*)-1-(3,5-difluoro-4-(piperidin-1-yl)phenyl)pyrrolidine-2,5-diyl)bis(2-((2*S*,4*R*)-4-methoxypyrrolidin-2-yl)-1*H*-benzo[*d*]imidazole);

(*S*)-6,6'-((2*R*,5*R*)-1-(4-*tert*-butylphenyl)pyrrolidine-2,5-diyl)bis(2-((*S*)-4-methylenepyrrolidin-2-yl)-1*H*-benzo[*d*]imidazole);

(*S*)-6,6'-((2*R*,5*R*)-1-(4-(4,4-diphenylpiperidin-1-yl)-3,5-difluorophenyl)pyrrolidine-2,5-diyl)bis(2-((*S*)-pyrrolidin-2-yl)-1*H*-benzo[*d*]imidazole);

1-(1-(4-((2*R*,5*R*)-2,5-bis(2-((*S*)-pyrrolidin-2-yl)-1*H*-benzo[*d*]imidazol-6-yl)pyrrolidin-1-yl)-2,6-difluorophenyl)-4-phenylpiperidin-4-yl)ethanone;

(*S*)-6,6'-((2*R*,5*R*)-1-(3,5-difluoro-4-(piperidin-1-yl)phenyl)pyrrolidine-2,5-diyl)bis(2-((*S*)-pyrrolidin-2-yl)-1*H*-benzo[*d*]imidazole);

(*S*,*S*,*S*)-6,6'-((2*R*,5*R*)-1-(3,5-difluoro-4-(piperidin-1-yl)phenyl)pyrrolidine-2,5-diyl)bis(2-((2*S*,3a*S*,6a*S*)-octahydrocyclopenta[b]pyrrol-2-yl)-1*H*-benzo[*d*]imidazole);

(*S*,*S*,*S*)-6,6'-((2*R*,5*R*)-1-(4-*tert*-butylphenyl)pyrrolidine-2,5-diyl)bis(2-((2*S*,3a*S*,6a*S*)-octahydrocyclopenta[b]pyrrol-2-yl)-1*H*-benzo[*d*]imidazole);

(*S*)-6,6'-((2*R*,5*R*)-1-(3,5-difluoro-4-(3-azaspiro[5.5]undecan-3-yl)phenyl)pyrrolidine-2,5-diyl)bis(2-((*S*)-pyrrolidin-2-yl)-1*H*-benzo[*d*]imidazole);

(*S*)-6,6'-((2*R*,5*R*)-1-(3-fluoro-4-(4-phenylpiperidin-1-yl)phenyl)pyrrolidine-2,5-diyl)bis(2-((*S*)-pyrrolidin-2-yl)-1*H*-benzo[*d*]imidazole);

(S,S,S)-6,6'-((2R,5R)-1-(3,5-difluoro-4-(4-phenylpiperidin-1-yl)phenyl)pyrrolidine-2,5-diyl)bis(2-((2S,3aS,6aS)-octahydrocyclopenta[b]pyrrol-2-yl)-1H-benzo[d]imidazole);

(S)-6,6'-((2R,5R)-1-(3,5-difluoro-4-(3-phenylpiperidin-1-yl)phenyl)pyrrolidine-2,5-diyl)bis(2-((S)-pyrrolidin-2-yl)-1H-benzo[d]imidazole);

(S)-6,6'-((2R,5R)-1-(3,5-difluoro-4-(3-phenylpyrrolidin-1-yl)phenyl)pyrrolidine-2,5-diyl)bis(2-((S)-pyrrolidin-2-yl)-1H-benzo[d]imidazole);

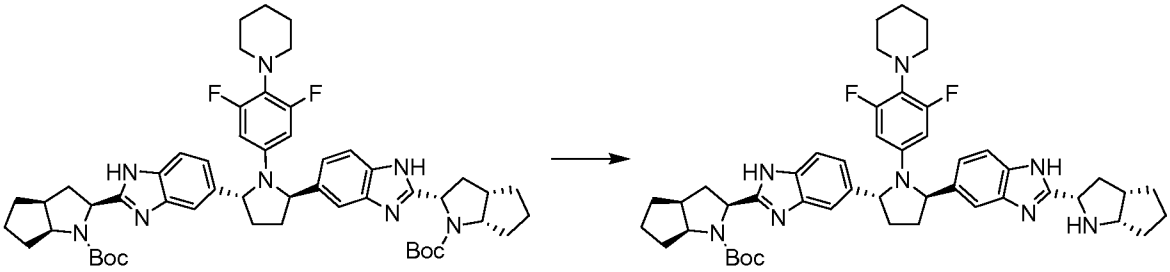
(S)-6,6'-((2R,5R)-1-(3,5-difluoro-4-(4-(pyrimidin-2-yl)piperazin-1-yl)phenyl)pyrrolidine-2,5-diyl)bis(5-fluoro-2-((S)-pyrrolidin-2-yl)-1H-benzo[d]imidazole);

(S)-6,6'-((2S,5R)-1-(2-(4-phenylpiperidin-1-yl)pyrimidin-5-yl)pyrrolidine-2,5-diyl)bis(5-fluoro-2-((S)-pyrrolidin-2-yl)-1H-benzo[d]imidazole); and

(S)-6,6'-((2S,5R)-1-(2-(piperidin-1-yl)pyrimidin-5-yl)pyrrolidine-2,5-diyl)bis(5-fluoro-2-((S)-pyrrolidin-2-yl)-1H-benzo[d]imidazole).

The following compounds as free base or salt can be made using General Procedure 8, General Procedure 9E (Fe/NH_4Cl), General Procedure 10/10A, and General Procedure 11/11A:
(S)-6,6'-((2R,5R)-1-(3,5-difluoro-4-(4-(3-phenylpropyl)piperidin-1-yl)phenyl)pyrrolidine-2,5-diyl)bis(5-fluoro-2-((S)-pyrrolidin-2-yl)-1H-benzo[d]imidazole);
(S)-6,6'-((2R,5R)-1-(3,5-difluoro-4-(6-azaspiro[2.5]octan-6-yl)phenyl)pyrrolidine-2,5-diyl)bis(5-fluoro-2-((S)-pyrrolidin-2-yl)-1H-benzo[d]imidazole);
(S)-6,6'-((2R,5R)-1-(4-(4-*tert*-butylpiperidin-1-yl)-3,5-difluorophenyl)pyrrolidine-2,5-diyl)bis(5-fluoro-2-((S)-pyrrolidin-2-yl)-1H-benzo[d]imidazole);
(S)-6,6'-((2R,5R)-1-(3,5-difluoro-4-(4-(naphthalen-2-yl)piperidin-1-yl)phenyl)pyrrolidine-2,5-diyl)bis(5-fluoro-2-((S)-pyrrolidin-2-yl)-1H-benzo[d]imidazole); and
(S)-6,6'-((2R,5R)-1-(4-(benzyloxy)phenyl)pyrrolidine-2,5-diyl)bis(2-((S)-pyrrolidin-2-yl)-1H-benzo[d]imidazole).

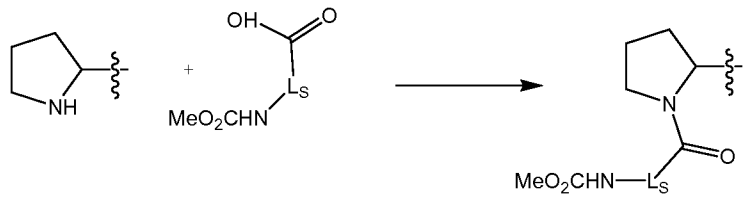
Illustration of General Procedure 11. General Procedure 11C (monodeprotection)



(2S,3aS,6aS)-*tert*-butyl 2-(5-((2R,5R)-1-(3,5-difluoro-4-(piperidin-1-yl)phenyl)-5-(2-((2S,3aS,6aS)-octahydrocyclopenta[b]pyrrol-2-yl)-1H-benzo[d]imidazol-5-yl)pyrrolidin-2-yl)-1H-benzo[d]imidazol-2-yl)hexahydrocyclopenta[b]pyrrole-1(2H)-carboxylate

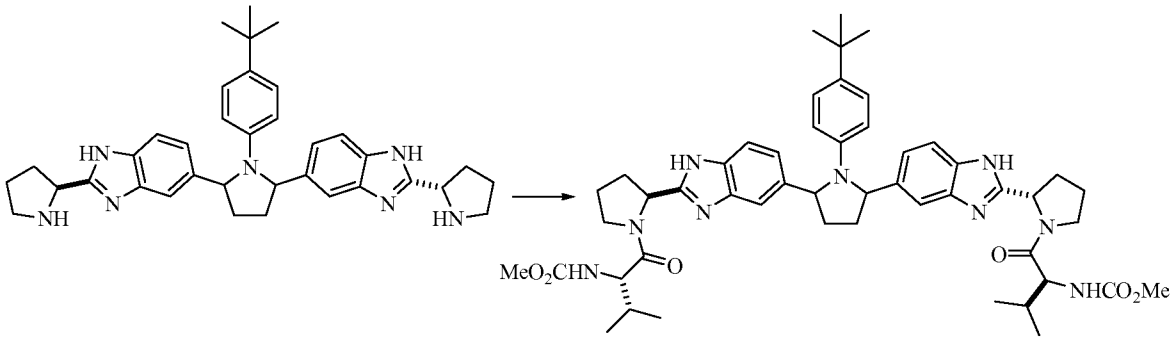
The starting di-Boc-protected amine (1.24 g, 1.36 mmol) was dissolved in dichloromethane (12 mL) at ambient temperature and treated with aliquots of trifluoroacetic acid (0.10 mL, 1.35 mmol) every thirty minutes for 1.5 hours. The solution was concentrated to dryness then re-dissolved into dichloromethane and washed with sodium bicarbonate solution. After concentration, the residue was purified by chromatography, eluting with 0-20% methanol in dichloromethane to give 425 mg (38%) of the title mono-deprotected amine as a yellow powder.

General Procedure 12. Endcap addition.



Reaction of an amine with an acid to form an amide as depicted above can be effected as described generally in Scheme 1 and other foregoing Schemes. The reaction can be promoted by a peptide coupling reagent, such as EDAC/HOBT, PyBOP, HATU, T3P or DEPBT, in a solvent such as THF, DMF, dichloromethane, ethyl acetate, or DMSO, with or without the addition of an amine base such as Hunig's base, *N*-methylmorpholine, pyridine, 2,6-lutidine, or triethylamine, to give amide products. For example, an amine (1 equivalent) can be reacted with acids (2 equivalents) such as, but not limited to, 2-(methoxycarbonylamino)-3-methylbutanoic acid, 2-(methoxycarbonylamino)-3,3-dimethylbutanoic acid, 2-cyclohexyl-2-(methoxycarbonylamino)acetic acid, 2-(methoxycarbonylamino)-2-(tetrahydro-2*H*-pyran-4-yl)acetic acid, or those listed below under General Procedure 19. Final coupling products may contain varying amounts of stereoisomers with respect to the pyrrolidine ring. In the case of fluoro-substituted benzimidazole-containing products (e.g. Example 6.1, Example 6.12, Example 6.16), final purification to remove residual amounts of another stereoisomer may require chiral chromatography as described below in General Procedure 12C.

Illustration of General Procedure 12. General Procedure 12A

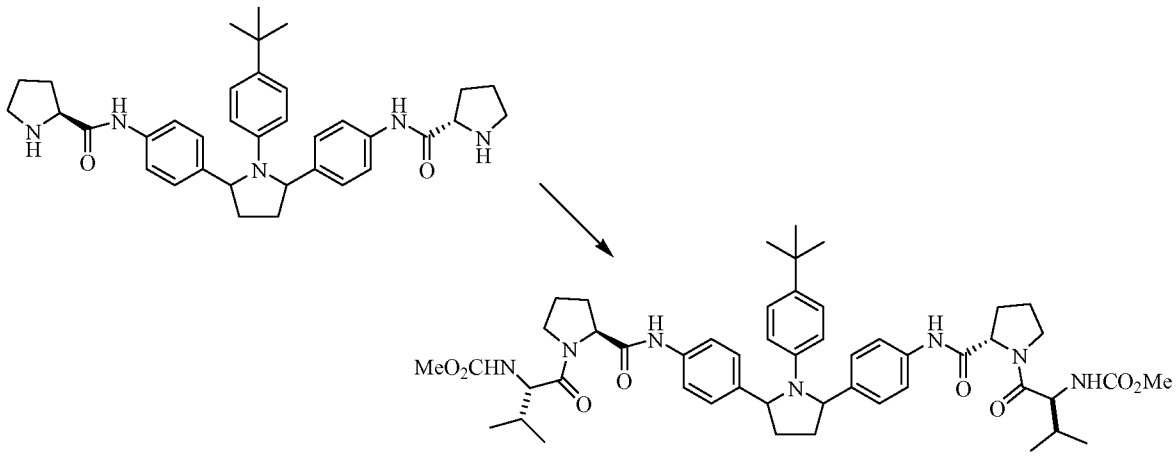


dimethyl (2*S*,2'*S*)-1,1'-((2*S*,2'*S*)-2,2'-(5,5'-((2*R*,5*R*)-1-(4-*tert*-butylphenyl)pyrrolidine-2,5-diyl)bis(1*H*-benzo[*d*]imidazole-5,2-diyl))bis(pyrrolidine-2,1-diyl))bis(3-methyl-1-oxobutane-2,1-diyl)dicarbamate and dimethyl (2*S*,2'*S*)-1,1'-((2*S*,2'*S*)-2,2'-(5,5'-((2*S*,5*S*)-1-(4-*tert*-butylphenyl)pyrrolidine-2,5-diyl)bis(1*H*-benzo[*d*]imidazole-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

(*S*)-5,5'-(1-(4-*tert*-butylphenyl)pyrrolidine-2,5-diyl)bis(2-((*S*)-pyrrolidin-2-yl)-1*H*-benzo[*d*]imidazole) (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 hour at room temperature then diluted with water. The solid product was filtered off and purified by chromatography on silica gel with a 12 g column, eluting with 0-8% methanol in dichloromethane to give 0.143 g (60%) of a yellow solid as a mixture of trans diastereomers. ^{1}H NMR (400 MHz, DMSO-d_6) 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).

Illustration of General Procedure 12. General Procedure 12B

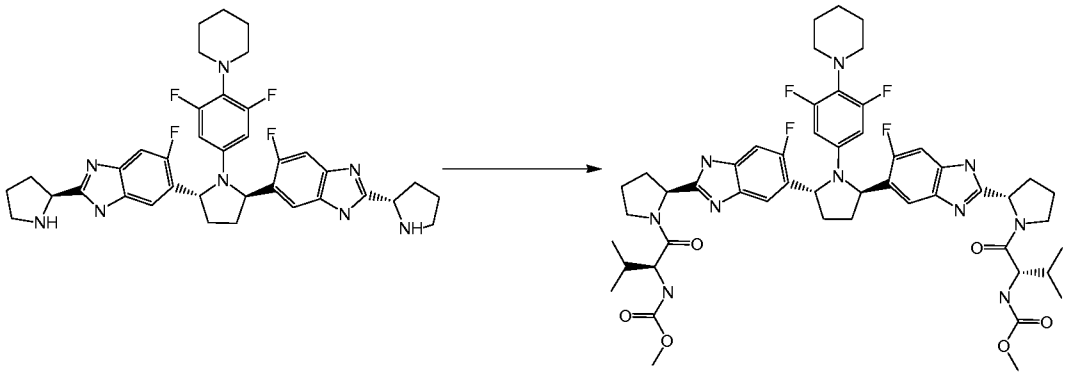


dimethyl (2*S*,2'*S*)-1,1'-((2*S*,2'*S*)-2,2'-(4,4'-((2*S*,5*S*)-1-(4-*tert*-butylphenyl)pyrrolidine-2,5-diyl)bis(4,1-phenylene))bis(azanediyl)bis(oxomethylene)bis(pyrrolidine-2,1-diyl))bis(3-methyl-1-oxobutane-2,1-diyl)dicarbamate and dimethyl (2*S*,2'*S*)-1,1'-((2*S*,2'*S*)-2,2'-(4,4'-((2*R*,5*R*)-1-(4-*tert*-butylphenyl)pyrrolidine-2,5-diyl)bis(4,1-phenylene)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

(2*S*,2'*S*)-*N*,*N*'-(4,4'-((2*S*,5*S*)-1-(4-*tert*-Butylphenyl)pyrrolidine-2,5-diyl)bis(4,1-phenylene))dipyrrolidine-2-carboxamide and (2*S*,2'*S*)-*N*,*N*'-(4,4'-((2*R*,5*R*)-1-(4-*tert*-butylphenyl)pyrrolidine-2,5-diyl)bis(4,1-phenylene))dipyrrolidine-2-carboxamide (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 hours. The 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 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%) as a mixture of trans diastereomers. ^{1}H NMR (400 MHz, DMSO-d_6) 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); MS (ESI+) *m/z* 895 $(M+H)^+$.

Illustration of General Procedure 12. General Procedure 12C



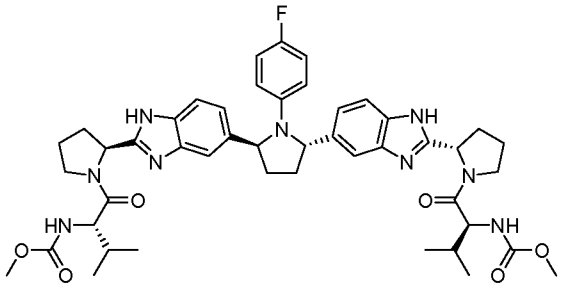
methyl {(2*S*)-1-[(2*S*)-2-{5-[(2*R*,5*R*)-1-[3,5-difluoro-4-(piperidin-1-yl)phenyl]-5-{6-fluoro-2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1*H*-benzimidazol-5-yl}pyrrolidin-2-yl]-6-fluoro-1*H*-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

To a solution of (*S*)-2-(methoxycarbonylamino)-3-methylbutanoic acid (116 mg, 0.660 mmol) in CH_2Cl_2 (1.0 mL) was added EDC (127 mg, 0.660 mmol) and the solution was stirred at room temperature for 20 minutes. This solution was then cannulated into a solution of 6,6'-{(2*R*,5*R*)-1-[3,5-difluoro-4-(piperidin-1-yl)phenyl]pyrrolidine-2,5-diyl}bis{5-fluoro-2-[(2*S*)-pyrrolidin-2-yl]-1*H*-benzimidazole} (ACD Name v12) (148 mg, 0.220 mmol) and Hunig's base (0.231 ml, 1.320 mmol) in CH_2Cl_2 (1.000 mL) followed by the addition of HOBT (101 mg, 0.660 mmol), and the solution was then stirred at room temperature for 1 hour. The solution was diluted with CH_2Cl_2, washed with H_2O, dried (Na_2SO_4), filtered and concentrated. The product may be subject to further purification.

From a separate experiment using the above coupling procedure, crude product (about 4 mmol) was purified on a Teledyne/ISCO Combiflash® Rf System using a C18 cartridge eluting with 0-30% CH_3CN/(0.1%TFA/H_2O) over 30 minutes. The desired fractions were made basic with 10% $NaHCO_3$ solution and extracted with EtOAc. The combined extracts were dried (Na_2SO_4), filtered and concentrated to give a white solid (545 mg). This material was then re-purified on a Waters preparative HPLC system using a C18 column eluting with 0-95% CH_3CN/(0.1% TFA/H_2O) over 40 minutes to give material (195 mg) containing mostly the title compound and a residual amount of a diastereomeric product. To remove remaining amounts of the diastereomer, chiral chromatography was run on this sample using a Chiralpak® IA column (5 cm×15 cm, 20 mL/minute) and eluting with 55/30/15 hexane/THF/[CH_3OH/EtOH 8:2] to give the title compound (116 mg, 0.118 mmol). ^1H NMR (400 MHz, $CDCl_3$) δ ppm 10.51-10.60 (m, 1H) 10.33-10.41 (m, 1H) 7.43-7.50 (m, 1H) 7.32 (t,

1H) 7.13 (d, 1H) 6.93 (t, 1H) 5.82 (d, 2H) 5.28-5.48 (m, 6H) 4.26-4.39 (m, 2H) 3.78-3.90 (m, 2H) 3.70-3.71 (d, 6H) 3.57-3.67 (m, 2H) 3.44-3.57 (m, 1H) 2.99-3.12 (m, 2H) 2.79-2.98 (m, 4H) 1.78-2.58 (m, 12H) 1.41-1.51 (m, 2H) 0.80-0.95 (m, 12H); MS (ESI) *m/z* 987 $(M+H)^+$.

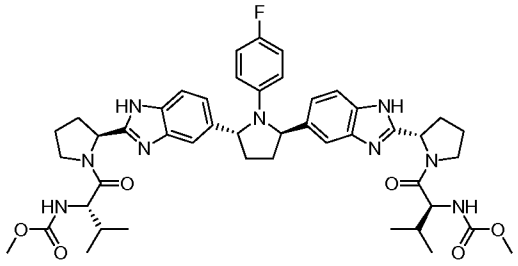
General Procedure 14. Chiral separation



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

The mixture of trans diastereomers was chromatographed by chiral chromatography on a Chiralpak IA column eluting with a mixture of hexane/EtOH/CH_3OH/1,2-dichloroethane/diethylamine (25/25/25/25/0.1) to give two separate isomers. ^{1}H NMR (400 MHz, DMSO-d_6) 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).

and



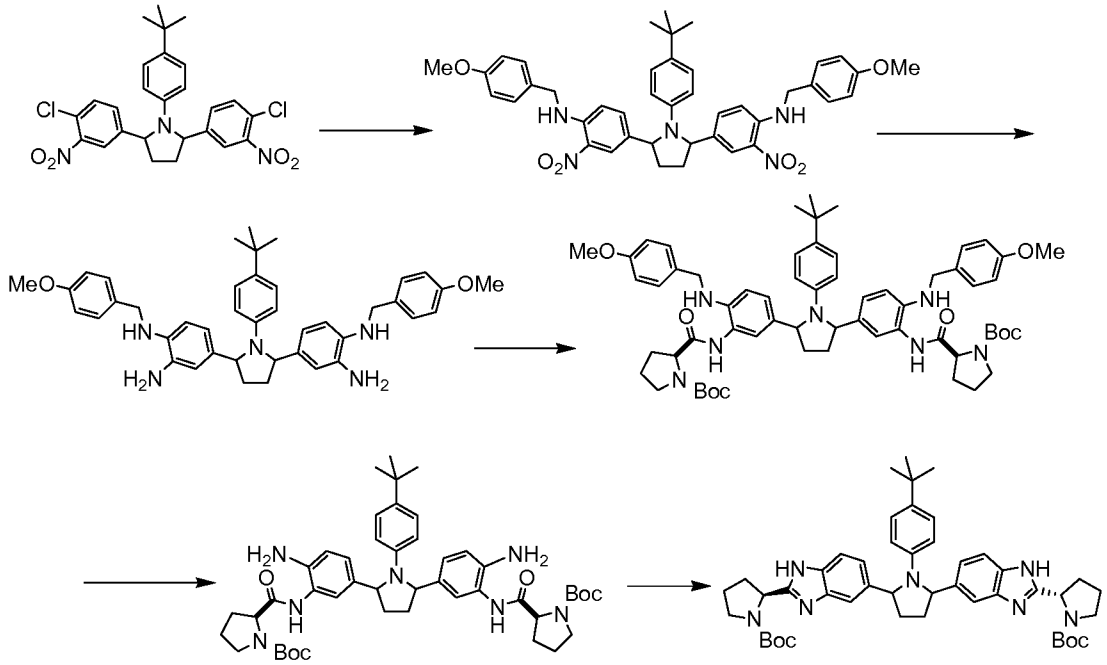
dimethyl (2*S*,2'*S*)-1,1'-((2*S*,2'*S*)-2,2'-(5,5'-((2*R*,5*R*)-1-(4-fluorophenyl)pyrrolidine-2,5-diyl)bis(1*H*-benzo[*d*]imidazole-5,2-diyl))bis(pyrrolidine-2,1-diyl))bis(3-methyl-1-oxobutane-2,1-diyl)dicarbamate

^{1}H NMR (400 MHz, DMSO-d_6) 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).

General Procedure 15. Benzimidazole synthesis through methoxybenzylamine displacement route I

Shown generally in Scheme VIII, is a method of preparing certain compounds (57) and (59). Illustrated below in General Procedure 15A is a representative synthesis of (57) where D is 4-*tert*-butylphenyl.

Illustration of General Procedure 15. General Procedure 15A



The five steps illustrated above are described by the following experimental procedures:

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

1-(4-*tert*-Butylphenyl)-2,5-bis(4-chloro-3-nitrophenyl)pyrrolidine (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 hour. The mixture was diluted with dichloromethane and filtered. The filtrate was washed with 0.5 *M* HCl, $NaHCO_3$ solution, and then brine. The organic phase was concentrated and purified by chromatography on silica gel with an 80 g column, eluting with 0-50% ethyl acetate/hexanes to give 4.13g (67%) of an orange foamy solid.

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

4,4'-(1-(4-*tert*-Butylphenyl)pyrrolidine-2,5-diyl)bis(*N*-(4-methoxybenzyl)-2-nitroaniline) (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 as a THF slurry. The flask was evacuated and purged with nitrogen twice, then evacuated and opened to a hydrogen balloon. The mixture was stirred at room temperature for 20 hours, then filtered through diatomaceous earth, concentrated, and

purified by chromatography on silica gel with an 80 g column, eluting with 0-40% ethyl acetate/dichloromethane to give the first peak of trans product (0.508 g, 28%).

(2*S*,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

4,4'-(1-(4-*tert*-Butylphenyl)pyrrolidine-2,5-diyl)bis(*N*1-(4-methoxybenzyl)benzene-1,2-diamine) (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 hour at room temperature and then diluted with water. The solid product was filtered off and purified by chromatography on silica gel with a 40 g column, eluting with 0-50% ethyl acetate in dichloromethane to give the title compound (0.565 g, 84%) as a yellow solid.

(2*S*,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

(2*S*,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 (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 40 g column, eluting with 0-15% methanol/dichloromethane to give the title compound (0.355 g, 81%) as a yellow solid.

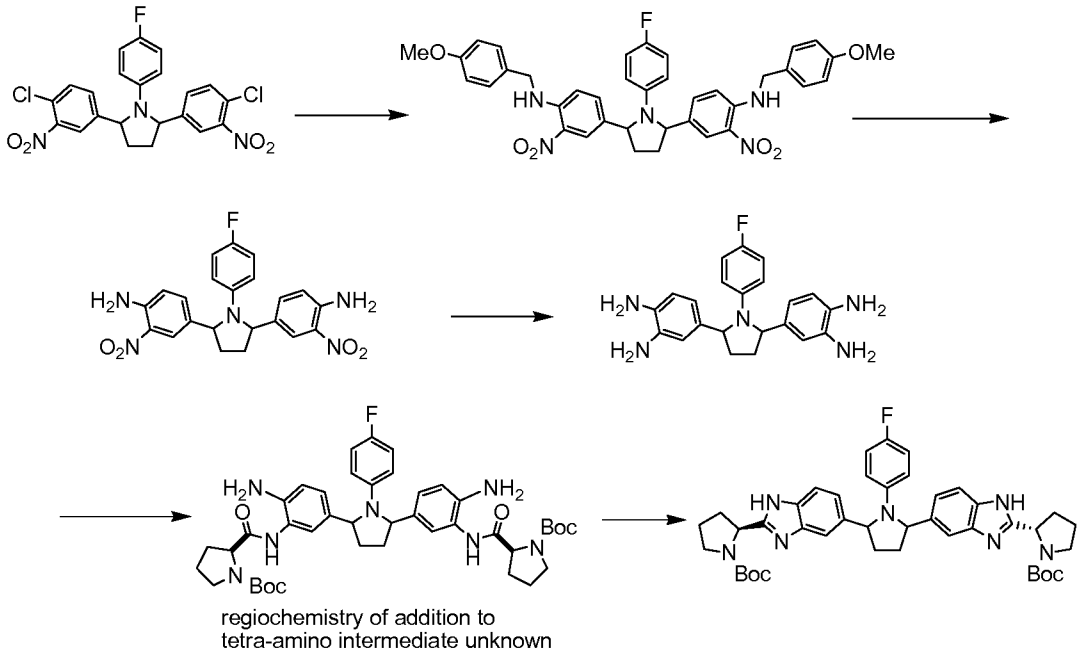
(2*S*,2'*S*)-*tert*-butyl 2,2'-(5,5'-(1-(4-*tert*-butylphenyl)pyrrolidine-2,5-diyl)bis(1*H*-benzo[*d*]imidazole-5,2-diyl))dipyrrolidine-1-carboxylate

(2*S*,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 was dissolved in neat acetic acid (3 mL) and heated at 72 ºC for 2 hours. The solution was concentrated and then poured into water. The pH was adjusted to ~7-8 with sodium bicarbonate. The product was extracted into dichloromethane, concentrated and purified by chromatography on silica gel with a 40 g column, eluting with 0-5%methanol/dichloromethane to give the title compound (0.185 g, 55%) as a light yellow solid.

General Procedure 16. Benzimidazole synthesis through methoxybenzylamine displacement route II

Shown generally in Scheme VIII, is a method of preparing certain compounds (57) and (59). Illustrated below in General Procedure 16A is a representative synthesis of (57) where D is 4-fluorophenyl.

Illustration of General Procedure 16. General Procedure 16A



The five steps illustrated above are described by the following experimental procedures:

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

2,5-Bis(4-chloro-3-nitrophenyl)-1-(4-fluorophenyl)pyrrolidine (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 hour 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 330 g column, eluting with 0-60% ethyl acetate/hexanes to give 0.79g (62%) of an orange foam solid.

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

4,4'-(1-(4-Fluorophenyl)pyrrolidine-2,5-diyl)bis(*N*-(4-methoxybenzyl)-2-nitroaniline) (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 hours. 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 40 g column, eluting with dichloromethane to give 0.218 g (43%) of the trans isomer.

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

4,4'-(1-(4-Fluorophenyl)pyrrolidine-2,5-diyl)bis(2-nitroaniline) (0.218 g, 0.50 mmol) was dissolved in DMF (5 mL) then platinum oxide (0.226 g, 0.99 mmol) was added as a 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 hours. The solution was taken on to the next step without purification.

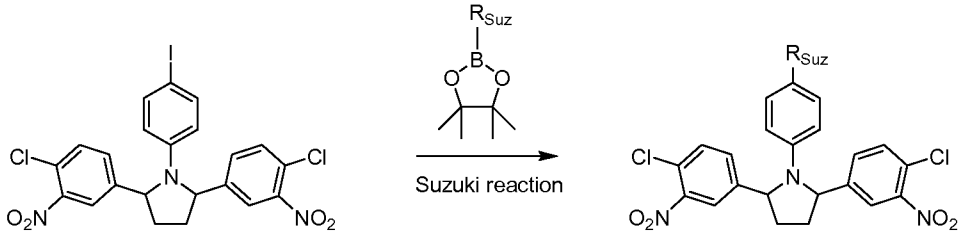
(2*S*,2'*S*)-*tert*-butyl 2,2'-(5,5'-(1-(4-fluorophenyl)pyrrolidine-2,5-diyl)bis(2-amino-5,1-phenylene))bis(azanediyl)bis(oxomethylene)dipyrrolidine-1-carboxylate

The crude DMF solution of 4,4'-(1-(4-fluorophenyl)pyrrolidine-2,5-diyl)dibenzene-1,2-diamine 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 hours at room temperature, and then the reaction mixture was diluted with water. The solid product was filtered off and purified by chromatography on silica gel with a 12 g column, eluting with 0-3% methanol in dichloromethane to give 0.235 g (72%) of a yellow solid, for which the regiochemistry of acylation was arbitrarily assigned as reacting at the meta-amino group.

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

(2*S*,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 was dissolved in neat acetic acid (2 mL) and heated at 60 °C for 1 hour. 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 12 g column, eluting with 0-20% ethyl acetate in dichloromethane to give the title compound (0.124 g, 55%) as a light yellow solid.

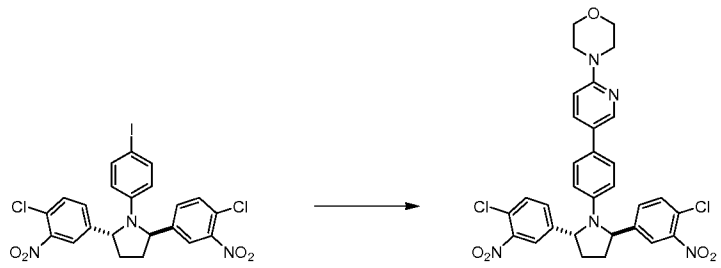
General Procedure 17. Suzuki Couplings off N-Aryl group



Intermediate compounds such as 2,5-bis(4-chloro-3-nitrophenyl)-1-(4-iodophenyl)pyrrolidine (or the corresponding triflate, nonaflate, or bromide) can be further elaborated through a Suzuki reaction as shown with an appropriate boronic acid or ester where R_{Suz} represents a suitable

cycloalkyl, aryl, cycloalkenyl, or heteroaryl group. Suitable conditions for effecting this Suzuki reaction include those described in Scheme V for the synthesis of compounds (37).

Illustration of General Procedure 17: General Procedure 17A



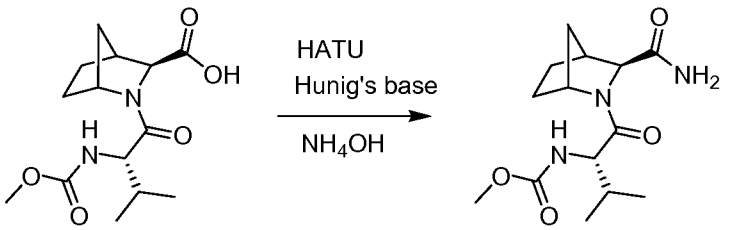
4-(5-(4-((2*R*,5*R*)-2,5-bis(4-chloro-3-nitrophenyl)pyrrolidin-1-yl)phenyl)pyridin-2-yl)morpholine

(2*R*,5*R*)-2,5-Bis(4-chloro-3-nitrophenyl)-1-(4-iodophenyl)pyrrolidine (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.

General Procedure 18. Proline amide synthesis

Particular substituted proline amides can be made using methods such as those shown in General Procedures 18A-18C.

Illustration of General Procedure 18. General Procedure 18A

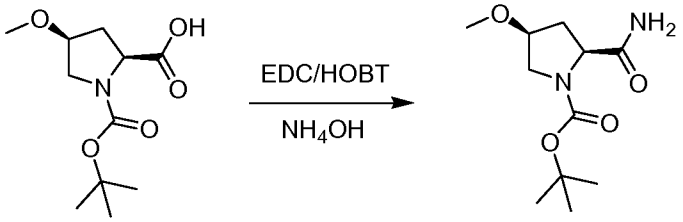


methyl (2*S*)-1-((3*S*)-3-carbamoyl-2-azabicyclo[2.2.1]heptan-2-yl)-3-methyl-1-oxobutan-2-ylcarbamate

(3*S*)-2-((*S*)-2-(Methoxycarbonylamino)-3-methylbutanoyl)-2-azabicyclo[2.2.1]heptane-3-carboxylic acid (1.78 g, 5.97 mmol), 2-(3H-[1,2,3]triazolo[4,5-*b*]pyridin-3-yl)-1,1,3,3-tetramethylisouronium hexafluorophosphate (2.49 g, 5.56 mmol), and diisopropylethylamine (2.61

mL, 14.92 mmol) were dissolved in acetonitrile (30 mL) at ambient temperature and treated by dropwise addition with 28% ammonium hydroxide solution (2.49 g, 17.98 mmol). The resulting mixture was stirred for 1 hour and then diluted with water and extracted into dichloromethane. The organic layer was washed with brine, dried over sodium sulfate, filtered, and concentrated to give methyl (2*S*)-1-((3*S*)-3-carbamoyl-2-azabicyclo[2.2.1]heptan-2-yl)-3-methyl-1-oxobutan-2-ylcarbamate as a white waxy solid.

Illustration of General Procedure 18. General Procedure 18B

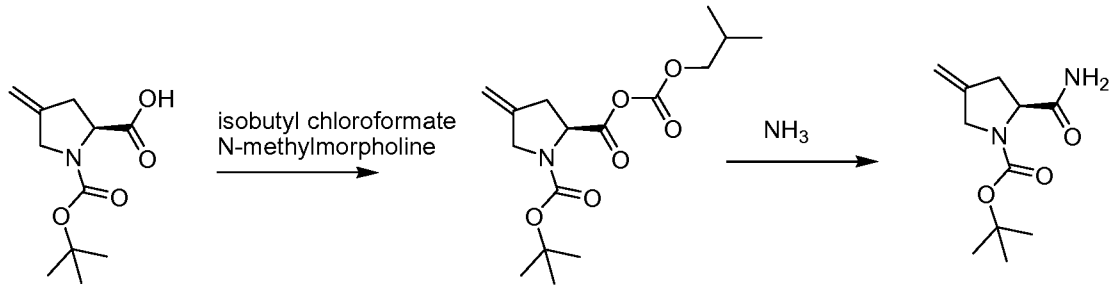


(2*S*,4*S*)-*tert*-butyl 2-carbamoyl-4-methoxypyrrolidine-1-carboxylate

(2*S*,4*S*)-1-(*tert*-Butoxycarbonyl)-4-methoxypyrrolidine-2-carboxylic acid (2.9 g, 11.82 mmol) was dissolved in acetonitrile (150 mL) and cooled in an ice bath. N^1-((Ethylimino)methylene)-N^3,N^3-dimethylpropane-1,3-diamine hydrochloride (2.72 g, 14.19 mmol) and 1*H*-benzo[*d*][1,2,3]triazol-1-ol hydrate (2.17 g, 14.19 mmol) were added, and the mixture was stirred at ambient temperature for 15 hours, becoming clear. 28% Ammonium hydroxide (4.93 mL, 35.5 mmol) was added dropwise resulting in a precipitate. After stirring for 2 hours, then mixture was concentrated, diluted with water and extracted into ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate, filtered, and concentrated to give 100% yield of (2*S*,4*S*)-*tert*-butyl 2-carbamoyl-4-methoxypyrrolidine-1-carboxylate as a white waxy solid.

Other amides that can be prepared using General Procedure 18B include:
(2*S*,4*R*)-*tert*-butyl 2-carbamoyl-4-methoxypyrrolidine-1-carboxylate;
(2*S*,4*S*)-*tert*-butyl 2-carbamoyl-4-fluoropyrrolidine-1-carboxylate; and
(*S*)-*tert*-butyl 5-carbamoyl-2,2-dimethylpyrrolidine-1-carboxylate.

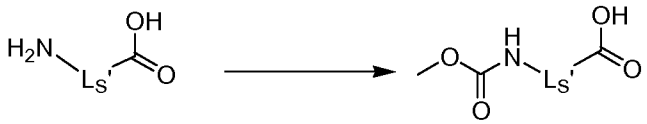
Illustration of General Procedure 18. General Procedure 18C



(*S*)-*tert*-butyl 2-carbamoyl-4-methylenepyrrolidine-1-carboxylate

(*S*)-1-(*tert*-Butoxycarbonyl)-4-methylenepyrrolidine-2-carboxylic acid (1.05 g, 4.48 mmol) and *N*-methylmorpholine (0.64 mL, 5.83 mmol) were dissolved in tetrahydrofuran (25 mL) and cooled to −15 °C in a dry ice/acetone bath. Isobutyl chloroformate (0.65 mL, 4.93 mmol) was added dropwise and the solution was stirred for 15 minutes. The internal temperature was lowered to −25 °C and ammonia (g) was bubbled through the solution for 2 minutes, then the flask was transferred to an ice bath and stirred for another 20 minutes. The solution was poured into brine and extracted into ethyl acetate, dried over magnesium sulfate, filtered and concentrated. This residue was triturated with ether/hexanes, filtered, and dried to give 0.97 g (81%) of (*S*)-*tert*-butyl 2-carbamoyl-4-methylenepyrrolidine-1-carboxylate as a white solid.

General Procedure 19



Amino acid carbamate intermediates can be made using the method and general illustration shown above to prepare Intermediate 2.

The following compounds can be made following General Procedure 19 starting from the appropriate amino acid:

(*S*)-2-(methoxycarbonylamino)-2-(tetrahydro-2*H*-pyran-4-yl)acetic acid;

(*S*)-2-cyclohexyl-2-(methoxycarbonylamino)acetic acid;

(*S*)-2-cyclopentyl-2-(methoxycarbonylamino)acetic acid;

(*S*)-2-cyclobutyl-2-(methoxycarbonylamino)acetic acid;

(*S*)-2-cyclopropyl-2-(methoxycarbonylamino)acetic acid;

(*S*)-2-(methoxycarbonylamino)-3,3-dimethylbutanoic acid;

(2*S*,3*R*)-3-methoxy-2-(methoxycarbonylamino)butanoic acid;

(2*S*,3*S*)-3-methoxy-2-(methoxycarbonylamino)butanoic acid;

(*S*)-2-(methoxycarbonylamino)-2-((*R*)-tetrahydrofuran-3-yl)acetic acid;

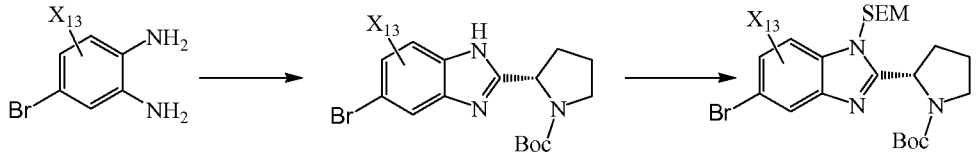
(*S*)-2-(methoxycarbonylamino)-2-((*S*)-tetrahydrofuran-3-yl)acetic acid;

(*S*)-2-(2,3-dihydro-1*H*-inden-2-yl)-2-(methoxycarbonylamino)acetic acid.

(S)-3-ethyl-2-(methoxycarbonylamino)pentanoic acid; and

(S)-2-(ethoxycarbonylamino)-3-methylbutanoic acid.

General Procedure 20



(79) (80) (81)

As described above generally in Scheme XIII, diamines (79) can be converted to benzimidazoles (81) in two steps.

Illustration of General Procedure 20. General Procedure 20A

(*S*)-*tert*-butyl 2-(6-bromo-5-fluoro-1*H*-benzo[*d*]imidazol-2-yl)pyrrolidine-1-carboxylate

To a solution of 4-bromo-5-fluorobenzene-1,2-diamine (1.7 g, 8.4 mmol) in DMSO (42 mL) was added (*S*)-1-(*tert*-butoxycarbonyl)pyrrolidine-2-carboxylic acid (1.8 g, 8.4 mmol) followed by HATU (3.5 g, 9.3 mmol) and *N*,*N*-diisopropyl-*N*-ethylamine (3.7 mL, 21.1 mmol), and the solution was stirred for 16 hours. The reaction mixture was diluted with EtOAc, washed with H_2O and brine, dried (Na_2SO_4), filtered and concentrated. Acetic acid (40 mL) was added, and the mixture was stirred at 60 °C for 4 hours. Then, the reaction mixture was cooled and concentrated. The residue was azeotroped 2 times with toluene to give crude product which was purified by flash chromatography (0-50% EtOAc/hexane) to give the title compound (2.5g, 6.4 mmol, 77%).

(*S*)-*tert*-butyl 2-(5-bromo-6-fluoro-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-benzo[*d*]imidazol-2-yl)pyrrolidine-1-carboxylate

To a solution of (*S*)-*tert*-butyl 2-(6-bromo-5-fluoro-1*H*-benzo[*d*]imidazol-2-yl)pyrrolidine-1-carboxylate (2.5 g, 6.4 mmol) in THF (32 mL) was added sodium hydride (0.27 g, 6.8 mmol) and stirring was continued for 30 minutes. 2-(Trimethylsilyl)-ethoxymethyl chloride (1.2 mL, 6.8 mmol) was added and stirring was continued for 30 minutes. Water was added to quench the reaction. The mixture was diluted with EtOAc, washed with 1*N* HCl, H_2O, and brine, dried (Na_2SO_4), filtered and concentrated to an oil. The oil was purified by flash chromatography (0-30% EtOAc/hexane) to give the title compound (2.9 g, 5.7 mmol, 89%).

The following compounds of general formula (81) can be made following General Procedure 20 starting from the appropriate diamine:

(*S*)-*tert*-butyl 2-(5-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-benzo[*d*]imidazol-2-yl)pyrrolidine-1-carboxylate;

(*S*)-*tert*-butyl 2-(5-bromo-4-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-benzo[*d*]imidazol-2-yl)pyrrolidine-1-carboxylate;

(*S*)-*tert*-butyl 2-(5-bromo-4-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-benzo[*d*]imidazol-2-yl)pyrrolidine-1-carboxylate;

(*S*)-*tert*-butyl 2-(5-bromo-4-fluoro-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-benzo[*d*]imidazol-2-yl)pyrrolidine-1-carboxylate;

(*S*)-*tert*-butyl 2-(6-bromo-3-((2-(trimethylsilyl)ethoxy)methyl)-3H-imidazo[4,5-*b*]pyridin-2-yl)pyrrolidine-1-carboxylate;

(*S*)-*tert*-butyl 2-(5-bromo-7-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-benzo[*d*]imidazol-2-yl)pyrrolidine-1-carboxylate;

(*S*)-*tert*-butyl 2-(5-bromo-6-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-benzo[*d*]imidazol-2-yl)pyrrolidine-1-carboxylate;

(*S*)-*tert*-butyl 2-(5-bromo-6-(trifluoromethyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-benzo[*d*]imidazol-2-yl)pyrrolidine-1-carboxylate;

(*S*)-*tert*-butyl 2-(5-bromo-7-(trifluoromethyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-benzo[*d*]imidazol-2-yl)pyrrolidine-1-carboxylate;

(*S*)-*tert*-butyl 2-(5-bromo-6-methoxy-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-benzo[*d*]imidazol-2-yl)pyrrolidine-1-carboxylate;

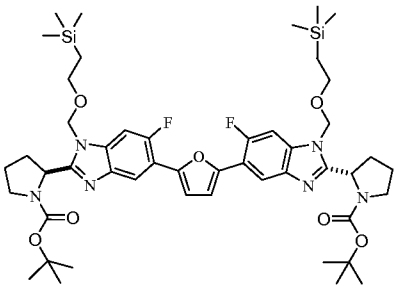
(*S*)-*tert*-butyl 2-(5-bromo-7-methoxy-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-benzo[*d*]imidazol-2-yl)pyrrolidine-1-carboxylate; and

(*S*)-methyl 5-bromo-2-(1-(*tert*-butoxycarbonyl)pyrrolidin-2-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-benzo[*d*]imidazole-7-carboxylate.

General Procedure 21

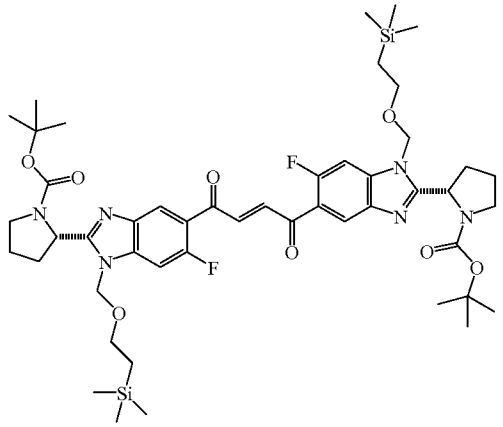
As described above generally in Scheme XIII, compounds (81) can be converted to compounds (82.2). Illustrated below in General Procedure 21A is a representative synthesis of compounds (82.2) where X_{13} is fluoro at the 6-position of the benzimidazole moiety. For convenient illustration, the SEM protecting groups on the benzimidazoles are shown attached to particular nitrogens of the benzimidazole. In General Procedures 21A and 22A, the actual substitution positions of the SEM groups were not determined and may be at either nitrogen.

Illustration of General Procedure 21. General Procedure 21A.



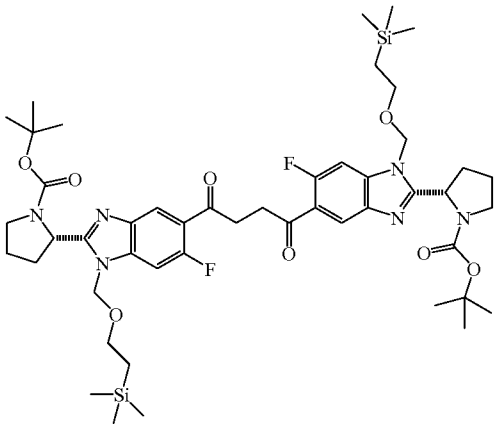
(2*S*,2'*S*)-*tert*-butyl 2,2'-(5,5'-(furan-2,5-diyl)bis(6-fluoro-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-benzo[*d*]imidazole-5,2-diyl))dipyrrolidine-1-carboxylate

In a pressure tube were combined (*S*)-*tert*-butyl 2-(5-bromo-6-fluoro-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-benzo[*d*]imidazol-2-yl)pyrrolidine-1-carboxylate (600 mg, 1.2 mmol), 2,5-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)furan (186 mg, 0.6 mmol), cesium fluoride (353 mg, 2.3 mmol) and DMF (4 mL), and the mixture was de-gassed with N_2 gas for 30 minutes. To this mixture was added $[(t\text{-Bu})_2PCl]_2PdCl_2$ (PXPd) (15.7 mg, 0.03 mmol) and the tube was sealed and heated at 100 °C for 18 hours. The cooled solution was diluted with EtOAc, filtered through diatomaceous earth. The filtrate was washed with H_2O and brine, dried (Na_2SO_4), filtered and treated with 3-mercaptopropyl silica gel for 30 minutes. The mixture was filtered, and the filtrate concentrated to give crude product which was purified by flash chromatography (0-50% EtOAc/hexane) to give the title compound (269mg, 0.29 mmol, 50%).



di-*tert*-butyl (2*S*,2'*S*)-2,2'-{[(2*E*)-1,4-dioxobut-2-ene-1,4-diyl]bis(6-fluoro-1-{[2-(trimethylsilyl)ethoxy]methyl}-1*H*-benzimidazole-5,2-diyl)}dipyrrolidine-1-carboxylate (ACD Name v12)

To a solution of (2*S*,2'*S*)-*tert*-butyl 2,2'-(5,5'-(furan-2,5-diyl)bis(6-fluoro-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-benzo[*d*]imidazole-5,2-diyl)dipyrrolidine-1-carboxylate (340 mg, .36 mmol) in THF (8 mL) was added Selectfluor® (1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate)) (258 mg, 0.73 mmol) followed by H_2O (1 mL). The solution was stirred for 1 hour, diluted with EtOAc, washed with H_2O and brine, dried (Na_2SO_4), filtered and concentrated to give the title compound.



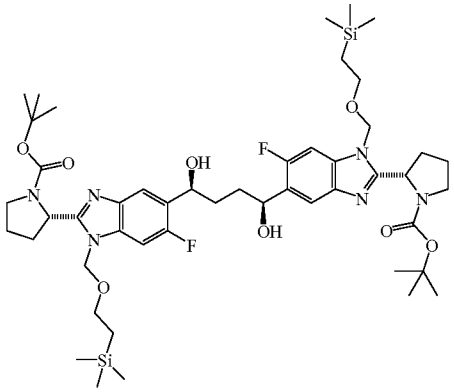
di-*tert*-butyl (2*S*,2'*S*)-2,2'-[(1,4-dioxobutane-1,4-diyl)bis(6-fluoro-1-{[2-(trimethylsilyl)ethoxy]methyl}-1*H*-benzimidazole-5,2-diyl)]dipyrrolidine-1-carboxylate (ACD Name v12)

To a solution of di-*tert*-butyl (2*S*,2'*S*)-2,2'-{[(2*E*)-1,4-dioxobut-2-ene-1,4-diyl]bis(6-fluoro-1-{[2-(trimethylsilyl)ethoxy]methyl}-1*H*-benzimidazole-5,2-diyl)}dipyrrolidine-1-carboxylate (346 mg, 0.36 mmol) in EtOAc (7 mL) was added platinum (3% on carbon) (71 mg, 0.36 mmol) and the solution was stirred under H_2 gas at 1 atm for 2 hours. The solution was filtered, washed with EtOAc and the filtrate concentrated to give a residue which was purified by flash chromatography (0-50% EtOAc/hexane) to give the title compound (269 mg, 0.28 mmol, 78%).

General Procedure 22

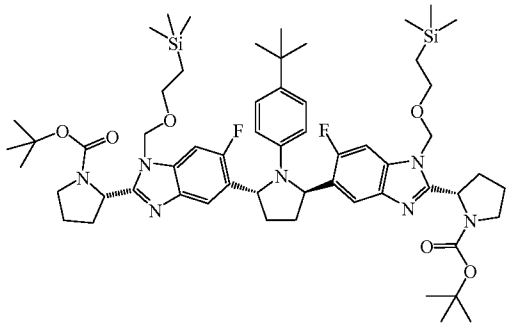
As described above generally in Scheme XIII, compounds (82.2) can be converted to compounds (84). Illustrated below in General Procedure 22A is a representative synthesis of compounds (84) where D is 4-*tert*-butylphenyl, the stereochemistries of the alcohols on the butane-1,4-diyl group are both (*S*), and X_{13} is 6-fluoro. The cyclization to form the pyrrolidine can form the trans-pyrrolidine along with varying amounts of the cis-pyrrolidine. The cis-pyrrolidine may be separated after deprotection (see General Procedure 23) or after any step following the deprotection.

Illustration of General Procedure 22. General Procedure 22A



di-*tert*-butyl (2*S*,2'*S*)-2,2'-{[(1*S*,4*S*)-1,4-dihydroxybutane-1,4-diyl]bis(6-fluoro-1-{[2-(trimethylsilyl)ethoxy]methyl}-1*H*-benzimidazole-5,2-diyl)}dipyrrolidine-1-carboxylate (ACD Name v12)

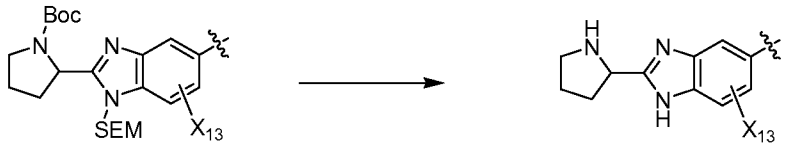
To a solution of (*R*)-(+)-α,α-diphenyl-2-pyrrolidinemethanol (59.9 mg, 0.24 mmol) in THF (2.8 mL) was added trimethylborate (0.034 mL, 0.31 mmol), and the resultant solution was stirred for 90 minutes. The solution was cooled to 0 °C and *N*,*N*-diethylaniline borane (0.4 mL, 2.2 mmol) was added in portions over 30 minutes with stirring continued at 0 °C. This solution was added via cannula to a 0°C solution of di-*tert*-butyl (2*S*,2'*S*)-2,2'-[(1,4-dioxobutane-1,4-diyl)bis(6-fluoro-1-{[2-(trimethylsilyl)ethoxy]methyl}-1*H*-benzimidazole-5,2-diyl)]dipyrrolidine-1-carboxylate (265 mg, .28 mmol) in THF (2.8 mL) and then warmed to room temperature and stirred for 16 hours. The solution was cooled to 0 °C and CH_3OH (0.09 mL, 2.2 mmol) was added, and the solution was warmed to room temperature and stirred for 2 hours. 1*N* HCl was added, and the aqueous solution was extracted with EtOAc. The combined extracts were washed with brine, dried (Na_2SO_4), filtered and concentrated. Purification was run by flash chromatography (0-3% CH_3OH/CH_2Cl_2) to give the title compound (248 mg, 0.26 mmol, 93%).



di-*tert*-butyl (2*S*,2'*S*)-2,2'-{[(2*R*,5*R*)-1-(4-*tert*-butylphenyl)pyrrolidine-2,5-diyl]bis(6-fluoro-1-{[2-(trimethylsilyl)ethoxy]methyl}-1*H*-benzimidazole-5,2-diyl)}dipyrrolidine-1-carboxylate (ACD Name v12)

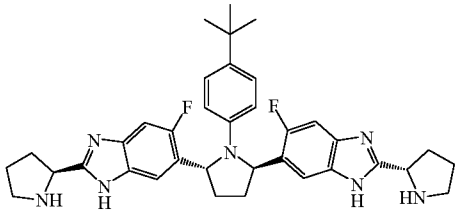
To a solution of di-*tert*-butyl (2*S*,2'*S*)-2,2'-{[(1*S*,4*S*)-1,4-dihydroxybutane-1,4-diyl]bis(6-fluoro-1-{[2-(trimethylsilyl)ethoxy]methyl}-1*H*-benzimidazole-5,2-diyl)}dipyrrolidine-1-carboxylate (100 mg, .10 mmol) in CH_2Cl_2 (1 mL) at -20 °C was added triethylamine (0.044 mL, 0.31 mmol) followed by mesyl chloride (0.018 mL, 0.23 mmol) and the solution stirred at -20 °C for 1 hour. 4-*tert*-Butyl aniline (0.083 mL, 0.52 mmol) was added in one portion, and the solution was allowed to warm to room temperature overnight, with stirring. The solution was diluted with EtOAc, washed with 1*N* HCl, H_2O, and brine, dried (Na_2SO_4), filtered and concentrated. Purification by flash chromatography (0-50% EtOAc/hexane) gave the title compound (46 mg, 0.04 mmol, 41%).

General Procedure 23. De-boc/de-SEM Procedure



Simultaneous removal of Boc and SEM protecting groups, according to the above depiction can be effected using standard conditions such as by treatment with an acid, such as HCl in solvents such as dioxane or methanol or mixtures thereof at temperature from about room temperature to about 60 °C. The compounds obtained on deprotection may consist of a mixture of stereoisomers that may be separated by reverse-phase HPLC. The de-protected compounds obtained may be isolated as either the salt directly from the reaction or reverse-phase HPLC or as the free base following neutralization, extraction into organic solvent and standard isolation.

Illustration of General Procedure 23. General Procedure 23A



6,6'-[(2*R*,5*R*)-1-(4-*tert*-butylphenyl)pyrrolidine-2,5-diyl]bis{5-fluoro-2-[(2*S*)-pyrrolidin-2-yl]-1*H*-benzimidazole} (ACD Name v12)

To a solution of di-*tert*-butyl (2*S*,2'*R*)-2,2'-{[(2*R*,5*R*)-1-(4-*tert*-butylphenyl)pyrrolidine-2,5-diyl]bis(6-fluoro-1-{[2-(trimethylsilyl)ethoxy]methyl}-1*H*-benzimidazole-5,2-diyl)}dipyrrolidine-1-carboxylate (44 mg, 0.04 mmol) in dioxane (1 mL) was added 4 *M* HCl/dioxane (1 mL, 4.0 mmol) and the solution was stirred at 50 °C for 2 hours. The cooled solution was concentrated and placed under vacuum for 1 hour to provide the crude title compound that was used without purification.

The following list of diamines

4-bromo-3-methylbenzene-1,2-diamine;

5-bromo-3-fluorobenzene-1,2-diamine;

4-bromo-3-fluorobenzene-1,2-diamine;

4-bromo-3-chlorobenzene-1,2-diamine; and

4-bromo-5-fluorobenzene-1,2-diamine.

can be subjected to a sequence of General Procedures 20/20A, 21/21A, 22/22A, 23/23A to give the following compounds:

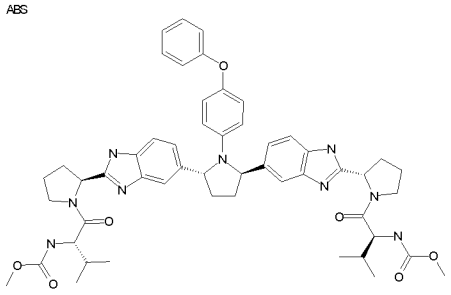
6,6'-[1-(4-*tert*-butylphenyl)pyrrolidine-2,5-diyl]bis{4-fluoro-2-[(2*S*)-pyrrolidin-2-yl]-1*H*-benzimidazole} (ACD Name v12);

6,6'-[(2*R*,5*R*)-1-(4-*tert*-butylphenyl)pyrrolidine-2,5-diyl]bis{7-fluoro-2-[(2*S*)-pyrrolidin-2-yl]-1*H*-benzimidazole} (ACD Name v12);
6,6'-[(2*R*,5*S*)-1-(4-*tert*-butylphenyl)pyrrolidine-2,5-diyl]bis{7-fluoro-2-[(2*S*)-pyrrolidin-2-yl]-1*H*-benzimidazole} (ACD Name v12);
6,6'-[(2*R*,5*R*)-1-(4-*tert*-butylphenyl)pyrrolidine-2,5-diyl]bis{7-chloro-2-[(2*S*)-pyrrolidin-2-yl]-1*H*-benzimidazole} (ACD Name v12);
6,6'-[(2*R*,5*S*)-1-(4-*tert*-butylphenyl)pyrrolidine-2,5-diyl]bis{7-chloro-2-[(2*S*)-pyrrolidin-2-yl]-1*H*-benzimidazole} (ACD Name v12);
6,6'-[(2*R*,5*R*)-1-(4-*tert*-butylphenyl)pyrrolidine-2,5-diyl]bis{7-methyl-2-[(2*S*)-pyrrolidin-2-yl]-1*H*-benzimidazole} (ACD Name v12);
6,6'-[(2*R*,5*S*)-1-(4-*tert*-butylphenyl)pyrrolidine-2,5-diyl]bis{7-methyl-2-[(2*S*)-pyrrolidin-2-yl]-1*H*-benzimidazole} (ACD Name v12);
6,6'-{(2*R*,5*R*)-1-[3-fluoro-4-(piperidin-1-yl)phenyl]pyrrolidine-2,5-diyl}bis{5-fluoro-2-[(2*S*)-pyrrolidin-2-yl]-1*H*-benzimidazole} (ACD Name v12);
6,6'-{(2*R*,5*R*)-1-[3,5-difluoro-4-(piperidin-1-yl)phenyl]pyrrolidine-2,5-diyl}bis{5-fluoro-2-[(2*S*)-pyrrolidin-2-yl]-1*H*-benzimidazole} (ACD Name v12); and
6,6'-{(2*R*,5*R*)-1-[3,5-difluoro-4-(4-phenylpiperidin-1-yl)phenyl]pyrrolidine-2,5-diyl}bis{5-fluoro-2-[(2*S*)-pyrrolidin-2-yl]-1*H*-benzimidazole} (ACD Name v12).

Examples

The following example compounds 1.1-1.8 can be made from the appropriate listed substituted pyrrolidine following the methods of General Procedure 8.1, General Procedure 9C (Raney-nickel), and General Procedure 10B.

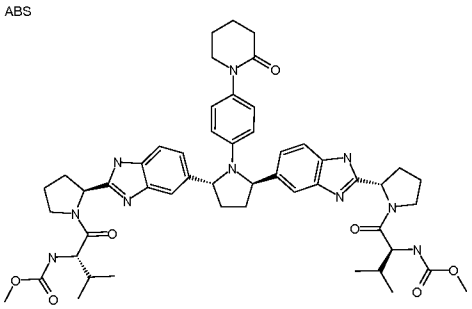
Pyrrolidines:
(2*R*,5*R*)-2,5-bis(4-chloro-3-nitrophenyl)-1-(4-phenoxyphenyl)pyrrolidine;
1-(4-((2*R*,5*R*)-2,5-bis(4-chloro-3-nitrophenyl)pyrrolidin-1-yl)phenyl)pyridin-2(1H)-one;
(2*R*,5*R*)-2,5-bis(4-chloro-3-nitrophenyl)-1-(2,5-difluoro-4-(trifluoromethyl)phenyl)pyrrolidine;
4-((2*R*,5*R*)-2,5-bis(4-chloro-3-nitrophenyl)pyrrolidin-1-yl)-2-fluoropyridine;
1-(4-((2*R*,5*R*)-2,5-bis(4-chloro-3-nitrophenyl)pyrrolidin-1-yl)-2,6-difluorophenyl)-4,4-difluoropiperidine;
1-(4-((2*R*,5*R*)-2,5-bis(4-chloro-3-nitrophenyl)pyrrolidin-1-yl)-2,6-difluorophenyl)-4-fluoropiperidine;
(2*R*,5*R*)-2,5-bis(4-chloro-3-nitrophenyl)-1-(4-((3-ethyloxetan-3-yl)methoxy)phenyl)pyrrolidine; and
(1*R*,5*S*)-3-(4-((2*R*,5*R*)-2,5-bis(4-chloro-3-nitrophenyl)pyrrolidin-1-yl)-2,6-difluorophenyl)-3-azabicyclo[3.2.0]heptane.



Example 1.1

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-phenoxyphenyl)pyrrolidin-2-yl]-1*H*-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

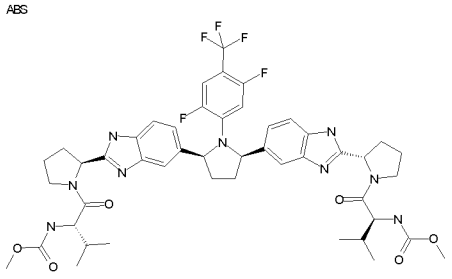
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.78 - 0.91 (m, 12 H) 1.70 (d, J=6.83 Hz, 2 H) 1.86 - 1.96 (m, 2 H) 1.99 (d, J=2.17 Hz, 4 H) 2.15 - 2.25 (m, 4 H) 2.55 - 2.61 (m, 2 H) 3.54 (s, 6 H) 3.82 (s, 4 H) 4.06 (t, J=8.40 Hz, 2 H) 5.13 (t, J=7.26 Hz, 2 H) 5.35 - 5.43 (m, 2 H) 6.35 (d, J=9.11 Hz, 2 H) 6.62 - 6.69 (m, 2 H) 6.71 (d, J=8.02 Hz, 2 H) 6.93 (t, J=7.43 Hz, 1 H) 7.08 (t, J=9.43 Hz, 2 H) 7.18 - 7.25 (m, 3 H) 7.27 - 7.34 (m, 3 H) 7.39 (d, J=8.13 Hz, 1 H) 7.47 (d, J=8.02 Hz, 1 H) 12.05 (d, J=12.04 Hz, 2 H); MS (ESI+) *m/z* 924.4 $(M+H)^+$.



Example 1.2

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-(2-oxopiperidin-1-yl)phenyl]pyrrolidin-2-yl}-1*H*-benzimidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

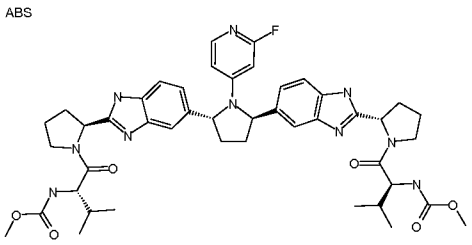
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.76 - 0.92 (m, 12 H) 1.66 - 1.76 (m, 6 H) 1.91 (dd, J=13.61, 7.54 Hz, 2 H) 1.95 - 2.04 (m, 4 H) 2.20 (dd, J=16.26, 3.80 Hz, 6 H) 2.58 - 2.64 (m, 2 H) 3.39 - 3.45 (m, 2 H) 3.54 (s, 6 H) 3.82 (s, 4 H) 4.02 - 4.09 (m, 2 H) 5.09 - 5.19 (m, 2 H) 5.35 - 5.43 (m, 2 H) 6.29 (d, J=8.89 Hz, 2 H) 6.70 - 6.78 (m, 2 H) 7.07 (d, J=8.13 Hz, 2 H) 7.22 (s, 1 H) 7.29 (d, J=8.35 Hz, 2 H) 7.33 (s, 1 H) 7.38 (d, J=8.35 Hz, 1 H) 7.47 (d, J=8.13 Hz, 1 H) 12.04 (s, 2 H); MS (ESI+) *m/z* 929.5 $(M+H)^+$.



Example 1.3

methyl {(2*S*)-1-[(2*S*)-2-{5-[(2*S*,5*R*)-1-[2,5-difluoro-4-(trifluoromethyl)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

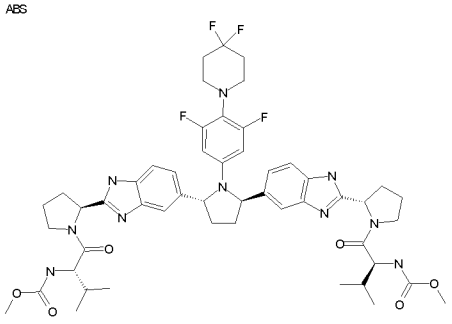
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.76 - 0.94 (m, 12 H) 1.83 - 2.07 (m, 8 H) 2.14 - 2.28 (m, 4 H) 2.35 - 2.45 (m, 2 H) 3.54 (s, 6 H) 3.75 - 3.94 (m, 4 H) 4.07 (dd, J=8.19, 4.93 Hz, 2 H) 5.19 (dd, J=31.50, 3.74 Hz, 4 H) 6.48 - 6.61 (m, 1 H) 7.20 - 7.35 (m, 5 H) 7.40 - 7.46 (m, 1 H) 7.49 - 7.56 (m, 2 H) 7.58 - 7.65 (m, 1 H) 12.12 (d, J=4.66 Hz, 2 H); MS (APCI+) *m/z* 936.24 $(M+H)^+$.



Example 1.4

methyl {(2*S*)-1-[(2*S*)-2-{5-[(2*R*,5*R*)-1-(2-fluoropyridin-4-yl)-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

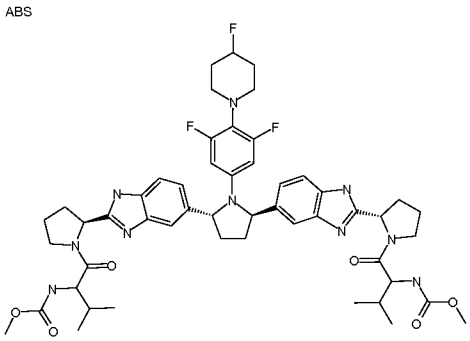
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.77 - 0.91 (m, 12 H) 1.32 (td, J=14.99, 7.43 Hz, 1 H) 1.53 (dt, J=21.23, 6.63 Hz, 1 H) 1.74 (dd, J=11.93, 6.07 Hz, 2 H) 1.86 - 2.05 (m, 6 H) 2.14 - 2.23 (m, 4 H) 3.54 (s, 6 H) 3.77 - 3.86 (m, 4 H) 4.05 - 4.10 (m, 2 H) 5.11 - 5.18 (m, 2 H) 5.45 - 5.59 (m, 2 H) 5.79 (s, 1 H) 6.18 - 6.23 (m, 1 H) 7.03 - 7.13 (m, 2 H) 7.23 (s, 1 H) 7.29 (d, J=8.35 Hz, 2 H) 7.34 (d, J=1.52 Hz, 1 H) 7.42 (d, J=8.35 Hz, 1 H) 7.47 - 7.56 (m, 2 H) 12.11 (s, 2 H); MS (ESI+) *m/z* 851.3 $(M+H)^+$.



Example 1.5

methyl {(2*S*)-1-[(2*S*)-2-{5-[(2*R*,5*R*)-1-[4-(4,4-difluoropiperidin-1-yl)-3,5-difluorophenyl]-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

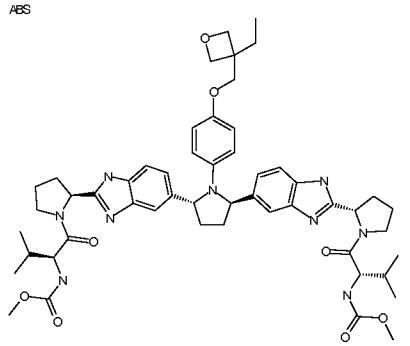
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.74 - 0.93 (m, 12 H) 1.63 - 1.74 (m, 2 H) 1.85 - 2.06 (m, 12 H) 2.19 (dd, J=9.49, 5.37 Hz, 4 H) 2.86 - 2.96 (m, 4 H) 3.54 (s, 6 H) 3.76 - 3.86 (m, 4 H) 4.07 (t, J=8.24 Hz, 2 H) 5.09 - 5.20 (m, 2 H) 5.33 - 5.42 (m, 2 H) 5.92 (d, J=12.90 Hz, 2 H) 7.07 (t, J=7.37 Hz, 2 H) 7.21 (s, 1 H) 7.26 - 7.33 (m, 3 H) 7.41 (d, J=8.13 Hz, 1 H) 7.49 (d, J=8.13 Hz, 1 H) 12.08 (d, J=12.90 Hz, 2 H); MS (ESI+) *m/z* 987.5 $(M+H)^+$.



Example 1.6

methyl {1-[(2*S*)-2-{5-[(2*R*,5*R*)-1-[3,5-difluoro-4-(4-fluoropiperidin-1-yl)phenyl]-5-{2-[(2*S*)-1-{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

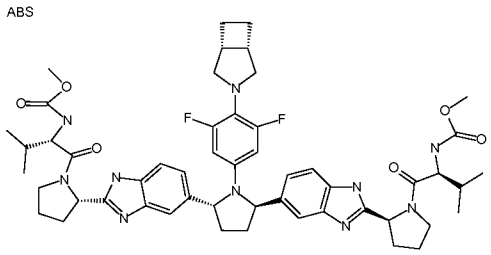
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.74 - 0.91 (m, 12 H) 1.63 - 1.71 (m, 6 H) 1.76 - 1.97 (m, 4 H) 1.98 - 2.07 (m, 4 H) 2.14 - 2.23 (m, 4 H) 2.71 - 2.78 (m, 2 H) 2.90 - 3.00 (m, 2 H) 3.54 (s, 6 H) 3.82 (s, 4 H) 4.06 (t, J=8.73 Hz, 2 H) 4.58 - 4.78 (m, 1 H) 5.11 - 5.18 (m, 2 H) 5.33 - 5.43 (m, 2 H) 5.90 (d, J=12.69 Hz, 2 H) 7.07 (t, J=7.37 Hz, 2 H) 7.20 (s, 1 H) 7.26 - 7.32 (m, 3 H) 7.41 (d, J=8.24 Hz, 1 H) 7.49 (d, J=8.24 Hz, 1 H) 12.07 (d, J=16.48 Hz, 2 H); MS (ESI+) *m/z* 969.5 $(M+H)^+$.



Example 1.7

methyl {(2*S*)-1-[(2*S*)-2-{5-[(2*R*,5*R*)-1-{4-[(3-ethyloxetan-3-yl)methoxy]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

^{1}H NMR (400 MHz, DMSO-d_6) δ 12.26 – 11.98 (m, 2H), 7.44 (d, J = 8.2, 1H), 7.37 (d, J = 8.2, 1H), 7.33 – 7.18 (m, 4H), 7.05 (t, J = 8.1, 2H), 6.62 – 6.53 (m, 2H), 6.26 (d, J = 8.8, 2H), 5.40 – 5.30 (m, 2H), 5.17 – 5.08 (m, 2H), 4.29 (d, J = 5.7, 2H), 4.22 (d, J = 5.8, 2H), 4.06 (t, J = 8.3, 2H), 3.86 – 3.75 (m, 6H), 3.53 (s, 6H), 2.54 (s, 2H), 2.24 – 2.12 (m, 4H), 2.06 – 1.83 (m, 6H), 1.75 – 1.62 (m, 4H), 0.91 – 0.74 (m, 15H); MS (ESI+) *m/z* 946.5 $(M+H)^+$.



Example 1.8

methyl {(2*S*)-1-[(2*S*)-2-{5-[(2*R*,5*R*)-1-{4-[(1*R*,5*S*)-3-azabicyclo[3.2.0]hept-3-yl]-3,5-difluorophenyl}-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

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.82 (s, 12 H) 1.61 (s, 3 H) 1.71 (d, 2 H) 1.97 (m, 9 H) 2.20 (s, 2 H) 2.74 - 2.78 (m, 2 H) 2.85 (s, 5 H) 3.53 (s, 6 H) 3.82 (s, 3 H) 4.06 (s, 2 H) 5.14 (s, 2 H) 5.38 (s, 2 H) 5.91 (s, 2 H) 7.09 (s, 1 H) 7.37 (m, 6 H) 7.63 (s, 1 H) 7.88 (s, 1 H) 12.05 (s, 2 H); MS (ESI+) *m/z* 963.5 $(M+H)^+$, (ESI-) *m/z* 961.4 $(M-H)^-$.

The following example compounds 2.1-2.17 can be made from the appropriate listed substituted pyrrolidine following the methods of General Procedure 8.1, General Procedure 9D (PtO2), and General Procedure 10B.

Pyrrolidines:

2-(4-((2*R*,5*R*)-2,5-bis(4-chloro-3-nitrophenyl)pyrrolidin-1-yl)phenyl)oxazole;

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

(2*R*,5*R*)-1-(4-(1,3-dioxan-5-yloxy)phenyl)-2,5-bis(4-chloro-3-nitrophenyl)pyrrolidine;

(2*R*,5*R*)-1-(4-((1,3-dioxolan-4-yl)methoxy)phenyl)-2,5-bis(4-chloro-3-nitrophenyl)pyrrolidine;

(2*R*,5*R*)-2,5-bis(4-chloro-3-nitrophenyl)-1-(4-((3-ethyloxetan-3-yl)methoxy)-3,5-difluorophenyl)pyrrolidine;

1-(4-((2*R*,5*R*)-2,5-bis(4-chloro-3-nitrophenyl)pyrrolidin-1-yl)-2,3,5,6-tetrafluorophenyl)piperidine;

(2*R*,5*R*)-2,5-bis(4-chloro-3-nitrophenyl)-1-(3-fluoro-4-(methylsulfonyl)phenyl)pyrrolidine (obtained by mCPBA oxidation of (2*R*,5*R*)-2,5-bis(4-chloro-3-nitrophenyl)-1-(3-fluoro-4-(methylthio)phenyl)pyrrolidine);

4-((2*R*,5*R*)-2,5-bis(4-chloro-3-nitrophenyl)pyrrolidin-1-yl)-*N*-*tert*-butyl-2-fluoroaniline;

1-(4-((2*R*,5*R*)-2,5-bis(4-chloro-3-nitrophenyl)pyrrolidin-1-yl)-2,6-difluorophenyl)-4-methylpiperidine;

1-(4-((2R,5R)-2,5-bis(4-chloro-3-nitrophenyl)pyrrolidin-1-yl)-2,6-difluorophenyl)-4-(3-phenylpropyl)piperidine;

8-(4-((2R,5R)-2,5-bis(4-chloro-3-nitrophenyl)pyrrolidin-1-yl)-2,6-difluorophenyl)-8-azaspiro[4.5]decane;

1-(4-((2R,5R)-2,5-bis(4-chloro-3-nitrophenyl)pyrrolidin-1-yl)-2,6-difluorophenyl)-4-(naphthalen-2-yl)piperidine;

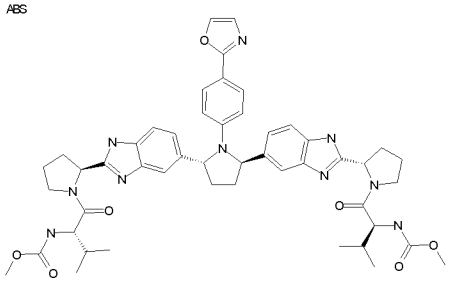
2-(1-(4-((2R,5R)-2,5-bis(4-chloro-3-nitrophenyl)pyrrolidin-1-yl)-2,6-difluorophenyl)piperidin-4-yl)pyridine;

1-(4-((2R,5R)-2,5-bis(4-chloro-3-nitrophenyl)pyrrolidin-1-yl)-2,6-difluorophenyl)-4-(4-(trimethylsilyl)phenyl)piperidine;

1-(4-((2R,5R)-2,5-bis(4-chloro-3-nitrophenyl)pyrrolidin-1-yl)-2,6-difluorophenyl)-4-(naphthalen-1-yl)piperidine;

1-(4-((2R,5R)-2,5-bis(4-chloro-2-fluoro-5-nitrophenyl)pyrrolidin-1-yl)-2,6-difluorophenyl)-3,5-dimethylpiperidine; and

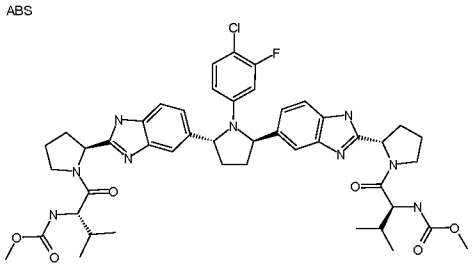
1-(4-((2R,5R)-2,5-bis(4-chloro-3-nitrophenyl)pyrrolidin-1-yl)-2,6-difluorophenyl)-4-(4-(trifluoromethyl)phenyl)piperazine.



Example 2.1

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-(1,3-oxazol-2-yl)phenyl]pyrrolidin-2-yl}-1*H*-benzimidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

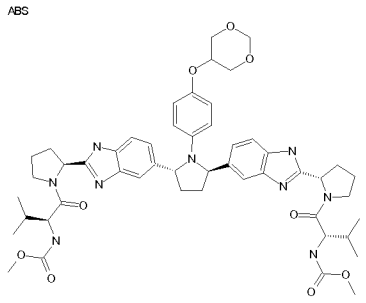
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.74 - 0.91 (m, 12 H) 1.70 - 1.79 (m, 2 H) 1.89 (ddd, J=14.20, 7.05, 6.94 Hz, 2 H) 1.95 - 2.04 (m, 4 H) 2.13 - 2.23 (m, 4 H) 2.55 - 2.61 (m, 2 H) 3.53 (s, 6 H) 3.77 - 3.84 (m, 4 H) 4.05 (t, J=8.67 Hz, 2 H) 5.09 - 5.18 (m, 2 H) 5.46 - 5.54 (m, 2 H) 6.45 (d, J=8.89 Hz, 2 H) 7.08 (t, J=7.75 Hz, 2 H) 7.13 (s, 1 H) 7.23 (s, 1 H) 7.28 (d, J=8.24 Hz, 2 H) 7.33 (s, 1 H) 7.39 (d, J=8.13 Hz, 1 H) 7.45 - 7.56 (m, 3 H) 7.94 (s, 1 H) 12.06 (s, 2 H); MS (ESI+) *m/z* 899.4 $(M+H)^+$.



Example 2.2

methyl {(2*S*)-1-[(2*S*)-2-{5-[(2*R*,5*R*)-1-(4-chloro-3-fluorophenyl)-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

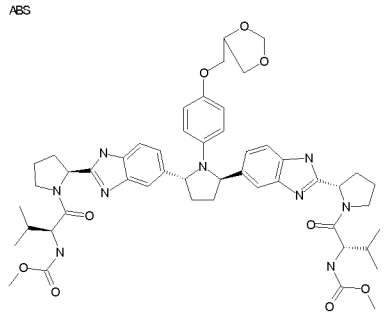
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.77 - 0.90 (m, 12 H) 1.66 - 1.78 (m, 2 H) 1.88 - 1.95 (m, 2 H) 1.96 - 2.06 (m, 4 H) 2.15 - 2.24 (m, 4 H) 2.54 - 2.60 (m, 2 H) 3.54 (s, 6 H) 3.79 - 3.86 (m, 4 H) 4.06 (t, J=8.46 Hz, 2 H) 5.10 - 5.18 (m, 2 H) 5.37 - 5.45 (m, 2 H) 6.16 (dd, J=9.49, 2.01 Hz, 1 H) 6.22 (dd, J=13.55, 2.06 Hz, 1 H) 7.00 - 7.11 (m, 3 H) 7.22 (s, 1 H) 7.28 (d, J=8.57 Hz, 2 H) 7.32 (s, 1 H) 7.40 (d, J=8.24 Hz, 1 H) 7.47 (d, J=8.13 Hz, 1 H) 12.07 (d, J=2.93 Hz, 2 H); MS (APCI+) *m/z* 884 $(M+H)^+$.



Example 2.3

methyl {(2*S*)-1-[(2*S*)-2-{5-[(2*R*,5*R*)-1-[4-(1,3-dioxan-5-yloxy)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

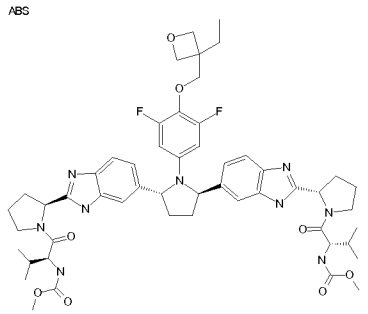
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.28 – 11.98 (m, 2H), 7.45 (d, *J* = 8.1, 1H), 7.37 (d, *J* = 8.2, 1H), 7.32 – 7.23 (m, 3H), 7.21 (s, 1H), 7.12 – 7.01 (m, 2H), 6.62 – 6.51 (m, 2H), 6.24 (d, *J* = 8.9, 2H), 5.40 – 5.27 (m, 2H), 5.18 – 5.09 (m, 2H), 4.72 (d, *J* = 6.1, 1H), 4.67 (d, *J* = 6.2, 1H), 4.06 (t, *J* = 8.4, 2H), 4.01 – 3.75 (m, 7H), 3.68 – 3.58 (m, 2H), 3.52 (d, *J* = 15.9, 6H), 2.28 – 1.83 (m, 12H), 1.74 – 1.62 (m, 2H), 0.93 – 0.73 (m, 12H); MS (ESI+) *m/z* 934.5 $(M+H)^+$.



Example 2.4

methyl {(2*S*)-1-[(2*S*)-2-{5-[(2*R*,5*R*)-1-[4-(1,3-dioxolan-4-ylmethoxy)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

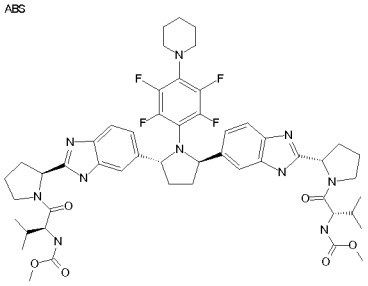
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.27 – 11.95 (m, 2H), 7.43 (d, *J* = 8.1, 1H), 7.35 (d, *J* = 8.2, 1H), 7.32 – 7.22 (m, 3H), 7.19 (s, 1H), 7.03 (t, *J* = 7.4, 2H), 6.59 – 6.47 (m, 2H), 6.23 (d, *J* = 8.8, 2H), 5.39 – 5.27 (m, 2H), 5.16 – 5.04 (m, 2H), 4.83 (d, *J* = 2.6, 1H), 4.74 (s, 1H), 4.22 – 4.12 (m, 1H), 4.04 (t, *J* = 8.3, 2H), 3.88 (t, *J* = 7.5, 1H), 3.83 – 3.67 (m, 6H), 3.57 – 3.47 (m, 7H), 2.29 – 1.80 (m, 12H), 1.74 – 1.60 (m, 2H), 0.93 – 0.71 (m, 12H); MS (ESI+) *m/z* 934.4 $(M+H)^+$.



Example 2.5

methyl {(2*S*)-1-[(2*S*)-2-{6-[(2*R*,5*R*)-1-{4-[(3-ethyloxetan-3-yl)methoxy]-3,5-difluorophenyl}-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

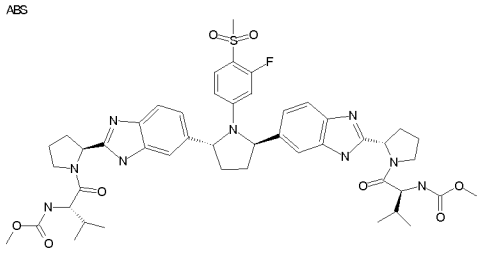
^{1}H NMR (400 MHz, DMSO-d_6) δ 12.30 – 12.02 (m, 2H), 7.47 (d, *J* = 8.3, 1H), 7.40 (d, *J* = 8.3, 1H), 7.34 – 7.16 (m, 4H), 7.06 (t, *J* = 7.0, 2H), 5.98 (d, *J* = 12.3, 2H), 5.46 – 5.30 (m, 2H), 5.24 – 5.05 (m, 2H), 4.29 (d, *J* = 5.5, 2H), 4.21 (d, *J* = 5.8, 2H), 4.05 (t, *J* = 8.2, 2H), 3.90 – 3.72 (m, 6H), 3.52 (s, 6H), 2.27 – 1.81 (m, 12H), 1.73 – 1.60 (m, 4H), 0.91 – 0.69 (m, 15H); MS (ESI+) *m/z* 982.4 $(M+H)^+$.



Example 2.6

methyl {(2*S*)-1-[(2*S*)-2-(6-{(2*R*,5*R*)-5-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1*H*-benzimidazol-6-yl}-1-[2,3,5,6-tetrafluoro-4-(piperidin-1-yl)phenyl]pyrrolidin-2-yl}-1*H*-benzimidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

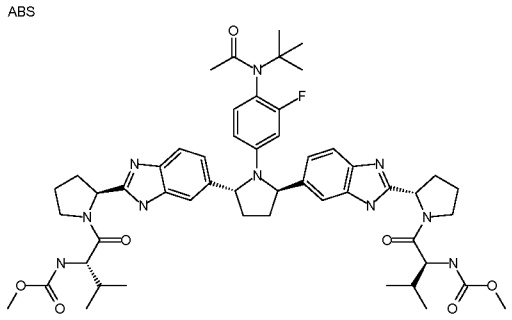
^{1}H NMR (400 MHz, DMSO-d_6) δ 12.10 (dd, *J* = 58.0, 37.7, 2H), 7.52 – 7.21 (m, 6H), 7.07 (t, *J* = 8.1, 2H), 5.52 – 5.29 (m, 2H), 5.17 – 5.03 (m, 2H), 4.12 – 3.93 (m, 2H), 3.88 – 3.66 (m, 4H), 3.53 (s, 6H), 2.87 – 2.71 (m, 4H), 2.27 – 1.76 (m, 14H), 1.50 – 1.32 (m, 6H), 0.93 – 0.70 (m, 12H); MS (ESI+) *m/z* 987.3 $(M+H)^+$.



Example 2.7

methyl {(2*S*)-1-[(2*S*)-2-{6-[(2*R*,5*R*)-1-[3-fluoro-4-(methylsulfonyl)phenyl]-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

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.81 - 0.97 (m, 12 H), 1.30 (s, 2 H), 1.82 (d, J=4.2 Hz, 2 H), 1.90 - 2.35 (m, 12 H), 3.60 (s, 6 H), 3.88 (s, 3 H), 4.13 (t, J=8.3 Hz, 2 H), 5.20 (t, J=7.3 Hz, 2 H), 5.62 (s, 2 H), 6.26 - 6.40 (m, J=9.5 Hz, 2 H), 7.15 (d, J=7.0 Hz, 2 H), 7.30 (s, 1 H), 7.32 - 7.45 (m, 4 H), 7.49 (d, J=8.2 Hz, 1 H), 7.56 (d, J=8.1 Hz, 1 H), 12.16 (s, 2 H); MS (ESI+) *m/z* 928.4 $(M+H)^+$, (ESI-) *m/z* 926.3 $(M-H)^-$.

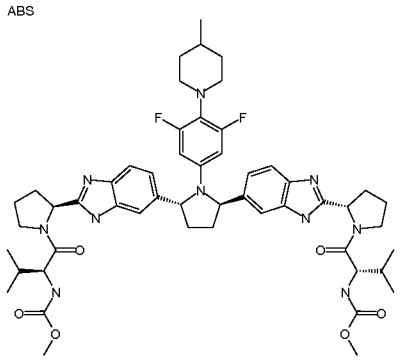


Example 2.8

methyl {(2*S*)-1-[(2*S*)-2-{6-[(2*R*,5*R*)-1-{4-[acetyl(*tert*-butyl)amino]-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

Starting from 4-((2*R*,5*R*)-2,5-bis(4-chloro-3-nitrophenyl)pyrrolidin-1-yl)-*N*-*tert*-butyl-2-fluoroaniline, the initial product of the sequence outlined above was 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 (ACD Name v12). The *N*-acetyl group was added by reaction with acetic anhydride/pyridine to provide the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.73 - 0.90 (m, 12 H), 1.13 (d, *J*=5.20 Hz, 9 H), 1.37 - 1.44 (m, 4 H), 1.62 - 1.72 (m, 2 H), 1.92 - 2.02 (m, 9 H), 2.10 - 2.26 (m, 5 H), 2.51 - 2.58 (m, 2 H), 3.52 (s, 6 H), 3.73 - 3.85 (m, 4 H), 3.98 - 4.12 (m, 2 H), 5.09 - 5.17 (m, 2 H), 5.36 - 5.48 (m, 3 H), 6.08 - 6.18 (m, 3 H), 6.74 - 6.87

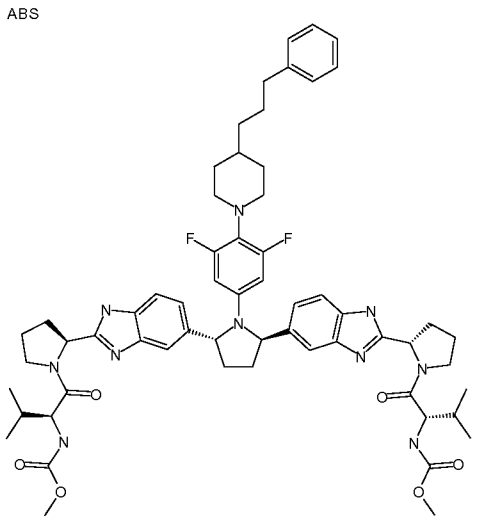
(m, 1 H), 7.08 (dd, *J*=13.72, 8.29 Hz, 3 H), 7.20 (s, 1 H), 7.24 - 7.31 (m, 4 H), 7.40 (d, *J*=8.24 Hz, 1 H), 7.48 (d, *J*=8.13 Hz, 1 H), 12.01 (s, 1 H), 12.17 (s, 1 H); MS (ESI+) *m/z* 964 $(M+H)^+$.



Example 2.9

methyl {(2*S*)-1-[(2*S*)-2-{6-[(2*R*,5*R*)-1-[3,5-difluoro-4-(4-methylpiperidin-1-yl)phenyl]-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

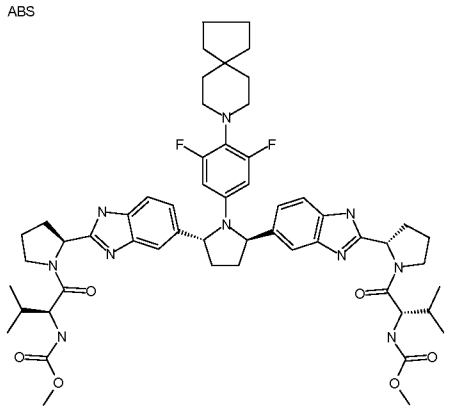
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.75 - 0.90 (m, 12 H), 1.05 - 1.18 (m, 2 H), 1.24 - 1.37 (m, 2 H), 1.45 - 1.54 (m, 2 H), 1.62 - 1.73 (m, 2 H), 1.84 - 2.05 (m, 7 H), 2.12 - 2.25 (m, 5 H), 2.69 - 2.81 (m, 4 H), 3.52 (s, 6 H), 3.77 - 3.86 (m, 4 H), 4.05 (t, J=8.35 Hz, 2 H), 5.10 - 5.18 (m, 2 H), 5.35 (q, J=7.34 Hz, 2 H), 5.87 (d, J=12.69 Hz, 2 H), 7.02 - 7.10 (m, 2 H), 7.19 (s, 1 H), 7.24 - 7.32 (m, 3 H), 7.39 (d, J=8.24 Hz, 1 H), 7.47 (d, J=8.13 Hz, 1 H), 12.06 (d, J=20.93 Hz, 2 H); MS (ESI+) *m/z* 966 $(M+H)^+$.



Example 2.10

methyl {(2*S*)-1-[(2*S*)-2-{5-[(2*R*,5*R*)-1-{3,5-difluoro-4-[4-(3-phenylpropyl)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

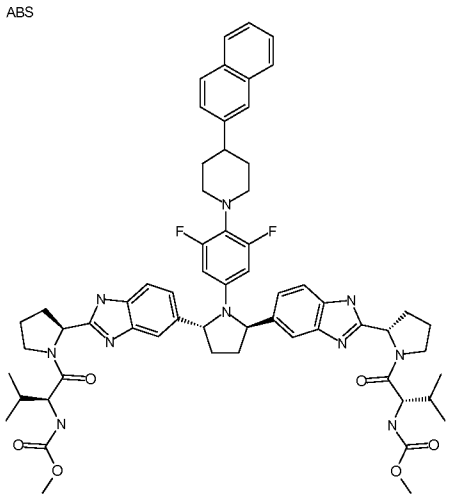
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.72 - 0.95 (m, 12 H), 1.00 - 1.31 (m, 9 H), 1.46 - 1.59 (m, 4 H), 1.61 - 1.79 (m, 2 H), 1.83 - 2.08 (m, 6 H), 2.11 - 2.27 (m, 4 H), 2.77 (s, 4 H), 3.54 (s, 6 H), 3.82 (s, 4 H), 4.06 (t, *J*=8.46 Hz, 2 H), 5.08 - 5.19 (m, 2 H), 5.28 - 5.46 (m, 2 H), 5.88 (d, *J*=12.79 Hz, 2 H), 7.01 - 7.10 (m, 2 H), 7.10 - 7.33 (m, 9 H), 7.40 (d, *J*=8.13 Hz, 1 H), 7.48 (d, *J*=8.13 Hz, 1 H), 11.71 - 12.51 (m, 2 H); MS (ESI+) *m/z* 1069 $(M+H)^+$; MS (ESI-) *m/z* 1067 $(M-H)^-$.



Example 2.11

methyl {(2*S*)-1-[(2*S*)-2-{5-[(2*R*,5*S*)-1-[4-(8-azaspiro[4.5]dec-8-yl)-3,5-difluorophenyl]-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

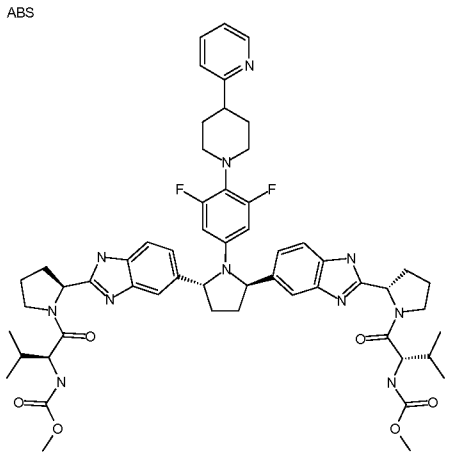
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.73 - 0.93 (m, 12 H), 1.29 - 1.43 (m, 9 H), 1.52 (t, *J*=6.83 Hz, 5 H), 1.68 (s, 2 H), 1.81 - 2.08 (m, 6 H), 2.10 - 2.26 (m, 4 H), 2.75 (s, 4 H), 3.54 (s, 6 H), 3.82 (s, 4 H), 4.06 (t, *J*=8.40 Hz, 2 H), 5.09 - 5.19 (m, 2 H), 5.29 - 5.46 (m, 2 H), 5.88 (d, *J*=12.58 Hz, 2 H), 7.03 - 7.11 (m, 2 H), 7.20 (s, 1 H), 7.25 - 7.33 (m, 3 H), 7.40 (d, *J*=8.24 Hz, 1 H), 7.49 (d, *J*=8.24 Hz, 1 H), 11.63 - 12.57 (m, 2 H); MS (ESI+) *m/z* 1005 $(M+H)^+$; MS (ESI-) *m/z* 1003 $(M-H)^-$.



Example 2.12

methyl {(2*S*)-1-[(2*S*)-2-{5-[(2*R*,5*R*)-1-{3,5-difluoro-4-[4-(2-naphthyl)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

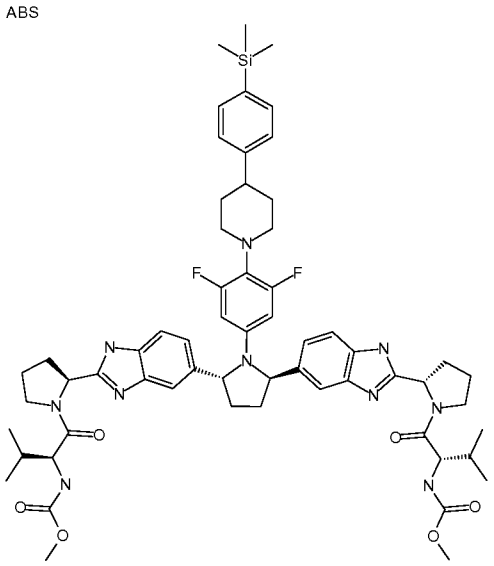
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.76 - 0.91 (m, 12 H), 1.24 (d, J=2.28 Hz, 2 H), 1.63 - 2.08 (m, 12 H), 2.20 (s, 4 H), 2.86 - 3.19 (m, 5 H), 3.53 (s, 6 H), 3.82 (s, 4 H), 4.06 (t, *J*=8.29 Hz, 2 H), 5.10 - 5.22 (m, 2 H), 5.32 - 5.48 (m, 2 H), 5.93 (d, *J*=12.90 Hz, 2 H), 7.03 - 7.16 (m, 2 H), 7.19 - 7.36 (m, 4 H), 7.39 - 7.55 (m, 5 H), 7.69 - 7.89 (m, 4 H), 11.71 - 12.63 (m, 2 H); MS (ESI+) *m/z* 1077 $(M+H)^+$; MS (ESI-) *m/z* 1075 $(M-H)^-$.



Example 2.13

methyl {(2*S*)-1-[(2*S*)-2-{5-[(2*R*,5*R*)-1-{3,5-difluoro-4-[4-(pyridin-2-yl)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

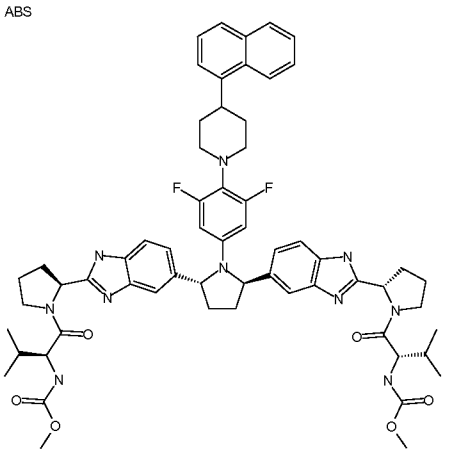
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.71 - 1.02 (m, 12 H), 1.62 - 1.83 (m, 6 H), 1.81 - 2.08 (m, 7 H), 2.10 - 2.29 (m, 4 H), 2.47 - 2.63 (m, 2 H), 2.81 - 3.07 (m, 4 H), 3.53 (s, 6 H), 3.82 (s, 4 H), 4.06 (t, *J*=8.89 Hz, 2 H), 5.10 - 5.21 (m, 2 H), 5.31 - 5.47 (m, 2 H), 5.91 (d, *J*=12.69 Hz, 2 H), 7.04 - 7.13 (m, 2 H), 7.14 - 7.20 (m, 1 H), 7.20 - 7.34 (m, 5 H), 7.41 (d, *J*=8.24 Hz, 1 H), 7.49 (d, *J*=8.35 Hz, 1 H), 7.62 - 7.72 (m, 1 H), 8.45 (d, *J*=4.55 Hz, 1 H), 11.74 - 12.57 (m, 2 H); MS (ESI+) *m/z* 1028 $(M+H)^+$; MS (ESI-) *m/z* 1026 $(M-H)^-$.



Example 2.14

methyl {(2*S*)-1-[(2*S*)-2-{5-[(2*R*,5*R*)-1-(3,5-difluoro-4-{4-[4-(trimethylsilyl)phenyl]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

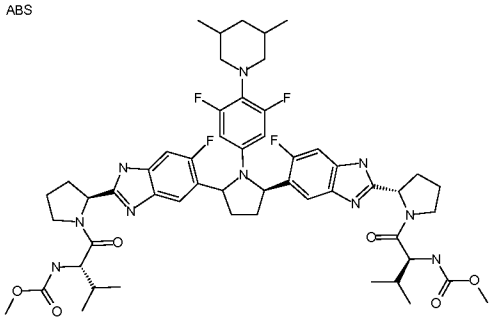
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.20 (s, 9 H), 0.74 - 0.94 (m, 12 H), 1.59 - 1.75 (m, 6 H), 1.83 - 2.09 (m, 7 H), 2.13 - 2.29 (m, 4 H), 2.44 - 2.59 (m, 2 H), 2.84 - 3.15 (m, 4 H), 3.53 (s, 6 H), 3.82 (s, 4 H), 4.06 (t, *J*=8.46 Hz, 2 H), 5.15 (d, *J*=3.04 Hz, 2 H), 5.31 - 5.47 (m, 2 H), 5.92 (d, *J*=12.79 Hz, 2 H), 7.04 - 7.14 (m, 2 H), 7.21 (d, *J*=7.92 Hz, 3 H), 7.27 - 7.37 (m, 3 H), 7.37 - 7.45 (m, 3 H), 7.50 (d, *J*=8.02 Hz, 1 H), 12.10 (d, *J*=17.57 Hz, 2 H); MS (ESI+) *m/z* 1099 $(M+H)^+$; MS (ESI-) *m/z* 1097 $(M-H)^-$.



Example 2.15

methyl {(2*S*)-1-[(2*S*)-2-{5-[(2*R*,5*R*)-1-{3,5-difluoro-4-[4-(1-naphthyl)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

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.74 - 0.94 (m, 12 H), 1.64 - 2.05 (m, 12 H), 2.13 - 2.29 (m, 3 H), 2.45 - 2.62 (m, 2 H), 2.90 - 3.01 (m, *J*=11.06 Hz, 2 H), 3.08 - 3.25 (m, 2 H), 3.53 (s, 6 H), 3.82 (s, 4 H), 4.06 (t, *J*=8.29 Hz, 2 H), 5.08 - 5.23 (m, 2 H), 5.32 - 5.52 (m, 2 H), 5.94 (d, *J*=12.69 Hz, 2 H), 7.04 - 7.17 (m, 2 H), 7.20 - 7.37 (m, 4 H), 7.38 - 7.59 (m, 6 H), 7.75 (d, *J*=8.35 Hz, 1 H), 7.86 - 7.95 (m, 1 H), 8.14 (d, *J*=8.24 Hz, 1 H), 11.61 - 12.69 (m, 2 H); MS (ESI+) *m/z* 1077 $(M+H)^+$; (ESI-) *m/z* 1075 $(M-H)^-$.

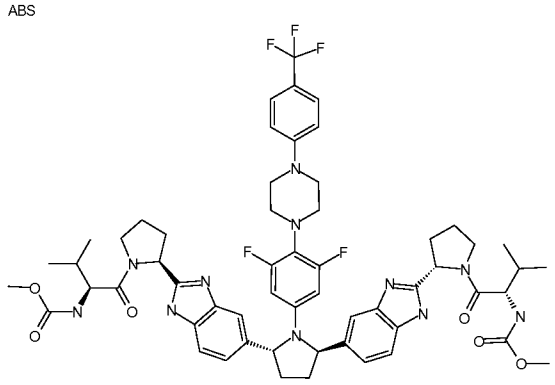


Example 2.16

methyl {(2*S*)-1-[(2*S*)-2-{5-[(5*R*)-1-[4-(3,5-dimethylpiperidin-1-yl)-3,5-difluorophenyl]-5-{6-fluoro-2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1*H*-benzimidazol-5-yl}pyrrolidin-2-yl]-6-fluoro-1*H*-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.64 - 0.94 (m, 18 H) 1.56 - 1.73 (m, 4 H) 1.75 - 1.93 (m, 6 H) 1.95 - 2.06 (m, 6 H) 2.12 - 2.26 (m, 4 H) 2.69 - 2.79 (m, 1 H) 3.20 - 3.29 (m, 1 H) 3.53 (s, 6 H) 3.74 -

3.89 (m, 4 H) 3.97 - 4.10 (m, 2 H) 5.05 - 5.19 (m, 2 H) 5.48 - 5.62 (m, 2 H) 5.87 (dd, J=11.49, 7.92 Hz, 2 H) 7.02 (dd, J=3.90, 1.95 Hz, 1 H) 7.12 (d, J=6.83 Hz, 1 H) 7.26 - 7.37 (m, 3 H) 7.40 (dd, J=11.11, 6.02 Hz, 1 H) 12.08 - 12.16 (m, 1 H) 12.23 - 12.31 (m, 1 H); MS (APCI+) *m/z* 1016 $(M+H)^+$.



Example 2.17

methyl {(2*S*)-1-[(2*S*)-2-{5-[(2*R*,5*R*)-1-(3,5-difluoro-4-{4-[4-(trifluoromethyl)phenyl]piperazin-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

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.69 - 0.96 (m, 14 H) 1.10 - 1.29 (m, 2 H) 1.69 (m, 2 H) 1.99 (m, 4 H) 2.20 (m, 2 H) 2.99 (m, 6 H) 3.22 - 3.26 (m, 6 H) 3.54 (s, 6 H) 3.82 (m, 6 H) 5.15 (m, 2 H) 5.39 (m, 2 H) 5.95 (m, 2 H) 7.03 (d, J=8.78 Hz, 2 H) 7.22 (m, 2 H) 7.24 - 7.36 (m, 2 H) 7.40 - 7.56 (m, 4 H) 12.06 (s, 2 H); MS (ESI+) *m/z* 1096.4, (ESI-) *m/z* 1094.3.

The following Example compounds 3.1-3.51 can be made from the appropriate listed intermediates following the methods of General Procedures 12/12A.

Intermediate amines:

(*S*)-6,6'-((2*R*,5*R*)-1-(4-(pyridin-2-yl)phenyl)pyrrolidine-2,5-diyl)bis(2-((*S*)-pyrrolidin-2-yl)-1*H*-benzo[*d*]imidazole);

(*S*)-6,6'-((2*R*,5*R*)-1-(3-chloro-4-(trifluoromethoxy)phenyl)pyrrolidine-2,5-diyl)bis(2-((*S*)-pyrrolidin-2-yl)-1*H*-benzo[*d*]imidazole);

(*S*)-6,6'-((2*R*,5*R*)-1-(4-(2-methoxyethoxy)phenyl)pyrrolidine-2,5-diyl)bis(2-((*S*)-pyrrolidin-2-yl)-1*H*-benzo[*d*]imidazole);

(*S*)-6,6'-((2*R*,5*R*)-1-(4-chlorophenyl)pyrrolidine-2,5-diyl)bis(2-((*S*)-pyrrolidin-2-yl)-1*H*-benzo[*d*]imidazole);

(*S*)-6,6'-((2*R*,5*R*)-1-(biphenyl-4-yl)pyrrolidine-2,5-diyl)bis(2-((*S*)-pyrrolidin-2-yl)-1*H*-benzo[*d*]imidazole);

(*S*)-6,6'-((2*R*,5*R*)-1-(4-*tert*-butylphenyl)pyrrolidine-2,5-diyl)bis(2-((*S*)-pyrrolidin-2-yl)-1*H*-benzo[*d*]imidazole);

(*S*,*S*)-6,6'-((2*R*,5*R*)-1-(3,5-difluoro-4-(piperidin-1-yl)phenyl)pyrrolidine-2,5-diyl)bis(2-((2*S*,4*S*)-4-methoxypyrrolidin-2-yl)-1*H*-benzo[*d*]imidazole);

(*S*,*S*)-6,6'-((2*R*,5*R*)-1-(3,5-difluoro-4-(piperidin-1-yl)phenyl)pyrrolidine-2,5-diyl)bis(2-((2*S*,4*S*)-4-fluoropyrrolidin-2-yl)-1*H*-benzo[*d*]imidazole);

(*S*,*S*)-6,6'-((2*R*,5*R*)-1-(4-fluorophenyl)pyrrolidine-2,5-diyl)bis(2-((2*S*,4*S*)-4-fluoropyrrolidin-2-yl)-1*H*-benzo[*d*]imidazole);

(*S*,*S*)-6,6'-((2*R*,5*R*)-1-(4-fluorophenyl)pyrrolidine-2,5-diyl)bis(2-((2*S*,4*S*)-4-methoxypyrrolidin-2-yl)-1*H*-benzo[*d*]imidazole);

(*S*)-6,6'-((2*R*,5*R*)-1-(4-*tert*-butylphenyl)pyrrolidine-2,5-diyl)bis(2-((*S*)-5,5-dimethylpyrrolidin-2-yl)-1*H*-benzo[*d*]imidazole);

(*S*,*S*)-6,6'-((2*R*,5*R*)-1-(4-*tert*-butylphenyl)pyrrolidine-2,5-diyl)bis(2-((2*S*,4*S*)-4-fluoropyrrolidin-2-yl)-1*H*-benzo[*d*]imidazole);

(*S*)-6,6'-((2*S*,5*S*)-1-(4-cyclopropyl-2-fluorophenyl)pyrrolidine-2,5-diyl)bis(2-((*S*)-pyrrolidin-2-yl)-1*H*-benzo[*d*]imidazole);

(*S*)-6,6'-((2*R*,5*R*)-1-(3-fluoro-4-(piperidin-1-yl)phenyl)pyrrolidine-2,5-diyl)bis(2-((*S*)-pyrrolidin-2-yl)-1*H*-benzo[*d*]imidazole);

(*S*)-6,6'-((2*R*,5*R*)-1-(3,5-difluoro-4-(piperidin-1-yl)phenyl)pyrrolidine-2,5-diyl)bis(2-((*S*)-pyrrolidin-2-yl)-1*H*-benzo[*d*]imidazole);

(*S*)-6,6'-((2*R*,5*R*)-1-(3-fluoro-4-(4-phenylpiperidin-1-yl)phenyl)pyrrolidine-2,5-diyl)bis(2-((*S*)-pyrrolidin-2-yl)-1*H*-benzo[*d*]imidazole);

(*S*)-6,6'-((2*R*,5*R*)-1-(3,5-difluoro-4-(4-phenylpiperidin-1-yl)phenyl)pyrrolidine-2,5-diyl)bis(2-((*S*)-pyrrolidin-2-yl)-1*H*-benzo[*d*]imidazole);

(*S*)-6,6'-((2*R*,5*R*)-1-(3,5-difluoro-4-(piperidin-1-yl)phenyl)pyrrolidine-2,5-diyl)bis(2-((3*S*)-2-azabicyclo[2.2.1]heptan-3-yl)-1*H*-benzo[*d*]imidazole);

(*S*)-6,6'-((2*R*,5*R*)-1-(3,5-difluoro-4-(piperidin-1-yl)phenyl)pyrrolidine-2,5-diyl)bis(2-((*S*)-indolin-2-yl)-1*H*-benzo[*d*]imidazole);

(*S*)-6,6'-((2*R*,5*R*)-1-(4-*tert*-butylphenyl)pyrrolidine-2,5-diyl)bis(2-((*S*)-4-methylenepyrrolidin-2-yl)-1*H*-benzo[*d*]imidazole);

(S,S,S)-6,6'-((2R,5R)-1-(3,5-difluoro-4-(4-phenylpiperidin-1-yl)phenyl)pyrrolidine-2,5-diyl)bis(2-((2S,3aS,6aS)-octahydrocyclopenta[b]pyrrol-2-yl)-1H-benzo[d]imidazole);

(S,S,S)-6,6'-((2R,5R)-1-(3,5-difluoro-4-(piperidin-1-yl)phenyl)pyrrolidine-2,5-diyl)bis(2-((2S,3aS,6aS)-octahydrocyclopenta[b]pyrrol-2-yl)-1H-benzo[d]imidazole);

(*S*)-6,6'-((2*R*,5*R*)-1-(3,5-difluoro-4-(4-phenylpiperidin-1-yl)phenyl)pyrrolidine-2,5-diyl)bis(2-((*S*)-pyrrolidin-2-yl)-1*H*-benzo[*d*]imidazole);

6,6'-{(2*R*,5*R*)-1-[3,5-difluoro-4-(piperidin-1-yl)phenyl]pyrrolidine-2,5-diyl}bis{5-fluoro-2-[(2*S*)-pyrrolidin-2-yl]-1*H*-benzimidazole} (ACD Name v12);

(S,S,S)-6,6'-((2R,5R)-1-(3,5-difluoro-4-(piperidin-1-yl)phenyl)pyrrolidine-2,5-diyl)bis(5-fluoro-2-((2S,3aS,6aS)-octahydrocyclopenta[b]pyrrol-2-yl)-1H-benzo[d]imidazole);

(S)-6,6'-((2R,5R)-1-(3,5-difluoro-4-(4-(4-fluorophenyl)piperidin-1-yl)phenyl)pyrrolidine-2,5-diyl)bis(2-((S)-pyrrolidin-2-yl)-1H-benzo[d]imidazole);

(S)-6,6'-((2R,5R)-1-(3,5-difluoro-4-(4-(3-(trimethylsilyl)phenyl)piperidin-1-yl)phenyl)pyrrolidine-2,5-diyl)bis(2-((S)-pyrrolidin-2-yl)-1H-benzo[d]imidazole);

(S)-6,6'-((2R,5R)-1-(4-(4-(3,4-difluorophenyl)piperidin-1-yl)-3,5-difluorophenyl)pyrrolidine-2,5-diyl)bis(2-((S)-pyrrolidin-2-yl)-1H-benzo[d]imidazole);

(S)-6,6'-((2R,5R)-1-(4-(4-(3,5-difluorophenyl)piperidin-1-yl)-3,5-difluorophenyl)pyrrolidine-2,5-diyl)bis(2-((S)-pyrrolidin-2-yl)-1H-benzo[d]imidazole);

(S)-6,6'-((2S,5R)-1-(2-(4-phenylpiperidin-1-yl)pyrimidin-5-yl)pyrrolidine-2,5-diyl)bis(5-fluoro-2-((S)-pyrrolidin-2-yl)-1H-benzo[d]imidazole);

(S)-6,6'-((2S,5R)-1-(2-(piperidin-1-yl)pyrimidin-5-yl)pyrrolidine-2,5-diyl)bis(5-fluoro-2-((S)-pyrrolidin-2-yl)-1H-benzo[d]imidazole);

(S)-6,6'-((2R,5R)-1-(4-(4-(2,6-difluorophenyl)piperazin-1-yl)-3,5-difluorophenyl)pyrrolidine-2,5-diyl)bis(5-fluoro-2-((S)-pyrrolidin-2-yl)-1H-benzo[d]imidazole);

(S)-6,6'-((2S,5S)-1-(4-(4-(2,6-difluorophenyl)piperazin-1-yl)-3,5-difluorophenyl)pyrrolidine-2,5-diyl)bis(5-fluoro-2-((S)-pyrrolidin-2-yl)-1H-benzo[d]imidazole); and

(S)-6,6'-((2R,5R)-1-(3,5-difluoro-4-(4-(4-fluorophenyl)piperidin-1-yl)phenyl)pyrrolidine-2,5-diyl)bis(5-fluoro-2-((S)-pyrrolidin-2-yl)-1H-benzo[d]imidazole).

Intermediate acids:

(*S*)-2-(methoxycarbonylamino)-3-methylbutanoic acid;

(*S*)-2-(methoxycarbonylamino)-2-(tetrahydro-2*H*-pyran-4-yl)acetic acid;

(*S*)-2-cyclohexyl-2-(methoxycarbonylamino)acetic acid;

(*S*)-2-cyclopentyl-2-(methoxycarbonylamino)acetic acid;

(*S*)-2-(methoxycarbonylamino)-3,3-dimethylbutanoic acid;

(2*S*,3*R*)-3-methoxy-2-(methoxycarbonylamino)butanoic acid;

(2*S*,3*S*)-3-methoxy-2-(methoxycarbonylamino)butanoic acid;

(*S*)-2-(methoxycarbonylamino)-2-((*R*)-tetrahydrofuran-3-yl)acetic acid;

(*S*)-2-(methoxycarbonylamino)-2-((*S*)-tetrahydrofuran-3-yl)acetic acid;

(*S*)-2-(2,3-dihydro-1*H*-inden-2-yl)-2-(methoxycarbonylamino)acetic acid;

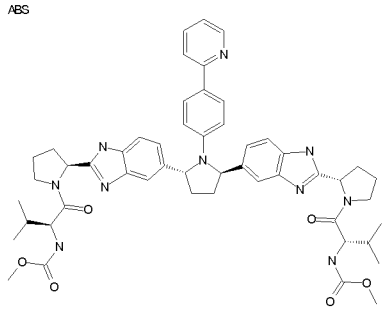
2-(*tert*-butoxycarbonylamino)acetic acid;

2-(methoxycarbonylamino)-3-methylbut-2-enoic acid;

(S)-tetrahydrofuran-2-carboxylic acid

(S)-3-ethyl-2-(methoxycarbonylamino)pentanoic acid; and

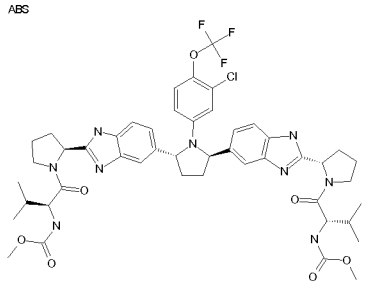
(S)-2-(ethoxycarbonylamino)-3-methylbutanoic acid.



Example 3.1

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-(pyridin-2-yl)phenyl]pyrrolidin-2-yl}-1*H*-benzimidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

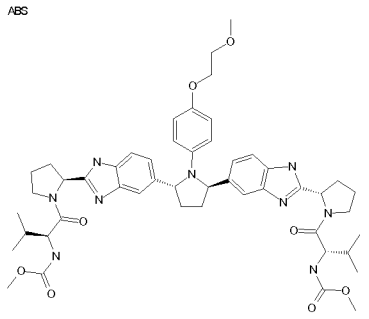
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.28 – 11.98 (m, 2H), 8.42 (d, *J* = 4.4, 1H), 7.70 – 7.56 (m, 4H), 7.46 (d, *J* = 8.2, 1H), 7.38 (d, *J* = 8.2, 1H), 7.34 (s, 1H), 7.30 – 7.20 (m, 3H), 7.16 – 7.02 (m, 3H), 6.42 (d, *J* = 8.7, 2H), 5.56 – 5.42 (m, 2H), 5.18 – 5.06 (m, 2H), 4.03 (t, *J* = 9.3, 2H), 3.88 – 3.73 (m, 4H), 3.52 (s, 6H), 2.25 – 1.62 (m, 14H), 0.92 – 0.67 (m, 12H); MS (ESI+) *m/z* 909.5 $(M+H)^+$.



Example 3.2

methyl {(2*S*)-1-[(2*S*)-2-{5-[(2*R*,5*R*)-1-[3-chloro-4-(trifluoromethoxy)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

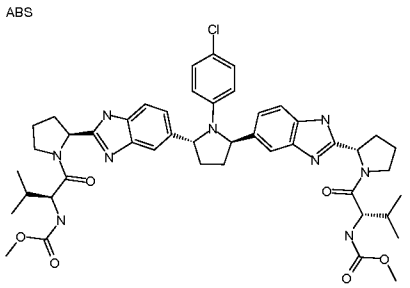
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.31 – 12.01 (m, 2H), 7.48 (d, *J* = 7.9, 1H), 7.40 (d, *J* = 8.2, 1H), 7.34 – 7.17 (m, 4H), 7.15 – 6.99 (m, 3H), 6.44 (s, 1H), 6.30 (d, *J* = 8.9, 1H), 5.55 – 5.37 (m, 2H), 5.19 – 5.04 (m, 2H), 4.04 (t, *J* = 7.8, 2H), 3.89 – 3.73 (m, 4H), 3.52 (s, 6H), 2.28 – 1.79 (m, 12H), 1.77 – 1.59 (m, 2H), 0.92 – 0.64 (m, 12H); MS (ESI+) *m/z* 950.4 $(M+H)^+$.



Example 3.3

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-(2-methoxyethoxy)phenyl]pyrrolidin-2-yl}-1*H*-benzimidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

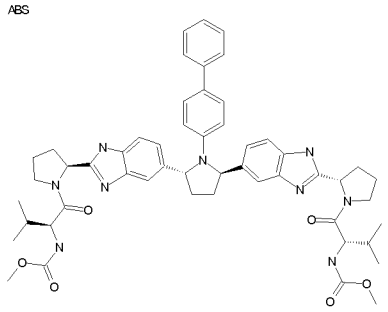
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.27 – 11.97 (m, 2H), 7.44 (d, *J* = 8.4, 1H), 7.36 (d, *J* = 7.7, 1H), 7.33 – 7.25 (m, 3H), 7.20 (s, 1H), 7.12 – 7.00 (m, 2H), 6.58 – 6.47 (m, 2H), 6.24 (d, *J* = 9.0, 2H), 5.40 – 5.27 (m, 2H), 5.19 – 5.08 (m, 2H), 4.06 (t, *J* = 8.3, 2H), 3.88 – 3.76 (m, 6H), 3.54 (s, 6H), 3.51 – 3.45 (m, 2H), 3.21 (s, 3H), 2.26 – 1.83 (m, 12H), 1.75 – 1.64 (m, 2H), 0.93 – 0.74 (m, 12H); MS (ESI+) *m/z* 906.4 $(M+H)^+$.



Example 3.4

methyl {(2*S*)-1-[(2*S*)-2-{5-[(2*R*,5*R*)-1-(4-chlorophenyl)-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

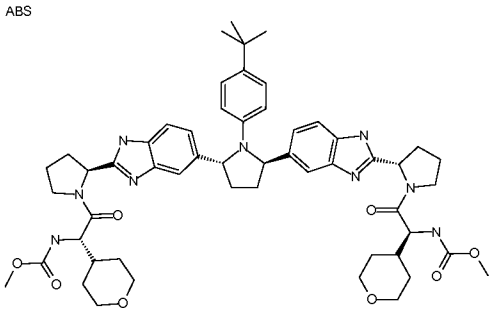
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.05 (s, 2H), 7.44 (d, *J* = 8.2, 1H), 7.36 (d, *J* = 8.1, 1H), 7.31 – 7.22 (m, 3H), 7.19 (s, 1H), 7.03 (t, *J* = 8.2, 2H), 6.94 – 6.83 (m, 2H), 6.29 (d, *J* = 9.1, 2H), 5.42 – 5.32 (m, 2H), 5.16 – 5.04 (m, 2H), 4.04 (t, *J* = 8.4, 2H), 3.85 – 3.75 (m, 4H), 3.51 (s, 6H), 2.25 – 1.58 (m, 14H), 0.90 – 0.73 (m, 12H); MS (ESI+) *m/z* 866.4 $(M+H)^+$.



Example 3.5

methyl {(2*S*)-1-[(2*S*)-2-{5-[(2*R*,5*R*)-1-(biphenyl-4-yl)-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

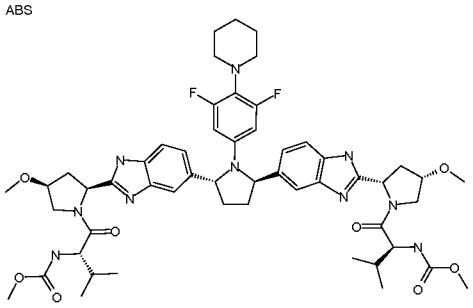
^{1}H NMR (400 MHz, DMSO-d_6) δ 12.11 – 11.66 (m, 2H), 7.47 (d, *J* = 8.3, 1H), 7.43 – 7.33 (m, 4H), 7.32 – 7.19 (m, 7H), 7.17 – 7.06 (m, 3H), 6.43 (d, *J* = 8.8, 2H), 5.52 – 5.41 (m, 2H), 5.18 – 5.09 (m, 2H), 4.05 (t, *J* = 8.2, 2H), 3.87 – 3.76 (m, 4H), 3.53 (s, 6H), 2.25 – 2.11 (m, 4H), 2.05 – 1.62 (m, 10H), 0.91 – 0.74 (m, 12H); MS (ESI+) *m/z* 908.5 $(M+H)^+$.



Example 3.6

dimethyl ([(2*R*,5*R*)-1-(4-*tert*-butylphenyl)pyrrolidine-2,5-diyl]bis{1*H*-benzimidazole-5,2-diyl(2*S*)pyrrolidine-2,1-diyl[(1*S*)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethane-2,1-diyl]})biscarbamate

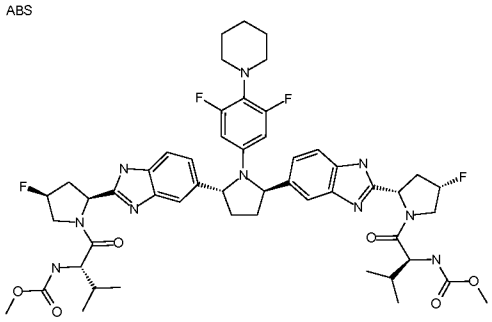
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.07 (s, 9 H) 1.22 - 1.32 (m, 2 H) 1.42 - 1.57 (m, 4 H) 1.64 - 1.72 (m, 2 H) 1.82 (dd, J=21.90, 10.63 Hz, 4 H) 1.92 - 2.02 (m, 4 H) 2.10 - 2.25 (m, 4 H) 2.90 - 2.99 (m, 1 H) 3.04 - 3.19 (m, 4 H) 3.53 (s, 6 H) 3.56 - 3.63 (m, 1 H) 3.66 - 3.79 (m, 4 H) 3.83 (d, J=3.04 Hz, 4 H) 4.14 (q, J=8.10 Hz, 2 H) 5.07 - 5.15 (m, 2 H) 5.33 - 5.40 (m, 2 H) 6.24 (d, J=8.89 Hz, 2 H) 6.85 - 6.94 (m, 2 H) 7.09 (dd, J=14.10, 8.46 Hz, 2 H) 7.16 - 7.22 (m, 2 H) 7.30 - 7.41 (m, 3 H) 7.44 (d, J=9.43 Hz, 1 H) 11.99 - 12.12 (m, 2 H); MS (ESI+) *m/z* 972.5 $(M+H)^+$.



Example 3.7

methyl {(2*S*)-1-[(2*S*,4*S*)-2-{5-[(2*R*,5*R*)-1-[3,5-difluoro-4-(piperidin-1-yl)phenyl]-5-{2-[(2*S*,4*S*)-4-methoxy-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-methoxypyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 0.76 - 0.87 (m, 12 H) 1.35 - 1.40 (m, 2 H) 1.45 (s, 4 H) 1.66 - 1.72 (m, 2 H) 1.95 (dd, J=13.28, 7.17 Hz, 2 H) 2.14 (td, J=12.32, 5.87 Hz, 2 H) 2.41 - 2.46 (m, 2 H) 2.76 (s, 4 H) 3.03 - 3.18 (m, 2 H) 3.25 (d, J=3.66 Hz, 6 H) 3.54 (s, 6 H) 3.64 (td, J=11.14, 5.65 Hz, 2 H) 4.05 - 4.13 (m, 4 H) 4.19 - 4.27 (m, 2 H) 5.10 - 5.16 (m, 2 H) 5.31 - 5.39 (m, 2 H) 5.88 (d, J=12.66 Hz, 2 H) 7.06 (t, J=8.47 Hz, 2 H) 7.21 - 7.31 (m, 4 H) 7.41 (d, J=8.09 Hz, 1 H) 7.48 (dd, J=8.39, 1.83 Hz, 1 H) 11.81 - 11.91 (m, 2 H); MS (ESI+) *m/z* 1011.6 $(M+H)^+$.

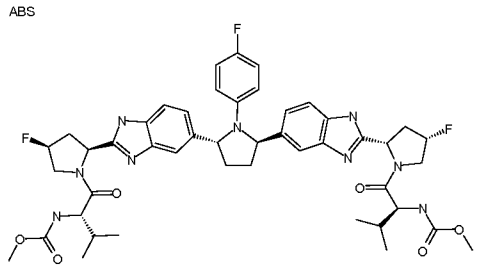


Example 3.8

methyl {(2*S*)-1-[(2*S*,4*S*)-2-{5-[(2*R*,5*R*)-1-[3,5-difluoro-4-(piperidin-1-yl)phenyl]-5-{2-[(2*S*,4*S*)-4-fluoro-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-fluoropyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 0.80 - 0.99 (m, 12 H) 1.38 (d, J=4.73 Hz, 2 H) 1.45 (s, 4 H) 1.64 - 1.74 (m, 2 H) 2.00 - 2.08 (m, 2 H) 2.37 - 2.45 (m, 2 H) 2.76 (s, 4 H) 3.08 - 3.19 (m, 2 H) 3.55 (s, 6 H) 3.99 - 4.26 (m, 6 H) 5.30 - 5.39 (m, 4 H) 5.47 (d, J=53.41 Hz, 4 H) 5.89 (d, J=12.66 Hz, 2 H)

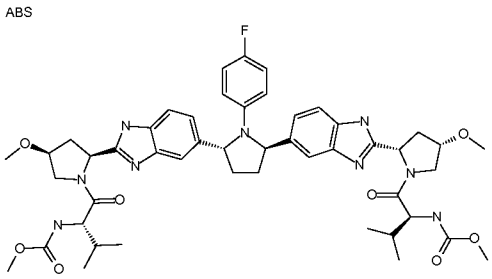
7.02 - 7.11 (m, 2 H) 7.27 (d, J=25.02 Hz, 2 H) 7.41 (d, J=8.09 Hz, 3 H) 7.47 (d, J=7.93 Hz, 1 H) 11.85 (d, J=31.74 Hz, 2 H); MS (ESI+) *m/z* 987.5 $(M+H)^+$.



Example 3.9

methyl {(2*S*)-1-[(2*S*,4*S*)-4-fluoro-2-{5-[(2*R*,5*R*)-5-{2-[(2*S*,4*S*)-4-fluoro-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1*H*-benzimidazol-5-yl}-1-(4-fluorophenyl)pyrrolidin-2-yl]-1*H*-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

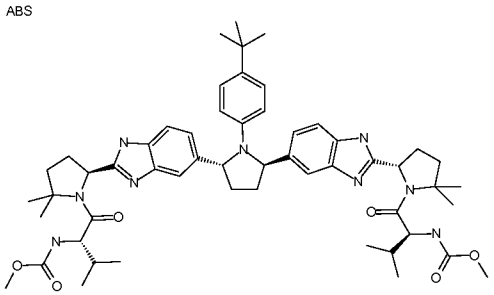
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.82 - 0.98 (m, 12 H) 1.68 - 1.77 (m, 2 H) 1.91 - 2.09 (m, 4 H) 2.36 - 2.44 (m, 2 H) 2.59 - 2.66 (m, 2 H) 3.52 - 3.57 (m, 6 H) 3.72 - 3.98 (m, 2 H) 4.07 - 4.18 (m, 4 H) 5.19 (t, J=8.08 Hz, 1 H) 5.31 - 5.44 (m, 4 H) 5.48 - 5.57 (m, 1 H) 6.24 - 6.31 (m, 2 H) 6.70 - 6.78 (m, 2 H) 7.02 - 7.12 (m, 2 H) 7.17 (s, 1 H) 7.24 - 7.34 (m, 2 H) 7.39 (t, J=7.92 Hz, 2 H) 7.47 (dd, J=20.38, 8.35 Hz, 1 H) 11.78 - 12.06 (m, 2 H); MS (ESI+) *m/z* 886.4 $(M+H)^+$.



Example 3.10

methyl {(2*S*)-1-[(2*S*,4*S*)-2-{5-[(2*R*,5*R*)-1-(4-fluorophenyl)-5-{2-[(2*S*,4*S*)-4-methoxy-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-methoxypyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

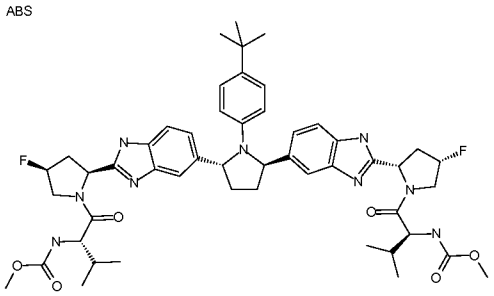
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.77 - 0.90 (m, 12 H) 1.66 - 1.76 (m, 2 H) 1.88 - 2.01 (m, 2 H) 2.06 - 2.19 (m, 2 H) 2.54 - 2.62 (m, 2 H) 3.25 (d, J=5.86 Hz, 6 H) 3.54 (s, 6 H) 3.59 - 3.72 (m, 2 H) 3.97 - 4.14 (m, 6 H) 4.16 - 4.30 (m, 2 H) 5.05 - 5.19 (m, 2 H) 5.36 (d, J=3.25 Hz, 2 H) 6.28 (dd, J=7.26, 4.34 Hz, 2 H) 6.69 - 6.79 (m, 2 H) 7.04 (d, J=8.57 Hz, 2 H) 7.22 - 7.33 (m, 4 H) 7.38 (d, J=8.02 Hz, 1 H) 7.45 (d, J=8.24 Hz, 1 H) 11.81 (s, 2 H); MS (ESI+) *m/z* 910.4 $(M+H)^+$.



Example 3.11

methyl {(2*S*)-1-[(5*S*)-5-{5-[(2*R*,5*R*)-1-(4-*tert*-butylphenyl)-5-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}-5,5-dimethylpyrrolidin-2-yl]-1*H*-benzimidazol-5-yl}pyrrolidin-2-yl]-1*H*-benzimidazol-2-yl}-2,2-dimethylpyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

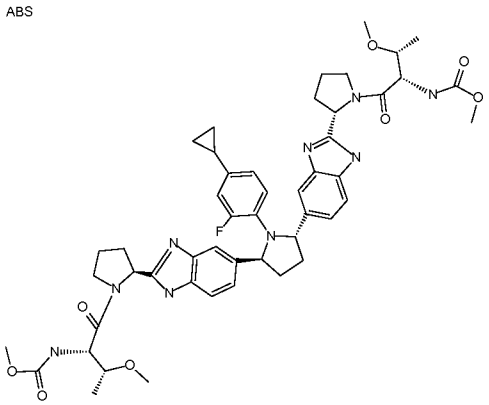
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.81 (d, J=6.61 Hz, 6 H) 0.89 (d, J=6.72 Hz, 6 H) 1.07 (s, 9 H) 1.38 (s, 6 H) 1.62 (s, 6 H) 1.68 - 1.77 (m, 4 H) 1.82 (s, 2 H) 1.94 (dd, J=13.61, 6.78 Hz, 2 H) 2.10 - 2.18 (m, 2 H) 2.27 (dd, J=4.12, 2.60 Hz, 2 H) 3.15 (d, J=3.36 Hz, 6 H) 3.96 - 4.03 (m, 2 H) 5.30 - 5.43 (m, 6 H) 6.24 - 6.31 (m, 2 H) 6.70 (t, J=6.67 Hz, 2 H) 6.84 - 6.91 (m, 2 H) 7.05 - 7.13 (m, 2 H) 7.24 (s, 1 H) 7.36 (d, J=1.08 Hz, 1 H) 7.40 (d, J=7.59 Hz, 1 H) 7.49 (d, J=8.78 Hz, 1 H) 12.16 (d, J=29.28 Hz, 2 H); MS (ESI+) *m/z* 944.5 $(M+H)^+$.



Example 3.12

methyl {(2*S*)-1-[(2*S*,4*S*)-2-{5-[(2*R*,5*R*)-1-(4-*tert*-butylphenyl)-5-{2-[(2*S*,4*S*)-4-fluoro-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-fluoropyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

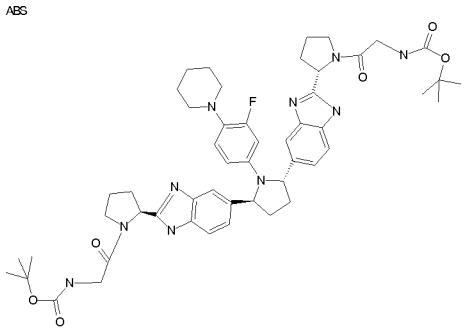
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.79 - 0.97 (m, 12 H) 1.07 (s, 9 H) 1.66 - 1.75 (m, 2 H) 1.99 - 2.08 (m, 2 H) 2.40 (dd, J=17.02, 3.04 Hz, 2 H) 3.09 - 3.21 (m, 4 H) 3.55 (s, 6 H) 4.05 - 4.13 (m, 4 H) 4.16 - 4.27 (m, 2 H) 5.35 (dd, J=8.51, 3.09 Hz, 4 H) 5.46 (d, J=53.24 Hz, 2 H) 6.23 - 6.29 (m, 2 H) 6.91 (d, J=8.89 Hz, 2 H) 7.03 - 7.11 (m, 2 H) 7.23 (d, J=3.47 Hz, 1 H) 7.28 (s, 1 H) 7.39 (dd, J=8.08, 4.72 Hz, 3 H) 7.44 (d, J=8.57 Hz, 1 H) 11.80 (d, J=20.06 Hz, 2 H); MS (ESI+) *m/z* 924.4 $(M+H)^+$.



Example 3.13

methyl {(2*S*,3*R*)-1-[(2*S*)-2-{5-[(2*S*,5*S*)-1-(4-cyclopropyl-2-fluorophenyl)-5-(2-{(2*S*)-1-[*N*-(methoxycarbonyl)-O-methyl-L-threonyl]pyrrolidin-2-yl}-1*H*-benzimidazol-5-yl)pyrrolidin-2-yl]-1*H*-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methoxy-1-oxobutan-2-yl}carbamate

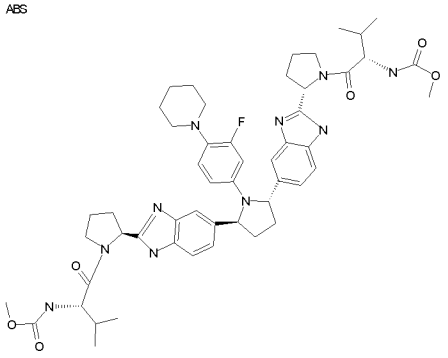
^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 0.35 - 0.57 (m, 2 H) 0.66 - 0.85 (m, 2 H) 1.07 - 1.17 (m, 7 H) 1.59 - 1.69 (m, 1 H) 1.82 (s, 2 H) 1.95 - 2.12 (m, 5 H) 2.13 - 2.33 (m, 5 H) 3.17 - 3.35 (m, 6 H) 3.48 - 3.65 (m, 6 H) 3.85 - 3.95 (m, 4 H) 4.29 - 4.38 (m, 2 H) 5.11 - 5.25 (m, 2 H) 5.58 (s, 2 H) 6.44 - 6.57 (m, 2 H) 6.59 - 6.70 (m, 1 H) 7.07 - 7.19 (m, 2 H) 7.25 - 7.32 (m, 2 H) 7.35 - 7.41 (m, 2 H) 7.45 (d, *J*=8.24 Hz, 2 H) 12.05 (d, *J*=16.63 Hz, 2 H); MS (ESI+) *m/z* 922.4 $(M+H)^+$, (ESI-) *m/z* 920.3 $(M-H)^-$.



Example 3.14

tert-butyl {2-[(2*S*)-2-(5-{(2*S*,5*S*)-5-{2-[(2*S*)-1-{[(*tert*-butoxycarbonyl)amino]acetyl}pyrrolidin-2-yl]-1*H*-benzimidazol-5-yl}-1-[3-fluoro-4-(piperidin-1-yl)phenyl]pyrrolidin-2-yl}-1*H*-benzimidazol-2-yl)pyrrolidin-1-yl]-2-oxoethyl}carbamate

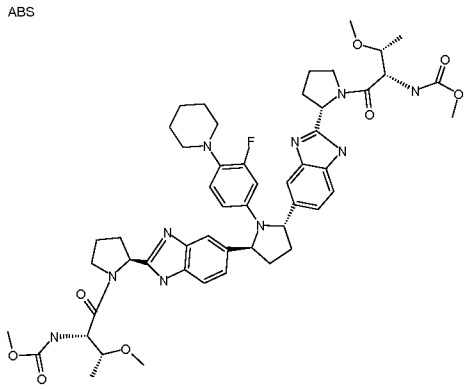
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.16 - 1.43 (m, 18 H) 1.42 - 2.27 (m, 14 H) 2.58 - 2.70 (m, 5 H) 3.38 - 4.02 (m, 9 H) 5.14 (s, 2 H) 5.33 (s, 3 H) 6.04 (s, 2 H) 6.74 (s, 3 H) 7.04 - 7.60 (m, 7 H) 11.83 - 12.43 (m, 2 H); MS (ESI+) *m/z* 933.4 $(M+H)^+$, (ESI-) *m/z* 931.4 $(M-H)^-$.



Example 3.15

methyl {(2*S*)-1-[(2*S*)-2-{5-[(2*S*,5*S*)-1-[3-fluoro-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

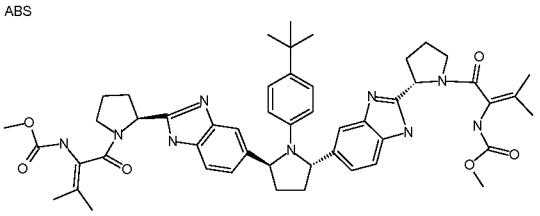
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.73 - 0.93 (m, 12 H) 1.32 - 1.57 (m, 6 H) 1.58 - 2.06 (m, 14 H) 2.18 (s, 4 H) 2.67 (dd, *J*=3.69, 1.95 Hz, 4 H) 3.75 - 3.87 (m, 6 H) 4.07 (t, 2 H) 5.13 (s, 2 H) 5.37 (dd, *J*=6.02, 2.11 Hz, 2 H) 6.04 (s, 2 H) 6.65 (s, 1 H) 7.09 (s, 2 H) 7.16 - 7.23 (m, 1 H) 7.23 - 7.48 (m, 5 H) 12.01 (s, 2 H); MS (ESI+) *m/z* 933.5 $(M+H)^+$, (ESI-) *m/z* 931.4 $(M-H)^-$.



Example 3.16

methyl {(2*S*,3*R*)-1-[(2*S*)-2-{5-[(2*S*,5*S*)-1-[3-fluoro-4-(piperidin-1-yl)phenyl]-5-(2-{(2*S*)-1-[*N*-(methoxycarbonyl)-O-methyl-L-threonyl]pyrrolidin-2-yl}-1*H*-benzimidazol-5-yl)pyrrolidin-2-yl]-1*H*-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methoxy-1-oxobutan-2-yl}carbamate

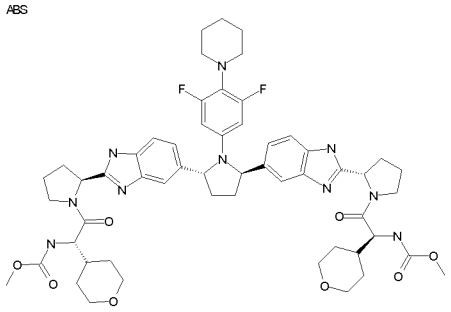
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.00 - 1.14 (m, 6 H) 1.33 - 1.55 (m, 6 H) 1.59 - 2.28 (m, 14 H) 2.58 - 2.71 (m, 4 H) 3.10 - 3.27 (m, 6 H) 3.54 (d, *J*=1.41 Hz, 6 H) 3.71 - 3.90 (m, 6 H) 4.21 - 4.33 (m, 2 H) 5.02 - 5.22 (m, 2 H) 5.37 (dd, *J*=6.02, 2.01 Hz, 2 H) 6.04 (s, 2 H) 6.58 - 6.84 (m, 1 H) 7.06 (d, *J*=22.88 Hz, 2 H) 7.16 - 7.32 (m, 2 H) 7.39 (d, *J*=8.13 Hz, 2 H) 11.90 - 12.34 (m, 2 H); MS (ESI+) *m/z* 965.5 $(M+H)^+$, (ESI-) *m/z* 963.3 $(M-H)^-$.



Example 3.17

dimethyl {[(2*S*,5*S*)-1-(4-*tert*-butylphenyl)pyrrolidine-2,5-diyl]bis[1*H*-benzimidazole-5,2-diyl(2*S*)pyrrolidine-2,1-diyl(3-methyl-1-oxobut-2-ene-1,2-diyl)]}biscarbamate

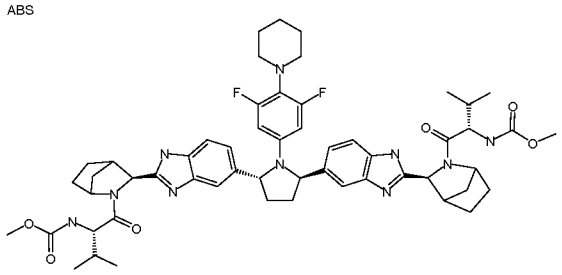
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.87 - 1.20 (m, 9 H) 1.60 - 1.77 (m, 14 H) 1.80 - 2.35 (m, 10 H) 3.16 - 3.79 (m, 10 H) 5.14 (s, 2 H) 5.37 (s, 2 H) 6.24 (d, *J*=3.04 Hz, 2 H) 6.92 (dd, *J*=8.57, 6.29 Hz, 2 H) 7.11 (s, 3 H) 7.31 (s, 1 H) 7.39 (d, *J*=8.13 Hz, 1 H) 7.50 (d, *J*=8.24 Hz, 1 H) 8.89 (d, 2 H) 11.64 - 12.14 (m, 2 H); MS (ESI+) *m/z* 884.5 $(M+H)^+$, 918.4 $(M+NH_3+NH_4)^+$.



Example 3.18

dimethyl ({(2*R*,5*R*)-1-[3,5-difluoro-4-(piperidin-1-yl)phenyl]pyrrolidine-2,5-diyl}bis{1*H*-benzimidazole-5,2-diyl(2*S*)pyrrolidine-2,1-diyl[(1*S*)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethane-2,1-diyl]})biscarbamate

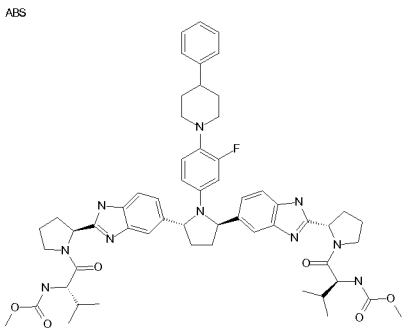
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.13 - 1.33 (m, 4 H) 1.36 - 1.57 (m, 10 H) 1.65 - 1.71 (m, 2 H) 1.79 - 1.90 (m, 2 H) 1.96 - 2.03 (m, 4 H) 2.13 - 2.26 (m, 4 H) 2.76 (s, 4 H) 2.93 - 3.15 (m, 4 H) 3.53 (s, 6 H) 3.62 (dd, J=10.03, 2.01 Hz, 2 H) 3.68 - 3.80 (m, 4 H) 3.81 - 3.88 (m, 4 H) 4.11 - 4.18 (m, 2 H) 5.10 - 5.18 (m, 2 H) 5.33 - 5.40 (m, 2 H) 5.82 - 5.92 (m, 2 H) 7.09 (dd, J=12.52, 8.29 Hz, 2 H) 7.17 - 7.24 (m, 2 H) 7.35 (t, J=8.35 Hz, 2 H) 7.41 (d, J=7.92 Hz, 1 H) 7.47 (d, J=6.94 Hz, 1 H) 12.05 (d, J=1.73 Hz, 1 H) 12.15 (d, J=2.17 Hz, 1 H); MS (ESI+) *m/z* 1035.5 $(M+H)^+$.



Example 3.19

methyl {(2*S*)-1-[(3*S*)-3-{5-[(2*R*,5*R*)-1-[3,5-difluoro-4-(piperidin-1-yl)phenyl]-5-{2-[(3*S*)-2-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}-2-azabicyclo[2.2.1]hept-3-yl]-1*H*-benzimidazol-5-yl}pyrrolidin-2-yl]-1*H*-benzimidazol-2-yl}-2-azabicyclo[2.2.1]hept-2-yl]-3-methyl-1-oxobutan-2-yl}carbamate

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.80 - 0.87 (m, 6 H) 0.93 (t, J=7.05 Hz, 6 H) 1.36 - 1.48 (m, 10 H) 1.49 - 1.57 (m, 2 H) 1.64 - 1.70 (m, 4 H) 1.72 - 1.79 (m, 4 H) 1.84 - 1.90 (m, 2 H) 1.92 - 1.98 (m, 2 H) 2.61 (s, 2 H) 2.72 - 2.78 (m, 4 H) 3.54 (s, 6 H) 4.10 - 4.17 (m, 2 H) 4.50 (s, 2 H) 4.59 (d, J=7.48 Hz, 2 H) 5.32 - 5.41 (m, 2 H) 5.89 (d, J=12.58 Hz, 2 H) 7.07 (d, J=7.70 Hz, 2 H) 7.18 (d, J=9.65 Hz, 2 H) 7.21 (s, 1 H) 7.32 (s, 1 H) 7.40 (d, J=8.13 Hz, 1 H) 7.49 (d, J=8.02 Hz, 1 H) 12.01 (dd, J=12.58, 1.08 Hz, 2 H); MS (ESI+) *m/z* 1003.4 $(M+H)^+$.

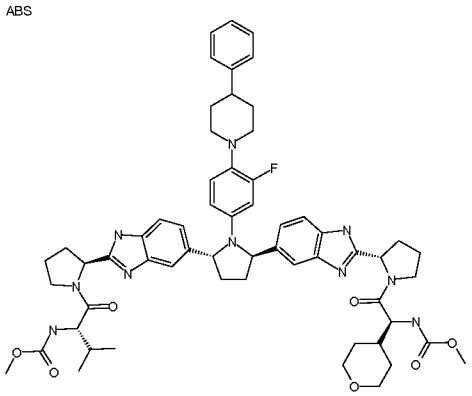


Example 3.20

methyl {(2*S*)-1-[(2*S*)-2-{5-[(2*R*,5*R*)-1-[3-fluoro-4-(4-phenylpiperidin-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

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.77 - 0.90 (m, 12 H) 1.66 - 1.75 (m, 8 H) 1.86 - 1.95 (m, 2 H) 1.96 - 2.05 (m, 4 H) 2.14 - 2.24 (m, 4 H) 3.04 - 3.14 (m, 4 H) 3.53 (s, 6 H) 3.77 - 3.86 (m, 4 H) 4.06 (t, J=8.40 Hz, 2 H) 5.11 - 5.17 (m, 2 H) 5.35 (q, J=6.83 Hz, 2 H) 6.05 - 6.12 (m, 2 H) 6.71 (ddd, J=13.99, 9.22, 4.34 Hz, 1 H) 7.07 (t, J=7.05 Hz, 2 H) 7.16 (t, J=6.94 Hz, 2 H) 7.20 - 7.32 (m, 8 H)

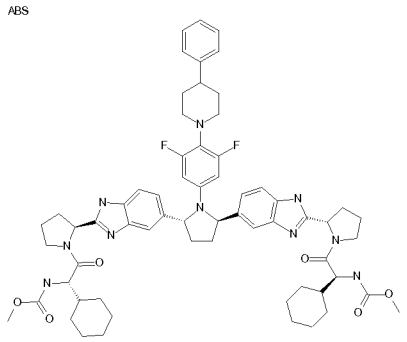
7.39 (d, J=8.13 Hz, 1 H) 7.47 (d, J=8.46 Hz, 1 H) 12.05 (d, J=5.64 Hz, 2 H); MS (ESI+) *m/z* 1009.4 $(M+H)^+$.



Example 3.21

methyl [(1*S*)-2-[(2*S*)-2-{5-[(2*R*,5*R*)-1-[3-fluoro-4-(4-phenylpiperidin-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]-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl]carbamate

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.76 - 0.92 (m, 6 H) 1.47 - 1.57 (m, 2 H) 1.65 - 1.76 (m, 8 H) 1.81 - 1.94 (m, 2 H) 1.94 - 2.04 (m, 4 H) 2.15 - 2.23 (m, 4 H) 3.03 - 3.15 (m, 4 H) 3.53 (s, 6 H) 3.57 - 3.67 (m, 2 H) 3.70 - 3.79 (m, 2 H) 3.79 - 3.89 (m, 4 H) 4.07 - 4.20 (m, 2 H) 5.10 - 5.19 (m, 2 H) 5.32 - 5.41 (m, 2 H) 6.04 - 6.11 (m, 2 H) 6.66 - 6.75 (m, 1 H) 7.03 - 7.36 (m, 12 H) 7.39 (dd, J=8.78, 1.63 Hz, 1 H) 7.46 (t, J=8.78 Hz, 1 H) 12.02 - 12.14 (m, 2 H); MS (APCI+) *m/z* 1051 $(M+H)^+$.

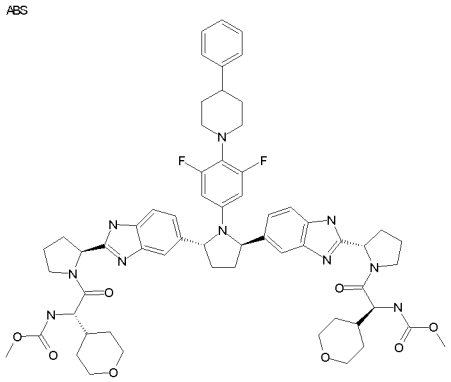


Example 3.22

dimethyl ({(2*R*,5*R*)-1-[3,5-difluoro-4-(4-phenylpiperidin-1-yl)phenyl]pyrrolidine-2,5-diyl}bis{1*H*-benzimidazole-5,2-diyl(2*S*)pyrrolidine-2,1-diyl[(1*S*)-1-cyclohexyl-2-oxoethane-2,1-diyl]})biscarbamate

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.81 - 1.14 (m, 11 H) 1.40 - 1.71 (m, 20 H) 1.94 - 2.05 (m, 4 H) 2.14 - 2.26 (m, 4 H) 2.83 - 2.91 (m, 2 H) 2.93 - 3.02 (m, 2 H) 3.52 (d, J=3.80 Hz, 6 H) 3.76 - 3.87

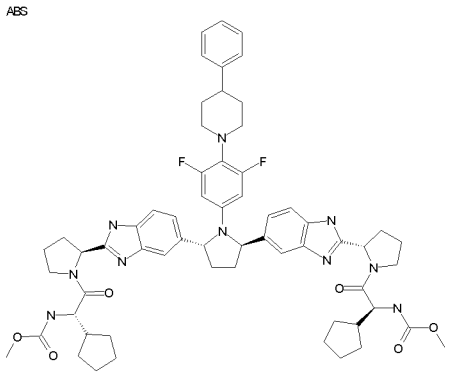
(m, 4 H) 4.08 (q, J=8.53 Hz, 2 H) 5.14 (d, J=5.86 Hz, 2 H) 5.33 - 5.45 (m, 2 H) 5.85 - 5.98 (m, 2 H) 7.05 - 7.31 (m, 11 H) 7.42 (d, J=9.76 Hz, 1 H) 7.49 (d, J=8.24 Hz, 1 H) 12.00 (s, 1 H) 12.16 (d, J=3.58 Hz, 1 H); MS (ESI+) *m/z* 1107.5 $(M+H)^+$.



Example 3.23

dimethyl ({(2*R*,5*R*)-1-[3,5-difluoro-4-(4-phenylpiperidin-1-yl)phenyl]pyrrolidine-2,5-diyl}bis{1*H*-benzimidazole-5,2-diyl(2*S*)pyrrolidine-2,1-diyl[(1*S*)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethane-2,1-diyl]})biscarbamate

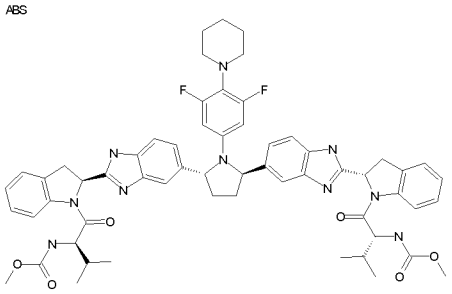
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.14 - 1.37 (m, 4 H) 1.43 - 1.57 (m, 4 H) 1.61 - 1.72 (m, 6 H) 1.77 - 1.91 (m, 2 H) 1.96 - 2.05 (m, 4 H) 2.14 - 2.25 (m, 4 H) 2.87 - 3.02 (m, 6 H) 3.06 - 3.22 (m, 2 H) 3.53 (s, 6 H) 3.58 - 3.67 (m, 2 H) 3.68 - 3.79 (m, 5 H) 3.81 - 3.89 (m, 4 H) 4.11 - 4.19 (m, 2 H) 5.14 (dd, J=7.32, 2.98 Hz, 2 H) 5.34 - 5.42 (m, 2 H) 5.85 - 5.95 (m, 2 H) 7.06 - 7.17 (m, 3 H) 7.19 - 7.29 (m, 6 H) 7.35 (t, J=9.05 Hz, 2 H) 7.42 (d, J=8.57 Hz, 1 H) 7.47 (d, J=8.78 Hz, 1 H) 12.05 (s, 1 H) 12.16 (d, J=1.41 Hz, 1 H); MS (ESI+) *m/z* 1111.5 $(M+H)^+$.



Example 3.24

dimethyl ({(2*R*,5*R*)-1-[3,5-difluoro-4-(4-phenylpiperidin-1-yl)phenyl]pyrrolidine-2,5-diyl}bis{1*H*-benzimidazole-5,2-diyl(2*S*)pyrrolidine-2,1-diyl[(1*S*)-1-cyclopentyl-2-oxoethane-2,1-diyl]})biscarbamate

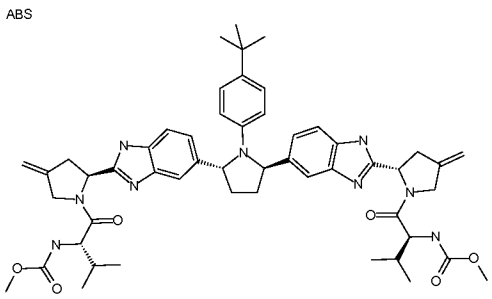
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.16 - 1.28 (m, 4 H) 1.31 - 1.54 (m, 10 H) 1.55 - 1.73 (m, 10 H) 1.95 - 2.06 (m, 4 H) 2.09 - 2.24 (m, 7 H) 2.85 - 3.07 (m, 4 H) 3.53 (s, 6 H) 3.82 (s, 4 H) 4.15 (t, J=8.51 Hz, 2 H) 5.11 - 5.18 (m, 2 H) 5.34 - 5.43 (m, 2 H) 5.92 (d, J=12.69 Hz, 2 H) 7.06 - 7.18 (m, 3 H) 7.19 - 7.31 (m, 6 H) 7.37 - 7.45 (m, 3 H) 7.50 (d, J=8.35 Hz, 1 H) 12.01 (s, 1 H) 12.08 (s, 1 H); MS (ESI+) *m/z* 1079.4 $(M+H)^+$.



Example 3.25

methyl {(2*R*)-1-[(2*S*)-2-{5-[(2*R*,5*R*)-1-[3,5-difluoro-4-(piperidin-1-yl)phenyl]-5-{2-[(2*S*)-1-{(2*R*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}-2,3-dihydro-1*H*-indol-2-yl]-1*H*-benzimidazol-5-yl}pyrrolidin-2-yl]-1*H*-benzimidazol-2-yl}-2,3-dihydro-1*H*-indol-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

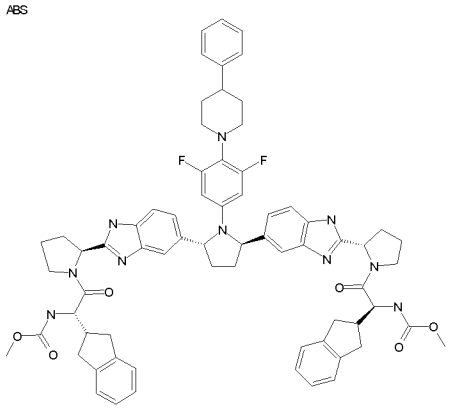
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.90 (dd, J=31.72, 6.23 Hz, 12 H) 1.31 - 1.51 (m, 7 H) 1.52 - 1.70 (m, 2 H) 2.06 - 2.29 (m, 4 H) 2.74 (s, 6 H) 3.08 (d, J=15.40 Hz, 6 H) 3.69 - 3.89 (m, 2 H) 4.27 (s, 1 H) 5.26 - 5.39 (m, 2 H) 5.77 - 6.01 (m, 4 H) 7.01 - 7.33 (m, 12 H) 7.37 - 7.53 (m, 2 H) 8.12 - 8.25 (m, 2 H) 12.34 (d, J=42.07 Hz, 2 H); MS (ESI+) *m/z* 1047.4 $(M+H)^+$.



Example 3.26

methyl {(2*S*)-1-[(2*S*)-2-{5-[(2*R*,5*R*)-1-(4-*tert*-butylphenyl)-5-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}-4-methylidenepyrrolidin-2-yl]-1*H*-benzimidazol-5-yl}pyrrolidin-2-yl]-1*H*-benzimidazol-2-yl}-4-methylidenepyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

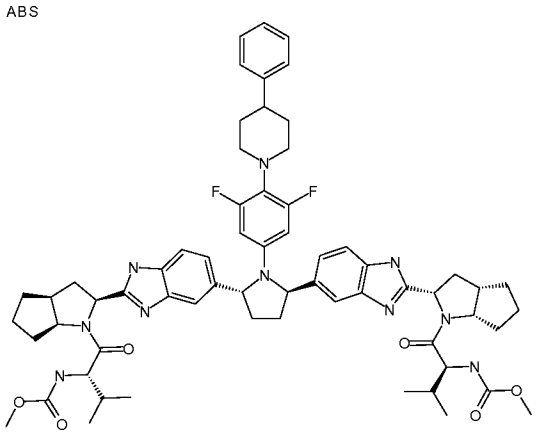
1H NMR (400 MHz, DMSO-d_6) δ ppm 0.74 - 0.92 (m, 12 H) 1.07 (s, 9 H) 1.68 (s, 2 H) 1.91 (ddd, J=14.64, 7.64, 7.43 Hz, 2 H) 2.61 - 2.75 (m, 2 H) 2.97 - 3.09 (m, 2 H) 3.13 (s, 1 H) 3.54 (s, 6 H) 3.94 - 4.08 (m, 2 H) 4.46 (d, J=12.36 Hz, 2 H) 4.60 (d, J=14.20 Hz, 2 H) 5.02 (s, 3 H) 5.10 (s, 2 H) 5.31 - 5.45 (m, 4 H) 6.24 (d, J=8.67 Hz, 2 H) 6.86 - 6.94 (m, 2 H) 7.07 (t, J=8.51 Hz, 2 H) 7.20 (s, 1 H) 7.26 (s, 1 H) 7.34 - 7.50 (m, 4 H) 12.05 (d, J=15.72 Hz, 2 H); MS (ESI+) *m/z* 912.4 $(M+H)^+$.



Example 3.27

dimethyl ({(2*R*,5*R*)-1-[3,5-difluoro-4-(4-phenylpiperidin-1-yl)phenyl]pyrrolidine-2,5-diyl}bis{1*H*-benzimidazole-5,2-diyl(2*S*)pyrrolidine-2,1-diyl[(1*S*)-1-(2,3-dihydro-1*H*-inden-2-yl)-2-oxoethane-2,1-diyl]})biscarbamate

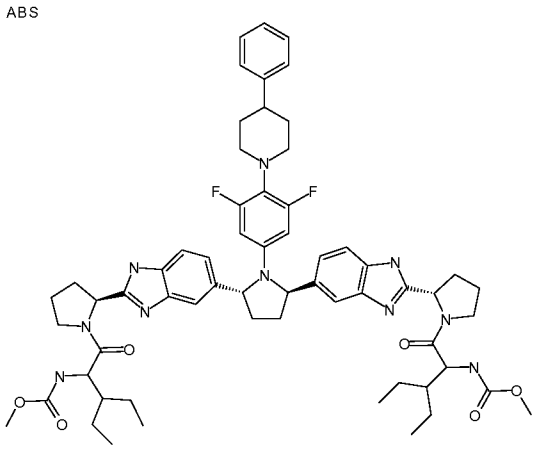
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.51 - 1.76 (m, 6 H) 1.94 - 2.06 (m, 4 H) 2.12 - 2.28 (m, 8 H) 2.69 - 2.89 (m, 12 H) 2.92 - 3.05 (m, 1 H) 3.55 (s, 6 H) 3.77 - 3.86 (m, 4 H) 4.36 - 4.43 (m, 2 H) 5.16 - 5.24 (m, 2 H) 5.35 - 5.48 (m, 2 H) 5.97 (d, J=12.90 Hz, 2 H) 7.01 - 7.30 (m, 17 H) 7.34 (s, 1 H) 7.46 (d, J=8.35 Hz, 1 H) 7.54 - 7.60 (m, 2 H) 12.07 (s, 1 H) 12.18 (s, 1 H); MS (ESI+) *m/z* 1175.5 $(M+H)^+$.



Example 3.28

methyl {(2*S*)-1-[(2*S*,3a*S*,6a*S*)-2-{5-[(2*R*,5*R*)-1-[3,5-difluoro-4-(4-phenylpiperidin-1-yl)phenyl]-5-{2-[(2*S*,3a*S*,6a*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}octahydrocyclopenta[*b*]pyrrol-2-yl]-1*H*-benzimidazol-5-yl}pyrrolidin-2-yl]-1*H*-benzimidazol-2-yl}hexahydrocyclopenta[*b*]pyrrol-1(2*H*)-yl]-3-methyl-1-oxobutan-2-yl}carbamate

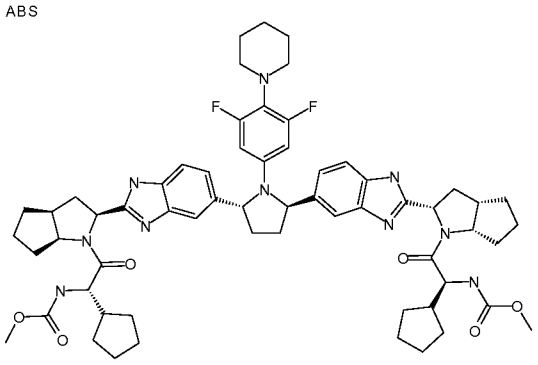
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.72 - 0.92 (m, 12 H) 1.50 - 1.59 (m, 4 H) 1.62 - 1.72 (m, 8 H) 1.73 - 1.81 (m, 2 H) 1.83 - 1.92 (m, 4 H) 1.95 - 2.03 (m, 2 H) 2.06 - 2.15 (m, 4 H) 2.38 - 2.46 (m, 2 H) 2.75 - 2.83 (m, 1 H) 2.86 - 3.01 (m, 4 H) 3.54 (s, 6 H) 4.01 (td, J=13.28, 6.83 Hz, 4 H) 4.78 (dd, J=7.70, 4.23 Hz, 2 H) 5.13 (t, J=8.24 Hz, 2 H) 5.33 - 5.45 (m, 2 H) 5.92 (dd, J=12.90, 2.82 Hz, 2 H) 7.07 (d, J=8.67 Hz, 2 H) 7.15 (t, J=6.94 Hz, 1 H) 7.20 - 7.29 (m, 5 H) 7.34 (d, J=4.01 Hz, 1 H) 7.39 - 7.47 (m, 3 H) 7.50 (d, J=8.02 Hz, 1 H) 11.97 (s, 1 H) 12.06 (s, 1 H);MS (ESI+) *m/z* 1107.4 $(M+H)^+$.



Example 3.29

methyl {1-[(2*S*)-2-{5-[(2*R*,5*R*)-1-[3,5-difluoro-4-(4-phenylpiperidin-1-yl)phenyl]-5-{2-[(2*S*)-1-{3-ethyl-2-[(methoxycarbonyl)amino]pentanoyl}pyrrolidin-2-yl]-1*H*-benzimidazol-5-yl}pyrrolidin-2-yl]-1*H*-benzimidazol-2-yl}pyrrolidin-1-yl]-3-ethyl-1-oxopentan-2-yl}carbamate

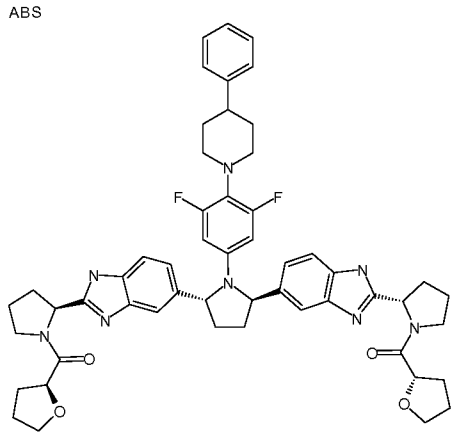
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.16 (t, *J*=6.02 Hz, 1 H) 0.34 (t, *J*=6.89 Hz, 1 H) 0.56 - 0.99 (m, 10 H) 1.16 - 1.36 (m, 4 H) 1.53 - 1.80 (m, 8 H) 1.93 - 2.09 (m, 4 H) 2.14 - 2.30 (m, 4 H) 2.80 - 3.13 (m, 11 H) 3.53 (s, 6 H) 3.73 - 3.95 (m, 4 H) 4.24 - 4.41 (m, 2 H) 5.09 - 5.20 (m, 2 H) 5.30 - 5.44 (m, 2 H) 5.83 - 5.96 (m, 2 H) 7.03 - 7.36 (m, 11 H) 7.39 - 7.62 (m, 2 H) 12.00 (s, 1 H) 12.13 - 12.20 (m, 1 H); MS (ESI+) *m/z* 1083.5 $(M+H)^+$.



Example 3.30

dimethyl ({(2*R*,5*R*)-1-[3,5-difluoro-4-(piperidin-1-yl)phenyl]pyrrolidine-2,5-diyl}bis{1*H*-benzimidazole-5,2-diyl(2*S*,3a*S*,6a*S*)hexahydrocyclopenta[*b*]pyrrole-2,1(2*H*)-diyl[(1*S*)-1-cyclopentyl-2-oxoethane-2,1-diyl]})biscarbamate

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.17 - 1.32 (m, 10 H) 1.36 - 1.49 (m, 10 H) 1.51 - 1.79 (m, 10 H) 1.87 (dd, J=15.83, 7.26 Hz, 2 H) 1.98 (dd, J=13.07, 8.40 Hz, 2 H) 2.05 - 2.16 (m, 6 H) 2.36 - 2.46 (m, 4 H) 2.72 - 2.81 (m, 6 H) 3.54 (s, 6 H) 4.11 (q, J=9.40 Hz, 2 H) 4.75 - 4.85 (m, 2 H) 5.08 - 5.18 (m, 2 H) 5.36 (dt, J=13.66, 6.83 Hz, 2 H) 5.88 (ddd, J=12.69, 3.52, 3.42 Hz, 2 H) 7.07 (d, J=8.35 Hz, 2 H) 7.21 (s, 1 H) 7.31 (d, J=4.01 Hz, 1 H) 7.41 (d, J=8.24 Hz, 1 H) 7.46 - 7.56 (m, 3 H) 11.88 (d, J=2.49 Hz, 1 H) 12.01 (d, J=3.36 Hz, 1 H); MS (ESI+) *m/z* 1083.5 $(M+H)^+$.

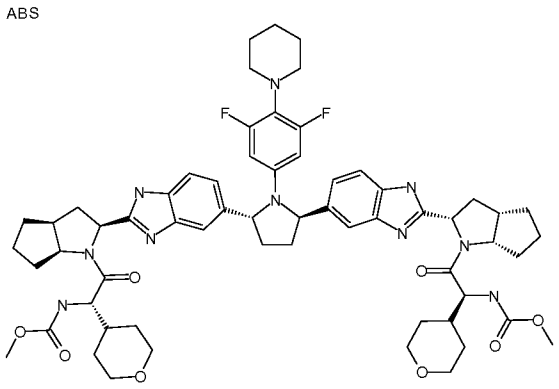


Example 3.31

({(2*R*,5*R*)-1-[3,5-difluoro-4-(4-phenylpiperidin-1-yl)phenyl]pyrrolidine-2,5-diyl}bis[1*H*-benzimidazole-5,2-diyl(2*S*)pyrrolidine-2,1-diyl])bis[(2*S*)-tetrahydrofuran-2-ylmethanone]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.36 - 1.49 (m, J=15.83 Hz, 2 H) 1.60 - 1.75 (m, 8 H) 1.77 - 1.91 (m, 6 H) 1.94 - 2.12 (m, 8 H) 2.16 - 2.27 (m, 2 H) 2.86 - 3.08 (m, 5 H) 3.74 (t, J=6.99 Hz, 6 H) 4.57 - 4.63 (m, 2 H) 5.13 (dd, J=9.00, 1.30 Hz, 2 H) 5.33 - 5.43 (m, 2 H) 5.93 (d, J=13.34 Hz, 2 H)

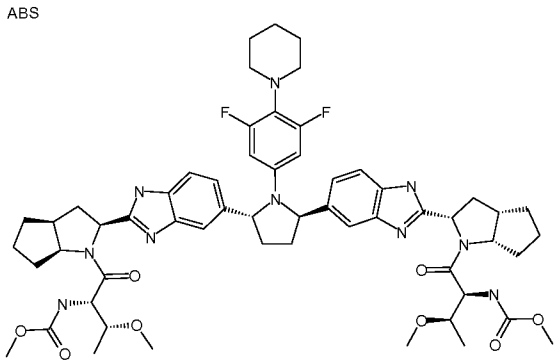
7.06 - 7.16 (m, 3 H) 7.20 - 7.29 (m, 5 H) 7.32 (s, 1 H) 7.42 (d, J=8.57 Hz, 1 H) 7.52 (d, J=8.13 Hz, 1 H) 12.00 (s, 1 H) 12.08 (s, 1 H); MS (ESI+) *m/z* 909.4 $(M+H)^+$.



Example 3.32

dimethyl ({(2*R*,5*R*)-1-[3,5-difluoro-4-(piperidin-1-yl)phenyl]pyrrolidine-2,5-diyl}bis{1*H*-benzimidazole-5,2-diyl(2*S*,3a*S*,6a*S*)hexahydrocyclopenta[*b*]pyrrole-2,1(2*H*)-diyl[(1*S*)-2-oxo-1-(tetrahydro-2*H*-pyran-4-yl)ethane-2,1-diyl]})biscarbamate

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.10 - 1.27 (m, 4 H) 1.33 - 1.51 (m, 12 H) 1.51 - 1.65 (m, 6 H) 1.67 - 1.80 (m, 4 H) 1.83 - 2.00 (m, 6 H) 2.08 - 2.17 (m, 4 H) 2.39 - 2.45 (m, 2 H) 2.73 - 2.85 (m, 8 H) 3.03 - 3.12 (m, 2 H) 3.53 (s, 6 H) 3.70 - 3.87 (m, 2 H) 4.04 - 4.17 (m, 2 H) 4.74 - 4.83 (m, 2 H) 5.08 - 5.17 (m, 2 H) 5.31 - 5.42 (m, 2 H) 5.83 - 5.93 (m, 2 H) 7.04 - 7.11 (m, 2 H) 7.21 (d, J=15.83 Hz, 2 H) 7.41 (d, J=8.02 Hz, 1 H) 7.46 - 7.55 (m, 3 H) 11.96 (d, J=4.12 Hz, 1 H) 12.11 (d, J=4.55 Hz, 1 H); MS (ESI+) *m/z* 1115.4 $(M+H)^+$.

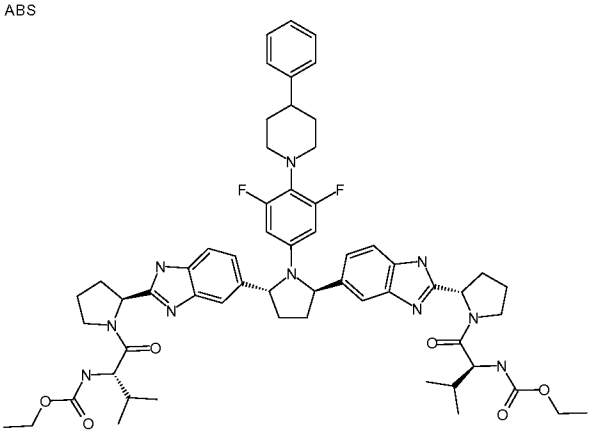


Example 3.33

methyl {(2*S*,3*R*)-1-[(2*S*,3a*S*,6a*S*)-2-{5-[(2*R*,5*R*)-1-[3,5-difluoro-4-(piperidin-1-yl)phenyl]-5-(2-{(2*S*,3a*S*,6a*S*)-1-[*N*-(methoxycarbonyl)-*O*-methyl-L-threonyl]octahydrocyclopenta[*b*]pyrrol-2-yl}-1*H*-benzimidazol-5-yl)pyrrolidin-2-yl]-1*H*-benzimidazol-2-yl}hexahydrocyclopenta[*b*]pyrrol-1(2*H*)-yl]-3-methoxy-1-oxobutan-2-yl}carbamate

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.95 (d, J=6.18 Hz, 3 H) 1.03 (d, J=5.75 Hz, 3 H) 1.35 - 1.49 (m, 8 H) 1.50 - 1.64 (m, 4 H) 1.66 - 1.81 (m, 6 H) 1.84 - 2.01 (m, 6 H) 2.07 - 2.16 (m, 4 H) 2.73 - 2.84 (m, 6 H) 3.13 (s, 3 H) 3.17 (s, 3 H) 3.54 (s, 6 H) 4.20 - 4.29 (m, 2 H) 4.76 - 4.84 (m, 2 H) 5.12 (t, J=8.19 Hz, 2 H) 5.37 (dd, J=6.51, 4.88 Hz, 2 H) 5.88 (d, J=13.45 Hz, 2 H) 7.05 (d, J=8.13 Hz, 2 H) 7.20 (s, 1 H) 7.30 (s, 1 H) 7.40 (d, J=7.81 Hz, 1 H) 7.47 - 7.57 (m, 3 H) 11.98 - 12.15 (m, 2 H); MS (APCI+) *m/z* 1063.4 $(M+H)^+$.

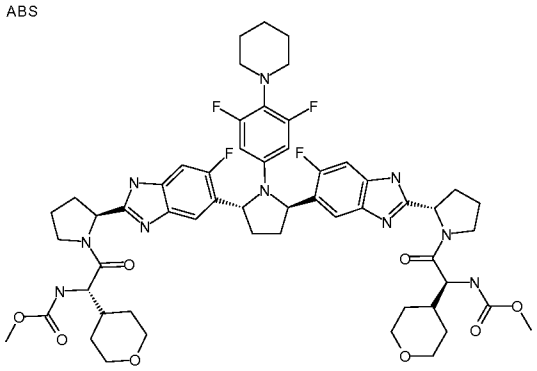
ABS



Example 3.34

ethyl {(2*S*)-1-[(2*S*)-2-{5-[(2*R*,5*R*)-1-[3,5-difluoro-4-(4-phenylpiperidin-1-yl)phenyl]-5-{2-[(2*S*)-1-{(2*S*)-2-[(ethoxycarbonyl)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

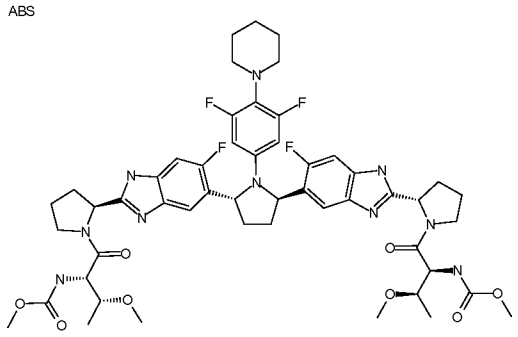
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.75 - 0.91 (m, 12 H) 1.15 (t, J=7.43 Hz, 6 H) 1.60 - 1.74 (m, 6 H) 1.85 - 2.07 (m, 8 H) 2.16 - 2.27 (m, 4 H) 2.86 - 3.04 (m, 4 H) 3.40 - 3.48 (m, 1 H) 3.76 - 3.85 (m, 4 H) 3.98 (q, J=7.08 Hz, 4 H) 4.05 (t, J=8.29 Hz, 2 H) 5.11 - 5.19 (m, 2 H) 5.34 - 5.44 (m, 2 H) 5.92 (d, J=12.69 Hz, 2 H) 7.05 - 7.11 (m, 2 H) 7.15 (t, J=6.94 Hz, 1 H) 7.20 - 7.27 (m, 7 H) 7.31 (s, 1 H) 7.42 (d, J=8.24 Hz, 1 H) 7.50 (d, J=7.92 Hz, 1 H) 12.07 (s, 1 H) 12.12 (s, 1 H); MS (ESI+) *m/z* 1055.4 $(M+H)^+$.



Example 3.35

dimethyl ({(2*R*,5*R*)-1-[3,5-difluoro-4-(piperidin-1-yl)phenyl]pyrrolidine-2,5-diyl}bis{(6-fluoro-1*H*-benzimidazole-5,2-diyl)(2*S*)pyrrolidine-2,1-diyl[(1*S*)-2-oxo-1-(tetrahydro-2*H*-pyran-4-yl)ethane-2,1-diyl]})biscarbamate

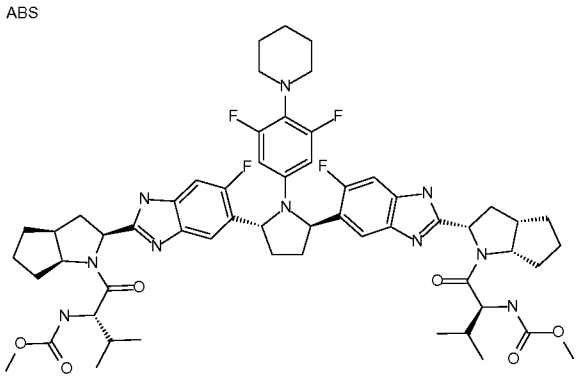
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.12 - 1.33 (m, 4 H) 1.38 - 1.55 (m, 10 H) 1.66 - 1.90 (m, 6 H) 1.94 - 2.04 (m, 4 H) 2.11 - 2.24 (m, 2 H) 2.75 - 2.85 (m, 6 H) 3.01 - 3.19 (m, 2 H) 3.52 (s, 6 H) 3.63 - 3.77 (m, 4 H) 3.78 - 3.89 (m, 6 H) 4.08 - 4.18 (m, 2 H) 5.07 - 5.16 (m, 2 H) 5.46 - 5.63 (m, 2 H) 5.81 - 5.93 (m, 2 H) 6.99 - 7.12 (m, 2 H) 7.31 - 7.44 (m, 4 H) 12.04 - 12.15 (m, 1 H) 12.28 - 12.35 (m, 1 H); MS (APCI+) *m/z* 1071.2 $(M+H)^+$.



Example 3.36

methyl {(2*S*,3*R*)-1-[(2*S*)-2-{5-[(2*R*,5*R*)-1-[3,5-difluoro-4-(piperidin-1-yl)phenyl]-5-(6-fluoro-2-{(2*S*)-1-[*N*-(methoxycarbonyl)-*O*-methyl-L-threonyl]pyrrolidin-2-yl}-1*H*-benzimidazol-5-yl)pyrrolidin-2-yl]-6-fluoro-1*H*-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methoxy-1-oxobutan-2-yl}carbamate

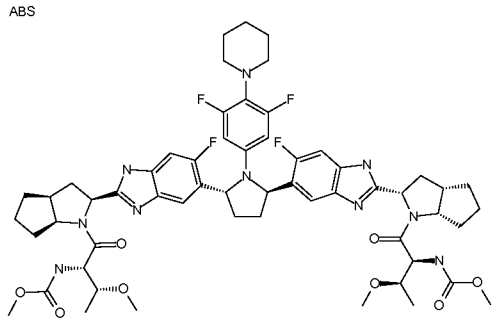
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.87 - 1.11 (m, 8 H) 1.35 - 1.52 (m, 6 H) 1.71 - 1.84 (m, 2 H) 1.91 - 2.07 (m, 4 H) 2.12 - 2.26 (m, 4 H) 2.79 (s, 4 H) 3.08 (d, J=37.41 Hz, 6 H) 3.41 - 3.48 (m, 2 H) 3.53 (s, 6 H) 3.82 (d, J=4.88 Hz, 4 H) 4.18 - 4.30 (m, 2 H) 5.11 (s, 2 H) 5.47 - 5.63 (m, 2 H) 5.81 - 5.97 (m, 2 H) 6.99 - 7.28 (m, 4 H) 7.37 (dd, J=25.54, 9.60 Hz, 2 H) 12.10 (s, 1 H) 12.22 - 12.35 (m, 1 H); MS (ESI+) *m/z* 1019.4 $(M+H)^+$.



Example 3.37

methyl {(2*S*)-1-[(2*S*,3a*S*,6a*S*)-2-{5-[(2*R*,5*R*)-1-[3,5-difluoro-4-(piperidin-1-yl)phenyl]-5-{6-fluoro-2-[(2*S*,3a*S*,6a*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}octahydrocyclopenta[*b*]pyrrol-2-yl]-1*H*-benzimidazol-5-yl}pyrrolidin-2-yl]-6-fluoro-1*H*-benzimidazol-2-yl}hexahydrocyclopenta[*b*]pyrrol-1(2*H*)-yl]-3-methyl-1-oxobutan-2-yl}carbamate

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.80 (dd, J=24.13, 6.45 Hz, 12 H) 1.36 - 1.67 (m, 10 H) 1.69 - 1.87 (m, 8 H) 1.92 - 2.17 (m, 6 H) 2.37 - 2.47 (m, 2 H) 2.78 (s, 6 H) 3.53 (s, 6 H) 3.92 - 4.07 (m, 2 H) 4.69 - 4.84 (m, 2 H) 5.08 (t, J=8.29 Hz, 2 H) 5.36 - 5.68 (m, 4 H) 5.86 (dd, J=11.71, 8.67 Hz, 2 H) 7.10 (dd, J=31.39, 6.89 Hz, 2 H) 7.28 - 7.51 (m, 4 H) 12.02 (s, 1 H) 12.21 (d, J=7.27 Hz, 1 H); MS (ESI+) *m/z* 1067.4 $(M+H)^+$.

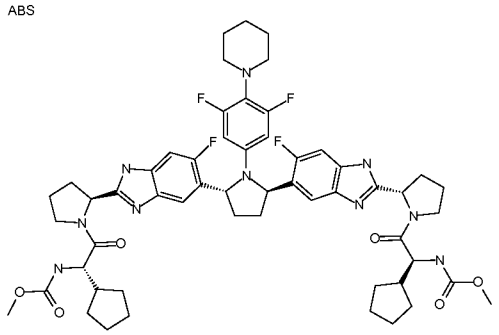


Example 3.38

methyl {(2*S*,3*R*)-1-[(2*S*,3a*S*,6a*S*)-2-{5-[(2*R*,5*R*)-1-[3,5-difluoro-4-(piperidin-1-yl)phenyl]-5-(6-fluoro-2-{(2*S*,3a*S*,6a*S*)-1-[*N*-(methoxycarbonyl)-*O*-methyl-L-threonyl]octahydrocyclopenta[*b*]pyrrol-2-yl}-1*H*-benzimidazol-5-yl)pyrrolidin-2-yl]-6-fluoro-1*H*-benzimidazol-2-yl}hexahydrocyclopenta[*b*]pyrrol-1(2*H*)-yl]-3-methoxy-1-oxobutan-2-yl}carbamate

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.78 - 1.07 (m, 8 H) 1.36 - 1.51 (m, 8 H) 1.51 - 1.67 (m, 4 H) 1.75 (dd, J=12.20, 6.56 Hz, 4 H) 1.90 (dd, J=20.22, 8.95 Hz, 4 H) 2.00 - 2.14 (m, 4 H) 2.37 - 2.47 (m, 2 H) 2.79 (s, 6 H) 3.04 - 3.20 (m, 6 H) 3.54 (s, 6 H) 4.14 - 4.29 (m, 2 H) 4.77 (dd, J=18.00, 7.48 Hz, 2

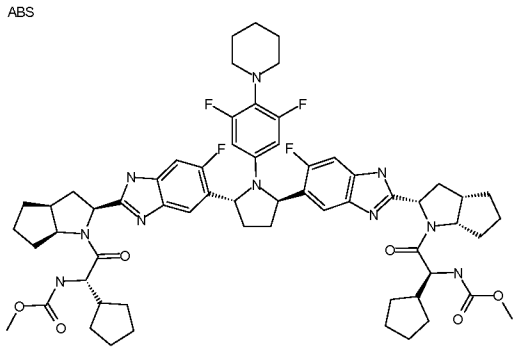
H) 5.07 (t, J=8.24 Hz, 2 H) 5.47 - 5.65 (m, 2 H) 5.80 - 5.94 (m, 2 H) 7.08 (dd, J=27.27, 6.78 Hz, 2 H) 7.28 - 7.57 (m, 4 H) 12.04 (s, 1 H) 12.26 (s, 1 H); MS (ESI+) *m/z* 1099.4 $(M+H)^+$.



Example 3.39

dimethyl ({(2*R*,5*R*)-1-[3,5-difluoro-4-(piperidin-1-yl)phenyl]pyrrolidine-2,5-diyl}bis{(6-fluoro-1*H*-benzimidazole-5,2-diyl)(2*S*)pyrrolidine-2,1-diyl[(1*S*)-1-cyclopentyl-2-oxoethane-2,1-diyl]})biscarbamate

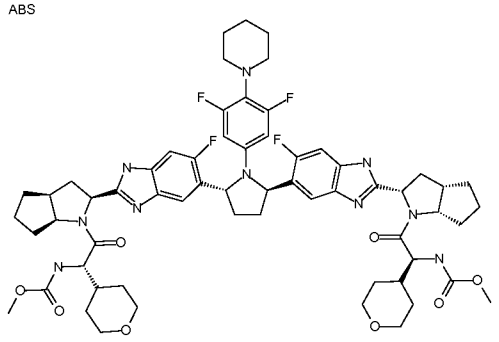
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.10 - 1.29 (m, 6 H) 1.34 - 1.62 (m, 18 H) 1.71 - 1.86 (m, 2 H) 1.94 - 2.10 (m, 4 H) 2.11 - 2.24 (m, 4 H) 2.74 - 2.84 (m, 4 H) 2.94 - 3.12 (m, 2 H) 3.53 (s, 6 H) 3.73 - 3.87 (m, 4 H) 4.06 - 4.17 (m, 2 H) 5.07 - 5.18 (m, 2 H) 5.47 - 5.63 (m, 2 H) 5.82 - 5.95 (m, 2 H) 7.03 (d, J=6.40 Hz, 1 H) 7.13 (d, J=7.37 Hz, 1 H) 7.30 - 7.46 (m, 4 H) 12.07 (s, 1 H) 12.23 (s, 1 H); MS (APCI+) *m/z* 1040.3 $(M+H)^+$.



Example 3.40

dimethyl ({(2*R*,5*R*)-1-[3,5-difluoro-4-(piperidin-1-yl)phenyl]pyrrolidine-2,5-diyl}bis{(6-fluoro-1*H*-benzimidazole-5,2-diyl)(2*S*,3a*S*,6a*S*)hexahydrocyclopenta[*b*]pyrrole-2,1(2*H*)-diyl[(1*S*)-1-cyclopentyl-2-oxoethane-2,1-diyl]})biscarbamate

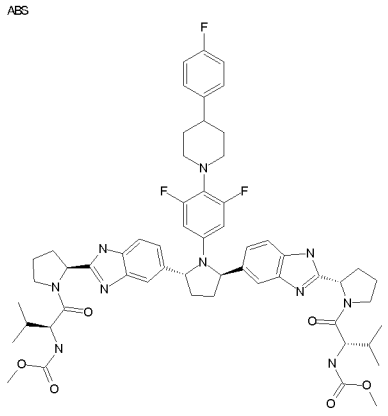
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.12 - 1.25 (m, 8 H) 1.35 - 1.64 (m, 18 H) 1.70 - 1.88 (m, 6 H) 1.92 - 2.15 (m, 8 H) 2.36 - 2.46 (m, 4 H) 2.78 (s, 6 H) 3.53 (s, 6 H) 4.07 (dt, J=18.38, 9.24 Hz, 2 H) 4.72 - 4.83 (m, 2 H) 5.07 (t, J=8.08 Hz, 2 H) 5.46 - 5.65 (m, 2 H) 5.81 - 5.91 (m, 2 H) 7.06 (d, J=6.07 Hz, 1 H) 7.11 - 7.19 (m, 1 H) 7.34 (dd, J=10.63, 4.88 Hz, 1 H) 7.43 (dd, J=11.22, 7.21 Hz, 1 H) 7.51 (dd, J=13.99, 7.92 Hz, 2 H) 11.95 (s, 1 H) 12.20 (s, 1 H); MS (ESI+) *m/z* 1119.4 $(M+H)^+$.



Example 3.41

dimethyl ({(2*R*,5*R*)-1-[3,5-difluoro-4-(piperidin-1-yl)phenyl]pyrrolidine-2,5-diyl}bis{(6-fluoro-1*H*-benzimidazole-5,2-diyl)(2*S*,3a*S*,6a*S*)hexahydrocyclopenta[*b*]pyrrole-2,1(2*H*)-diyl[(1*S*)-2-oxo-1-(tetrahydro-2*H*-pyran-4-yl)ethane-2,1-diyl]})biscarbamate

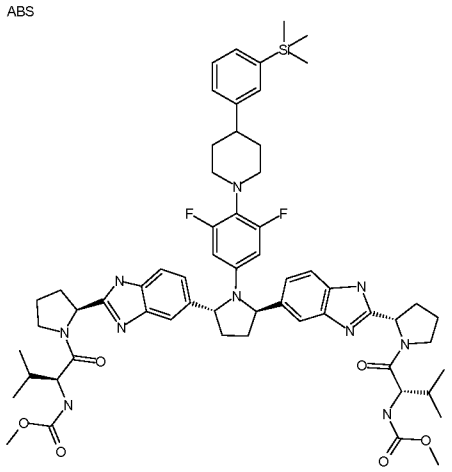
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.30 - 1.65 (m, 18 H) 1.69 - 1.94 (m, 12 H) 2.05 - 2.15 (m, 4 H) 2.37 - 2.45 (m, 4 H) 2.73 - 2.87 (m, 6 H) 2.97 - 3.11 (m, 3 H) 3.53 (s, 6 H) 3.77 (dd, J=27.65, 10.08 Hz, 4 H) 4.06 - 4.14 (m, 2 H) 4.71 - 4.81 (m, 2 H) 5.07 (t, J=8.35 Hz, 2 H) 5.43 - 5.65 (m, 2 H) 5.78 - 5.92 (m, 2 H) 6.99 - 7.05 (m, 1 H) 7.09 (t, J=6.94 Hz, 1 H) 7.33 (dd, J=10.03, 6.13 Hz, 1 H) 7.50 (dd, J=18.16, 7.86 Hz, 2 H) 11.99 (s, 1 H) 12.29 (d, J=5.75 Hz, 1 H); MS (ESI+) *m/z* 1151.4 $(M+H)^+$.



Example 3.42

methyl {(2*S*)-1-[(2*S*)-2-{5-[(2*R*,5*R*)-1-{3,5-difluoro-4-[4-(4-fluorophenyl)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

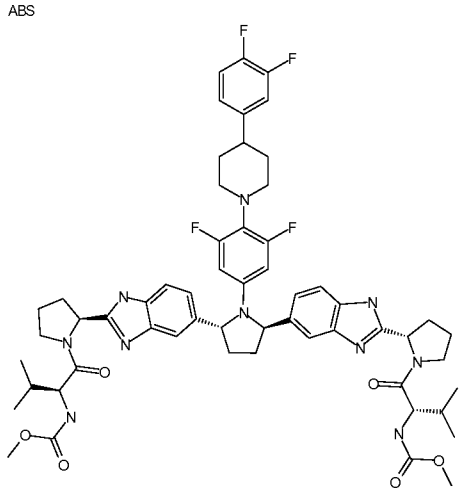
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.08 (d, *J* = 18.9, 2H), 7.50 (d, *J* = 8.0, 1H), 7.41 (d, *J* = 8.3, 1H), 7.33 – 7.18 (m, 6H), 7.13 – 7.01 (m, 4H), 5.91 (d, *J* = 13.1, 2H), 5.42 – 5.33 (m, 2H), 5.19 – 5.10 (m, 2H), 4.06 (t, *J* = 8.6, 2H), 3.86 – 3.77 (m, 4H), 3.53 (s, 6H), 3.03 – 2.83 (m, 5H), 2.28 – 1.54 (m, 18H), 0.91 – 0.73 (m, 12H); MS (ESI+) *m/z* 1045.4 $(M+H)^+$.



Example 3.43

methyl {(2*S*)-1-[(2*S*)-2-{5-[(2*R*,5*R*)-1-(3,5-difluoro-4-{4-[3-(trimethylsilyl)phenyl]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

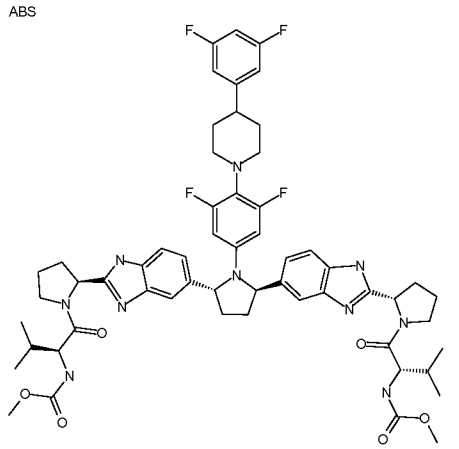
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.31 – 12.04 (m, 2H), 7.49 (d, *J* = 8.4, 1H), 7.40 (d, *J* = 8.2, 1H), 7.34 – 7.17 (m, 8H), 7.11 – 7.04 (m, 2H), 5.95 – 5.86 (m, 2H), 5.43 – 5.31 (m, 2H), 5.18 – 5.09 (m, 2H), 4.05 (t, *J* = 8.3, 2H), 3.86 – 3.76 (m, 4H), 3.52 (s, 6H), 3.12 – 2.82 (m, 4H), 2.58 – 2.52 (m, 2H), 2.26 – 1.83 (m, 11H), 1.72 – 1.58 (m, 6H), 0.90 – 0.73 (m, 12H), 0.20 (s, 9H); MS (ESI+) *m/z* 1099.4 $(M+H)^+$.



Example 3.44

methyl {(2*S*)-1-[(2*S*)-2-{5-[(2*R*,5*R*)-1-{4-[4-(3,4-difluorophenyl)piperidin-1-yl]-3,5-difluorophenyl}-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

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.32 – 12.04 (m, 2H), 7.50 (d, *J* = 8.5, 1H), 7.41 (d, *J* = 8.3, 1H), 7.36 – 7.25 (m, 5H), 7.21 (s, 1H), 7.12 – 7.05 (m, 3H), 5.91 (d, *J* = 12.8, 2H), 5.37 (dd, *J* = 6.0, 2.1, 2H), 5.18 – 5.11 (m, 2H), 4.06 (t, *J* = 8.3, 2H), 3.86 – 3.79 (m, 4H), 3.53 (s, 6H), 3.12 – 2.83 (m, 4H), 2.27 – 2.10 (m, 4H), 2.08 – 1.49 (m, 15H), 0.93 – 0.67 (m, 12H); MS (ESI+) *m/z* 1063.3 $(M+H)^+$.

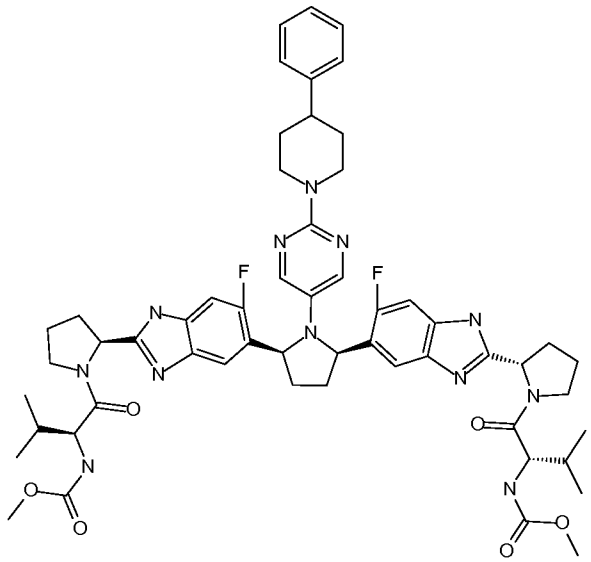


Example 3.45

methyl {(2*S*)-1-[(2*S*)-2-{5-[(2*R*,5*R*)-1-{4-[4-(3,5-difluorophenyl)piperidin-1-yl]-3,5-difluorophenyl}-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

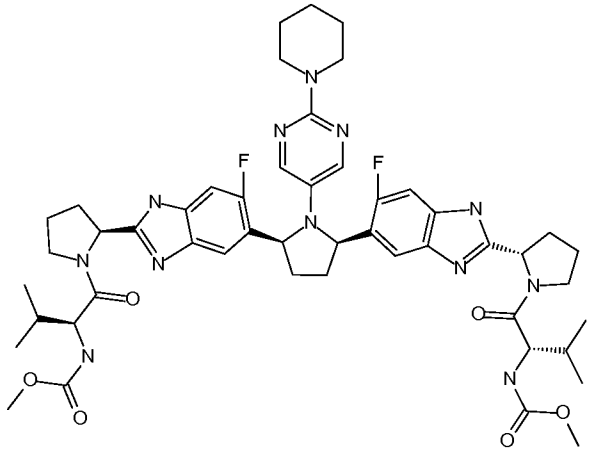
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.47 – 11.91 (m, 2H), 7.52 – 7.40 (m, 2H), 7.36 – 7.19 (m, 4H), 7.10 (d, *J* = 7.9, 2H), 7.04 – 6.92 (m, 3H), 5.92 (d, *J* = 12.7, 2H), 5.46 – 5.32 (m, 2H), 5.20 – 5.10 (m, 2H), 4.06 (t, *J* = 8.3, 2H), 3.89 – 3.75 (m, 4H), 3.53 (s, 6H), 3.13 – 2.82 (m, 4H), 2.63 – 2.54 (m, 3H), 2.28 – 2.12 (m, 4H), 2.08 – 1.84 (m, 6H), 1.77 – 1.56 (m, 6H), 0.91 – 0.71 (m, 12H); MS (ESI+) *m/z* 1063.4 $(M+H)^+$.



Example 3.46

methyl {(2*S*)-1-[(2*S*)-2-(6-fluoro-5-{(2*R*,5*S*)-5-{6-fluoro-2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1*H*-benzimidazol-5-yl}-1-[2-(4-phenylpiperidin-1-yl)pyrimidin-5-yl]pyrrolidin-2-yl}-1*H*-benzimidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

1H NMR (400 MHz, DMSO) δ = 12.42 – 12.16 (m, 2H), 7.81 – 7.55 (m, 4H), 7.45 – 7.12 (m, 9H), 5.23 – 5.06 (m, 2H), 5.02 – 4.86 (m, 2H), 4.57 – 4.45 (m, 2H), 4.13 – 3.96 (m, 2H), 3.92 – 3.70 (m, 4H), 3.53 (s, 6H), 2.75 (t, J=12.8, 2H), 2.62 – 2.54 (m, J=8.1, 2H), 2.28 – 1.59 (m, 15H), 1.53 – 1.36 (m, 2H), 0.98 – 0.66 (m, 12H). MS (ESI; M+H) m/z = 1029.4.

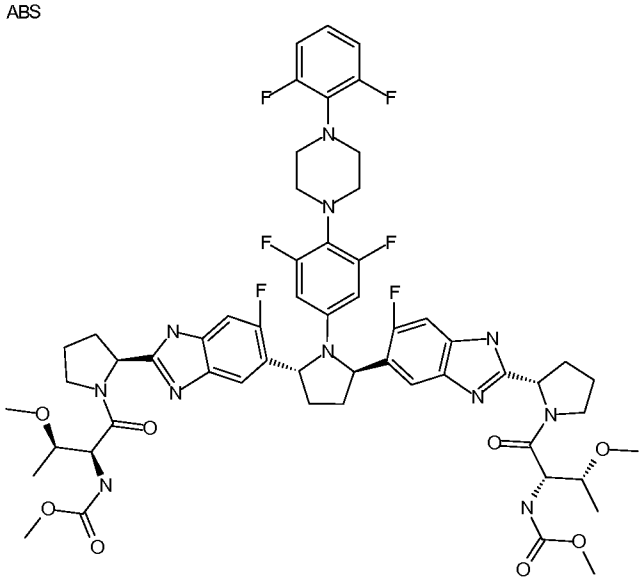


Example 3.47

methyl {(2*S*)-1-[(2*S*)-2-(6-fluoro-5-{(2*R*,5*S*)-5-{6-fluoro-2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1*H*-benzimidazol-5-yl}-1-[2-(piperidin-1-yl)pyrimidin-5-yl]pyrrolidin-2-yl}-1*H*-benzimidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

1H NMR (400 MHz, DMSO) δ 12.41 – 12.15 (m, 2H), 7.79 – 7.54 (m, 4H), 7.45 – 7.24 (m, 4H), 5.20 – 5.06 (m, 2H), 5.01 – 4.85 (m, 2H), 4.12 – 4.01 (m, 2H), 3.88 – 3.73 (m, 4H), 3.52 (s, 6H), 3.50 – 3.42 (m, 4H), 2.55 (s, 2H), 2.27 – 1.77 (m, 12H), 1.51 (s, 2H), 1.38 (s, 4H), 0.93 – 0.73 (m, 12H). MS (ESI; M+H) m/z = 953.4.

ABS

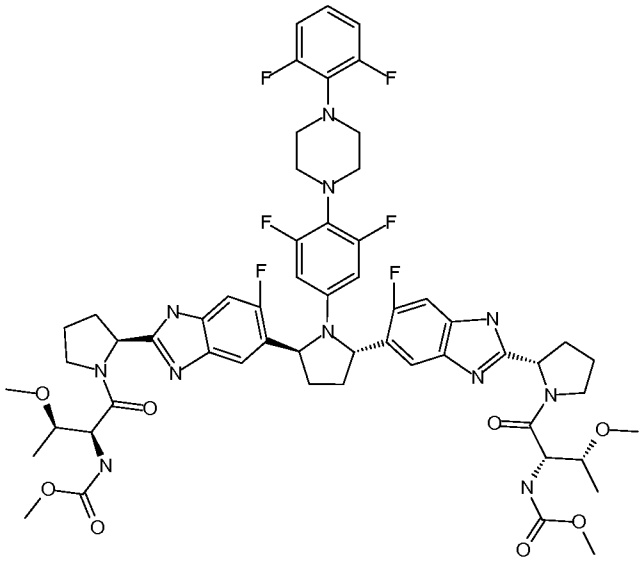


Example 3.48

methyl {(2*S*,3*R*)-1-[(2*S*)-2-{5-[(2*R*,5*R*)-1-{4-[4-(2,6-difluorophenyl)piperazin-1-yl]-3,5-difluorophenyl}-5-(6-fluoro-2-{(2*S*)-1-[*N*-(methoxycarbonyl)-*O*-methyl-L-threonyl]pyrrolidin-2-yl}-1*H*-benzimidazol-5-yl)pyrrolidin-2-yl]-6-fluoro-1*H*-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methoxy-1-oxobutan-2-yl}carbamate

1H NMR (400 MHz, DMSO) δ 12.37 – 12.08 (m, 2H), 7.41 (dd, J = 11.2, 6.3, 1H), 7.34 (dd, J = 10.4, 4.7, 1H), 7.24 (d, J = 8.3, 1H), 7.18 – 6.97 (m, 6H), 5.90 (dd, J = 22.3, 9.7, 2H), 5.57 (s, 2H), 5.16 – 5.06 (m, 2H), 4.25 (dd, J = 15.5, 8.2, 2H), 3.87 – 3.76 (m, 3H), 3.53 (s, 6H), 3.50 – 3.40 (m, 2H), 3.25 (d, J = 3.5, 1H), 3.13 (d, J = 1.1, 3H), 3.09 (s, 4H), 3.04 (d, J = 2.6, 3H), 2.96 (s, 4H), 2.55 – 2.47 (m, 2H), 2.26 – 1.71 (m, 10H), 1.08 – 0.89 (m, 6H). MS (ESI; M+H) m/z = 1132.4.

ABS

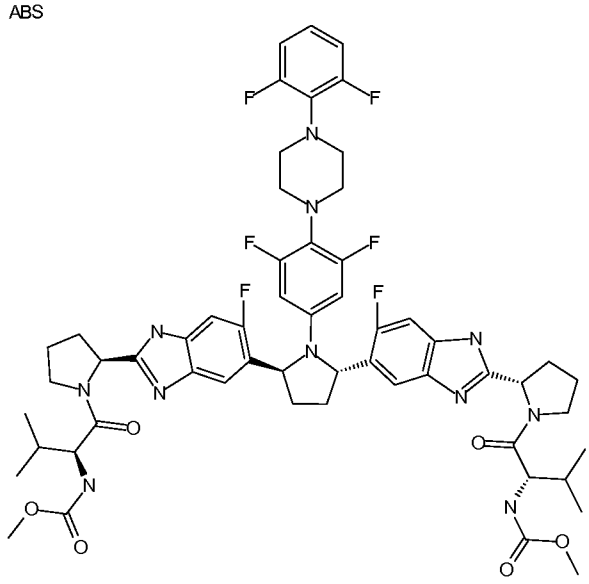


Example 3.49

methyl {(2*S*,3*R*)-1-[(2*S*)-2-{5-[(2*S*,5*S*)-1-{4-[4-(2,6-difluorophenyl)piperazin-1-yl]-3,5-difluorophenyl}-5-(6-fluoro-2-{(2*S*)-1-[*N*-(methoxycarbonyl)-*O*-methyl-L-threonyl]pyrrolidin-2-yl}-1*H*-benzimidazol-5-yl)pyrrolidin-2-yl]-6-fluoro-1*H*-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methoxy-1-oxobutan-2-yl}carbamate

1H NMR (400 MHz, DMSO) δ 12.33 – 12.04 (m, 2H), 7.41 (dd, J = 11.3, 4.7, 1H), 7.36 (dd, J = 10.5, 3.0, 1H), 7.28 (d, J = 7.9, 1H), 7.21 (d, J = 8.1, 1H), 7.16 (t, J = 7.8, 1H), 7.10 – 6.96 (m, 4H), 5.92 (q, J = 10.7, 2H), 5.69 – 5.49 (m, 2H), 5.12 (dd, J = 7.6, 4.1, 2H), 4.27 (t, J = 7.6, 2H), 3.82 (s, 3H), 3.53 (d, J = 3.1, 6H), 3.47 (d, J = 6.3, 2H), 3.24 (d, J = 2.3, 1H), 3.19 (s, 3H), 3.13 (s, 3H), 3.09 (s, 4H), 2.96 (s, 4H), 2.46 (s, 2H), 2.28 – 1.71 (m, 10H), 1.09 – 1.00 (m, 6H). MS (ESI; M+H) m/z = 1132.4.

ABS

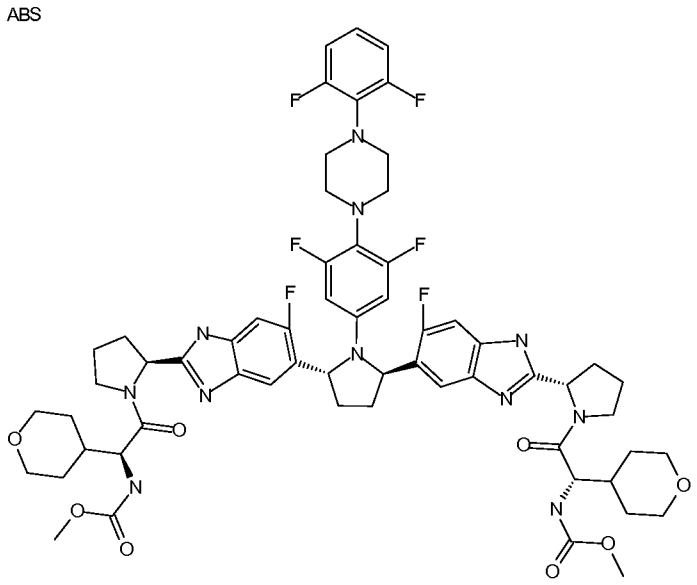


Example 3.50

methyl {(2*S*)-1-[(2*S*)-2-{5-[(2*S*,5*S*)-1-{4-[4-(2,6-difluorophenyl)piperazin-1-yl]-3,5-difluorophenyl}-5-{6-fluoro-2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1*H*-benzimidazol-5-yl}pyrrolidin-2-yl]-6-fluoro-1*H*-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

1H NMR (400 MHz, DMSO) δ 12.47 – 11.97 (m, 2H), 7.44 – 7.26 (m, 4H), 7.19 – 6.96 (m, 5H), 5.93 (q, J = 12.0, 2H), 5.67 – 5.48 (m, 2H), 5.18 – 5.07 (m, 2H), 4.05 (dd, J = 14.8, 8.3, 2H), 3.87 – 3.71 (m, 4H), 3.53 (d, J = 3.1, 6H), 3.09 (s, 4H), 2.96 (s, 4H), 2.46 (s, 2H), 2.25 – 1.70 (m, 12H), 0.89 – 0.76 (m, 12H). MS (ESI; M+H) m/z = 1100.4.

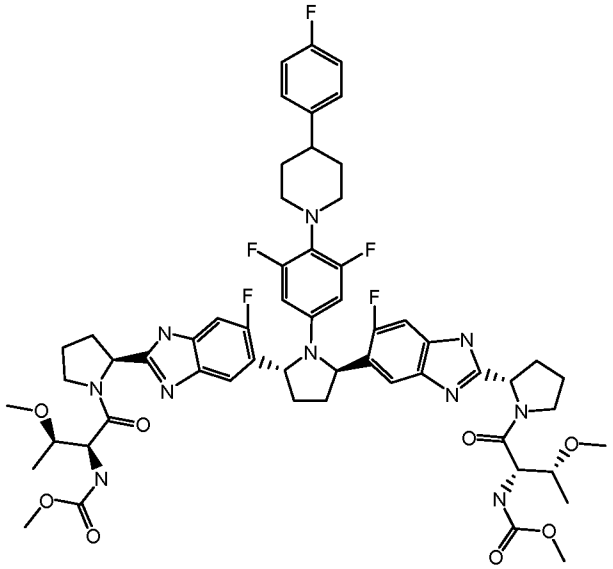
ABS



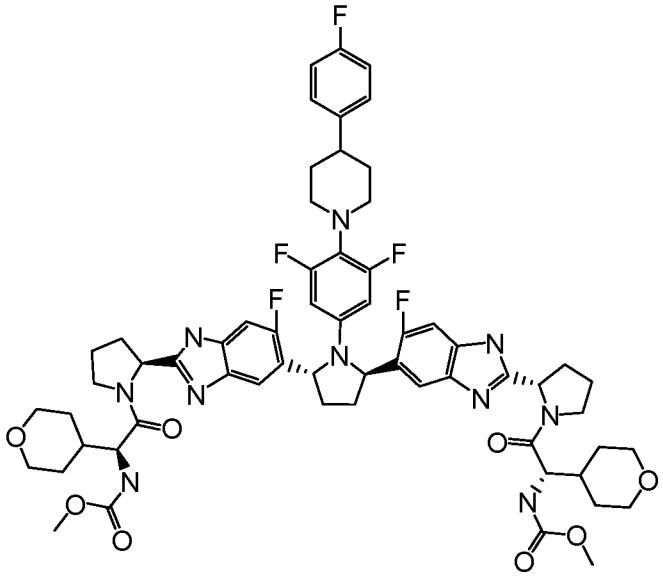
Example 3.51

dimethyl ([(2*R*,5*R*)-1-{4-[4-(2,6-difluorophenyl)piperazin-1-yl]-3,5-difluorophenyl}pyrrolidine-2,5-diyl]bis{(6-fluoro-1*H*-benzimidazole-5,2-diyl)(2*S*)pyrrolidine-2,1-diyl[(1*S*)-2-oxo-1-(tetrahydro-2*H*-pyran-4-yl)ethane-2,1-diyl]})biscarbamate

1H NMR (400 MHz, DMSO) δ 12.37 – 12.08 (m, 2H), 7.44 – 7.30 (m, 4H), 7.12 – 6.95 (m, 5H), 5.90 (q, J = 11.6, 2H), 5.66 – 5.47 (m, 2H), 5.16 – 5.05 (m, 2H), 4.17 – 4.04 (m, 2H), 3.88 – 3.61 (m, 7H), 3.52 (d, J = 3.1, 6H), 3.23 – 2.80 (m, 13H), 2.26 – 1.67 (m, 12H), 1.55 – 1.05 (m, 10H). MS (ESI; M+H) m/z = 1184.4



Example 3.52 methyl {(2*S*,3*R*)-1-[(2*S*)-2-{5-[(2*R*,5*R*)-1-{3,5-difluoro-4-[4-(4-fluorophenyl)piperidin-1-yl]phenyl}-5-(6-fluoro-2-{(2*S*)-1-[*N*-(methoxycarbonyl)-*O*-methyl-L-threonyl]pyrrolidin-2-yl}-1*H*-benzimidazol-5-yl)pyrrolidin-2-yl]-6-fluoro-1*H*-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methoxy-1-oxobutan-2-yl}carbamate1H NMR (400 MHz, DMSO) δ 12.36 – 12.06 (m, 2H), 7.41 (dd, J = 11.2, 6.3, 1H), 7.34 (dd, J = 10.4, 4.8, 1H), 7.30 – 7.20 (m, 3H), 7.17 – 6.98 (m, 5H), 5.98 – 5.82 (m, 2H), 5.65 – 5.47 (m, 2H), 5.17 – 5.06 (m, 2H), 4.25 (dd, J = 15.6, 8.1, 2H), 3.88 – 3.74 (m, 3H), 3.53 (d, J = 1.3, 6H), 3.49 – 3.38 (m, 2H), 3.31 (d, 1H), 3.25 (d, J = 3.7, 1H), 3.13 (d, J = 1.3, 3H), 3.03 (d, J = 2.3, 3H), 3.00 – 2.84 (m, 3H), 2.60 – 2.53 (m, J = 2.5, 2H), 2.26 – 1.55 (m, 14H), 1.28 – 1.13 (m, 1H), 1.10 – 0.88 (m, 6H). MS (ESI; M+H) m/z = 1113.4.



Example 3.53 dimethyl ([(2*R*,5*R*)-1-{3,5-difluoro-4-[4-(4-fluorophenyl)piperidin-1-yl]phenyl}pyrrolidine-2,5-diyl]bis{(6-fluoro-1*H*-benzimidazole-5,2-diyl)(2*S*)pyrrolidine-2,1-diyl[(1*S*)-2-oxo-1-(tetrahydro-2*H*-pyran-4-yl)ethane-2,1-diyl]})biscarbamate1H NMR (400 MHz, DMSO) δ 12.36 – 12.07 (m, 2H), 7.44 – 7.22 (m, 6H), 7.12 – 6.99 (m, 4H), 5.88 (dd, J = 23.6, 11.2, 2H), 5.64 – 5.47 (m, 2H), 5.15 – 5.06 (m, 2H), 4.17 – 4.06 (m, 2H), 3.89 – 3.61 (m, 7H), 3.52 (d, J = 3.3, 6H), 3.25 – 2.82 (m, 9H), 2.26 – 2.08 (m, 4H), 2.05 – 1.92 (m, 4H), 1.91 – 1.57 (m, 9H), 1.54 – 1.38 (m, 4H), 1.38 – 1.02 (m, 6H). MS (ESI; M+H) m/z = 1165.5.

The following Example compounds 4.1-4.62 can be made from the appropriate listed intermediate following the methods of General Procedures 12/12B.

Intermediate amines:

(*S*)-6,6'-((2*R*,5*R*)-1-(4-(cyclopentyloxy)-3-fluorophenyl)pyrrolidine-2,5-diyl)bis(2-((*S*)-pyrrolidin-2-yl)-1*H*-benzo[*d*]imidazole);

(*S*)-6,6'-((2*R*,5*R*)-1-(3-methyl-4-(piperidin-1-yl)phenyl)pyrrolidine-2,5-diyl)bis(2-((*S*)-pyrrolidin-2-yl)-1*H*-benzo[*d*]imidazole);

(*S*)-6,6'-((2*R*,5*R*)-1-(3,5-difluoro-4-((3a*R*,7a*S*)-1*H*-isoindol-2(3*H*,3a*H*,4*H*,5*H*,6*H*,7*H*,7a*H*)-yl)phenyl)pyrrolidine-2,5-diyl)bis(2-((*S*)-pyrrolidin-2-yl)-1*H*-benzo[*d*]imidazole);

(*S*)-6,6'-((2*R*,5*R*)-1-(3,5-dichloro-4-(piperidin-1-yl)phenyl)pyrrolidine-2,5-diyl)bis(2-((*S*)-pyrrolidin-2-yl)-1*H*-benzo[*d*]imidazole);

(*S*)-6,6'-((2*R*,5*R*)-1-(2,5-difluoro-4-(piperidin-1-yl)phenyl)pyrrolidine-2,5-diyl)bis(2-((*S*)-pyrrolidin-2-yl)-1*H*-benzo[*d*]imidazole);

(*S*)-6,6'-((2*R*,5*R*)-1-(4-((2*R*,6*S*)-2,6-dimethylpiperidin-1-yl)-3,5-difluorophenyl)pyrrolidine-2,5-diyl)bis(2-((*S*)-pyrrolidin-2-yl)-1*H*-benzo[*d*]imidazole);

(*S*)-6,6'-((2*R*,5*R*)-1-(2,3,5-trifluoro-4-(piperidin-1-yl)phenyl)pyrrolidine-2,5-diyl)bis(2-((*S*)-pyrrolidin-2-yl)-1*H*-benzo[*d*]imidazole);

(*S*)-6,6'-((2*R*,5*R*)-1-(4-cyclohexyl-3-fluorophenyl)pyrrolidine-2,5-diyl)bis(2-((*S*)-pyrrolidin-2-yl)-1*H*-benzo[*d*]imidazole);

(*S*)-6,6'-((2*R*,5*R*)-1-(3,4-difluorophenyl)pyrrolidine-2,5-diyl)bis(2-((*S*)-pyrrolidin-2-yl)-1*H*-benzo[*d*]imidazole);

(*S*)-6,6'-((2*R*,5*R*)-1-(4-ethoxyphenyl)pyrrolidine-2,5-diyl)bis(2-((*S*)-pyrrolidin-2-yl)-1*H*-benzo[*d*]imidazole);

(*S*)-6,6'-((2*R*,5*R*)-1-(4-(2,2-difluoroethoxy)phenyl)pyrrolidine-2,5-diyl)bis(2-((*S*)-pyrrolidin-2-yl)-1*H*-benzo[*d*]imidazole);

(*S*)-6,6'-((2*R*,5*R*)-1-(4-(3,5-dimethylpiperidin-1-yl)-3,5-difluorophenyl)pyrrolidine-2,5-diyl)bis(2-((*S*)-pyrrolidin-2-yl)-1*H*-benzo[*d*]imidazole);

6,6'-{(2*R*,5*R*)-1-[4-(pentafluoro-λ^6-sulfanyl)phenyl]pyrrolidine-2,5-diyl}bis{2-[(2*S*)-pyrrolidin-2-yl]-1*H*-benzimidazole} (ACD Name v12);

(*S*)-6,6'-((2*S*,5*S*)-1-(4-cyclopropylphenyl)pyrrolidine-2,5-diyl)bis(2-((*S*)-pyrrolidin-2-yl)-1*H*-benzo[*d*]imidazole);

(*S*)-6,6'-((2*S*,5*S*)-1-(4-cyclopropyl-3,5-difluorophenyl)pyrrolidine-2,5-diyl)bis(2-((*S*)-pyrrolidin-2-yl)-1*H*-benzo[*d*]imidazole);

(*S*)-6,6'-((2*R*,5*R*)-1-(4-*tert*-butylphenyl)pyrrolidine-2,5-diyl)bis(2-((*S*)-pyrrolidin-2-yl)-1*H*-benzo[*d*]imidazole);

1-(1-(4-((2*R*,5*R*)-2,5-bis(2-((*S*)-pyrrolidin-2-yl)-1*H*-benzo[*d*]imidazol-6-yl)pyrrolidin-1-yl)-2,6-difluorophenyl)-4-phenylpiperidin-4-yl)ethanone;

(*S*,*S*,*S*)-6,6'-((2*R*,5*R*)-1-(3,5-difluoro-4-(piperidin-1-yl)phenyl)pyrrolidine-2,5-diyl)bis(2-((2*S*,3a*S*,6a*S*)-octahydrocyclopenta[b]pyrrol-2-yl)-1*H*-benzo[*d*]imidazole);

(*S*,*S*,*S*)-6,6'-((2*R*,5*R*)-1-(4-*tert*-butylphenyl)pyrrolidine-2,5-diyl)bis(2-((2*S*,3a*S*,6a*S*)-octahydrocyclopenta[b]pyrrol-2-yl)-1*H*-benzo[*d*]imidazole);

2-(4-((2*R*,5*R*)-2,5-bis(2-((*S*)-pyrrolidin-2-yl)-1*H*-benzo[*d*]imidazol-6-yl)pyrrolidin-1-yl)-2,6-difluorophenyl)-2-azabicyclo[2.2.2]octane;

(*S*)-6,6'-((2*R*,5*R*)-1-(3,5-difluoro-4-(4-isopropylpiperidin-1-yl)phenyl)pyrrolidine-2,5-diyl)bis(2-((*S*)-pyrrolidin-2-yl)-1*H*-benzo[*d*]imidazole);

(*S*)-6,6'-((2*R*,5*R*)-1-(4-(4,4-dimethylpiperidin-1-yl)-3,5-difluorophenyl)pyrrolidine-2,5-diyl)bis(2-((*S*)-pyrrolidin-2-yl)-1*H*-benzo[*d*]imidazole);

(*S*)-6,6'-((2*R*,5*R*)-1-(4-(3,3-dimethylazetidin-1-yl)-3,5-difluorophenyl)pyrrolidine-2,5-diyl)bis(2-((*S*)-pyrrolidin-2-yl)-1*H*-benzo[*d*]imidazole);

(*S*)-6,6'-((2*R*,5*R*)-1-(4-(4-phenylpiperidin-1-yl)phenyl)pyrrolidine-2,5-diyl)bis(2-((*S*)-pyrrolidin-2-yl)-1*H*-benzo[*d*]imidazole);

(S)-6,6'-((2R,5R)-1-(3,5-difluoro-4-(4-(3-phenylpropyl)piperidin-1-yl)phenyl)pyrrolidine-2,5-diyl)bis(5-fluoro-2-((S)-pyrrolidin-2-yl)-1H-benzo[d]imidazole);

(S)-6,6'-((2R,5R)-1-(4-(4-*tert*-butylpiperidin-1-yl)-3,5-difluorophenyl)pyrrolidine-2,5-diyl)bis(5-fluoro-2-((S)-pyrrolidin-2-yl)-1H-benzo[d]imidazole);

(S)-6,6'-((2R,5R)-1-(3,5-difluoro-4-(4-(naphthalen-2-yl)piperidin-1-yl)phenyl)pyrrolidine-2,5-diyl)bis(5-fluoro-2-((S)-pyrrolidin-2-yl)-1H-benzo[d]imidazole);

(S)-6,6'-((2R,5R)-1-(4-(2,3-dihydrospiro[indene-1,4'-piperidine]-1'-yl)-3,5-difluorophenyl)pyrrolidine-2,5-diyl)bis(5-fluoro-2-((S)-pyrrolidin-2-yl)-1H-benzo[d]imidazole);

(S)-6,6'-((2R,5R)-1-(3,5-difluoro-4-(3-phenylpiperidin-1-yl)phenyl)pyrrolidine-2,5-diyl)bis(2-((S)-pyrrolidin-2-yl)-1H-benzo[d]imidazole);

(S)-6,6'-((2R,5R)-1-(3,5-difluoro-4-(3-phenylpyrrolidin-1-yl)phenyl)pyrrolidine-2,5-diyl)bis(2-((S)-pyrrolidin-2-yl)-1H-benzo[d]imidazole);

(S)-6,6'-((2R,5R)-1-(3,5-difluoro-4-(4-(4-methoxyphenyl)piperidin-1-yl)phenyl)pyrrolidine-2,5-diyl)bis(2-((S)-pyrrolidin-2-yl)-1H-benzo[d]imidazole);

(S)-6,6'-((2R,5R)-1-(3,5-difluoro-4-(4-fluoro-4-phenylpiperidin-1-yl)phenyl)pyrrolidine-2,5-diyl)bis(2-((S)-pyrrolidin-2-yl)-1H-benzo[d]imidazole);

(S)-6,6'-((2R,5R)-1-(4-(4-fluoro-4-phenylpiperidin-1-yl)phenyl)pyrrolidine-2,5-diyl)bis(2-((S)-pyrrolidin-2-yl)-1H-benzo[d]imidazole);

(S)-6,6'-((2R,5R)-1-(3,5-difluoro-4-(4-(fluorodiphenylmethyl)piperidin-1-yl)phenyl)pyrrolidine-2,5-diyl)bis(5-fluoro-2-((S)-pyrrolidin-2-yl)-1H-benzo[d]imidazole);

(S)-6,6'-((2R,5R)-1-(3,5-difluoro-4-(4-phenylpiperidin-1-yl)phenyl)pyrrolidine-2,5-diyl)bis(5-fluoro-2-((S)-pyrrolidin-2-yl)-1H-benzo[d]imidazole);

(S)-6,6'-((2R,5R)-1-(4-(benzyloxy)phenyl)pyrrolidine-2,5-diyl)bis(2-((S)-pyrrolidin-2-yl)-1H-benzo[d]imidazole);

(S)-6,6'-((2R,5R)-1-(3,5-difluoro-4-(4-(4-(trifluoromethyl)phenyl)piperazin-1-yl)phenyl)pyrrolidine-2,5-diyl)bis(5-fluoro-2-((S)-pyrrolidin-2-yl)-1H-benzo[d]imidazole);

6-((2R,5R)-1-(3,5-difluoro-4-(piperidin-1-yl)phenyl)-5-(2-((S)-pyrrolidin-2-yl)-1H-benzo[d]imidazol-6-yl)pyrrolidin-2-yl)-5-fluoro-2-((S)-pyrrolidin-2-yl)-1H-benzo[d]imidazole;

(S)-6,6'-((2R,5R)-1-(4-(4-benzylpiperidin-1-yl)-3,5-difluorophenyl)pyrrolidine-2,5-diyl)bis(5-fluoro-2-((S)-pyrrolidin-2-yl)-1H-benzo[d]imidazole);

(S)-6,6'-((2R,5R)-1-(4-(4-benzylpiperidin-1-yl)-3,5-difluorophenyl)pyrrolidine-2,5-diyl)bis(2-((S)-pyrrolidin-2-yl)-1H-benzo[d]imidazole);

(S)-6,6'-((2S,5R)-1-(3,5-difluoro-4-(4-phenylpiperidin-1-yl)phenyl)pyrrolidine-2,5-diyl)bis(2-((S)-pyrrolidin-2-yl)-1H-benzo[d]imidazole);

4-(4-((2R,5R)-2,5-bis(2-((S)-pyrrolidin-2-yl)-1H-benzo[d]imidazol-6-yl)pyrrolidin-1-yl)-2,6-difluorophenyl)-2-phenylmorpholine;

(S)-6,6'-((2R,5R)-1-(3,5-difluoro-4-(2-phenylpiperidin-1-yl)phenyl)pyrrolidine-2,5-diyl)bis(2-((S)-pyrrolidin-2-yl)-1H-benzo[d]imidazole);

(2S,6R)-4-(4-((2R,5R)-2,5-bis(5-fluoro-2-((S)-pyrrolidin-2-yl)-1H-benzo[d]imidazol-6-yl)pyrrolidin-1-yl)-2,6-difluorophenyl)-2,6-dimethylmorpholine;

(S)-6,6'-((2R,5R)-1-(3,5-difluoro-4-(3-azaspiro[5.5]undecan-3-yl)phenyl)pyrrolidine-2,5-diyl)bis(5-fluoro-2-((S)-pyrrolidin-2-yl)-1H-benzo[d]imidazole);

(S)-6,6'-((2R,5R)-1-(4-(4-cyclohexylpiperidin-1-yl)-3,5-difluorophenyl)pyrrolidine-2,5-diyl)bis(5-fluoro-2-((S)-pyrrolidin-2-yl)-1H-benzo[d]imidazole);

(S)-4-(4-((2R,5R)-2,5-bis(5-fluoro-2-((S)-pyrrolidin-2-yl)-1H-benzo[d]imidazol-6-yl)pyrrolidin-1-yl)-2,6-difluorophenyl)-2-phenylmorpholine;

(S)-6,6'-((2S,5R)-1-(3,5-difluoro-4-(piperidin-1-yl)phenyl)pyrrolidine-2,5-diyl)bis(5-fluoro-2-((S)-pyrrolidin-2-yl)-1H-benzo[d]imidazole);

(S)-6,6'-((2R,5R)-1-(3,5-difluoro-4-(4-phenylpiperazin-1-yl)phenyl)pyrrolidine-2,5-diyl)bis(2-((S)-pyrrolidin-2-yl)-1H-benzo[d]imidazole);

(S,R)-6,6'-((2R,5R)-1-(3,5-difluoro-4-(piperidin-1-yl)phenyl)pyrrolidine-2,5-diyl)bis(2-((2S,4R)-4-fluoropyrrolidin-2-yl)-1H-benzo[d]imidazole);

(S)-6,6'-((2R,5R)-1-(3,5-difluoro-4-(4-(pyrimidin-2-yl)piperazin-1-yl)phenyl)pyrrolidine-2,5-diyl)bis(5-fluoro-2-((S)-pyrrolidin-2-yl)-1H-benzo[d]imidazole);

(S)-6,6'-((2R,5R)-1-(4-(4-(2,4-difluorophenyl)piperidin-1-yl)-3,5-difluorophenyl)pyrrolidine-2,5-diyl)bis(5-fluoro-2-((S)-pyrrolidin-2-yl)-1H-benzo[d]imidazole);

(S)-6,6'-((2R,5R)-1-(3,5-difluoro-4-(4-(4-fluorophenyl)piperidin-1-yl)phenyl)pyrrolidine-2,5-diyl)bis(5-fluoro-2-((S)-pyrrolidin-2-yl)-1H-benzo[d]imidazole).

(S)-6,6'-((2R,5R)-1-(3,5-difluoro-4-(4-(5-methylthiophen-2-yl)piperidin-1-yl)phenyl)pyrrolidine-2,5-diyl)bis(5-fluoro-2-((S)-pyrrolidin-2-yl)-1H-benzo[d]imidazole); and

(S)-6,6'-((2R,5R)-1-(3,5-difluoro-4-(4-fluoro-4-phenylpiperidin-1-yl)phenyl)pyrrolidine-2,5-diyl)bis(5-fluoro-2-((S)-pyrrolidin-2-yl)-1H-benzo[d]imidazole).

Intermediate acids:

(*S*)-2-(methoxycarbonylamino)-3-methylbutanoic acid;

(*S*)-2-(methoxycarbonylamino)-2-(tetrahydro-2H-pyran-4-yl)acetic acid;

(2*S*,3*R*)-3-methoxy-2-(methoxycarbonylamino)butanoic acid;

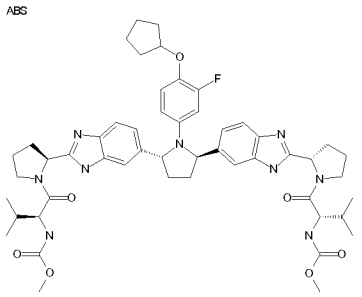
(*S*)-2-cyclopropyl-2-(methoxycarbonylamino)acetic acid;

(2S,3R)-3-*tert*-butoxy-2-(methoxycarbonylamino)butanoic acid;

(*S*)-2-(methoxycarbonylamino)-2-(tetrahydro-2*H*-pyran-4-yl)acetic acid;

(*S*)-2-cyclopentyl-2-(methoxycarbonylamino)acetic acid; and

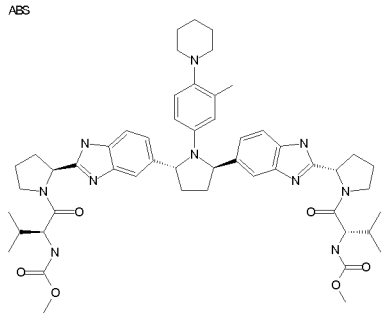
(2*S*,3*R*)-3-methoxy-2-(methoxycarbonylamino)butanoic acid.



Example 4.1

methyl {(2*S*)-1-[(2*S*)-2-{6-[(2*R*,5*R*)-1-[4-(cyclopentyloxy)-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

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.74 - 0.89 (m, 12 H), 1.37 - 1.77 (m, 12 H), 1.81 - 2.06 (m, 6 H), 2.11 - 2.29 (m, 4 H), 3.54 (s, 6 H), 3.72 - 3.92 (m, 4 H), 3.95 - 4.16 (m, 2 H), 4.40 - 4.52 (m, 1 H), 5.07 - 5.23 (m, 2 H), 5.26 - 5.44 (m, 2 H), 5.96 - 6.17 (m, 2 H), 6.63 - 6.98 (m, 2 H), 7.00 - 7.16 (m, 2 H), 7.16 - 7.35 (m, 4 H), 7.35 - 7.54 (m, *J*=31.23 Hz, 2 H), 11.93 - 12.32 (m, 2 H); MS (ESI) *m/z* = 934.5 $(M+H)^+$.

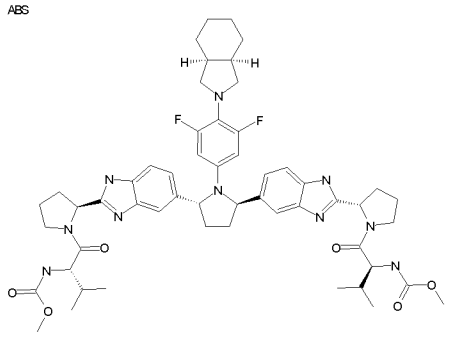


Example 4.2

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-[3-methyl-4-(piperidin-1-yl)phenyl]pyrrolidin-2-yl}-1*H*-benzimidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.74 - 0.89 (m, 12 H) 1.35 - 1.41 (m, 2 H) 1.44 - 1.52 (m, 4 H) 1.62 - 1.67 (m, 2 H) 1.86 - 1.93 (m, 5 H) 1.94 - 2.03 (m, 4 H) 2.15 - 2.24 (m, 4 H) 2.48 - 2.54 (m, 6 H) 3.52 (s, 6 H) 3.74 - 3.84 (m, 4 H) 4.00 - 4.09 (m, 2 H) 5.06 - 5.18 (m, 2 H) 5.28 - 5.37 (m, 2 H) 6.07 -

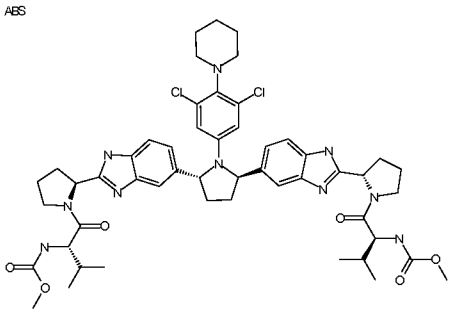
6.12 (m, 1 H) 6.17 - 6.21 (m, 1 H) 6.56 - 6.62 (m, 1 H) 6.99 - 7.30 (m, 6 H) 7.35 (d, J=8.24 Hz, 1 H) 7.44 (d, J=8.24 Hz, 1 H) 11.94 - 12.04 (m, 2 H); MS (ESI+) *m/z* 929.5 $(M+H)^+$.



Example 4.3

methyl {(2*S*)-1-[(2*S*)-2-{5-[(2*R*,5*R*)-1-{3,5-difluoro-4-[(3a*R*,7a*S*)-octahydro-2H-isoindol-2-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

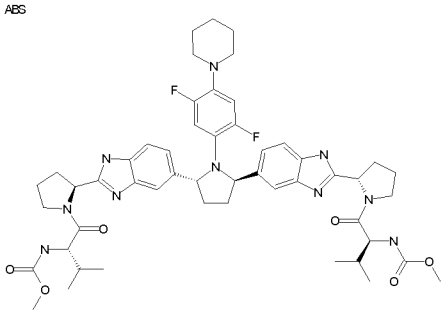
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.71 - 0.94 (m, 12 H) 1.22 - 1.31 (m, 2 H) 1.35 - 1.53 (m, 6 H) 1.66 - 1.74 (m, 2 H) 1.86 - 2.24 (m, 12 H) 2.90 - 2.97 (m, 2 H) 3.05 - 3.15 (m, 2 H) 3.36 - 3.42 (m, 2 H) 3.54 (s, 6 H) 3.77 - 3.86 (m, 4 H) 4.06 (t, J=8.29 Hz, 2 H) 5.09 - 5.20 (m, 2 H) 5.29 - 5.40 (m, 2 H) 5.89 (d, J=12.25 Hz, 2 H) 7.03 - 7.13 (m, 2 H) 7.18 - 7.33 (m, 4 H) 7.40 (d, J=8.13 Hz, 1 H) 7.48 (d, J=8.24 Hz, 1 H) 11.95 - 12.25 (m, 2 H); MS (ESI+) *m/z* 991.5 $(M+H)^+$.



Example 4.4

methyl {(2*S*)-1-[(2*S*)-2-{5-[(2*R*,5*R*)-1-[3,5-dichloro-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

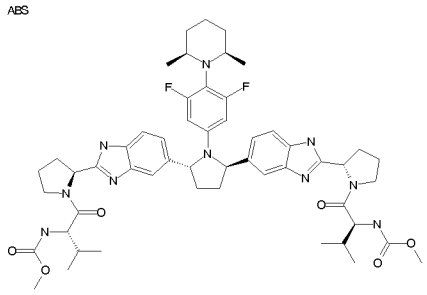
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.68 - 0.94 (m, 12 H) 1.36 - 2.28 (m, 20 H) 2.84 (s, 4 H) 3.54 (s, 6 H) 3.82 (s, 4 H) 4.04 - 4.09 (m, 2 H) 5.09 - 5.19 (m, 2 H) 5.33 - 5.50 (m, 2 H) 6.30 (t, *J*=2.49 Hz, 2 H) 6.99 - 7.57 (m, 8 H) 12.04 (s, 1 H) 12.09 (s, 1 H); MS (ESI+) *m/z* 983 $(M+H)^+$.



Example 4.5

methyl {(2*S*)-1-[(2*S*)-2-{5-[(2*R*,5*R*)-1-[2,5-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

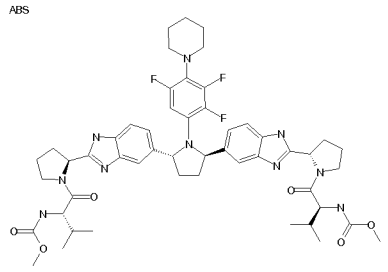
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.80 (s, 12 H) 1.08 - 2.71 (m, 24 H) 3.53 (s, 6 H) 3.81 (s, 4 H) 3.97 - 4.11 (m, 2 H) 5.13 (s, 2 H) 5.51 (s, 2 H) 6.34 - 6.70 (m, 2 H) 7.00 - 7.60 (m, 8 H) 11.87 - 12.30 (m, 2 H); MS (ESI+) *m/z* 952 $(M+H)^+$.



Example 4.6

methyl {(2*S*)-1-[(2*S*)-2-{5-[(2*R*,5*R*)-1-{4-[(2*R*,6*S*)-2,6-dimethylpiperidin-1-yl]-3,5-difluorophenyl}-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

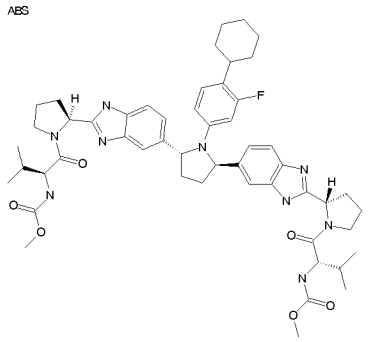
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.58 (s, 6 H) 0.73 - 0.92 (m, 12 H) 1.08 - 2.37 (m, 20 H) 3.53 (s, 6 H) 3.82 (s, 4 H) 4.06 (q, *J*=7.92 Hz, 2 H) 5.15 (s, 2 H) 5.39 (s, 2 H) 5.88 (d, *J*=13.01 Hz, 2 H) 7.02 - 7.58 (m, 10 H) 12.01 (s, 1 H) 12.18 (s, 1 H); MS (ESI+) *m/z* 979 $(M+H)^+$.



Example 4.7

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-[2,3,5-trifluoro-4-(piperidin-1-yl)phenyl]pyrrolidin-2-yl}-1*H*-benzimidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

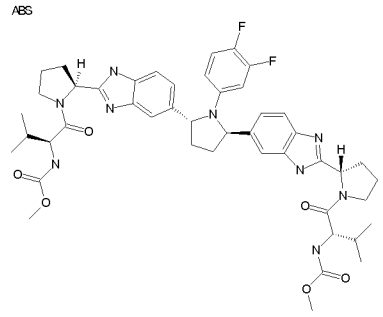
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.72 - 0.93 (m, 12 H) 1.34 - 2.38 (m, 20 H) 2.77 (s, 4 H) 3.53 (s, 6 H) 3.82 (s, 4 H) 4.00 - 4.13 (m, 2 H) 5.14 (s, 2 H) 5.56 (s, 2 H) 6.27 - 6.47 (m, 1 H) 6.97 - 7.49 (m, 8 H) 12.01 (s, 1 H) 12.08 (d, *J*=1.84 Hz, 1 H); MS (ESI+) *m/z* 970 $(M+H)^+$.



Example 4.8

methyl {(2*S*)-1-[(2*S*)-2-{5-[(2*R*,5*R*)-1-(4-cyclohexyl-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

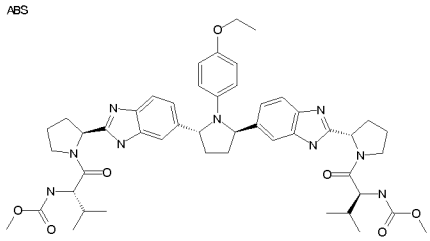
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 10.48 (m, 1 H), 10.32 (s, 1 H), 7.70 (d, *J* = 8.0 Hz, 1 H), 7.53 (s, 1 H), 7.34 (d, *J* = 8.1 Hz, 1 H), 7.13 (d, *J* = 5.5 Hz, 3 H), 6.72 (s, 1 H), 6.03 (m, 2 H), 5.40 (m, 5 H), 5.26 (d, *J* = 1.7 Hz, 3 H), 4.34 (dd, *J* = 8.7, 7.0 Hz, 2 H), 3.84 (d, *J* = 7.6 Hz, 2 H), 3.70 (s, 6 H), 3.62 (m, 3 H), 3.09 (m, 2 H), 2.57 (m, 4 H), 2.33 (m, 2 H), 2.17 (m, 5 H), 1.97 (m, 3 H), 1.73 (m, 8 H), 1.17 (m, 8 H), 0.89 (t, J = 6.4, 12 H); MS (ESI+) *m/z* (rel abundance) 933 (100, M+H), 934 (53).



Example 4.9

methyl {(2*S*)-1-[(2*S*)-2-{5-[(2*R*,5*R*)-1-(3,4-difluorophenyl)-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

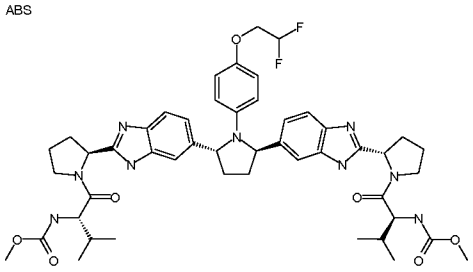
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 10.49 (d, *J* = 9.0 Hz, 1 H), 10.38 (s, 1 H), 7.70 (d, *J* = 8.1 Hz, 1 H), 7.51 (s, 1 H), 7.35 (d, *J* = 8.3 Hz, 1 H), 7.12 (dd, *J* = 10.9, 6.3 Hz, 3 H), 6.69 (dd, *J* = 9.4, 5.7 Hz, 1 H), 6.13 (d, *J* = 7.2 Hz, 1 H), 6.00 (s, 1 H), 5.41 (m, 4 H), 5.27 (m, 2 H), 4.34 (m, 2 H), 4.06 (d, *J* = 6.6 Hz, 1 H), 3.85 (m, 2 H), 3.73 (s, 6 H), 3.64 (m, 2 H), 3.08 (m, 2 H), 2.61 (m, 2 H), 2.34 (m, 2 H), 2.19 (m, 4 H), 1.96 (m, 2 H), 1.79 (m, 2 H), 1.64 (m, 4 H), 0.92 (m, 12 H); MS (ESI+) *m/z* (rel abundance) 868 (100, M+H), 869 (43).



Example 4.10

methyl {(2*S*)-1-[(2*S*)-2-{6-[(2*R*,5*R*)-1-(4-ethoxyphenyl)-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

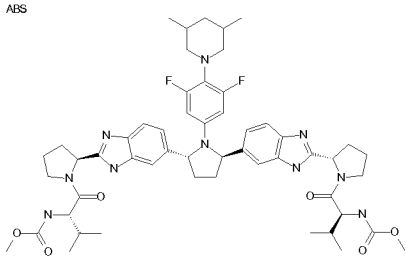
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.92 - 0.75 (m, 12H), 1.21 - 1.10 (m, 3H), 1.33 - 1.21 (m, 1H), 1.76 - 1.64 (m, 2H), 2.06 - 1.85 (m, 7H), 2.28 - 2.08 (m, 4H), 3.54 (s, 6H), 3.73 (q, J = 7.0, 2H), 3.81 (s, 4H), 4.11 - 3.99 (m, 2H), 5.18 - 5.06 (m, 2H), 5.33 (s, 2H), 6.24 (d, J = 8.9, 2H), 6.51 (dt, J = 4.9, 9.4, 2H), 7.04 (t, J = 7.7, 2H), 7.34 - 7.18 (m, 4H), 7.36 (d, J = 8.2, 1H), 7.44 (d, J = 8.2, 1H), 12.02 (s, 2H); MS (ESI) *m/z* 876 $(M+H)^+$, 874 $(M-H)^-$.



Example 4.11

methyl {(2*S*)-1-[(2*S*)-2-{6-[(2*R*,5*R*)-1-[4-(2,2-difluoroethoxy)phenyl]-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

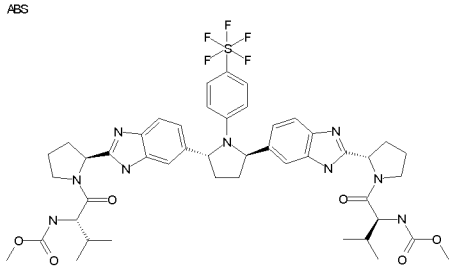
^{1}H NMR (400 MHz, methanol-d_4) δ ppm 0.85 (dd, J = 6.7, 20.0, 12H), 1.88 - 1.75 (m, 2H), 2.06 - 1.95 (m, 3H), 2.22 - 2.06 (m, 3H), 2.34 - 2.23 (m, 2H), 2.49 - 2.34 (m, 2H), 2.71 - 2.56 (m, 2H), 3.64 (s, 6H), 4.13 - 3.76 (m, 6H), 4.22 (dd, J = 5.4, 10.3, 1H), 5.28 - 5.17 (m, 2H), 5.37 (t, J = 6.4, 2H), 5.96 (tt, J = 3.9, 55.2, 1H), 6.31 (t, J = 9.7, 2H), 6.60 - 6.51 (m, 2H), 6.98 (d, J = 8.4, 1H), 7.23 (d, J = 8.3, 2H), 7.35 (d, J = 17.8, 2H), 7.50 (d, J = 8.3, 2H); MS (ESI) *m/z* 912 $(M+H)^+$, 910 $(M-H)^-$.



Example 4.12

methyl {(2*S*)-1-[(2*S*)-2-{6-[(2*R*,5*R*)-1-[4-(3,5-dimethylpiperidin-1-yl)-3,5-difluorophenyl]-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

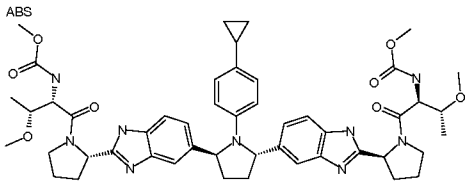
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.50 (q, J = 11.9, 1H), 0.97 - 0.64 (m, 18H), 1.32 - 1.20 (m, 2H), 1.81 - 1.46 (m, 5H), 2.09 - 1.80 (m, 6H), 2.32 - 2.13 (m, 5H), 2.75 (dd, J = 10.0, 40.2, 2H), 3.18 - 3.05 (m, 1H), 3.54 (s, 6H), 3.82 (s, 4H), 4.14 - 3.95 (m, 2H), 5.14 (s, 2H), 5.36 (d, J = 7.2, 2H), 5.88 (d, J = 12.8, 2H), 7.14 - 7.02 (m, 2H), 7.19 (s, 1H), 7.33 - 7.23 (m, 3H), 7.41 (d, J = 8.2, 1H), 7.49 (d, J = 8.2, 1H), 12.37 - 11.98 (m, 2H); MS (ESI) *m/z* 979 $(M+H)^+$.



Example 4.13

methyl {(2*S*)-1-[(2*S*)-2-(6-{(2*R*,5*R*)-5-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1*H*-benzimidazol-6-yl}-1-[4-(pentafluoro-lambda~6~-sulfanyl)phenyl]pyrrolidin-2-yl}-1*H*-benzimidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

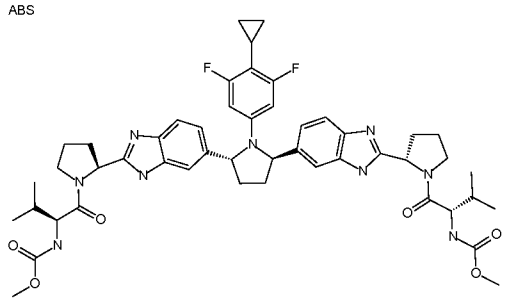
^{1}H NMR (400 MHz, DMSO-d_6) δppm 0.92 - 0.69 (m, 12H), 2.08 - 1.61 (m, 8H), 2.20 (s, 4H), 3.53 (s, 6H), 3.82 (s, 4H), 4.05 (t, J = 8.0, 2H), 5.13 (dt, J = 4.9, 9.8, 2H), 5.49 (dd, J = 10.8, 15.8, 2H), 6.37 (d, J = 8.6, 2H), 7.13 - 6.81 (m, 3H), 7.20 (d, J = 8.8, 1H), 7.28 (dd, J = 4.6, 9.9, 3H), 7.45 - 7.34 (m, 4H), 7.48 (d, J = 8.2, 1H), 12.16 (dd, J = 22.6, 68.2, 2H); MS (ESI) *m/z* 958 $(M+H)^+$, 956 $(M-H)^-$.



Example 4.14

methyl {(2*S*,3*R*)-1-[(2*S*)-2-{5-[(2*S*,5*S*)-1-(4-cyclopropylphenyl)-5-(2-{(2*S*)-1-[*N*-(methoxycarbonyl)-O-methyl-L-threonyl]pyrrolidin-2-yl}-1*H*-benzimidazol-5-yl)pyrrolidin-2-yl]-1*H*-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methoxy-1-oxobutan-2-yl}carbamate

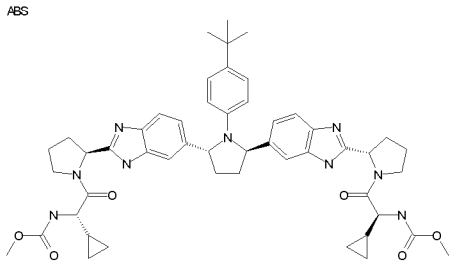
^{1}H NMR (400 MHz, DMSO- d_6) δ ppm 0.37 (m, 2 H) 0.68, (s, 2 H) 1.08 (d, 6 H) 1.54 -1.64 (m, 2 H) 1.69 (s, 2 H) 1.99 (s, 4 H) 2.17 (s, 7 H) 3.18 (s, 6 H) 3.42 - 3.53 (m, 2 H) 3.54 (s, J=1.41 Hz, 6 H) 3.84 (s, 3 H) 4.28 (s, 2 H) 5.12 (s, 2 H) 5.34 (s, 2 H) 6.22 (s, 2 H) 6.61 (s, 2 H) 7.05 (s, 2 H) 7.16 (s, 2 H) 7.36 (s, 2 H) 11.97 (s, 1 H),12.08 (s, 1H); MS (ESI+) *m/z* 904.5 $(M+H)^+$, (ESI-) *m/z* 902.3 $(M-H)^-$.



Example 4.15

methyl {(2*S*)-1-[(2*S*)-2-{6-[(2*R*,5*R*)-1-(4-cyclopropyl-3,5-difluorophenyl)-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

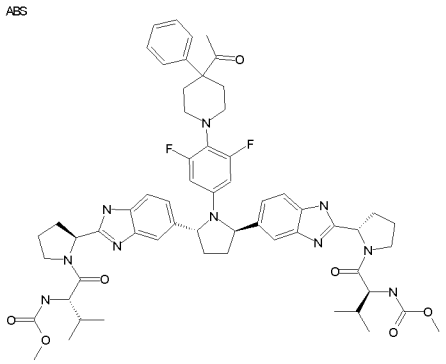
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 10.47 (br s, 1H) 10.30-10.41 (br s, 1H) 7.69 (br s, 1H) 7.49 (s, 1H) 7.30-7.43 (br s, 1H) 7.04-7.20 (m, 3H) 5.75-5.89 (m, 2H) 5.37 (m, 4H) 5.23 (s, 2H) 4.34 (t, 2H) 3.83 (m, 2H) 3.71 (s, 6H) 3.56-3.67 (m, 2H) 3.11 (m, 2H) 2.58 (br s, 2H) 2.33 (m, 2H) 2.08-2.27 (m, 4H) 2.01 (m, 2H) 1.78 (br s, 2H) 0.82-0.96 (m, 12H) 0.71 (m, 4H).



Example 4.16

dimethyl ([(2*R*,5*R*)-1-(4-*tert*-butylphenyl)pyrrolidine-2,5-diyl]bis{1*H*-benzimidazole-6,2-diyl(2*S*)pyrrolidine-2,1-diyl[(1*S*)-1-cyclopropyl-2-oxoethane-2,1-diyl]})biscarbamate

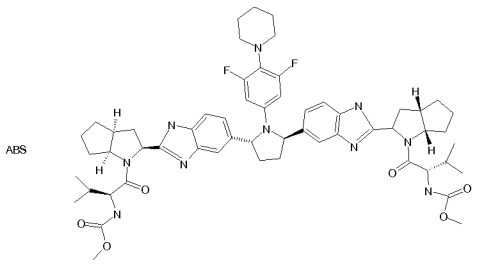
^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 0.48 - 0.24 (m, 7H), 0.89 - 0.81 (m, 1H), 1.01 (s, 3H), 1.07 (s, 6H), 1.14 (dd, J = 8.7, 16.6, 1H), 1.32 - 1.17 (m, 4H), 1.75 - 1.64 (m, 1H), 2.05 - 1.78 (m, 4H), 2.24 - 2.09 (m, 3H), 2.45 - 2.39 (m, 2H), 3.21 - 3.12 (m, 1H), 3.53 (s, 6H), 3.72 - 3.63 (m, 2H), 3.76 (s, 2H), 4.03 - 3.85 (m, 2H), 5.17 - 5.04 (m, 1H), 5.44 - 5.26 (m, 2H), 6.26 (d, J = 8.8, 1H), 6.95 - 6.81 (m, 2H), 7.06 - 6.95 (m, 1H), 7.09 (t, J = 8.3, 1H), 7.20 (d, J = 4.3, 1H), 7.35 - 7.25 (m, 1H), 7.55 - 7.36 (m, 4H), 12.28 - 11.84 (m, 2H); MS (ESI+) *m/z* 884 $(M+H)^+$, (ESI-) *m/z* 882 $(M-H)^-$.



Example 4.17

methyl {(2*S*)-1-[(2*S*)-2-{5-[(2*R*,5*R*)-1-[4-(4-acetyl-4-phenylpiperidin-1-yl)-3,5-difluorophenyl]-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

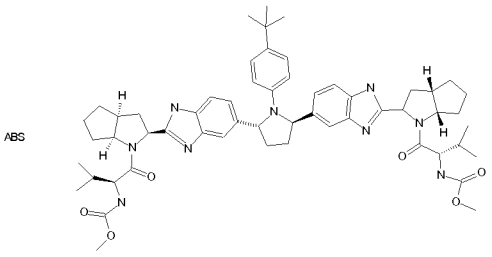
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.75 - 0.91 (m, 12 H) 1.68 (d, J=4.66 Hz, 2 H) 1.83 (s, 3 H) 1.87 - 2.38 (m, 16 H) 2.78 - 2.90 (m, 4 H) 3.54 (s, 6 H) 3.82 (s, 4 H) 4.06 (t, J=8.35 Hz, 2 H) 5.09 - 5.18 (m, 2 H) 5.27 - 5.41 (m, 2 H) 5.88 (d, J=12.90 Hz, 2 H) 7.02 - 7.51 (m, 13 H) 12.07 (d, J=16.91 Hz, 2 H); MS (ESI+) *m/z* 1070 $(M+H)^+$.



Example 4.18

methyl {(2*S*)-1-[(2*S*,3a*S*,6a*S*)-2-{5-[(2*R*,5*R*)-1-[3,5-difluoro-4-(piperidin-1-yl)phenyl]-5-{2-[(3a*S*,6a*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}octahydrocyclopenta[*b*]pyrrol-2-yl]-1*H*-benzimidazol-5-yl}pyrrolidin-2-yl]-1*H*-benzimidazol-2-yl}hexahydrocyclopenta[*b*]pyrrol-1(2*H*)-yl]-3-methyl-1-oxobutan-2-yl}carbamate

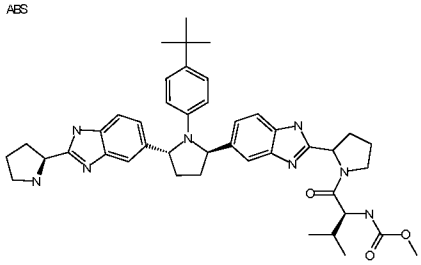
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.64 - 0.96 (m, 13 H) 1.31 - 2.18 (m, 21 H) 3.50 - 3.57 (m, 6 H) 3.93 - 4.07 (m, 2 H) 4.72 - 4.85 (m, 1 H) 5.13 (t, 1 H) 5.37 (s, 2 H) 5.90 (dd, 2 H) 7.06 (d, 2 H) 7.21 (s, 1 H) 7.33 (d, 1 H) 7.36 - 7.56 (m, *J*=8.13 Hz, 4 H) 11.96 (s, 1 H) 12.03 - 12.08 (m, 1 H) 12.24 (none, 1 H); MS (ESI+) *m/z* 1031.5 $(M+H)^+$, (ESI-) *m/z* 1029.4 $(M-H)^-$.



Example 4.19

methyl {(2*S*)-1-[(2*S*,3a*S*,6a*S*)-2-{5-[(2*R*,5*R*)-1-(4-*tert*-butylphenyl)-5-{2-[(3a*S*,6a*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}octahydrocyclopenta[*b*]pyrrol-2-yl]-1*H*-benzimidazol-5-yl}pyrrolidin-2-yl]-1*H*-benzimidazol-2-yl}hexahydrocyclopenta[*b*]pyrrol-1(2*H*)-yl]-3-methyl-1-oxobutan-2-yl}carbamate

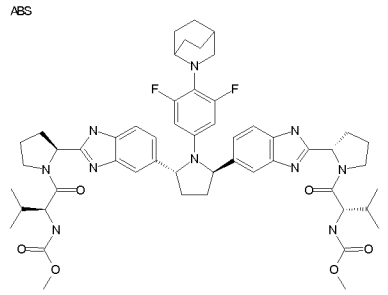
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.62 - 0.93 (m, 13 H) 1.42 - 2.16 (m, 25 H) 2.78 (s, 1 H) 3.54 (s, 6 H) 4.01 (s, 2 H) 4.77 (s, 1 H) 5.11 (t, *J*=8.08 Hz, 2 H) 5.35 (s, 2 H) 6.26 (d, *J*=8.67 Hz, 2 H) 6.83 - 6.97 (m, 2 H) 7.05 (s, 2 H) 7.21 (s, 1 H) 7.27 - 7.32 (m, 1 H) 7.34 - 7.55 (m, 4 H) 11.92 (s, 1 H) 12.01 (s, 1 H); MS (ESI+) *m/z* 968.5 $(M+H)^+$, (ESI-) *m/z* 966.4 $(M-H)^-$, 1011.7 $(M+COOH-H)^-$.



Example 4.20

methyl [(2*S*)-1-(2-{5-[(2*R*,5*R*)-1-(4-*tert*-butylphenyl)-5-{2-[(2*S*)-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

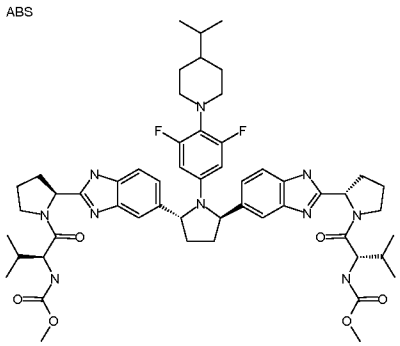
The title compound can be prepared by reacting the amine with one equivalent of an acid instead of two. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.67 - 0.90 (m, 6 H) 0.97 - 1.17 (m, 9 H) 1.53 - 2.46 (m, 13 H) 3.26 - 3.42 (m, *J*=11.39 Hz, 2 H) 3.54 (s, 3 H) 3.85 (d, *J*=4.34 Hz, 2 H) 4.07 - 4.13 (m, 1 H) 4.88 - 4.98 (m, 1 H) 5.15 - 5.23 (m, 1 H) 5.45 (d, *J*=7.16 Hz, 1 H) 5.50 (d, *J*=6.94 Hz, 1 H) 6.26 (d, *J*=8.78 Hz, 2 H) 6.92 (d, *J*=8.78 Hz, 2 H) 7.19 - 7.77 (m, 7 H) 9.15 (s, 1 H) 9.66 (s, 1 H); MS (ESI+) *m/z* 731 $(M+H)^+$.



Example 4.21

methyl {(2*S*)-1-[(2*S*)-2-{5-[(2*R*,5*R*)-1-[4-(2-azabicyclo[2.2.2]oct-2-yl)-3,5-difluorophenyl]-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

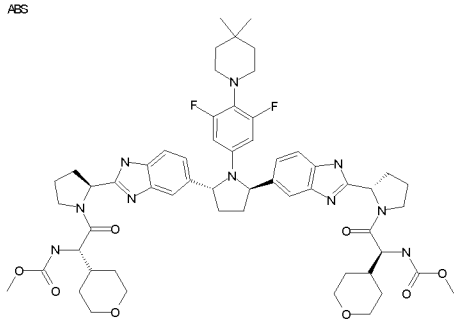
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.74 - 1.02 (m, 12 H), 1.41 - 2.27 (m, 26 H), 2.65 (s, 1 H), 3.05 - 3.26 (m, 3 H), 3.54 (s, 6 H), 4.06 (t, *J*=8.35 Hz, 2 H), 5.07 - 5.20 (m, 2 H), 5.26 - 5.45 (m, 2 H), 5.89 (d, *J*=12.36 Hz, 2 H), 7.00 - 7.14 (m, 2 H), 7.16 - 7.33 (m, 4 H), 7.44 (dd, *J*=32.42, 8.24 Hz, 2 H), 12.06 (two s, 2 H); MS (ESI+) *m/z* 977 $(M+H)^+$, (ESI-) *m/z* 975 $(M-H)^-$.



Example 4.22

methyl {(2*S*)-1-[(2*S*)-2-{5-[(2*R*,5*R*)-1-{3,5-difluoro-4-[4-(propan-2-yl)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

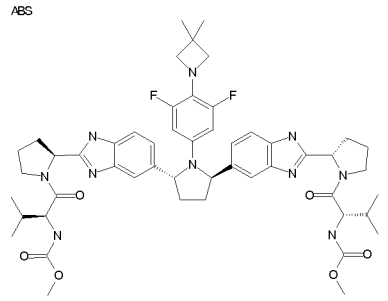
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.74 - 0.91 (m, 18 H), 0.91 - 1.05 (m, 1 H), 1.07 - 1.21 (m, 3 H), 1.31 - 1.43 (m, 1 H), 1.51 (d, *J*=11.17 Hz, 2 H), 1.63 - 1.77 (m, 2 H), 1.84 - 2.26 (m, 11 H), 2.72 - 2.88 (m, 4 H), 3.54 (s, 6 H) 3.82 (br s, 4 H), 4.06 (t, *J*=8.35 Hz, 2 H), 5.07 - 5.23 (m, 2 H), 5.29 - 5.45 (m, 2 H), 5.88 (d, *J*=12.79 Hz, 2 H), 7.02 - 7.12 (m, 2 H), 7.16 - 7.32 (m, 4 H), 7.41 (d, *J*=8.13 Hz, 1 H), 7.49 (d, *J*=8.13 Hz, 1 H), 12.07 (two s, 2 H); MS (ESI+) *m/z* 994 $(M+H)^+$.



Example 4.23

dimethyl ({(2*R*,5*R*)-1-[4-(4,4-dimethylpiperidin-1-yl)-3,5-difluorophenyl]pyrrolidine-2,5-diyl}bis{1*H*-benzimidazole-5,2-diyl(2*S*)pyrrolidine-2,1-diyl[(1*S*)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethane-2,1-diyl]})biscarbamate

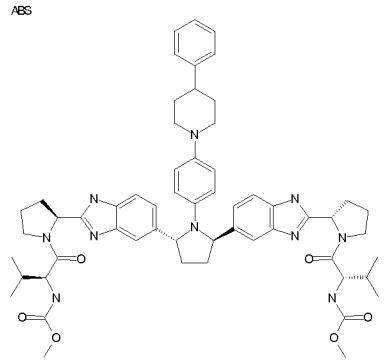
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.87 (s, 6 H), 1.18 - 1.34 (m, 9 H), 1.34 - 1.59 (m, 4 H), 1.61 - 1.93 (m, 5 H), 1.93 - 2.06 (m, 4 H), 2.09 - 2.27 (m, 4 H), 2.77 (s, 4 H), 2.90 - 3.27 (m, 4 H), 3.53 (s, 6 H), 3.62 (d, *J*=11.71 Hz, 1 H), 3.67 - 3.89 (m, 7 H), 4.14 (q, *J*=8.10 Hz, 2 H), 5.08 - 5.20 (m, 2 H), 5.30 - 5.43 (m, 2 H), 5.81 - 5.94 (m, 2 H), 7.03 - 7.52 (m, 8 H), 12.10 (two s, 2 H); MS (ESI+) *m/z* 1063 $(M+H)^+$, (ESI-) *m/z* 1061 $(M-H)^-$.



Example 4.24

methyl {(2*S*)-1-[(2*S*)-2-{5-[(2*R*,5*R*)-1-[4-(3,3-dimethylazetidin-1-yl)-3,5-difluorophenyl]-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

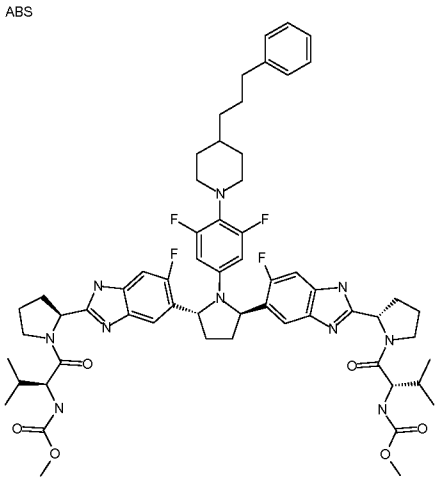
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.76-0.94 (m, 12 H), 1.13 (s, 6 H), 1.61-1.74 (m, 2 H), 1.81-2.28 (m, 9 H), 3.07-3.18 (m, 1 H), 3.49 (s, 4 H), 3.54 (s, 6 H), 3.82 (br s, 4 H), 4.07 (t, *J*=8.24 Hz, 2 H), 5.14 (t, *J*=7.54 Hz, 2 H), 5.25-5.40 (m, 2 H), 5.79-5.94 (m, 2 H), 7.01-7.07 (m, 2 H), 7.08-7.34 (m, 4 H), 7.39 (d, *J*=8.13 Hz, 1 H), 7.47 (d, *J*=8.24 Hz, 1 H), 12.05 (two s, 2 H); MS (ESI+) *m/z* 951 $(M+H)^+$.



Example 4.25

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-(4-phenylpiperidin-1-yl)phenyl]pyrrolidin-2-yl}-1*H*-benzimidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

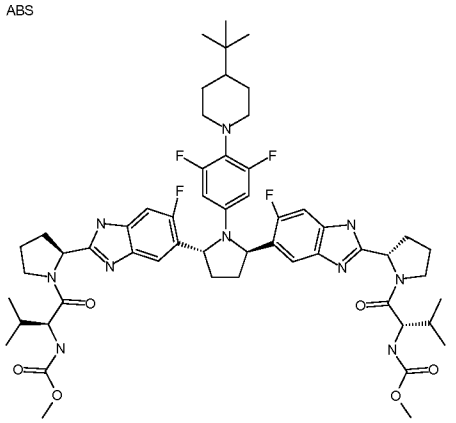
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.74 - 0.93 (m, 12 H), 1.61 - 1.79 (m, 6 H), 1.84 - 2.09 (m, 6 H), 2.11 - 2.27 (m, 4 H), 2.40 - 2.60 (m, 4 H), 3.35 (s, 3 H), 3.53 (s, 6 H), 3.82 (s, 4 H), 4.06 (t, *J*=8.29 Hz, 2 H), 5.08 - 5.19 (m, 2 H), 5.28 - 5.46 (m, 2 H), 6.26 (d, *J*=8.67 Hz, 2 H), 6.55 - 6.67 (m, 2 H), 7.06 (t, *J*=7.32 Hz, 2 H), 7.13 - 7.32 (m, 9 H), 7.37 (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* 991 $(M+H)^+$, (ESI-) *m/z* 989 $(M-H)^-$.



Example 4.26

methyl {(2*S*)-1-[(2*S*)-2-{5-[(2*R*,5*R*)-1-{3,5-difluoro-4-[4-(3-phenylpropyl)piperidin-1-yl]phenyl}-5-{6-fluoro-2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1*H*-benzimidazol-5-yl}pyrrolidin-2-yl]-6-fluoro-1*H*-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

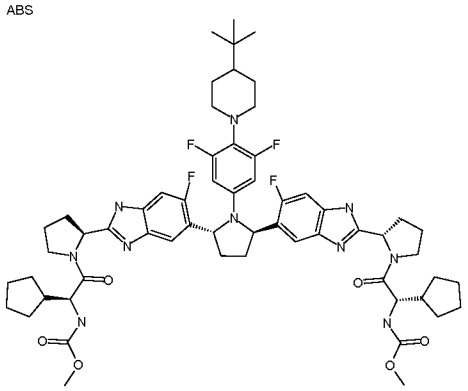
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.68 - 0.84 (m, 12 H), 0.98 - 1.30 (m, 8 H), 1.47 - 1.60 (m, 5 H), 1.63 - 2.07 (m, 9 H), 2.09 - 2.24 (m, 3 H), 2.78 (s, 4 H), 3.51 (s, 6 H), 3.71 - 3.87 (m, 4 H), 3.97 - 4.12 (m, 2 H), 5.03 - 5.17 (m, 2 H), 5.43 - 5.63 (m, 2 H), 5.78 - 5.96 (m, 2 H), 7.02 (dd, *J*=6.78, 2.33 Hz, 1 H), 7.08 - 7.19 (m, 4 H), 7.19 - 7.35 (m, 5 H), 7.39 (dd, *J*=11.28, 6.29 Hz, 1 H), 11.50 - 12.73 (m, 2 H); MS (ESI+) *m/z* 1105 $(M+H)^+$; MS (ESI-) *m/z* 1103 $(M-H)^-$.



Example 4.27

methyl {(2*S*)-1-[(2*S*)-2-{5-[(2*R*,5*R*)-1-[4-(4-*tert*-butylpiperidin-1-yl)-3,5-difluorophenyl]-5-{6-fluoro-2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1*H*-benzimidazol-5-yl}pyrrolidin-2-yl]-6-fluoro-1*H*-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

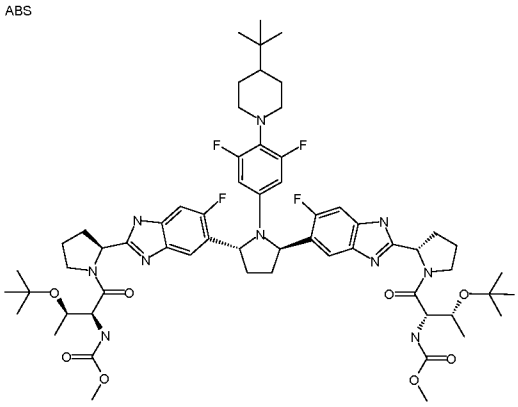
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.69 - 0.76 (m, 4 H), 0.76 - 0.91 (m, 17 H), 1.13 - 1.27 (m, 3 H), 1.55 (d, *J*=11.39 Hz, 2 H), 1.67 - 2.09 (m, 9 H), 2.11 - 2.26 (m, 4 H), 2.72 - 2.94 (m, 4 H), 3.50 - 3.57 (m, 6 H), 3.62 - 3.86 (m, 5 H), 3.99 - 4.11 (m, 2 H), 5.03 - 5.17 (m, 2 H), 5.46 - 5.63 (m, 2 H), 5.87 (dd, *J*=12.52, 7.21 Hz, 2 H), 7.03 (d, *J*=6.40 Hz, 1 H), 7.13 (d, *J*=6.94 Hz, 1 H), 7.25 - 7.37 (m, 3 H), 7.40 (dd, *J*=11.17, 6.29 Hz, 1 H), 11.67 - 12.63 (m, 2 H); MS (ESI+) *m/z* 1043 $(M+H)^+$; MS (ESI-) *m/z* 1041 $(M-H)^-$.



Example 4.28

dimethyl ({(2*R*,5*R*)-1-[4-(4-*tert*-butylpiperidin-1-yl)-3,5-difluorophenyl]pyrrolidine-2,5-diyl}bis{(6-fluoro-1*H*-benzimidazole-5,2-diyl)(2*S*)pyrrolidine-2,1-diyl[(1*S*)-1-cyclopentyl-2-oxoethane-2,1-diyl]})biscarbamate

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.80 (s, 9 H), 1.08 - 1.63 (m, 24 H), 1.65 - 1.87 (m, 3 H), 1.92 - 2.25 (m, 10 H), 2.37 - 2.45 (m, 1 H), 2.73 - 2.93 (m, 4 H), 3.60 - 3.91 (m, 4 H), 4.13 (t, *J*=8.24 Hz, 2 H), 5.11 (d, *J*=6.83 Hz, 2 H), 5.45 - 5.63 (m, 2 H), 5.80 - 5.97 (m, 2 H), 6.95 - 7.08 (m, 1 H), 7.13 (d, *J*=6.61 Hz, 1 H), 7.34 (dd, *J*=10.25, 3.74 Hz, 1 H), 7.37 - 7.46 (m, 3 H), 11.73 - 12.50 (m, 2 H); MS (ESI+) *m/z* 1095 $(M+H)^+$; MS (ESI-) *m/z* 1093 $(M-H)^-$.

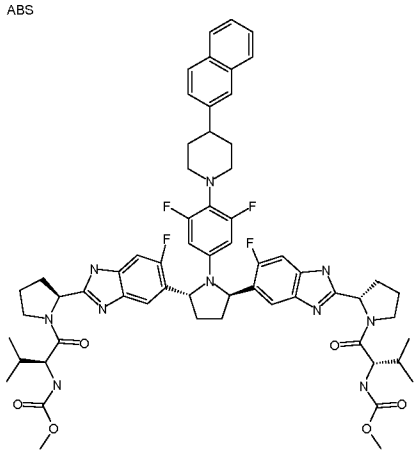


Example 4.29

methyl {(2*S*,3*R*)-3-*tert*-butoxy-1-[(2*S*)-2-(5-{(2*R*,5*R*)-5-{2-[(2*S*)-1-{(2*S*,3*R*)-3-*tert*-butoxy-2-[(methoxycarbonyl)amino]butanoyl}pyrrolidin-2-yl]-6-fluoro-1*H*-benzimidazol-5-yl}-1-[4-(4-*tert*-butylpiperidin-1-yl)-3,5-difluorophenyl]pyrrolidin-2-yl}-6-fluoro-1*H*-benzimidazol-2-yl)pyrrolidin-1-yl]-1-oxobutan-2-yl}carbamate

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.82 (d, *J*=14.64 Hz, 13 H), 0.88 - 0.96 (m, 4 H), 1.02 (s, 7 H), 1.12 (d, *J*=33.83 Hz, 11 H), 1.49 - 2.31 (m, 9 H), 2.69 - 2.93 (m, 4 H), 3.27 (s, 1 H), 3.50 - 3.57 (m, 6 H), 3.64 - 3.94 (m, 9 H), 4.03 - 4.31 (m, 3 H), 5.06 - 5.23 (m, 1 H), 5.38 - 5.69 (m, 2 H), 5.78 - 5.95

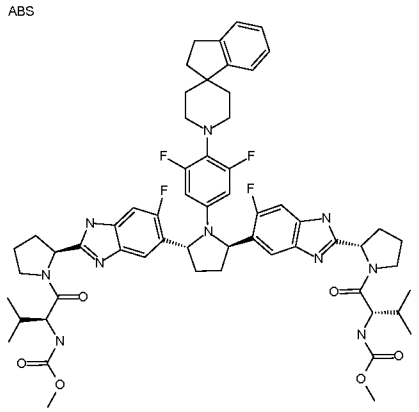
(m, 2 H), 6.46 - 6.63 (m, 1 H), 6.70 - 6.87 (m, 1 H), 6.92 - 7.04 (m, 1 H), 7.08 - 7.29 (m, 1 H), 7.34 (dd, *J*=10.63, 1.84 Hz, 1 H), 7.38 - 7.55 (m, 1 H), 11.40 - 12.88 (m, 2 H); MS (ESI+) *m/z* 1159 $(M+H)^+$.



Example 4.30

methyl {(2*S*)-1-[(2*S*)-2-{5-[(2*R*,5*R*)-1-{3,5-difluoro-4-[4-(2-naphthyl)piperidin-1-yl]phenyl}-5-{6-fluoro-2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1*H*-benzimidazol-5-yl}pyrrolidin-2-yl]-6-fluoro-1*H*-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

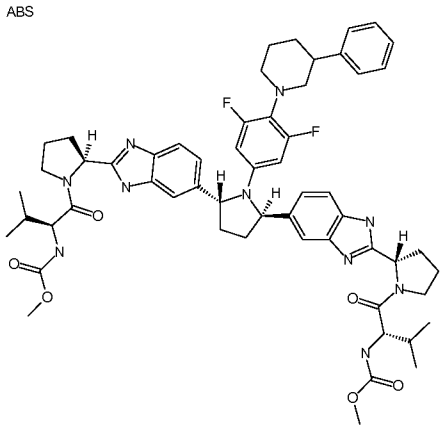
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.73 (d, J=6.51 Hz, 4 H), 0.76 - 0.85 (m, 8 H), 1.19 - 1.32 (m, 2 H), 1.69 - 2.08 (m, 12 H), 2.11 - 2.25 (m, 3 H), 2.67 - 2.78 (m, 1 H), 2.92 - 3.18 (m, 5 H), 3.52 (d, *J*=1.19 Hz, 6 H), 3.72 - 3.87 (m, 4 H), 3.99 - 4.11 (m, 2 H), 5.06 - 5.19 (m, 2 H), 5.49 - 5.67 (m, 2 H), 5.83 - 6.00 (m, 2 H), 7.01 - 7.09 (m, 1 H), 7.16 (d, *J*=7.05 Hz, 1 H), 7.25 - 7.37 (m, 3 H), 7.38 - 7.53 (m, 4 H), 7.68 - 7.93 (m, 4 H), 11.88 - 12.65 (m, 2 H); MS (ESI+) *m/z* 1113 $(M+H)^+$; MS (ESI-) *m/z* 1111 $(M-H)^-$.



Example 4.31

methyl {(2*S*)-1-[(2*S*)-2-{5-[(2*R*,5*R*)-1-[4-(2,3-dihydro-1'*H*-spiro[indene-1,4'-piperidin]-1'-yl)-3,5-difluorophenyl]-5-{6-fluoro-2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1*H*-benzimidazol-5-yl}pyrrolidin-2-yl]-6-fluoro-1*H*-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

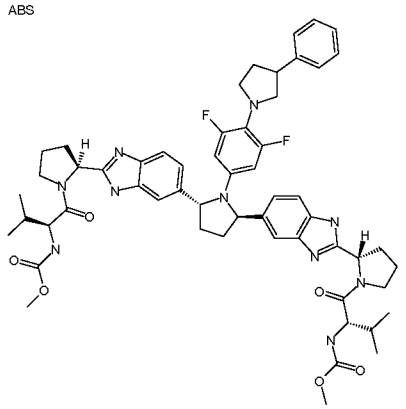
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 10.53-10.63 (m, 1H) 10.31-10.41 (m, 1H) 7.43-7.52 (m, 1H) 7.30-7.40 (m, 1H) 7.10-7.25 (m, 5H) 6.92-7.00 (m, 1H) 5.86 (d, 2H) 5.23-5.51 (m, 6H) 4.26-4.40 (m, 2H) 3.77-3.91 (m, 2H) 3.68-3.72 (m, 6H) 3.56-3.66 (m, 2H) 2.83-3.26 (m, 8H) 1.81-2.61 (m, 16H) 0.71-1.10 (m, 12H); MS (ESI) *m/z* 1089 $(M+H)^+$.



Example 4.32

methyl {(2*S*)-1-[(2*S*)-2-{5-[(2*R*,5*R*)-1-[3,5-difluoro-4-(3-phenylpiperidin-1-yl)phenyl]-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

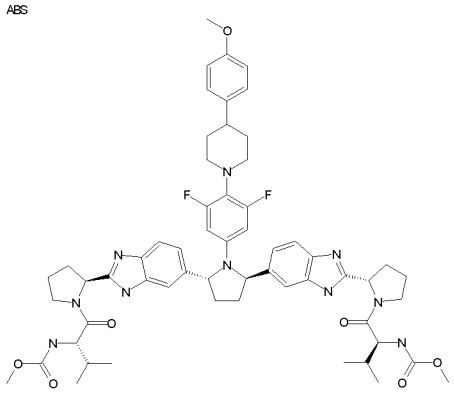
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.07 (s, 1 H), 12.01 (s, 1 H), 7.48 (d, J = 8.3 Hz, 1 H), 7.38 (m, 2 H), 7.20 (s, 8 H), 7.09 (m, 2 H), 5.90 (d, J = 12.9 Hz, 2 H), 5.36 (d, J = 7.5 Hz, 2 H), 5.14 (s, 2 H), 4.05 (t, J = 8.1 Hz, 2 H), 3.81 (s, 4 H), 3.54 (s, 6 H), 2.85 (s, 4 H), 2.18 (s, 5 H), 1.94 (m, 7 H), 1.61 (m, 5 H), 0.77 (m, 12 H); MS (ESI+) *m/z* (rel abundance) 1027 (100, $M+H)^+$.



Example 4.33

methyl {(2*S*)-1-[(2*S*)-2-{5-[(2*R*,5*R*)-1-[3,5-difluoro-4-(3-phenylpyrrolidin-1-yl)phenyl]-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

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.09 (d, J = 14.8 Hz, 2 H), 7.47 (m, 2 H), 7.45 (m, 2 H), 7.24 (m, 8 H), 7.08 (s, 2 H), 5.93 (d, J = 12.1 Hz, 2 H), 5.38 (s, 2 H), 5.15 (s, 2 H), 4.06 (t, J = 8.4 Hz, 2 H), 3.82 (s, 4 H), 3.53 (s, 6 H), 3.13 (m, 4 H), 2.19 (s, 4 H), 1.90 (m, 6 H), 1.70 (s, 2 H), 0.80 (m, 12 H); MS (ESI+) *m/z* (rel abundance) 1013 (100, M+H)$^+$, 1014 (58).

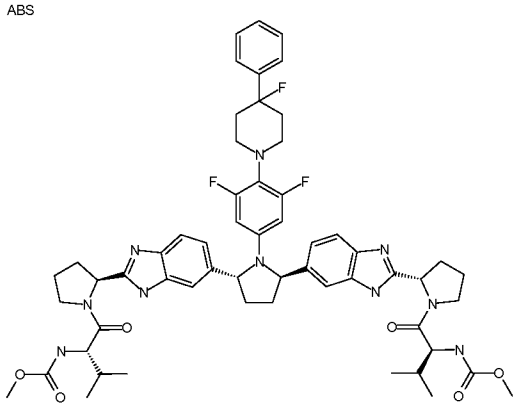


Example 4.34

methyl {(2*S*)-1-[(2*S*)-2-{6-[(2*R*,5*R*)-1-{3,5-difluoro-4-[4-(4-methoxyphenyl)piperidin-1-yl]phenyl}-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

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.97 - 0.69 (m, 12H), 1.24 (s, 1H), 1.78 - 1.50 (m, 6H), 2.10 - 1.85 (m, 7H), 2.19 (s, 4H), 2.47 - 2.38 (m, 1H), 3.03 - 2.80 (m, 4H), 3.53 (s, 6H), 3.69 (s, 3H), 3.82 (s, 4H), 4.17 - 3.93 (m, 2H), 5.22 - 5.08 (m, 2H), 5.45 - 5.29 (m, 2H), 5.91 (d, J = 12.8, 2H), 6.81 (d, J =

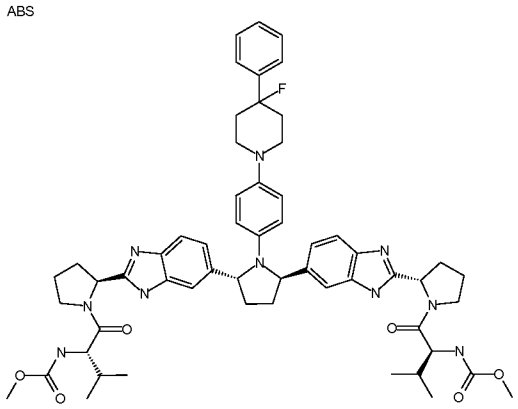
8.7, 2H), 7.17 - 7.02 (m, 4H), 7.21 (s, 1H), 7.34 - 7.26 (m, 3H), 7.41 (d, J = 8.2, 1H), 7.50 (d, J = 8.2, 1H), 12.17 (dd, J = 19.9, 74.7, 2H); MS (ESI) *m/z* 1057 $(M+H)^+$, 1055 $(M-H)^+$.



Example 4.35

methyl {(2*S*)-1-[(2*S*)-2-{6-[(2*R*,5*R*)-1-[3,5-difluoro-4-(4-fluoro-4-phenylpiperidin-1-yl)phenyl]-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

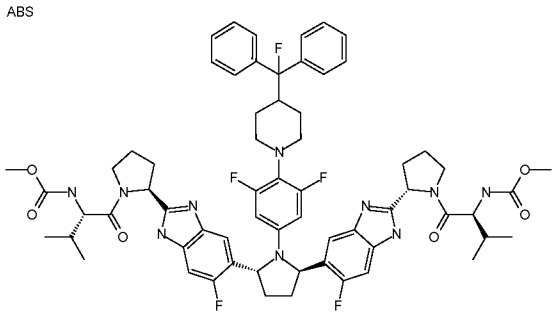
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.91 - 0.75 (m, 12H), 2.11 - 1.60 (m, 12H), 2.28 - 2.12 (m, 4H), 2.55 (d, J = 5.5, 2H), 2.84 - 2.71 (m, 2H), 3.28 - 3.06 (m, 2H), 3.53 (s, 6H), 3.83 (s, 4H), 4.11 - 3.99 (m, 2H), 5.19 - 5.09 (m, 2H), 5.45 - 5.30 (m, 2H), 5.94 (d, J = 12.8, 2H), 7.13 - 7.05 (m, 2H), 7.45 - 7.18 (m, 10H), 7.50 (d, J = 8.3, 1H), 12.11 (d, J = 15.2, 2H); MS (ESI) *m/z* 1045 $(M+H)^+$, 1043 $(M-H)^+$.



Example 4.36

methyl {(2*S*)-1-[(2*S*)-2-{6-[(2*R*,5*R*)-1-[4-(4-fluoro-4-phenylpiperidin-1-yl)phenyl]-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

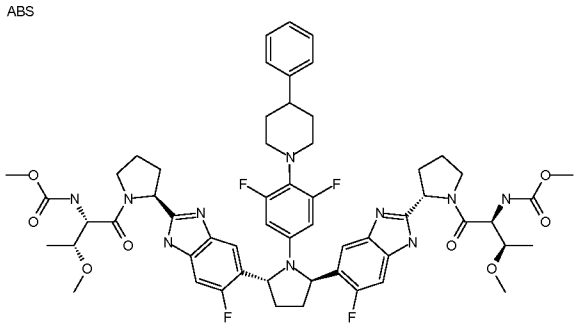
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.92 - 0.74 (m, 12H), 1.23 (d, J = 3.9, 1H), 1.69 (d, J = 3.6, 2H), 2.09 - 1.80 (m, 9H), 2.26 - 2.09 (m, 5H), 2.81 - 2.69 (m, 2H), 3.26 - 3.10 (m, 3H), 3.53 (s, 6H), 3.89 - 3.74 (m, 4H), 4.05 (t, J = 8.4, 2H), 5.18 - 5.06 (m, 2H), 5.34 (d, J = 4.5, 2H), 6.27 (d, J = 8.7, 2H), 6.65 (dt, J = 4.2, 8.6, 2H), 7.06 (t, J = 7.8, 2H), 7.21 (s, 1H), 7.43 - 7.26 (m, 9H), 7.45 (d, J = 8.2, 1H), 12.04 (s, 2H); MS (ESI) *m/z* 1009 $(M+H)^+$, 1007 $(M-H)^+$.



Example 4.37

methyl {(2*S*)-1-[(2*S*)-2-{5-[(2*R*,5*R*)-1-(3,5-difluoro-4-{4-[fluoro(diphenyl)methyl]piperidin-1-yl}phenyl)-5-{6-fluoro-2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1*H*-benzimidazol-5-yl}pyrrolidin-2-yl]-6-fluoro-1*H*-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

^{1}H NMR (400 MHz, methanol-d_4) δ ppm 0.99 - 0.69 (m, 12H), 1.42 - 1.26 (m, 3H), 1.55 (dd, J = 12.0, 24.4, 2H), 2.42 - 1.85 (m, 12H), 2.62 - 2.43 (m, 3H), 3.01 - 2.74 (m, 4H), 3.63 (s, 6H), 3.90 - 3.77 (m, 2H), 4.05 - 3.90 (m, 2H), 4.20 (d, J = 7.4, 1H), 5.24 - 5.08 (m, 2H), 5.52 (t, J = 5.8, 2H), 5.92 - 5.72 (m, 2H), 7.07 (s, 1H), 7.18 (t, J = 7.3, 2H), 7.29 (t, J = 7.5, 6H), 7.33 (s, 1H), 7.43 (d, J = 7.3, 4H); MS (ESI) *m/z* 1171 $(M+H)^+$.

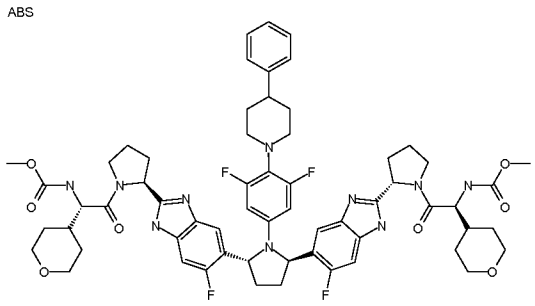


Example 4.38

methyl {(2*S*,3*R*)-1-[(2*S*)-2-{5-[(2*R*,5*R*)-1-[3,5-difluoro-4-(4-phenylpiperidin-1-yl)phenyl]-5-(6-fluoro-2-{(2*S*)-1-[*N*-(methoxycarbonyl)-*O*-methyl-L-threonyl]pyrrolidin-2-yl}-1*H*-benzimidazol-5-

yl)pyrrolidin-2-yl]-6-fluoro-1*H*-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methoxy-1-oxobutan-2-yl}carbamate

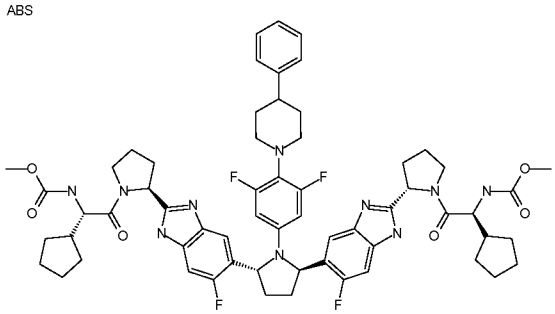
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.92 (d, J = 5.5, 2H), 1.04 (dd, J = 5.8, 12.0, 4H), 1.68 (s, 4H), 1.80 (s, 2H), 2.09 - 1.91 (m, 4H), 2.27 - 2.10 (m, 4H), 3.01 - 2.82 (m, 3H), 3.03 (s, 4H), 3.13 (s, 4H), 3.25 (s, 2H), 3.44 (dd, J = 6.5, 12.8, 3H), 3.53 (s, 6H), 3.81 (s, 3H), 4.31 - 4.14 (m, 2H), 5.17 - 5.02 (m, 2H), 5.66 - 5.41 (m, 2H), 5.97 - 5.80 (m, 2H), 7.13 - 6.99 (m, 2H), 7.19 - 7.13 (m, 2H), 7.31 - 7.19 (m, 5H), 7.38 (dd, J = 9.8, 26.3, 2H), 12.39 - 12.01 (m, 2H); MS (ESI) *m/z* 1095 $(M+H)^+$, 1093 $(M-H)^+$.



Example 4.39

dimethyl ({(2*R*,5*R*)-1-[3,5-difluoro-4-(4-phenylpiperidin-1-yl)phenyl]pyrrolidine-2,5-diyl}bis{(6-fluoro-1*H*-benzimidazole-5,2-diyl)(2*S*)pyrrolidine-2,1-diyl[(1*S*)-2-oxo-1-(tetrahydro-2*H*-pyran-4-yl)ethane-2,1-diyl]})biscarbamate

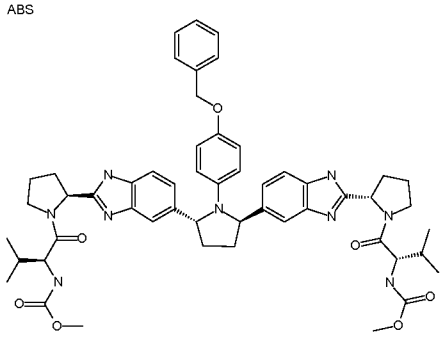
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.37 - 1.07 (m, 6H), 1.56 - 1.36 (m, 4H), 1.73 - 1.60 (m, 4H), 1.78 (s, 4H), 2.06 - 1.93 (m, 4H), 2.26 - 2.06 (m, 4H), 3.26 - 2.81 (m, 8H), 3.52 (s, 6H), 3.91 - 3.60 (m, 8H), 4.12 (dd, J = 6.9, 15.8, 2H), 5.11 (s, 2H), 5.54 (d, J = 10.0, 2H), 5.99 - 5.81 (m, 2H), 7.05 (dd, J = 6.3, 23.5, 2H), 7.16 (t, J = 6.9, 1H), 7.31 - 7.20 (m, 5H), 7.45 - 7.30 (m, 4H), 12.23 (d, J = 83.3, 2H); MS (ESI) *m/z* 1147 $(M+H)^+$.



Example 4.40

dimethyl ({(2*R*,5*R*)-1-[3,5-difluoro-4-(4-phenylpiperidin-1-yl)phenyl]pyrrolidine-2,5-diyl}bis{(6-fluoro-1*H*-benzimidazole-5,2-diyl)(2*S*)pyrrolidine-2,1-diyl[(1*S*)-1-cyclopentyl-2-oxoethane-2,1-diyl]})biscarbamate

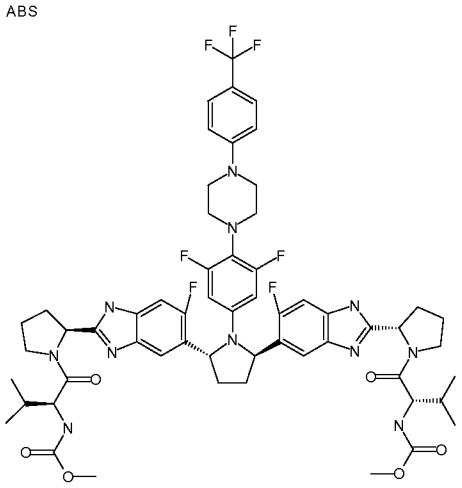
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.61 - 1.10 (m, 18H), 1.67 (s, 4H), 1.90 - 1.72 (m, 2H), 2.13 - 1.93 (m, 6H), 2.18 (s, 4H), 3.08 - 2.86 (m, 4H), 3.17 (d, J = 5.1, 1H), 3.52 (s, 6H), 3.89 - 3.70 (m, 4H), 4.20 - 4.01 (m, 2H), 5.11 (s, 2H), 5.56 (d, J = 21.5, 2H), 5.96 - 5.83 (m, 2H), 7.04 (d, J = 6.7, 1H), 7.16 (t, J = 7.0, 2H), 7.31 - 7.20 (m, 4H), 7.39 (dt, J = 8.1, 25.5, 4H), 12.16 (d, J = 61.1, 2H); MS (ESI) *m/z* 1115 $(M+H)^+$, 1113 $(M-H)^+$.



Example 4.41

methyl {(2*S*)-1-[(2*S*)-2-{5-[(2*R*,5*R*)-1-[4-(benzyloxy)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

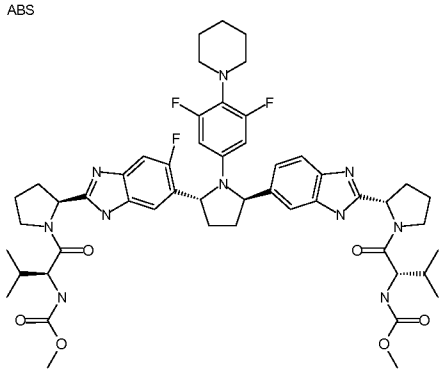
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.02 (s, 2H), 7.28 (m, 13H), 6.60 (m, 2H), 6.23 (m, 2H), 5.33 (m, 2H), 5.14 (m, 2H), 4.90 (m, 2H), 3.81 (m, 4H), 3.56 (s, 6H), 2.20 (m, 6H), 1.98 (m, 6H), 1.70 (m, 2H), 0.86 (m, 12H); MS (ESI) *m/z* 938 $(M+H)^+$.



Example 4.42

methyl {(2*S*)-1-[(2*S*)-2-{5-[(2*R*,5*R*)-1-(3,5-difluoro-4-{4-[4-(trifluoromethyl)phenyl]piperazin-1-yl}phenyl)-5-{6-fluoro-2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1*H*-benzimidazol-5-yl}pyrrolidin-2-yl]-6-fluoro-1*H*-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

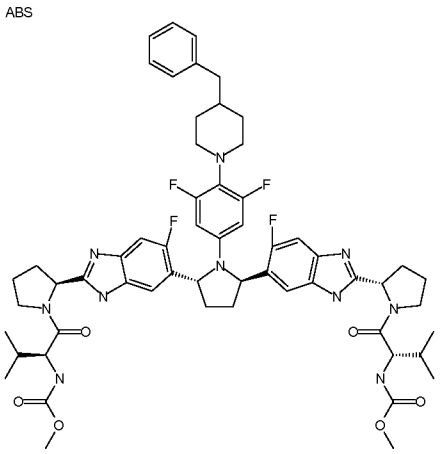
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.55 (m, 2H), 7.48 (d, J=8.8Hz, 2H), 7.34 (m, 2H), 7.18 (m, 2H), 7.04 (d, J=7.8Hz, 2H), 5.99 (m, 2H), 5.63 (m, 2H), 5.13 (m, 2H), 4.06 (m, 2H), 3.80 (m, 2H), 3.53 (s, 6H), 3.25 (m, 8H), 2.99 (m, 4H), 2.05 (m, 12H), 0.81 (m, 12H); MS (ESI) *m/z* 1132 $(M+H)^+$.



Example 4.43

methyl {(2*S*)-1-[(2*S*)-2-{6-[(2*R*,5*R*)-1-[3,5-difluoro-4-(piperidin-1-yl)phenyl]-5-{5-fluoro-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

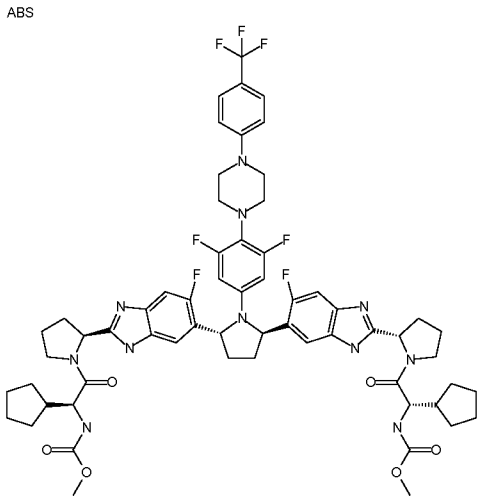
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.68 - 0.89 (m, 12 H) 1.34 - 1.50 (m, 6 H) 1.65 - 2.06 (m, 9 H) 2.12 - 2.24 (m, 4 H) 2.70 - 2.82 (m, 4 H) 3.52 (d, J=2.49 Hz, 6 H) 3.73 - 3.86 (m, 4 H) 3.99 - 4.08 (m, 2 H) 5.06 - 5.19 (m, 2 H) 5.26 - 5.43 (m, 1 H) 5.46 - 5.56 (m, 1 H) 5.86 (d, J=12.04 Hz, 2 H) 6.98 (d, J=6.51 Hz, 1 H) 7.02 - 7.11 (m, 1 H) 7.21 (d, J=6.94 Hz, 1 H) 7.26 - 7.35 (m, 2 H) 7.39 (d, J=8.35 Hz, 1 H) 7.45 - 7.51 (m, 1 H) 12.01 - 12.26 (m, 2 H); MS (ESI+) *m/z* 969 $(M+H)^+$.



Example 4.44

methyl {(2*S*)-1-[(2*S*)-2-{6-[(2*R*,5*R*)-1-[4-(4-benzylpiperidin-1-yl)-3,5-difluorophenyl]-5-{5-fluoro-2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1*H*-benzimidazol-6-yl}pyrrolidin-2-yl]-5-fluoro-1*H*-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

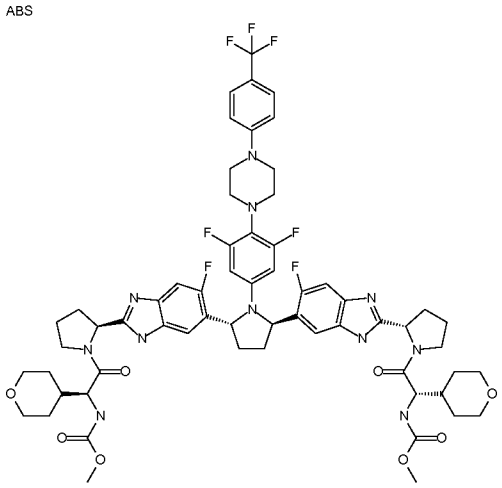
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.67 - 0.88 (m, 12 H) 1.22 (s, 12 H) 1.42 - 1.51 (m, 5 H) 1.73 - 2.04 (m, 12 H) 2.12 - 2.21 (m, 4 H) 2.72 - 2.81 (m, 5 H) 3.48 - 3.54 (m, 6 H) 3.72 - 3.83 (m, 3 H) 3.97 - 4.06 (m, 2 H) 5.05 - 5.13 (m, 2 H) 5.46 - 5.58 (m, 2 H) 5.79 - 5.89 (m, 2 H) 6.99 - 7.04 (m, 1 H) 7.09 - 7.16 (m, 5 H) 7.20 - 7.34 (m, 6 H) 7.35 - 7.42 (m, 1 H) 7.51 - 7.64 (m, 3 H) 12.10 (s, 1 H) 12.23 (s, 1 H); MS (ESI+) *m/z* 1077 $(M+H)^+$.



Example 4.45

dimethyl ([(2*R*,5*R*)-1-(3,5-difluoro-4-{4-[4-(trifluoromethyl)phenyl]piperazin-1-yl}phenyl)pyrrolidine-2,5-diyl]bis{(5-fluoro-1*H*-benzimidazole-6,2-diyl)(2*S*)pyrrolidine-2,1-diyl[(1*S*)-1-cyclopentyl-2-oxoethane-2,1-diyl]})biscarbamate

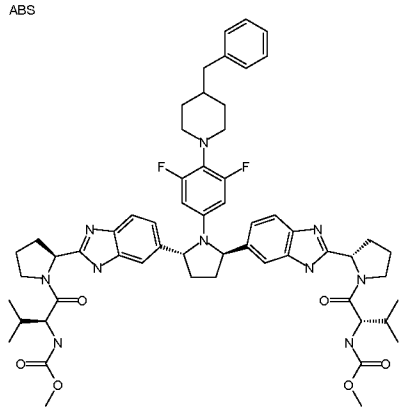
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.09 - 1.64 (m, 18 H) 1.71 - 1.86 (m, 2 H) 1.92 - 2.23 (m, 10 H) 2.91 - 3.03 (m, 5 H) 3.22 - 3.30 (m, 4 H) 3.52 (s, 6 H) 3.71 - 3.87 (m, 4 H) 4.12 (t, J=8.40 Hz, 2 H) 5.05 - 5.16 (m, 2 H) 5.48 - 5.65 (m, 2 H) 5.85 - 5.99 (m, 2 H) 7.03 (d, J=8.89 Hz, 3 H) 7.14 (d, J=6.29 Hz, 1 H) 7.30 - 7.38 (m, 1 H) 7.40 (d, J=9.54 Hz, 2 H) 7.46 (d, J=8.67 Hz, 2 H) 12.08 (s, 1 H) 12.20 (s, 1 H); MS (ESI+) *m/z* 1184 $(M+H)^+$.



Example 4.46

dimethyl ([(2*R*,5*R*)-1-(3,5-difluoro-4-{4-[4-(trifluoromethyl)phenyl]piperazin-1-yl}phenyl)pyrrolidine-2,5-diyl]bis{(5-fluoro-1*H*-benzimidazole-6,2-diyl)(2*S*)pyrrolidine-2,1-diyl[(1*S*)-2-oxo-1-(tetrahydro-2*H*-pyran-4-yl)ethane-2,1-diyl]})biscarbamate

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.09 - 1.33 (m, 4 H) 1.38 - 1.54 (m, 4 H) 1.70 - 1.88 (m, 4 H) 1.92 - 2.05 (m, 4 H) 2.10 - 2.25 (m, 3 H) 2.95 - 3.03 (m, 4 H) 3.03 - 3.20 (m, 3 H) 3.21 - 3.29 (m, 4 H) 3.51 (s, 6 H) 3.62 - 3.89 (m, 6 H) 4.05 - 4.17 (m, 2 H) 5.06 - 5.15 (m, 2 H) 5.48 - 5.64 (m, 2 H) 5.83 - 5.98 (m, 2 H) 7.03 (d, J=8.67 Hz, 3 H) 7.07 (d, J=6.29 Hz, 1 H) 7.29 - 7.42 (m, 3 H) 7.46 (d, J=8.78 Hz, 2 H) 12.11 (s, 1 H) 12.32 (s, 1 H); MS (ESI+) *m/z* 1216 $(M+H)^+$.

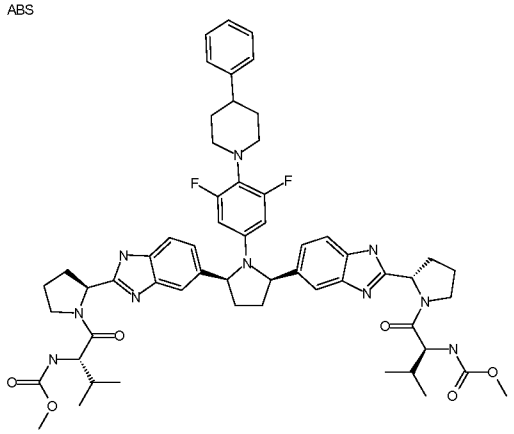


Example 4.47

methyl {(2*S*)-1-[(2*S*)-2-{6-[(2*R*,5*R*)-1-[4-(4-benzylpiperidin-1-yl)-3,5-difluorophenyl]-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

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.07 (d, J = 19.1, 2H), 7.48 (d, J = 8.3, 2H), 7.40 (d, J = 8.1, 2H), 7.34 – 7.10 (m, 8H), 7.07 (s, 2H), 5.87 (d, J = 12.3, 2H), 5.35 (s, 2H), 5.14 (s, 1H), 3.78 (d, J = 28.9, 2H), 3.54 (s, 6H), 2.76 (s, 3H), 2.19 (s, 4H), 2.07 – 1.80 (m, 6H), 1.68 (s, 2H), 1.46 (d, J = 10.4, 3H), 1.25 – 1.08 (m, 2H), 0.92 – 0.71 (m, 12H); MS (ESI+) *m/z* 1041.4 $(M+H)^+$, (ESI-) *m/z* 1039.3 $(M-H)^-$.

ABS

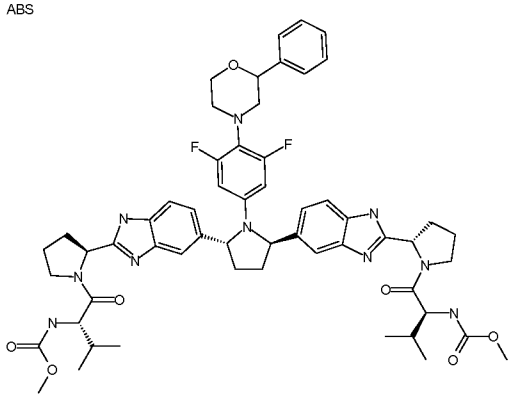


Example 4.48

methyl {(2*S*)-1-[(2*S*)-2-{5-[(2*S*,5*R*)-1-[3,5-difluoro-4-(4-phenylpiperidin-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

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.76 - 0.94 (m, 12 H), 1.60 - 2.30 (m, 14 H), 2.88 - 3.09 (m, 4 H), 3.54 (s, 6 H), 3.84 (s, 3 H), 4.02 - 4.15 (m, *J*=8.1, 8.1 Hz, 2 H), 4.77 - 4.97 (m, 2 H), 5.17 (d, *J*=2.9 Hz, 2 H), 5.95 - 6.10 (m, 2 H), 7.08 - 7.70 (m, 13 H), 12.09 - 12.23 (m, 2 H).

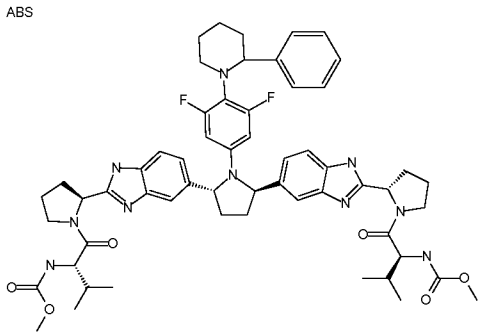
ABS



Example 4.49

methyl {(2*S*)-1-[(2*S*)-2-{5-[(2*R*,5*R*)-1-[3,5-difluoro-4-(2-phenylmorpholin-4-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

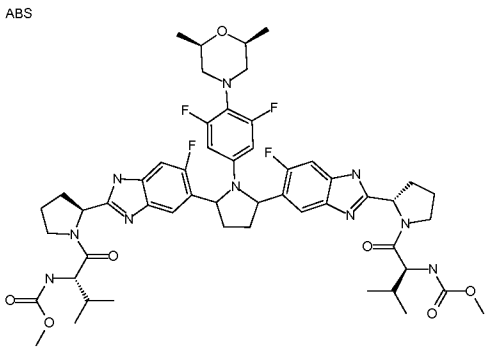
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.69 - 0.92 (m, 12 H), 1.69 (d, *J*=5.1 Hz, 2 H), 1.82 - 2.30 (m, 12 H), 2.70 - 3.16 (m, *J*=63.6 Hz, 6 H), 3.54 (s, 6 H), 3.81 (s, 3 H), 3.99 - 4.12 (m, 2 H), 4.47 (dd, *J*=9.1, 3.7 Hz, 1 H), 5.08 - 5.19 (m, 2 H), 5.29 - 5.48 (m, 2 H), 5.92 (d, *J*=13.4 Hz, 2 H), 7.07 (t, *J*=7.9 Hz, 2 H), 7.16 - 7.35 (m, *J*=0.8 Hz, 10 H), 7.40 (d, *J*=8.1 Hz, 1 H), 7.49 (d, *J*=8.3 Hz, 1 H), 12.06 (s, 1 H), 12.11 (s, 1 H); MS (APCI+) *m/z* 1030.1(M+H).



Example 4.50

methyl {(2*S*)-1-[(2*S*)-2-{5-[(2*R*,5*R*)-1-[3,5-difluoro-4-(2-phenylpiperidin-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

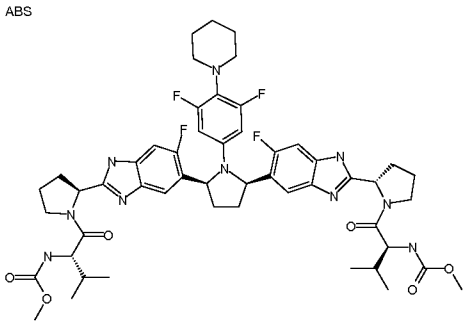
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.81 - 1.01 (m, 12 H), 1.24 - 2.35 (m, 22 H), 3.60 (s, 6 H), 3.89 (s, 4 H), 3.94 - 4.20 (m, 3 H), 5.22 (s, 2 H), 5.30 (d, *J*=4.3 Hz, 2 H), 5.73 (dd, *J*=13.1, 3.6 Hz, 2 H), 6.92 - 7.44 (m, 13 H), 7.48 (d, *J*=8.1 Hz, 1 H), 12.08 (s, 1 H), 12.17 (s, 1 H); MS (APCI+) *m/z* 1028.2 $(M+H)^+$.



Example 4.51

methyl [(2*S*)-1-{(2*S*)-2-[5-(1-{4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]-3,5-difluorophenyl}-5-{6-fluoro-2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1*H*-benzimidazol-5-yl}pyrrolidin-2-yl)-6-fluoro-1*H*-benzimidazol-2-yl]pyrrolidin-1-yl}-3-methyl-1-oxobutan-2-yl]carbamate

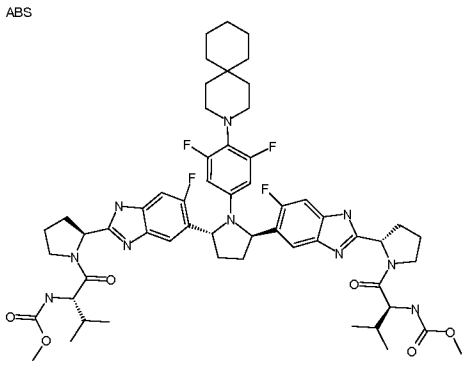
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.67 - 0.90 (m, 12 H), 0.96 (s, 6 H), 1.01 - 1.31 (m, 2 H), 1.68 - 2.25 (m, 12 H), 3.51 (s, 6 H), 3.78 (s, 3 H), 4.01 (q, *J*=7.2 Hz, 2 H), 5.10 (d, *J*=4.8 Hz, 2 H), 5.43 - 5.65 (m, 2 H), 5.79 - 5.97 (m, 2 H), 7.02 (d, *J*=5.3 Hz, 1 H), 7.11 (d, *J*=6.8 Hz, 1 H), 7.21 - 7.46 (m, 4 H), 12.11 (s, 1 H), 12.24 (s, 1 H); MS (ESI) *m/z* 1017.4 $(M+H)^+$.



Example 4.52

methyl {(2*S*)-1-[(2*S*)-2-{5-[(2*S*,5*R*)-1-[3,5-difluoro-4-(piperidin-1-yl)phenyl]-5-{6-fluoro-2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1*H*-benzimidazol-5-yl}pyrrolidin-2-yl]-6-fluoro-1*H*-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

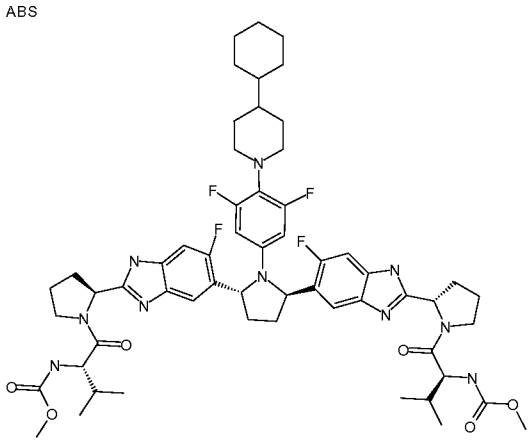
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.72 - 0.94 (m, *J*=10.5, 10.5 Hz, 12 H), 1.36 - 1.58 (m, 6 H), 1.77 - 2.28 (m, 14 H), 2.83 (s, 4 H), 3.53 (s, 6 H), 3.82 (s, 4 H), 3.97 - 4.14 (m, 2 H), 4.92 - 5.07 (m, 2 H), 5.09 - 5.20 (m, 2 H), 5.83 - 6.02 (m, 2 H), 7.21 - 7.79 (m, 6 H), 12.14 - 12.44 (m, 2 H); MS (APCI+) *m/z* 987.8 $(M+H)^+$.



Example 4.53

methyl {(2*S*)-1-[(2*S*)-2-{5-[(2*R*,5*R*)-1-[4-(3-azaspiro[5.5]undec-3-yl)-3,5-difluorophenyl]-5-{6-fluoro-2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1*H*-benzimidazol-5-yl}pyrrolidin-2-yl]-6-fluoro-1*H*-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

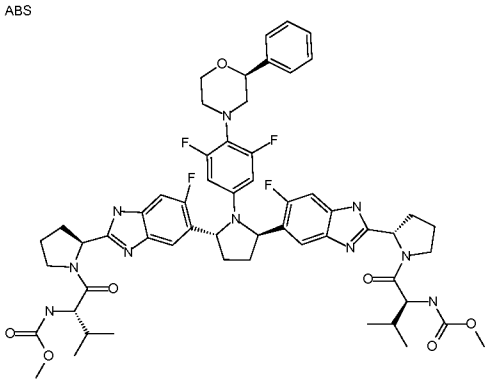
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.64 - 0.94 (m, 12 H), 1.21 - 1.44 (m, 16 H), 1.68 - 2.25 (m, *J*=78.0 Hz, 12 H), 2.78 (s, 4 H), 3.53 (s, 6 H), 3.80 (s, 4 H), 4.04 (t, *J*=7.1 Hz, 2 H), 5.11 (s, 2 H), 5.55 (dd, *J*=19.8, 4.2 Hz, 2 H), 5.79 - 5.99 (m, 2 H), 7.03 (d, *J*=6.0 Hz, 1 H), 7.13 (d, *J*=6.5 Hz, 1 H), 7.24 - 7.48 (m, 4 H), 12.12 (s, 1 H), 12.24 (s, 1 H); MS (ESI) *m/z* 1055.4 $(M+H)^+$.



Example 4.54

methyl {(2*S*)-1-[(2*S*)-2-{5-[(2*R*,5*R*)-1-[4-(4-cyclohexylpiperidin-1-yl)-3,5-difluorophenyl]-5-{6-fluoro-2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1*H*-benzimidazol-5-yl}pyrrolidin-2-yl]-6-fluoro-1*H*-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

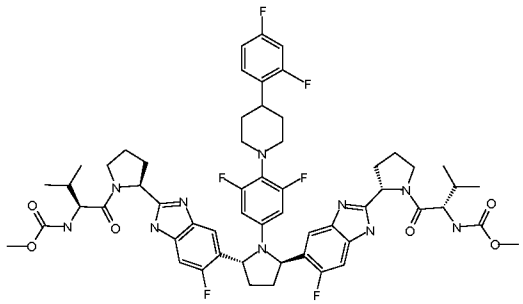
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.65 - 0.97 (m, 12 H), 0.98 - 1.33 (m, 10 H), 1.50 - 2.25 (m, 20 H), 2.72 - 2.91 (m, 4 H), 3.53 (s, 6 H), 3.79 (s, 4 H), 4.04 (t, *J*=8.1 Hz, 2 H), 5.11 (s, 2 H), 5.54 (dd, *J*=14.7, 6.7 Hz, 2 H), 5.79 - 5.97 (m, 2 H), 7.03 (d, *J*=6.7 Hz, 1 H), 7.13 (d, *J*=6.9 Hz, 1 H), 7.24 - 7.46 (m, 4 H), 12.11 (s, 1 H), 12.23 (s, 1 H); MS (ESI+) *m/z* 1069.5 $(M+H)^+$.



Example 4.55

methyl {(2*S*)-1-[(2*S*)-2-{5-[(2*R*,5*R*)-1-{3,5-difluoro-4-[(2*S*)-2-phenylmorpholin-4-yl]phenyl}-5-{6-fluoro-2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1*H*-benzimidazol-5-yl}pyrrolidin-2-yl]-6-fluoro-1*H*-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

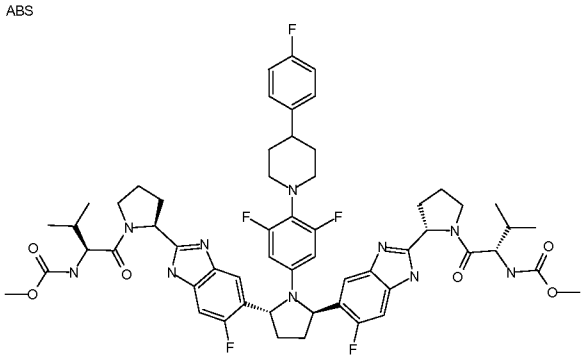
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.60 - 0.95 (m, 12 H), 1.64 - 2.08 (m, 10 H), 2.09 - 2.25 (m, 4 H), 2.70 - 3.18 (m, 4 H), 3.53 (s, 6 H), 3.64 - 3.86 (m, 4 H), 3.91 (d, *J*=11.4 Hz, 1 H), 4.03 (t, *J*=8.2 Hz, 2 H), 4.48 (d, *J*=7.5 Hz, 1 H), 5.10 (s, 2 H), 5.43 - 5.69 (m, 2 H), 5.80 - 6.03 (m, 2 H), 7.03 (d, *J*=6.8 Hz, 1 H), 7.14 (d, *J*=6.7 Hz, 1 H), 7.20 - 7.45 (m, 10 H), 12.10 (s, 1 H), 12.24 (s, 1 H); MS (ESI+) *m/z* 1065.4 $(M+H)^+$.



Example 4.56

methyl {(2*S*)-1-[(2*S*)-2-{5-[(2*R*,5*R*)-1-{4-[4-(2,4-difluorophenyl)piperidin-1-yl]-3,5-difluorophenyl}-5-{6-fluoro-2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1*H*-benzimidazol-5-yl}pyrrolidin-2-yl]-6-fluoro-1*H*-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

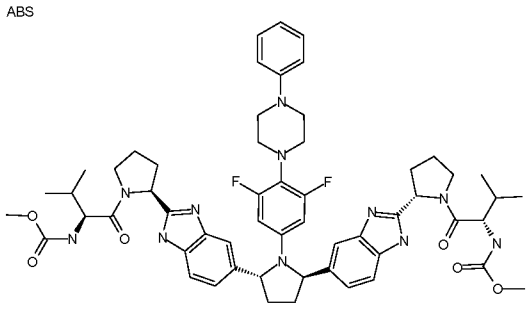
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.68 - 0.92 (m, 14 H), 1.58 - 2.08 (m, 11 H), 2.09 - 2.27 (m, 4 H), 2.71 - 3.14 (m, 6 H), 3.52 (s, 6 H), 3.68 - 3.89 (m, 4 H), 3.98 - 4.10 (m, 2 H), 5.05 - 5.17 (m, 2 H), 5.48 - 5.68 (m, 2 H), 5.83 - 5.99 (m, 2 H), 6.95 - 7.08 (m, 2 H), 7.09 - 7.21 (m, 2 H), 7.25 - 7.46 (m, 5 H), 12.06 - 12.39 (m, 2 H); MS (ESI+) *m/z* 1099.3 $(M+H)^+$.



Example 4.57

methyl {(2*S*)-1-[(2*S*)-2-{5-[(2*R*,5*R*)-1-{3,5-difluoro-4-[4-(4-fluorophenyl)piperidin-1-yl]phenyl}-5-{6-fluoro-2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1*H*-benzimidazol-5-yl}pyrrolidin-2-yl]-6-fluoro-1*H*-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

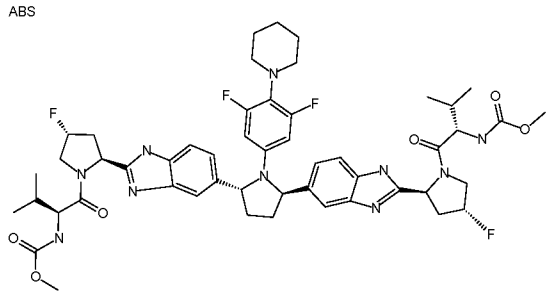
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.67 - 0.93 (m, 14 H), 1.53 - 2.09 (m, 11 H), 2.10 - 2.25 (m, 4 H), 2.83 - 3.15 (m, 6 H), 3.53 (s, 6 H), 3.69 - 3.88 (m, 4 H), 3.98 - 4.10 (m, 2 H), 5.05 - 5.17 (m, 2 H), 5.48 - 5.67 (m, 2 H), 5.83 - 5.99 (m, 2 H), 6.99 - 7.20 (m, 4 H), 7.22 - 7.47 (m, 6 H), 12.02 - 12.47 (m, 2 H); MS (ESI+) *m/z* 1081.4 $(M+H)^+$.



Example 4.58

methyl {(2*S*)-1-[(2*S*)-2-{5-[(2*R*,5*R*)-1-[3,5-difluoro-4-(4-phenylpiperazin-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

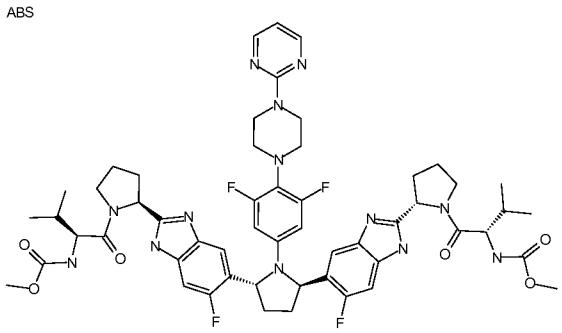
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.72 - 0.95 (m, 12 H) 1.69 (s, 1 H) 1.84 - 2.11 (m, 2 H) 2.20 (s, 4 H) 2.97 (s, 4 H) 3.09 (s, 4 H) 3.54 (s, 6 H) 3.82 (s, 4 H) 4.03 (q, J=7.05 Hz, 6 H) 5.15 (s, 2 H) 5.39 (s, 2 H) 5.95 (s, 2 H) 6.75 (s, 2 H) 6.90 (d, J=8.24 Hz, 2 H) 7.08 (t, 2 H) 7.17 (t, J=7.92 Hz, 2 H) 7.30 (s, 2 H) 7.48 (s, 2 H) 7.66 (s, 2 H) 7.92 (s, 2 H) 12.09 (s, 2 H); MS (ESI+) *m/z* 1028.4, (ESI-) *m/z* 1026.4 $(M-H)^-$.



Example 4.59

methyl {(2*S*)-1-[(2*S*,4*R*)-2-{5-[(2*R*,5*R*)-1-[3,5-difluoro-4-(piperidin-1-yl)phenyl]-5-{2-[(2*S*,4*R*)-4-fluoro-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-fluoropyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.76 (m,16 H) 0.89 (m, 3 H) 1.45 (m, 5 H) 1.70 (m, 2 H) 1.85 (m, 1 H) 2.76 (d, 2 H) 3.17 (d, J=5.10 Hz, 2 H) 3.53 (s, 6 H) 3.87 - 4.13 (m, 4 H) 4.31 (m, 1 H) 5.17 (d, 2 H) 5.36 (m, 3 H) 5.57 (s, 1 H) 5.89 (d, 2 H) 7.09 (m, 2 H) 7.18 - 7.25 (m, 1 H) 7.29 (m, 3 H) 7.48 (m, 3 H) 12.22 (s, 2 H); MS (ESI+) *m/z* 987.4, (ESI-) *m/z* 985.2 $(M-H)^-$.

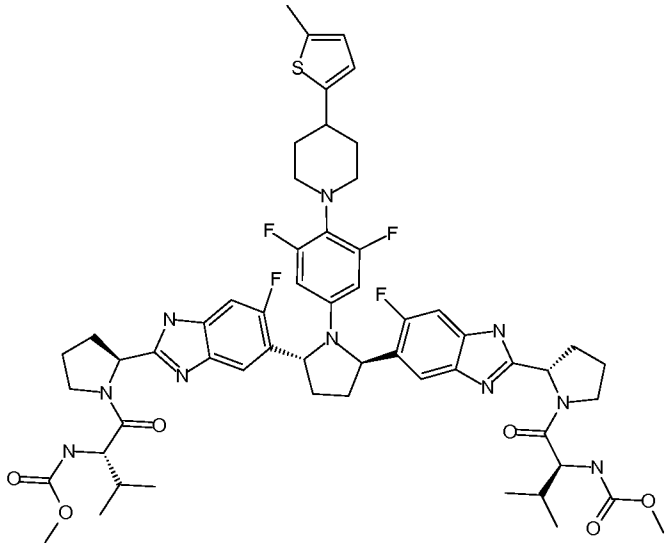


Example 4.60

methyl {(2*S*)-1-[(2*S*)-2-{5-[(2*R*,5*R*)-1-{3,5-difluoro-4-[4-(pyrimidin-2-yl)piperazin-1-yl]phenyl}-5-{6-fluoro-2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1*H*-benzimidazol-5-yl}pyrrolidin-2-yl]-6-fluoro-1*H*-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.67 - 0.93 (m, 12 H) 1.99 (m, 16 H) 2.18 (m, 4 H) 2.87 (m, 4 H) 3.53 (s, 6 H) 3.56 m, 2H) 3.74 (m, 10 H) 5.11 (m, 2 H) 5.53 (m, 2 H) 5.90 (m, 2 H) 6.60 (t, J=4.72 Hz, 1 H) 7.04 (m, 2 H) 7.32 (m, 4 H) 8.33 (d, J=4.77 Hz, 2 H) 12.14 (s, 1 H) 12.22 (s, 1H); MS (ESI+) *m/z* 1066.4, (ESI-) *m/z* 1064.1 $(M-H)^-$.

ABS

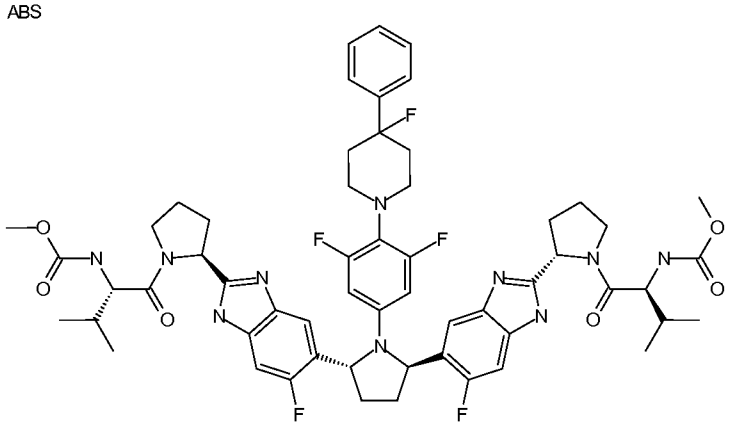


Example 4.61

methyl {(2*S*)-1-[(2*S*)-2-{5-[(2*R*,5*R*)-1-{3,5-difluoro-4-[4-(5-methyl-2-thienyl)piperidin-1-yl]phenyl}-5-{6-fluoro-2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1*H*-benzimidazol-5-yl}pyrrolidin-2-yl]-6-fluoro-1*H*-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

1H NMR (400 MHz, DMSO-D6) δ ppm 0.71 - 0.98 (m, 12 H), 1.49 - 2.31 (m, 18 H), 2.42 (s, 3 H), 2.87 - 3.11 (m, *J*=14.1 Hz, 5 H), 3.59 (s, 6 H), 3.77 - 3.94 (m, *J*=9.1 Hz, 4 H), 4.05 - 4.17 (m, 2 H), 5.08 - 5.26 (m, 2 H), 5.53 - 5.74 (m, 2 H), 5.89 - 6.05 (m, 2 H), 6.64 (d, *J*=2.4 Hz, 1 H), 6.68 (d, *J*=3.5 Hz, 1 H), 7.04 - 7.14 (m, 1 H), 7.16 - 7.25 (m, 1 H), 7.31 - 7.53 (m, 4 H), 12.09 - 12.23 (m, 1 H), 12.26 - 12.41 (m, 1 H); MS (ESI) m/z 1083.3 (M+H).

ABS

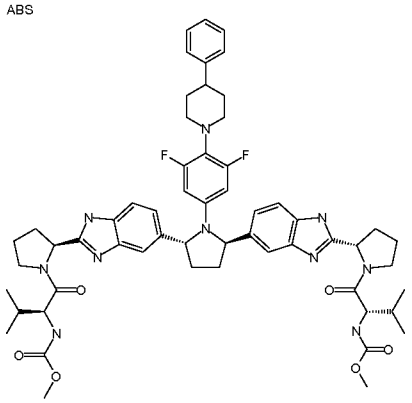


Example 4.62

methyl {(2*S*)-1-[(2*S*)-2-{5-[(2*R*,5*R*)-1-[3,5-difluoro-4-(4-fluoro-4-phenylpiperidin-1-yl)phenyl]-5-{6-fluoro-2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1*H*-

benzimidazol-5-yl}pyrrolidin-2-yl]-6-fluoro-1*H*-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

^{1}H NMR (400 MHz, DMSO) δ 0.84 - 0.69 (m, 12H), 0.90 - 0.84 (m, 2H), 1.93 - 1.76 (m, 7H), 2.00 (dd, *J* = 6.8, 14.5, 8H), 2.23 - 2.12 (m, 5H), 3.52 (s, 6H), 3.87 - 3.73 (m, 4H), 4.08 - 3.97 (m, 2H), 5.16 - 5.06 (m, 2H), 5.65 - 5.48 (m, 2H), 5.99 - 5.86 (m, 2H), 7.06 (d, *J* = 6.7, 1H), 7.15 (d, *J* = 6.9, 1H), 7.31 (d, *J* = 7.0, 3H), 7.36 (d, *J* = 7.7, 2H), 7.41 (t, *J* = 7.6, 4H), 12.19 (d, *J* = 44.3, 2H). MS (ESI) *m/z* 1081 $(M+H)^+$.

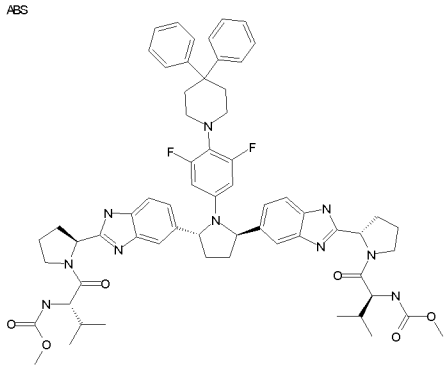


Example 5.1

methyl {(2*S*)-1-[(2*S*)-2-{5-[(2*R*,5*R*)-1-[3,5-difluoro-4-(4-phenylpiperidin-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

In a 250 mL round-bottomed flask cooled in an ice bath was added (*S*)-6,6'-((2*R*,5*R*)-1-(3,5-difluoro-4-(4-phenylpiperidin-1-yl)phenyl)pyrrolidine-2,5-diyl)bis(2-((*S*)-pyrrolidin-2-yl)-1*H*-benzo[*d*]imidazole) (2.57 mmol), (*S*)-2-(methoxycarbonylamino)-3-methylbutanoic acid (0.945 g, 5.40 mmol) and 1*H*-benzo[*d*][1,2,3]triazol-1-ol hydrate (0.984 g, 6.43 mmol) in DMF (25 mL) to give an orange solution. 4-Methylmorpholine (2.83 mL, 25.7 mmol) and N^1-((ethylimino)methylene)-N^3,N^3-dimethylpropane-1,3-diamine hydrochloride (1.232 g, 6.43 mmol) were added, and the mixture was stirred at ambient temperature for 2 hours and then diluted into EtOAc. The EtOAc layer was washed with aqueous saturated $NaHCO_3$, H_2O, and saturated NaCl. The organic layer was treated with 3-mercaptopropyl silica for 1 hour, dried (Na_2SO_4), filtered and concentrated to a yellow foam (2.74 g). Purification by flash chromatography on a 120 g silica cartridge eluting with 2-5% methanol in dichloromethane afforded 1.7 g (61%) of the title compound as a yellow powder. The title compound can additionally be purified by recrystallization from acetonitrile. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.73 - 0.91 (m, 12 H) 1.60 - 1.74 (m, 6 H) 1.86 - 2.04 (m, 6 H) 2.17 - 2.30 (m, 4 H) 2.52 - 2.53 (m, 4 H) 2.84 - 3.02 (m, 4 H) 3.52 - 3.56 (m, 6 H) 3.78 - 3.87 (m, 3 H) 4.00 - 4.12 (m, 2 H)

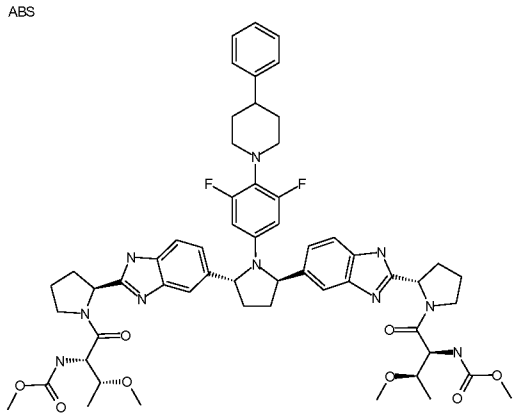
5.10 - 5.18 (m, 2 H) 5.32 - 5.42 (m, 2 H) 5.88 - 5.95 (m, 2 H) 7.05 - 7.33 (m, 11 H) 7.41 (d, J=8.24 Hz, 1 H) 7.50 (d, J=8.35 Hz, 1 H) 11.97 - 12.30 (m, 2 H); MS (ESI+) *m/z* 1027 $(M+H)^+$.



Example 5.2

methyl {(2*S*)-1-[(2*S*)-2-{5-[(2*R*,5*R*)-1-[4-(4,4-diphenylpiperidin-1-yl)-3,5-difluorophenyl]-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

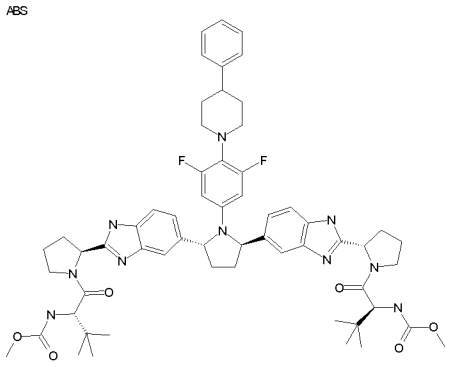
In a 100 mL round bottom was added (*S*)-6,6'-((2*R*,5*R*)-1-(4-(4,4-diphenylpiperidin-1-yl)-3,5-difluorophenyl)pyrrolidine-2,5-diyl)bis(2-((*S*)-pyrrolidin-2-yl)-1*H*-benzo[*d*]imidazole) (0.385 g, 0.488 mmol), (*S*)-2-(methoxycarbonylamino)-3-methylbutanoic acid (0.180 g, 1.025 mmol), and 1*H*-benzo[*d*][1,2,3]triazol-1-ol hydrate (0.187 g, 1.220 mmol) in DMF (25 mL) to give an orange solution. 4-Methylmorpholine (0.537 mL, 4.88 mmol) and N^1-((ethylimino)methylene)-N^3,N^3-dimethylpropane-1,3-diamine hydrochloride (0.234 g, 1.220 mmol) were added, and the mixture was stirred at ambient temperature for 2 hours and then diluted with EtOAc. The organic solution was washed sequentially with saturated $NaHCO_3$, H_2O, and saturated NaCl. The organic layer was treated with 3-mercaptopropyl silica for 1 hour, dried (Na2SO4), filtered and concentrated to a yellow foam. Purification by flash chromatography on a 24 g silica cartridge eluting with 2-7% methanol in CH_2Cl_2 provided material that was 90% pure by HPLC. A second chromatography of selected fractions on a 12 g silica cartridge eluting with 2-5% methanol in CH_2Cl_2 gave the title compound as a cream colored solid (100 mg, 17%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.76 - 0.91 (m, 12 H) 1.68 (d, J=4.01 Hz, 2 H) 1.85 - 2.07 (m, 6 H) 2.19 (s, 4 H) 2.38 (s, 4 H) 2.86 (s, 4 H) 3.54 (s, 6 H) 3.82 (s, 4 H) 4.06 (t, J=8.35 Hz, 2 H) 5.10 - 5.17 (m, 2 H) 5.34 (d, J=7.16 Hz, 2 H) 5.85 (d, J=12.79 Hz, 2 H) 6.84 - 7.54 (m, 20 H) 12.06 (d, J=18.98 Hz, 2 H); MS (ESI+) *m/z* 1103 $(M+H)^+$.



Example 5.3

methyl {(2*S*,3*R*)-1-[(2*S*)-2-{5-[(2*R*,5*R*)-1-[3,5-difluoro-4-(4-phenylpiperidin-1-yl)phenyl]-5-(2-{(2*S*)-1-[*N*-(methoxycarbonyl)-O-methyl-L-threonyl]pyrrolidin-2-yl}-1*H*-benzimidazol-5-yl)pyrrolidin-2-yl]-1*H*-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methoxy-1-oxobutan-2-yl}carbamate

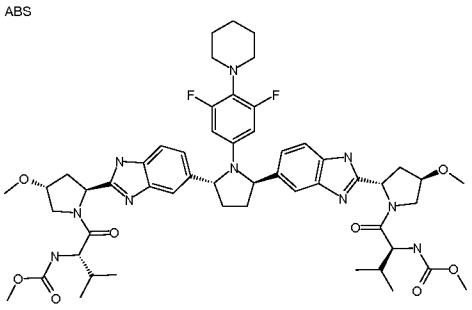
(*S*)-6,6'-((2*R*,5*R*)-1-(3,5-Difluoro-4-(4-phenylpiperidin-1-yl)phenyl)pyrrolidine-2,5-diyl)bis(2-((*S*)-pyrrolidin-2-yl)-1*H*-benzo[*d*]imidazole) hydrochloride (0.12 g) was dissolved in dimethyl sulfoxide (2 mL) and treated with diisopropylethylamine (0.195 mL, 1.12 mmol) at ambient temperature followed by (2*S*,3*R*)-3-methoxy-2-(methoxycarbonylamino)butanoic acid (0.059 g, 0.307 mmol) and HATU (0.112 g, 0.293 mmol). After 1 hour, the solution was diluted with water and extracted into dichloromethane, concentrated and purified by chromatography, eluting with 0-8% methanol in dichloromethane to give 0.071 g of a yellow solid (48%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.03 (dd, J=18.22, 6.18 Hz, 6 H) 1.63 - 1.72 (m, 6 H) 1.99 - 2.08 (m, 6 H) 2.15 - 2.26 (m, 6 H) 2.87 - 3.00 (m, 2 H) 3.10 (s, 3 H) 3.15 (s, 3 H) 3.17 - 3.20 (m, 1 H) 3.43 - 3.52 (m, 2 H) 3.54 (s, 6 H) 3.79 - 3.89 (m, 4 H) 4.25 - 4.30 (m, 2 H) 5.11 - 5.18 (m, 2 H) 5.35 - 5.42 (m, 2 H) 5.87 - 5.95 (m, 2 H) 7.09 (t, J=8.19 Hz, 2 H) 7.12 - 7.32 (m, 9 H) 7.41 (d, J=8.35 Hz, 1 H) 7.49 (d, J=8.78 Hz, 1 H) 12.03 (s, 1 H) 12.10 (s, 1 H); MS (ESI+) *m/z* 1059.4 $(M+H)^+$.



Example 5.4

methyl {(2*S*)-1-[(2*S*)-2-{5-[(2*R*,5*R*)-1-[3,5-difluoro-4-(4-phenylpiperidin-1-yl)phenyl]-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

(*S*)-6,6'-((2*R*,5*R*)-1-(3,5-Difluoro-4-(4-phenylpiperidin-1-yl)phenyl)pyrrolidine-2,5-diyl)bis(2-((*S*)-pyrrolidin-2-yl)-1*H*-benzo[*d*]imidazole) hydrochloride (0.12 g) was dissolved in dimethyl sulfoxide (2 mL) and treated with diisopropylethylamine (0.195 mL, 1.12 mmol) at ambient temperature followed by (*S*)-2-(methoxycarbonylamino)-3,3-dimethylbutanoic acid (0.058 g, 0.307 mmol) and HATU (0.112 g, 0.293 mmol). After 1 hour, the solution was diluted with water and extracted into dichloromethane. The organic phases were concentrated and purified by chromatography, eluting with 0-6% methanol in dichloromethane to give the title compound (0.065 g, 44%) as a yellow solid . ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.89 (d, J=13.88 Hz, 18 H) 1.61 - 1.73 (m, 8 H) 1.95 - 2.08 (m, 4 H) 2.15 - 2.24 (m, 6 H) 2.86 - 3.02 (m, 4 H) 3.55 (s, 6 H) 3.78 - 3.85 (m, 4 H) 4.23 (dd, J=8.89, 4.66 Hz, 2 H) 5.13 - 5.22 (m, 2 H) 5.33 - 5.43 (m, 2 H) 5.92 (dd, J=12.85, 2.98 Hz, 2 H) 7.05 - 7.18 (m, 4 H) 7.20 - 7.29 (m, 5 H) 7.33 (s, 1 H) 7.42 (d, J=8.13 Hz, 1 H) 7.49 (d, J=8.46 Hz, 1 H) 12.05 (d, J=1.63 Hz, 1 H) 12.09 (d, J=1.30 Hz, 1 H); MS (ESI+) *m/z* 1055.4 $(M+H)^+$.

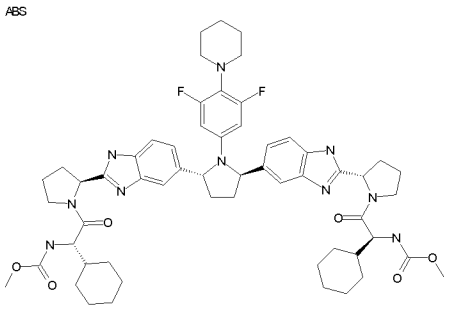


Example 5.5

methyl {(2*S*)-1-[(2*S*,4*R*)-2-{5-[(2*R*,5*R*)-1-[3,5-difluoro-4-(piperidin-1-yl)phenyl]-5-{2-[(2*S*,4*R*)-4-methoxy-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-methoxypyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

(*S*,*R*)-6,6'-((2*R*,5*R*)-1-(3,5-Difluoro-4-(piperidin-1-yl)phenyl)pyrrolidine-2,5-diyl)bis(2-((2*S*,4*R*)-4-methoxypyrrolidin-2-yl)-1*H*-benzo[*d*]imidazole) (0.20g, 0.287 mmol) was dissolved in dimethyl sulfoxide (3 mL) and treated with diisopropylethylamine (0.400 mL, 2.29 mmol) at ambient temperature followed by (*S*)-2-(methoxycarbonylamino)-3-methylbutanoic acid (0.111 g, 0.631 mmol) and HATU (0.229 g, 0.603 mmol). After 2 hours, the solution was diluted with water and extracted into dichloromethane. The organic layer was concentrated and purified by chromatography, eluting with 0-6% methanol in dichloromethane to give the title compound (0.163 g, 56%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.71 - 0.84 (m, 12 H) 1.35 - 1.49 (m, 8 H) 1.69 (d,

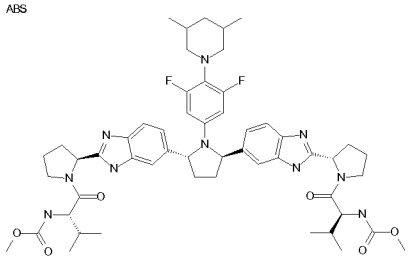
J=5.42 Hz, 2 H) 1.83 - 1.94 (m, 2 H) 2.22 - 2.32 (m, 4 H) 2.76 (s, 4 H) 3.29 (s, 6 H) 3.54 (s, 6 H) 3.87 (dd, J=11.11, 3.85 Hz, 2 H) 4.03 (q, J=7.05 Hz, 4 H) 4.21 (s, 2 H) 5.02 - 5.15 (m, 2 H) 5.36 (d, J=3.25 Hz, 2 H) 5.84 - 5.94 (m, 2 H) 7.04 - 7.11 (m, 2 H) 7.19 (s, 1 H) 7.27 - 7.34 (m, 3 H) 7.41 (d, J=8.24 Hz, 1 H) 7.48 (d, J=8.24 Hz, 1 H) 12.13 (s, 1 H) 12.19 (s, 1 H); MS (ESI+) *m/z* 1011.6 $(M+H)^+$.



Example 5.6

dimethyl ({(2*R*,5*R*)-1-[3,5-difluoro-4-(piperidin-1-yl)phenyl]pyrrolidine-2,5-diyl}bis{1*H*-benzimidazole-5,2-diyl(2*S*)pyrrolidine-2,1-diyl[(1*S*)-1-cyclohexyl-2-oxoethane-2,1-diyl]})biscarbamate

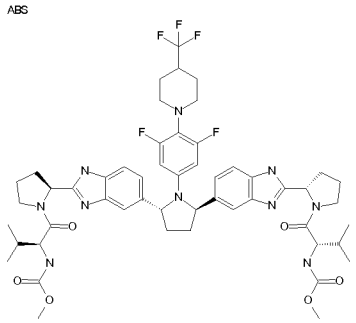
(*S*)-6,6'-((2*R*,5*R*)-1-(3,5-Difluoro-4-(piperidin-1-yl)phenyl)pyrrolidine-2,5-diyl)bis(2-((*S*)-pyrrolidin-2-yl)-1*H*-benzo[*d*]imidazole) (0.192 g, 0.302 mmol) was dissolved in dimethyl sulfoxide (4 mL) and treated with diisopropylethylamine (0.421 mL, 2.41 mmol) at ambient temperature followed by (*S*)-2-cyclohexyl-2-(methoxycarbonylamino)acetic acid (0.143 g, 0.663 mmol) and HATU (0.241 g, 0.633 mmol). After 1 hour, the solution was diluted with water and extracted into dichloromethane. The organic phase was concentrated, and the residue was purified by chromatography, eluting with 0-8% methanol in dichloromethane to give the title compound (0.166 g, 53%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.80 - 1.12 (m, 8 H) 1.36 - 1.70 (m, 24 H) 1.98 (d, J=4.45 Hz, 4 H) 2.15 - 2.25 (m, 4 H) 2.75 (s, 4 H) 3.52 (s, 6 H) 3.81 (d, J=2.39 Hz, 4 H) 4.08 (q, J=8.57 Hz, 2 H) 5.14 (d, J=4.23 Hz, 2 H) 5.36 (d, J=3.58 Hz, 2 H) 5.82 - 5.93 (m, 2 H) 7.10 (dd, J=13.93, 8.30 Hz, 2 H) 7.15 - 7.28 (m, 4 H) 7.42 (d, J=7.37 Hz, 1 H) 7.48 (dd, J=8.35, 1.84 Hz, 1 H) 12.00 (s, 1 H) 12.16 (s, 1 H); MS (ESI+) *m/z* 1031.4 $(M+H)^+$.



Example 5.7

methyl {(2*S*)-1-[(2*S*)-2-{6-[(2*R*,5*R*)-1-[4-(3,5-dimethylpiperidin-1-yl)-3,5-difluorophenyl]-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

Diisopropylethylamine (3 mL, 17.18 mmol) was added to a suspension of (*S*)-6,6'-((2*R*,5*R*)-1-(4-(3,5-dimethylpiperidin-1-yl)-3,5-difluorophenyl)pyrrolidine-2,5-diyl)bis(2-((*S*)-pyrrolidin-2-yl)-1*H*-benzo[*d*]imidazole) (1.045 g, 1.572 mmol), (*S*)-2-(methoxycarbonylamino)-3-methylbutanoic acid (0.6852 g, 3.91 mmol), and HATU (1.4995 g, 3.94 mmol) in dichloromethane (20 mL). The reaction mixture was stirred at ambient temperature for 30 minutes. The reaction was diluted with dichloromethane, washed with water (2×), brine (1×), and concentrated. The residue was purified by flash chromatography (2–5% methanol/dichloromethane) to afford the title compound (0.7107 g, 46%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.50 (q, J = 11.9, 1H), 0.97 - 0.64 (m, 18H), 1.32 - 1.20 (m, 2H), 1.81 - 1.46 (m, 5H), 2.09 - 1.80 (m, 6H), 2.32 - 2.13 (m, 5H), 2.75 (dd, J = 10.0, 40.2, 2H), 3.18 - 3.05 (m, 1H), 3.54 (s, 6H), 3.82 (s, 4H), 4.14 - 3.95 (m, 2H), 5.14 (s, 2H), 5.36 (d, J = 7.2, 2H), 5.88 (d, J = 12.8, 2H), 7.14 - 7.02 (m, 2H), 7.19 (s, 1H), 7.33 - 7.23 (m, 3H), 7.41 (d, J = 8.2, 1H), 7.49 (d, J = 8.2, 1H), 12.37 - 11.98 (m, 2H); MS (ESI+) *m/z* 979 $(M+H)^+$.

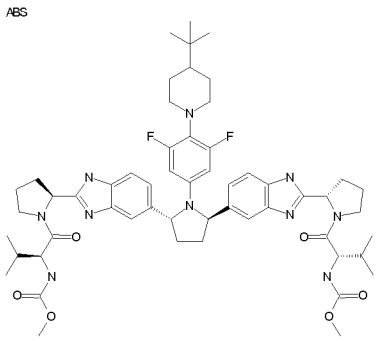


Example 5.8

methyl {(2*S*)-1-[(2*S*)-2-{5-[(2*R*,5*R*)-1-{3,5-difluoro-4-[4-(trifluoromethyl)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

(*S*)-6,6'-((2*R*,5*R*)-1-(3,5-Difluoro-4-(4-(trifluoromethyl)piperidin-1-yl)phenyl)pyrrolidine-2,5-diyl)bis(2-((*S*)-pyrrolidin-2-yl)-1*H*-benzo[*d*]imidazole) tetrahydrochloride (250 mg, 0.294 mmol) and (*S*)-2-(methoxycarbonylamino)-3-methylbutanoic acid (113 mg, 0.647 mmol) were combined in anhydrous DMF (3 mL) under nitrogen. HOBT hydrate (113 mg, 0.735 mmol) and EDAC (144 mg, 0.735 mmol) were added. The amber-colored solution was cooled to 0 °C. 4-Methylmorpholine (0.323 mL, 2.94 mmol) was added, the cooling bath was removed, and the reaction mixture was stirred at 20 °C. After 2 hours, the reaction was diluted with EtOAc (50 mL) and washed with water (3×25 mL) and brine (25 mL). The organic phase was dried over anhydrous $MgSO_4$, filtered, and

concentrated by rotary evaporation to a tan solid (300 mg). An aliquot (50 mg) of crude material was dissolved in 2 mL acetonitrile and 2 mL 0.1% TFA in H_2O, and purified by RP-C18 HPLC (Waters Prep LC, 40 mm Module with Nova-Pak HR C18 6μm 40×100 mm Prep Pak cartridge) eluting with a 30 minutes gradient of 95:5 0.1% TFA in H_2O/acetonitrile to 25:75 0.1% TFA in H_2O/acetonitrile, then 10 minutes to 100% acetonitrile at 20 mL/minute (10 mL fractions). Pure fractions were treated with saturated aq $NaHCO_3$ (2 mL/tube), each tube was vortexed to thoroughly neutralize TFA, and the neutralized solutions were combined in a 250-mL round bottom flask. The acetonitrile was removed by rotary evaporation, and extracted the remaining aqueous phase with EtOAc (2×50 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated by rotary evaporation to afford the title compound as a white solid (18 mg). Repeated purification of an additional 100 mg as above by prep-HPLC in two 50-mg injections. Workup as above afforded additional title compound as a white solid (34 mg). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.73 - 0.90 (m, 12 H), 1.23 (s, 1 H), 1.34 - 1.49 (m, 2 H), 1.63 - 1.76 (m, 4 H), 1.83 - 2.04 (m, 6 H), 2.11 - 2.25 (m, 4 H), 2.84 (m, 4 H), 3.52 (s, 6 H), 3.81 (br s, 4 H), 4.00 - 4.09 (m, 2 H), 5.08 - 5.18 (m, 2 H), 5.28 - 5.42 (m, 2 H), 5.89 (d, *J*=12.79 Hz, 2 H), 7.06 (t, *J*=7.26 Hz, 2 H), 7.16 - 7.32 (m, 4 H), 7.39 (d, *J*=8.24 Hz, 1 H), 7.47 (d, *J*=8.13 Hz, 1 H), 12.06 (two s, 2 H); MS (ESI+) *m/z* 1019 $(M+H)^+$.

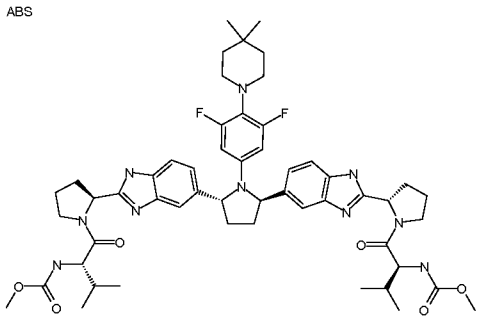


Example 5.9

methyl {(2*S*)-1-[(2*S*)-2-{5-[(2*R*,5*R*)-1-[4-(4-*tert*-butylpiperidin-1-yl)-3,5-difluorophenyl]-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

(*S*)-6,6'-((2*R*,5*R*)-1-(4-(4-*tert*-Butylpiperidin-1-yl)-3,5-difluorophenyl)pyrrolidine-2,5-diyl)bis(2-((*S*)-pyrrolidin-2-yl)-1*H*-benzo[*d*]imidazole) tetrahydrochloride (250 mg, 0.298 mmol) and (*S*)-2-(methoxycarbonylamino)-3-methylbutanoic acid (115 mg, 0.656 mmol) were combined in anhydrous DMF (3 mL) under nitrogen. HOBT hydrate (114 mg, 0.745 mmol) and EDAC (146 mg, 0.745 mmol) were added, and then the amber-colored solution was cooled to 0 °C. 4-Methylmorpholine (0.328 mL, 2.98 mmol) was added, the cooling bath was removed, and the reaction mixture was stirred at 20 °C. After 18 hours, the reaction mixture was diluted with EtOAc (50 mL),

washed with water (3×25 mL) and brine (25 mL). The organic phase was dried over anhydrous $MgSO_4$, filtered, and concentrated by rotary evaporation to a yellow solid. Pre-purified by SiO_2 flash chromatography (Alltech Extract-Clean™ column, 10 g bed) eluting with 3% CH_3OH/CH_2Cl_2 afforded a yellow solid (119 mg). An aliquot (50 mg) of the residue was dissolved in 2 mL acetonitrile and 2 mL 0.1% TFA in H_2O, and purified by RP-C18 HPLC (Waters Prep LC, 40 mm Module with Nova-Pak HR C18 6 μm 40×100 mm Prep Pak cartridge) eluting with a 30 minutes gradient of 95:5 0.1% TFA in H_2O/acetonitrile to 25:75 0.1% TFA in H_2O/acetonitrile, then 10 minutes to 100% acetonitrile at 20 mL/minute (10 mL fractions). Pure fractions were treated with saturated aq $NaHCO_3$ (2 mL/tube), each tube was vortexed to thoroughly neutralize TFA, and the solutions were combined in a 250-mL round bottom flask. The remaining 69 mg of material was purified by prep-HPLC as described above. The pure product-containing fractions were treated with saturated aq $NaHCO_3$ as above and combined in the same 250-mL round bottom flask. The acetonitrile was removed by rotary evaporation, the remaining aqueous phase was extracted with EtOAc (2×50 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated by rotary evaporation to afford the title compound as a white solid (56 mg). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.68 - 0.93 (m, 22 H), 1.09 - 1.25 (m, 2 H), 1.53 (d, J=11.93 Hz, 2 H), 1.63 - 1.75 (m, 2 H), 1.80 - 2.08 (m, 7 H), 2.12 - 2.27 (m, 4 H), 2.71 - 2.91 (m, 5 H), 3.54 (s, 6 H), 3.82 (br s, 4 H), 4.06 (t, J=8.35 Hz, 2 H), 5.09 - 5.19 (m, 2 H), 5.30 - 5.44 (m, 2 H), 5.89 (d, J=12.69 Hz, 2 H), 7.02 - 7.11 (m, 2 H), 7.17 - 7.32 (m, 4 H), 7.40 (d, J=8.24 Hz, 1 H), 7.49 (d, J=8.13 Hz, 1 H), 12.07 (two s, 2 H); MS (ESI+) m/z 1007 $(M+H)^+$.

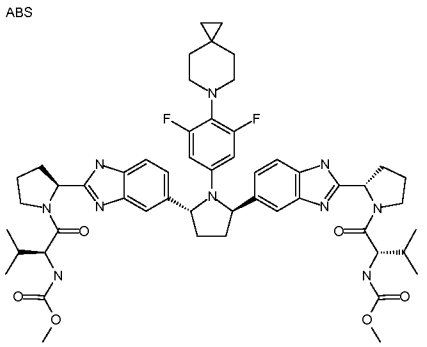


Example 5.10

methyl {(2*S*)-1-[(2*S*)-2-{5-[(2*R*,5*R*)-1-[4-(4,4-dimethylpiperidin-1-yl)-3,5-difluorophenyl]-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

(*S*)-6,6'-((2*R*,5*R*)-1-(4-(4,4-Dimethylpiperidin-1-yl)-3,5-difluorophenyl)pyrrolidine-2,5-diyl)bis(2-((*S*)-pyrrolidin-2-yl)-1*H*-benzo[*d*]imidazole) pentahydrochloride (250 mg, 0.295 mmol) and (*S*)-2-(methoxycarbonylamino)-3-methylbutanoic acid (109 mg, 0.620 mmol) were combined in anhydrous DMF (3 mL) under nitrogen. HOBT hydrate (104 mg, 0.679 mmol), and EDAC (133 mg,

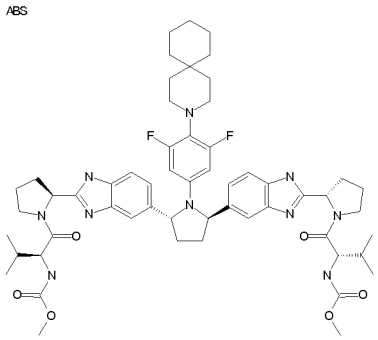
0.679 mmol) were added, and then the amber-colored solution was cooled to 0 °C. 4-Methylmorpholine (0.325 mL, 2.95 mmol) was added, the cooling bath was removed, and the reaction mixture was stirred at 20 °C. After 2 hours, the reaction mixture was diluted with EtOAc (50 mL), and washed with water (3×25 mL) and brine (25 mL). The organic phase was dried over anhydrous $MgSO_4$, filtered, and concentrated by rotary evaporation to a tan solid. Purification by SiO_2 flash chromatography (3.8 cm×15 cm) eluting with a step gradient of 3% to 4% CH_3OH/CH_2Cl_2 afforded the title compound as a solid (115 mg). An aliquot (50 mg) was dissolved in 1.5 mL acetonitrile and 1.5 mL 0.1% TFA in H_2O, and purified by RP-C18 HPLC (Waters Prep LC, 40 mm Module with Nova-Pak HR C18 6 μm 40x100 mm Prep Pak cartridge) eluting with a 30 minutes gradient of 95:5 0.1% TFA in H_2O/acetonitrile to 25:75 0.1% TFA in H_2O/acetonitrile, then 10 minutes to 100% acetonitrile at 20 mL/minute (10 mL fractions). Pure fractions were treated with saturated aq $NaHCO_3$ (2 mL/tube), each tube was vortexed to thoroughly neutralize TFA, and the solutions were combined in a 250-mL round bottom flask. Acetonitrile was removed by concentration in vacuo. The remaining aqueous phase was extracted with EtOAc (2×50 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated by rotary evaporation to afford the title compound as a white solid (33 mg). The remaining 65 mg of impure product (from silica gel column) were purified by RP-C18 prep HPLC as described above to obtain additional title compound as a white solid (33mg). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.75 - 0.91 (m, 12 H), 0.87 (s, 6 H), 1.21 - 1.35 (m, 4 H), 1.63 - 1.77 (m, 2 H), 1.81 - 2.09 (m, 6 H), 2.11 - 2.29 (m, 4 H), 2.49 - 2.59 (m, 2 H), 2.76 (s, 4 H), 3.54 (s, 6 H), 3.82 (br s, 4 H), 4.06 (t, *J*=8.46 Hz, 2 H), 5.09 - 5.22 (m, 2 H), 5.30 - 5.44 (m, 2 H), 5.89 (d, *J*=12.79 Hz, 2 H), 7.03 - 7.11 (m, 2 H), 7.17 - 7.32 (m, 4 H), 7.41 (d, *J*=8.13 Hz, 1 H), 7.49 (d, *J*=8.02 Hz, 1 H), 12.07 (two s, 2 H); (ESI+) *m/z* 979 $(M+H)^+$; MS (ESI-) *m/z* 977 $(M-H)^-$.



Example 5.11

methyl {(2*S*)-1-[(2*S*)-2-{5-[(2*R*,5*R*)-1-[4-(6-azaspiro[2.5]oct-6-yl)-3,5-difluorophenyl]-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

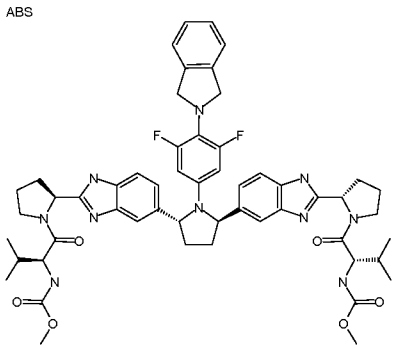
(*S*)-6,6'-((2*R*,5*R*)-1-(3,5-Difluoro-4-(6-azaspiro[2.5]octan-6-yl)phenyl)pyrrolidine-2,5-diyl)bis(2-((*S*)-pyrrolidin-2-yl)-1*H*-benzo[*d*]imidazole) tetrahydrochloride (250 mg, 0.309 mmol) and (*S*)-2-(methoxycarbonylamino)-3-methylbutanoic acid (119 mg, 0.680 mmol) were combined in anhydrous DMF (3 mL) under nitrogen. HOBT hydrate (118 mg, 0.773 mmol) and EDAC (151 mg, 0.773 mmol), were added, and then the amber-colored solution was cooled to 0 °C. 4-Methylmorpholine (0.340 mL, 3.09 mmol) was added, the cooling bath was removed, and the reaction mixture was stirred at 20 °C. After 16.5 hours, the reaction mixture was diluted with EtOAc (50 mL), and washed with water (3×25 mL) and brine (25 mL). The organic phase was dried over anhydrous $MgSO_4$, filtered, and concentrated by rotary evaporation to a yellow solid. Pre-purification by SiO_2 flash chromatography (Alltech Extract-Clean™ column, 10 g bed) eluting with 3% CH_3OH/CH_2Cl_2 to afforded a beige solid (172 mg). An aliquot (50 mg) was dissolved in 1.5 mL acetonitrile and 1.5 mL 0.1% TFA in H_2O, and purified by RP-C18 HPLC (Waters Prep LC, 40 mm Module with Nova-Pak HR C18 6 μm 40×100mm Prep Pak cartridge) eluting with a 30 minutes gradient of 95:5 0.1% TFA in H_2O/acetonitrile to 25:75 0.1% TFA in H_2O/acetonitrile, then 10 minutes to 100% acetonitrile at 20 mL/minute (10 mL fractions). Pure fractions were treated with saturated aq $NaHCO_3$ (2 mL/tube), each tube was vortexed to thoroughly neutralize TFA, and the solutions were combined in a 250-mL round bottom flask. Two additional 50 mg lots were purified by prep-HPLC as described above, and the pure product-containing fractions were treated with saturated aq $NaHCO_3$ as above and combined in the same 250-mL round bottom flask. The acetonitrile was removed by concentration in vacuo, and the remaining aqueous phase was extracted with EtOAc (2×50 mL). The combined organic phases were dried over anhydrous $MgSO_4$, filtered, and concentrated by rotary evaporation to afford the title compound as a white solid (42 mg). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.22 (s, 4 H), 0.72 - 0.93 (m, 12 H), 1.21 - 1.36 (m, 5 H), 1.61 - 1.78 (m, 2 H), 1.83 - 2.08 (m, 7 H), 2.13 - 2.27 (m, 4 H), 2.81 (br s, 4 H), 3.53 (s, 6 H), 3.82 (br s, 4 H), 4.06 (t, *J*=8.40 Hz, 2 H), 5.10-5.19 (m, 2 H), 5.29 - 5.45 (m, 2 H), 5.90 (d, *J*=12.79 Hz, 2 H), 7.02 - 7.32 (m, 6 H), 7.41 (d, *J*=8.24 Hz, 1 H), 7.49 (d, *J*=8.24 Hz, 1 H), 12.07 (two s, 2 H); MS (ESI+) *m/z* 977 $(M+H)^+$.



Example 5.12

methyl {(2*S*)-1-[(2*S*)-2-{5-[(2*R*,5*R*)-1-[4-(3-azaspiro[5.5]undec-3-yl)-3,5-difluorophenyl]-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

(*S*)-6,6'-((2*R*,5*R*)-1-(3,5-Difluoro-4-(3-azaspiro[5.5]undecan-3-yl)phenyl)pyrrolidine-2,5-diyl)bis(2-((*S*)-pyrrolidin-2-yl)-1*H*-benzo[*d*]imidazole) tetrahydrochloride (250 mg, 0.294 mmol) and (*S*)-2-(methoxycarbonylamino)-3-methylbutanoic acid (113 mg, 0.646 mmol) were combined in anhydrous DMF (3 mL) under nitrogen. HOBT hydrate (113 mg, 0.735 mmol) and EDAC (144 mg, 0.735 mmol), were added, and then the mixture was cooled to 0 °C. 4-Methylmorpholine (0.323 mL, 2.94 mmol) was added, the cooling bath was removed, and the reaction mixture was stirred at 20 °C for 18 hours. The reaction mixture was diluted with EtOAc (50 mL) and washed with water (3×25 mL) and brine (25 mL). The organic phase was dried over anhydrous $MgSO_4$, filtered, and concentrated by rotary evaporation to a beige foam. The crude material was purified by SiO_2 flash chromatography (3.8 cm×15 cm) eluting with 4% CH_3OH/CH_2Cl_2 to afford the title compound as a white solid (82 mg). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.72 - 0.93 (m, 12 H), 1.22 - 1.41 (m, 15 H), 1.63 - 1.74 (m, 2 H), 1.80 - 2.07 (m, 7 H), 2.12 - 2.27 (m, 4 H), 2.75 (s, 4 H), 3.54 (s, 6 H), 3.82 (s, 4 H), 4.06 (t, *J*=8.40 Hz, 2 H), 5.14 (d, *J*=1.19 Hz, 2 H), 5.27 - 5.42 (m, 2 H), 5.88 (d, *J*=12.69 Hz, 2 H), 7.03 - 7.11 (m, 2 H), 7.20 (s, 1 H), 7.29 (d, *J*=5.96 Hz, 3 H), 7.40 (d, *J*=8.24 Hz, 1 H), 7.49 (d, *J*=8.24 Hz, 1 H), 12.07 (m, 2 H); MS (ESI+) *m/z* 1019 $(M+H)^+$, (ESI-) *m/z* 1017 $(M-H)^-$.

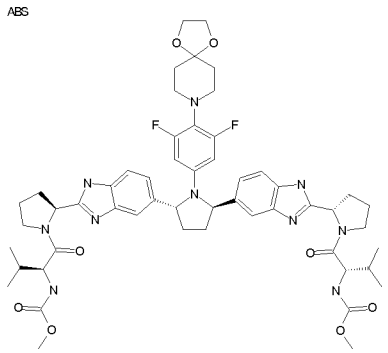


Example 5.13

methyl {(2*S*)-1-[(2*S*)-2-{5-[(2*R*,5*R*)-1-[4-(1,3-dihydro-2H-isoindol-2-yl)-3,5-difluorophenyl]-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

(*S*)-6,6'-((2*R*,5*R*)-1-(3,5-Difluoro-4-(isoindolin-2-yl)phenyl)pyrrolidine-2,5-diyl)bis(2-((*S*)-pyrrolidin-2-yl)-1*H*-benzo[*d*]imidazole) tetrahydrochloride (250 mg, 0.306 mmol) and (*S*)-2-(methoxycarbonylamino)-3-methylbutanoic acid (118 mg, 0.673 mmol) were combined in anhydrous DMF (3 mL) under nitrogen. HOBT hydrate (117 mg, 0.765 mmol) and EDAC (150 mg, 0.765 mmol) were added, then the amber-colored solution was cooled to 0 °C. 4-Methylmorpholine (0.337

mL, 3.06 mmol) was added, the cooling bath was removed, and the reaction mixture was stirred at 20 °C for 16 hours. The reaction mixture was diluted with EtOAc (50 mL) and this mixture was washed with water (3×25 mL) and brine (25 mL). The organic phase over dried over anhydrous $MgSO_4$, filtered, and concentrated by rotary evaporation to a greenish-yellow solid. The solid was purified by SiO_2 flash chromatography (3.8 cm×15 cm) eluting with 4% CH_3OH/CH_2Cl_2 to afford an off-white solid (104 mg). An aliquot (52 mg) was dissolved acetonitrile (2 mL) and 0.1% TFA in H_2O (2 mL) and purified by RP-C18 HPLC (Waters Prep LC, 40 mm Module with Nova-Pak HR C18 6 μm 40x100 mm Prep Pak cartridge) eluting with a 30 minutes gradient of 95:5 0.1% TFA in H_2O/acetonitrile to 25:75 0.1% TFA in H_2O/acetonitrile, then 10 minutes to 100% acetonitrile at 20 mL/minute (10 mL fractions). Pure fractions were treated with saturated aq $NaHCO_3$ (2 mL/tube), each tube was vortexed to thoroughly neutralize TFA, and the solutions were combined in a 500-mL round bottom flask. The remaining 52 mg of material were purified by prep-HPLC as described above and the pure product-containing fractions were treated with saturated aq $NaHCO_3$ as described above. The product containing fractions were combined in the same 500-mL round bottom flask. The acetonitrile was removed by rotary evaporation. The remaining aqueous phase was extracted with EtOAc (2×50 mL). The combined organic phases were dried over anhydrous $MgSO_4$, filtered, and concentrated by rotary evaporation to afford the title compound as a white solid (88 mg). ^1H NMR (400 MHz, DMSO-d_6) δ ppm 0.75 - 0.92 (m, 12 H), 1.61 - 2.08 (m, 8 H), 2.11 - 2.26 (m, 3 H), 2.57 (s, 2 H), 3.54 (s, 6 H), 3.83 (s, 4 H), 4.07 (t, *J*=8.29 Hz, 2 H), 4.26 - 4.43 (m, 4 H), 5.10 - 5.23 (m, 2 H), 5.33 - 5.50 (m, 2 H), 5.99 (d, *J*=12.79 Hz, 2 H), 7.09 (t, *J*=6.83 Hz, 2 H), 7.20 (s, 4 H), 7.22 - 7.37 (m, 4 H), 7.42 (d, *J*=8.24 Hz, 1 H), 7.50 (d, *J*=8.13 Hz, 1 H), 12.09 (m, 2 H); MS (ESI+) *m/z* 985 $(M+H)^+$, (ESI-) *m/z* 983 $(M-H)^-$.



Example 5.14

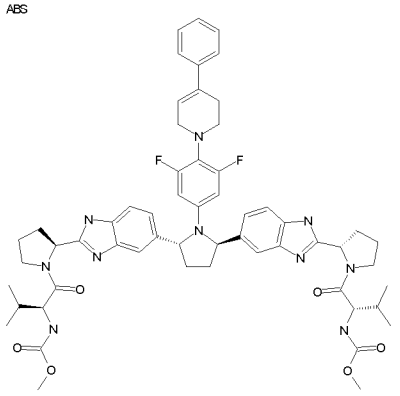
methyl {(2*S*)-1-[(2*S*)-2-{5-[(2*R*,5*R*)-1-[4-(1,4-dioxa-8-azaspiro[4.5]dec-8-yl)-3,5-difluorophenyl]-5-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1*H*-benzimidazol-5-yl}pyrrolidin-2-yl]-1*H*-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

Part A

The compound 8-(4-((2*R*,5*R*)-2,5-bis(4-chloro-3-nitrophenyl)pyrrolidin-1-yl)-2,6-difluorophenyl)-1,4-dioxa-8-azaspiro[4.5]decane can be transformed following the methods of General Procedure 8.1 and General Procedure 9D (PtO2) to obtain dimethyl (2*S*,2'*S*)-1,1'-((2*S*,2'*S*)-2,2'-(4,4'-((2*R*,5*R*)-1-(3,5-difluoro-4-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)phenyl)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.

Part B

In an oven-dried 10-mL round bottom flask, dimethyl (2*S*,2'*S*)-1,1'-((2*S*,2'*S*)-2,2'-(4,4'-((2*R*,5*R*)-1-(3,5-difluoro-4-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)phenyl)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 (200 mg, 0.191 mmol) was dissolved in anhydrous toluene (2 mL) under nitrogen. Glacial acetic acid (0.110 mL, 1.914 mmol) was added, and the solution was stirred in an oil bath at 60 °C. After 1.5 hours, the reaction mixture was cooled to room temperature, diluted with EtOAc (50 mL), and washed with saturated aq $NaHCO_3$ (25 mL). The organic phase was dried over anhydrous $MgSO_4$, filtered, and concentrated by rotary evaporation to afford the crude title compound as a tan solid (185 mg). An aliquot (93 mg) of the impure material was dissolved acetonitrile (2 mL) and 0.1% TFA in H_2O (2 mL) and purified by RP-C18 HPLC (Waters Prep LC, 40 mm Module with Nova Pak HR C18 6 μm 40x100 mm Prep Pak cartridge) eluting with a 30 minutes gradient of 95:5 0.1% TFA in H_2O/acetonitrile to 25:75 0.1% TFA in H_2O/acetonitrile, then 10 minutes to 100% acetonitrile at 20 mL/minute. Pure fractions were immediately treated with saturated aq $NaHCO_3$ (2 mL/tube), each tube was vortexed to thoroughly neutralize TFA, and the solutions were combined in a 500-mL round bottom flask. The remaining 92 mg were purified by preparative-HPLC as described above and the pure product-containing fractions were treated with saturated aq $NaHCO_3$ as described above. The additional fractions were combined in the same 500-mL round bottom flask. The acetonitrile was removed by rotary evaporation, and the remaining aqueous phase was extracted with EtOAc (2×50 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated by rotary evaporation to afford the title compound as a white solid (103 mg). 1H NMR (400 MHz, DMSO-d_6) δ ppm 0.73 - 0.94 (m, 12 H), 1.51 - 1.61 (m, 4 H), 1.63 - 1.75 (m, 2 H), 1.83 - 2.10 (m, 8 H), 2.13 - 2.29 (m, 4 H), 2.86 (s, 4 H), 3.54 (s, 6 H), 3.83 (s, 8 H), 4.06 (t, *J*=8.51 Hz, 2 H), 5.09 - 5.21 (m, 2 H), 5.30 - 5.42 (m, 2 H), 5.90 (d, *J*=12.69 Hz, 2 H), 7.01 - 7.12 (m, 2 H), 7.17 - 7.32 (m, 4 H), 7.40 (s, 1 H), 7.49 (d, *J*=8.24 Hz, 1 H), 11.71 - 12.53 (m, 2 H); MS (ESI+) *m/z* 1009 $(M+H)^+$, (ESI-) *m/z* 1007 $(M-H)^-$.



Example 5.15

methyl {(2*S*)-1-[(2*S*)-2-{5-[(2*R*,5*R*)-1-[3,5-difluoro-4-(4-phenyl-3,6-dihydropyridin-1(2H)-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

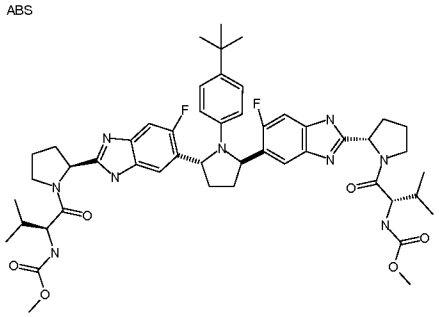
Part A

The compound 1-(4-((2*R*,5*R*)-2,5-bis(4-chloro-3-nitrophenyl)pyrrolidin-1-yl)-2,6-difluorophenyl)-4-phenyl-1,2,3,6-tetrahydropyridine can be transformed following the methods of General Procedure 8.1 and General Procedure 9E to obtain dimethyl (2*S*,2'*S*)-1,1'-((2*S*,2'*S*)-2,2'-(4,4'-((2*R*,5*R*)-1-(3,5-difluoro-4-(4-phenyl-5,6-dihydropyridin-1(2H)-yl)phenyl)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.

PartB

In an oven-dried 5-mL round bottom flask, dimethyl (2*S*,2'*S*)-1,1'-((2*S*,2'*S*)-2,2'-(4,4'-((2*R*,5*R*)-1-(3,5-difluoro-4-(4-phenyl-5,6-dihydropyridin-1(2H)-yl)phenyl)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 (75 mg, 0.071 mmol) was dissolved in anhydrous toluene (1 mL) under nitrogen. Glacial acetic acid (0.041 mL, 0.707 mmol) was added, and the solution was stirred in an oil bath at 60 °C. After 1.5 hours, the yellow reaction mixture was cooled to room temperature, diluted in EtOAc (50 mL), and washed with saturated aq $NaHCO_3$ (25 mL). The organic phase was dried over anhydrous $MgSO_4$, filtered, and concentrated by rotary evaporation to a yellow solid (~80 mg). The residue was dissolved in 2 mL acetonitrile and 2 mL 0.1% TFA in H_2O, and purified by RP-C18 HPLC (Waters Prep LC, 40 mm Module with Nova-Pak HR C18 6 μm 40x100 mm Prep Pak cartridge) eluting with a 30 minutes gradient of 95:5 0.1% TFA in H_2O/acetonitrile to 25:75 0.1% TFA in H_2O/acetonitrile, then 10 minutes to 100% acetonitrile at 20 mL/minute (10 mL fractions). Pure fractions were treated with saturated aq $NaHCO_3$ (2 mL/tube), each tube was vortexed to thoroughly neutralize TFA, and the solutions were combined in a 250-mL round bottom flask. The

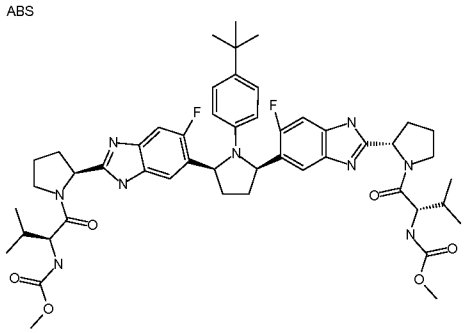
acetonitrile was removed by rotary evaporation, and the remaining aqueous phase was extracted with EtOAc (2×50 mL). The organic phase was dried over anhydrous $MgSO_4$, filtered, and concentrated by rotary evaporation to afford the product as an off-white solid (34 mg). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.76 - 0.94 (m, 12 H), 1.70 (d, *J*=4.55 Hz, 2 H), 1.83 - 2.10 (m, 6 H), 2.11 - 2.26 (m, 3 H), 2.44 (s, 1 H), 2.56 (s, 4 H), 3.09 (s, 2 H), 3.48 (s, 2 H), 3.54 (s, 6 H), 3.82 (s, 4 H), 4.07 (t, *J*=8.35 Hz, 2 H), 5.09 - 5.22 (m, 2 H), 5.30 - 5.46 (m, 2 H), 5.95 (d, *J*=12.90 Hz, 2 H), 6.09 (s, 1 H), 7.04 - 7.17 (m, 2 H), 7.19 - 7.25 (m, 2 H), 7.26 - 7.34 (m, 5 H), 7.36 - 7.45 (m, 3 H), 7.50 (d, *J*=8.35 Hz, 1 H), 11.71 - 12.63 (m, 2 H); MS (ESI+) *m/z* 1025 $(M+H)^+$, (ESI-) *m/z* 1023 $(M-H)^-$.



Example 6.1

methyl {(2*S*)-1-[(2*S*)-2-{5-[(2*R*,5*R*)-1-(4-*tert*-butylphenyl)-5-{5-fluoro-2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1*H*-benzimidazol-6-yl}pyrrolidin-2-yl]-6-fluoro-1*H*-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

To 6,6'-[(2*R*,5*R*)-1-(4-*tert*-butylphenyl)pyrrolidine-2,5-diyl]bis{5-fluoro-2-[(2*S*)-pyrrolidin-2-yl]-1*H*-benzimidazole} was added DMF (1.0 mL) followed by *N*-methylmorpholine (0.045mL, 0.41 mmol), (*S*)-2-(methoxycarbonylamino)-3-methylbutanoic acid (15mg, 0.09 mmol), EDC (20mg, 0.1 mmol) and HOBT (16mg, 0.1 mmol). The solution was stirred at room temperature for 18 hours. The reaction mixture was diluted with EtOAc, washed with H_2O and brine, dried (Na_2SO_4), filtered and concentrated. The product was purified by reverse-phase HPLC chromatography (5-100% CH_3CN/0.1%TFA-H_2O); the desired fractions were neutralized with aqueous $NaHCO_3$ solution, extracted with EtOAc, dried, filtered and solvent evaporated to give the title compound (6.7mg, 7.2 μmol, 18%): ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 10.48 (m, 1H) 10.25 (m, 1H) 7.39 (m, 1H) 7.14 (m, 1H) 6.98 (m, 3H) 6.29 (m, 1H) 5.54 (br s, 1H) 5.34 (br s, 4H) 4.31 (m, 1H) 3.82 (m, 2H) 3.70 (s, 6H) 3.51-3.65 (m, 2H) 3.03 (br s, 2H) 2.51 (br s, 2H) 2.23-2.40 (m, 2H) 2.14 (m, 4H) 1.95 (m, 4H) 1.27 (m, 2H) 1.09-1.23 (m, 9H) 1.07 (m, 3H) 0.87 (m, 9H) 0.67-0.79 (m, 2H); MS (ESI) *m/z* 924 $(M+H)^+$.



Example 6.2

methyl {(2*S*)-1-[(2*S*)-2-{5-[(2*R*,5*S*)-1-(4-*tert*-butylphenyl)-5-{5-fluoro-2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1*H*-benzimidazol-6-yl}pyrrolidin-2-yl]-6-fluoro-1*H*-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

From the HPLC purification of Example 6.1, the cis isomer (6.4mg, 6.9μmol, 17%) was also obtained: ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 11.62 (s, 1H) 11.37 (s, 1H) 7.45-7.55 (m, 3H) 7.36 (d, 1H) 7.04 (d, 2H) 6.92 (d, 1H) 6.77 (d, 1H) 6.41 (d, 2H) 5.36-5.40 (m, 2H) 5.33 (m, 1H) 5.07 (t, 1H) 3.98-4.07 (m, 1H) 3.93 (m, 1H) 3.74-3.86 (m, 2H) 3.72 (m, 1H) 3.59 (m, 2H) 2.80 (m, 1H) 2.50 (s, 6H) 2.32 (s, 4H) 1.86-2.27 (m, 7H) 1.78 (m, 1H) 1.17 (s, 9H) 0.86-1.01 (m, 9H); MS (ESI) *m/z* 924 $(M+H)^+$.

The following example compounds 6.3-6.11 can be made from the appropriate listed intermediate amine following generally the method of Example 6.1:

Intermediate amines:

6,6'-[(2*R*,5*R*)-1-(4-*tert*-butylphenyl)pyrrolidine-2,5-diyl]bis{7-fluoro-2-[(2*S*)-pyrrolidin-2-yl]-1*H*-benzimidazole} (ACD Name v12);

6,6'-[(2*R*,5*S*)-1-(4-*tert*-butylphenyl)pyrrolidine-2,5-diyl]bis{7-fluoro-2-[(2*S*)-pyrrolidin-2-yl]-1*H*-benzimidazole} (ACD Name v12);

6,6'-[(2*R*,5*R*)-1-(4-*tert*-butylphenyl)pyrrolidine-2,5-diyl]bis{7-chloro-2-[(2*S*)-pyrrolidin-2-yl]-1*H*-benzimidazole} (ACD Name v12);

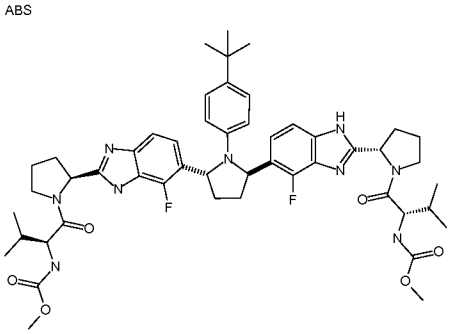
6,6'-[(2*R*,5*S*)-1-(4-*tert*-butylphenyl)pyrrolidine-2,5-diyl]bis{7-chloro-2-[(2*S*)-pyrrolidin-2-yl]-1*H*-benzimidazole} (ACD Name v12);

6,6'-[(2*R*,5*R*)-1-(4-*tert*-butylphenyl)pyrrolidine-2,5-diyl]bis{7-methyl-2-[(2*S*)-pyrrolidin-2-yl]-1*H*-benzimidazole} (ACD Name v12);

6,6'-[(2*R*,5*S*)-1-(4-*tert*-butylphenyl)pyrrolidine-2,5-diyl]bis{7-methyl-2-[(2*S*)-pyrrolidin-2-yl]-1*H*-benzimidazole} (ACD Name v12);

6,6'-{(2*R*,5*R*)-1-[3-fluoro-4-(piperidin-1-yl)phenyl]pyrrolidine-2,5-diyl}bis{5-fluoro-2-[(2*S*)-pyrrolidin-2-yl]-1*H*-benzimidazole} (ACD Name v12);

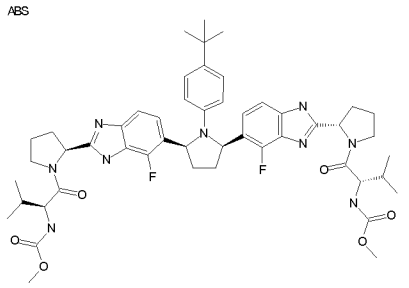
6,6'-{(2*R*,5*R*)-1-[3,5-difluoro-4-(piperidin-1-yl)phenyl]pyrrolidine-2,5-diyl}bis{5-fluoro-2-[(2*S*)-pyrrolidin-2-yl]-1*H*-benzimidazole} (ACD Name v12); and
6,6'-{(2*R*,5*R*)-1-[3,5-difluoro-4-(4-phenylpiperidin-1-yl)phenyl]pyrrolidine-2,5-diyl}bis{5-fluoro-2-[(2*S*)-pyrrolidin-2-yl]-1*H*-benzimidazole} (ACD Name v12).



Example 6.3

methyl {(2*S*)-1-[(2*S*)-2-{5-[(2*R*,5*R*)-1-(4-*tert*-butylphenyl)-5-{7-fluoro-2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1*H*-benzimidazol-6-yl}pyrrolidin-2-yl]-4-fluoro-1*H*-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

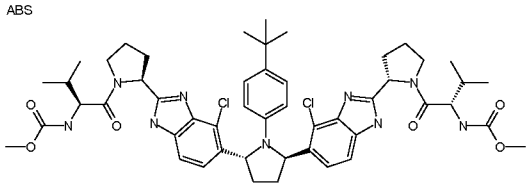
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 10.41-10.64 (m, 2H) 6.84-7.06 (m, 6H) 6.25-6.36 (m, 2H) 5.55-5.68 (m, 1H) 5.25-5.46 (m, 4H) 4.27-4.40 (m, 1H) 3.79-3.92 (m, 2H) 3.71 (s, 6H) 3.56-3.67 (m, 2H) 3.03-3.27 (m, 2H) 1.83-2.66 (m, 10H) 1.14 (s, 9H) 0.77-1.31 (m, 14H); MS (ESI) *m/z* 924 $(M+H)^+$.



Example 6.4

methyl {(2*S*)-1-[(2*S*)-2-{5-[(2*R*,5*S*)-1-(4-*tert*-butylphenyl)-5-{7-fluoro-2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1*H*-benzimidazol-6-yl}pyrrolidin-2-yl]-4-fluoro-1*H*-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

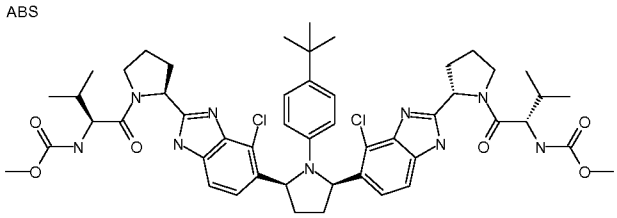
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 10.54-10.71 (m, 2H) 7.54-7.68 (m, 2H) 7.00-7.21 (m, 4H) 6.43-6.54 (m, 2H) 5.27-5.50 (m, 4H) 5.20 (br s, 2H) 4.29-4.42 (m, 1H) 3.80-3.94 (m, 2H) 3.71 (s, 6H) 3.59-3.69 (m, 2H) 3.04-3.29 (m, 2H) 1.86-2.66 (m, 10H) 1.18 (s, 9H) 0.79-1.33 (m, 14H); MS (ESI) *m/z* 924 $(M+H)^+$.



Example 6.5

methyl {(2*S*)-1-[(2*S*)-2-{5-[(2*R*,5*R*)-1-(4-*tert*-butylphenyl)-5-{4-chloro-2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1*H*-benzimidazol-5-yl}pyrrolidin-2-yl]-4-chloro-1*H*-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

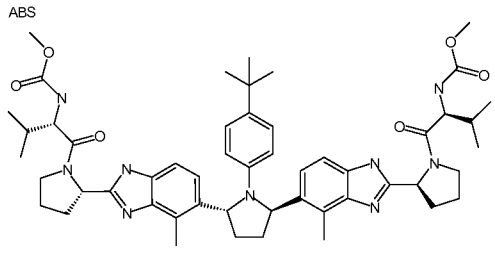
^{1}H NMR (400 MHz, DMSO-d_6) δ 12.70 (s, 0H), 12.39 (s, 1H), 8.07 (s, 1H), 7.32 (dd, J = 26.1, 8.1, 3H), 6.91 (d, J = 37.0, 4H), 6.08 (d, J = 7.9, 1H), 5.64 (s, 1H), 5.17 (s, 1H), 4.66 (s, 1H), 4.10 (d, J = 5.2, 1H), 3.86 (s, 3H), 3.52 (d, J = 14.1, 6H), 3.17 (d, J = 5.2, 1H), 2.30 – 2.10 (m, 2H), 2.00 (s, 4H), 1.77 (s, 1H), 1.23 (s, 1H), 1.18 – 1.01 (m, 9H), 1.01 – 0.72 (m, 11H); MS (APCI+) *m/z* 958.76 $(M+H)^+$.



Example 6.6

methyl {(2*S*)-1-[(2*S*)-2-{5-[(2*R*,5*S*)-1-(4-*tert*-butylphenyl)-5-{4-chloro-2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1*H*-benzimidazol-5-yl}pyrrolidin-2-yl]-4-chloro-1*H*-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

^{1}H NMR (400 MHz, DMSO-d_6) δ 12.45 (s, 1H), 8.06 (d, J = 3.3, 1H), 7.68 (d, J = 8.6, 2H), 7.48 (t, J = 12.5, 2H), 7.31 (d, J = 8.2, 2H), 7.00 (d, J = 8.1, 2H), 6.20 (d, J = 8.7, 2H), 5.16 (d, J = 32.0, 4H), 4.66 (s, 1H), 4.11 (s, 1H), 3.88 (s, 3H), 3.56 (d, J = 8.1, 6H), 2.30 – 2.09 (m, 5H), 2.02 (s, 7H), 1.80 (s, 2H), 1.23 (s, 2H), 1.09 (s, 9H), 1.00 – 0.78 (m, 12H); MS(APCI+) *m/z* 958.64 $(M+H)^+$.

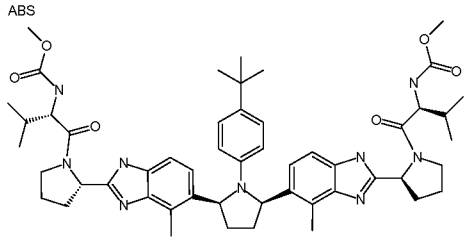


Example 6.7

methyl {(2*S*)-1-[(2*S*)-2-{5-[(2*R*,5*R*)-1-(4-*tert*-butylphenyl)-5-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-4-methyl-1*H*-benzimidazol-5-

yl}pyrrolidin-2-yl]-4-methyl-1*H*-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

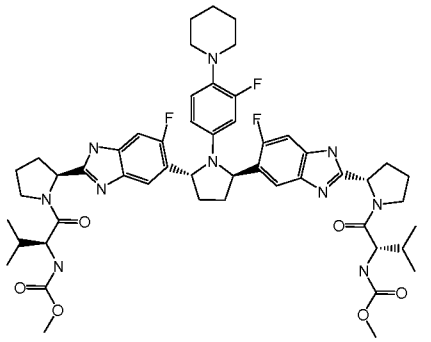
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.78 - 1.05 (m, 14 H), 1.06 (s, 9 H), 1.86 - 2.06 (m, 8 H), 2.09 - 2.31 (m, 4 H), 2.58 - 2.72 (m, 6 H), 3.54 (s, 6 H), 3.79 - 3.93 (m, 4 H), 4.02 - 4.17 (m, 2 H), 5.11 - 5.23 (m, 2 H), 5.42 - 5.51 (m, 2 H), 6.02 - 6.12 (m, 2 H), 6.71 - 6.83 (m, 2 H), 6.83 - 6.96 (m, 2 H), 7.04 - 7.19 (m, 2 H), 7.24 - 7.35 (m, 2 H), 11.84 - 12.26 (m, 2 H).



Example 6.8

methyl {(2*S*)-1-[(2*S*)-2-{5-[(2*R*,5*S*)-1-(4-*tert*-butylphenyl)-5-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-4-methyl-1*H*-benzimidazol-5-yl}pyrrolidin-2-yl]-4-methyl-1*H*-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.79 - 1.06 (m, 12 H), 1.23 (s, 9 H), 1.87 - 2.31 (m, *J*=30.69 Hz, 12 H), 2.58 - 2.65 (m, *J*=3.25 Hz, 6 H), 3.55 (s, 6 H), 3.81 - 3.96 (m, 4 H), 4.01 - 4.19 (m, 2 H), 4.92 (s, 2 H), 5.12 - 5.26 (m, 2 H), 6.14 - 6.26 (m, 2 H), 6.86 - 7.02 (m, 2 H), 7.22 - 7.39 (m, 4 H), 7.57 - 7.79 (m, 2 H), 11.90 - 12.32 (m, 2 H); MS (ESI) *m/z* = 916.4 $(M+H)^+$.

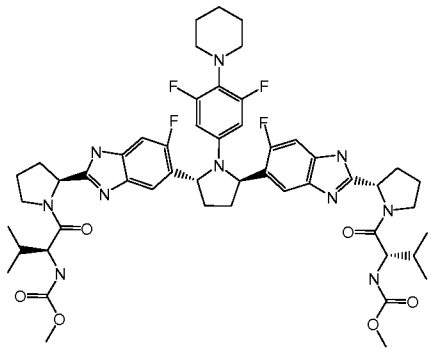


Example 6.9

methyl {(2*S*)-1-[(2*S*)-2-(6-fluoro-5-{(2*R*,5*R*)-5-{6-fluoro-2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1*H*-benzimidazol-5-yl}-1-[3-fluoro-4-(piperidin-1-yl)phenyl]pyrrolidin-2-yl}-1*H*-benzimidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 10.21-10.67 (m, 2H) 6.55-7.99 (m, 6H) 5.95-6.14 (m, 1H) 5.19-5.56 (m, 6H) 4.25-4.39 (m, 1H) 3.77-3.92 (m, 2H) 3.70 (s, 6H) 3.42-3.76 (m, 3H) 2.95-3.17 (m, 2H)

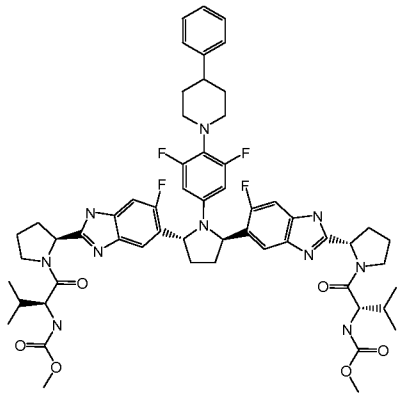
2.64-2.95 (m, 2H) 2.43-2.64 (m, 1H) 1.78-2.42 (m, 11H) 0.62-1.78 (m, 18H); MS (ESI) *m/z* 969 $(M+H)^+$.



Example 6.10

methyl {(2*S*)-1-[(2*S*)-2-{5-[(2*R*,5*R*)-1-[3,5-difluoro-4-(piperidin-1-yl)phenyl]-5-{6-fluoro-2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1*H*-benzimidazol-5-yl}pyrrolidin-2-yl]-6-fluoro-1*H*-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

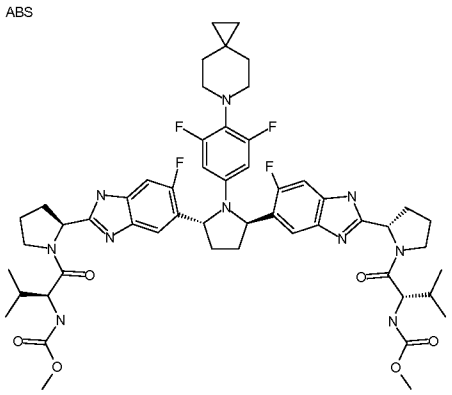
To a solution of 6,6'-{(2*R*,5*R*)-1-[3,5-difluoro-4-(piperidin-1-yl)phenyl]pyrrolidine-2,5-diyl}bis{5-fluoro-2-[(2*S*)-pyrrolidin-2-yl]-1*H*-benzimidazole} (64 mg, 0.095 mmol) in DMF (2378 μL) was added (*S*)-2-(methoxycarbonylamino)-3-methylbutanoic acid (35.0 mg, 0.200 mmol), EDC (45.6 mg, 0.238 mmol), HOBT (36.4 mg, 0.238 mmol) and *N*-methylmorpholine (105 μL, 0.951 mmol), and the resultant solution was stirred at ambient temperature overnight. The reaction solution was diluted with EtOAc, washed with H_2O and brine, dried (MgSO4), filtered and concentrated. The crude material was dissolved in 1:1 CH_3CN:0.1% TFA/H_2O and purified by HPLC (C18, 0-100% CH_3CN/0.1%TFA/H_2O). The product containing fractions were combined, made basic with saturated sodium bicarbonate solution, and extracted with EtOAc. The organic layer was dried ($MgSO_4$), filtered and concentrated to give the title compound (43.3 mg, 0.044 mmol, 46.1 % yield). The title compound can also be prepared according to General Procedure 12C described above. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 10.25-10.70 (m, 2H) 6.83-7.53 (m, 4H) 5.70-5.91 (m, 2H) 5.20-5.52 (m, 4H) 4.21-4.42 (m, 2H) 3.70 (s, 6H) 3.53-3.94 (m, 6H) 1.75-3.17 (m, 16H) 0.63-1.74 (m, 18H); MS (ESI) *m/z* 987 $(M+H)^+$.



Example 6.11

methyl {(2*S*)-1-[(2*S*)-2-{5-[(2*R*,5*R*)-1-[3,5-difluoro-4-(4-phenylpiperidin-1-yl)phenyl]-5-{6-fluoro-2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1*H*-benzimidazol-5-yl}pyrrolidin-2-yl]-6-fluoro-1*H*-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 10.54 (br s, 2H) 7.09-7.33 (m, 9H) 5.77-5.92 (m, 2H) 5.23-5.52 (m, 4H) 4.24-4.39 (m, 2H) 3.79-3.91 (m, 2H) 3.70 (s, 6H) 3.55-3.67 (m, 2H) 2.92-3.21 (m, 5H) 1.73-2.65 (m, 10H) 0.97-1.74 (m, 8H) 0.76-0.96 (m, 12H); MS (ESI) *m/z* 1063 $(M+H)^+$.

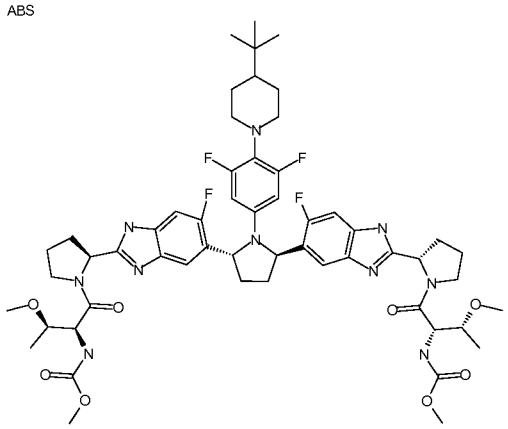


Example 6.12

methyl {(2*S*)-1-[(2*S*)-2-{5-[(2*R*,5*R*)-1-[4-(6-azaspiro[2.5]oct-6-yl)-3,5-difluorophenyl]-5-{6-fluoro-2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1*H*-benzimidazol-5-yl}pyrrolidin-2-yl]-6-fluoro-1*H*-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

In an oven-dried 5-mL pear-shaped flask, dissolved (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (56.6 mg, 0.323 mmol) in anhydrous CH_2Cl_2 (1 mL) under nitrogen, added EDAC (63.2 mg, 0.323 mmol), and stirred at 20 °C for 20 min. The resulting solution was added via gas-tight syringe to a solution of (S)-6,6'-((2R,5R)-1-(3,5-difluoro-4-(6-azaspiro[2.5]octan-6-yl)phenyl)pyrrolidine-2,5-diyl)bis(5-fluoro-2-((S)-pyrrolidin-2-yl)-1H-benzo[d]imidazole)

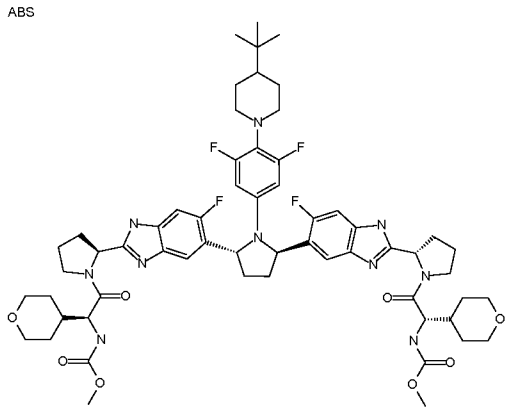
hydrochloride (91 mg) and diisopropylethylamine (0.188 mL, 1.077 mmol) in anhydrous CH_2Cl_2 (2 mL) under nitrogen, added HOBt hydrate (49.5 mg, 0.323 mmol), and stirred at 20 °C for 1 hr. The reaction was diluted with CH_2Cl_2 (50 mL), washed with water (25 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated by rotary evaporation to a dark yellow foam (~140 mg). Dissolved 70 mg of the impure material in 2 mL Acetonitrile and 2 mL 0.1% TFA in H_2O, and purified by RP-C_{18} HPLC (Waters Prep LC, 40mm Module with Nova Pak HR C18 6μm 40x100mm Prep Pak cartridge) eluting with a 30 min gradient of 95:5 0.1% TFA in H_2O/Acetonitrile to 25:75 0.1% TFA in H_2O/Acetonitrile, then 10 min to 100% Acetonitrile at 20 mL/min. Pure fractions were treated with saturated aqueous $NaHCO_3$ (2 mL/tube), vortexed each tube to thoroughly neutralize TFA, and combined the solutions in a 500-mL round bottom flask. Purified the remaining 70 mg by prep-HPLC as above and the pure product-containing fractions were treated with saturated aqueous $NaHCO_3$ as above and combined in the same 500-mL round bottom flask. Removed the Acetonitrile by rotary evaporation, extracted the remaining aqueous phase with EtOAc (2 x 50 mL), dried the combined organic extracts over anhydrous $MgSO_4$, filtered, and concentrated by rotary evaporation to afford the product as a white solid (49 mg, 0.048 mmol). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.24 (s, 4 H), 0.68 - 0.91 (m, 12 H), 1.21 - 1.35 (m, 5 H), 1.67 - 2.07 (m, 9 H), 2.13 - 2.24 (m, 4 H), 2.84 (s, 4 H), 3.53 (s, 6 H), 3.73 - 3.87 (m, 4 H), 3.99 - 4.11 (m, 2 H), 5.02 - 5.23 (m, 2 H), 5.45 - 5.65 (m, 2 H), 5.81 - 5.99 (m, 2 H), 7.04 (d, *J*=6.07 Hz, 1 H), 7.14 (d, *J*=6.94 Hz, 1 H), 7.26 - 7.36 (m, 3 H), 7.41 (dd, *J*=11.06, 6.18 Hz, 1 H), 11.73 - 12.63 (m, 2 H); MS (ESI+) *m/z* 1013 $(M+H)^+$; MS (ESI-) *m/z* 1011 $(M-H)^-$.



Example 6.13

methyl {(2*S*,3*R*)-1-[(2*S*)-2-{5-[(2*R*,5*R*)-1-[4-(4-*tert*-butylpiperidin-1-yl)-3,5-difluorophenyl]-5-(6-fluoro-2-{(2*S*)-1-[*N*-(methoxycarbonyl)-*O*-methyl-L-threonyl]pyrrolidin-2-yl}-1*H*-benzimidazol-5-yl)pyrrolidin-2-yl]-6-fluoro-1*H*-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methoxy-1-oxobutan-2-yl}carbamate

(2S,3R)-3-Methoxy-2-(methoxycarbonylamino)butanoic acid (65.6 mg, 0.343 mmol) was dissolved in anhydrous CH_2Cl_2 (1 mL) under nitrogen. EDAC (67.1 mg, 0.343 mmol) was added, and the mixture was stirred at 20 °C for 20 minutes. The resulting solution was added via to a solution of (S)-6,6'-((2R,5R)-1-(4-(4-*tert*-butylpiperidin-1-yl)-3,5-difluorophenyl)pyrrolidine-2,5-diyl)bis(5-fluoro-2-((S)-pyrrolidin-2-yl)-1H-benzo[d]imidazole) hydrochloride (100 mg) and diisopropylamine (0.200 mL, 1.143 mmol) in anhydrous CH_2Cl_2 (2 mL) under nitrogen. HOBt hydrate (52.5 mg, 0.343 mmol) was added, and the mixture was stirred at 20 °C for 1 hour. The reaction was diluted with CH_2Cl_2 (50 mL), washed with water (25 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated by rotary evaporation to a dark yellow foam (140 mg). The crude material (70 mg) was dissolved in acetonitrile (2 mL) and 0.1% TFA in H_2O (2 mL), and purified by RP-C_{18} HPLC (Waters Prep LC, 40 mm module with Nova-Pak® HR C18 6μm 40×100mm Prep Pak cartridge) eluting with a 30 minute gradient of 95:5 0.1% TFA in H_2O/acetonitrile to 25:75 0.1% TFA in H_2O/acetonitrile, then 10 minutes to 100% acetonitrile at 20 mL/minute. Pure fractions were treated with saturated aqueous $NaHCO_3$ (2 mL/tube), each tube was vortexed to thoroughly neutralize TFA, and the fractions were combined in a 500-mL round bottom flask. The remaining 70 mg of material was purified by prep-HPLC as described above and the pure product-containing fractions were treated with saturated aqueous $NaHCO_3$ as above and combined in the same 500-mL round bottom flask. The acetonitrile was removed by rotary evaporation, the remaining aqueous phase was extracted with EtOAc (2×50 mL), the combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated by rotary evaporation to afford the product as a white solid (62 mg, 0.057 mmol). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.80 (s, 9 H), 0.92 (d, *J*=6.07 Hz, 2 H), 0.98 - 1.09 (m, 4 H), 1.12 - 1.22 (m, 2 H), 1.44 - 1.63 (m, 3 H), 1.65 - 1.89 (m, 3 H), 1.91 - 2.10 (m, 4 H), 2.11 - 2.28 (m, 4 H), 2.73 - 2.92 (m, 4 H), 3.04 (d, *J*=1.73 Hz, 2 H), 3.13 (s, 3 H), 3.25 (d, *J*=3.47 Hz, 1 H), 3.41 - 3.50 (m, 3 H), 3.53 (s, 6 H), 3.72 - 3.92 (m, 4 H), 4.25 (q, *J*=7.99 Hz, 2 H), 5.02 - 5.17 (m, 2 H), 5.46 - 5.63 (m, 2 H), 5.79 - 6.00 (m, 2 H), 7.02 (d, *J*=6.72 Hz, 1 H), 7.08 - 7.18 (m, 2 H), 7.24 (d, *J*=8.02 Hz, 1 H), 7.33 (dd, *J*=10.36, 4.50 Hz, 1 H), 7.40 (dd, *J*=11.22, 6.23 Hz, 1 H), 11.84 - 12.63 (m, 2 H); MS (ESI+) *m/z* 1075 $(M+H)^+$; MS (ESI-) *m/z* 1073 $(M-H)^-$.

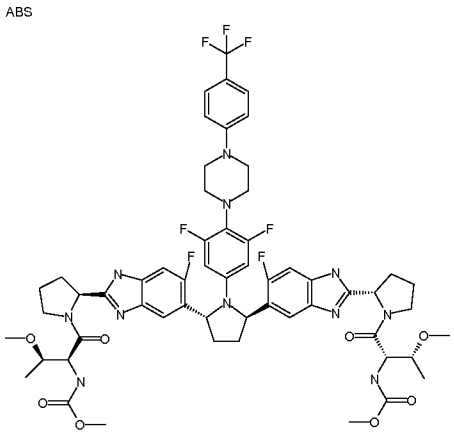


Example 6.14

dimethyl ({(2*R*,5*R*)-1-[4-(4-*tert*-butylpiperidin-1-yl)-3,5-difluorophenyl]pyrrolidine-2,5-diyl}bis{(6-fluoro-1*H*-benzimidazole-5,2-diyl)(2*S*)pyrrolidine-2,1-diyl[(1*S*)-2-oxo-1-(tetrahydro-2*H*-pyran-4-yl)ethane-2,1-diyl]})biscarbamate

(S)-2-(Methoxycarbonylamino)-2-(tetrahydro-2H-pyran-4-yl)acetic acid (74.5 mg, 0.343 mmol) was dissolved in anhydrous CH_2Cl_2 (1 mL) under nitrogen. EDAC (67.1 mg, 0.343 mmol) was added, and the mixture was stirred at 20 °C for 20 minutes. The resulting solution was added to a solution of (S)-6,6'-((2R,5R)-1-(4-(4-*tert*-butylpiperidin-1-yl)-3,5-difluorophenyl)pyrrolidine-2,5-diyl)bis(5-fluoro-2-((S)-pyrrolidin-2-yl)-1H-benzo[d]imidazole) hydrochloride (100 mg) and diisopropylethylamine (0.200 mL, 1.143 mmol) in anhydrous CH_2Cl_2 (2 mL) under nitrogen. HOBt hydrate (52.5 mg, 0.343 mmol) was added, and the mixture was stirred at 20 °C for 1 hour. The reaction was diluted with CH_2Cl_2 (50 mL), washed with water (25 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated by rotary evaporation to a dark yellow solid (210 mg). The impure material (70 mg) was dissolved in 2 mL acetonitrile and 2 mL 0.1% TFA in H_2O, and purified by RP-C_{18} HPLC (Waters Prep LC, 40mm module with Nova-Pak® HR C18 6μm 40×100mm Prep Pak cartridge) eluting with a 30 minute gradient of 95:5 0.1% TFA in H_2O/acetonitrile to 25:75 0.1% TFA in H_2O/acetonitrile, then 10 minutes to 100% acetonitrile at 20 mL/minute. Pure fractions were treated with saturated aqueous $NaHCO_3$ (2 mL/tube), each tube was vortexed to thoroughly neutralize TFA, and the fractions were combined in a 500-mL round bottom flask. The remaining material was purified in two 70 mg injections by prep-HPLC as described above, and the pure product-containing fractions were treated with saturated aqueous $NaHCO_3$ as above and combined in the same 500-mL round bottom flask. The acetonitrile was removed by rotary evaporation, the remaining aqueous phase was extracted with EtOAc (2×50 mL), the combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated by rotary evaporation to afford the product as a white solid (69 mg, 0.060 mmol). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.80 (s, 9 H), 0.89 - 1.01 (m, 1 H), 1.07 - 1.38 (m, 7 H), 1.39 - 1.63 (m, 6 H), 1.67 - 1.91 (m, 5 H), 1.92 - 2.05 (m, 4 H), 2.10 - 2.26 (m, 4 H), 2.71 - 2.95 (m, 5 H), 2.96 - 3.25 (m, 3 H), 3.52 (s, 6 H), 3.62 - 3.92 (m, 8 H), 4.06 - 4.23 (m,

2 H), 5.10 (t, *J*=6.23 Hz, 2 H), 5.39 - 5.65 (m, 2 H), 5.77 - 5.99 (m, 2 H), 7.01 (d, *J*=6.72 Hz, 1 H), 7.07 (d, *J*=7.05 Hz, 1 H), 7.28 - 7.49 (m, 4 H), 11.78 - 12.42 (m, 2 H); MS (ESI+) *m/z* 1127 $(M+H)^+$; MS (ESI-) *m/z* 1125 $(M-H)^-$.

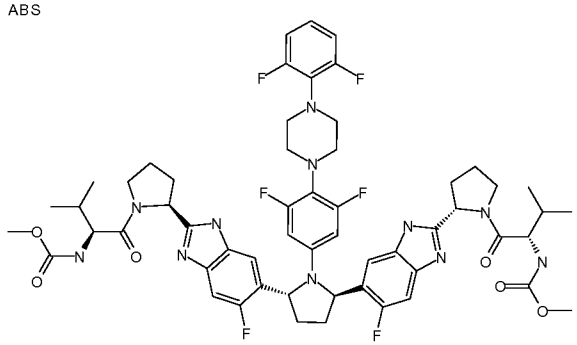


Example 6.15

methyl {(2*S*,3*R*)-1-[(2*S*)-2-{5-[(2*R*,5*R*)-1-(3,5-difluoro-4-{4-[4-(trifluoromethyl)phenyl]piperazin-1-yl}phenyl)-5-(6-fluoro-2-{(2*S*)-1-[*N*-(methoxycarbonyl)-*O*-methyl-L-threonyl]pyrrolidin-2-yl}-1*H*-benzimidazol-5-yl)pyrrolidin-2-yl]-6-fluoro-1*H*-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methoxy-1-oxobutan-2-yl}carbamate

(S)-6,6'-((2R,5R)-1-(3,5-Difluoro-4-(4-(4-(trifluoromethyl)phenyl)piperazin-1-yl)phenyl)pyrrolidine-2,5-diyl)bis(5-fluoro-2-((S)-pyrrolidin-2-yl)-1H-benzo[d]imidazole) hydrochloride (88 mg), (2S,3R)-3-methoxy-2-(methoxycarbonylamino)butanoic acid (41 mg, 0.216 mmol), N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (46 mg, 0.238 mmol), 1-hydroxybenzotriazole hydrate (36 mg, 0.238 mmol) and 4-methylmorpholine (0.095 mL, 0.864 mmol) were dissolved in DMF (3.0 mL), and the mixture stirred at room temperature for 3 hours. Afterwards, an isopropyl alcohol and chloroform mixture was added then extracted with 1 *N* aqueous hydrochloric acid. The organic extract was dried, filtered and concentrated, and then the residue was purified by chromatography (silica gel, methanol in dichloromethane) which afforded 71 mg of the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.56 (m, 2H), 7.48 (d, J=8.8Hz, 2H), 7.34 (m, 2H), 7.18 (m, 2H), 7.04 (d, J=8.6Hz, 2H), 5.97 (m, 2H), 5.62 (m, 2H), 5.17 (m, 2H), 4.28 (m, 2H), 3.82 (m, 2H), 3.60 (m, 2H), 3.54 (s, 6H), 3.25 (m, 8H), 3.17 (s, 6H), 2.99 (m, 4H), 2.05 (m, 12H), 1.25 (m, 6H); MS (ESI) *m/z* 1164 $(M+H)^+$.

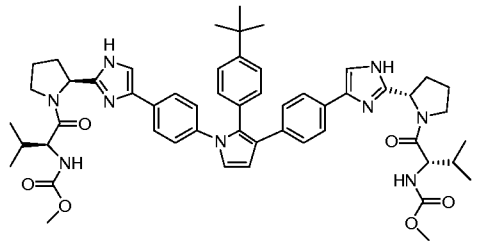
ABS



Example 6.16

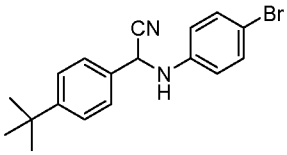
methyl {(2*S*)-1-[(2*S*)-2-{6-[(2*R*,5*R*)-1-{4-[4-(2,6-difluorophenyl)piperazin-1-yl]-3,5-difluorophenyl}-5-{5-fluoro-2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1*H*-benzimidazol-6-yl}pyrrolidin-2-yl]-5-fluoro-1*H*-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

(S)-2-(Methoxycarbonylamino)-3-methylbutanoic acid (0.072 g, 0.410 mmole) and HOBt (0.063 g, 0.410 mmole) were combined in DMF (2 mL). To the clear solution was added EDAC (0.079 g, 0.410 mmole) with a 0.2 ml DMF rinse, and the resulting clear solution was stirred at room temperature for 20 minutes. (S)-6,6'-((2R,5R)-1-(4-(4-(2,6-Difluorophenyl)piperazin-1-yl)-3,5-difluorophenyl)pyrrolidine-2,5-diyl)bis(5-fluoro-2-((S)-pyrrolidin-2-yl)-1H-benzo[d]imidazole) hydrochloride (0.160 g) was dissolved in 2 ml DMF, treated with N-methylmorpholine (1.863 mmol, 0.205 ml), and then treated with the activated amino acid solution and the resulting clear brown solution was stirred at room temperature for 1 hour. The pH of the solution was measured to be 8 by pH paper. Reaction progress was determined by LC-MS at 1 hour and analysis deemed reaction complete. The reaction mixture was concentrated in vacuo to a brown mobile oil. The oil was diluted with 50 ml EtOAc and washed with 30 mL 10% $NaHCO_3$. The layers were separated and the aqueous layer was extracted with another 50 mL EtOAc. The combined organic extracts were washed with 10% NaCl, dried over anhydrous Na_2SO_4(s), filtered and solvent removed in vacuo leaving a brown oily residue. The residue was purified on a 12 g silica gel column eluted with a gradient of CH_2Cl_2/CH_3OH, 99/1 to 95/5 over 13 minutes, then 95/5 to 90/10 over 8 minutes. The fractions containing product were combined and repurified on a 12 g gold column eluted with a gradient of CH_2Cl_2/CH_3OH, 98/2 to 90/10 over 15 minutes. The fractions were concentrated in vacuo leaving a light brown solid as the title compound (50.3 mg). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.82 (m, 12 H) 1.99 (m, 9 H) 2.18 (m, 2 H) 2.95 (m, 4 H) 3.05 - 3.17 (m, 5 H) 3.53 (s, 6 H) 3.79 (m, 4 H) 3.95 - 4.11 (m, 4 H) 5.11 (m, 2 H) 5.55 (m, 2 H) 5.91 (m, 2 H) 7.01 (m, 5 H) 7.29 (m, 4 H) 12.14 (m, 2 H); MS (ESI+) *m/z* 1100.3, (ESI-) *m/z* 1098.3(M-H)$^-$.



Example 7.1

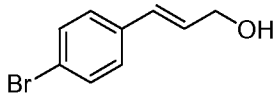
methyl {(2*S*)-1-[(2*S*)-2-(4-{4-[2-(4-*tert*-butylphenyl)-1-(4-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1*H*-imidazol-4-yl}phenyl)-1*H*-pyrrol-3-yl]phenyl}-1*H*-imidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate



Example 7.1A

2-(4-bromophenylamino)-2-(4-*tert*-butylphenyl)acetonitrile

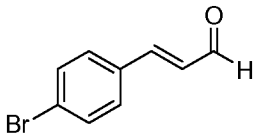
To a solution of 4-bromoaniline (10.0 g, 58.1 mmol) in THF (100 mL) was added 4-*tert*-butylbenzaldehyde (9.72 mL, 58.1 mmol), acetic acid (13.3 mL, 233 mmol), potassium cyanide (3.79 g, 58.1 mmol) and water (50 mL). The resultant mixture was stirred at room temperature for 16 hours. The resultant solid that formed was collected by vacuum filtration, washed with hexane, and then dried to afford 15.3 g, (77%) of the title compound. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.49 (m, 4H), 7.37 (d, J=8.7 Hz, 2H), 6.66 (d, J=8.8 Hz, 2H), 5.34 (d, J=8.1 Hz, 1H), 4.02 (d, J=8.0 Hz, 1H), 1.34 (s, 9H).



Example 7.1B

(*E*)-3-(4-bromophenyl)prop-2-en-1-ol

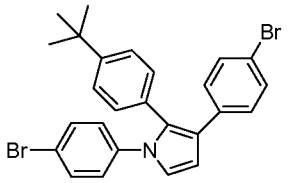
To a solution of (*E*)-ethyl 3-(4-bromophenyl)acrylate (10.0 g, 39.2 mmol) in dichloromethane (151 mL) cooled to -78°C was added a solution of diisobutylaluminum hydride (1.0 *M* in dichloromethane, 82 mL, 82 mmol) dropwise over 15 minutes time. The solution was then stirred for an additional 2 hours followed by the addition of a solution of 10% aqueous sodium hydroxide (250 mL). The mixture was allowed to warm to room temperature, and then the mixture was extracted with dichloromethane. The organic layer was dried and concentrated to afford 8.35 g (100%) of the title compound used directly in the next reaction.



Example 7.1C

(*E*)-3-(4-bromophenyl)acrylaldehyde

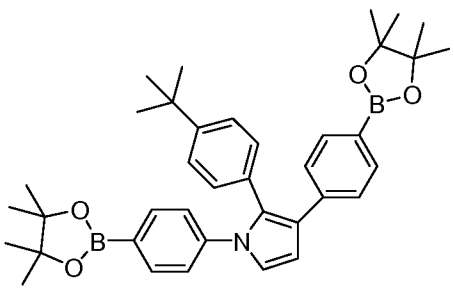
To the product of Example 7.1B (8.35 g, 39.2 mmol) dissolved in dichloromethane (151 mL) was added pyridinium dichromate (22.11 g, 58.8 mmol), and the resultant mixture was stirred for 16 hours at room temperature. A solution of hexane was added, and the resultant mixture filtered through diatomaceous earth, and then concentrated. Water was added to the residue, and the mixture was extracted with ethyl acetate. The organic layers were combined, dried and then concentrated. The residue was purified by chromatography (silica gel, hexanes in ethyl acetate) which afforded 5.5 g, (67%) of the title compound. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 9.62 (d, J=7.6 Hz, 1H), 7.57 (d, J=8.5 Hz, 2H), 7.42 (m, 3H), 6.70 (dd, J=15.9, 7.6 Hz, 1H).



Example 7.1D

1,3-bis(4-bromophenyl)-2-(4-*tert*-butylphenyl)-1*H*-pyrrole

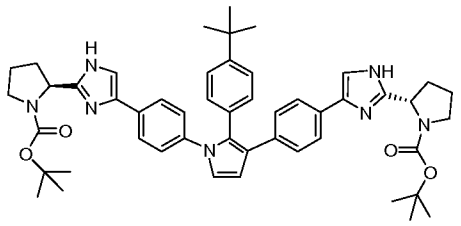
To the product of Example 7.1C (0.676 g, 3.2 mmol) and the product from Example 7.1A (1.0 g, 2.91 mmol) was added ethanol (30 mL) followed by potassium hydroxide (0.163 g, 2.91 mmol), and the mixture was stirred at room temperature for 16 hours. Afterwards the mixture was concentrated. The residue was partitioned between water and ethyl acetate. The organic layers were combined, dried and then concentrated. The residue was purified by chromatography (silica gel, hexanes in ethyl acetate) which afforded 150 mg, (10%) of the title compound. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.37 (m, 3H), 7.32 (d, J=8.5, 2H), 7.21 (d, J=8.4 Hz, 2H), 7.06 (d, J=8.3 Hz, 2H), 6.93 (m, 4H), 6.51 (dd, J=2.9 Hz, 1H), 1.29 (s, 9H).



Example 7.1E

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

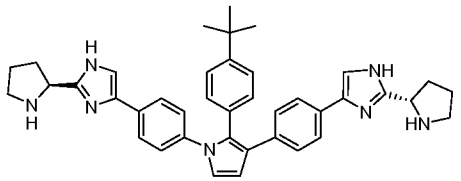
A solution of the product from Example 7.1D (150 mg, 0.295 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (165 mg, 0.648 mmol), potassium acetate (87 mg, 8.84 mmol) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane (21.6 mg, 0.029 mmol) in dioxane (5.5 mL) was heated at 100°C for 18 hours. The mixture was then filtered through diatomaceous earth and concentrated to an oil which was dissolved in EtOAc and extracted with brine. The organic extract was concentrated to afford 230 mg of the title compound that was used directly in the next step.



Example 7.1F

di-*tert*-butyl (2*S*,2'*S*)-2,2'-{[2-(4-*tert*-butylphenyl)-1*H*-pyrrole-1,3-diyl]bis(benzene-4,1-diyl-1*H*-imidazole-4,2-diyl)}dipyrrolidine-1-carboxylate (ACD Name v12)

The product from Example 7.1E (227 mg, 0.376 mmol), (*S*)-*tert*-butyl 2-(5-bromo-1*H*-imidazol-2-yl)pyrrolidine-1-carboxylate or (*S*)-*tert*-butyl 2-(4-bromo-1*H*-imidazol-2-yl)pyrrolidine-1-carboxylate (357 mg, 1.13 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane (27.5 mg, 0.038 mmol), and a solution of sodium carbonate (1.0 M in water, 1.13 mL, 1.13 mmol) were heated in a solution of ethanol (3 mL) and toluene (3 mL) at 85°C for 18 hours. The mixture then had water (10 mL) added followed by extraction with EtOAc (2×10 mL). The organic extract was dried, filtered and concentrated, and then the residue was purified by chromatography (silica gel, methanol in dichloromethane) which afforded 29 mg, (9 %) of the title compound; MS (ESI) *m/z* 823 $(M+H)^+$.



Example 7.1G

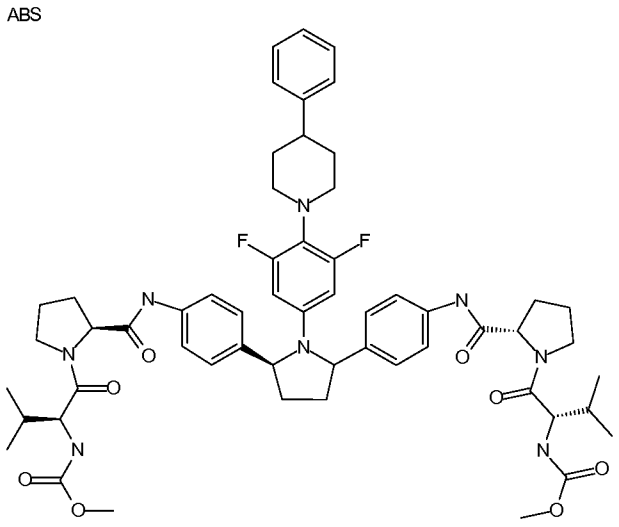
4,4'-{[2-(4-*tert*-butylphenyl)-1*H*-pyrrole-1,3-diyl]dibenzene-4,1-diyl}bis{2-[(2*S*)-pyrrolidin-2-yl]-1*H*-imidazole} (ACD Name v12)

The product of Example 7.1F (29 mg, 0.035 mmol) was dissolved in dioxane (0.5 mL) and hydrochloric acid in dioxane (4.0 *N*, 0.14 mL, 0.54 mmol) was added. The mixture was stirred at room temperature for 4 hours. Afterwards the mixture was concentrated to afford the title compound as a hydrochloride salt. MS (ESI) *m/z* 622 $(M+H)^+$.

Example 7.1H

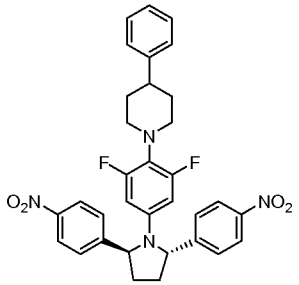
methyl {(2*S*)-1-[(2*S*)-2-(4-{4-[2-(4-*tert*-butylphenyl)-1-(4-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1*H*-imidazol-4-yl}phenyl)-1*H*-pyrrol-3-yl]phenyl}-1*H*-imidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

The product from Example 7.1G (22 mg, 0.036 mmol), (*S*)-2-(methoxycarbonylamino)-3-methylbutanoic acid (12.7 mg, 0.072 mmol), *N*-(3-dimethylaminopropyl)-*N*'-ethylcarbodiimide hydrochloride (15.2 mg, 0.079 mmol), 1-hydroxybenzotriazole hydrate (12.2 mg, 0.079 mmol) and 4-methylmorpholine (0.021 mL, 0.29 mmol) were dissolved in DMF (0.7 mL), and the mixture was stirred at room temperature for 3 hours. Afterwards, 1 *N* aqueous hydrochloric acid (5 mL) was added followed by extraction with dichloromethane (2×5 mL). The organic extract was dried, filtered and concentrated. Then the residue was purified by chromatography (silica gel, methanol in dichloromethane) which afforded 3.3 mg, (10 %) of the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.57 (s, 1H), 10.26 (s, 1H), 7.62 (m, 4H), 7.20 (m, 8H), 6.99 (m, 4H), 5.37 (m, 2H), 5.24 (m, 2H), 4.30 (m, 2H), 3.80 (m, 2H), 3.08 (m, 1H), 2.96 (s, 3H), 2.88 (s, 3H), 2.30 (m, 2H), 2.19 (m, 2H), 2.08 (m, 2H), 1.92 (m, 2H), 1.23 (m, 9H), 0.85 (m, 12H); MS (ESI) *m/z* 936 $(M+H)^+$.



Example 8

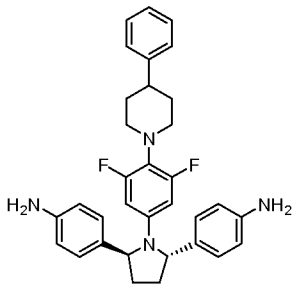
dimethyl ({(2*S*)-1-[3,5-difluoro-4-(4-phenylpiperidin-1-yl)phenyl]pyrrolidine-2,5-diyl}bis{4,1-phenylenecarbamoyl(2*S*)pyrrolidine-2,1-diyl[(2*S*)-3-methyl-1-oxobutane-1,2-diyl]})biscarbamate



Example 8A

1-(4-((2S,5S)-2,5-bis(4-nitrophenyl)pyrrolidin-1-yl)-2,6-difluorophenyl)-4-phenylpiperidine

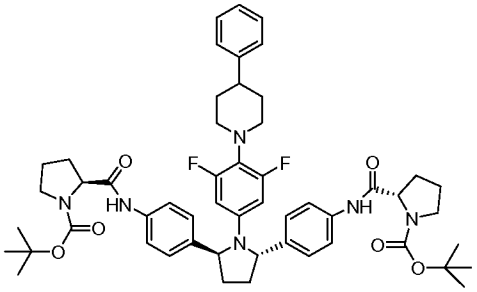
A mixture of Intermediate 6 (2.68 g, 5.49 mmol), 3,5-difluoro-4-(4-phenylpiperidin-1-yl)aniline (1.90 g, 6.58 mmol) and diisopropylethylamine (9.58 mL, 54.9 mmol) in DMF (18.3 mL) was heated at 60 °C for 18 hours. Afterwards ethyl acetate was added to the solution followed by extraction with water. The organic extract was dried, filtered and concentrated then the residue purified by chromatography (silica gel, ethyl acetate in hexanes) which afforded 197 mg, (6 %) of the title compound. MS (ESI) *m/z* 585 $(M+H)^+$.



Example 8B

4,4'-((2S,5S)-1-(3,5-difluoro-4-(4-phenylpiperidin-1-yl)phenyl)pyrrolidine-2,5-diyl)dianiline

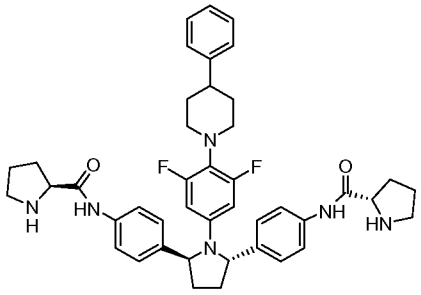
The product of Example 8A (197 mg, 0.337 mmol) was dissolved in a mixture of THF (3 mL), ethanol (3 mL) and water (0.5 mL), and then iron (95 mg, 1.69 mmol) and ammonium chloride (27 mg, 0.506 mmol) were added and the mixture heated at 80 °C for 3 hours. Afterwards ethyl acetate was added to the solution followed by extraction with sodium bicarbonate. The organic extract was dried, filtered and concentrated which afforded 177 mg (100%) of the title compound. MS (ESI) *m/z* 525 $(M+H)^+$.



Example 8C

(2S,2'S)-*tert*-butyl 2,2'-(4,4'-((2S,5S)-1-(3,5-difluoro-4-(4-phenylpiperidin-1-yl)phenyl)pyrrolidine-2,5-diyl)bis(4,1-phenylene))bis(azanediyl)bis(oxomethylene)dipyrrolidine-1-carboxylate

The product from Example 8B (177 mg, 0.337 mmol), (S)-1-(*tert*-butoxycarbonyl)pyrrolidine-2-carboxylic acid (160 mg, 0.742 mmol), N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (162 mg, 0.843 mmol), 1-hydroxybenzotriazole hydrate (129 mg, 0.843 mmol) and 4-methylmorpholine (0.370 mL, 3.37 mmol) were dissolved in dichloromethane (3.5 mL), and the mixture stirred at room temperature for 19 hours. Afterwards, aqueous sodium bicarbonate was added followed by extraction with dichloromethane. The organic extract was dried, filtered and concentrated, and then the residue was purified by chromatography (silica gel, methanol in dichloromethane) which afforded 130 mg, (42 %) of the title compound. MS (ESI) *m/z* 920 $(M+H)^+$.



Example 8D

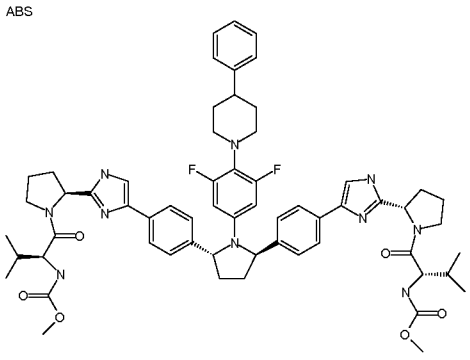
(2S,2'S)-N,N'-(4,4'-((2S,5S)-1-(3,5-difluoro-4-(4-phenylpiperidin-1-yl)phenyl)pyrrolidine-2,5-diyl)bis(4,1-phenylene))dipyrrolidine-2-carboxamide

The product of Example 8C (130 mg, 0.141 mmol) was dissolved in dichloromethane (2.7 mL) and trifluoroacetic acid (0.27 mL, 3.5 mmol) and the mixture was stirred at room temperature for 1 hour. Afterwards the mixture was concentrated, the residue was dissolved in an isopropyl alcohol and chloroform mixture and then extracted with aqueous sodium bicarbonate. The organic phase was then dried and concentrated to afford 100 mg (99%) of the title compound. MS (ESI) *m/z* 719 $(M+H)^+$.

Example 8E

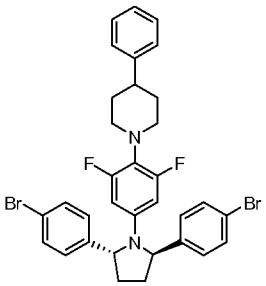
dimethyl ({(2*S*)-1-[3,5-difluoro-4-(4-phenylpiperidin-1-yl)phenyl]pyrrolidine-2,5-diyl}bis{4,1-phenylenecarbamoyl(2*S*)pyrrolidine-2,1-diyl[(2*S*)-3-methyl-1-oxobutane-1,2-diyl]})biscarbamate

The product from Example 8D (100 mg, 0.142 mmol), (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (60 mg, 0.341 mmol), N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (68 mg, 0.355 mmol), 1-hydroxybenzotriazole hydrate (54 mg, 0.355 mmol) and 4-methylmorpholine (0.156 mL, 1.42 mmol) were dissolved in DMF (1.5 mL), and the mixture was stirred at room temperature for 19 hours. Afterwards, an isopropyl alcohol and chloroform mixture was added and then extracted with aqueous sodium bicarbonate. The organic extract was dried, filtered and concentrated, and then the residue was purified by chromatography (silica gel, methanol in dichloromethane) which afforded 20 mg, (14 %) of the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.03 (s, 2H), 7.53 (d, J = 8.5Hz, 4H), 7.30 (m, 9H), 5.83 (d, J= 12.6 Hz, 2H), 5.18 (m, 2H), 5.08 (m, 2H), 4.43 (m, 2H), 4.02 (m, 4H), 3.61 (m, 2H), 3.54 (s, 6H), 2.98 (m, 4H), 2.18 (m, 2H), 1.93 (m, 6H), 1.70 (m, 6H), 0.81 (m, 12H); MS (ESI) *m/z* 1033 $(M+H)^+$.



Example 9

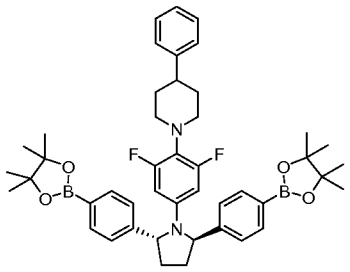
methyl {(2*S*)-1-[(2*S*)-2-(4-{4-[(2*R*,5*R*)-1-[3,5-difluoro-4-(4-phenylpiperidin-1-yl)phenyl]-5-(4-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1*H*-imidazol-4-yl}phenyl)pyrrolidin-2-yl]phenyl}-1*H*-imidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate



Example 9A

1-(4-((2R,5R)-2,5-bis(4-bromophenyl)pyrrolidin-1-yl)-2,6-difluorophenyl)-4-phenylpiperidine

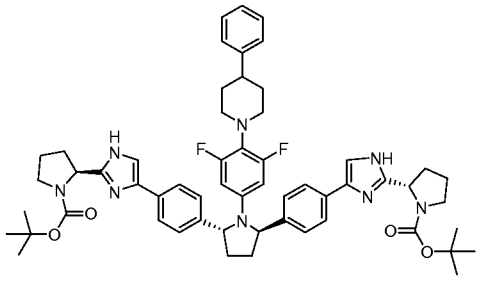
A mixture of Intermediate 7 (2.35 g, 4.22 mmol), 3,5-difluoro-4-(4-phenylpiperidin-1-yl)aniline (2.44 g, 8.45 mmol) and diisopropylethylamine (2.21 mL, 12.67 mmol) in acetonitrile (25 mL) was heated at 80°C for 9 hours. Afterwards the resultant solid was removed by filtration and purified by chromatography (silica gel, hexanes in ethyl acetate then dichloromethane in hexanes) which afforded 130 mg, (4.7%) of the title compound. MS (ESI+) *m/z* 653 $(M+H)^+$.



Example 9B

1-(4-((2R,5R)-2,5-bis(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)pyrrolidin-1-yl)-2,6-difluorophenyl)-4-phenylpiperidine

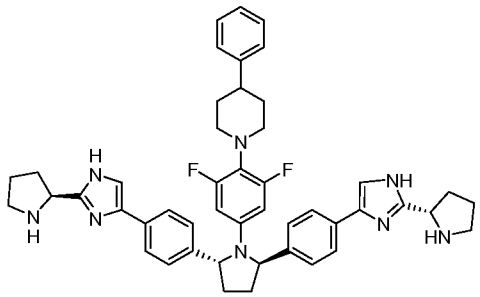
A solution of the product from Example 9A (130 mg, 0.199 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (121 mg, 0.478 mmol), potassium acetate (59 mg, 0.598 mmol) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (29 mg, 0.04 mmol) in dioxane (4.5 mL) was heated at 100 °C for 3 hours. The mixture was then filtered through diatomaceous earth and concentrated to an oil which was dissolved in EtOAc and extracted with 1 *N* aqueous hydrochloric acid. The organic extract was dried, filtered and concentrated, and then the residue was purified by chromatography (silica gel, ethyl acetate in hexanes) which afforded 50 mg, (34 %) of the title compound. MS (ESI) *m/z* 747 $(M+H)^+$.



Example 9C

(2S,2'S)-*tert*-butyl 2,2'-(4,4'-(4,4'-((2R,5R)-1-(3,5-difluoro-4-(4-phenylpiperidin-1-yl)phenyl)pyrrolidine-2,5-diyl)bis(4,1-phenylene))bis(1H-imidazole-4,2-diyl))dipyrrolidine-1-carboxylate

The product from Example 9B (50 mg, 0.067 mmol), Intermediate 1 (64 mg, 0.201 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (6.1 mg, 0.0084 mmol), and sodium carbonate (1.0 M in water, 0.27 mL, 0.27 mmol) were heated in ethanol (1.5 mL) and toluene (1.5 mL) at 85 °C for 17 hours. Water (10 mL) was added to the mixture followed by extraction with dichloromethane. The organic extract was dried, filtered and concentrated, and then the residue was purified by chromatography (silica gel, methanol in dichloromethane) which afforded 51 mg, (79 %) of the title compound. MS (ESI) *m/z* 966 $(M+H)^+$.



Example 9D

1-(4-((2R,5R)-2,5-bis(4-(2-((S)-pyrrolidin-2-yl)-1H-imidazol-4-yl)phenyl)pyrrolidin-1-yl)-2,6-difluorophenyl)-4-phenylpiperidine

The product of Example 9C (50 mg, 0.052 mmol) was dissolved in dioxane (1.5 mL) and hydrochloric acid in dioxane (4.0 *N*, 0.65 mL, 2.6 mmol), and the mixture was stirred at room temperature for 4 hours. Afterwards the mixture was concentrated to afford the title compound as a hydrochloride salt. MS (ESI) *m/z* 765 $(M+H)^+$.

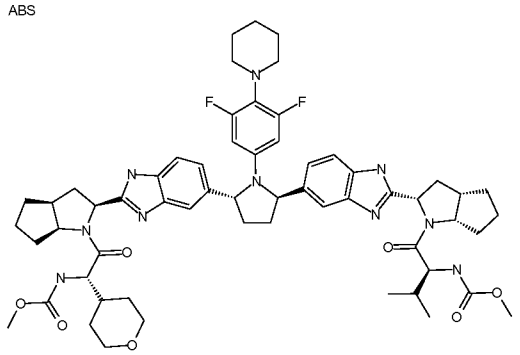
Example 9E

methyl {(2*S*)-1-[(2*S*)-2-(4-{4-[(2*R*,5*R*)-1-[3,5-difluoro-4-(4-phenylpiperidin-1-yl)phenyl]-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 9D (40 mg, 0.052 mmol), (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid (18.3 mg, 0.105 mmol), N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (22.1 mg, 0.115 mmol), 1-hydroxybenzotriazole hydrate (17.6 mg, 0.115 mmol) and 4-methylmorpholine (0.046 mL, 0.418 mmol) were dissolved in DMF (1.5 mL), and the mixture was stirred at room temperature for 19 hours. Afterwards, 1 *N* aqueous hydrochloric acid was added followed by extraction with dichloromethane. The organic extract was dried, filtered and concentrated, and then the residue was purified by chromatography (silica gel, methanol in dichloromethane) which afforded 25 mg, (44 %) of the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.64 (m, 5H), 7.23 (m, 11H), 5.89 (d, J= 12.8 Hz, 2H), 5.23 (m, 2H), 5.08 (m, 2H), 4.06 (m,

2H), 3.80 (m, 4H), 3.53 (s, 6H), 2.96 (m, 4H), 2.18 (m, 2H), 1.99 (m, 6H), 1.70 (m, 6H), 0.83 (m, 12H); MS (ESI) *m/z* 1080 $(M+H)^+$.

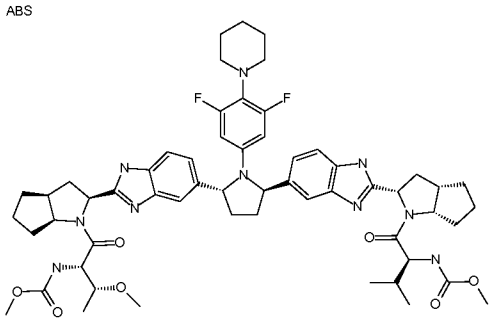
From the product of General Procedure 11C, the compounds of Examples 10.1 and 10.2 can be obtained by the steps of: (1) coupling with (S)-2-(methoxycarbonylamino)-3-methylbutanoic acid; (2) removal of the single Boc protecting group; and (3) coupling with a second selected carbamate-protected amino acid.



Example 10.1

methyl [(1*S*)-2-[(2*S*,3a*S*,6a*S*)-2-{5-[(2*R*,5*R*)-1-[3,5-difluoro-4-(piperidin-1-yl)phenyl]-5-{2-[(2*S*,3a*S*,6a*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}octahydrocyclopenta[*b*]pyrrol-2-yl]-1*H*-benzimidazol-5-yl}pyrrolidin-2-yl]-1*H*-benzimidazol-2-yl}hexahydrocyclopenta[*b*]pyrrol-1(2*H*)-yl]-2-oxo-1-(tetrahydro-2*H*-pyran-4-yl)ethyl]carbamate

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.70 - 0.91 (m, 6 H) 1.10 - 1.27 (m, 2 H) 1.34 - 1.49 (m, 8 H) 1.50 - 1.64 (m, 4 H) 1.65 - 1.81 (m, 4 H) 1.84 - 2.03 (m, 6 H) 2.05 - 2.18 (m, 4 H) 2.36 - 2.46 (m, 4 H) 2.72 - 2.86 (m, 6 H) 3.02 - 3.21 (m, 2 H) 3.54 (s, 6 H) 3.70 - 3.89 (m, 2 H) 3.97 - 4.17 (m, 2 H) 4.72 - 4.86 (m, 2 H) 5.07 - 5.20 (m, 2 H) 5.32 - 5.43 (m, 2 H) 5.84 - 5.94 (m, 2 H) 7.07 (t, J=10.08 Hz, 2 H) 7.17 - 7.27 (m, 2 H) 7.30 - 7.56 (m, 4 H) 11.92 - 11.99 (m, 1 H) 12.03 - 12.13 (m, 1 H); MS (ESI+) *m/z* 1073.4 $(M+H)^+$.

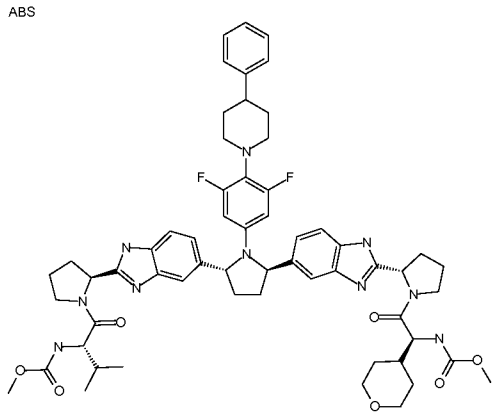


Example 10.2

methyl {(2*S*,3*R*)-1-[(2*S*,3a*S*,6a*S*)-2-{5-[(2*R*,5*R*)-1-[3,5-difluoro-4-(piperidin-1-yl)phenyl]-5-{2-[(2*S*,3a*S*,6a*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}octahydrocyclopenta[*b*]pyrrol-2-yl]-1*H*-benzimidazol-5-yl}pyrrolidin-2-yl]-1*H*-benzimidazol-2-yl}hexahydrocyclopenta[*b*]pyrrol-1(2*H*)-yl]-3-methoxy-1-oxobutan-2-yl}carbamate

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.70 - 0.89 (m, 6 H) 0.99 (ddd, J=34.43, 6.29, 3.31 Hz, 3 H) 1.35 - 1.48 (m, 6 H) 1.50 - 1.63 (m, 4 H) 1.66 - 1.80 (m, 6 H) 1.83 - 2.00 (m, 6 H) 2.05 - 2.16 (m, 4 H) 2.72 - 2.83 (m, 4 H) 3.17 (s, 3 H) 3.21 - 3.28 (m, 4 H) 3.54 (s, 6 H) 4.02 (t, J=7.48 Hz, 1 H) 4.20 - 4.30 (m, 1 H) 4.80 (t, J=7.97 Hz, 2 H) 5.08 - 5.17 (m, 2 H) 5.32 - 5.43 (m, 2 H) 5.83 - 5.94 (m, 2 H) 7.05 (dd, J=8.24, 1.30 Hz, 2 H) 7.21 (s, 1 H) 7.30 (d, J=3.14 Hz, 1 H) 7.40 (d, J=7.92 Hz, 1 H) 7.45 - 7.56 (m, 3 H) 11.99 (dd, J=9.87, 1.63 Hz, 1 H) 12.04 - 12.13 (m, 1 H); MS (ESI+) *m/z* 1047.5 $(M+H)^+$.

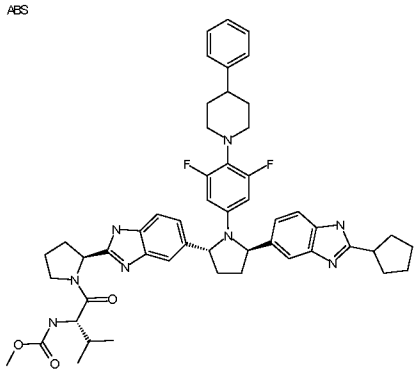
From the product of General Procedure 8B, Example 1B (mono-displacement), the compounds of Examples 11.1 and 11.2 can be obtained by the steps of: (1) Buchwald reaction with an appropriate second amide (see General Procedure 8); (2) nitro reduction (see General Procedure 9); and (3) cyclization (see General Procedure 10).



Example 11.1

methyl [(1*S*)-2-[(2*S*)-2-{5-[(2*R*,5*R*)-1-[3,5-difluoro-4-(4-phenylpiperidin-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]-2-oxo-1-(tetrahydro-2*H*-pyran-4-yl)ethyl]carbamate

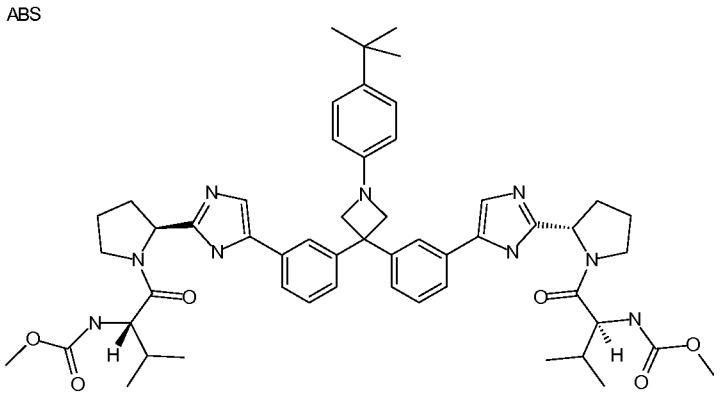
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.74 - 0.91 (m, 6 H) 1.44 - 1.56 (m, 2 H) 1.62 - 1.75 (m, 6 H) 1.82 - 1.95 (m, 2 H) 1.97 - 2.07 (m, 4 H) 2.16 - 2.26 (m, 4 H) 2.87 - 3.16 (m, 7 H) 3.43 - 3.50 (m, 2 H) 3.53 (s, 6 H) 3.58 - 3.66 (m, 2 H) 3.70 - 3.78 (m, 2 H) 3.80 - 3.89 (m, 4 H) 4.06 (t, J=8.51 Hz, 2 H) 5.11 - 5.19 (m, 2 H) 5.33 - 5.43 (m, 2 H) 5.86 - 5.95 (m, 2 H) 7.06 - 7.11 (m, 2 H) 7.12 - 7.37 (m, 9 H) 7.42 (dd, J=7.92, 1.73 Hz, 1 H) 7.46 - 7.53 (m, 1 H) 12.04 - 12.20 (m, 2 H); MS (ESI+) *m/z* 1069.4 $(M+H)^+$.



Example 11.2

methyl {(2*S*)-1-[(2*S*)-2-(5-{(2*R*,5*R*)-5-(2-cyclopentyl-1*H*-benzimidazol-5-yl)-1-[3,5-difluoro-4-(4-phenylpiperidin-1-yl)phenyl]pyrrolidin-2-yl}-1*H*-benzimidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.76 - 0.91 (m, 6 H) 1.59 - 1.73 (m, 10 H) 1.73 - 1.80 (m, 2 H) 1.83 - 1.94 (m, 4 H) 1.97 - 2.08 (m, 4 H) 2.16 - 2.24 (m, 1 H) 2.86 - 3.04 (m, 6 H) 3.19 - 3.29 (m, 1 H) 3.53 (s, 3 H) 3.79 - 3.87 (m, 2 H) 5.11 - 5.19 (m, 1 H) 5.34 - 5.42 (m, 2 H) 5.88 - 5.95 (m, 2 H) 7.03 - 7.11 (m, 2 H) 7.13 - 7.19 (m, 2 H) 7.20 - 7.27 (m, 4 H) 7.28 - 7.34 (m, 2 H) 7.40 (dd, J=13.88, 8.24 Hz, 1 H) 7.50 (d, J=8.02 Hz, 1 H) 12.05 (d, J=10.63 Hz, 1 H) 12.12 (d, J=3.90 Hz, 1 H); MS (ESI+) *m/z* 869.4 $(M+H)^+$.



Example 12.1

methyl {(2*S*)-1-[(2*S*)-2-(5-{3-[1-(4-tert-butylphenyl)-3-(3-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1*H*-imidazol-5-yl}phenyl)azetidin-3-yl]phenyl}-1*H*-imidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

Example 12.1A

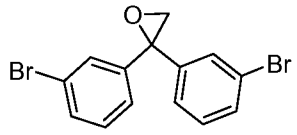
bis(3-bromophenyl)methanol

n-BuLi (26.5 mL, 42.4 mmol, 1.6M in hexane) was added to a solution of 1,3-dibromobenzene (10 g, 42.4 mmol) in THF (50 mL) at -78 °C. After stirred for 2 h at -78 °C, the 3-bromobenzaldehyde (7.84 g, 42.4 mmol) was added to the reaction mixture. The reaction mixture was allowed to warm up to r.t. and stirred at 30 °C for 12 h. The reaction was quenched with aq.NH_4Cl (100 mL). The mixture was extracted with dichloromethane (80 mLx5). The combined organic layers were dried and concentrated. The residue was purified by column chromatography (on silica gel, eluent with Petroleum ether ~Petroleum ether: EtOAc=20:1) to afford 8.4 g of the title compound (24.5 mmol, 58%). LC/MS: [M-18+1] = 325. ^{1}HNMR (DMSO-d_6), 400MHz: δ 5.74 (d, 1H, J=4.0 Hz), 6.19 (d, 1H, J=4.4 Hz), 7.26-7.31 (m, 2H), 7.37-7.43 (m, 4H), 7.59 (s, 2 H).

Example 12.1B

bis(3-bromophenyl)methanone

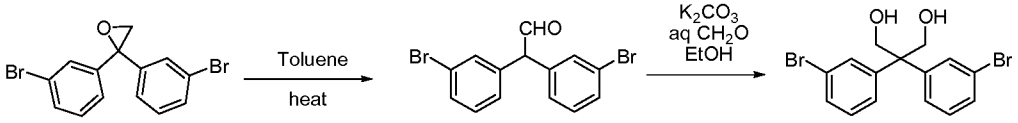
MnO_2 (21.61 g, 249 mmol) was added to a solution of bis(3-bromophenyl)methanol (8.4 g, 24.5 mmol) in dichloromethane (80 mL). The mixture was stirred at 25 °C for 12 h and then filtered. The filter cake was washed with dichloromethane (60 mLx5). The filtrate was concentrated to afford 7.6 g of the title compound (22.3 mmol, 90%). LC/MS: [M+1] = 341. ^{1}HNMR (DMSO-d_6), 400MHz: δ 7.52-7.56 (m, 2H), 7.71 (d, 2H, J=7.2 Hz), 7.88-7.92 (m, 4H).



Example 12.1C

2,2-bis(3-bromophenyl)oxirane

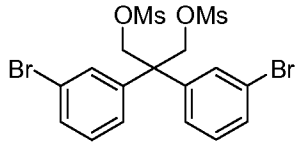
KOt-Bu (2.72 g, 24.26 mmol) was added to a stirred suspension of bis(3-bromophenyl)methanone (7.5 g, 22.06 mmol) and trimethylsulfonium iodide (4.50 g, 22.06 mmol) in DMSO (20 mL) and the resulting mixture was stirred at 30 °C for 8 h. The mixture was diluted with ethyl acetate (500mL), washed with water (500 mL x 3) and brine (500 mL). The organic layer was separated and evaporated in *vacuo* to afford the title compound which was used directly without further purification.



Example 12.1D

2,2-bis(3-bromophenyl)propane-1,3-diol

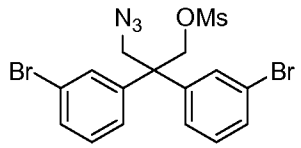
A mixture of the crude 2,2-bis(3-bromophenyl)oxirane (7.4 g, 20.90 mmol) and *p*-toluenesulfonic acid monohydrate (360 mg, 2.1 mmol) in toluene (25 mL) was stirred at 95 °C for 1 h. The solution was washed with aq $NaHCO_3$ (10 mL) and water (20 mL). The organic layer was dried and concentrated. The residue was dissolved in EtOH (20 mL). To the solution was added formaldehyde (15.56 mL, 209 mmol, 37% aqueous solution) and K_2CO_3 (1.44 g, 10.45 mmol). The mixture was stirred at 85°C for 12h. After cooling to room temperature, the reaction mixture was diluted with water (50 mL) and extracted with dichloromethane (60 mLx4). The combined organic layers were dried and concentrated. The residue was purified by column chromatography (on silica gel, eluent with Petroleum ether~Petroleum ether: EtOAc=2:1) to afford 4.6 g of 2,2-bis(3-bromophenyl)propane-1,3-diol (11.9 mmol, 57% after two steps). LC/MS: [M-18+1] = 368. ^{1}HNMR ($CDCl_3$), 400MHz: δ 2.53 (brs, 2H), 2.41 (s, 4H), 7.09-7.20 (m, 4H), 7.36-7.40 (m, 4H).



Example 12.1E

2,2-bis(3-bromophenyl)propane-1,3-diyl dimethanesulfonate

To a stirred solution of 2,2-bis(3-bromophenyl)propane-1,3-diol (6.0 g, 15.54 mmol) in dichloromethane (50 mL) at 0°C was added methanesulfonic chloride (27.1 g, 155 mmol) and Et_3N (17.3 mL, 124 mmol)to give an orange solution. The reaction mixture was stirred at 0 °C for 1h, then at 40 °C for 8 h. The reaction was washed with aq. NH_4Cl (80 mL). The aqueous layer was extracted with dichloromethane (50 mLx3). The combined organic layers were dried and concentrated. The residue was purified by chromatography (on silica gel column, Petroleum ether: EtOAc=2:1) to afford 3.2 g of the title compound (5.9 mmol, 38%). LC/MS: [M+18] = 560. ^{1}HNMR ($CDCl_3$), 400MHz: δ 2.93 (s, 6H), 4.49 (s, 4H), 7.15-7.48 (m, 8H).

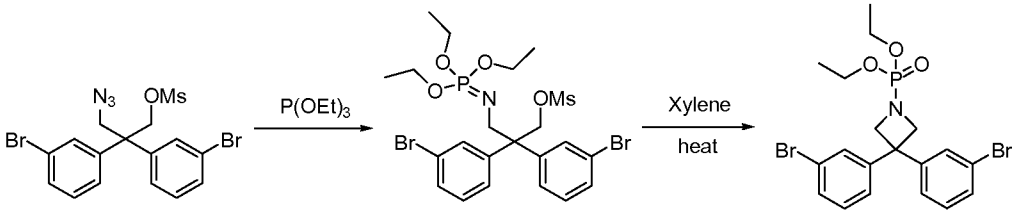


Example 12.1F

3-azido-2,2-bis(3-bromophenyl)propyl methanesulfonate

To a solution of 2,2-bis(3-bromophenyl)propane-1,3-diyl dimethanesulfonate (3.6 g, 6.64 mmol) in DMPU (25 mL, 207 mmol) under N_2 was added NaN_3 (0.52 g, 7.97 mmol) with stirring. The mixture was heated to 110 °C for 5 h. After cooling to room temperature, the reaction mixture was diluted with EtOAc (100 mL), and washed with water (30 mLx2) and brine (25 mL), dried and concentrated. The residue was purified by column chromatography (on silica gel, eluent with

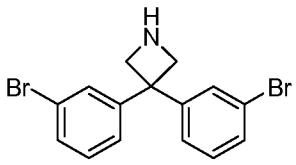
Petroleum ether: EtOAc=3:1) to afford 1.3 g of the title compound (2.66 mmol, 40%). LC/MS: [M+18] = 507. ^{1}HNMR ($CDCl_3$), 400MHz: δ 2.83 (s, 3H), 4.07 (s, 2H), 4.77 (s, 2H), 7.07-7.09 (m, 2H), 7.21-7.31 (m, 4H), 7.44-7.46 (m, 2H).



Example 12.1G

diethyl 3,3-bis(3-bromophenyl)azetidin-1-ylphosphonate

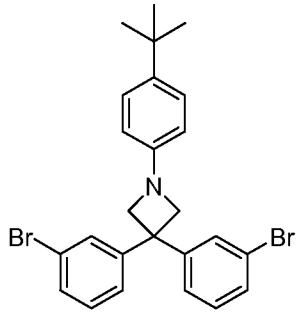
To a solution of 3-azido-2,2-bis(3-bromophenyl)propyl methanesulfonate (1.3 g, 2.66 mmol) in anhydrous toluene (10 mL) and anhydrous THF (5 mL) under N_2 was added triethyl phosphite (0.49 mL, 2.79 mmol) at 25 °C. The mixture was stirred for 18 h. The reaction was concentrated by rotary evaporation in a dried apparatus. The residue was dried in *vacuo*, and used in the next reaction without further purification. The crude triethyl phosphorimidate was dissolved in anhydrous m-xylene (5 mL) under N_2 and heated in an oil bath at 150 °C for 12h. After cooled to room temperature, the solvent was removed by rotary evaporation (vacuum pump assisted) to give a thick light orange oil which was purified by prep-TLC (eluent with EtOAc: dichloromethane=1:5) to afford 960 mg of diethyl 3,3-bis(3-bromophenyl)azetidin-1-ylphosphonate (1.9 mmol, 71% after two steps). LC/MS: [M+1] = 504. ^{1}HNMR ($CDCl_3$), 400MHz: δ 1.25-1.36 (m, 6H), 4.05-4.39 (m, 4H), 4.40 (d, 2H, J=5.2 Hz), 7.09-7.11 (m, 2H), 7.20-7.27 (m, 2H), 7.40-7.42 (m, 4H).



Example 12.1H

3,3-bis(3-bromophenyl)azetidine

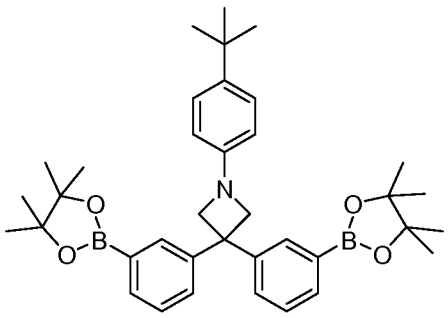
To a solution of diethyl 3,3-bis(3-bromophenyl)azetidin-1-ylphosphonate (960 mg, 1.9 mmol) in anhydrous dichloromethane (5 mL) under N_2 was added TFA (5 mL). The mixture was stirred at 20 °C for 3 h, then concentrated by rotary evaporation. The residue was dissolved in dichloromethane (20 mL) and washed with aq. $NaHCO_3$ (30 mL). The organic layer was dried and concentrated to afford 595 mg of the title compound (1.6 mmol, 85%) as a yellow oil which was used directly to next step without purification. LC/MS: [M+1] = 368.



Example 12.1I

3,3-bis(3-bromophenyl)-1-(4-tert-butylphenyl)azetidine

A mixture of 3,3-bis(3-bromophenyl)azetidine (60 mg, 0.163 mmol), 1-tert-butyl-4-iodobenzene (85 mg, 0.327 mmol), xantphos (9.46 mg, 0.016 mmol), $Pd_2(dba)_3$ (3.74 mg, 4.09 μmol) and tert-butoxide (18.85 mg, 0.196 mmol) in dioxane (5 mL) was stirred at 110 °C for 12 h. After the reaction was cooled to room temperature, water (15 mL) and dichloromethane (15 mL) was added. The aqueous phase was extracted with dichloromethane (15mLx3). The combined organic layers were dried and concentrated. The residue was purified by prep-HPLC (Instrument waters 2767 PHW004 Column YMC-Triart C18 150*20mm S-5um.12nm Mobile Phase A: water (0.05% NH_4HCO_3) B: ACN Gradient 95-95% B in 8 min stop in 14 min Flow Rate(ml/min) 20.00 Detective Wavalength(nm) 214\254 Retention Time(min) 7.4 to afford 26 mg of the title compound (0.052 mmol, 31.8 % yield). LC/MS: [M+1] = 500.



Example 12.1J

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

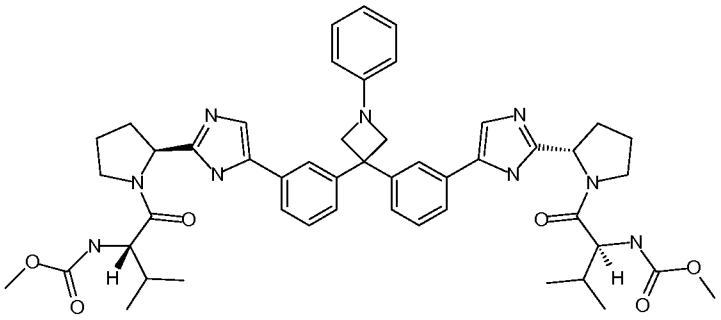
A mixture of 3,3-bis(3-bromophenyl)-1-(4-tert-butylphenyl)azetidine (50 mg, 0.100 mmol), bis(pinacolato)diboron (65.9 mg, 0.260 mmol), KOAc (58.8 mg, 0.599 mmol) and $PdCl_2(dppf)$-CH_2Cl_2 adduct (20.39 mg, 0.025 mmol) was stirred at 100 °C for 2 h under N_2. After cooling to room temperature, water (15 mL) and dichloromethane (15 mL) was added. The aqueous layer was extracted with dichloromethane (15mLx3). The combined organic layers were dried and concentrated. The residue was purified by prep-TLC (eluent with dichloromethane: hexane=1:1) to afford 50 mg of the title compound (0.078 mmol, 78 % yield). LC/MS: [M-$C_{12}H_{20}$+1] = 430; [M-C_6H_{10}+1] = 512.

Example 12.1K

methyl {(2*S*)-1-[(2*S*)-2-(5-{3-[1-(4-tert-butylphenyl)-3-(3-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1*H*-imidazol-5-yl}phenyl)azetidin-3-yl]phenyl}-1*H*-imidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

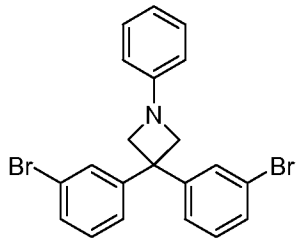
A mixture of 1-(4-tert-butylphenyl)-3,3-bis(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)azetidine (50 mg, 0.084 mmol), Intermediate 4 (66.0 mg, 0.177 mmol), $PdCl_2$(dppf)-CH_2Cl_2 adduct (13.76 mg, 0.017 mmol) and K_2CO_3 (69.9 mg, 0.506 mmol) in dioxane (5 mL) was stirred at 100 °C for 2 h. After cooling to room temperature, the reaction mixture was diluted with dichloromethane (20 mL) and washed with aq. NH_4Cl (15 mLl). The aqueous layer was extracted with dichloromethane (15 mLx3), and the combined organic layers were washed with brine (25 mL), dried and concentrated. The residue was purified by prep-HPLC: Instrument waters 2767 PHW003 Column Boston C18 10um 21*250mm Mobile Phase A:water(0.05%NH_4HCO_3); B:ACN Gradient 60-82% B in 8min, stop at 14min Flow Rate(ml/min) 30.00 Detective Wavelength(nm) 214\254 Retention Time(min) 8.32. The purity was 83% after first purification by prep-HPLC. The compound was further purified by prep-TLC (eluent with MeOH: dichloromethane=1:15) to afford 22 mg of the title compound (0.024 mmol, 28.2 % yield). LC/MS: [M+1] = 926. ^{1}HNMR (MeOD-d_4), 400MHz: δ 0.77-0.85 (m, 12H), 1.18 (s, 9H), 1.88-2.23 (m, 10H), 3.07 (d, 2H, J= 6.4 Hz), 3.56 (s, 6H), 3.75-3.89 (m, 4H), 4.12-4.14 (m, 2H), 4.36-4.42 (m, 4H), 5.03-5.07 (m, 2H), 6.46-6.48 (m, 2H), 6.73-6.77 (m, 1H), 7.10-7.23 (m, 9H), 7.39-7.41 (m, 2H), 7.68-7.72 (m, 2H).

ABS



Example 12.2

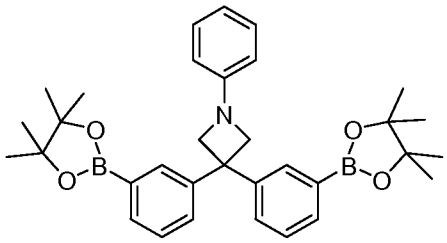
methyl {(2*S*)-1-[(2*S*)-2-(5-{3-[3-(3-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1*H*-imidazol-5-yl}phenyl)-1-phenylazetidin-3-yl]phenyl}-1*H*-imidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate



Example 12.2A

3,3-bis(3-bromophenyl)-1-phenylazetidine

A mixture of 3,3-bis(3-bromophenyl)azetidine (200 mg, 0.545 mmol), iodobenzene (222 mg, 1.090 mmol), xantphos (31.5 mg, 0.054 mmol), $Pd_2(dba)_3$ (12.47 mg, 0.014 mmol) and sodium tert-butoxide (62.8 mg, 0.654 mmol) in dioxane (3 ml) was stirred for 12 h at 100 °C. After cooling to room temperature, water (15 mL) and dichloromethane (15 mL) was added. The aqueous layer was extracted with dichloromethane (15mLx3). The combined organic layers were dried and concentrated. The residue was purified by prep-TLC (eluent with dichloromethane: EtOAc=5:1) to afford 140 mg of the title compound (0.31 mmol, 58%). LC/MS: [M+1] = 444, Ret. Time: 2.69 min. ^{1}HNMR ($CDCl_3$), 400MHz: 4.42 (s, 4H), 6.54 (d, 2H, *J*=7.6 Hz), 7.09-7.11 (m, 2H), 6.79 (t, 1H, *J*=7.2 Hz), 7.17-7.26 (m, 6H), 7.37-7.45 (m, 4H).



Example 12.2B

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

A mixture of 3,3-bis(3-bromophenyl)-1-phenylazetidine (140 mg, 0.284 mmol), KOAc (167 mg, 1.705 mmol), $PdCl_2$(dppf)-CH_2Cl_2 adduct (58.0 mg, 0.071 mmol) and bis(pinacolato)diboron (188 mg, 0.739 mmol) in dioxane (3 mL) was stirred at 110 °C for 2h. After cooling to room temperature, the reaction mixture was diluted with dichloromethane (20 mL) and washed with aq. NH_4Cl (15 mL). The aqueous layer was extracted with dichloromethane (15 mLx3). The combined organic layers were washed with brine (25 mL). The organic layers was dried and concentrated. The crude product was purified by prep-TLC (eluent with dichloromethane: Hexane=1:2) to afford 142 mg of the title compound (0.209 mmol, 73.6 % yield). LC/MS: [M+1] = 538.

Example 12.2C

methyl {(2*S*)-1-[(2*S*)-2-(5-{3-[3-(3-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1*H*-imidazol-5-yl}phenyl)-1-phenylazetidin-3-yl]phenyl}-1*H*-imidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

A mixture of 1-phenyl-3,3-bis(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)azetidine (60 mg, 0.112 mmol), Intermediate 4 (88 mg, 0.235 mmol), $PdCl_2$(dppf)-CH_2Cl_2 adduct (18.24 mg, 0.022 mmol) and K_2CO_3 (93 mg, 0.670 mmol) in dioxane (5 mL) and water (1 mL) was stirred at 100 °C for 2 h under N_2. The reaction mixture was diluted with dichloromethane (20 mL) and washed with aq. NH_4Cl (15 mL). The aqueous phase was extracted with dichloromethane (15 mLx3). The combined organic layers was washed with brine (25 mL). The organic layers was dried and concentrated. The crude product was purified by prep-HPLC (Instrument waters 2767 PHW003 Column Boston C18 10um 21*250mm Mobile Phase A:water (0.05%NH4HCO3);B:ACN Gradient 45-70% B in 8min,stop at 14min Flow Rate(ml/min) 30.00 Detective Wavalength(nm) 214\254 Retention Time(min) 8.47. Then the compound was further purified by prep-TLC (eluent with MeOH : dichloromethane=1:15) to afford 20 mg of the title compound (0.022 mmol, 19.53 % yield). LC/MS: [M+1] = 870. ^{1}HNMR (MeOD-d_4), 400MHz: δ 0.86-0.97 (m, 12H), 1.97-2.33 (m, 10H), 3.07 (d, 2H, *J*= 6.4 Hz), 3.66 (s, 6H), 3.83-3.99 (m, 5H), 4.21-4.23 (m, 2H), 4.49-4.55 (m, 5H), 5.13-5.16 (m, 2H), 6.61-6.63 (m, 2H), 6.73-6.77 (m, 1H), 7.19-7.58 (m, 12H), 7.78-7.80 (m, 2H).

The present invention also contemplates pharmaceutically acceptable salts of each title compound described in the above examples. All of the examples disclosed in U.S. Patent Application Publication No. 2010/0317568 and U.S. Patent Application Serial Nos. 12/903,822 and 12/964,027 are also incorporated herein by reference.

When tested using HCV 1b-Con1 replicon assays in the presence of 5% FBS, each title compound in 1.1, 1.3, 1.5, 1.6, 1.7, 1.8, 2.1, 2.2, 2.4, 2.5, 2.6, 2.9, 2.10, 2.11, 2.12, 2.13, 2.14, 2.15, 2.16, 2.17, 3.1, 3.2, 3.4, 3.5, 3.6, 3.7, 3.8, 3.11, 3.12, 3.13, 3.15, 3.17, 3.18, 3.19, 3.20, 3.21, 3.22, 3.23, 3.24, 3.25, 3.26, 3.27, 3.28, 3.29, 3.30, 3.31, 3.32, 3.33, 3.34, 3.35, 3.36, 3.37, 3.38, 3.39, 3.40, 3.41, 3,42, 3.43, 3.44, 3.45, 3.46, 3.47, 3.48, 3.49, 3.50, 3.51, 3.52, 3.53, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 4.10, 4.11, 4.12, 4.13, 4.14, 4.15, 4.16, 4.17, 4.18, 4.19, 4.20, 4.21, 4.22, 4.23, 4.24, 4.26, 4.27, 4.28, 4.29, 4.30, 4.31, 4.32, 4.33, 4.34, 4.35, 4.36, 4.37, 4.38, 4.39, 4.40, 4.41, 4.42, 4.43, 4.44, 4.45, 4.46, 4.47, 4.49, 4.50, 4.51, 4.52, 4.53, 4.54, 4.55, 4.56, 4.57, 4.58, 4.59, 4.60, 4.61, 4.62, 5.1, 5.2, 5.3, 5.4, 5.5, 5.6, 5.7, 5.8, 5.9, 5.10, 5.11, 5.12, 5.13, 5.14, 5.15, 6.1, 6.2, 6.3, 6.4, 6.5, 6.6, 6.7, 6.8, 6.9, 6.10, 6.11, 6.12, 6.13, 6.14, 6.15, 6.16, 7.1, 8, 9, 10.1, 10.2, 11.1, and 11.2 showed an EC_{50} value of less than about 0.1 nM. When tested using HCV 1b-Con1 replicon assays in the presence of 5% FBS, each title compound in Examples 1.4, 2.8, 3.3, 3.9, 3.10, 3.16 and 4.25 showed an EC_{50} value of from about 0.1 to about 1 nM. When tested using HCV 1b-Con1 replicon assays in the presence of 5% FBS, each title compound in Examples 2.3, 2.7, 12.1 and 12.2 showed an EC_{50} value

of from about 1 to about 10 nM. The tile compounds of Example 1.2 and 3.14 showed an EC_{50} value of over 10 μM when tested using HCV 1b-Con1 replicon assays in the presence of 5% FBS.

When tested using HCV 2a, 2b, 3a and 4a replicon assays in the absence of human plasma (HP), the EC_{50} values of Example 5.1 were about at least 50-fold less than those of Example 4.25 (about 200-500 pM); and the EC_{50} values of Example 3.20 were about at least 15 fold less than those of Example 4.25. The AUC value (as defined above) of Example 5.1 was about 30 fold greater than that of Example 2.9. When tested using HCV 1a replicon assays in the presence of 40% HP, the EC_{50} value of Example 6.1 against L31M, Y93H or Y93N mutant was at least 5-fold less than that of Example 109 (about 10-100 nM) of U.S. Patent Application Publication No. 2010/0317568 (U.S. Patent Application Serial No. 12/813,301, hereinafter the '301 application); and the AUC value of Example 6.1 was about 9-fold greater than that of Example 109 of the '301 application. When tested using HCV 2a, 2b, 3a and 4a replicon assays in the absence of HP, the EC_{50} values of Example 4.15, as well as Example 302 of the '301 application, were about 2-4 fold less than those of Example 163 (about 10-50 pM) of the '301 application. When tested using HCV 2b and 4a replicon assays in the absence of HP, the EC_{50} values of Example 251 of the '301 application were about 2-fold less than those of Example 163 of the '301 application. When tested using HCV 2a, 2b, 3a and 4a replicon assays in the absence of HP, the EC_{50} values of Example 120 of the '301 application were about at least 2-fold less than those of Example 164 (about 300-1200 pM) of the '301 application, and the EC_{50} values of Examples 245, 256 and 271 of the '301 application were at least about 10-fold less than those of Example 164 of the '301 application; the AUC values of Example 245, 256 and 271 were at least about 10-fold greater than that of Example 164.

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 FMDV 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, I_D, I_E, I_F or I_G).

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-7977 (Pharmasset) (nucleoside polymerase inhibitor), 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-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, I_D, I_E, I_F or I_G (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, I_D, I_E, I_F or I_G, or preferably a compound described hereinabove, 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, I_D, I_E, I_F or I_G, or preferably a compound described hereinabove, 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, I_D, I_E, I_F or I_G, or preferably a compound described hereinabove, 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.

In still another embodiment, a pharmaceutical composition of the invention comprises (1) a compound of Formula I, I_A, I_B, I_C, I_D, I_E, I_F or I_G, or preferably a compound selected from the title compounds of the above Examples or Table 5, or a salt, solvate or prodrug thereof, and (2) one or more HCV inhibitors/modulators selected from ABT-072 (Abbott), ABT-333 (Abbott), ACH-1095 (Achillion), ACH-1625 (Achillion), ACH-2684 (Achillion), ACH-2928 (Achillion), alisporovir, ANA-598 (Anadys), ANA-773 (Anadys), AVL-181 (Avila), AVL-192 (Avila), AZD2836 (Astra-Zeneca), AZD7295 (Astra-Zeneca), BCX-4678 (BioCryst), BI-201335 (Boehringer Ingelheim), BI-207127 (Boehringer Ingelheim), BILB-1941 (Boehringer Ingelheim), BMS-650032 (BMS), BMS-790052 (BMS), BMS-791325 (BMS), BMS-824393 (BMS), boceprevir, CTS-1027 (Conatus), danoprevir, EDP-239 (Enanta), filibuvir, GL59728 (Glaxo), GL60667 (Glaxo), GS-5885 (Gilead),

GS-6620 (Gilead), GS-9132 (Gilead), GS-9256 (Gilead), GS-9451 (Gilead), GS-9620 (Gilead), GS-9669 (Gilead), GSK625433 (GlaxoSmithKline), IDX-102 (Idenix), IDX-136 (Idenix), IDX-184 (Idenix), IDX-316 (Idenix), IDX-320 (Idenix), IDX-375 (Idenix), INX-189 (Inhibitex), ITX-4520 (iTherx), ITX-5061 (iTherx), MK-0608 (Merck), MK-3281 (Merck), MK-5172 (Merck), narlaprevir, NM-811 (Novartis), PF-4878691 (Pfizer), PHX-1766 (Phenomix), PPI-1301 (Presidio), PPI-461 (Presidio), PSI-7977 (Pharmasset), PSI-938 (Pharmasset), RG7128 (Roche), RO5303253 (Roche), SCY-635 (Scynexis), tegobuvir, telaprevir, TMC-435 (Tibotec), TMC-647055 (Tibotec), TMC64912 (Medivir), vaniprevir, VBY708 (Virobay), VCH-759 (Vertex & ViraChem), VCH-916 (ViraChem), VX-222 (VCH-222) (Vertex & ViraChem), VX-500 (Vertex), VX-759 (Vertex), VX-813 (Vertex), VX-985 (Vertex), or a combination thereof.

In another embodiment, a pharmaceutical composition of the invention comprises (1) a compound of Formula I, I_A, I_B, I_C, I_D, I_E, I_F or I_G, or preferably a compound selected from the title compounds of the above Examples or Table 5, or a salt, solvate or prodrug thereof, and (2) one or more HCV protease inhibitors selected from ACH-1095 (Achillion), ACH-1625 (Achillion), ACH-2684 (Achillion), AVL-181 (Avila), AVL-192 (Avila), BI-201335 (Boehringer Ingelheim), BMS-650032 (BMS), boceprevir, danoprevir, GS-9132 (Gilead), GS-9256 (Gilead), GS-9451 (Gilead), IDX-136 (Idenix), IDX-316 (Idenix), IDX-320 (Idenix), MK-5172 (Merck), narlaprevir, PHX-1766 (Phenomix), telaprevir, TMC-435 (Tibotec), vaniprevir, VBY708 (Virobay), VX-500 (Vertex), VX-813 (Vertex), VX-985 (Vertex), or a combination thereof.

In yet another preferred embodiment, a pharmaceutical composition of the invention comprises (1) a compound of Formula I, I_A, I_B, I_C, I_D, I_E, I_F or I_G, or preferably a compound selected from the title compounds of the above Examples or Table 5, or a salt, solvate or prodrug thereof, and (2) one or more HCV polymerase inhibitors selected from ABT-072 (Abbott), ABT-333 (Abbott), ANA-598 (Anadys), BI-207127 (Boehringer Ingelheim), BILB-1941 (Boehringer Ingelheim), BMS-791325 (BMS), filibuvir, GL59728 (Glaxo), GL60667 (Glaxo), GS-9669 (Gilead), IDX-375 (Idenix), MK-3281 (Merck), tegobuvir, TMC-647055 (Tibotec), VCH-759 (Vertex & ViraChem), VCH-916 (ViraChem), VX-222 (VCH-222) (Vertex & ViraChem), VX-759 (Vertex), GS-6620 (Gilead), IDX-102 (Idenix), IDX-184 (Idenix), INX-189 (Inhibitex), MK-0608 (Merck), PSI-7977 (Pharmasset), PSI-938 (Pharmasset), RG7128 (Roche), TMC64912 (Medivir), GSK625433 (GlaxoSmithKline), BCX-4678 (BioCryst), or a combination thereof. The polymerase inhibitor(s) can include (i) one or more nucleotide polymerase inhibitors selected from GS-6620 (Gilead), IDX-102 (Idenix), IDX-184 (Idenix), INX-189 (Inhibitex), MK-0608 (Merck), PSI-7977 (Pharmasset), PSI-938 (Pharmasset), RG7128 (Roche), TMC64912 (Medivir), or a combination therefore; or (ii) one or more non-nucleoside polymerase inhibitors selected from ABT-072 (Abbott), ABT-333 (Abbott), ANA-598 (Anadys), BI-207127 (Boehringer Ingelheim), BILB-1941 (Boehringer Ingelheim), BMS-791325 (BMS), filibuvir, GL59728 (Glaxo), GL60667 (Glaxo), GS-9669 (Gilead), IDX-375 (Idenix), MK-

3281 (Merck), tegobuvir, TMC-647055 (Tibotec), VCH-759 (Vertex & ViraChem), VCH-916 (ViraChem), VX-222 (VCH-222) (Vertex & ViraChem), VX-759 (Vertex), or a combination thereof; or (iii) both a nucleotide polymerase inhibitor(s) and a non-nucleoside polymerase inhibitor(s).

In a further embodiment, a pharmaceutical composition of the invention comprises (1) a compound of Formula I, I_A, I_B, I_C, I_D, I_E, I_F or I_G, or preferably a compound selected from the title compounds of the above Examples or Table 5, or a salt, solvate or prodrug thereof, (2) one or more HCV protease inhibitors selected from ACH-1095 (Achillion), ACH-1625 (Achillion), ACH-2684 (Achillion), AVL-181 (Avila), AVL-192 (Avila), BI-201335 (Boehringer Ingelheim), BMS-650032 (BMS), boceprevir, danoprevir, GS-9132 (Gilead), GS-9256 (Gilead), GS-9451 (Gilead), IDX-136 (Idenix), IDX-316 (Idenix), IDX-320 (Idenix), MK-5172 (Merck), narlaprevir, PHX-1766 (Phenomix), telaprevir, TMC-435 (Tibotec), vaniprevir, VBY708 (Virobay), VX-500 (Vertex), VX-813 (Vertex), VX-985 (Vertex), or a combination thereof, and (3) one or more HCV polymerase inhibitors selected from ABT-072 (Abbott), ABT-333 (Abbott), ANA-598 (Anadys), BI-207127 (Boehringer Ingelheim), BILB-1941 (Boehringer Ingelheim), BMS-791325 (BMS), filibuvir, GL59728 (Glaxo), GL60667 (Glaxo), GS-9669 (Gilead), IDX-375 (Idenix), MK-3281 (Merck), tegobuvir, TMC-647055 (Tibotec), VCH-759 (Vertex & ViraChem), VCH-916 (ViraChem), VX-222 (VCH-222) (Vertex & ViraChem), VX-759 (Vertex), GS-6620 (Gilead), IDX-102 (Idenix), IDX-184 (Idenix), INX-189 (Inhibitex), MK-0608 (Merck), PSI-7977 (Pharmasset), PSI-938 (Pharmasset), RG7128 (Roche), TMC64912 (Medivir), GSK625433 (GlaxoSmithKline), BCX-4678 (BioCryst), ore a combination thereof. The polymerase inhibitor(s) can include (i) one or more nucleotide polymerase inhibitors selected from GS-6620 (Gilead), IDX-102 (Idenix), IDX-184 (Idenix), INX-189 (Inhibitex), MK-0608 (Merck), PSI-7977 (Pharmasset), PSI-938 (Pharmasset), RG7128 (Roche), TMC64912 (Medivir), or a combination therefore; or (ii) one or more non-nucleoside polymerase inhibitors selected from ABT-072 (Abbott), ABT-333 (Abbott), ANA-598 (Anadys), BI-207127 (Boehringer Ingelheim), BILB-1941 (Boehringer Ingelheim), BMS-791325 (BMS), filibuvir, GL59728 (Glaxo), GL60667 (Glaxo), GS-9669 (Gilead), IDX-375 (Idenix), MK-3281 (Merck), tegobuvir, TMC-647055 (Tibotec), VCH-759 (Vertex & ViraChem), VCH-916 (ViraChem), VX-222 (VCH-222) (Vertex & ViraChem), VX-759 (Vertex), or a combination thereof; or (iii) both a nucleotide polymerase inhibitor(s) and a non-nucleoside polymerase inhibitor(s).

In still another embodiment, a pharmaceutical composition of the invention comprises (1) a compound of Formula I, I_A, I_B, I_C, I_D, I_E, I_F or I_G, or preferably a compound selected from the title compounds of the above Examples or Table 5, or a salt, solvate or prodrug thereof, and (2) an cyclophilin inhibitor (e.g., alisporovir, NM-811 (Novartis), SCY-635 (Scynexis)), an entry inhibitor (e.g., ITX-4520 (iTherx) or ITX-5061 (iTherx)), another NS5A inhibitor (e.g.,), or a TLR-7 agonist (e.g., GS-9620 (Gilead) or PF-4878691 (Pfizer)), and (3) optionally one or more HCV protease or polymerase inhibitors described above.

A pharmaceutical composition containing multiple active ingredients can be either a co-formulated product, a co-packaged product, or a combination thereof.

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, I_D, I_E, I_F or I_G, or preferably a compound described hereinabove, 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, I_D, I_E, I_F or I_G, or preferably a compound described hereinabove, 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, I_D, I_E, I_F or I_G, or preferably a compound described hereinabove, 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, I_D, I_E, I_F or I_G, or preferably a compound described hereinabove, 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).

In another 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, I_D, I_E, I_F or I_G, or preferably a compound selected from the title compounds of the above Examples or Table 5, or a salt, solvate or prodrug thereof), and one or more HCV inhibitors/modulators described above, with or without interferon.

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.

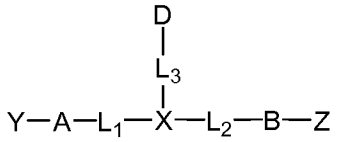
In addition, the present invention features use of the compounds or salts of the present invention for the manufacture of medicaments for the treatment of HCV infection. Any compound described herein, or a pharmaceutically acceptable salt thereof, can be used to make medicaments of the present invention.

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 compounds having 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 or R_F;

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 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 $-SF_5$; 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 $-O-R_S$, $-S-R_S$, $-C(O)R_S$, $-OC(O)R_S$, $-C(O)OR_S$, $-N(R_SR_S')$, $-S(O)R_S$, $-SO_2R_S$, $-C(O)N(R_SR_S')$, $-N(R_S)C(O)R_S'$, $-N(R_S)C(O)N(R_S'R_S'')$, $-N(R_S)SO_2R_S'$, $-SO_2N(R_SR_S')$, $-N(R_S)SO_2N(R_S'R_S'')$, $-N(R_S)S(O)N(R_S'R_S'')$, $-OS(O)-R_S$, $-OS(O)_2-R_S$, $-S(O)_2OR_S$, $-S(O)OR_S$, $-OC(O)OR_S$, $-N(R_S)C(O)OR_S'$, $-OC(O)N(R_SR_S')$, $-N(R_S)S(O)-R_S'$, $-S(O)N(R_SR_S')$, $-P(O)(OR_S)_2$, 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 $-N(R_SR_S')$;

R_F is independently selected at each occurrence from 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; or $-(R_X-R_Y)_Q-(R_X-R_Y')$, wherein Q is 0, 1, 2, 3 or 4, and each R_X is independently O, S or $N(R_B)$, wherein each R_Y is independently C_1-C_6alkylene, C_2-C_6alkenylene or C_2-C_6alkynylene each of which is independently optionally substituted with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl or cyano, and wherein each R_Y' is independently C_1-C_6alkyl, C_2-C_6alkenyl or C_2-

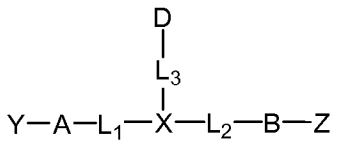
C_6alkynyl each of which is independently optionally substituted with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl or cyano;

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 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; 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, –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.

2. A compounds having Formula I_E, or a pharmaceutically acceptable salt thereof,



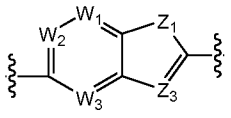
I_E

wherein:

X is 4- to 8-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 which is independently optionally substituted at each occurrence with one or more halo, hydroxy, –O–C_1-C_6alkyl, or –O–C_1-C_6haloalkyl;

L_3 is bond or C_1-C_6alkylene;

A and B are each independently phenyl, pyridinyl, thiazolyl, or  where Z_1 is independently selected at each occurrence from O, S, NH or CH_2, Z_3 is independently selected at each occurrence from N or CH, and W_1, W_2, and W_3 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.

D is C_6-C_{10}carbocycle or 5- to 12-membered heterocycle, each of which is optionally substituted with one or more R_M;

Y is –T'–$C(R_1R_2)N(R_5)$–T–R_D;

Z is –T'–$C(R_8R_9)N(R_{12})$–T–R_D;

R_1 is hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, or 3- to 6-membered carbocycle or heterocycle, wherein each said 3- to 6-membered carbocycle or heterocycle is independently optionally substituted at each occurrence with one or more substituents selected from halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, –O–C_1-C_6alkyl or –O–C_1-C_6haloalkyl;

R_2 and R_5 are each independently hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, or 3- to 6-membered carbocycle or heterocycle, wherein each said 3- to 6-membered carbocycle or heterocycle is independently optionally substituted at each occurrence with one or more substituents selected from halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, –O–C_1-C_6alkyl or –O–C_1-C_6haloalkyl; or 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_8 is hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, or 3- to 6-membered carbocycle or heterocycle, wherein each said 3- to 6-membered carbocycle or heterocycle is independently optionally substituted at each occurrence with one or more substituents selected from halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, –O–C_1-C_6alkyl or –O–C_1-C_6haloalkyl;

R_9 and R_{12} are each independently hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, or 3- to 6-membered carbocycle or heterocycle, wherein each said 3- to 6-membered carbocycle or heterocycle is independently optionally substituted at each occurrence with one or more substituents selected from halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, –O–C_1-C_6alkyl or –O–C_1-C_6haloalkyl; or 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;

T is independently selected at each occurrence from bond or –C(O)–L_S'–;

T' is independently selected at each occurrence from bond, $-C(O)N(R_B)-$, $-N(R_B)C(O)-$, or 3- to 12-membered heterocycle, wherein said 3- to 12-membered heterocycle 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 $-L_S-R_E$;

R_B and R_B' are each independently selected at each occurrence from hydrogen; or C_1-C_6alkyl which is independently optionally substituted at each occurrence with one or more substituents selected from halogen 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, C_1-C_6alkyl, C_1-C_6haloalkyl, $-O-C_1$-C_6alkyl, or $-O-C_1$-C_6haloalkyl;

R_E is independently selected at each occurrence from $-O-R_S$, $-S-R_S$, $-C(O)R_S$, $-OC(O)R_S$, $-C(O)OR_S$, $-N(R_SR_S')$, $-S(O)R_S$, $-SO_2R_S$, $-C(O)N(R_SR_S')$, $-N(R_S)C(O)R_S'$, $-N(R_S)C(O)N(R_S'R_S'')$, $-N(R_S)SO_2R_S'$, $-SO_2N(R_SR_S')$, $-N(R_S)SO_2N(R_S'R_S'')$, $-N(R_S)S(O)N(R_S'R_S'')$, $-OS(O)-R_S$, $-OS(O)_2-R_S$, $-S(O)_2OR_S$, $-S(O)OR_S$, $-OC(O)OR_S$, $-N(R_S)C(O)OR_S'$, $-OC(O)N(R_SR_S')$, $-N(R_S)S(O)-R_S'$, $-S(O)N(R_SR_S')$, $-C(O)N(R_S)C(O)-R_S'$, or $=C(R_SR_S')$; 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_{12}carbocycle or 3- to 12-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_{12}carbocycle or 3- to 12-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 is independently selected at each occurrence from bond; or C_1-C_6alkylene, C_2-C_6alkenylene or C_2-C_6alkynylene, each independently optionally substituted with halogen;

L_S' is 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;

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_6haloalkyl, or 3- to 12-membered carbocycle or heterocycle; or 3- to 12-membered carbocycle or heterocycle; wherein each 3- to 12-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;

R_M is independently selected at each occurrence from:

halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, cyano, SF_5, –N($R_S$$R_S$'), –O–$R_S$, –OC(O)$R_S$, –OC(O)O$R_S$, –OC(O)N($R_S$$R_S$'), –C(O)$R_S$, –C(O)O$R_S$, –C(O)N($R_S$$R_S$'), –N($R_S$)C(O)$R_S$', –N($R_S$)C(O)O$R_S$', –N($R_S$)$SO_2$$R_S$', –S(O)$R_S$, –$SO_2$$R_S$, –S(O)N($R_S$$R_S$'), –S$R_S$, –Si($R_S$)$_3$, or –P(O)(O$R_S$)$_2$;

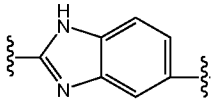
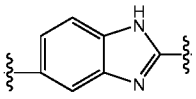
C_1-C_6alkyl, C_2-C_6alkenyl or C_2-C_6alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl, cyano, –N($R_S$$R_S$'), –O–$R_S$, –OC(O)$R_S$, –OC(O)O$R_S$, –OC(O)N($R_S$$R_S$'), –C(O)$R_S$, –C(O)O$R_S$, –C(O)N($R_S$$R_S$'), –N($R_S$)C(O)$R_S$', –N($R_S$)C(O)O$R_S$', –N($R_S$)$SO_2$$R_S$', –S(O)$R_S$, –$SO_2$$R_S$, –S(O)N($R_S$$R_S$'), –S$R_S$, or –P(O)(O$R_S$)$_2$; or

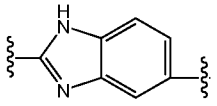
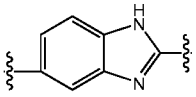
G_2, wherein G_2 is a C_3-C_{12}carbocycle or 3- to 12-membered heterocycle, each of which is independently optionally substituted at each occurrence with one or more R_{G2}, and each R_{G2} is independently selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, 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, –O–R_S, –C(O)OR_S, –C(O)R_S, –N($R_S$$R_S$'), or –$L_4$–$G_3$;

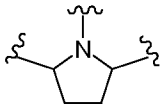
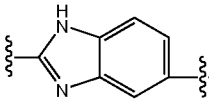
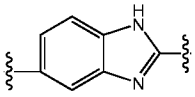
L_4 is a bond, C_1-C_6alkylene, C_2-C_6alkenylene, C_2-C_6alkynylene, –O–, –S–, –N(R_B)–, –C(O)–, –S(O)$_2$–, –S(O)–, –C(O)O–, –OC(O)–, –OC(O)O–, –C(O)N(R_B)–, –N(R_B)C(O)–, –N(R_B)C(O)O–, –OC(O)N(R_B)–, –N(R_B)S(O)–, –N(R_B)S(O)$_2$–, –S(O)N(R_B)–, –S(O)$_2$N(R_B)–, –N(R_B)C(O)N(R_B')–, –N(R_B)SO_2N(R_B')–, or –N(R_B)S(O)N(R_B')–;

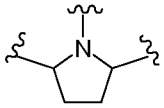
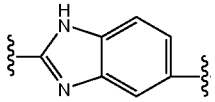
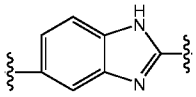
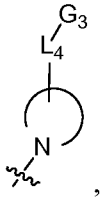
G_3 is a C_3-C_{12}carbocycle or 3- to 12-membered heterocycle, and is optionally substituted with one or more R_{G3}; and

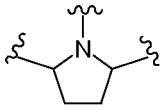
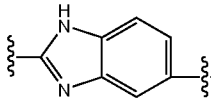
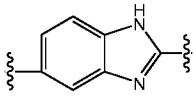
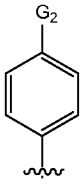
R_{G3} is each independently, at each occurrence, halogen, –C_1-C_6alkyl, –C(O)C_1-C_6alkyl, –C_1-C_6haloalkyl, –O–C_1-C_6alkyl, –O–C_1-C_6haloalkyl, C_3-C_6carbocycle, or 3- to 6-membered heterocycle.

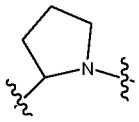
3. The compound or salt according to claim 2, wherein A is  and is optionally substituted with one or more R_A, and B is  and is optionally substituted with one or more R_A, and D is C_6-C_{10}aryl or 5- to 10-membered heteroaryl and is substituted with one or more R_M.

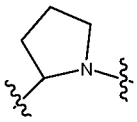
4. The compound or salt according to claim 2, wherein A is  and is optionally substituted with one or more R_A, and B is  and is optionally substituted with one or more R_A, and D is phenyl or pyridyl and is substituted by one or more R_M, wherein at least one R_M is G_2 which is substituted with L_4–G_3 and optionally substituted with one or more R_{G2}.

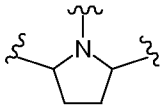
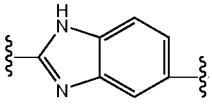
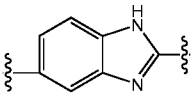
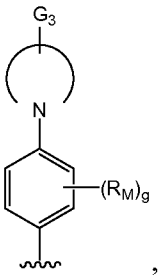
5. The compound or salt according to claim 2, wherein X is  and is optionally substituted with one or more R_A, A is  and is optionally substituted with one or more R_A, and B is  and is optionally substituted with one or more R_A, and D is phenyl or pyridyl and is substituted by one or more R_M, and wherein at least one R_M is  which is a monocyclic 4-8 membered nitrogen-containing heterocycle optionally substituted with one or more R_{G2}.

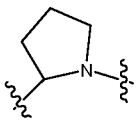
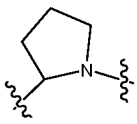
6. The compound or salt according to claim 2, wherein X is  and is optionally substituted with one or more R_A, A is  and is optionally substituted with one or more R_A, and B is  and is optionally substituted with one or more R_A, and D is phenyl or pyridyl and is substituted by one or more R_M, and at least one R_M is  , wherein  is a monocyclic 4-8 membered nitrogen-containing heterocycle optionally substituted with one or more R_{G2}.

7. The compound or salt according to claim 2, wherein X is  and is optionally substituted with one or more R_A, A is  and is optionally substituted with one or more R_A, and B is  and is optionally substituted with one or more R_A, and D is  and is optionally substituted by one or more additional R_M.

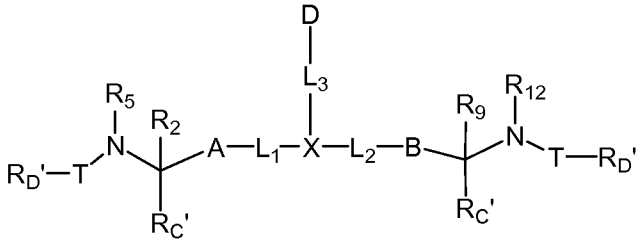
8. The compound or salt according to claim 7, wherein R_1 is hydrogen, and R_2 and R_5 taken together with the atoms to which they are attached form  which is substituted with 0, 1, 2, 3, or 4 R_A, wherein R_8 is hydrogen, and R_9 and R_{12} taken together with the atoms to which

they are attached form  which is substituted with 0, 1, 2, 3, or 4 R_A, and wherein each T' is bond.

9. The compound or salt according to claim 2, wherein X is  and is optionally substituted with one or more R_A, A is  and is optionally substituted with one or more R_A, and B is  and is optionally substituted with one or more R_A, and D is  , wherein G_3 is phenyl optionally substituted with one or two R_{G3}; g is 0, 1, or 2; R_M is each independently fluoro, chloro, methyl, methoxy, trifluoromethyl, or trifluoromethoxy; and  is a monocyclic 4-8 membered nitrogen-containing heterocycle optionally substituted with one or more R_{G2}.

10. The compound or salt according to claim 9, wherein R_1 is hydrogen, and R_2 and R_5 taken together with the atoms to which they are attached form  which is substituted with 0, 1, 2, 3, or 4 R_A, wherein R_8 is hydrogen, and R_9 and R_{12} taken together with the atoms to which they are attached form  which is substituted with 0, 1, 2, 3, or 4 R_A, and wherein each T' is bond.

11. A compounds having Formula I_B, or a pharmaceutically acceptable salt thereof,



I_B

wherein:

R_C' is each independently selected from R_C;

R_D' is each independently selected from R_D;

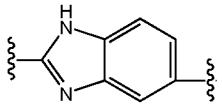
R_2 and R_5, taken together with the atoms to which they are attached, form a 3- to 12-membered heterocycle which is optionally substituted with one or more R_A;

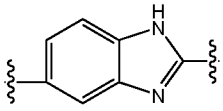
R_9 and R_{12}, taken together with the atoms to which they are attached, form a 3- to 12-membered heterocycle which is optionally substituted with one or more R_A;

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

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 is  and is optionally substituted with one or more R_A;

B is  and is optionally substituted with one or more R_A;

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;

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, 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_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)(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 $-N(R_SR_S')$;

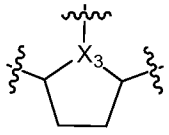
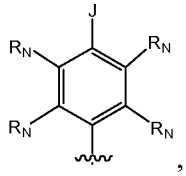
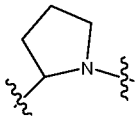
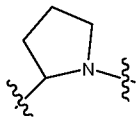
R_F is independently selected at each occurrence from C_1-C_{10}alkyl, C_2-C_{10}alkenyl or C_2-C_{10}alkynyl, each of which contains 0, 1, 2, 3, 4 or 5 heteroatoms selected from O, S or N and is optionally substituted with one or more R_L; or $-(R_X-R_Y)_Q-(R_X-R_Y')$, wherein Q is 0, 1, 2, 3 or 4, and each R_X is independently O, S or $N(R_B)$, wherein each R_Y is independently C_1-C_6alkylene, C_2-C_6alkenylene or C_2-C_6alkynylene each of which is independently optionally substituted with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl or cyano, and wherein each R_Y' is independently C_1-C_6alkyl, C_2-C_6alkenyl or C_2-C_6alkynyl each of which is independently optionally substituted with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxo, formyl or cyano;

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 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; 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, –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.

12. The compound or salt according to claim 11, wherein X is  and is optionally substituted with one or more R_A or R_F, and X_3 is N and is directly linked to –L_3–D, wherein L_1, L_2 and L_3 are bond, wherein D is  , and each R_N is independently R_D, wherein J is C_3-C_6carbocycle or 3- to 6-membered heterocycle and is substituted with a C_3-C_6carbocycle or 3- to 6-membered heterocycle which is independently 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, C_2-C_6haloalkynyl, C(O)OR_S or –N($R_S$$R_S$'), and J is optionally substituted with one or more R_A, wherein 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, wherein 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, wherein -T-R_D' is –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', and wherein L_Y' is each independently L_S'.

13. A process of making a compound of the invention, comprising a step described in one of the Schemes, General Procedures or Examples described herein.

14. An intermediate described in one of Schemes, General Procedures or Examples described herein.

15. methyl {(2*S*,3*R*)-1-[(2*S*)-2-{5-[(2*R*,5*R*)-1-{3,5-difluoro-4-[4-(4-fluorophenyl)piperidin-1-yl]phenyl}-5-(6-fluoro-2-{(2*S*)-1-[*N*-(methoxycarbonyl)-*O*-methyl-L-threonyl]pyrrolidin-2-yl}-1*H*-benzimidazol-5-yl)pyrrolidin-2-yl]-6-fluoro-1*H*-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methoxy-1-oxobutan-2-yl}carbamate, or a pharmaceutically acceptable salt thereof.

16. A pharmaceutical composition comprising the compound of claim 15 or said salt.

17. methyl {(2*S*)-1-[(2*S*)-2-{5-[(2*R*,5*R*)-1-[3,5-difluoro-4-(4-phenylpiperidin-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, or a pharmaceutically acceptable salt thereof.

18. A pharmaceutical composition comprising the compound of claim 17 or said salt.

19. methyl {(2*S*,3*R*)-1-[(2*S*)-2-{5-[(2*R*,5*R*)-1-{4-[4-(2,6-difluorophenyl)piperazin-1-yl]-3,5-difluorophenyl}-5-(6-fluoro-2-{(2*S*)-1-[*N*-(methoxycarbonyl)-*O*-methyl-L-threonyl]pyrrolidin-2-yl}-1*H*-benzimidazol-5-yl)pyrrolidin-2-yl]-6-fluoro-1*H*-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methoxy-1-oxobutan-2-yl}carbamate, or a pharmaceutically acceptable salt thereof.

20. A pharmaceutical composition comprising the compound of claim 19 or said salt.

21. methyl {(2*S*)-1-[(2*S*)-2-{5-[(2*R*,5*R*)-1-(4-*tert*-butylphenyl)-5-{5-fluoro-2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1*H*-benzimidazol-6-yl}pyrrolidin-2-yl]-6-fluoro-1*H*-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate, or a pharmaceutically acceptable salt thereof.

22. A pharmaceutical composition comprising the compound of claim 21 or said salt.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2011/056045

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D403/14 C07D401/14 C07D417/14 A61K31/4184 A61K31/4439
A61K31/454 A61K31/506 A61K31/496 A61K31/4178 A61P31/14
ADD.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2008/144380 A1 (SQUIBB BRISTOL MYERS CO [US]; BACHAND CAROL [CA]; BELEMA MAKONEN [US];) 27 November 2008 (2008-11-27)	1,13,14
A	see compounds of claim 1 and e.g. examples 30, 31, 33, 34, 36 and 37 as inhibitors of HCV replication -----	11
X,P	WO 2010/144646 A2 (ABBOTT LAB [US]; DEGOEY DAVID A [US]; KATI WARREN M [US]; HUTCHINS CHA) 16 December 2010 (2010-12-16) see the claims, the examples and the pharmacological acitivity as inhibitors of HCV replication -----	1-22

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
5 March 2012	02/04/2012

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

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2011/056045

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1, 11, 13, 14(all partially)

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2011/056045

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2008144380 A1	27-11-2008	CN 101754966 A	23-06-2010
		EP 2146984 A1	27-01-2010
		JP 2010527373 A	12-08-2010
		US 2008311075 A1	18-12-2008
		WO 2008144380 A1	27-11-2008
WO 2010144646 A2	16-12-2010	AR 077060 A1	27-07-2011
		AU 2010258769 A1	16-12-2010
		CA 2737601 A1	16-12-2010
		CN 102333772 A	25-01-2012
		DO P2011000087 A	30-04-2011
		EA 201170401 A1	31-10-2011
		EC SP110937 A	31-05-2011
		EP 2337781 A2	29-06-2011
		EP 2368890 A1	28-09-2011
		PE 06792011 A1	20-10-2011
		SG 171708 A1	28-07-2011
		TW 201102063 A	16-01-2011
		US 2010317568 A1	16-12-2010
		UY 32699 A	31-12-2010
		WO 2010144646 A2	16-12-2010

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1, 11, 13, 14(all partially)

   Claims 1, 13 and 14 (all of them partly), i.e. compounds of formula I wherein X is a carbocycle and process for preparation

   ---

2. claims: 2-10, 12, 15-22(completely); 1, 11, 13, 14(partially)

   Claims 2 to 10, 13 and 14 (all partly), i.e. the compounds of formula I wherein X is a heterocycle and process for preparation

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COMPUESTOS ANTIVIRALES

Esta Solicitud invoca la prioridad de la Solicitud de la Patente de los EE.UU. N° Acta: 13/100.827, presentada el 4 de mayo, 2011, la Solicitud Provisional de Patente de los EE.UU. N° Acta: 61/446.800, presentada el 25 de febrero, 2011, la Solicitud de Patente de los EE.UU. N° Acta: 12/964.027, presentada el 9 de diciembre, 2010, y la Solicitud de Patente de los EE.UU. N° Acta: 12/903.822, presentada el 13 de octubre, 2010, cuya divulgación pompleta se incorpora a la presente a modo de referencia.

CAMPO DE LA INVENCIÓN

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 proteína no estructural NS5A es una fosfoproteína asociada a membrana presente en las formas basalmente fosforiladas e hiperfosforiladas. Es un componente crítico de la replicación del HCV y se cree que ejerce múltiples funciones en diversas etapas del ciclo de vida viral. Una proteína NS5A de longitud completa comprende tres dominios, a saber, el Dominio I, el Dominio II y el Dominio III. El Dominio I (residuos 1 a 213) contiene un motivo de unión a zinc y una hélice anfipática N-terminal que puede

promover la asociación a membrana. El Dominio II (residuos 250 a 342) tiene funciones reguladoras, tales como interacciones con las proteína quinasas PKR y PI3K, así como NS5B, y también contiene a la región determinante de sensibilidad al interferón. El Dominio III (residuos 356 a 447) cumple un rol en el ensamblaje del virión infeccioso, y puede ser modulado por fosforilación dentro del dominio. La NS5A ha sido identificada como un blanco terapéutico promisorio para el tratamiento del HCV.

RESUMEN

La presente invención está dirigida a compuestos de las fórmulas I, IA, IB, IC, ID, IE, IF y IG 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.

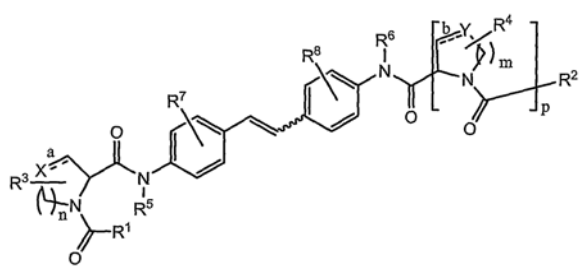
Además, la presente invención está dirigida a procesos de elaboración de los compuestos o las sales de la invención.

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.

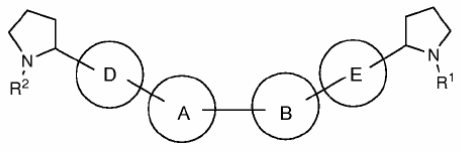
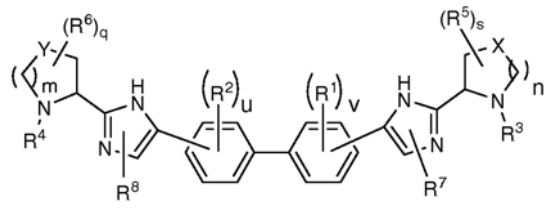
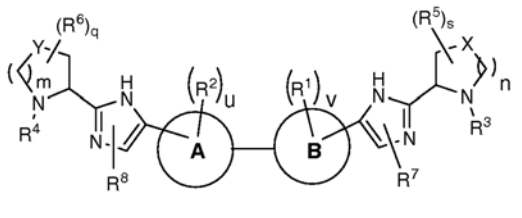
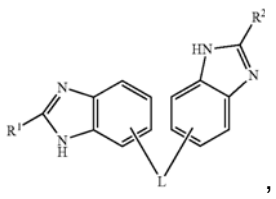
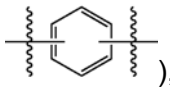
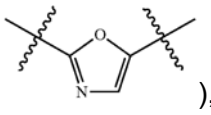
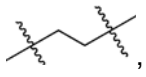
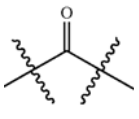
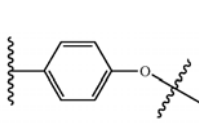
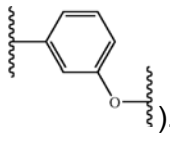
DESCRIPCIÓN DETALLADA

Tellinghuisen et al., Nature 435: 374-379 (2005), describen una estructura cristalina de la proteína NS5A en la cual hay dos monómeros NS5A empaquetados como un dímero por medio de contactos cercanos a los extremos N-terminales de las moléculas. En WO2006093867 se postula el uso de la estructura cristalina de la proteína NS5A junto con modelación computada para diseñar o seleccionar inhibidores de NS5A.

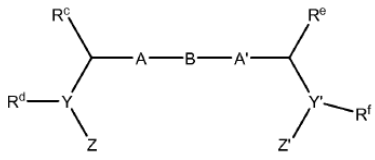
Para mejorar las interacciones con la proteína NS5A, se han diseñado muchos inhibidores de NS5A para que tengan estructuras diméricas o de tipo dímero. Por ejemplo, en WO2006133326 (BMS) se describen compuestos de la fórmula:

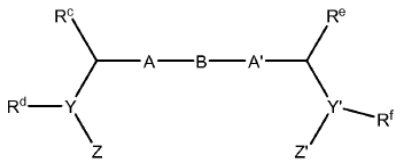
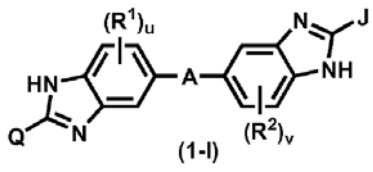
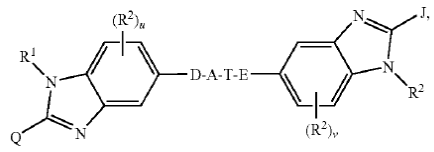


; en WO2008144380 (BMS) se indican

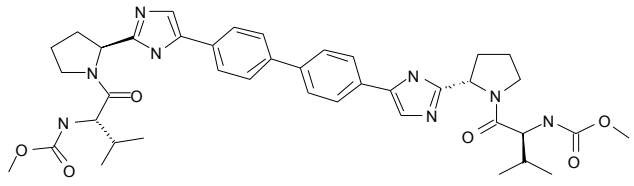
compuestos de la fórmula:  ; en WO2008021927 (BMS) se muestran compuestos de la fórmula:  ; en WO2008021927 (BMS) se describen compuestos de la fórmula:  ; y en US20100068176 (BMS) se muestran compuestos de la fórmula:  , en donde L se selecciona entre arilos (por ejemplo, ), heteroarilos (por ejemplo,  o ), grupos alifáticos (por ejemplo,  ,  ,  o ), o una combinación de los mismos (por ejemplo,  o ).

También se han provisto determinadas modificaciones de las fórmulas anteriores. Por ejemplo, en WO2010065681 (Presidio) se divulga la fórmula:



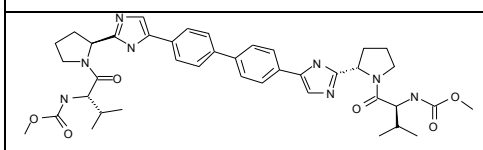
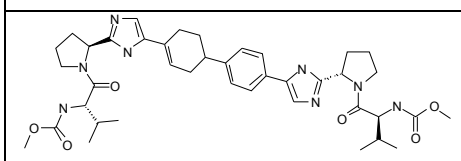
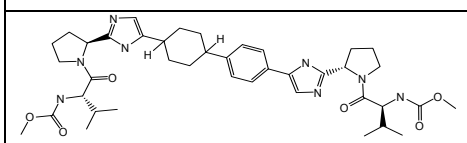
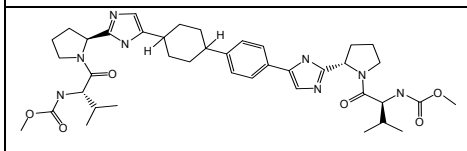
, en donde B es Q o Q-Q, y cada Q se selecciona de manera independiente entre cicloalquilo, cicloalquenilo, heterociclo, arilo o heteroarilo, con la salvedad que solamente una Q sea un anillo aromático de seis miembros cuando B es Q-Q y con la salvedad que si B es Q-Q, cualquier Q que sea policíclico se una al resto de la molécula a través de un solo ciclo del policiclo; en WO2010096777 (Presidio) se describe una fórmula similar: 
, en donde B es W-W o W-X''-W, y en donde cada W es arilo o heteroarilo opcionalmente sustituido, y X'' se selecciona entre -O-, -S(O)k, -N(RN)- y –CR'2-; en WO2010091413 (Enanta) y US20100266543 (Enanta) se muestra la siguiente fórmula: 
(1-I)
, en donde A es arilo, heteroarilo, heterocíclico, C3-C8cicloalquilo o C3-C8cicloalquenilo sustituido y está opcionalmente sustituido con sustituyentes seleccionados; y en US20100221215 (Enanta) se muestra la fórmula: 
, en donde A se selecciona entre arilo, heteroarilo, heterocíclico, C3-C8cicloalquilo o C3-C8cicloalquenilo, cada uno opcionalmente sustituido, D está ausente o es un grupo alifático opcionalmente sustituido, T está ausente o es un grupo alifático lineal opcionalmente sustituido que contiene entre cero y ocho carbonos, E está ausente o se selecciona de manera independiente entre arilo opcionalmente sustituido y heteroarilo opcionalmente sustituido, y en donde uno o dos entre D, E y T está ausente.

En las Tablas 1-4 se comparan las actividades antivirales de diferentes compuestos NS5A. Según se demuestra en estas tablas, hay diversos compuestos protegidos genéricamente por WO2010065681 (Presidio), WO2010096777 (Presidio), WO2010096462 (Enanta), US20100266543 (Enanta), WO2010096462 (Enanta) y US20100266543 (Enanta) que parecen tener actividades anti-HCV comparables o inferiores que los correspondientes compuestos que se describen en las Solicitudes BMS. En las Patentes WO2010065681 (Presidio) WO2010096777 (Presidio), WO2010096462 (Enanta), US20100266543 (Enanta), WO2010096462 (Enanta) y US20100266543 (Enanta) tampoco se identifica ninguna ventaja de estos compuestos frente a los que se describen en las Solicitudes BMS.

El compuesto  (BMS-790052) emplea un conector de bifenilo entre los grupos imidazol. Véase WO2008021927 (BMS). Los valores de EC50 de BMS-790052 contra diferentes genotipos de HCV fueron descritos por Nettles et al., “BMS-790052 is a First-in-class Potent Hepatitis C Virus (HCV) NS5A Inhibitor for Patients with Chronic HCV Infection: Results from a Proof-of-concept Study”, 59th Annual Meeting of the American Asociation for the Study of Liver Diseases (Oct 31-Nov 1, 2008, San Francisco, CA; www.natap.org/2008/AASLD/AASLD_06.htm). Específicamente, Nettles et al., observaron que los valores de EC50 de BMS-790052 contra los genotipos 1ª, 1b, 3a, 4a y 5a del HCV eran de 0,05, 0,009, 0,127, 0,012 y 0,033 nM, respectivamente. Véase también Gao et al., Nature 465: 96–100 (2010). Los compuestos de la Tabla 1 emplean diferentes conectores entre los grupos imidazol. En la Tabla 1 se muestran los valores de EC50 de estos compuestos cuando se evalúan usando respectivos ensayos con replicones en la presencia de 5% (v/v) de suero fetal bovino (FBS). En comparación con BMS-790052, el reemplazo del conector de bifenilo por otros conectores puede reducir significativamente las actividades de los compuestos

contra diversos genotipos del HCV.

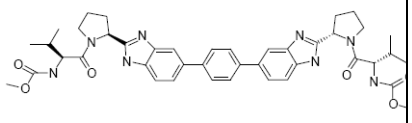
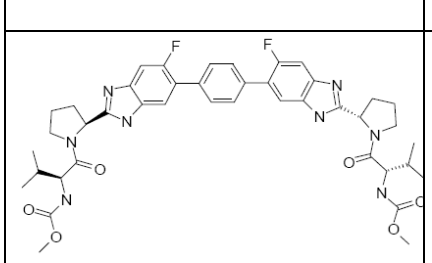
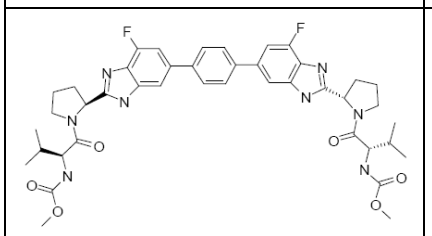
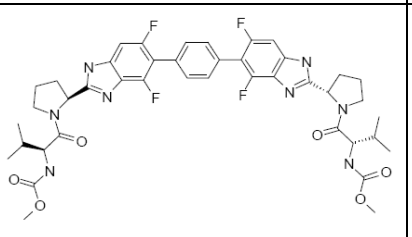
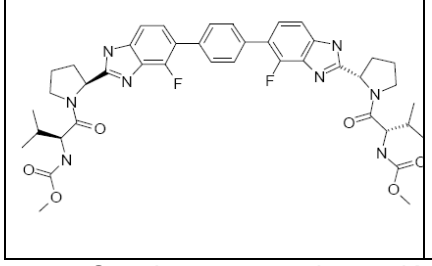
Tabla 1. Conector de bifenilo versus otros conectores

	EC50 (nM)							
	1a	1b	2a	2b	3a	4a	5a	6a
 (BMS-790052)	Véase Nettles et al., supra.							
	0,12	0,03	16	0,09	1,5	0,03	0,05	0,5
 (isómero 1, en el cual el grupo ciclohexanilo tiene una configuración cis/trans diferente del isómero 2)	0,71	0,06	9,0	0,4	2,3	0,04	0,08	0,5
 (isómero 2, en el cual el grupo ciclohexanilo tiene una configuración cis/trans diferente del isómero 1)	>10	8,5	>100	>10	>10	4,0	>10	>10

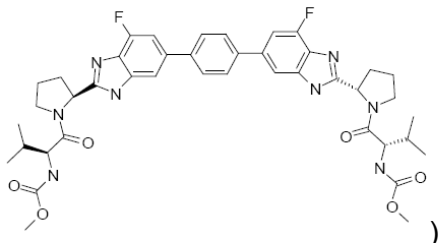
En la Tabla 2 se comparan compuestos que contienen benzimidazol no sustituido con aquellos que contienen benzimidazol sustituido con halo. Las actividades anti-virales fueron evaluadas usando replicones de tipo salvaje (por ejemplo, 1b WT o 1a WT), así como replicones que contienen mutaciones NS5A específicas (por ejemplo, 1b L28T, 1b Y93H, 1a L31V, 1a Y93C, 1a M28V o 1a Q30E) en la ausencia de FBS. En comparación con el compuesto de referencia que contiene benzimidazol no sustituido, los compuestos

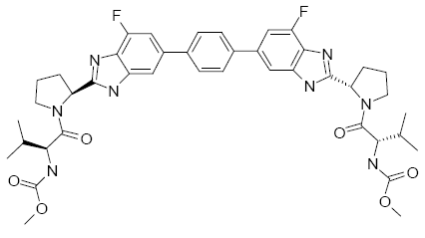
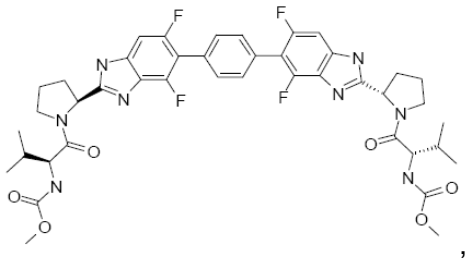
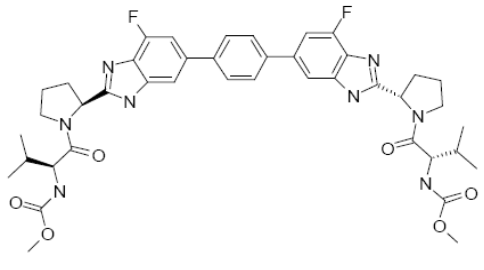
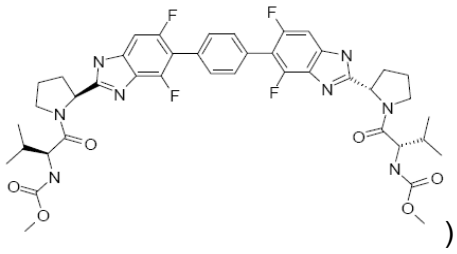
que contienen benzimidazol sustituido en general exhibieron actividades comparables o inferiores contra muchos de estos virus HCV.

Tabla 2. Benzimidazol no sustituido versus benzimidazol sustituido con halo

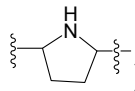
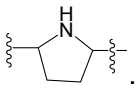
	EC50 (nM)							
	1b WT	1b L28 T	1b Y93 H	1a WT	1a L31 V	1a Y93 C	1a M28 V	1a Q30 E
 (compuesto de referencia)	0,01	2,7	0,9	0,09	36	40	1,0	40
	0,003	1,8	0,5	0,14	109	26	2,4	119
	0,004	4,3	2,4	0,26	5,5	34	1,8	59
	0,005	>10	5,7	0,28	33	103	11,6	306
	0,007	>10	3,6	0,1	80	141	5,8	52

Con la presente invención se descubrió sorprendentemente que los compuestos

que contienen benzimidazol sustituido con halo (por ejemplo, ) pueden presentar una mejor actividad contra determinadas variantes del HCV que contienen mutaciones NS5A (por ejemplo, 1a L31V).

Pruebas similares también mostraron que  y  , en comparación con el compuesto de referencia en la Tabla 2, exhibieron una actividad significativamente mejorada contra la variante 1a del HCV que contiene a la mutación M28T de NS5A. Estas mejoras no fueron descritas ni sugeridas en ninguna de las Solicitudes BMS, Presidio o Enanta mencionadas previamente. Por consiguiente, la presente invención está dirigida a métodos para usar los compuestos que contienen benzimidazol sustituido con halo (por ejemplo,  o ) en el tratamiento de variantes del HCV (por ejemplo, 1a M28T o 1a L31V). Estos métodos comprenden administrar una cantidad eficaz de dicho compuesto a un paciente infectado

con dicha variante del HCV (por ejemplo, 1a M28T o 1a L31V).

Se encontró asimismo que cuando el conector de fenilo entre los grupos de benzimidazol era reemplazado por un conector de pirrolidinilo (por ejemplo, ), la química del proceso para introducir las substituciones halo en los grupos benzimidazol se volvía extremadamente difícil. En las Solicitudes BMS, Presidio y Enanta mencionadas previamente no se provee ninguna divulgación habilitante que pudiera permitir substituciones halo sobre los grupos benzimidazol en un compuesto en el cual el conector de fenilo fue reemplazado por  . El esquema XXIV y diversos ejemplos de la presente solicitud (por ejemplo, los ejemplos 2.16, 3.35-3.41, 3.46-3.53, 4.26-4.31, 4.37-4.40, 4.42-4.46 y 4.51-4.57) proporcionan una divulgación habilitante que permite tales substituciones en los compuestos con conectores de pirrolidinilo sustituido.

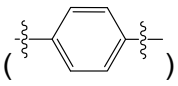
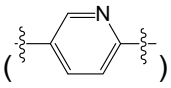
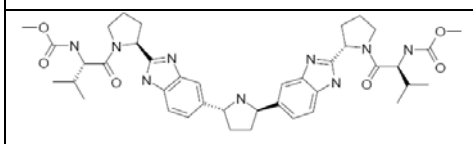
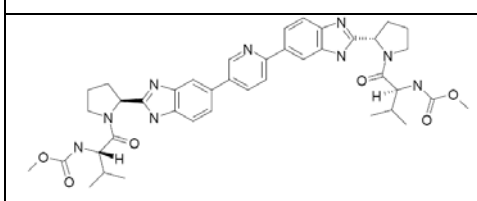
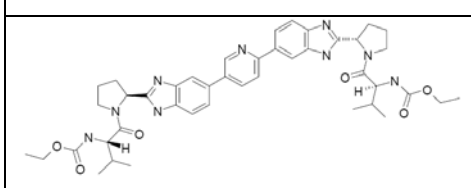
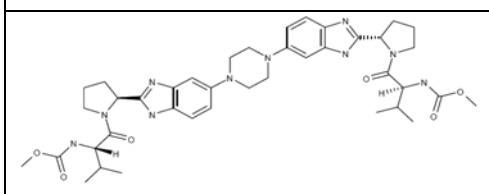
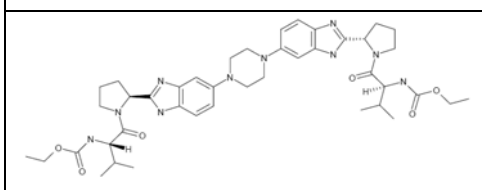
En la Tabla 3 se comparan compuestos con diferentes conectores entre los grupos benzimidazol. Las actividades anti-virales se determinaron usando ensayos con replicones 1a y 1b. "HP" se refiere a plasma humano. El compuesto que contiene al conector de pirrolidinilo mostró actividades anti-HCV significativamente inferiores que los que contienen al conector de piridinilo. En comparación con el conector de fenilo () usado en US20100068176 (BMS), se espera que el conector de piridinilo () o los conectores tipo aromáticos de 6 miembros proporcionen actividades anti-HCV similares o comparables.

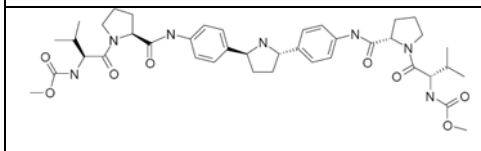
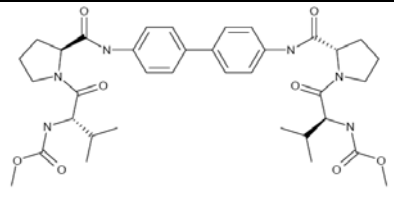
Tabla 3. Conector heterocíclico no aromático versus conector heterocíclico aromático

	EC50 (nM, en la presencia de FBS	EC50 (nM, en la presencia de FBS 5% y HP 40%)

	5%)			
	1a	1b	1a	1b
	> 250	> 250	2500 - 8000	> 4500
	< 0,32	< 0,32	< 3,2	< 3,2
	6,8	2,9	83	190
	1,7	1,7	< 3,2	6
	82	73	166	548

En la Tabla 4 se muestra además que cuando el conector de fenilo se reemplaza por un conector de pirrolidinilo, se puede reducir significativamente la actividad del compuesto contra el HCV. El compuesto de la Tabla 4 contiene un conector de pirrolidinilo y tiene valores de EC50 de más de 200 nM. En comparación, BMS-790052, que contiene un conector de bifenilo, tiene valores de EC50 no mayores que 0,2 nM. Véase Nettles et al., supra. Por lo tanto, en las Tablas 3 y 4 se demuestra claramente que el uso de un conector de pirrolidinilo no sustituido en un inhibidor de NS5A dimérico o de tipo dímero puede conducir a actividades anti-HCV pobres.

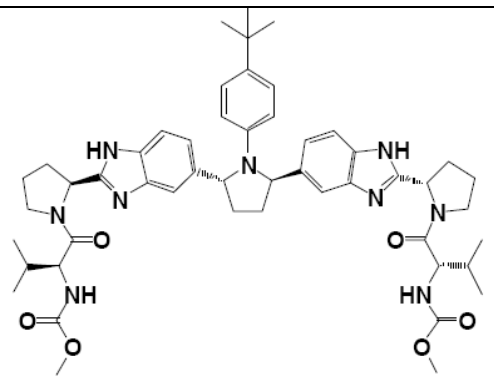
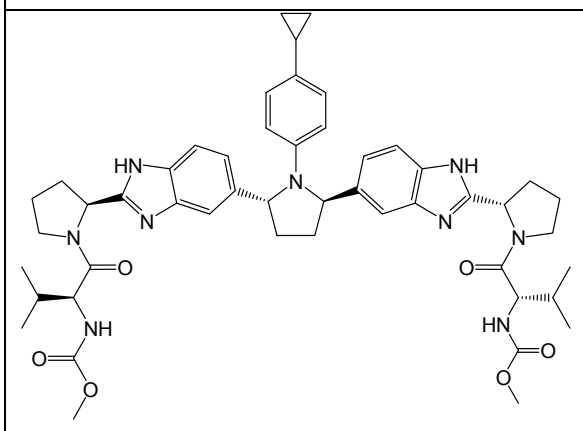
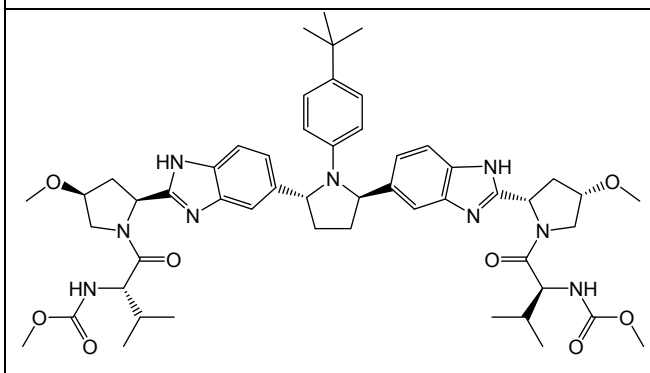
Tabla 4. Conector heterocíclico no aromático versus conector heterocíclico aromático

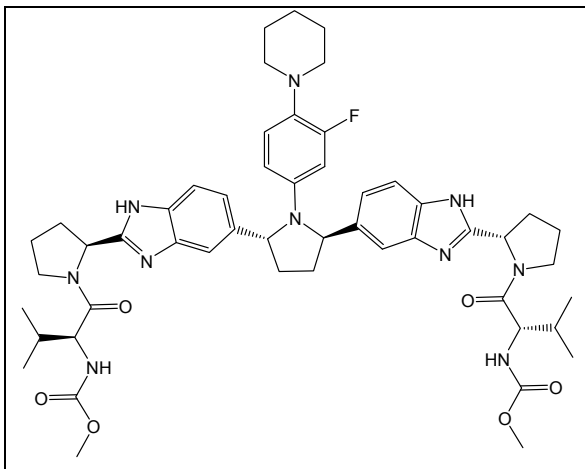
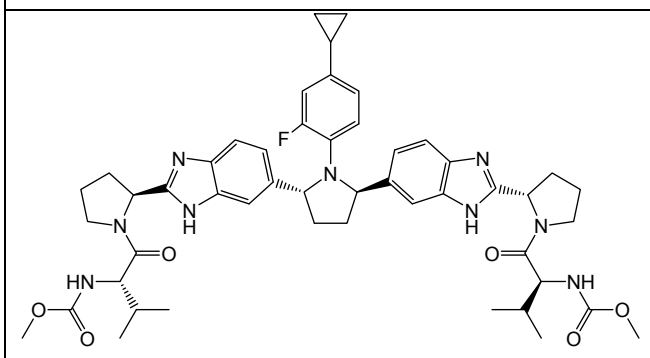
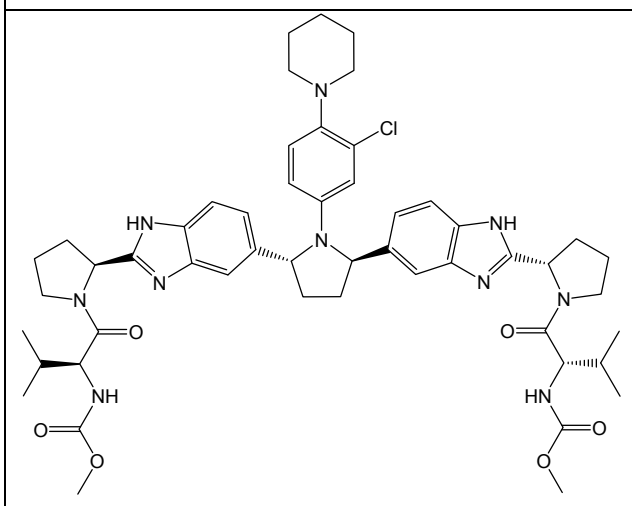
	EC50 (nM, en la presencia de FBS 5%)		EC50 (nM, en la presencia de FBS 5% y HP 40%)	
	1a	1b	1a	1b
	290	320	1200	2400
	> 1000	10	> 10000	60

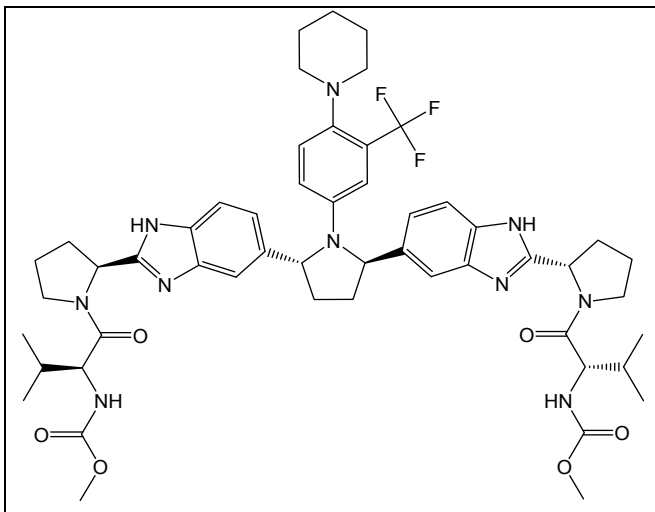
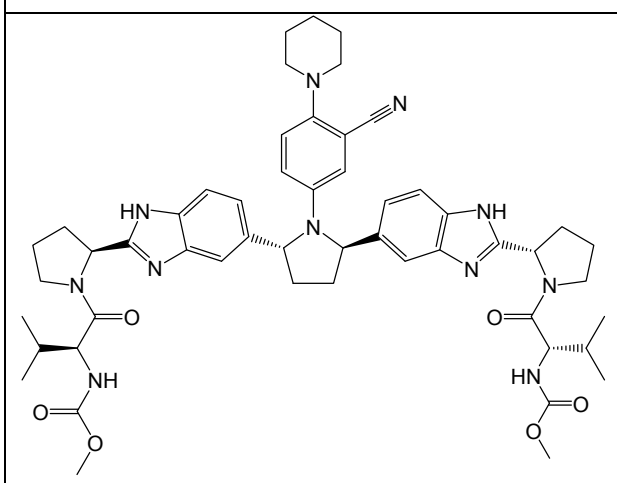
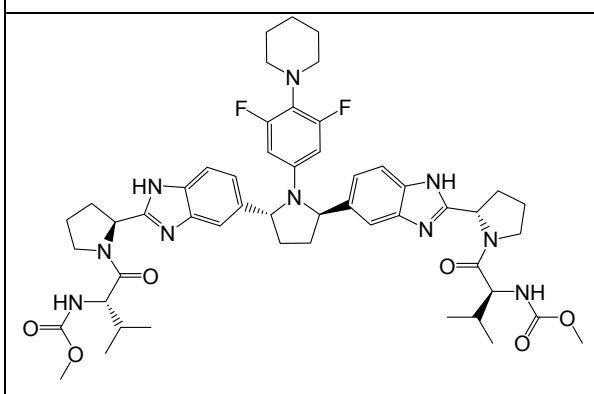
Se descubrió inesperadamente que cuando el átomo de nitrógeno en el conector de pirrolidinilo es sustituido por un carbociclo o heterociclo, es posible mejorar drásticamente las actividades anti-virales del compuesto. En la Tabla 5 se muestran las actividades anti-HCV de compuestos en los cuales el conector de pirrolidinilo fue sustituido por un carbociclo o heterociclo sustituido.

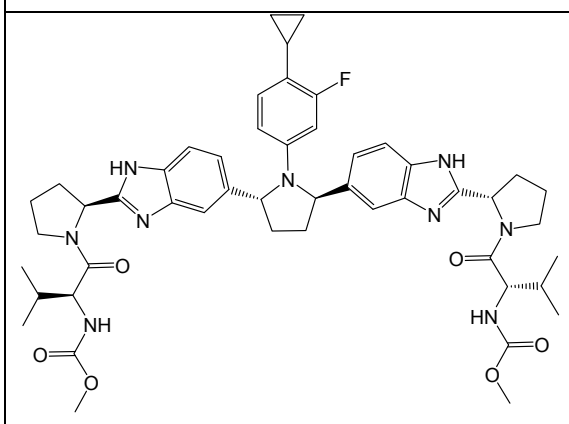
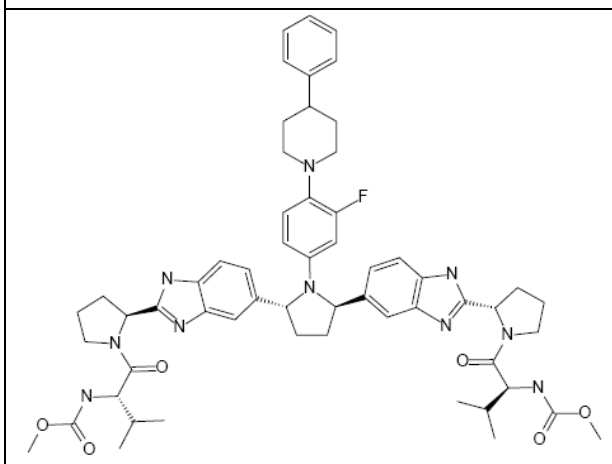
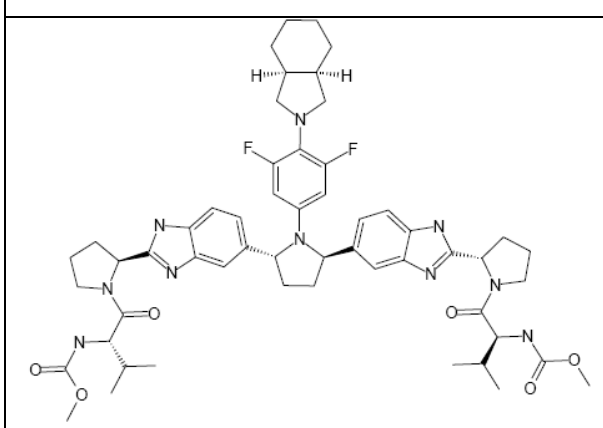
Tabla 5. Conector de pirrolidinilo sustituido

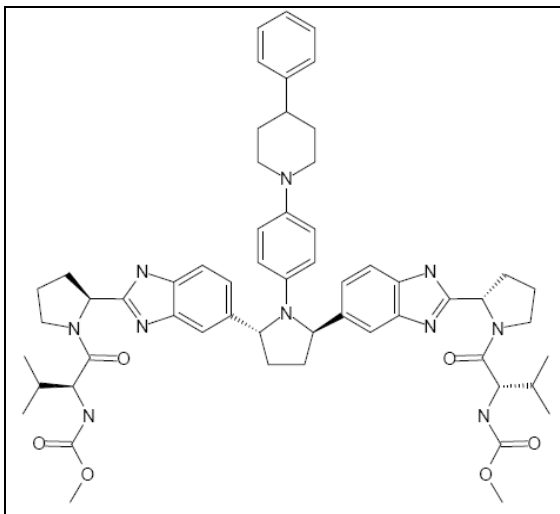
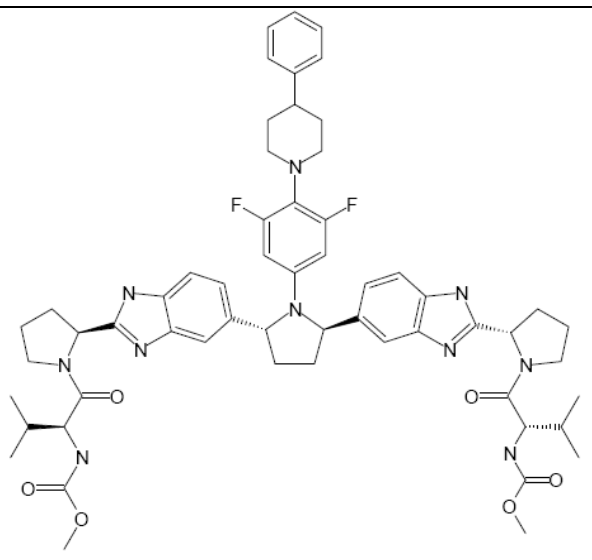
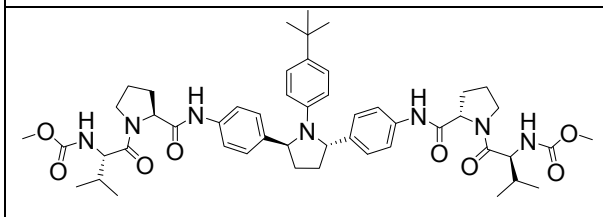
	EC50 (nM, en la presencia de HP 40%)		EC50 (nM, en la ausencia de HP)			
	1a	1b	2a	2b	3a	4a

 (Ejemplo 109 de la publicación de la Solicitud de Patente de los EE.UU. N°: 2010/0317568)	0,1	0,3	0,2	≤ 0,05	≤ 0,05	≤ 0,05
 (Ejemplo 163 de la publicación de la Solicitud de Patente de los EE.UU. N°: 2010/0317568)	0,1	0,3	≤ 0,05	≤ 0,05	≤ 0,05	≤ 0,05
 (Ejemplo 236 de la publicación de la Solicitud de Patente de los EE.UU. N°: 2010/0317568)	0,3	0,8				

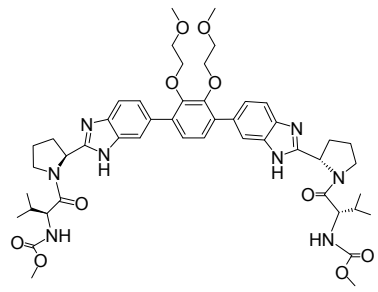
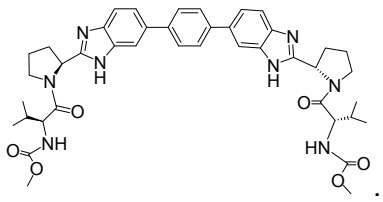
 (Ejemplo 245 de la publicación de la Solicitud de Patente de los EE.UU. N°: 2010/0317568)	0,2	0,4	≤ 0,05	≤ 0,05	≤ 0,05	≤ 0,05
 (Ejemplo 251 de la publicación de la Solicitud de Patente de los EE.UU. N°: 2010/0317568)	0,1	0,2	≤ 0,05	≤ 0,05	≤ 0,05	≤ 0,05
 (Ejemplo 256 de la publicación de la Solicitud de Patente de los EE.UU. N°: 2010/0317568)	0,2	0,2	≤ 0,05	≤ 0,05	≤ 0,05	≤ 0,05

 (Ejemplo 257 de la publicación de la Solicitud de Patente de los EE.UU. N°: 2010/0317568)	0,6	0,3	0,5	≤ 0,05	≤ 0,05	≤ 0,05
 (Ejemplo 258 de la publicación de la Solicitud de Patente de los EE.UU. N°: 2010/0317568)	0,4	0,5	0,07	≤ 0,05	≤ 0,05	≤ 0,05
 (Ejemplo 271 de la publicación de la Solicitud de	0,1	0,2	≤ 0,05	≤ 0,05	≤ 0,05	≤ 0,05

Patente de los EE.UU. N°: 2010/0317568)						
 (Ejemplo 302 de la publicación de la Solicitud de Patente de los EE.UU. N°: 2010/0317568)	0,1	0,1	≤ 0,05	≤ 0,05	≤ 0,05	≤ 0,05
 (Ejemplo 3.20 descrito más adelante)	0,5	0,6	≤ 0,05	≤ 0,05	≤ 0,05	≤ 0,05
 (Ejemplo 4.3 descrito más adelante)	0,1	0,2				

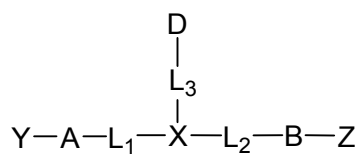
 (Ejemplo 4.25 descrito más adelante)	1,5	1,5	0,5	0,5	0,5	0,2
 (Ejemplo 5.1 descrito más adelante)	0,1	0,2	≤ 0,05	≤ 0,05	≤ 0,05	≤ 0,05
 (Ejemplo 37 de la publicación de la Solicitud de Patente de los EE.UU. N°: 2010/0317568)	0,2	0,1	≤ 0,05	≤ 0,05	≤ 0,05	≤ 0,05

Se hace notar que no se ha demostrado que la actividad anti-HCV de

 fuera mejor que la actividad de  .

En la Tabla 5 también se demuestra que una o más substituciones halo adicionales sobre los sustituyentes carbociclo/heterociclo en el conector de pirrolidinilo pueden mejorar significativamente las actividades anti-HCV de los compuestos (por ejemplo, compárese el Ejemplo 4.25 con el Ejemplo 3.20 o con el Ejemplo 5.1).

La presente invención presenta compuestos de Fórmula I, y sales aceptables farmacéuticamente de los mismos,



I

donde:

X es C3-C12carbociclo o heterociclo de entre 3 y 12 miembros, y está opcionalmente sustituido con uno o más RA o RF;

L1 y L2 se seleccionan en forma independiente entre sí entre un enlace; o C1-C6alquileno, C2-C6alquenileno o C2-C6alquinileno, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más RL;

L3 es un enlace o –LS–K–LS'–, donde K se selecciona entre un enlace, –O–, –S–, –N(RB)–, –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(RB)–, –N(RB)C(O)–, –N(RB)C(O)O–, –OC(O)N(RB)–, –N(RB)S(O)–, –N(RB)S(O)2–, –S(O)N(RB)–, –S(O)2N(RB)–, –C(O)N(RB)C(O)–, –N(RB)C(O)N(RB')–, –N(RB)SO2N(RB')–, o –

N(RB)S(O)N(RB')–;

A y B son en forma independiente entre sí C3-C12carbociclo o heterociclo de entre 3 y 12 miembros, y están opcionalmente sustituidos en forma independiente entre sí con uno o más RA;

D es C3-C12carbociclo o heterociclo de entre 3 y 12 miembros, y está opcionalmente sustituido con uno o más RA; o D es C3-C12carbociclo o heterociclo de entre 3 y 12 miembros que está sustituido con J y opcionalmente sustituido con uno o más RA, donde J es C3-C12carbociclo o heterociclo de entre 3 y 12 miembros y está opcionalmente sustituido con uno o más RA, o J es –SF5; o D es hidrógeno o RA;

Y se selecciona entre –T'–C(R1R2)N(R5)–T–RD, –T'–C(R3R4)C(R6R7)–T–RD, –LK–T–RD, o –LK–E;

R1 y R2 son en forma independiente entre sí RC, y R5 es RB; o R1 es RC, y R2 y R5, tomados junto con los átomos a los cuales están unidos, forman un heterociclo de entre 3 y 12 miembros que está opcionalmente sustituido con uno o más RA;

R3, R4, R6, y R7 son en forma independiente entre sí RC; o R3 y R6 son en forma independiente entre sí RC, y R4 y R7, tomados junto con los átomos a los cuales están unidos, forman un carbociclo o heterociclo de entre 3 y 12 miembros que está opcionalmente sustituido con uno o más RA;

Z se selecciona entre –T'–C(R8R9)N(R12)–T–RD, –T'–C(R10R11)C(R13R14)–T–RD, –LK–T–RD, o –LK–E;

R8 y R9 son en forma independiente entre sí RC, y R12 es RB; o R8 es RC, y R9 y R12, tomados junto con los átomos a los cuales están unidos, forman un heterociclo de entre 3 y 12 miembros que está opcionalmente sustituido con uno o más RA;

R10, R11, R13, y R14 son en forma independiente entre sí RC; o R10 y R13 son

en forma independiente entre sí RC, y R11 y R14, tomados junto con los átomos a los cuales están unidos, forman un carbociclo o heterociclo de entre 3 y 12 miembros que está opcionalmente sustituido con uno o más RA;

T y T' se seleccionan en forma independiente entre sí en cada caso entre un enlace, –LS–, –LS–M–LS'–, o –LS–M–LS'–M'–LS''–, donde M y M' se seleccionan en forma independiente entre sí en cada caso entre un enlace, –O–, –S–, –N(RB)–, –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(RB)–, –N(RB)C(O)–, –N(RB)C(O)O–, –OC(O)N(RB)–, –N(RB)S(O)–, –N(RB)S(O)2–, –S(O)N(RB)–, –S(O)2N(RB)–, –C(O)N(RB)C(O)–, –N(RB)C(O)N(RB')–, –N(RB)SO2N(RB')–, –N(RB)S(O)N(RB')–, C3-C12carbociclo o heterociclo de entre 3 y 12 miembros, y donde dicho C3-C12carbociclo y heterociclo de entre 3 y 12 miembros están opcionalmente sustituidos en forma independiente entre sí en cada caso con uno o más RA;

LK se selecciona en forma independiente en cada caso entre un enlace, –LS–N(RB)C(O)–LS'– o –LS–C(O)N(RB)–LS'–; o C1-C6alquileno, C2-C6alquenileno o C2-C6alquinileno, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más RL; o C3-C12carbociclo o heterociclo de entre 3 y 12 miembros, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más RA;

E se selecciona en forma independiente en cada caso entre C3-C12carbociclo o heterociclo de entre 3 y 12 miembros, y está opcionalmente sustituido en forma independiente en cada caso con uno o más RA;

RD se selecciona en forma independiente en cada caso entre hidrógeno o RA;

RA se selecciona en forma independiente en cada caso entre halógeno, nitro, oxo, fosfonoxi, fosfono, tioxo, ciano, o –LS–RE, donde dos RA adyacentes, tomados

junto con los átomos a los cuales están unidos y cualquier otro átomo entre los átomos a los cuales están unidos, pueden formar opcionalmente carbociclo o heterociclo;

RB y RB' se seleccionan en forma independiente entre sí en cada caso entre hidrógeno; o C1-C6alquilo, C2-C6alquenilo o C2-C6alquinilo, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano o carbociclo o heterociclo de entre 3 y 6 miembros; o carbociclo o heterociclo de entre 3 y 6 miembros; donde cada carbociclo o heterociclo de entre 3 y 6 miembros en RB o RB' está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C1-C6alquilo, C2-C6alquenilo, C2-C6alquinilo, C1-C6haloalquilo, C2-C6haloalquenilo o C2-C6haloalquinilo;

RC se selecciona en forma independiente en cada caso entre hidrógeno, halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo o ciano; o C1-C6alquilo, C2-C6alquenilo o C2-C6alquinilo, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano o carbociclo o heterociclo de entre 3 y 6 miembros; o carbociclo o heterociclo de entre 3 y 6 miembros; donde cada carbociclo o heterociclo de entre 3 y 6 miembros en RC está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C1-C6alquilo, C2-C6alquenilo, C2-C6alquinilo, C1-C6haloalquilo, C2-

C6haloalquenilo o C2-C6haloalquinilo;

RE se selecciona en forma independiente en cada caso entre –O–RS, –S–RS, –C(O)RS, –OC(O)RS, –C(O)ORS, –N(RSRS'), –S(O)RS, –SO2RS, –C(O)N(RSRS'), –N(RS)C(O)RS', –N(RS)C(O)N(RS'RS''), –N(RS)SO2RS', –SO2N(RSRS'), –N(RS)SO2N(RS'RS''), –N(RS)S(O)N(RS'RS''), –OS(O)–RS, –OS(O)2–RS, –S(O)2ORS, –S(O)ORS, –OC(O)ORS, –N(RS)C(O)ORS', –OC(O)N(RSRS'), –N(RS)S(O)–RS', –S(O)N(RSRS'), –P(O)(ORS)2, o –C(O)N(RS)C(O)–RS'; o C1-C6alquilo, C2-C6alquenilo o C2-C6alquinilo, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo o ciano; o C3-C6carbociclo o heterociclo de entre 3 y 6 miembros, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C1-C6alquilo, C2-C6alquenilo, C2-C6alquinilo, C1-C6haloalquilo, C2-C6haloalquenilo, C2-C6haloalquinilo, C(O)ORS, o –N(RSRS');

RF se selecciona en forma independiente en cada caso entre C1-C10alquilo, C2-C10alquenilo o C2-C10alquinilo, cada uno de los cuales contiene 0, 1, 2, 3, 4 o 5 herteroátomos seleccionados entre O, S o N y está opcionalmente sustituido en forma independiente con uno o más RL; o –(RX–RY)Q–(RX–RY'), donde Q es 0, 1, 2, 3 o 4, y cada RX es en forma independiente O, S o N(RB), donde cada RY es en forma independiente C1-C6alquileno, C2-C6alquenileno o C2-C6alquinileno cada uno de los cuales está opcionalmente sustituido en forma independiente con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo o ciano, y donde cada RY' es en forma independiente C1-C6alquilo, C2-

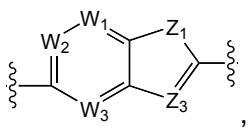
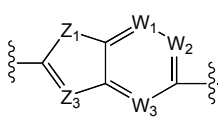
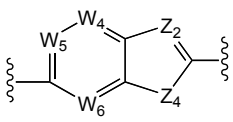
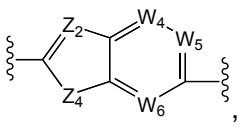
C6alquenilo o C2-C6alquinilo cada uno de los cuales está opcionalmente sustituido en forma independiente con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo o ciano;

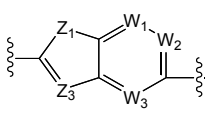
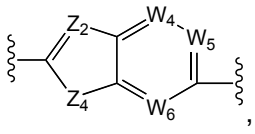
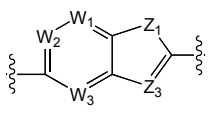
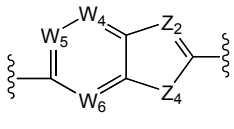
RL se selecciona en forma independiente en cada caso entre halógeno, nitro, oxo, fosfonoxi, fosfono, tioxo, ciano, –O–RS, –S–RS, –C(O)RS, –OC(O)RS, –C(O)ORS, –N(RSRS'), –S(O)RS, –SO2RS, –C(O)N(RSRS') o –N(RS)C(O)RS'; o C3-C6carbociclo o heterociclo de entre 3 y 6 miembros, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C1-C6alquilo, C2-C6alquenilo, C2-C6alquinilo, C1-C6haloalquilo, C2-C6haloalquenilo o C2-C6haloalquinilo; donde dos RL adyacentes, tomados junto con los átomos a los cuales están unidos y cualquier otro átomo entre los átomos a los cuales están unidos, pueden formar opcionalmente carbociclo o heterociclo;

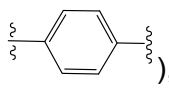
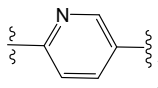
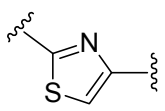
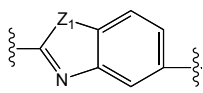
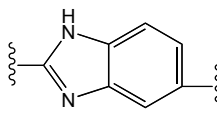
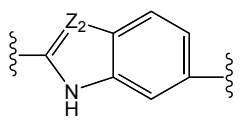
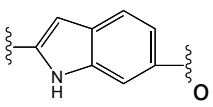
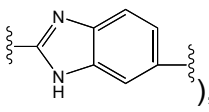
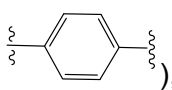
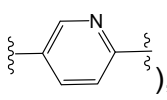
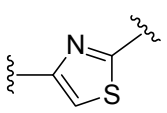
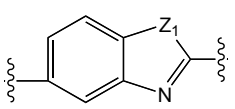
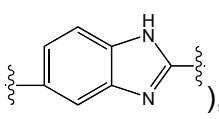
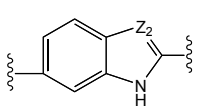
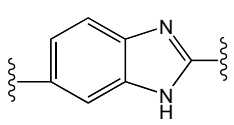
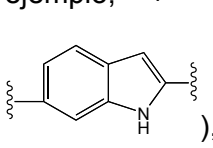
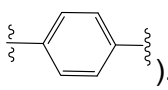
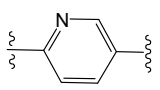
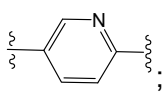
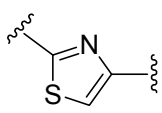
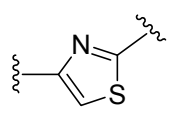
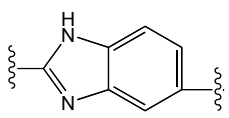
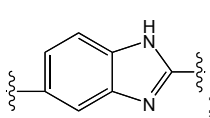
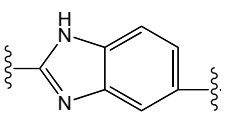
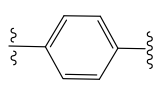
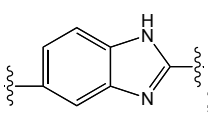
LS, LS' y LS'' se seleccionan en forma independiente entre sí en cada caso entre un enlace; o C1-C6alquileno, C2-C6alquenileno o C2-C6alquinileno, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más RL; y

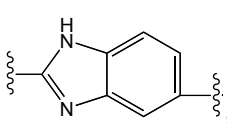
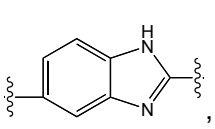
RS, RS' y RS'' se seleccionan en forma independiente entre sí en cada caso entre hidrógeno; C1-C6alquilo, C2-C6alquenilo o C2-C6alquinilo, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, –O–C1-C6alquilo, –O–C1-C6alquilen–O–C1-C6alquilo, o carbociclo o heterociclo de entre 3 y 6 miembros; o carbociclo o heterociclo de entre 3 y 6 miembros;

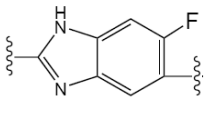
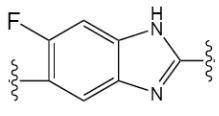
donde cada carbociclo o heterociclo de entre 3 y 6 miembros en RS , RS' o RS' está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C1-C6alquilo, C2-C6alquenilo, C2-C6alquinilo, C1-C6haloalquilo, C2-C6haloalquenilo o C2-C6haloalquinilo.

A y B preferiblemente se seleccionan en forma independiente entre C5-C6carbociclo (por ejemplo, fenilo), heterociclo de 5 o 6 miembros (por ejemplo, piridinilo o tiazolilo), o biciclos de entre 8 y 12 miembros como por ejemplo  ,  ,  o  , donde Z1 se selecciona en forma independiente en cada caso entre O, S, NH o CH2, Z2 se selecciona en forma independiente en cada caso entre N o CH, Z3 se selecciona en forma independiente en cada caso entre N o CH, Z4 se selecciona en forma independiente en cada caso entre O, S, NH o CH2, y W1, W2, W3, W4, W5 y W6 se seleccionan en forma independiente entre sí en cada caso entre CH o N. A y B están opcionalmente sustituidos en forma independiente entre sí con uno o más RA.

Más preferiblemente, A se selecciona entre C5-C6carbociclo, heterociclo de 5 o 6 miembros,  o  , y está opcionalmente sustituido con uno o más RA; B se selecciona entre C5-C6carbociclo, heterociclo de 5 o 6 miembros,  o  , y está opcionalmente sustituido con uno o más RA; donde Z1, Z2, Z3, Z4, W1, W2, W3, W4, W5, W6 son como se definen precedentemente. Preferiblemente, Z3 es N y Z4 es NH. Por ejemplo, A se puede seleccionar entre fenilo

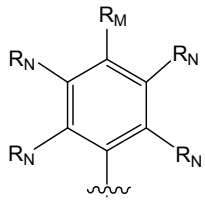
(por ejemplo, ), piridinilo (por ejemplo, ), tiazolilo (por ejemplo, ),  (por ejemplo, ), o  (por ejemplo,  o ), y está opcionalmente sustituido con uno o más RA; y B se puede seleccionar entre fenilo (por ejemplo, ), piridinilo (por ejemplo, ), tiazolilo (por ejemplo, ),  (por ejemplo, ), o  (por ejemplo,  o ), y está opcionalmente sustituido con uno o más RA. Más preferiblemente, A y B son fenilo (por ejemplo, A y B son ). También más preferiblemente, 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 está opcionalmente sustituido en forma independiente con uno o más RA.

También preferiblemente, A es  , B es  , y A y B están sustituidos con uno o más halógeno, como por ejemplo F o Cl. Sorprendentemente se ha descubierto que cuando A y/o B son benzimidazol halosustituido (por ejemplo, A es

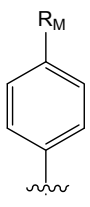
 y B es ), los compuestos de Fórmula I (así como también los compuestos de Fórmula IA, IB, IC, ID, IE, IF o IG que se describen más adelante, y los compuestos de cada forma de realización descrita bajo las mismas) en forma inesperada mostró propiedades farmacocinéticas significativamente mejoradas, en comparación con los compuestos con benzimidazol no sustituido. Las mejoras en la farmacocinética pueden observarse, por ejemplo, como un mayor nivel exposición en plasma medido como el área bajo la curva (AUC) a lo largo de un período de 24 horas luego de la administración oral en ratones (por ejemplos véase más adelante). De manera sorprendente también se descubrió que estos compuestos con benzimidazol sustituido con halo en forma inesperada presentan una actividad inhibitoria mejorada contra viertas variantes HCV genotipo 1a (por ejemplo, variantes que contienen mutaciones NS5A L31M, Y93H, o Y93N). De manera acorde, la presente invención contempla métodos para usar dichos compuestos para tratar una infección de HCV genotipo 1a (por ejemplo, variante de infección L31M, Y93H, o Y93N 1a). Estos métodos comprenden administrar tal compuesto a un paciente que tenga variante HCV genotipo 1a (por ejemplo, variante L31M, Y93H, o Y93N 1a). La presente invención también contempla el uso de dichos compuestos para la fabricación de un medicamento para el tratamiento de una infección de variante genotipo 1a (por ejemplo, variante de infección L31M, Y93H, o Y93N 1a).

D preferiblemente se selecciona entre C5-C6carbociclo, heterociclo de 5 o 6 miembros, o biciclos de entre 6 y 12 miembros, y está opcionalmente sustituido con uno o más RA. D también puede seleccionarse preferiblemente entre C1-C6alquilo, C2-C6alquenilo o C2-C6alquinilo, y está opcionalmente sustituido con uno o más sustituyentes seleccionados entre RL. Más preferiblemente, D es C5-C6carbociclo (por ejemplo, fenilo), heterociclo de 5 o 6 miembros (por ejemplo, piridinilo, pirimidinilo, tiazolilo), o biciclos de entre 6 y 12 miembros (por ejemplo, indanilo, 4,5,6,7-tetrahidrobenzo[d]tiazolilo, benzo[d]tiazolilo, indazolilo, benzo[d][1,3]dioxol-5-ilo), y está

sustituido con uno o más RM, donde RM es halógeno, nitro, oxo, fosfonoxi, fosfono, tioxo, ciano, o –LS–RE. También preferiblemente, D es fenilo, y está opcionalmente sustituido con uno o más RA. Más preferiblemente, D es fenilo, y está sustituido con uno o más RM, donde RM es como se define precedentemente. Más preferiblemente, D es

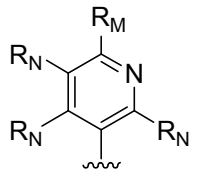


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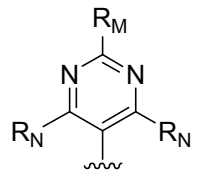


, donde RM es como se define precedentemente, y cada RN se selecciona en forma independiente entre RD y preferiblemente es hidrógeno. Uno o más RN también puede ser preferiblemente halo como por ejemplo F.

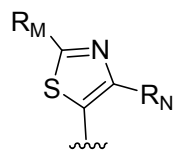
D es también preferiblemente piridinilo, pirimidinilo, o tiazolilo, opcionalmente sustituido con uno o más RA. Más preferiblemente D es piridinilo, pirimidinilo, o tiazolilo, y está sustituido con uno o más RM. Más preferiblemente, D es



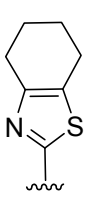
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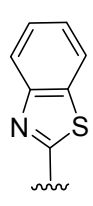
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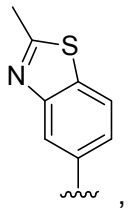
, donde RM es como se define precedentemente, y cada RN se selecciona en forma independiente entre RD y preferiblemente es hidrógeno. Uno o más RN también puede ser preferiblemente halo como por ejemplo F. D es también preferiblemente indanilo, 4,5,6,7-tetrahidrobenzo[d]tiazolilo, benzo[d]tiazolilo, o indazolilo, y está opcionalmente sustituido con uno o más RA. Más preferiblemente D es indanilo, 4,5,6,7-tetrahidrobenzo[d]tiazolilo, benzo[d]tiazolilo, indazolilo, o benzo[d][1,3]dioxol-5-ilo, y está sustituido con uno o más RM. Más preferiblemente, D es



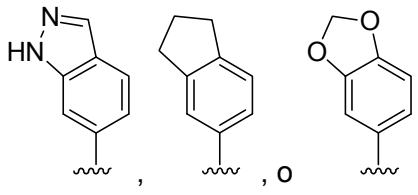
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, , o , y está opcionalmente sustituido con uno o más RM.

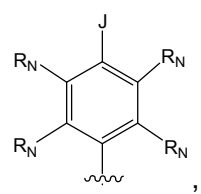
Preferiblemente, RM es halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, ciano; o C1-C6alquilo, C2-C6alquenilo o C2-C6alquinilo, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo o ciano; o C3-C6carbociclo o heterociclo de entre 3 y 6 miembros, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C1-C6alquilo, C2-C6alquenilo, C2-C6alquinilo, C1-C6haloalquilo, C2-C6haloalquenilo o C2-C6haloalquinilo. Más preferiblemente, RM es halógeno, hidroxi, mercapto, amino, carboxi; o C1-C6alquilo, C2-C6alquenilo o C2-C6alquinilo, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino o carboxi. Más preferiblemente, RM es C1-C6alquilo el cual está opcionalmente sustituido con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino o carboxi.

También preferiblemente, RM es halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, o ciano; o RM es –LS–RE, donde LS es una unión o C1-C6alquileno, y RE es –N(RSRS'), –O–RS, –C(O)RS, –C(O)ORS, –C(O)N(RSRS'), –N(RS)C(O)RS', –N(RS)C(O)ORS', –N(RS)SO2RS', –SO2RS, –SRS, o –P(O)(ORS)2, donde RS y RS' pueden seleccionarse en forma independiente entre sí, por ejemplo, entre (1) hidrógeno o (2) C1-C6alquilo opcionalmente sustituido en cada caso con uno o más halógeno, hidroxi, –O–C1-C6alquilo o heterociclo de entre 3 y 6 miembros; o RM es C1-C6alquilo, C2-C6alquenilo o C2-C6alquinilo, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes

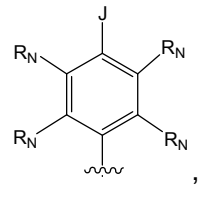
seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo o ciano; o RM es C3-C6carbociclo o heterociclo de entre 3 y 6 miembros, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C1-C6alquilo, C2-C6alquenilo, C2-C6alquinilo, C1-C6haloalquilo, C2-C6haloalquenilo, C2-C6haloalquinilo, –C(O)ORS, o –N(RSRS'). Más preferiblemente, RM es halógeno (por ejemplo, fluoro, cloro, bromo, yodo), hidroxi, mercapto, amino, carboxi, o C1-C6alquilo (por ejemplo, metilo, isopropilo, tert-butilo), C2-C6alquenilo o C2-C6alquinilo, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, ciano, o carboxi. Por ejemplo RM es CF3, –C(CF3)2–OH, –C(CH3)2–CN, –C(CH3)2–CH2OH, o –C(CH3)2–CH2NH2. También preferiblemente RM es –LS–RE donde LS es una unión y RE es –N(RSRS'), –O–RS, –N(RS)C(O)ORS', –N(RS)SO2RS', –SO2RS, o –SRS. Por ejemplo donde LS es una unión, RE es –N(C1-C6alquil)2 (por ejemplo, –NMe2); –N(C1-C6alquilen–O–C1-C6alquil)2 (por ejemplo –N(CH2CH2OMe)2); –N(C1-C6alquil)(C1-C6alquilen–O–C1-C6alquilo) (por ejemplo –N(CH3)(CH2CH2OMe)); –O–C1-C6alquilo (por ejemplo, –O–Me, –O–Et, –O–isopropilo, –O–tert-butilo, –O–n-hexilo); –O–C1-C6haloalquilo (por ejemplo, – OCF3, –OCH2CF3); –O–C1-C6alquilen–piperidina (por ejemplo, –O–CH2CH2–1-piperidilo); –N(C1-C6alquil)C(O)OC1-C6alquilo (por ejemplo, –N(CH3)C(O)O–CH2CH(CH3)2), –N(C1-C6alquil)SO2C1-C6alquilo (por ejemplo, –N(CH3)SO2CH3); –SO2C1-C6alquilo (por ejemplo, –SO2Me); –SO2C1-C6haloalquilo (por ejemplo, –SO2CF3); o –S–C1-C6haloalquilo (por ejemplo, SCF3). También preferiblemente RM es –LS–RE donde LS es C1-C6alquileno (por ejemplo, –CH2–, –C(CH3)2–, –C(CH3)2–CH2–) y RE es –O–RS, –C(O)ORS, –N(RS)C(O)ORS', o –P(O)(ORS)2. Por ejemplo RM es –C1-C6alquilen–O–RS (por ejemplo, –C(CH3)2–CH2–OMe); –C1-C6alquilen–C(O)ORS (por ejemplo, –C(CH3)2–C(O)OMe); –C1-C6alquilen–

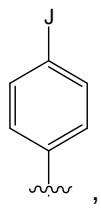
N(RS)C(O)ORS' (por ejemplo, –C(CH3)2–CH2–NHC(O)OCH3); o –C1-C6alquilen–P(O)(ORS)2 (por ejemplo, –CH2–P(O)(OEt)2). También más preferiblemente RM es C3-C6carbociclo o heterociclo de entre 3 y 6 miembros, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C1-C6alquilo, C2-C6alquenilo, C2-C6alquinilo, C1-C6haloalquilo, C2-C6haloalquenilo, C2-C6haloalquinilo, –C(O)ORS, o –N(RSRS'). Por ejemplo RM 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). Más preferiblemente, RM es C1-C6alquilo el cual está opcionalmente sustituido con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino o carboxi (por ejemplo, tert-butilo, CF3).

Más preferiblemente, D es C5-C6carbociclo, heterociclo de 5 o 6 miembros o biciclo de entre 6 y 12 miembros y está sustituido con J y opcionalmente sustituido con uno o más RA, donde J es C3-C6carbociclo, heterociclo de entre 3 y 6 miembros o biciclo de entre 6 y 12 miembros y está opcionalmente sustituido con uno o más RA. Preferiblemente, J está sustituido con un C3-C6carbociclo o heterociclo de entre 3 y 6 miembros, donde dicho C3-C6carbociclo o heterociclo de entre 3 y 6 miembros está opcionalmente sustituido en forma independiente con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C1-C6alquilo, C2-C6alquenilo, C2-C6alquinilo, C1-C6haloalquilo, C2-C6haloalquenilo, C2-C6haloalquinilo, C(O)ORS o –N(RSRS'), y J también puede estar opcionalmente sustituido con uno o más RA. También preferiblemente, D es C5-C6carbociclo o heterociclo de 5 o 6 miembros y está sustituido

con J y opcionalmente sustituido con uno o más RA, y J es C3-C6carbociclo o heterociclo de entre 3 y 6 miembros y está opcionalmente sustituido con uno o más RA, y preferiblemente, J está sustituido con al menos un C3-C6carbociclo o heterociclo de entre 3 y 6 miembros que está opcionalmente sustituido en forma independiente con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C1-C6alquilo, C2-C6alquenilo, C2-C6alquinilo, C1-C6haloalquilo, C2-C6haloalquenilo, C2-C6haloalquinilo, C(O)ORS o –N(RSRS'). También preferiblemente, D es C5-C6carbociclo o heterociclo de 5 o 6 miembros y está sustituido con J y opcionalmente sustituido con uno o más RA, y J es biciclo de entre 6 y 12 miembros (por ejemplo, un biciclo fusionado, en puente o espiro de entre 7 y 12 miembros que comprende un átomo del anillo nitrógeno a través del cual J se enlaza por unión covalente con D) y está opcionalmente sustituido con uno o más RA. Más preferiblemente, D es fenilo y está sustituido con J y opcionalmente sustituido con uno o más RA, y J es C3-C6carbociclo, heterociclo de entre 3 y 6 miembros o biciclo de entre 6 y 12 miembros y está opcionalmente sustituido con uno o más RA, y preferiblemente J está sustituido con al menos un C3-C6carbociclo o heterociclo de entre 3 y 6 miembros que está opcionalmente sustituido en forma independiente con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C1-C6alquilo, C2-C6alquenilo, C2-C6alquinilo, C1-C6haloalquilo, C2-C6haloalquenilo, C2-C6haloalquinilo, C(O)ORS o –N(RSRS'). Más preferiblemente, D es 

, donde cada RN se selecciona en forma independiente entre RD y preferiblemente es hidrógeno o halógeno, y J es C3-C6carbociclo, heterociclo de entre 3 y 6 miembros o biciclo de entre 6 y 12 miembros y está opcionalmente sustituido con uno o más RA, y preferiblemente J está sustituido con al menos un C3-C6carbociclo o heterociclo de entre 3 y 6 miembros que está

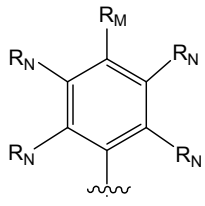
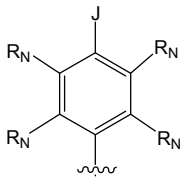
opcionalmente sustituido en forma independiente con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C1-C6alquilo, C2-C6alquenilo, C2-C6alquinilo, C1-C6haloalquilo, C2-C6haloalquenilo, C2-C6haloalquinilo, C(O)ORS o –N(RSRS'). También preferiblemente, D es 

, donde cada RN se selecciona en forma independiente entre RD y preferiblemente es hidrógeno o halógeno, y J es C3-C6carbociclo o heterociclo de entre 3 y 6 miembros y está sustituido con un C3-C6carbociclo o heterociclo de entre 3 y 6 miembros que está opcionalmente sustituido en forma independiente con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C1-C6alquilo, C2-C6alquenilo, C2-C6alquinilo, C1-C6haloalquilo, C2-C6haloalquenilo, C2-C6haloalquinilo, C(O)ORS o –N(RSRS'), y J también puede estar opcionalmente sustituido con uno o más RA. También preferiblemente, D es 

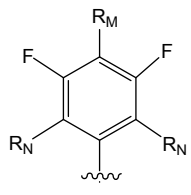
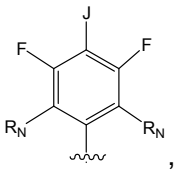
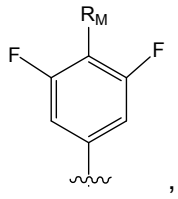
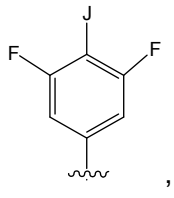
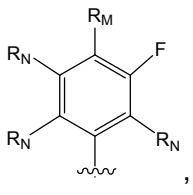
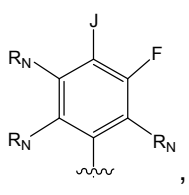
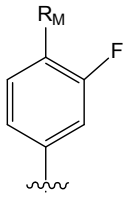
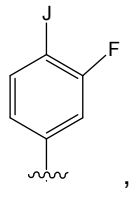
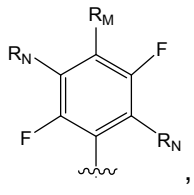
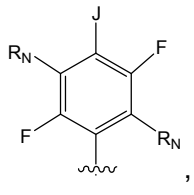
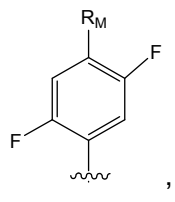
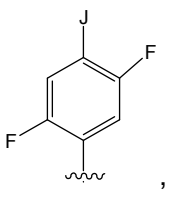
, y J es C3-C6carbociclo o heterociclo de entre 3 y 6 miembros y está opcionalmente sustituido con uno o más RA, y preferiblemente J está sustituido con al menos un C3-C6carbociclo o heterociclo de entre 3 y 6 miembros que está opcionalmente sustituido en forma independiente con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C1-C6alquilo, C2-C6alquenilo, C2-C6alquinilo, C1-C6haloalquilo, C2-C6haloalquenilo, C2-C6haloalquinilo, C(O)ORS o –N(RSRS').

Sorprendentemente se ha descubierto que cuando D contiene un carbociclo o heterociclo sustituido con halo (por ejemplo, un carbociclo o heterociclo de 5 o 6

miembros sustituido con halo unido directamente a X), el compuesto de Fórmula I (así como también los compuestos de Fórmula IA, IB, IC, ID, IE, IF o IG que se describen más adelante, y los compuestos de cada forma de realización descrita bajo las mismas) pueden exhibir una actividad inhibitoria mejorada significativamente contra HCV genotipos 2a, 2b, 3a o 4a y/o propiedades farmacocinéticas mejoradas. Por lo tanto, la presente invención contempla métodos para usar dichos compuestos para tratar HCV genotipo 2a, 2b, 3a o 4a infection. Estos métodos comprenden administrar tal compuesto a un paciente que tenga HCV genotipo 2a, 2b, 3a o 4a. La presente invención también contempla el uso de dichos compuestos para la fabricación de un medicamento para el tratamiento de HCV genotipos 2a, 2b, 3a o 4a. Los D adecuados para este fin pueden ser, por ejemplo,

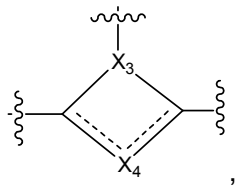
como se describe precedentemente, donde al menos un RN es halo como por ejemplo flúor. Los ejemplos específicos de D adecuados incluyen, sin que esto constituya limitación alguna,

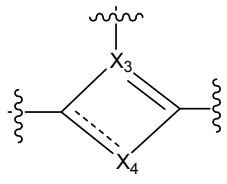
, donde RN, RM y J son como se describe precedentemente.

X preferiblemente es C5-C6carbociclo, heterociclo de 5 o 6 miembros, o biciclos de

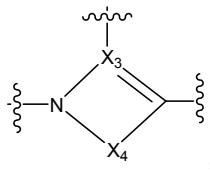
entre 6 y 12 miembros, y está opcionalmente sustituido con uno o más RA o RF. X también puede ser C5-C6carbociclo o heterociclo de 5 o 6 miembros que está opcionalmente sustituido con uno o más RA o RF, donde dos RA adyacentes sobre X, tomados junto con los átomos del anillo a los cuales están unidos, forman opcionalmente un carbociclo o heterociclo de 5 o 6 miembros. También preferiblemente, X es



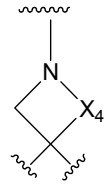
, donde X3 es C(H) o preferiblemente N y está directamente unido a –L3–D; X4 es C2-C4alquileno, C2-C4alquenileno o C2-C4alquinileno, cada uno de los cuales opcionalmente contiene uno o dos herteroátomos seleccionados entre O, S o N; y X está opcionalmente sustituido con uno o más RA o RF, y dos RA adyacentes sobre X, tomados junto con los átomos del anillo a los cuales están unidos, pueden formar opcionalmente un carbociclo o heterociclo de 5 o 6 miembros. Además, X puede ser



o

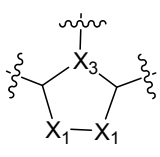
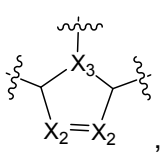
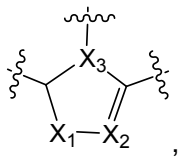
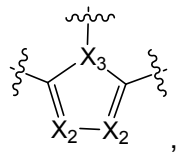
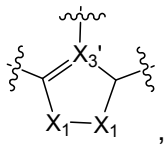
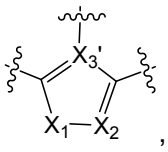
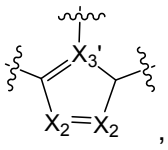
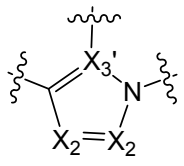
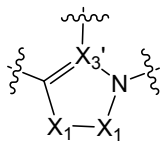


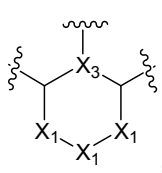
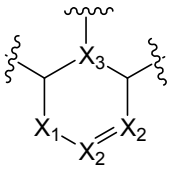
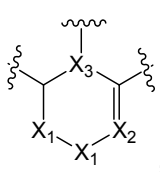
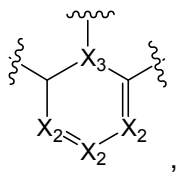
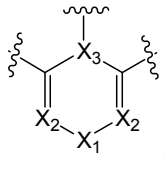
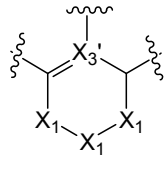
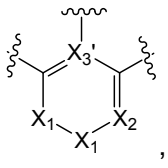
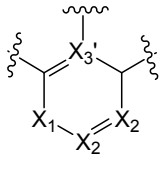
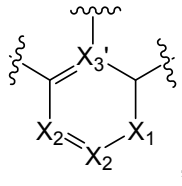
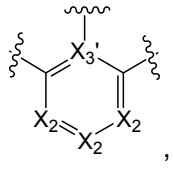
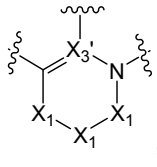
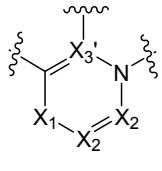
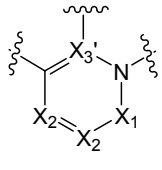
, donde X3 es C y está directamente unido a –L3–D, X4 es C2-C4alquileno, C2-C4alquenileno o C2-C4alquinileno cada uno de los cuales opcionalmente contiene uno o dos herteroátomos seleccionados entre O, S o N, y X está opcionalmente sustituido con uno o más RA o RF, y dos RA adyacentes sobre X, tomados junto con los átomos del anillo a los cuales están unidos, forman opcionalmente un carbociclo o heterociclo de 5 o 6 miembros. Además, X puede ser

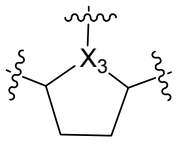
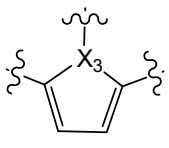
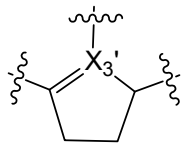


donde N está directamente unido a L3–D, X4 es C2-C4alquileno, C2-C4alquenileno o C2-C4alquinileno cada uno de los cuales opcionalmente contiene uno o dos herteroátomos seleccionados entre O, S o N, y X está opcionalmente sustituido con uno o más RA o RF, y dos RA

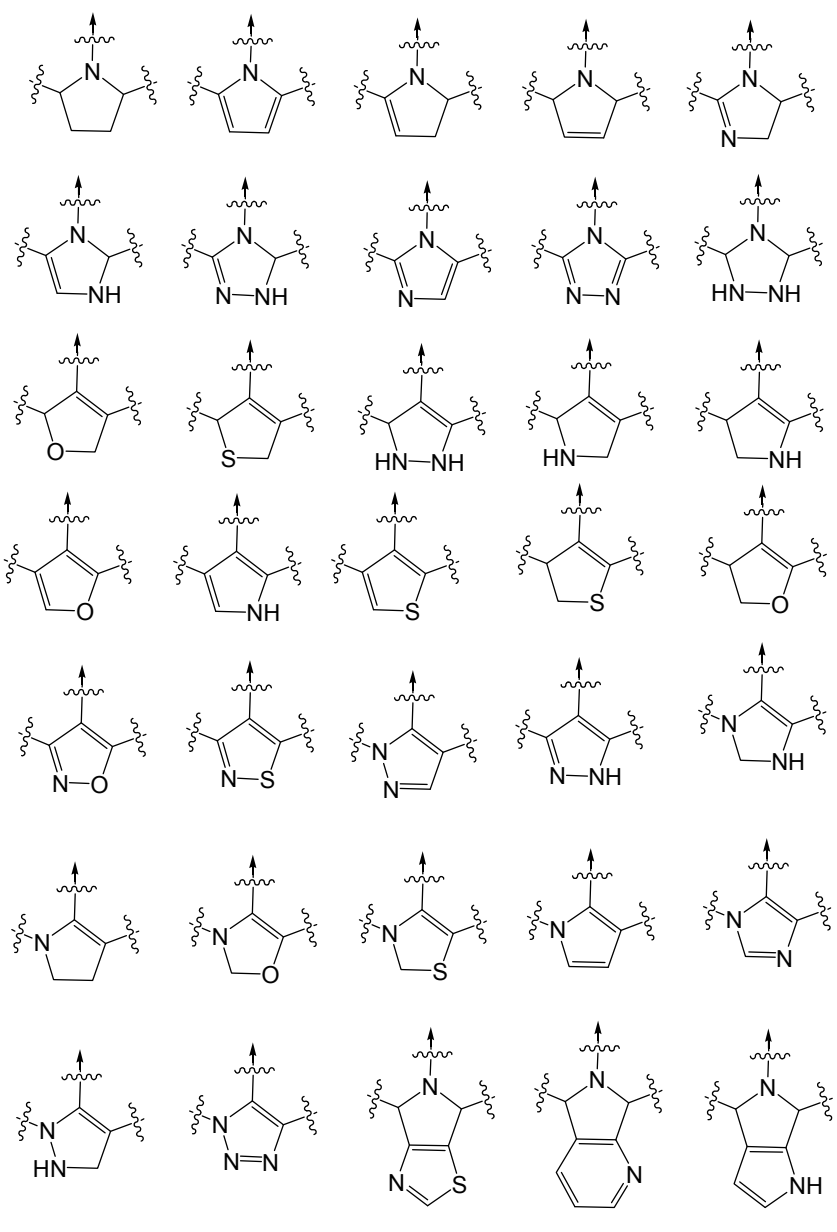
adyacentes sobre X, tomados junto con los átomos del anillo a los cuales están unidos, forman opcionalmente un carbociclo o heterociclo de 5 o 6 miembros.

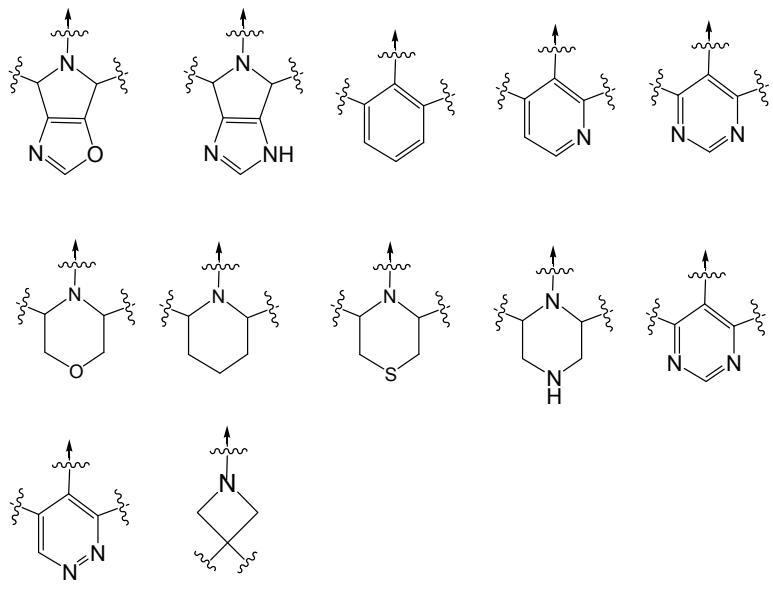
Por ejemplo, X puede ser  ,  ,  ,  ,  ,  ,  ,  o  , donde X1 se selecciona en forma independiente en cada caso entre CH2, O, S o NH, X2 se selecciona en forma independiente en cada caso entre CH o N, X3 es N y está directamente unido a –L3–D, y X3’ es C y está directamente unido a –L3–D; y X está opcionalmente sustituido con uno o más RA o RF, y dos RA adyacentes sobre X, tomados junto con los átomos del anillo a los cuales están unidos, forman opcionalmente un carbociclo o heterociclo de 5 o 6 miembros.

En otro ejemplo, X es  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  o  , donde X1 se selecciona en forma independiente en cada caso entre CH2, O, S o NH, X2 se selecciona en forma independiente en cada caso entre CH o N, X3 es N y está directamente unido a –L3–D, y X3’ es C y está directamente unido a –L3–D; y donde X está opcionalmente sustituido con uno o más RA o RF, y dos RA adyacentes sobre X, tomados junto con los átomos del anillo a los cuales están unidos, forman opcionalmente un carbociclo o heterociclo de 5 o 6 miembros.

Más preferiblemente, X es  ,  o  , donde X3 es C(H) o N y está directamente unido a –L3–D, X3’ es C y está directamente unido a –L3–D, y donde X está opcionalmente sustituido con uno o más RA o RF, y dos RA adyacentes sobre X, tomados junto con los átomos del anillo a los cuales están unidos, forman opcionalmente un carbociclo o heterociclo de 5 o 6 miembros. Más preferiblemente, X3 es N.

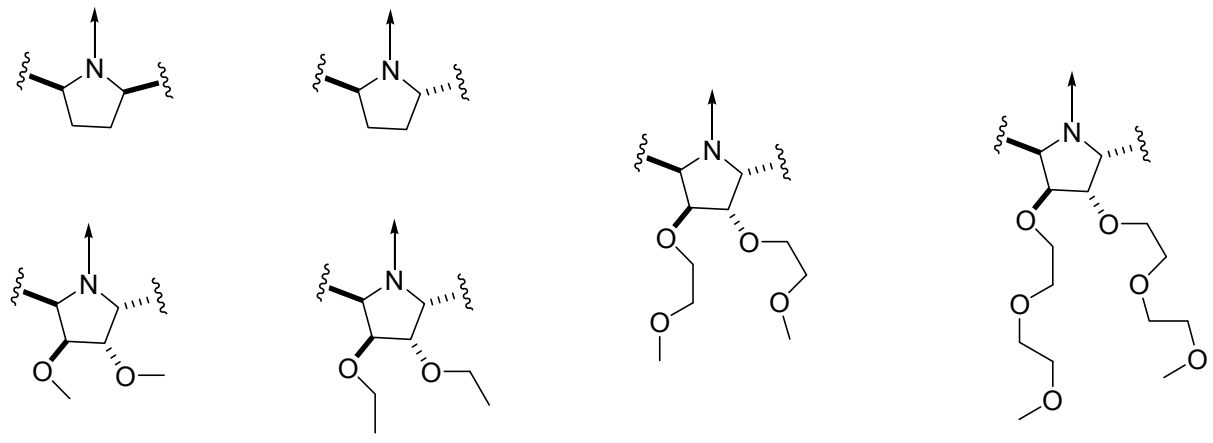
Los ejemplos no limitativos de X incluyen:





donde "→" indica la unión covalente a –L3–D. Cada X puede estar opcionalmente sustituido con uno o más RA o RF, y dos RA adyacentes sobre X, tomados junto con los átomos del anillo a los cuales están unidos, forman opcionalmente un carbociclo o heterociclo de 5 o 6 miembros.

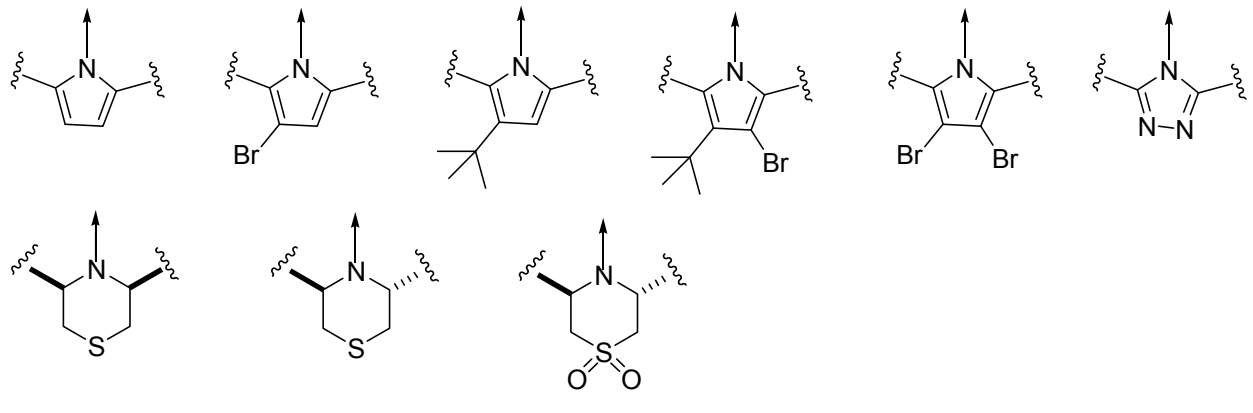
Los ejemplos no limitativos de los X preferidos incluyen los siguientes anillos pirrolidina, cada uno de los cuales está opcionalmente sustituido con uno o más RA o RF:



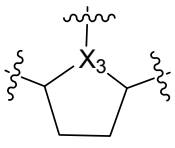
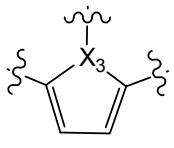
Como se muestra, la estereoquímica relativa en las posiciones 2 y 5 de estos anillos pirrolidina puede ser cis o trans. Las estereoquímicas de los sustituyentes opcionales RA en las posiciones 3 o 4 de la pirrolidina pueden variar en relación a cualquier sustituyente en cualquier otra posición del anilo pirrolidina. Dependiendo de los sustituyentes particulares unidos a la pirrolidina, la estereoquímica en cualquier carbono puede ser (R)

o (S).

Los ejemplos no limitativos de los X preferidos también incluyen los siguientes anillos pirrol, triazol o tiomorfolina, cada uno de los cuales está opcionalmente sustituido con uno o más RA o RF:



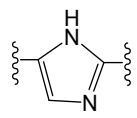
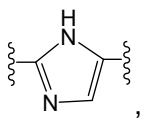
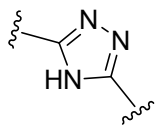
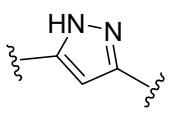
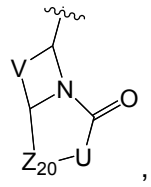
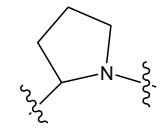
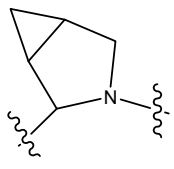
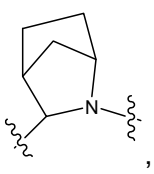
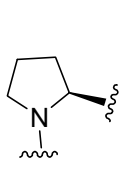
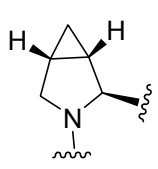
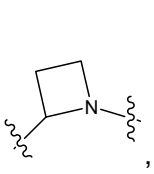
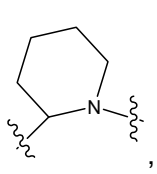
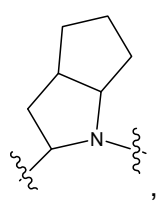
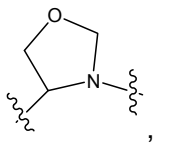
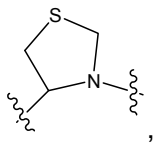
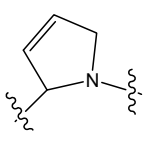
Como se muestra, la estereoquímica relativa en las posiciones 3 y 5 del anillo tiomorfolina puede ser cis o trans. Dependiendo de los sustituyentes particulares unidos a la tiomorfolina, la estereoquímica en cualquier carbono puede ser (R) o (S).

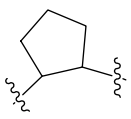
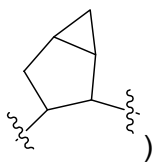
También preferiblemente, X es  o  donde X3 es N y está directamente unido a –L3–D, y X está opcionalmente sustituido con uno o más RA o RF. Preferiblemente, RF es C1-C10alquilo, C2-C10alquenilo o C2-C10alquinilo, cada uno de los cuales contiene 0, 1, 2, 3, 4 o 5 herteroátomos seleccionados entre O, S o N y está opcionalmente sustituido en forma independiente con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo o ciano. También preferiblemente, RF es C1-C10alquilo, C2-C10alquenilo o C2-C10alquinilo, cada uno de los cuales contiene 0, 1, 2, 3, 4 o 5 O y está opcionalmente sustituido en forma independiente con uno o más RL. También preferiblemente, RF es –(RX–RY)Q–(RX–RY'), donde Q es 0, 1, 2, 3 o 4; cada RX es en forma independiente O, S o N(RB); cada RY es en forma independiente C1-C6alquileno, C2-C6alquenileno o C2-C6alquinileno cada uno de los cuales está opcionalmente

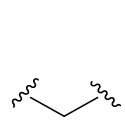
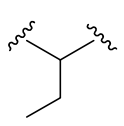
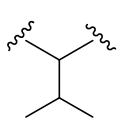
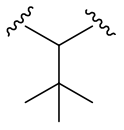
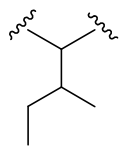
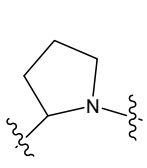
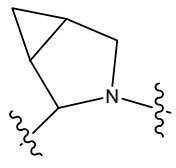
sustituido en forma independiente con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo o ciano; y cada RY' es en forma independiente C1-C6alquilo, C2-C6alquenilo o C2-C6alquinilo cada uno de los cuales está opcionalmente sustituido en forma independiente con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo o ciano. Preferiblemente, cada RX es O. Más preferiblemente, X está opcionalmente sustituido con uno o más RA o RF, cada RF se selecciona en forma independiente entre C1-C10alquilo, C2-C10alquenilo o C2-C10alquinilo, cada uno de los cuales contiene 0, 1, 2 o 3 O y está opcionalmente sustituido en forma independiente con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo o ciano. También preferiblemente, X está opcionalmente sustituido con uno o más RA o RF, cada RF se selecciona en forma independiente entre –(O–C1-C6alquilene)Q–(O–C1-C6alquilo), donde Q preferiblemente es 0, 1, 2 o 3.

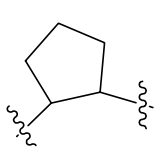
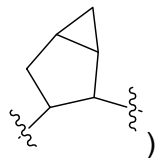
L1 y L2 son preferiblemente en forma independiente un enlace o C1-C6alquileno, L3 preferiblemente se selecciona entre un enlace, C1-C6alquileno o –C(O)–, y L1, L2, y L3 están opcionalmente sustituidos en forma independiente entre sí con uno o más RL. Más preferiblemente, L1, L2 y L3 son en forma independiente entre sí un enlace o C1-C6alquileno (por ejemplo, –CH2– o –CH2CH2–), y están opcionalmente sustituidos en forma independiente entre sí con uno o más RL. Más preferiblemente, L1, L2 y L3 son un enlace.

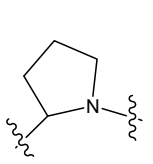
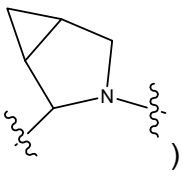
Y preferiblemente se selecciona entre –LS–C(R1R2)N(R5)–T–RD, –LS–C(R3R4)C(R6R7)–T–RD, –G–C(R1R2)N(R5)–T–RD, –G–C(R3R4)C(R6R7)–T–RD, –N(RB)C(O)C(R1R2)N(R5)–T–RD, –N(RB)C(O)C(R3R4)C(R6R7)–T–RD, –C(O)N(RB)C(R1R2)N(R5)–T–RD, –C(O)N(RB)C(R3R4)C(R6R7)–T–RD, –N(RB)C(O)–LS–E, o –C(O)N(RB)–LS–E. G es C5-C6carbociclo o heterociclo de 5 o 6 miembros,

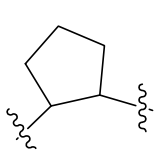
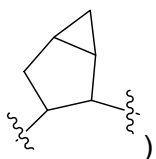
como por ejemplo  ,  ,  o  , y está opcionalmente sustituido con uno o más RA (por ejemplo, uno o más cloro o bromo). E preferiblemente es un biciclo de entre 7 y 12 miembros (como por ejemplo  , donde U se selecciona en forma independiente en cada caso entre -(CH2)- o -(NH)-; V y Z20 se seleccionan en forma independiente entre sí entre C1-C4alquileno, C2-C4alquenileno o C2-C4alquinileno, en donde al menos un átomo de carbono puede reemplazarse en forma independiente opcionalmente por O, S o N), y está opcionalmente sustituido en forma independiente con uno o más RA. Más preferiblemente, R1 es RC, y R2 y R5, tomados junto con los átomos a los cuales están unidos, forman un heterociclo de 5 o 6 miembros o biciclo de entre 6 y 12 miembros (por ejemplo,  o  ; o  ,  ,  ; o  ,  ,  ,  ,  , o ) que está opcionalmente sustituido con uno o más RA (como por ejemplo, sin que esto constituya limitación alguna, hidroxi, halo (por ejemplo, fluoro), C1-C6alquilo (por ejemplo, metilo), o C2-C6alquenilo (por ejemplo, alilo)); y R3 y R6 son en forma independiente entre sí RC, y R4 y R7, tomados junto con los átomos a los cuales están unidos, forman un carbociclo/heterociclo de 5 o 6 miembros o

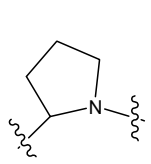
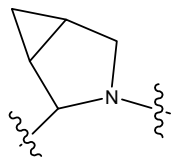
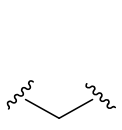
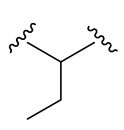
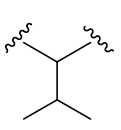
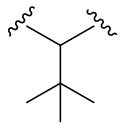
biciclo de entre 6 y 12 miembros (por ejemplo,  o ) que está opcionalmente sustituido con uno o más RA (como por ejemplo, sin que esto constituya limitación alguna, hidroxi, halo (por ejemplo, fluoro), C1-C6alquilo (por ejemplo, metilo), o C2-C6alquenilo (por ejemplo, alilo)).

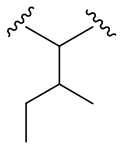
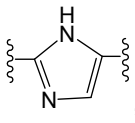
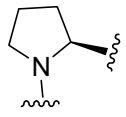
Y también puede seleccionarse entre –M–C(R1R2)N(R5)–C(O)–LY'–M'–RD, –M–C(R1R2)N(R5)–LY'–M'–RD, –LS–C(R1R2)N(R5)–C(O)–LY'–M'–RD, –LS–C(R1R2)N(R5)–LY'–M'–RD, –M–C(R3R4)C(R6R7)–C(O)–LY'–M'–RD, –M–C(R3R4)C(R6R7)–LY'–M'–RD, –LS–C(R3R4)C(R6R7)–C(O)–LY'–M'–RD, o –LS–C(R3R4)C(R6R7)–LY'–M'–RD, donde M preferiblemente es un enlace, –C(O)N(RB)– o –N(RB)C(O)–, M' preferiblemente es un enlace, –C(O)N(RB)–, –N(RB)C(O)–, –N(RB)C(O)O–, N(RB)C(O)N(RB')–, –N(RB)S(O)– o –N(RB)S(O)2–, y LY' preferiblemente es C1-C6alquileno que está opcionalmente sustituido con uno o más RL. LY', por ejemplo, es un C1-C6alquileno como por ejemplo, sin que esto constituya limitación alguna,  ,  ,  ,  , o  ; y el RL opcional es un sustituyente como por ejemplo, sin que esto constituya limitación alguna, fenilo, –SMe, o metoxi. La estereoquímica en un carbono dentro del grupo LY' puede ser (R) o (S). Más preferiblemente, R1 es RC, y R2 y R5, tomados junto con los átomos a los cuales están unidos, forman un heterociclo de 5 o 6 miembros o biciclo de entre 6 y 12 miembros (por ejemplo,  o ) que está opcionalmente sustituido con uno o más RA (por ejemplo, uno o más hidroxi); y R3 y R6 son en forma independiente entre sí RC, y R4 y R7, tomados junto con los átomos a los

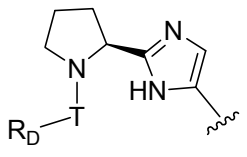
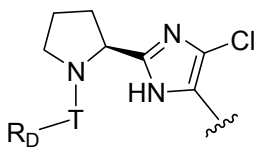
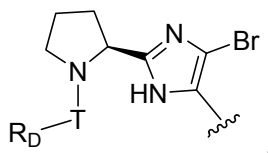
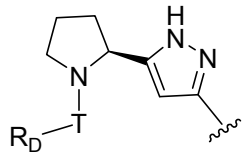
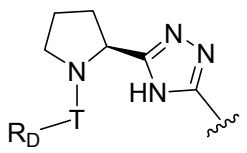
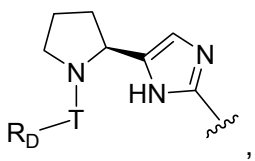
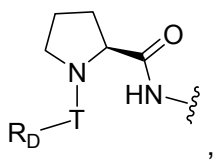
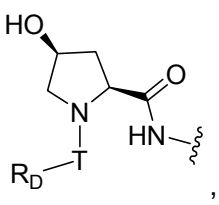
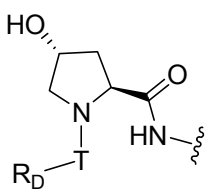
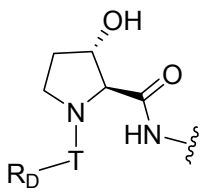
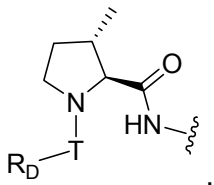
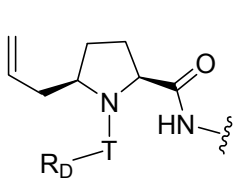
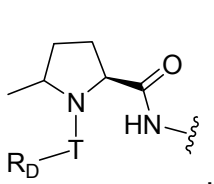
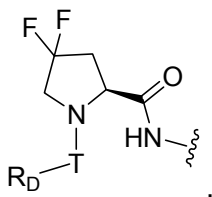
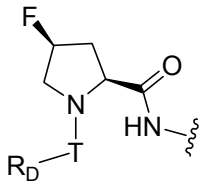
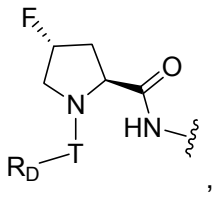
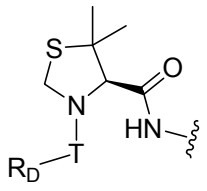
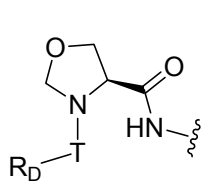
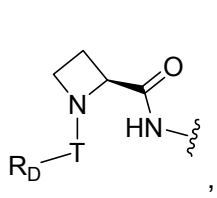
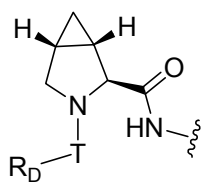
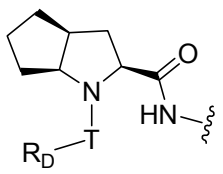
cuales están unidos, forman un carbociclo/heterociclo de 5 o 6 miembros o biciclo de entre 6 y 12 miembros (por ejemplo,  o ) que está opcionalmente sustituido con uno o más RA.

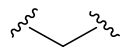
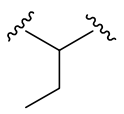
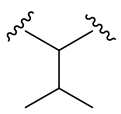
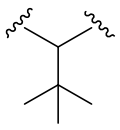
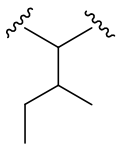
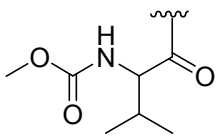
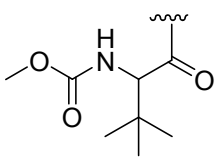
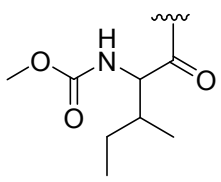
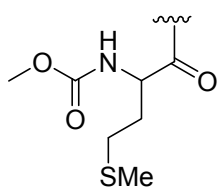
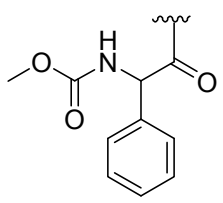
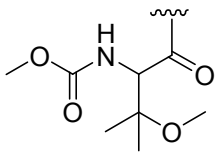
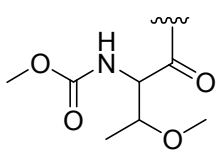
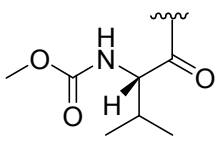
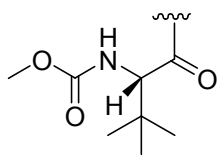
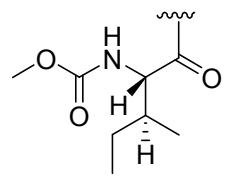
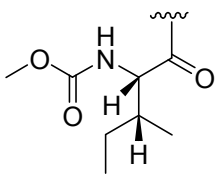
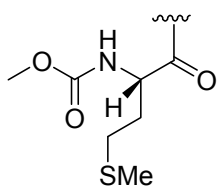
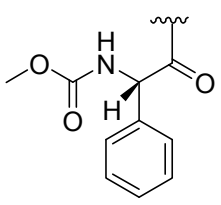
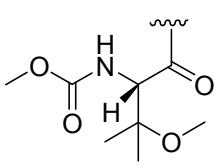
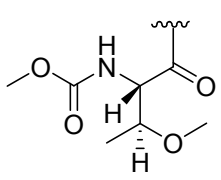
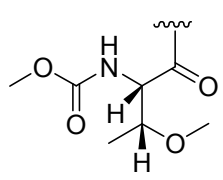
También preferiblemente, Y se selecciona entre –N(RB)CO–C(R1R2)N(R5)–C(O)–LY'–N(RB)C(O)O–RD, –N(RB)CO–C(R1R2)N(R5)–C(O)–LY'–N(RB)C(O)–RD, –N(RB)CO–C(R1R2)N(R5)–C(O)–LY'–N(RB)S(O)2–RD, –N(RB)CO–C(R1R2)N(R5)–C(O)–LY'–N(RBRB')–RD, –N(RB)CO–C(R1R2)N(R5)–C(O)–LY'–O–RD, –N(RB)CO–C(R1R2)N(R5)–C(O)–LY'–RD, –N(RB)CO–C(R1R2)N(R5)–RD, –LS–C(R1R2)N(R5)–C(O)–LY'–N(RB)C(O)O–RD, –LS–C(R1R2)N(R5)–C(O)–LY'–N(RB)C(O)–RD, –LS–C(R1R2)N(R5)–C(O)–LY'–N(RB)S(O)2–RD, –LS–C(R1R2)N(R5)–C(O)–LY'–N(RBRB')–RD, –LS–C(R1R2)N(R5)–C(O)–LY'–O–RD, –LS–C(R1R2)N(R5)–C(O)–LY'–RD, –LS–C(R1R2)N(R5)–RD, –N(RB)CO–C(R3R4)C(R6R7)–C(O)–LY'–N(RB)C(O)O–RD, –N(RB)CO–C(R3R4)C(R6R7)–C(O)–LY'–N(RB)C(O)–RD, –N(RB)CO–C(R3R4)C(R6R7)–C(O)–LY'–N(RB)S(O)2–RD, –N(RB)CO–C(R3R4)C(R6R7)–C(O)–LY'–N(RBRB')–RD, –N(RB)CO–C(R3R4)C(R6R7)–C(O)–LY'–O–RD, –N(RB)CO–C(R3R4)C(R6R7)–C(O)–LY'–RD, –N(RB)CO–C(R3R4)C(R6R7)–RD, –LS–C(R3R4)C(R6R7)–C(O)–LY'–N(RB)C(O)O–RD, –LS–C(R3R4)C(R6R7)–C(O)–LY'–N(RB)C(O)–RD, –LS–C(R3R4)C(R6R7)–C(O)–LY'–N(RB)S(O)2–RD, –LS–C(R3R4)C(R6R7)–C(O)–LY'–N(RBRB')–RD, –LS–C(R3R4)C(R6R7)–C(O)–LY'–O–RD, –LS–C(R3R4)C(R6R7)–C(O)–LY'–RD, o –LS–C(R3R4)C(R6R7)–RD, donde LY' preferiblemente es C1-C6alquileno que está opcionalmente sustituido con uno o más RL. R1 puede ser RC, y R2 y R5, tomados junto con los átomos a los cuales están unidos, pueden formar un heterociclo de 5 o 6 miembros o biciclo de entre 6 y 12 miembros (por ejemplo,  o )

que está opcionalmente sustituido con uno o más RA; y R3 y R6 pueden ser en forma independiente entre sí RC, y R4 y R7, tomados junto con los átomos a los cuales están unidos, pueden formar un carbociclo/heterociclo de 5 o 6 miembros o biciclo de entre 6 y 12 miembros (por ejemplo,  o ) que está opcionalmente sustituido con uno o más RA.

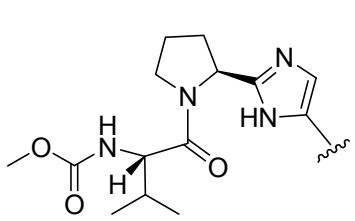
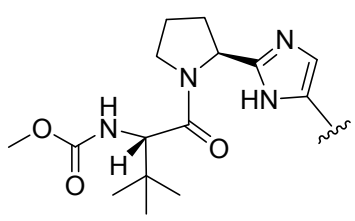
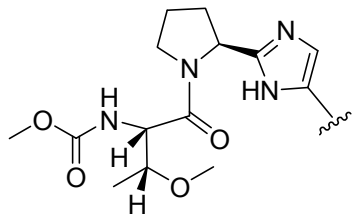
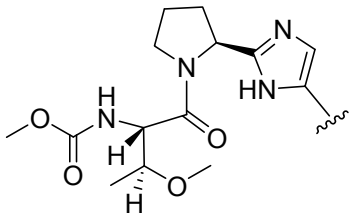
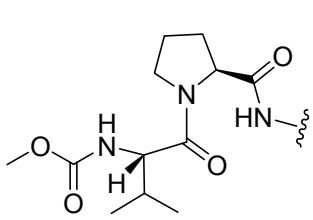
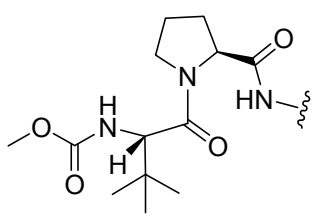
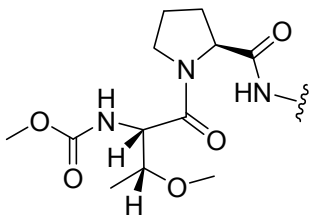
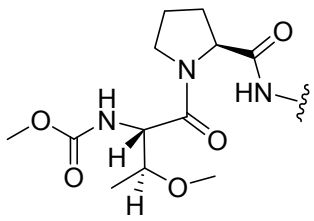
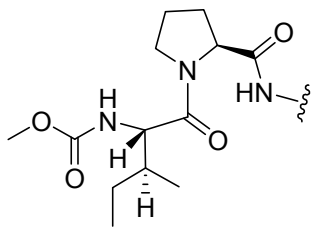
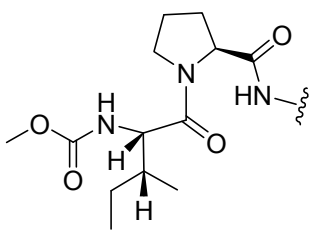
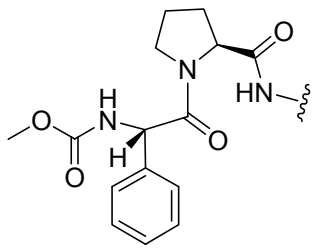
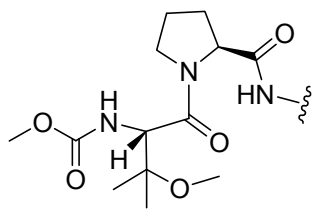
Más preferiblemente, Y se selecciona entre –N(RB'')CO–C(R1R2)N(R5)–C(O)–LY–N(RB'')C(O)–LS–RE o –C(R1R2)N(R5)–C(O)–LY–N(RB'')C(O)–LS–RE, o Y es –G–C(R1R2)N(R5)–C(O)–LY–N(RB'')C(O)–LS–RE, donde LY es C1-C6alquileno opcionalmente sustituido con uno o más RL, y RB'' es en forma independiente en cada caso RB. RB'' y R1 son cada uno preferiblemente hidrógeno o C1-C6alquilo, y R2 y R5, tomados junto con los átomos a los cuales están unidos, preferiblemente forman un heterociclo de 5 o 6 miembros o biciclo de entre 6 y 12 miembros (por ejemplo,  o ) que está opcionalmente sustituido con uno o más RA (como por ejemplo, sin que esto constituya limitación alguna, hidroxi, halo (por ejemplo, fluoro), C1-C6alquilo (por ejemplo, metilo), o C2-C6alquenilo (por ejemplo, alilo)). Preferiblemente, LY es C1-C6alquileno sustituido con uno o más RL como por ejemplo a C3-C6carbociclo o heterociclo de entre 3 y 6 miembros que está opcionalmente sustituido en forma independiente con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C1-C6alquilo, C2-C6alquenilo, C2-C6alquinilo, C1-C6haloalquilo, C2-C6haloalquenilo o C2-C6haloalquinilo. Más preferiblemente, LY es un C1-C6alquileno como por ejemplo, sin que esto constituya limitación alguna,  ,  ,  ,  , o

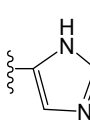
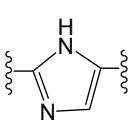
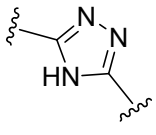
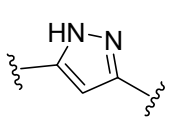
 (la estereoquímica en un carbono dentro del grupo LY puede ser (R) o (S)), LY está opcionalmente sustituido en forma independiente con uno o más RL (por ejemplo, uno o más fenilo o metoxi), G preferiblemente es  , RB'' es hidrógeno; –C(R1R2)N(R5)– es  ; LS es un enlace; y RE es metoxi.

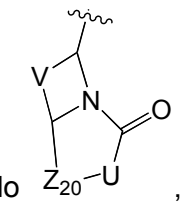
Los ejemplos no limitativos de los Y preferidos incluyen:  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , o  , donde T y RD son como se definen en la presente. T, por ejemplo,

puede ser –LS–M–LS'–M'–LS''– donde LS es un enlace; M es C(O); LS' es C1-C6alquileno como por ejemplo, sin que esto constituya limitación alguna,  ,  ,  ,  , o  , donde LS' está opcionalmente sustituido en forma independiente con uno o más RL; RL es un sustituyente como por ejemplo, sin que esto constituya limitación alguna, fenilo o metoxi; M' es –NHC(O)– o –NMeC(O)–; y LS'' es un enlace. La estereoquímica en un carbono dentro del grupo LS' puede ser (R) o (S). RD, por ejemplo es metoxi. T-RD incluye, sin que esto constituya limitación alguna:  ,  ,  ,  ,  ,  , o  . T-RD también puede incluir ciertas configuraciones estereoquímicas; por lo tanto T-RD incluye, sin que esto constituya limitación alguna:  ,  ,  ,  ,  ,  ,  ,  , y  .

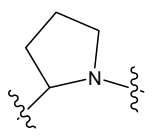
Los ejemplos no limitativos de los Y preferidos también incluyen:


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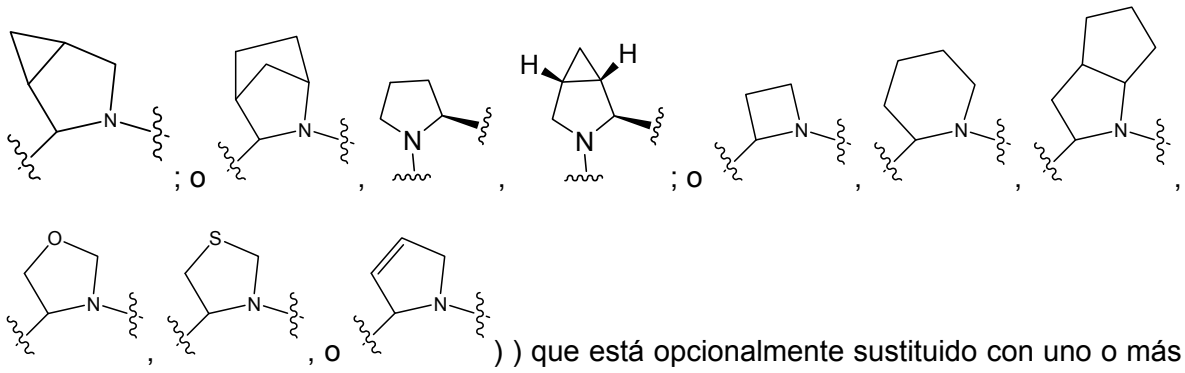
Z preferiblemente se selecciona entre –LS–C(R8R9)N(R12)–T–RD, –LS–C(R10R11)C(R13R14)–T–RD, –G–C(R8R9)N(R12)–T–RD, –G–C(R10R11)C(R13R14)–T–RD, –N(RB)C(O)C(R8R9)N(R12)–T–RD, –N(RB)C(O)C(R10R11)C(R13R14)–T–RD, –C(O)N(RB)C(R8R9)N(R12)–T–RD, –C(O)N(RB)C(R10R11)C(R13R14)–T–RD, –N(RB)C(O)–LS–E, o –C(O)N(RB)–LS–E. G es C5-C6carbociclo o heterociclo de 5 o 6 miembros, como por ejemplo  ,  ,  o  , y está opcionalmente sustituido con uno o más RA (por ejemplo, uno o más cloro o bromo). E



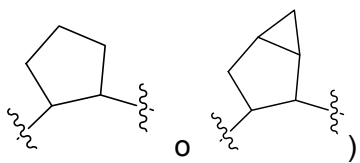
preferiblemente es un un biciclo de entre 8 y 12 miembros (como por ejemplo , donde U se selecciona en forma independiente en cada caso entre -(CH2)- o -(NH)-; y V y Z20 se seleccionan en forma independiente entre sí entre C1-C4alquileno, C2-C4alquenileno o C2-C4alquinileno, en donde al menos un átomo de carbono se reemplaza opcionalmente en forma independiente por O, S o N), y está opcionalmente sustituido en forma independiente con uno o más RA. Más preferiblemente, R8 es RC, y R9 y R12, tomados junto con los átomos a los cuales están unidos, forman un heterociclo



de 5 o 6 miembros o biciclo de entre 6 y 12 miembros (por ejemplo, o

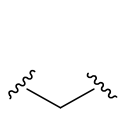
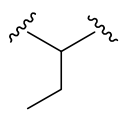
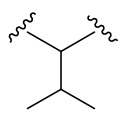
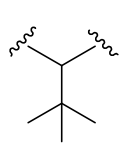
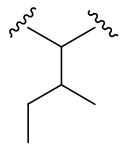
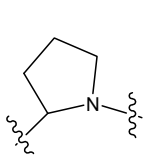


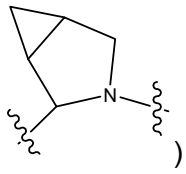
; o , , ; o , , , , , o)) que está opcionalmente sustituido con uno o más RA (como por ejemplo, sin que esto constituya limitación alguna, hidroxi, halo (por ejemplo, fluoro), C1-C6alquilo (por ejemplo, metilo), o C2-C6alquenilo (por ejemplo, alilo)); y R10 y R13 son en forma independiente entre sí RC, y R11 y R14, tomados junto con los átomos a los cuales están unidos, forman un carbociclo/heterociclo de 5 o 6 miembros o biciclo de entre 6 y 12 miembros (por ejemplo,

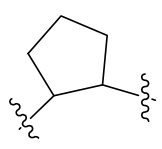
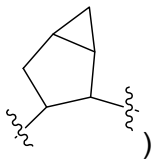


o) que está opcionalmente sustituido con uno o más RA (como por ejemplo, sin que esto constituya limitación alguna, hidroxi, halo (por ejemplo, fluoro), C1-C6alquilo (por ejemplo, metilo), o

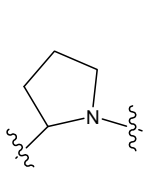
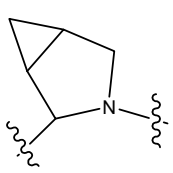
C2-C6alquenilo (por ejemplo, alilo)).

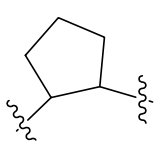
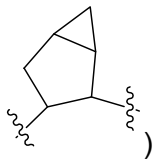
Z también puede seleccionarse entre –M–C(R8R9)N(R12)–C(O)–LY'–M'–RD, –M–C(R8R9)N(R12)–LY'–M'–RD, –LS–C(R8R9)N(R12)–C(O)–LY'–M'–RD, –LS–C(R8R9)N(R12)–LY'–M'–RD, –M–C(R10R11)C(R13R14)–C(O)–LY'–M'–RD, –M–C(R10R11)C(R13R14)–LY'–M'–RD, –LS–C(R10R11)C(R13R14)–C(O)–LY'–M'–RD, o –LS–C(R10R11)C(R13R14)–LY'–M'–RD, donde M preferiblemente es un enlace, –C(O)N(RB)– o –N(RB)C(O)–, M' preferiblemente es un enlace, –C(O)N(RB)–, –N(RB)C(O)–, –N(RB)C(O)O–, N(RB)C(O)N(RB')–, –N(RB)S(O)– o –N(RB)S(O)2–, y LY' preferiblemente es C1-C6alquileno que está opcionalmente sustituido en forma independiente con uno o más RL. LY', por ejemplo, es un C1-C6alquileno como por ejemplo, sin que esto constituya limitación alguna,  ,  ,  ,  , o  ; y el RL opcional es un sustituyente como por ejemplo, sin que esto constituya limitación alguna, fenilo, –SMe, o metoxi. La estereoquímica en un carbono dentro del grupo LY' puede ser (R) o (S). Más preferiblemente, R8 es RC, y R9 y R12, tomados junto con los átomos a los cuales están unidos, forman un heterociclo de 5 o 6 miembros o biciclo de entre 6 y 12 miembros (por ejemplo, 

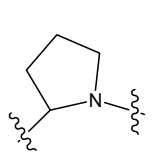
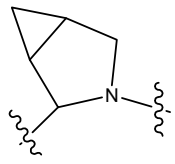
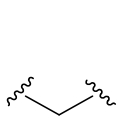
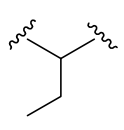
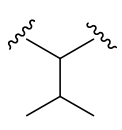
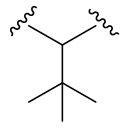
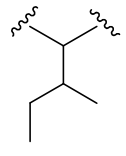
o 

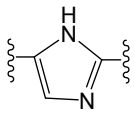
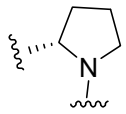
) que está opcionalmente sustituido con uno o más RA (por ejemplo, uno o más hidroxi); y R10 y R13 son en forma independiente entre sí RC, y R11 y R14, tomados junto con los átomos a los cuales están unidos, forman un carbociclo/heterociclo de 5 o 6 miembros o biciclo de entre 6 y 12 miembros (por ejemplo,  o ) que está

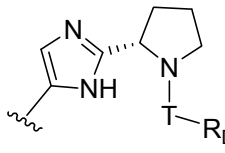
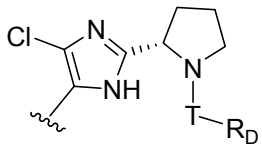
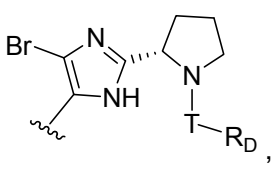
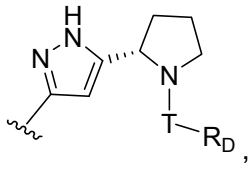
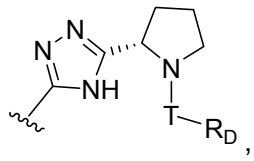
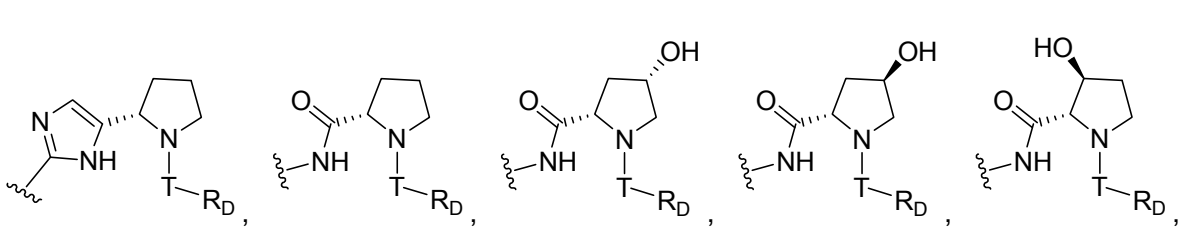
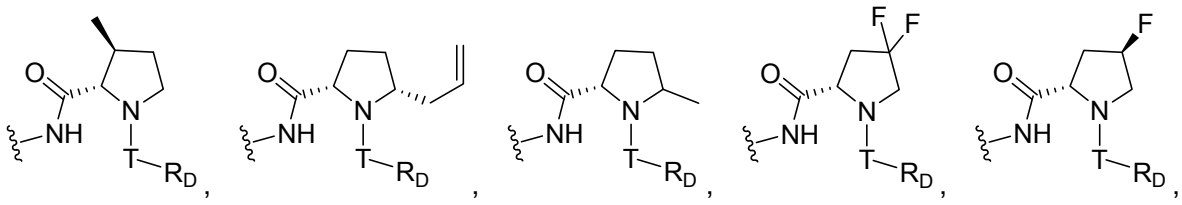
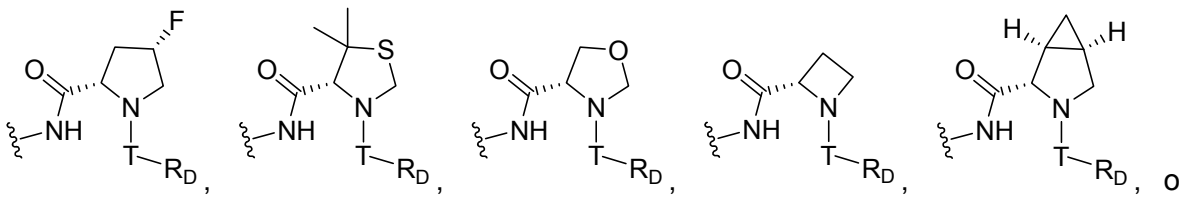
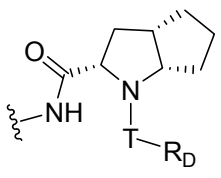
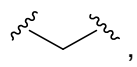
opcionalmente sustituido con uno o más RA.

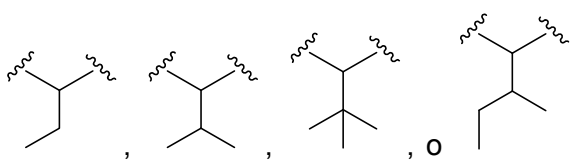
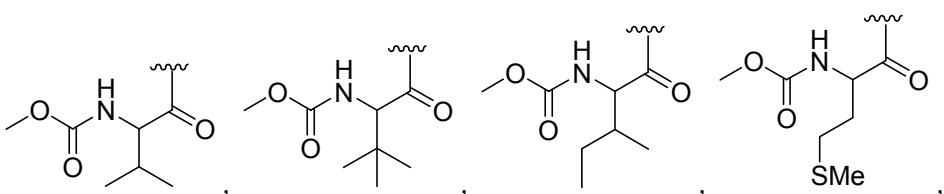
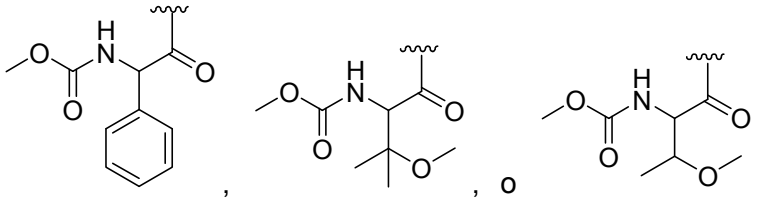
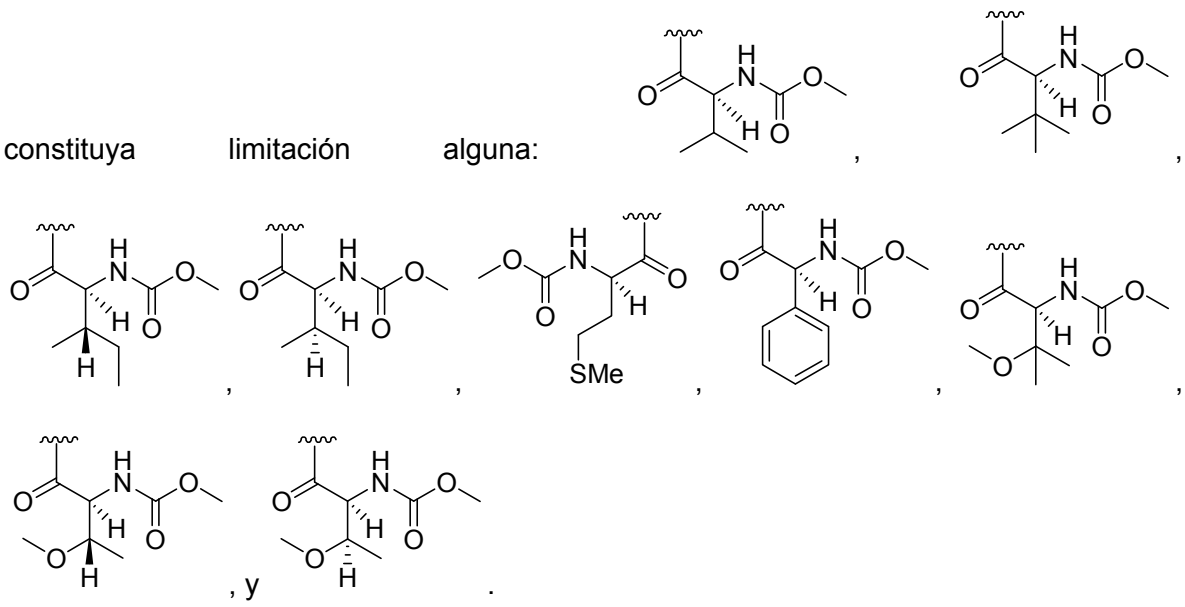
También preferiblemente, Z se selecciona entre –N(RB)CO–C(R8R9)N(R12)–C(O)–LY'–N(RB)C(O)O–RD, –N(RB)CO–C(R8R9)N(R12)–C(O)–LY'–N(RB)C(O)–RD, –N(RB)CO–C(R8R9)N(R12)–C(O)–LY'–N(RB)S(O)2–RD, –N(RB)CO–C(R8R9)N(R12)–C(O)–LY'–N(RBRB')–RD, –N(RB)CO–C(R8R9)N(R12)–C(O)–LY'–O–RD, –N(RB)CO–C(R8R9)N(R12)–C(O)–LY'–RD, –N(RB)CO–C(R8R9)N(R12)–RD, –LS–C(R8R9)N(R12)–C(O)–LY'–N(RB)C(O)O–RD, –LS–C(R8R9)N(R12)–C(O)–LY'–N(RB)C(O)–RD, –LS–C(R8R9)N(R12)–C(O)–LY'–N(RB)S(O)2–RD, –LS–C(R8R9)N(R12)–C(O)–LY'–N(RBRB')–RD, –LS–C(R8R9)N(R12)–C(O)–LY'–O–RD, –LS–C(R8R9)N(R12)–C(O)–LY'–RD, –LS–C(R8R9)N(R12)–RD, –N(RB)CO–C(R10R11)C(R13R14)–C(O)–LY'–N(RB)C(O)O–RD, –N(RB)CO–C(R10R11)C(R13R14)–C(O)–LY'–N(RB)C(O)–RD, –N(RB)CO–C(R10R11)C(R13R14)–C(O)–LY'–N(RB)S(O)2–RD, –N(RB)CO–C(R10R11)C(R13R14)–C(O)–LY'–N(RBRB')–RD, –N(RB)CO–C(R10R11)C(R13R14)–C(O)–LY'–O–RD, –N(RB)CO–C(R10R11)C(R13R14)–C(O)–LY'–RD, –N(RB)CO–C(R10R11)C(R13R14)–RD, –LS–C(R10R11)C(R13R14)–C(O)–LY'–N(RB)C(O)O–RD, –LS–C(R10R11)C(R13R14)–C(O)–LY'–N(RB)C(O)–RD, –LS–C(R10R11)C(R13R14)–C(O)–LY'–N(RB)S(O)2–RD, –LS–C(R10R11)C(R13R14)–C(O)–LY'–N(RBRB')–RD, –LS–C(R10R11)C(R13R14)–C(O)–LY'–O–RD, –LS–C(R10R11)C(R13R14)–C(O)–LY'–RD, o –LS–C(R10R11)C(R13R14)–RD, donde LY' preferiblemente es C1-C6alquileno que está opcionalmente sustituido en forma independiente con uno o más RL. R8 puede ser RC, y R9 y R12, tomados junto con los átomos a los cuales están unidos, pueden formar un heterociclo de 5 o 6 miembros o biciclo de entre 6 y 12 miembros (por ejemplo,  o ) que está opcionalmente sustituido con uno o más RA; y R10 y R13 pueden ser en forma independiente entre sí RC, y R11 y R14, tomados junto con los átomos a los cuales están unidos, pueden formar un carbociclo/heterociclo de 5 o 6 miembros o biciclo de entre 6 y

12 miembros (por ejemplo,  o ) que está opcionalmente sustituido con uno o más RA.

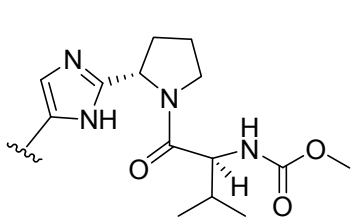
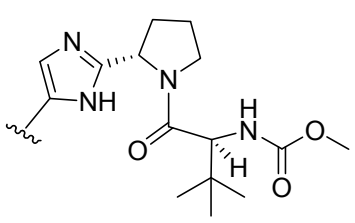
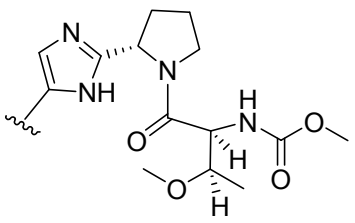
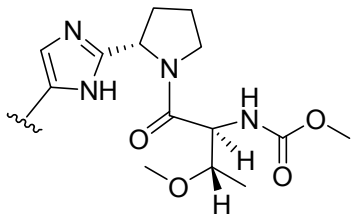
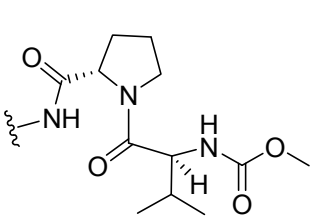
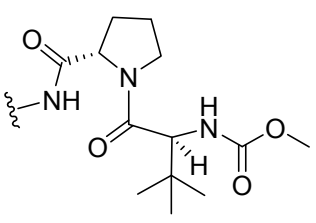
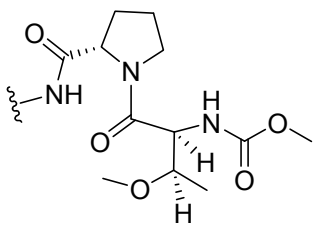
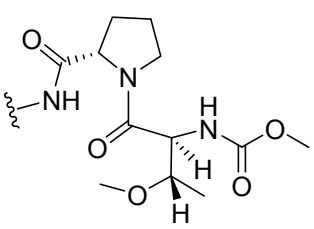
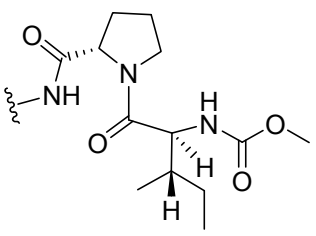
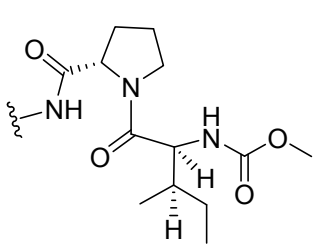
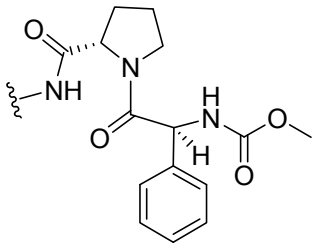
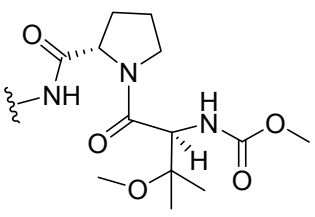
Más preferiblemente, Z se selecciona entre –N(RB'')CO–C(R8R9)N(R12)–C(O)–LY–N(RB'')C(O)–LS–RE o –C(R8R9)N(R12)–C(O)–LY–N(RB'')C(O)–LS–RE, o Z es –G–C(R8R9)N(R12)–C(O)–LY–N(RB'')C(O)–LS–RE, donde LY es C1-C6alquileno opcionalmente sustituido con uno o más RL, y RB'' es en forma independiente en cada caso RB. RB'' y R8 son cada uno preferiblemente hidrógeno o C1-C6alquilo, y R9 y R12, tomados junto con los átomos a los cuales están unidos, preferiblemente forman un heterociclo de 5 o 6 miembros o biciclo de entre 6 y 12 miembros (por ejemplo,  o ) que está opcionalmente sustituido con uno o más RA (como por ejemplo, sin que esto constituya limitación alguna, hidroxi, halo (por ejemplo, fluoro), C1-C6alquilo (por ejemplo, metilo), o C2-C6alquenilo (por ejemplo, alilo)). Preferiblemente, LY es C1-C6alquileno sustituido con uno o más RL como por ejemplo a C3-C6carbociclo o heterociclo de entre 3 y 6 miembros que está opcionalmente sustituido en forma independiente con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C1-C6alquilo, C2-C6alquenilo, C2-C6alquinilo, C1-C6haloalquilo, C2-C6haloalquenilo o C2-C6haloalquinilo. Más preferiblemente, LY es un C1-C6alquileno como por ejemplo, sin que esto constituya limitación alguna,  ,  ,  ,  , o  (la estereoquímica en un carbono dentro del grupo LY puede ser (R) o (S)); LY

está opcionalmente sustituido en forma independiente con uno o más RL (por ejemplo, uno o más fenilo o metoxi); G preferiblemente es  ; RB'' es hidrógeno; –C(R8R9)N(R12)– es  ; LS es un enlace; y RE es metoxi.

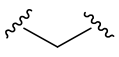
Los ejemplos no limitativos de los Z preferidos incluyen:  ,  ,  ,  ,  ,  ,  ,  , o  , donde T y RD son como se definen en la presente. T, por ejemplo, puede ser –LS–M–LS'–M'–LS''– donde LS es un enlace; M es C(O); LS' es C1-C6alquileno como por ejemplo, sin que esto constituya limitación alguna,  ,


, donde LS' está opcionalmente sustituido en forma independiente con uno o más RL; el RL opcional es un sustituyente como por ejemplo, sin que esto constituya limitación alguna, fenilo o metoxi; M' es –NHC(O)– o –NMeC(O)–; y LS'' es un enlace. La estereoquímica en un carbono dentro del grupo LS' puede ser (R) o (S). RD, por ejemplo es metoxi. T-RD incluye, sin que esto constituya limitación alguna: 

. T-RD también puede incluir ciertas configuraciones estereoquímicas; por lo tanto T-RD incluye, sin que esto constituya limitación alguna: 
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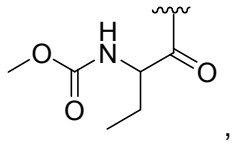
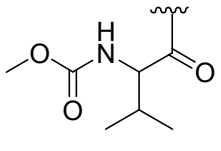
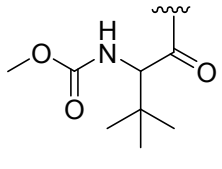
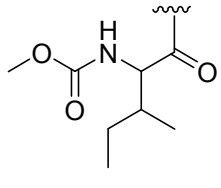
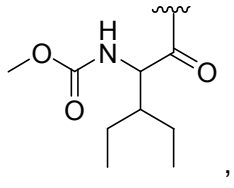
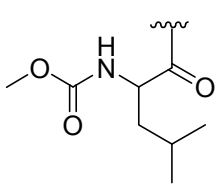
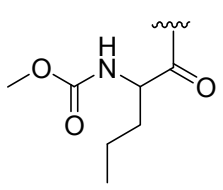
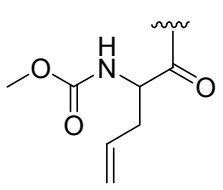
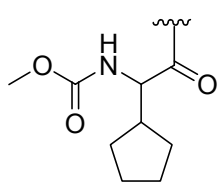
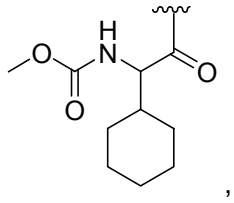
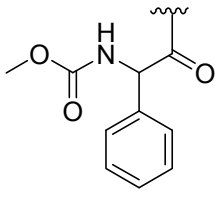
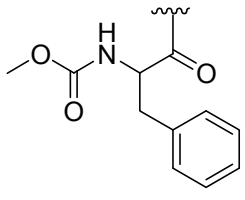
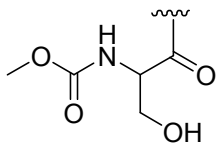
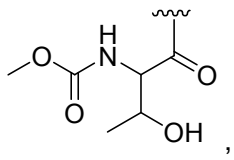
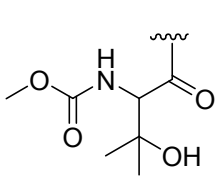
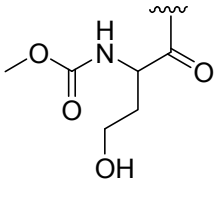
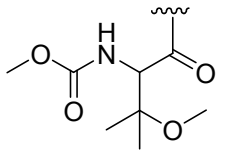
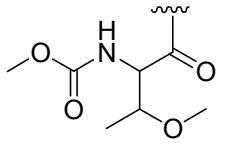
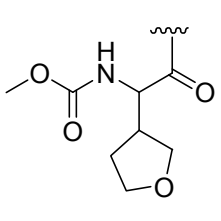
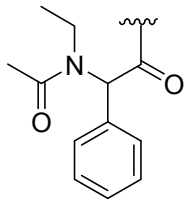
Los ejemplos no limitativos de los Z preferidos también incluyen:


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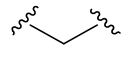
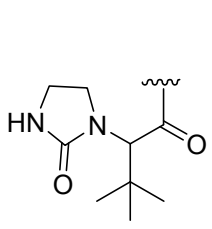
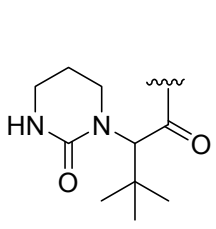
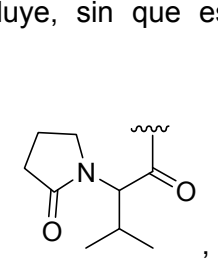
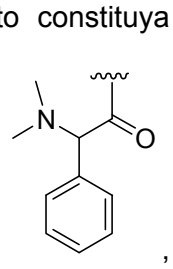
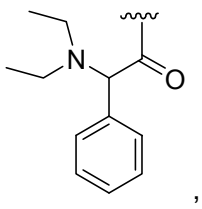
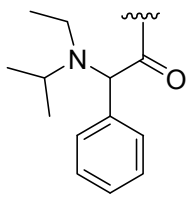
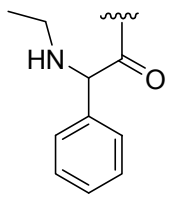
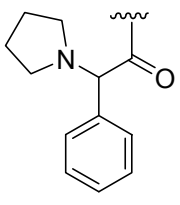
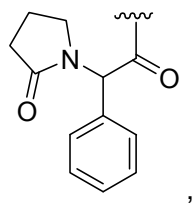
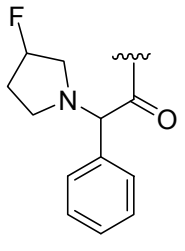
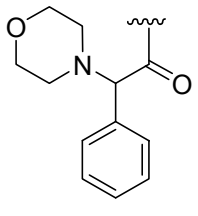
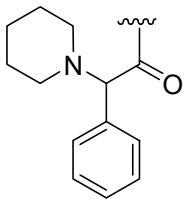
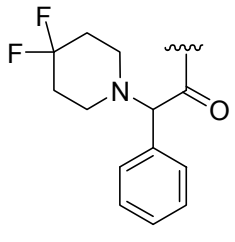
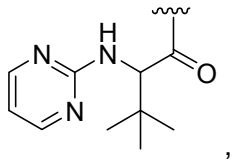
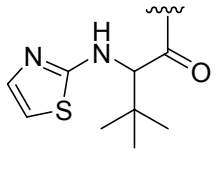
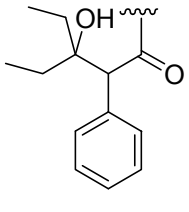
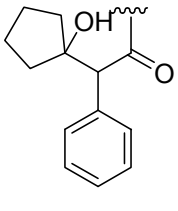
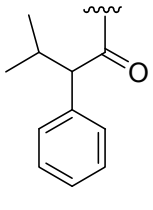
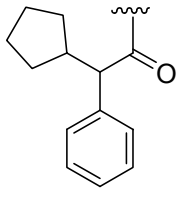
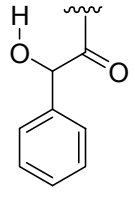
T puede seleccionarse en forma independiente en cada caso, sin que esto constituya limitación alguna, entre –C(O)–LS'–, –C(O)O–LS'–, –C(O)–LS'–N(RB)C(O)–LS''–, –C(O)–LS'–N(RB)C(O)O–LS''–, –N(RB)C(O)–LS'–N(RB)C(O)–LS''–, –N(RB)C(O)–LS'—N(RB)C(O)O–LS''–, o –N(RB)C(O)–LS'—N(RB)–LS''–. Preferiblemente, T se selecciona en forma independiente en cada caso entre –C(O)–LS'–M'–LS''– o –N(RB)C(O)–LS'–M'–LS''–. Más preferiblemente, T se selecciona en forma independiente en cada caso entre –C(O)–LS'–N(RB)C(O)–LS''– o –C(O)–LS'–N(RB)C(O)O–LS''–.

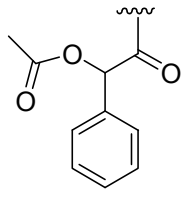
T también puede ser, por ejemplo, –LS–M–LS'–M'–LS''– donde LS es un enlace; M es C(O); LS' es C1-C6alquileno (por ejemplo, ), donde LS' está opcionalmente sustituido en forma independiente con RT; el RT opcional es un sustituyente seleccionado entre –C1-C6alquilo, –C2-C6alquenilo, –C1-C6alquil–OH, –C1-C6alquil–O–C1-C6alquilo,

heterociclo de entre 3 y 6 miembros (por ejemplo, tetrahidrofuranilo), o C3-C6carbociclilo (por ejemplo, fenilo, ciclohexilo); M' es –NHC(O)–, –N(Et)C(O)– o –N(Me)C(O)–; y LS'' es un enlace. RD preferiblemente es hidrógeno, –C1-C6alquilo (por ejemplo, metilo), –O–C1-C6alquilo (por ejemplo, metoxi, tert-butoxi), metoximetilo, o –N(C1-C6alquil)2 (por ejemplo, –NMe2).

T-RD puede ser, sin que esto constituya limitación alguna,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  .,  , o  , donde la estereoquímica en un carbono dentro del grupo T-RD puede ser (R) o (S).

T también puede ser, sin que esto constituya limitación alguna, –LS–M–LS'–

donde LS es un enlace; M es C(O); LS' es C1-C6alquileno (por ejemplo, ) donde LS' está opcionalmente sustituido en forma independiente con RT; el RT opcional es un sustituyente seleccionado entre –C1-C6alquilo, –C1-C6alquil–OH, –C1-C6alquil–O–C1-C6alquilo, o un C3-C6carbociclilo (por ejemplo, fenilo, ciclohexilo). RD, por ejemplo es –OH; –OC(O)Me; –NH(C1-C6alquilo) (por ejemplo, –NHMe, –NHEt); –N(C1-C6alquil)2 (por ejemplo, –NMe2, –NEt2); un heterociclilo de entre 3 y 10 miembros (por ejemplo, pirrolidinilo, imidazolidinilo, hexahidropirimidinilo, morfolinilo, piperidinilo) opcionalmente sustituido con uno o más halógeno, oxo; C3-C10carbociclo (por ejemplo, ciclopentilo) opcionalmente sustituido con –OH; –C1-C6alquilo (por ejemplo, isopropilo, 3-pentilo) opcionalmente sustituido con –OH; o NHRT donde RT es un heterociclilo de 3 a 6 miembros (por ejemplo, tiazolilo, pirimidinilo). T-RD incluye, sin que esto constituya limitación alguna:  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , o



, donde la estereoquímica en un carbono dentro del grupo T-RD puede ser (R) o (S).

Para cada compuesto de Fórmula I, LK también puede seleccionarse en forma independiente en cada caso entre un enlace; –LS'–N(RB)C(O)–LS–; –LS'–C(O)N(RB)–LS–; o C1-C6alquileno, C2-C6alquenileno, C2-C6alquinileno, C3-C10carbociclo o heterociclo de entre 3 y 10 miembros, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, RT, –O–RS, –S–RS, –N(RSRS'), –OC(O)RS, –C(O)ORS, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo o ciano, donde RT, RB, RS, RS', LS y LS' son como se definen precedentemente.

Para la Fórmula I así como también las Fórmulas IA, IB, IC, ID, IE, IF o IG que se describen más adelante, incluyendo todas las formas de forma de realización descritas bajo las mismas, RA preferiblemente es halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, ciano; o C1-C6alquilo, C2-C6alquenilo o C2-C6alquinilo, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo o ciano; o C3-C6carbociclo o heterociclo de entre 3 y 6 miembros, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C1-C6alquilo, C2-C6alquenilo, C2-C6alquinilo, C1-C6haloalquilo, C2-C6haloalquenilo o C2-C6haloalquinilo; o –LA–O–RS, –LA–S–RS, –LA–C(O)RS, –LA–OC(O)RS, –LA–C(O)ORS, –LA–N(RSRS'), –LA–S(O)RS, –LA–SO2RS, –LA–C(O)N(RSRS'), –LA–N(RS)C(O)RS', –LA–N(RS)C(O)N(RS'RS''), –LA–N(RS)SO2RS', –

LA–SO2N(RSRS’), –LA–N(RS)SO2N(RS’RS’’), –LA–N(RS)S(O)N(RS’RS’’), –LA–OS(O)–RS, –LA–OS(O)2–RS, –LA–S(O)2ORS, –LA–S(O)ORS, –LA–OC(O)ORS, –LA–N(RS)C(O)ORS’, –LA–OC(O)N(RSRS’), –LA–N(RS)S(O)–RS’, –LA–S(O)N(RSRS’) o –LA–C(O)N(RS)C(O)–RS’, donde LA es un enlace, C1-C6alquileno, C2-C6alquenileno o C2-C6alquinileno.

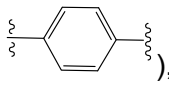
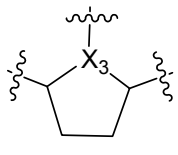
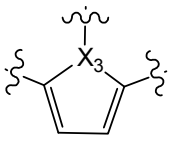
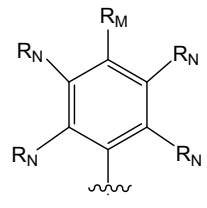
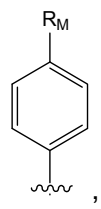
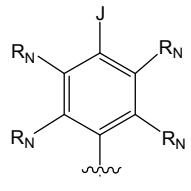
Más preferiblemente, RA es halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, ciano; o C1-C6alquilo, C2-C6alquenilo o C2-C6alquinilo, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo o ciano; o C3-C6carbociclo o heterociclo de entre 3 y 6 miembros, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C1-C6alquilo, C2-C6alquenilo, C2-C6alquinilo, C1-C6haloalquilo, C2-C6haloalquenilo o C2-C6haloalquinilo.

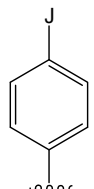
Más preferiblemente, RA es halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, ciano; o C1-C6alquilo, C2-C6alquenilo o C2-C6alquinilo, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo o ciano.

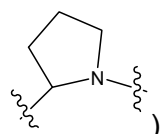
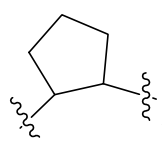
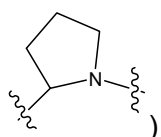
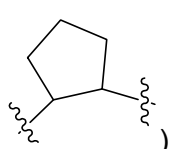
LS, LS’ y LS’’ preferiblemente se seleccionan en forma independiente entre sí en cada caso entre un enlace; o C1-C6alquileno, C2-C6alquenileno o C2-C6alquinileno.

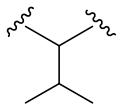
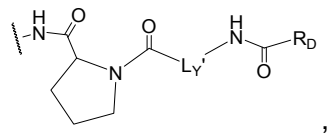
A y B pueden ser iguales o diferentes. De la misma manera, L1 y L2, o Y y Z, o Y–A– y Z–B–, o –A–L1– y –B–L2–, pueden ser iguales o diferentes. En algunas instancias, Y–A–L1– es idéntico a Z–B–L2–. En otras instancias, Y–A–L1– es distinto de Z–B–L2–.

En una forma de realización, A y B son en forma independiente entre sí carbociclo

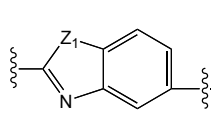
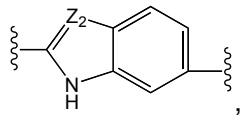
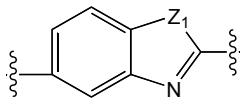
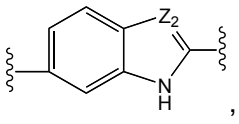
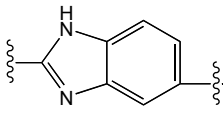
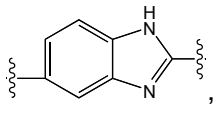
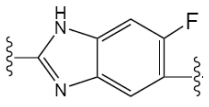
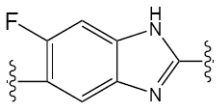
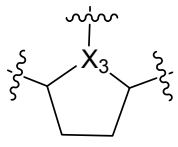
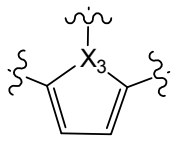
o heterociclo de 5 o 6 miembros (por ejemplo, fenilo como por ejemplo ), y están opcionalmente sustituidos en forma independiente entre sí con uno o más RA. X es carbociclo o heterociclo de 5 o 6 miembros o biciclo de entre 6 y 12 miembros (por ejemplo,  o  , donde X3 es N y está directamente unido a –L3–D) y está opcionalmente sustituido con uno o más RA. Los ejemplos específicos de X se describen precedentemente. D es C5-C6carbociclo o heterociclo de 5 o 6 miembros (por ejemplo, fenilo), y está opcionalmente sustituido con uno o más RA, o está sustituido con J y opcionalmente sustituido con uno o más RA, donde J es C3-C6carbociclo, heterociclo de entre 3 y 6 miembros o biciclo de entre 6 y 12 miembros y está opcionalmente sustituido con uno o más RA. Preferiblemente, J está sustituido con un C3-C6carbociclo o heterociclo de entre 3 y 6 miembros que está opcionalmente sustituido en forma independiente con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C1-C6alquilo, C2-C6alquenilo, C2-C6alquinilo, C1-C6haloalquilo, C2-C6haloalquenilo, C2-C6haloalquinilo, C(O)ORS o –N(RSRS'), y J también puede estar opcionalmente sustituido con uno o más RA. Preferiblemente, D es  o  , donde RM y RN son como se definen precedentemente. También preferiblemente, D es 

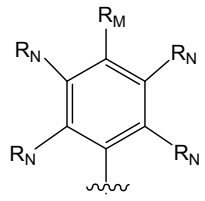
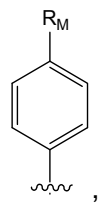
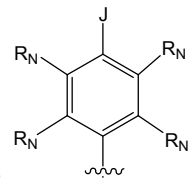
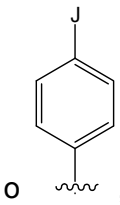
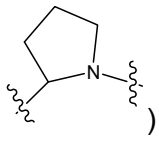


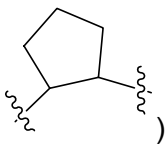
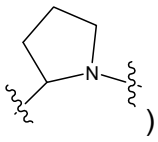
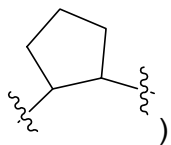
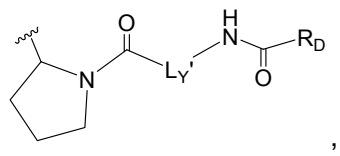
o , donde J y RN son como se definen precedentemente. L1 y L2 son en forma independiente entre sí un enlace o C1-C6alquileno, y L3 es un enlace, C1-C6alquileno o -C(O)-, y L1, L2, y L3 están opcionalmente sustituidos en forma independiente entre sí con uno o más RL. Preferiblemente, L1, L2, y L3 son un enlace. Y es –N(RB)C(O)C(R1R2)N(R5)–T–RD, o –N(RB)C(O)C(R3R4)C(R6R7)–T–RD, y Z es –N(RB)C(O)C(R8R9)N(R12)–T–RD, o –N(RB)C(O)C(R10R11)C(R13R14)–T–RD. R1 es RC, y R2 y R5, tomados junto con los átomos a los cuales están unidos, forman un anillo heterocíclico de 5 o 6 miembros (por ejemplo, ) que está opcionalmente sustituido con uno o más RA; R3 y R6 son en forma independiente entre sí RC, y R4 y R7, tomados junto con los átomos a los cuales están unidos, forman un anillo carbocíclico o heterocíclico de 5 o 6 miembros (por ejemplo, ) que está opcionalmente sustituido con uno o más RA. R8 es RC, y R9 y R12, tomados junto con los átomos a los cuales están unidos, forman un anillo heterocíclico de 5 o 6 miembros (por ejemplo, ) que está opcionalmente sustituido con uno o más RA; y R10 y R13 son en forma independiente entre sí RC, y R11 y R14, tomados junto con los átomos a los cuales están unidos, forman un anillo carbocíclico o heterocíclico de 5 o 6 miembros (por ejemplo, ) que está opcionalmente sustituido con uno o más RA. T preferiblemente se selecciona en forma independiente en cada caso entre –C(O)–LY'–

N(RB)C(O)–LS''– o –C(O)–LY'–N(RB)C(O)O–LS''–. LY' es en forma independiente en cada caso LS' y, preferiblemente, es en forma independiente en cada caso C1-C6alquileno (por ejemplo, -CH2- o ) y está opcionalmente sustituido con uno o más sustituyentes seleccionados entre RL. T también puede seleccionarse, sin que esto constituya limitación alguna, entre –C(O)–LY'–LS''–, –C(O)–LY'–O–LS''–, –C(O)–LY'–N(RB)–LS''–, o –C(O)–LY'–N(RB)S(O)2–LS''–. En algunos casos, al menos uno de Y y Z es, o Y y Z son ambos en forma independiente, 

, donde los ejemplos no limitativos de RD incluyen (1) –O–C1-C6alquilo, –O–C2-C6alquenilo, –O–C2-C6alquinilo, C1-C6alquilo, C2-C6alquenilo o C2-C6alquinilo, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C3-C6carbociclo o heterociclo de entre 3 y 6 miembros; o (2) C3-C6carbociclo o heterociclo de entre 3 y 6 miembros cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C1-C6alquilo, C2-C6alquenilo, C2-C6alquinilo, C1-C6haloalquilo, C2-C6haloalquenilo o C2-C6haloalquinilo; y los ejemplos no limitativos de LY' incluyen C1-C6alquileno opcionalmente sustituido con halógeno, hidroxi, mercapto, amino, carboxi, fosfonoxi, –O–C1-C6alquilo, –O–C2-C6alquenilo, –O–C2-C6alquinilo, o carbociclo o heterociclo de entre 3 y 6 miembros, donde dicho carbociclo o heterociclo de entre 3 y 6 miembros está opcionalmente sustituido con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C1-C6alquilo, C2-C6alquenilo, C2-C6alquinilo, C1-C6haloalquilo, C2-C6haloalquenilo o C2-C6haloalquinilo.

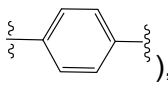
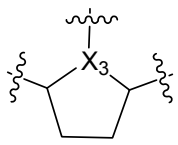
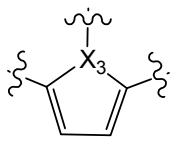
En otra forma de realización, A es  o  , y está opcionalmente sustituido con uno o más RA; B es  o  , y está opcionalmente sustituido con uno o más RA. Z1 se selecciona en forma independiente en cada caso entre O, S, NH o CH2; y Z2 se selecciona en forma independiente en cada caso entre N o CH. Preferiblemente, A es  , B es  , y A y B están sustituidos con uno o más halógeno, como por ejemplo F o Cl. Cuando A y/o B son benzimidazol sustituido con halo (por ejemplo, A es  y B es ), los compuestos de esta forma de realización pueden tener propiedades farmacocinéticas significativamente mejoradas así como también una actividad inhibitoria mejorada contra ciertos mutantes de HCV genotipo 1a, en comparación con los mismos compuestos pero con benzimidazol no sustituido. X es carbociclo o heterociclo de 5 o 6 miembros o biciclo de entre 6 y 12 miembros (por ejemplo,  o  , donde X3 es N y está directamente unido a –L3–D) y está opcionalmente sustituido con uno o más RA. Los ejemplos específicos de X se describen precedentemente. D es C5-C6carbociclo o heterociclo de 5 o 6 miembros (por ejemplo, fenilo), y está opcionalmente sustituido con uno o más RA, o está sustituido con J y opcionalmente sustituido con uno o más RA, donde J es C3-C6carbociclo, heterociclo de entre 3 y 6 miembros o biciclo de entre 6 y 12 miembros y está opcionalmente sustituido con uno o más RA. Preferiblemente, J está sustituido con un C3-C6carbociclo o

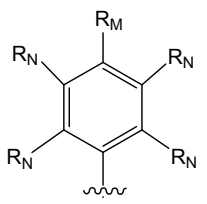
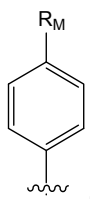
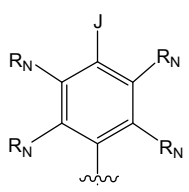
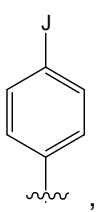
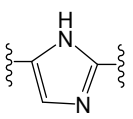
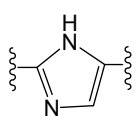
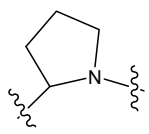
heterociclo de entre 3 y 6 miembros que está opcionalmente sustituido en forma independiente con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C1-C6alquilo, C2-C6alquenilo, C2-C6alquinilo, C1-C6haloalquilo, C2-C6haloalquenilo, C2-C6haloalquinilo, C(O)ORS o –N(RSRS'), y J también puede estar opcionalmente sustituido con uno o más RA. Preferiblemente, D es  o  , donde RM y RN son como se definen precedentemente. También preferiblemente, D es  o  , donde J y RN son como se definen precedentemente. L1 y L2 son en forma independiente entre sí un enlace o C1-C6alquileno, y L3 es un enlace, C1-C6alquileno o -C(O)-, y L1, L2, y L3 están opcionalmente sustituidos en forma independiente entre sí con uno o más RL. Preferiblemente, L1, L2, y L3 son un enlace. Y es –LS–C(R1R2)N(R5)–T–RD o –LS–C(R3R4)C(R6R7)–T–RD, y Z es –LS–C(R8R9)N(R12)–T–RD o –LS–C(R10R11)C(R13R14)–T–RD. R1 es RC, y R2 y R5, tomados junto con los átomos a los cuales están unidos, forman un anillo heterocíclico de 5 o 6 miembros (por ejemplo, ) que está opcionalmente sustituido con uno o más RA; R3 y R6 son en forma independiente entre sí RC, y R4 y R7, tomados junto con los átomos a los cuales están unidos, forman un anillo carbocíclico o heterocíclico de 5 o 6 miembros (por ejemplo,

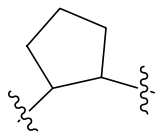
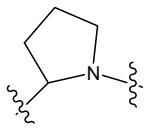
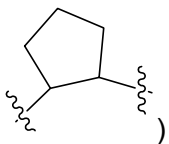
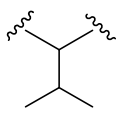
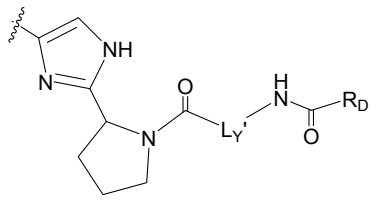
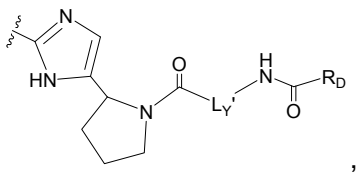

) que está opcionalmente sustituido con uno o más RA. R8 es RC, y R9 y R12, tomados junto con los átomos a los cuales están unidos, forman un anillo heterocíclico de 5 o 6 miembros (por ejemplo, 
) que está opcionalmente sustituido con uno o más RA; y R10 y R13 son en forma independiente entre sí RC, y R11 y R14, tomados junto con los átomos a los cuales están unidos, forman un anillo carbocíclico o heterocíclico de 5 o 6 miembros (por ejemplo, 
) que está opcionalmente sustituido con uno o más RA. T preferiblemente se selecciona en forma independiente en cada caso entre –C(O)–LY'–N(RB)C(O)–LS''– o –C(O)–LY'–N(RB)C(O)O–LS''–. LY' es en forma independiente en cada caso LS' y, preferiblemente, es en forma independiente C1-C6alquileno (por ejemplo, -CH2-) y está opcionalmente sustituido con uno o más sustituyentes seleccionados entre RL. T también puede seleccionarse, sin que esto constituya limitación alguna, entre –C(O)–LY'–LS''–, –C(O)–LY'–O–LS''–, –C(O)–LY'–N(RB)–LS''–, o –C(O)–LY'–N(RB)S(O)2–LS''–. En algunos casos, al menos uno de Y y Z es, o Y y Z son ambos en forma independiente, 

, donde los ejemplos no limitativos de RD incluyen (1) –O–C1-C6alquilo, –O–C2-C6alquenilo, –O–C2-C6alquinilo, C1-C6alquilo, C2-C6alquenilo o C2-C6alquinilo, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C3-C6carbociclo o heterociclo de entre 3 y 6 miembros; o (2) C3-C6carbociclo o heterociclo de entre 3 y 6 miembros cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o

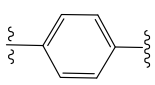
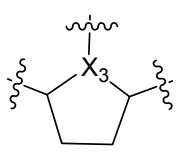
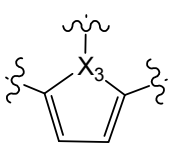
más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C1-C6alquilo, C2-C6alquenilo, C2-C6alquinilo, C1-C6haloalquilo, C2-C6haloalquenilo o C2-C6haloalquinilo; y los ejemplos no limitativos de LY' incluyen C1-C6alquileno opcionalmente sustituido con halógeno, hidroxi, mercapto, amino, carboxi, fosfonoxi, –O–C1-C6alquilo, –O–C2-C6alquenilo, –O–C2-C6alquinilo, o carbociclo o heterociclo de entre 3 y 6 miembros, donde dicho carbociclo o heterociclo de entre 3 y 6 miembros está opcionalmente sustituido con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C1-C6alquilo, C2-C6alquenilo, C2-C6alquinilo, C1-C6haloalquilo, C2-C6haloalquenilo o C2-C6haloalquinilo.

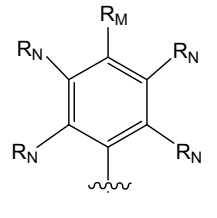
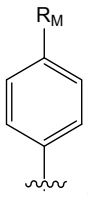
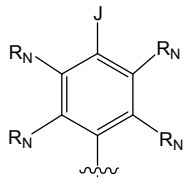
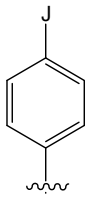
En aun otra forma de realización, A y B son en forma independiente entre sí carbociclo o heterociclo de 5 o 6 miembros (por ejemplo, A y B son en forma independiente entre sí fenilo, como por ejemplo ), y están opcionalmente sustituidos en forma independiente entre sí con uno o más RA. X es carbociclo o heterociclo de 5 o 6 miembros o biciclo de entre 6 y 12 miembros (por ejemplo,  o  , donde X3 es N y está directamente unido a –L3–D) y está opcionalmente sustituido con uno o más RA. Los ejemplos específicos de X se describen precedentemente. D puede ser, por ejemplo, C5-C6carbociclo o heterociclo de 5 o 6 miembros (por ejemplo, fenilo), y está opcionalmente sustituido con uno o más RA, o está sustituido con J y opcionalmente sustituido con uno o más RA, donde J es C3-C6carbociclo, heterociclo de entre 3 y 6 miembros o biciclo de entre 6 y 12 miembros y está opcionalmente sustituido con uno o más RA. Preferiblemente, J está sustituido con un C3-C6carbociclo o heterociclo de entre 3 y 6 miembros que está opcionalmente sustituido en forma independiente con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo,

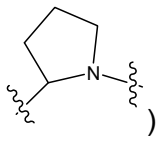
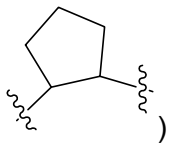
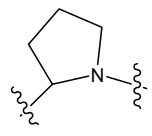
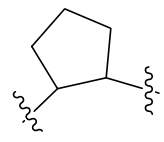
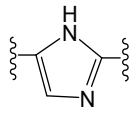
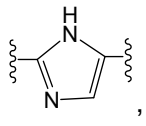
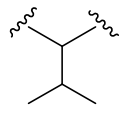
ciano, C1-C6alquilo, C2-C6alquenilo, C2-C6alquinilo, C1-C6haloalquilo, C2-C6haloalquenilo, C2-C6haloalquinilo, C(O)ORS o –N(RSRS'), y J también puede estar opcionalmente sustituido con uno o más RA. Preferiblemente, D es  o  , donde RM y RN son como se definen precedentemente. También preferiblemente, D es  o  , donde J y RN son como se definen precedentemente. L1 y L2 son en forma independiente entre sí un enlace o C1-C6alquileno, y L3 es un enlace, C1-C6alquileno o -C(O)-, y L1, L2, y L3 están opcionalmente sustituidos en forma independiente entre sí con uno o más RL. Preferiblemente, L1, L2, y L3 son un enlace. Y es –G–C(R1R2)N(R5)–T–RD o –G–C(R3R4)C(R6R7)–T–RD, y Z es –G–C(R8R9)N(R12)–T–RD o –G–C(R10R11)C(R13R14)–T–RD. G es en forma independiente C5-C6carbociclo o heterociclo de 5 o 6 miembros, como por ejemplo  o  , y está opcionalmente sustituido en forma independiente con uno o más RA. R1 es RC, y R2 y R5, tomados junto con los átomos a los cuales están unidos, forman un anillo heterocíclico de 5 o 6 miembros (por ejemplo, ) que está opcionalmente sustituido con uno o más RA; R3 y R6 son en forma independiente entre sí RC, y R4 y R7, tomados junto con los átomos a los cuales están unidos, forman un anillo carbocíclico o

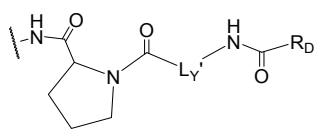
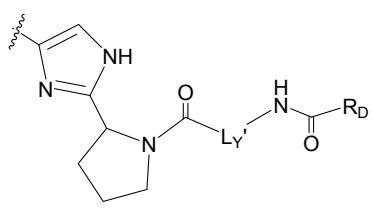
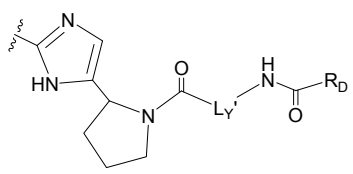
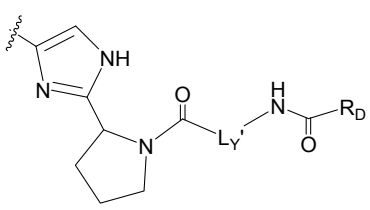
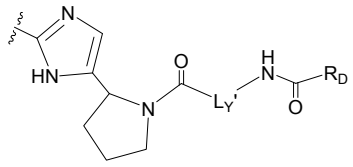
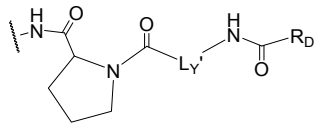
heterocíclico de 5 o 6 miembros (por ejemplo, ) que está opcionalmente sustituido con uno o más RA. R8 es RC, y R9 y R12, tomados junto con los átomos a los cuales están unidos, forman un anillo heterocíclico de 5 o 6 miembros (por ejemplo, ) que está opcionalmente sustituido con uno o más RA; y R10 y R13 son en forma independiente entre sí RC, y R11 y R14, tomados junto con los átomos a los cuales están unidos, forman un anillo carbocíclico o heterocíclico de 5 o 6 miembros (por ejemplo, ) que está opcionalmente sustituido con uno o más RA. T preferiblemente se selecciona en forma independiente en cada caso entre –C(O)–LY'–N(RB)C(O)–LS''– o –C(O)–LY'–N(RB)C(O)O–LS''–. LY' es en forma independiente en cada caso LS' y, preferiblemente, es en forma independiente en cada caso C1-C6alquileno (por ejemplo, -CH2- o ) y está opcionalmente sustituido con uno o más sustituyentes seleccionados entre RL. T también puede seleccionarse, sin que esto constituya limitación alguna, entre –C(O)–LY'–LS''–, –C(O)–LY'–O–LS''–, –C(O)–LY'–N(RB)–LS''–, o –C(O)–LY'–N(RB)S(O)2–LS''–. En algunos casos, al menos uno de Y y Z es, o Y y Z son ambos en forma independiente,  o  , donde los ejemplos no limitativos de RD incluyen (1) –O–C1-C6alquilo, –O–C2-C6alquenilo, –O–C2-C6alquinilo, C1-C6alquilo, C2-C6alquenilo o C2-

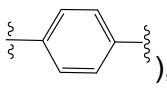
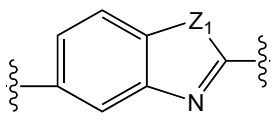
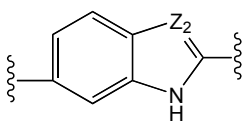
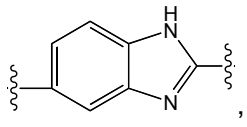
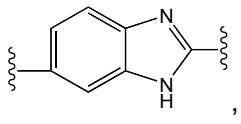
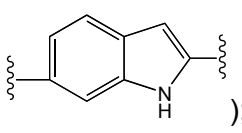
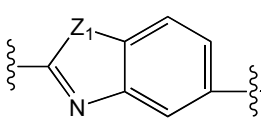
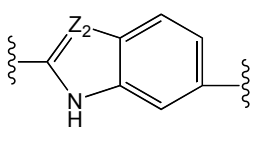
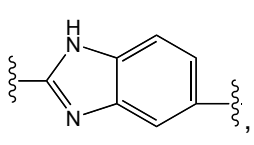
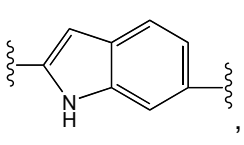
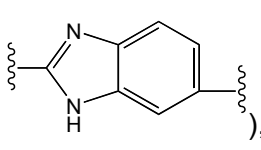
C6alquinilo, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C3-C6carbociclo o heterociclo de entre 3 y 6 miembros; o (2) C3-C6carbociclo o heterociclo de entre 3 y 6 miembros cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C1-C6alquilo, C2-C6alquenilo, C2-C6alquinilo, C1-C6haloalquilo, C2-C6haloalquenilo o C2-C6haloalquinilo; y los ejemplos no limitativos de LY' incluyen C1-C6alquileno opcionalmente sustituido con halógeno, hidroxi, mercapto, amino, carboxi, fosfonoxi, –O–C1-C6alquilo, –O–C2-C6alquenilo, –O–C2-C6alquinilo, o carbociclo o heterociclo de entre 3 y 6 miembros, donde dicho carbociclo o heterociclo de entre 3 y 6 miembros está opcionalmente sustituido con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C1-C6alquilo, C2-C6alquenilo, C2-C6alquinilo, C1-C6haloalquilo, C2-C6haloalquenilo o C2-C6haloalquinilo.

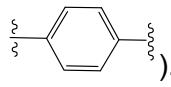
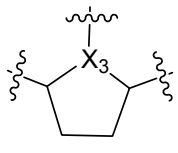
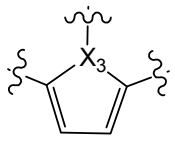
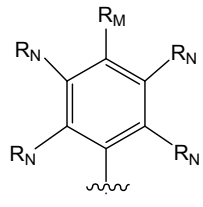
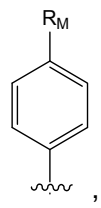
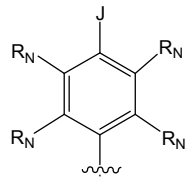
En aun otra forma de realización, A y B son en forma independiente entre sí carbociclo o heterociclo de 5 o 6 miembros (por ejemplo, A y B son en forma independiente entre sí fenilo, como por ejemplo ), y están opcionalmente sustituidos en forma independiente entre sí con uno o más RA. X es carbociclo o heterociclo de 5 o 6 miembros o biciclo de entre 6 y 12 miembros (por ejemplo,  o  , donde X3 es N y está directamente unido a –L3–D) y está opcionalmente sustituido con uno o más RA. Los ejemplos específicos de X se describen precedentemente. D puede ser, por ejemplo, C5-C6carbociclo o heterociclo de 5 o 6 miembros (por ejemplo, fenilo), y está opcionalmente sustituido con uno o más RA, o está

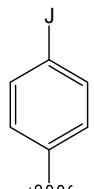
sustituido con J y opcionalmente sustituido con uno o más RA, donde J es C3-C6carbociclo, heterociclo de entre 3 y 6 miembros o biciclo de entre 6 y 12 miembros y está opcionalmente sustituido con uno o más RA. Preferiblemente, J está sustituido con un C3-C6carbociclo o heterociclo de entre 3 y 6 miembros que está opcionalmente sustituido en forma independiente con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C1-C6alquilo, C2-C6alquenilo, C2-C6alquinilo, C1-C6haloalquilo, C2-C6haloalquenilo, C2-C6haloalquinilo, C(O)ORS o –N(RSRS'), y J también puede estar opcionalmente sustituido con uno o más RA. Preferiblemente, D es  o  , donde RM y RN son como se definen precedentemente. También preferiblemente, D es  o  , donde J y RN son como se definen precedentemente. L1 y L2 son en forma independiente entre sí un enlace o C1-C6alquileno, y L3 es un enlace, C1-C6alquileno o -C(O)-, y L1, L2, y L3 están opcionalmente sustituidos en forma independiente entre sí con uno o más RL. Preferiblemente, L1, L2, y L3 son un enlace. Y es –N(RB)C(O)C(R1R2)N(R5)–T–RD o –N(RB)C(O)C(R3R4)C(R6R7)–T–RD, y Z es –G–C(R8R9)N(R12)–T–RD o –G–C(R10R11)C(R13R14)–T–RD; o Y es –G–C(R1R2)N(R5)–T–RD o –G–C(R3R4)C(R6R7)–T–RD, y Z es –N(RB)C(O)C(R8R9)N(R12)–T–RD o –N(RB)C(O)C(R10R11)C(R13R14)–T–RD. R1 es RC, y R2 y R5, tomados junto con los átomos a los cuales están unidos, forman un anillo heterocíclico de 5 o 6 miembros (por

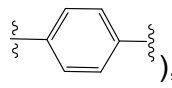
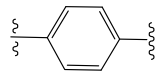
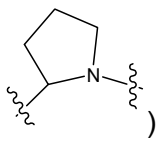
ejemplo, ) que está opcionalmente sustituido con uno o más RA; R3 y R6 son en forma independiente entre sí RC, y R4 y R7, tomados junto con los átomos a los cuales están unidos, forman un anillo carbocíclico o heterocíclico de 5 o 6 miembros (por ejemplo, ) que está opcionalmente sustituido con uno o más RA. R8 es RC, y R9 y R12, tomados junto con los átomos a los cuales están unidos, forman un anillo heterocíclico de 5 o 6 miembros (por ejemplo, ) que está opcionalmente sustituido con uno o más RA; y R10 y R13 son en forma independiente entre sí RC, y R11 y R14, tomados junto con los átomos a los cuales están unidos, forman un anillo carbocíclico o heterocíclico de 5 o 6 miembros (por ejemplo, ) que está opcionalmente sustituido con uno o más RA. G es en forma independiente C5-C6carbociclo o heterociclo de 5 o 6 miembros, como por ejemplo  o  , y está opcionalmente sustituido en forma independiente con uno o más RA. T preferiblemente se selecciona en forma independiente en cada caso entre –C(O)–LY'–N(RB)C(O)–LS''– o –C(O)–LY'–N(RB)C(O)O–LS''–. LY' es en forma independiente en cada caso LS' y, preferiblemente, es en forma independiente en cada caso C1-C6alquileno (por ejemplo, -CH2- o ) y está opcionalmente sustituido con uno o más sustituyentes seleccionados entre RL. T también puede seleccionarse, sin que esto constituya limitación alguna, entre –C(O)–LY'–LS''–, –C(O)–LY'–O–LS''–, –C(O)–LY'–

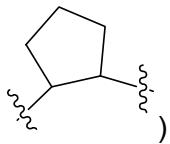
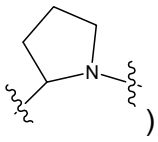
N(RB)–LS''–, o –C(O)–LY'–N(RB)S(O)2–LS''–. En algunos casos, Y es  como se describe precedentemente, y Z es  o  como se describe precedentemente. En algunos otros casos, Y es  o  como se describe precedentemente , y Z es  como se describe precedentemente.

En aun otra forma de realización, A es carbociclo o heterociclo de 5 o 6 miembros (por ejemplo, fenilo como por ejemplo ), y B es  o  (por ejemplo,  ,  , o ); o A es  o  (por ejemplo,  ,  , o ), y B es carbociclo o

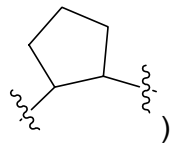
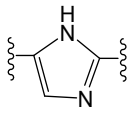
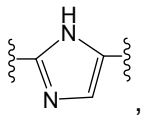
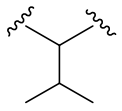
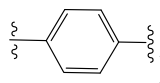
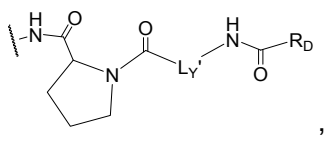
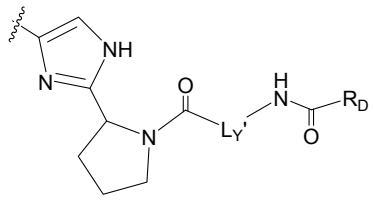
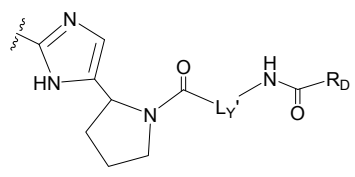
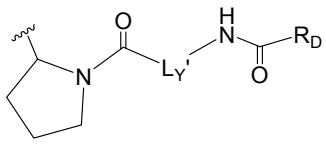
heterociclo de 5 o 6 miembros (por ejemplo, fenilo como por ejemplo ). A y B están opcionalmente sustituidos en forma independiente entre sí con uno o más RA. Z1 se selecciona en forma independiente en cada caso entre O, S, NH o CH2; y Z2 se selecciona en forma independiente en cada caso entre N o CH. X es carbociclo o heterociclo de 5 o 6 miembros o biciclo de entre 6 y 12 miembros (por ejemplo,  o  , donde X3 es N y está directamente unido a –L3–D) y está opcionalmente sustituido con uno o más RA. Los ejemplos específicos de X se describen precedentemente. D es C5-C6carbociclo o heterociclo de 5 o 6 miembros (por ejemplo, fenilo), y está opcionalmente sustituido con uno o más RA, o está sustituido con J y opcionalmente sustituido con uno o más RA, donde J es C3-C6carbociclo, heterociclo de entre 3 y 6 miembros o biciclo de entre 6 y 12 miembros y está opcionalmente sustituido con uno o más RA. Preferiblemente, J está sustituido con un C3-C6carbociclo o heterociclo de entre 3 y 6 miembros que está opcionalmente sustituido en forma independiente con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C1-C6alquilo, C2-C6alquenilo, C2-C6alquinilo, C1-C6haloalquilo, C2-C6haloalquenilo, C2-C6haloalquinilo, C(O)ORS o –N(RSRS'), y J también puede estar opcionalmente sustituido con uno o más RA. Preferiblemente, D es  o  , donde RM y RN son como se definen precedentemente. También preferiblemente, D es 

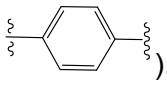
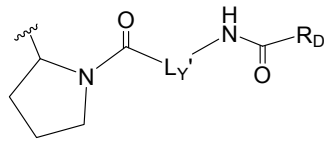
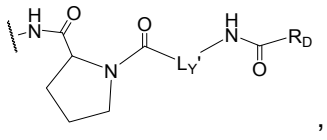
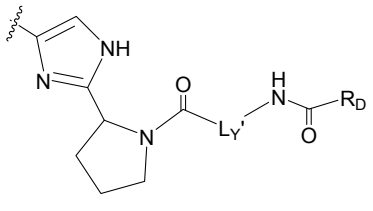
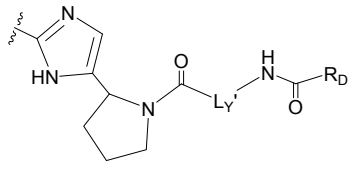


o , donde J y RN son como se definen precedentemente. L1 y L2 son en forma independiente entre sí un enlace o C1-C6alquileno, y L3 es un enlace, C1-C6alquileno o -C(O)-, y L1, L2, y L3 están opcionalmente sustituidos en forma independiente entre sí con uno o más RL. Preferiblemente, L1, L2, y L3 son un enlace. Cuando A es carbociclo o heterociclo de 5 o 6 miembros (por ejemplo, fenilo como por ejemplo ), Y es –N(RB)C(O)C(R1R2)N(R5)–T–RD, –N(RB)C(O)C(R3R4)C(R6R7)–T–RD, –G–C(R1R2)N(R5)–T–RD o –G–C(R3R4)C(R6R7)–T–RD, y Z es –LS–C(R8R9)N(R12)–T–RD o –LS–C(R10R11)C(R13R14)–T–RD. Cuando B es carbociclo o heterociclo de 5 o 6 miembros (por ejemplo, fenilo como por ejemplo ), Y es –LS–C(R1R2)N(R5)–T–RD o –LS–C(R3R4)C(R6R7)–T–RD, y Z es –N(RB)C(O)C(R8R9)N(R12)–T–RD, –N(RB)C(O)C(R10R11)C(R13R14)–T–RD, –G–C(R8R9)N(R12)–T–RD o –G–C(R10R11)C(R13R14)–T–RD. R1 es RC, y R2 y R5, tomados junto con los átomos a los cuales están unidos, forman un anillo heterocíclico de 5 o 6 miembros (por ejemplo, 

) que está opcionalmente sustituido con uno o más RA; R3 y R6 son en forma independiente entre sí RC, y R4 y R7, tomados junto con los átomos a los cuales están unidos, forman un anillo carbocíclico o heterocíclico de 5 o 6 miembros (por ejemplo, ) que está opcionalmente sustituido con uno o más RA. R8 es RC, y R9 y R12, tomados junto con los átomos a los cuales están unidos, forman un anillo heterocíclico de 5 o 6 miembros (por ejemplo, 

) que está opcionalmente sustituido con uno o

más RA; y R10 y R13 son en forma independiente entre sí RC, y R11 y R14, tomados junto con los átomos a los cuales están unidos, forman un anillo carbocíclico o heterocíclico de 5 o 6 miembros (por ejemplo, ) que está opcionalmente sustituido con uno o más RA. G es en forma independiente C5-C6carbociclo o heterociclo de 5 o 6 miembros, como por ejemplo  o  , y está opcionalmente sustituido en forma independiente con uno o más RA. T preferiblemente se selecciona en forma independiente en cada caso entre –C(O)–LY'–N(RB)C(O)–LS''– o –C(O)–LY'–N(RB)C(O)O–LS''–. LY' es en forma independiente en cada caso LS' y, preferiblemente, es en forma independiente en cada caso C1-C6alquileno (por ejemplo, -CH2- o ) y está opcionalmente sustituido con uno o más sustituyentes seleccionados entre RL. T también puede seleccionarse, sin que esto constituya limitación alguna, entre –C(O)–LY'–LS''–, –C(O)–LY'–O–LS''–, –C(O)–LY'–N(RB)–LS''–, o –C(O)–LY'–N(RB)S(O)2–LS''–. En algunos casos cuando A es carbociclo o heterociclo de 5 o 6 miembros (por ejemplo, fenilo como por ejemplo ), 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 como por ejemplo ), Y es  como se describe precedentemente, y Z es  ,  o  como se describe precedentemente.

La presente invención también presenta compuestos de las Fórmulas I, IA, IB, IC y ID como se describe aquí (incluyendo cada forma de realización descrita bajo las mismas) y sales aceptables farmacéuticamente de los mismos, donde:

D es C3-C12carbociclo o heterociclo de entre 3 y 12 miembros, y está opcionalmente sustituido con uno o más RA; o D es C3-C12carbociclo o heterociclo de entre 3 y 12 miembros que está sustituido con J y opcionalmente sustituido con uno o más RA, donde J es C3-C15carbociclo o heterociclo de entre 3 y 15 miembros (por ejemplo, un monociclo de entre 3 y 6 miembros, un bibiclo fusionado, en puente o espiro de entre 6 y 12 miembros, un anillo fusionado, en puente o espiro de entre 10 y 15 miembros que contiene un triciclo, o un carbociclo o heterociclo de entre 13 y 15 miembros) y está opcionalmente sustituido con uno o más RA, o J es –SF5; o D es hidrógeno o RA;

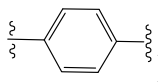
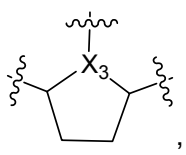
RA se selecciona en forma independiente en cada caso entre halógeno, nitro, oxo, fosfonoxi, fosfono, tioxo, ciano, o –LB–RE; donde dos RA adyacentes, tomados junto con los átomos a los cuales están unidos y cualquier otro átomo entre los átomos a los cuales están unidos, pueden formar opcionalmente carbociclo o heterociclo;

LB se selecciona en forma independiente en cada caso entre LS; o C1-C10alquileno, C2-C10alquenileno o C2-C10alquinileno, en cada uno de los cuales opcionalmente se reemplazan 1, 2, 3, 4 o 5 átomos de carbono en forma independiente por O, S o N(RB), y cada uno de dichos C1-C10alquileno, C2-C10alquenileno o C2-C10alquinileno está opcionalmente sustituido en forma independiente con uno o más RL;

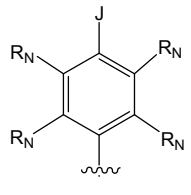
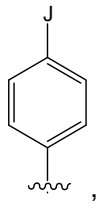
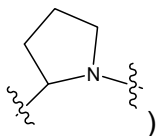
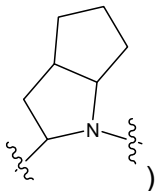
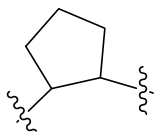
RE se selecciona en forma independiente en cada caso entre –O–RS, –S–RS, –C(O)RS, –OC(O)RS, –C(O)ORS, –N(RSRS'), –S(O)RS, –SO2RS, –C(O)N(RSRS'), –N(RS)C(O)RS', –N(RS)C(O)N(RS'RS''), –N(RS)SO2RS', –SO2N(RSRS'), –N(RS)SO2N(RS'RS''), –N(RS)S(O)N(RS'RS''), –OS(O)–RS, –OS(O)2–RS, –S(O)2ORS, –S(O)ORS, –OC(O)ORS, –N(RS)C(O)ORS', –OC(O)N(RSRS'), –N(RS)S(O)–RS', –S(O)N(RSRS'), –P(O)(ORS)2, =C(RSRS'), o –C(O)N(RS)C(O)–RS'; o C1-C6alquilo, C2-C6alquenilo o C2-C6alquinilo, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C3-C12carbociclo o heterociclo de entre 3 y 12 miembros; o C3-C12carbociclo o heterociclo de entre 3 y 12 miembros (por ejemplo, carbociclo o heterociclo de entre 7 y 12 miembros), cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, trimetilsililo, C1-C6alquilo, C2-C6alquenilo, C2-C6alquinilo, C1-C6haloalquilo, C2-C6haloalquenilo, C2-C6haloalquinilo, –O–RS, –S–RS, –C(O)RS, –C(O)ORS, o –N(RSRS').

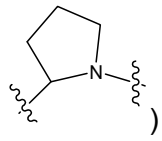
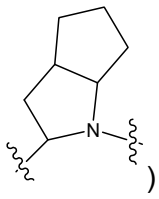
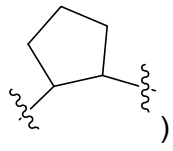
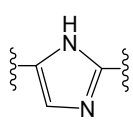
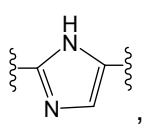
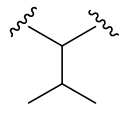
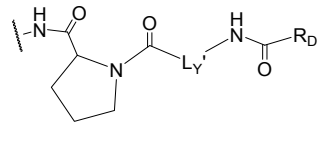
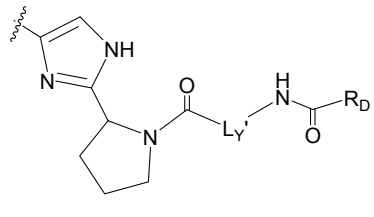
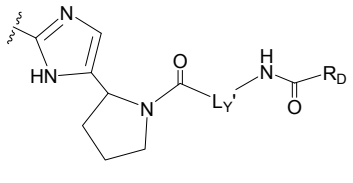
RL se selecciona en forma independiente en cada caso entre halógeno, nitro, oxo, fosfonoxi, fosfono, tioxo, ciano, –O–RS, –S–RS, –C(O)RS, –OC(O)RS, –

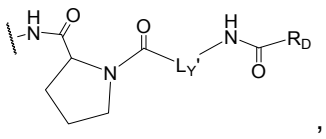
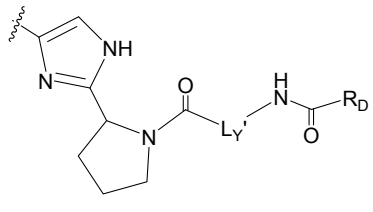
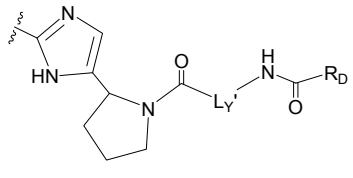
C(O)ORS, –N(RSRS'), –S(O)RS, –SO2RS, –C(O)N(RSRS') o –N(RS)C(O)RS'; o C3-C12carbociclo o heterociclo de entre 3 y 12 miembros (por ejemplo, C3-C6carbociclo o heterociclo de entre 3 y 6 miembros), cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C1-C6alquilo, C2-C6alquenilo, C2-C6alquinilo, C1-C6haloalquilo, C2-C6haloalquenilo o C2-C6haloalquinilo; donde dos RL adyacentes, tomados junto con los átomos a los cuales están unidos y cualquier otro átomo entre los átomos a los cuales están unidos, pueden formar opcionalmente carbociclo o heterociclo.

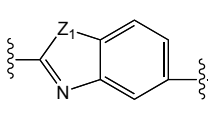
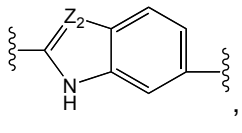
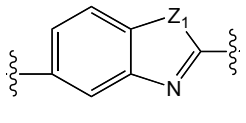
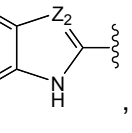
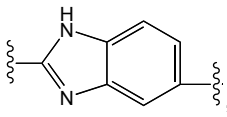
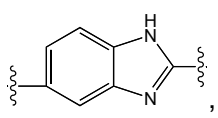
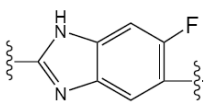
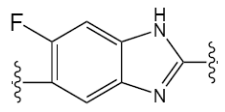
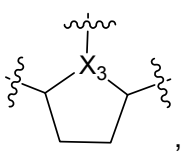
En una forma de realización, A y B son en forma independiente entre sí carbociclo o heterociclo de 5 o 6 miembros (preferiblemente, A y B son en forma independiente entre sí fenilo como por ejemplo ), y están opcionalmente sustituidos en forma independiente entre sí con uno o más RA (preferiblemente, A y B están sustituidos en forma independiente entre sí con al menos un halo como por ejemplo F). X es carbociclo o heterociclo de 5 o 6 miembros o biciclo de entre 6 y 12 miembros (preferiblemente, X es 

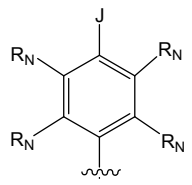
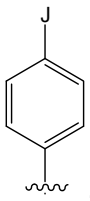
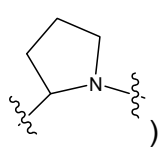
, donde X3 es N y está directamente unido a –L3–D), y está opcionalmente sustituido con uno o más RA. D es un C5-C6carbociclo o heterociclo de 5 o 6 miembros (por ejemplo, fenilo), y está sustituido con J y opcionalmente sustituido con uno o más RA. J es C3-C6carbociclo, heterociclo de entre 3 y 6 miembros, biciclo de entre 6 y 12 miembros, triciclo de entre 10 y 15 miembros, o carbociclo/heterociclo de entre 13 y 15 miembros, y J está opcionalmente sustituido con uno o más RA. Preferiblemente, J está sustituido con un C3-C6carbociclo, heterociclo de entre 3 y 6 miembros, biciclo de entre 6 y 12 miembros o carbociclo/heterociclo de entre 7 y 12 miembros, que está opcionalmente sustituido en forma independiente con uno o más sustituyentes seleccionados entre (1)

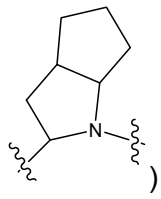
halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C1-C6alquilo, C2-C6alquenilo, C2-C6alquinilo, C1-C6haloalquilo, C2-C6haloalquenilo, C2-C6haloalquinilo, –C(O)ORS o –N(RSRS'), o (2) trimetilsililo, –O–RS, –S–RS, –C(O)RS; y J también puede estar opcionalmente sustituido con uno o más RA. Preferiblemente, D es  o  , donde J es como se define precedentemente, y cada RN se selecciona en forma independiente entre RD y preferiblemente es hidrógeno o halo como por ejemplo F. L1 y L2 son en forma independiente entre sí un enlace o C1-C6alquileno, y L3 es un enlace, C1-C6alquileno o -C(O)-, y L1, L2, y L3 están opcionalmente sustituidos en forma independiente entre sí con uno o más RL. Preferiblemente, L1, L2, y L3 son un enlace. Y es –N(RB)C(O)C(R1R2)N(R5)–T–RD, –N(RB)C(O)C(R3R4)C(R6R7)–T–RD, –G–C(R1R2)N(R5)–T–RD o –G–C(R3R4)C(R6R7)–T–RD. Z es –N(RB)C(O)C(R8R9)N(R12)–T–RD, –N(RB)C(O)C(R10R11)C(R13R14)–T–RD, –G–C(R8R9)N(R12)–T–RD o –G–C(R10R11)C(R13R14)–T–RD. R1 es RC; y R2 y R5, tomados junto con los átomos a los cuales están unidos, forman un anillo heterocíclico de 5 o 6 miembros (por ejemplo, ) o biciclo de entre 6 y 12 miembros (por ejemplo, ) que está opcionalmente sustituido con uno o más RA; R3 y R6 son en forma independiente entre sí RC, y R4 y R7, tomados junto con los átomos a los cuales están unidos, forman un anillo carbocíclico o heterocíclico de 5 o 6 miembros (por ejemplo, ) o biciclo de entre 6 y 12 miembros que está opcionalmente sustituido con uno o más RA. R8 es RC; y R9 y R12, tomados junto con los átomos a los cuales están unidos, forman un anillo

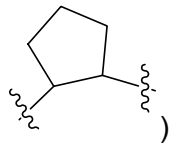
heterocíclico de 5 o 6 miembros (por ejemplo, ) o biciclo de entre 6 y 12 miembros (por ejemplo, ) que está opcionalmente sustituido con uno o más RA; y R10 y R13 son en forma independiente entre sí RC, y R11 y R14, tomados junto con los átomos a los cuales están unidos, forman un anillo carbocíclico o heterocíclico de 5 o 6 miembros (por ejemplo, ) o biciclo de entre 6 y 12 miembros que está opcionalmente sustituido con uno o más RA. G es en forma independiente C5-C6carbociclo o heterociclo de 5 o 6 miembros, como por ejemplo  o  , y está opcionalmente sustituido en forma independiente con uno o más RA. T preferiblemente se selecciona en forma independiente en cada caso entre –C(O)–LY'–N(RB)C(O)–LS''– o –C(O)–LY'–N(RB)C(O)O–LS''–. LY' es en forma independiente en cada caso LS' y, preferiblemente, es en forma independiente en cada caso C1-C6alquileno (por ejemplo, -CH2- o ) y está opcionalmente sustituido con uno o más sustituyentes seleccionados entre RL. T también puede seleccionarse, sin que esto constituya limitación alguna, entre –C(O)–LY'–LS''–, –C(O)–LY'–O–LS''–, –C(O)–LY'–N(RB)–LS''–, o –C(O)–LY'–N(RB)S(O)2–LS''–. En algunos casos, Y es  ,  o  como

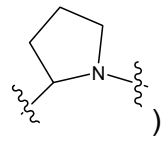
se describe precedentemente, y Z es  ,  o  como se describe precedentemente.

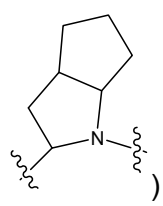
En otra forma de realización, A es  o  , y está opcionalmente sustituido con uno o más RA; B es  o  , y está opcionalmente sustituido con uno o más RA. Z1 se selecciona en forma independiente en cada caso entre O, S, NH o CH2; y Z2 se selecciona en forma independiente en cada caso entre N o CH. Preferiblemente, A y B están sustituidos en forma independiente entre sí con al menos un halo como por ejemplo F. También preferiblemente, A es  , B es  , y A y B están sustituidos con uno o más halógeno, como por ejemplo F o Cl. Cuando A y/o B son benzimidazol sustituido con halo (por ejemplo, A es  y B es ), los compuestos de esta forma de realización pueden tener propiedades farmacocinéticas significativamente mejoradas así como también una actividad inhibitoria mejorada contra ciertas mutaciones de HCV genotipo 1a, en comparación con los mismos compuestos pero con benzimidazol no sustituido. X es carbociclo o heterociclo de 5 o 6 miembros o biciclo de entre 6 y 12 miembros (preferiblemente, X es  , donde X3 es N y

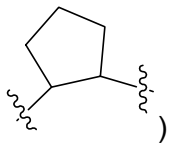
está directamente unido a –L3–D), y está opcionalmente sustituido con uno o más RA. D es un C5-C6carbociclo o heterociclo de 5 o 6 miembros (por ejemplo, fenilo), y está sustituido con J y opcionalmente sustituido con uno o más RA. J es C3-C6carbociclo, heterociclo de entre 3 y 6 miembros, biciclo de entre 6 y 12 miembros, triciclo de entre 10 y 15 miembros o carbociclo/heterociclo de entre 13 y 15 miembros, y J está opcionalmente sustituido con uno o más RA. Preferiblemente, J está sustituido con un C3-C6carbociclo, heterociclo de entre 3 y 6 miembros, biciclo de entre 6 y 12 miembros o carbociclo/heterociclo de entre 7 y 12 miembros, que está opcionalmente sustituido en forma independiente con uno o más sustituyentes seleccionados entre (1) halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C1-C6alquilo, C2-C6alquenilo, C2-C6alquinilo, C1-C6haloalquilo, C2-C6haloalquenilo, C2-C6haloalquinilo, –C(O)ORS o –N(RSRS'), o (2) trimetilsililo, –O–RS, –S–RS, o –C(O)RS; y J también puede estar opcionalmente sustituido con uno o más RA. Preferiblemente, D es  o  , donde J es como se define precedentemente, y cada RN se selecciona en forma independiente entre RD y preferiblemente es hidrógeno o halo como por ejemplo F. L1 y L2 son en forma independiente entre sí un enlace o C1-C6alquileno, y L3 es un enlace, C1-C6alquileno o -C(O)-, y L1, L2, y L3 están opcionalmente sustituidos en forma independiente entre sí con uno o más RL. Preferiblemente, L1, L2, y L3 son un enlace. Y es –LS–C(R1R2)N(R5)–T–RD o –LS–C(R3R4)C(R6R7)–T–RD. Z es –LS–C(R8R9)N(R12)–T–RD o –LS–C(R10R11)C(R13R14)–T–RD. R1 es RC; y R2 y R5, tomados junto con los átomos a los cuales están unidos, forman un anillo heterocíclico de 5 o 6 miembros (por ejemplo, ) o biciclo de entre 6 y 12 miembros (por ejemplo,

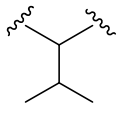

) que está opcionalmente sustituido con uno o más RA; R3 y R6 son en forma independiente entre sí RC, y R4 y R7, tomados junto con los átomos a los cuales están unidos, forman un anillo carbocíclico o heterocíclico de 5 o 6 miembros (por ejemplo,

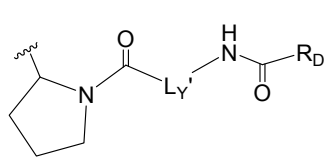
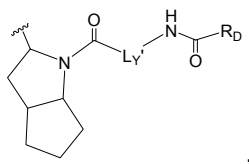

) o biciclo de entre 6 y 12 miembros que está opcionalmente sustituido con uno o más RA. R8 es RC; y R9 y R12, tomados junto con los átomos a los cuales están unidos, forman un anillo heterocíclico de 5 o 6 miembros (por ejemplo,


) o biciclo de entre 6 y 12 miembros (por ejemplo,

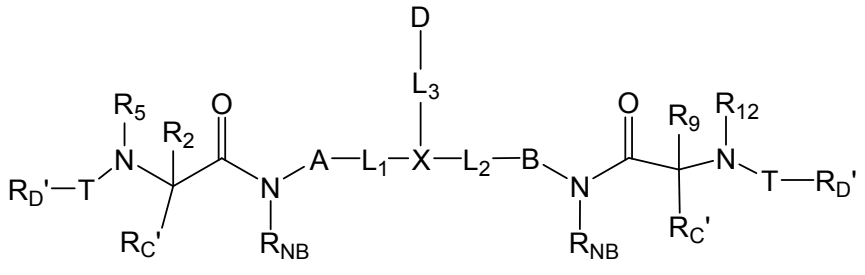

) que está opcionalmente sustituido con uno o más RA; y R10 y R13 son en forma independiente entre sí RC, y R11 y R14, tomados junto con los átomos a los cuales están unidos, forman un anillo carbocíclico o heterocíclico de 5 o 6 miembros (por ejemplo,


) o biciclo de entre 6 y 12 miembros que está opcionalmente sustituido con uno o más RA. T preferiblemente se selecciona en forma independiente en cada caso entre –C(O)–LY'–N(RB)C(O)–LS''– o –C(O)–LY'–N(RB)C(O)O–LS''–. LY' es en forma independiente en cada caso LS' y, preferiblemente, es en forma independiente en cada caso C1-C6alquileno (por ejemplo, -CH2- o


) y está opcionalmente sustituido con uno o más sustituyentes seleccionados entre RL. T también puede seleccionarse, sin que esto

constituya limitación alguna, entre –C(O)–LY'–LS''–, –C(O)–LY'–O–LS''–, –C(O)–LY'–N(RB)–LS''–, o –C(O)–LY'–N(RB)S(O)2–LS''–. En algunos casos, Y y Z son en forma independiente  o  , donde los ejemplos no limitativos de RD incluyen (1) –O–C1-C6alquilo, –O–C2-C6alquenilo, –O–C2-C6alquinilo, C1-C6alquilo, C2-C6alquenilo o C2-C6alquinilo, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C3-C6carbociclo o heterociclo de entre 3 y 6 miembros; o (2) C3-C6carbociclo o heterociclo de entre 3 y 6 miembros cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C1-C6alquilo, C2-C6alquenilo, C2-C6alquinilo, C1-C6haloalquilo, C2-C6haloalquenilo o C2-C6haloalquinilo; y los ejemplos no limitativos de LY' incluyen C1-C6alquileno opcionalmente sustituido con halógeno, hidroxi, mercapto, amino, carboxi, fosfonoxi, –O–C1-C6alquilo, –O–C2-C6alquenilo, –O–C2-C6alquinilo, o carbociclo o heterociclo de entre 3 y 6 miembros, donde dicho carbociclo o heterociclo de entre 3 y 6 miembros está opcionalmente sustituido con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C1-C6alquilo, C2-C6alquenilo, C2-C6alquinilo, C1-C6haloalquilo, C2-C6haloalquenilo o C2-C6haloalquinilo.

En otro aspecto, la presente invención presenta compuestos de Fórmula IA y sales aceptables farmacéuticamente del mismo.



IA

donde:

RNB se selecciona en forma independiente entre RB;

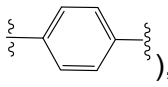
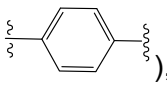
RC' se selecciona en forma independiente entre RC;

RD' se selecciona en forma independiente entre RD;

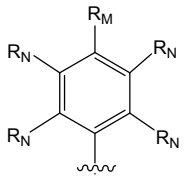
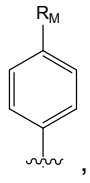
R2 y R5, tomados junto con los átomos a los cuales están unidos, forman un heterociclo de entre 3 y 12 miembros que está opcionalmente sustituido con uno o más RA;

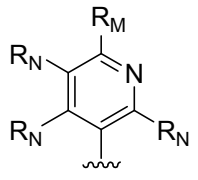
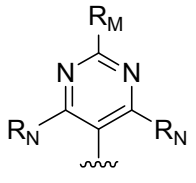
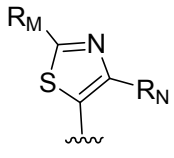
R9 y R12, tomados junto con los átomos a los cuales están unidos, forman un heterociclo de entre 3 y 12 miembros que está opcionalmente sustituido con uno o más RA;

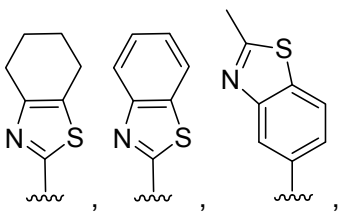
A, B, D, X, L1, L2, L3, T, RA, RB, RC, y RD son como se describe precedentemente en Fórmula I.

En este aspecto, A y B preferiblemente se seleccionan en forma independiente entre C5-C6carbociclo o heterociclo de 5 o 6 miembros, y están opcionalmente sustituidos en forma independiente entre sí con uno o más RA. Más preferiblemente, al menos uno de A y B es fenilo (por ejemplo, ), y está opcionalmente sustituido con uno o más RA. Más preferiblemente, A y B son en forma independiente entre sí fenilo (por ejemplo, ), y están opcionalmente sustituidos en forma independiente entre sí con uno o más RA.

D preferiblemente se selecciona entre C5-C6carbociclo, heterociclo de 5 o 6

miembros, o biciclos de entre 8 y 12 miembros, y está opcionalmente sustituido con uno o más RA. D también puede seleccionarse preferiblemente entre C1-C6alquilo, C2-C6alquenilo o C2-C6alquinilo, y está opcionalmente sustituido con uno o más RL. Más preferiblemente, D es C5-C6carbociclo, heterociclo de 5 o 6 miembros, o biciclos de entre 6 y 12 miembros, y está sustituido con uno o más RM, donde RM es halógeno, nitro, oxo, fosfonoxi, fosfono, tioxo, ciano, o –LS–RE. También preferiblemente, D es fenilo, y está opcionalmente sustituido con uno o más RA. Más preferiblemente, D es fenilo, y está sustituido con uno o más RM, donde RM es como se define precedentemente. Más preferiblemente, D es  o  , donde RM es como se define precedentemente, y cada RN se selecciona en forma independiente entre RD y preferiblemente es hidrógeno. Uno o más RN también puede ser preferiblemente halo como por ejemplo F.

D es también preferiblemente piridinilo, pirimidinilo, o tiazolilo, opcionalmente sustituido con uno o más RA. Más preferiblemente D es piridinilo, pirimidinilo, o tiazolilo, y está sustituido con uno o más RM. Más preferiblemente, D es  ,  , o  , donde RM es como se define precedentemente, y cada RN se selecciona en forma independiente entre RD y preferiblemente es hidrógeno. Uno o más RN también puede ser preferiblemente halo como por ejemplo F. D es también preferiblemente indanilo, 4,5,6,7-tetrahidrobenzo[d]tiazolilo, benzo[d]tiazolilo, o indazolilo, y está opcionalmente sustituido con uno o más RA. Más preferiblemente D es indanilo,

4,5,6,7-tetrahidrobenzo[d]tiazolilo, benzo[d]tiazolilo, indazolilo, o benzo[d][1,3]dioxol-5-ilo, y está sustituido con uno o más RM. Más preferiblemente, D es  , y está opcionalmente sustituido con uno o más RM.

Preferiblemente, RM es halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, ciano; o C1-C6alquilo, C2-C6alquenilo o C2-C6alquinilo, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo o ciano; o C3-C6carbociclo o heterociclo de entre 3 y 6 miembros, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C1-C6alquilo, C2-C6alquenilo, C2-C6alquinilo, C1-C6haloalquilo, C2-C6haloalquenilo o C2-C6haloalquinilo. Más preferiblemente, RM es halógeno, hidroxi, mercapto, amino, carboxi; o C1-C6alquilo, C2-C6alquenilo o C2-C6alquinilo, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino o carboxi. Más preferiblemente, RM es C1-C6alquilo que está opcionalmente sustituido en forma independiente con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino o carboxi.

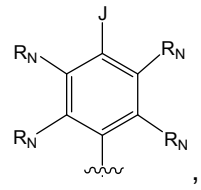
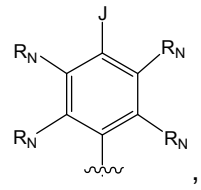
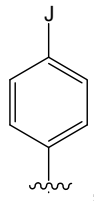
También preferiblemente, RM es halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, o ciano; o RM es –LS–RE, donde LS es una unión o C1-C6alquileno, y RE es –N(RSRS'), –O–RS, –C(O)RS, –C(O)ORS, –C(O)N(RSRS'), –

N(RS)C(O)RS', –N(RS)C(O)ORS', –N(RS)SO2RS', –SO2RS, –SRS, o –P(O)(ORS)2, donde RS y RS' pueden seleccionarse en forma independiente entre sí, por ejemplo, entre (1) hidrógeno o (2) C1-C6alquilo opcionalmente sustituido en cada caso con uno o más halógeno, hidroxi, –O–C1-C6alquilo o heterociclo de entre 3 y 6 miembros; o RM es C1-C6alquilo, C2-C6alquenilo o C2-C6alquinilo, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo o ciano; o RM es C3-C6carbociclo o heterociclo de entre 3 y 6 miembros, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C1-C6alquilo, C2-C6alquenilo, C2-C6alquinilo, C1-C6haloalquilo, C2-C6haloalquenilo, C2-C6haloalquinilo, –C(O)ORS, o –N(RSRS'). Más preferiblemente, RM es halógeno (por ejemplo, fluoro, cloro, bromo, yodo), hidroxi, mercapto, amino, carboxi, o C1-C6alquilo (por ejemplo, metilo, isopropilo, tert-butilo), C2-C6alquenilo o C2-C6alquinilo, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, ciano, o carboxi. Por ejemplo RM es CF3, –C(CF3)2–OH, –C(CH3)2–CN, –C(CH3)2–CH2OH, o –C(CH3)2–CH2NH2. También preferiblemente RM es –LS–RE donde LS es una unión y RE es –N(RSRS'), –O–RS, –N(RS)C(O)ORS', –N(RS)SO2RS', –SO2RS, o –SRS. Por ejemplo donde LS es una unión, RE es –N(C1-C6alquil)2 (por ejemplo, –NMe2); –N(C1-C6alquilen–O–C1-C6alquil)2 (por ejemplo –N(CH2CH2OMe)2); –N(C1-C6alquil)(C1-C6alquilen–O–C1-C6alquilo) (por ejemplo –N(CH3)(CH2CH2OMe)); –O–C1-C6alquilo (por ejemplo, –O–Me, –O–Et, –O–isopropilo, –O–tert-butilo, –O–n-hexilo); –O–C1-C6haloalquilo (por ejemplo, – OCF3, –OCH2CF3); –O–C1-C6alquilen–piperidina (por ejemplo, –O–CH2CH2–1-piperidilo); –N(C1-C6alquil)C(O)OC1-C6alquilo (por ejemplo, –N(CH3)C(O)O–CH2CH(CH3)2), –N(C1-C6alquil)SO2C1-C6alquilo (por ejemplo, –

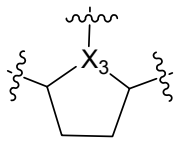
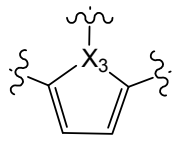
N(CH3)SO2CH3); –SO2C1-C6alquilo (por ejemplo, –SO2Me); –SO2C1-C6haloalquilo (por ejemplo, –SO2CF3); o –S–C1-C6haloalquilo (por ejemplo, SCF3). También preferiblemente RM es –LS–RE donde LS es C1-C6alquileno (por ejemplo, –CH2–, –C(CH3)2–, –C(CH3)2–CH2–) y RE es –O–RS, –C(O)ORS, –N(RS)C(O)ORS', o –P(O)(ORS)2. Por ejemplo RM es –C1-C6alquilen–O–RS (por ejemplo, –C(CH3)2–CH2–OMe); –C1-C6alquilen–C(O)ORS (por ejemplo, –C(CH3)2–C(O)OMe); –C1-C6alquilen–N(RS)C(O)ORS' (por ejemplo, –C(CH3)2–CH2–NHC(O)OCH3); o –C1-C6alquilen–P(O)(ORS)2 (por ejemplo, –CH2–P(O)(OEt)2). También más preferiblemente RM es C3-C6carbociclo o heterociclo de entre 3 y 6 miembros, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C1-C6alquilo, C2-C6alquenilo, C2-C6alquinilo, C1-C6haloalquilo, C2-C6haloalquenilo, C2-C6haloalquinilo, –C(O)ORS, o –N(RSRS'). Por ejemplo RM 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). Más preferiblemente, RM es C1-C6alquilo que está opcionalmente sustituido en forma independiente con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino o carboxi (por ejemplo, tert-butilo, CF3).

Más preferiblemente, D es C5-C6carbociclo, heterociclo de 5 o 6 miembros o biciclo de entre 6 y 12 miembros y está sustituido con J y opcionalmente sustituido con uno o más RA, donde J es C3-C6carbociclo, heterociclo de entre 3 y 6 miembros o biciclo de entre 6 y 12 miembros y está opcionalmente sustituido con uno o más RA. Preferiblemente, J está sustituido con un C3-C6carbociclo o heterociclo de entre 3 y 6 miembros, donde dicho C3-C6carbociclo o heterociclo de entre 3 y 6 miembros está

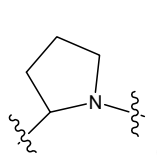
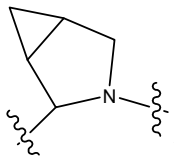
opcionalmente sustituido en forma independiente con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C1-C6alquilo, C2-C6alquenilo, C2-C6alquinilo, C1-C6haloalquilo, C2-C6haloalquenilo, C2-C6haloalquinilo, C(O)ORS o –N(RSRS'), y J también puede estar opcionalmente sustituido con uno o más RA. También preferiblemente, D es C5-C6carbociclo o heterociclo de 5 o 6 miembros y está sustituido con J y opcionalmente sustituido con uno o más RA, y J es C3-C6carbociclo o heterociclo de entre 3 y 6 miembros y está opcionalmente sustituido con uno o más RA, y preferiblemente, J está sustituido con al menos un C3-C6carbociclo o heterociclo de entre 3 y 6 miembros que está opcionalmente sustituido en forma independiente con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C1-C6alquilo, C2-C6alquenilo, C2-C6alquinilo, C1-C6haloalquilo, C2-C6haloalquenilo, C2-C6haloalquinilo, C(O)ORS o –N(RSRS'). También preferiblemente, D es C5-C6carbociclo o heterociclo de 5 o 6 miembros y está sustituido con J y opcionalmente sustituido con uno o más RA, y J es biciclo de entre 6 y 12 miembros (por ejemplo, un biciclo fusionado, en puente o espiro de entre 7 y 12 miembros que comprende un átomo del anillo nitrógeno a través del cual J se enlaza por unión covalente con D) y está opcionalmente sustituido con uno o más RA. Más preferiblemente, D es fenilo y está sustituido con J y opcionalmente sustituido con uno o más RA, y J es C3-C6carbociclo, heterociclo de entre 3 y 6 miembros o biciclo de entre 6 y 12 miembros y está opcionalmente sustituido con uno o más RA, y preferiblemente J está sustituido con al menos un C3-C6carbociclo o heterociclo de entre 3 y 6 miembros que está opcionalmente sustituido en forma independiente con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C1-C6alquilo, C2-C6alquenilo, C2-C6alquinilo, C1-C6haloalquilo, C2-C6haloalquenilo, C2-C6haloalquinilo, C(O)ORS o –N(RSRS'). Más

preferiblemente, D es  , donde cada RN se selecciona en forma independiente entre RD y preferiblemente es hidrógeno o halógeno, y J es C3-C6carbociclo, heterociclo de entre 3 y 6 miembros o biciclo de entre 6 y 12 miembros y está opcionalmente sustituido con uno o más RA, y preferiblemente J está sustituido con al menos un C3-C6carbociclo o heterociclo de entre 3 y 6 miembros que está opcionalmente sustituido en forma independiente con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C1-C6alquilo, C2-C6alquenilo, C2-C6alquinilo, C1-C6haloalquilo, C2-C6haloalquenilo, C2-C6haloalquinilo, C(O)ORS o –N(RSRS'). También preferiblemente, D es  , donde cada RN se selecciona en forma independiente entre RD y preferiblemente es hidrógeno o halógeno, y J es C3-C6carbociclo o heterociclo de entre 3 y 6 miembros y está sustituido con un C3-C6carbociclo o heterociclo de entre 3 y 6 miembros que está opcionalmente sustituido en forma independiente con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C1-C6alquilo, C2-C6alquenilo, C2-C6alquinilo, C1-C6haloalquilo, C2-C6haloalquenilo, C2-C6haloalquinilo, C(O)ORS o –N(RSRS'), y J también puede estar opcionalmente sustituido con uno o más RA. También preferiblemente, D es  , y J es C3-C6carbociclo o heterociclo de entre 3 y 6 miembros y está opcionalmente sustituido con uno o más RA, y preferiblemente J está sustituido con al menos un C3-C6carbociclo o

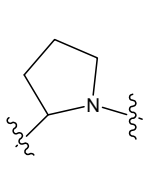
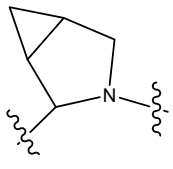
heterociclo de entre 3 y 6 miembros que está opcionalmente sustituido en forma independiente con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C1-C6alquilo, C2-C6alquenilo, C2-C6alquinilo, C1-C6haloalquilo, C2-C6haloalquenilo, C2-C6haloalquinilo, C(O)ORS o –N(RSRS').

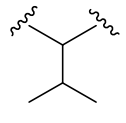
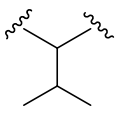
X preferiblemente es C5-C6carbociclo, heterociclo de 5 o 6 miembros, o biciclos de entre 6 y 12 miembros (por ejemplo,  o  , donde X3 es N y está directamente unido a –L3–D), y está opcionalmente sustituido con uno o más RA o RF. Los ejemplos no limitativos de X se describen precedentemente.

L1 y L2 son preferiblemente en forma independiente un enlace o C1-C6alquileno, L3 preferiblemente se selecciona entre un enlace, C1-C6alquileno o –C(O)–, y L1, L2, y L3 están opcionalmente sustituidos en forma independiente entre sí con uno o más RL. Más preferiblemente, L1, L2 y L3 son en forma independiente entre sí un enlace o C1-C6alquileno (por ejemplo, –CH2– o –CH2CH2–), y están opcionalmente sustituidos en forma independiente entre sí con uno o más RL. Más preferiblemente, L1, L2 y L3 son un enlace.

R2 y R5, tomados junto con los átomos a los cuales están unidos, preferiblemente forman un heterociclo de 5 o 6 miembros o biciclo de entre 6 y 12 miembros (por ejemplo,  o ), que está opcionalmente sustituido con uno o más RA.

R9 y R12, tomados junto con los átomos a los cuales están unidos, preferiblemente forman un heterociclo de 5 o 6 miembros o biciclo de entre 6 y 12

miembros (por ejemplo,  o ), que está opcionalmente sustituido con uno o más RA.

-T-RD' puede seleccionarse en forma independiente en cada caso, sin que esto constituya limitación alguna, entre –C(O)–LY'–, –C(O)O–LY'–RD', –C(O)–LY'–N(RB)C(O)–LS''–RD', –C(O)–LY'–N(RB)C(O)O–LS''–RD', –N(RB)C(O)–LY'–N(RB)C(O)–LS''–RD', –N(RB)C(O)–LY'—N(RB)C(O)O–LS''–RD', o –N(RB)C(O)–LY'—N(RB)–LS''–RD', donde LY' es en forma independiente en cada caso LS' y, preferiblemente, es en forma independiente en cada caso C1-C6alquileno (por ejemplo, -CH2- o ) y está opcionalmente sustituido con uno o más sustituyentes seleccionados entre RL. Preferiblemente, -T-RD' se selecciona en forma independiente en cada caso entre –C(O)–LY'–M'–LS''–RD' o –N(RB)C(O)–LY'–M'–LS''–RD'. Más preferiblemente, -T-RD' se selecciona en forma independiente en cada caso entre –C(O)–LY'–N(RB)C(O)–LS''–RD' o –C(O)–LY'–N(RB)C(O)O–LS''–RD'. Más preferiblemente, -T-RD' se selecciona en forma independiente en cada caso entre –C(O)–LY'–N(RB)C(O)–RD' o –C(O)–LY'–N(RB)C(O)O–RD', donde LY' preferiblemente es en forma independiente en cada caso C1-C6alquileno (por ejemplo, -CH2- o ) y está opcionalmente sustituido con uno o más sustituyentes seleccionados entre RL.

RNB y RC' son preferiblemente hidrógeno, y RD' preferiblemente se selecciona en forma independiente en cada caso entre RE. Más preferiblemente, RD' se selecciona en forma independiente en cada caso entre C1-C6alquilo, C2-C6alquenilo o C2-C6alquinilo, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C3-C6carbociclo o

heterociclo de entre 3 y 6 miembros; o C3-C6carbociclo o heterociclo de entre 3 y 6 miembros, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C1-C6alquilo, C2-C6alquenilo, C2-C6alquinilo, C1-C6haloalquilo, C2-C6haloalquenilo o C2-C6haloalquinilo.

RA preferiblemente es halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, ciano; o C1-C6alquilo, C2-C6alquenilo o C2-C6alquinilo, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo o ciano; o C3-C6carbociclo o heterociclo de entre 3 y 6 miembros, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C1-C6alquilo, C2-C6alquenilo, C2-C6alquinilo, C1-C6haloalquilo, C2-C6haloalquenilo o C2-C6haloalquinilo; o –LA–O–RS, –LA–S–RS, –LA–C(O)RS, –LA–OC(O)RS, –LA–C(O)ORS, –LA–N(RSRS’), –LA–S(O)RS, –LA–SO2RS, –LA–C(O)N(RSRS’), –LA–N(RS)C(O)RS’, –LA–N(RS)C(O)N(RS’RS’’), –LA–N(RS)SO2RS’, –LA–SO2N(RSRS’), –LA–N(RS)SO2N(RS’RS’’), –LA–N(RS)S(O)N(RS’RS’’), –LA–OS(O)–RS, –LA–OS(O)2–RS, –LA–S(O)2ORS, –LA–S(O)ORS, –LA–OC(O)ORS, –LA–N(RS)C(O)ORS’, –LA–OC(O)N(RSRS’), –LA–N(RS)S(O)–RS’, –LA–S(O)N(RSRS’) o –LA–C(O)N(RS)C(O)–RS’, donde LA es un enlace, C1-C6alquileno, C2-C6alquenileno o C2-C6alquinileno.

Más preferiblemente, RA es halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, ciano; o C1-C6alquilo, C2-C6alquenilo o C2-C6alquinilo, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo o ciano; o C3-C6carbociclo o

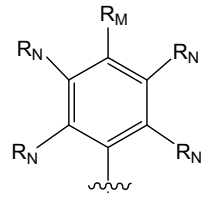
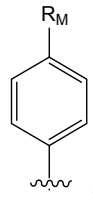
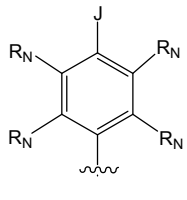
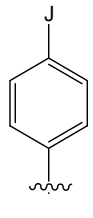
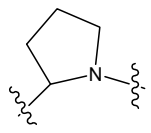
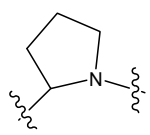
heterociclo de entre 3 y 6 miembros, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C1-C6alquilo, C2-C6alquenilo, C2-C6alquinilo, C1-C6haloalquilo, C2-C6haloalquenilo o C2-C6haloalquinilo.

Más preferiblemente, RA es halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, ciano; o C1-C6alquilo, C2-C6alquenilo o C2-C6alquinilo, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo o ciano.

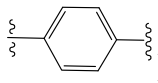
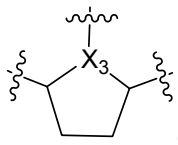
LS, LS' y LS'' preferiblemente se seleccionan en forma independiente entre sí en cada caso entre un enlace; o C1-C6alquileno, C2-C6alquenileno o C2-C6alquinileno.

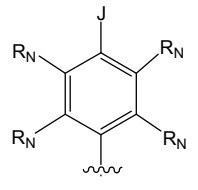
A y B pueden ser iguales o diferentes. De la misma manera, L1 y L2 pueden ser iguales o diferentes.

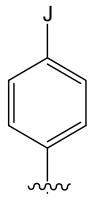
En una forma de realización de este aspecto, A y B son en forma independiente entre sí fenilo, y están opcionalmente sustituidos en forma independiente entre sí con uno o más RA; D es fenilo, y está opcionalmente sustituido con uno o más RA, o está sustituido con J y opcionalmente sustituido con uno o más RA, donde J es C3-C6carbociclo, heterociclo de entre 3 y 6 miembros o biciclo de entre 6 y 12 miembros y está opcionalmente sustituido con uno o más RA. Preferiblemente, J está sustituido con un C3-C6carbociclo o heterociclo de entre 3 y 6 miembros que está opcionalmente sustituido en forma independiente con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C1-C6alquilo, C2-C6alquenilo, C2-C6alquinilo, C1-C6haloalquilo, C2-C6haloalquenilo, C2-C6haloalquinilo, C(O)ORS o –N(RSRS'), y J también puede estar

opcionalmente sustituido con uno o más RA. Preferiblemente, D es  o  , donde RM y RN son como se definen precedentemente. También preferiblemente, D es  o  , donde J y RN son como se definen precedentemente. L1 y L2 son en forma independiente entre sí un enlace o C1-C6alquileno, y L3 es un enlace, C1-C6alquileno o -C(O)-, y L1, L2, y L3 están opcionalmente sustituidos en forma independiente entre sí con uno o más RL. Preferiblemente, L1, L2, y L3 son un enlace. -T-RD' se selecciona en forma independiente en cada caso entre –C(O)–LY'–N(RB)C(O)–LS''–RD' o –C(O)–LY'–N(RB)C(O)O–LS''–RD', donde LY' es C1-C6alquileno (por ejemplo, -CH2-) y está opcionalmente sustituido con uno o más sustituyentes seleccionados entre RL, y LS'' preferiblemente es un enlace. –T-RD' también puede seleccionarse, sin que esto constituya limitación alguna, entre –C(O)–LY'–LS''–RD', –C(O)–LY'–O–LS''–RD', –C(O)–LY'–N(RB)–LS''–RD', o –C(O)–LY'–N(RB)S(O)2–LS''–RD'. Preferiblemente, R2 y R5, tomados junto con los átomos a los cuales están unidos, forman  que está opcionalmente sustituido con uno o más RA; R9 y R12, tomados junto con los átomos a los cuales están unidos, forman  que está opcionalmente sustituido con uno o más RA.

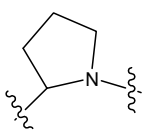
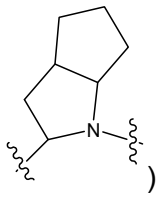
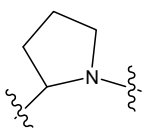
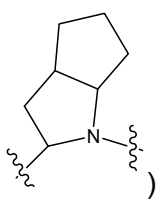
En otra forma de realización de este aspecto, A y B son en forma independiente

entre sí fenilo (por ejemplo, ), y están opcionalmente sustituidos en forma independiente entre sí con uno o más RA (preferiblemente, A y B están sustituidos en forma independiente entre sí con al menos un halo como por ejemplo F). X es 

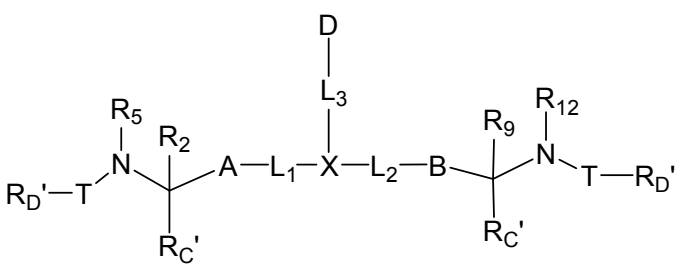
, donde X3 es N y está directamente unido a –L3–D, y X está opcionalmente sustituido con uno o más RA o RF. D es fenilo, y está sustituido con J y opcionalmente sustituido con uno o más RA. J es C3-C6carbociclo, heterociclo de entre 3 y 6 miembros, biciclo de entre 6 y 12 miembros, triciclo de entre 10 y 15 miembros o carbociclo/heterociclo de entre 13 y 15 miembros, y J está opcionalmente sustituido con uno o más RA. Preferiblemente, J está sustituido con un C3-C6carbociclo, heterociclo de entre 3 y 6 miembros, biciclo de entre 6 y 12 miembros o carbociclo/heterociclo de entre 7 y 12 miembros, que está opcionalmente sustituido en forma independiente con uno o más sustituyentes seleccionados entre (1) halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C1-C6alquilo, C2-C6alquenilo, C2-C6alquinilo, C1-C6haloalquilo, C2-C6haloalquenilo, C2-C6haloalquinilo, –C(O)ORS o –N(RSRS’), o (2) trimetilsililo, –O–RS, –S–RS o –C(O)RS; y J también puede estar opcionalmente sustituido con uno o más RA. Preferiblemente, D es 

o 

, donde J es como se define precedentemente, y cada RN se selecciona en forma independiente entre RD y preferiblemente es hidrógeno o halo como por ejemplo F. L1 y L2 son en forma independiente entre sí un enlace o C1-C6alquileno, y L3 es un enlace, C1-C6alquileno o -C(O)-, y L1, L2, y L3 están opcionalmente sustituidos en forma

independiente entre sí con uno o más RL. Preferiblemente, L1, L2, y L3 son un enlace. -T-RD' se selecciona en forma independiente en cada caso entre –C(O)–LY'–N(RB)C(O)–LS''–RD' o –C(O)–LY'–N(RB)C(O)O–LS''–RD', donde LY' es C1-C6alquileno (por ejemplo, -CH2-) y está opcionalmente sustituido con uno o más sustituyentes seleccionados entre RL, y LS'' preferiblemente es un enlace. –T-RD' también puede seleccionarse, sin que esto constituya limitación alguna, entre –C(O)–LY'–LS''–RD', –C(O)–LY'–O–LS''–RD', –C(O)–LY'–N(RB)–LS''–RD', o –C(O)–LY'–N(RB)S(O)2–LS''–RD'. R2 y R5, tomados junto con los átomos a los cuales están unidos, forman un anillo heterocíclico de 5 o 6 miembros (por ejemplo, ) o biciclo de entre 6 y 12 miembros (por ejemplo, ) que está opcionalmente sustituido con uno o más RA; y R9 y R12, tomados junto con los átomos a los cuales están unidos, forman un anillo heterocíclico de 5 o 6 miembros (por ejemplo, ) o biciclo de entre 6 y 12 miembros (por ejemplo, ) que está opcionalmente sustituido con uno o más RA.

En aun otro aspecto, la presente invención presenta compuestos de Fórmula IB y sales aceptables farmacéuticamente del mismo:



IB

donde:

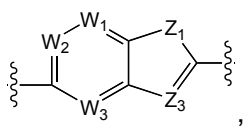
RC’ se selecciona en forma independiente entre RC;

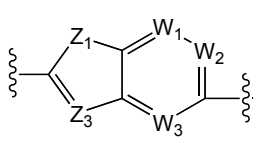
RD’ se selecciona en forma independiente entre RD;

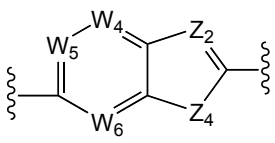
R2 y R5, tomados junto con los átomos a los cuales están unidos, forman un heterociclo de entre 3 y 12 miembros que está opcionalmente sustituido con uno o más RA;

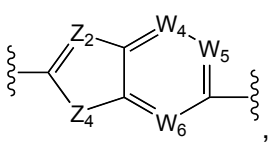
R9 y R12, tomados junto con los átomos a los cuales están unidos, forman un heterociclo de entre 3 y 12 miembros que está opcionalmente sustituido con uno o más RA;

A, B, D, X, L1, L2, L3, T, RA, RC, y RD son como se describe precedentemente en Fórmula I.

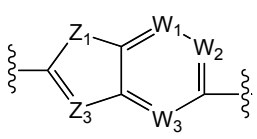
En este aspecto, A y B preferiblemente se seleccionan en forma independiente entre biciclos de entre 8 y 12 miembros como por ejemplo 

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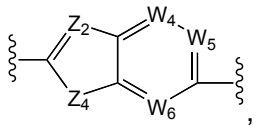
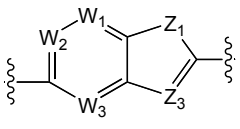
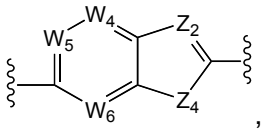
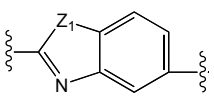
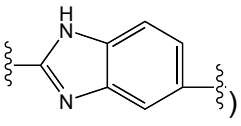
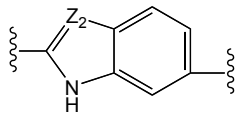
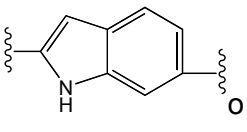
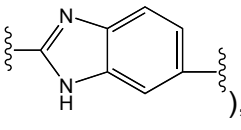
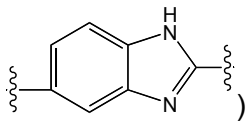
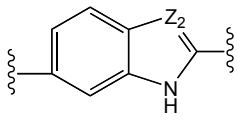
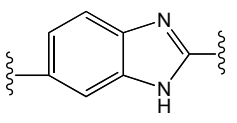
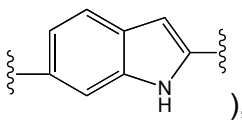
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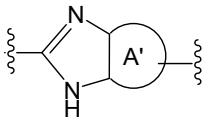
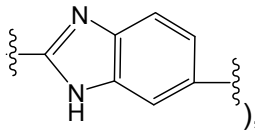
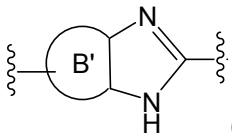
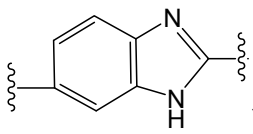
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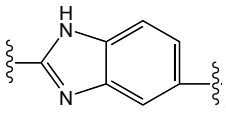
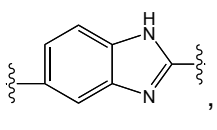
, donde Z1 se selecciona en forma independiente en cada caso entre O, S, NH o CH2, Z2 se selecciona en forma independiente en cada caso entre N o CH, Z3 se selecciona en forma independiente en cada caso entre N o CH, Z4 se selecciona en forma independiente en cada caso entre O, S, NH o CH2, y W1, W2, W3, W4, W5 y W6 se seleccionan en forma independiente entre sí en cada caso entre CH o N. A y B están opcionalmente sustituidos en forma independiente entre sí con uno o más RA.

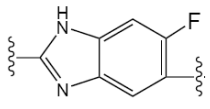
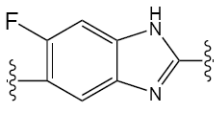
Más preferiblemente, A se selecciona entre 

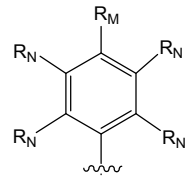
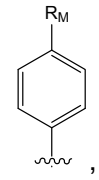
o


, y está opcionalmente sustituido con uno o más RA; B se selecciona entre  o  , y está opcionalmente sustituido con uno o más RA, donde Z1, Z2, Z3, Z4, W1, W2, W3, W4, W5, W6 son como se definen precedentemente. Preferiblemente, Z3 es N y Z4 es NH. Por ejemplo, A se puede seleccionar entre  (por ejemplo, ) o  (por ejemplo,  o ), y está opcionalmente sustituido con uno o más RA; y B se puede seleccionar entre (por ejemplo, ) o  (por ejemplo,  o ), y está opcionalmente sustituido con uno o más RA.

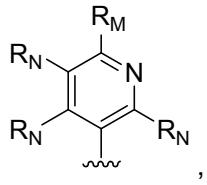
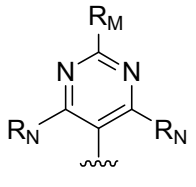
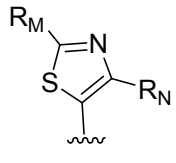
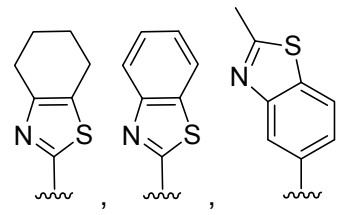
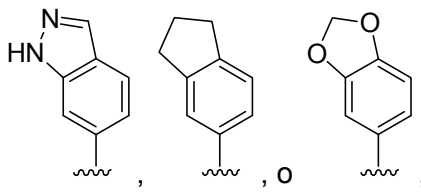
También preferiblemente, A es  (por ejemplo, ), y B es  (por ejemplo, ), donde A’ y B’ se seleccionan en forma independiente entre C5-C6carbociclo o heterociclo de 5 o 6 miembros, y A y B están opcionalmente sustituidos en forma independiente con uno o más RA.

Más preferiblemente, A es  , B es  , y A y B están

sustituidos con uno o más halógeno, como por ejemplo F o Cl. Cuando A y/o B son benzimidazol sustituido con halo (por ejemplo, A es  y B es ), los compuestos de Fórmula IB pueden tener propiedades farmacocinéticas significativamente mejoradas así como también una actividad inhibitoria mejorada contra ciertas mutaciones de HCV genotipo 1a, en comparación con los mismos compuestos pero con benzimidazol no sustituido.

D preferiblemente se selecciona entre C5-C6carbociclo, heterociclo de 5 o 6 miembros, o biciclos de entre 6 y 12 miembros, y está opcionalmente sustituido con uno o más RA. D también puede seleccionarse preferiblemente entre C1-C6alquilo, C2-C6alquenilo o C2-C6alquinilo, y está opcionalmente sustituido con uno o más sustituyentes seleccionados entre RL. Más preferiblemente, D es C5-C6carbociclo, heterociclo de 5 o 6 miembros, o biciclos de entre 6 y 12 miembros, y está sustituido con uno o más RM, donde RM es halógeno, nitro, oxo, fosfonoxi, fosfono, tioxo, ciano, o –LS–RE. También preferiblemente, D es fenilo, y está opcionalmente sustituido con uno o más RA. Más preferiblemente, D es fenilo, y está sustituido con uno o más RM, donde RM es como se define precedentemente. Más preferiblemente, D es  o  , donde RM es como se define precedentemente, y cada RN se selecciona en forma independiente entre RD y preferiblemente es hidrógeno. Uno o más RN también puede ser preferiblemente halo como por ejemplo F.

D es también preferiblemente piridinilo, pirimidinilo, o tiazolilo, opcionalmente sustituido con uno o más RA. Más preferiblemente D es piridinilo, pirimidinilo, o tiazolilo, y

está sustituido con uno o más RM. Más preferiblemente, D es  ,  , o  , donde RM es como se define precedentemente, y cada RN se selecciona en forma independiente entre RD y preferiblemente es hidrógeno. Uno o más RN también puede ser preferiblemente halo como por ejemplo F. D es también preferiblemente indanilo, 4,5,6,7-tetrahidrobenzo[d]tiazolilo, benzo[d]tiazolilo, o indazolilo, y está opcionalmente sustituido con uno o más RA. Más preferiblemente D es indanilo, 4,5,6,7-tetrahidrobenzo[d]tiazolilo, benzo[d]tiazolilo, indazolilo, o benzo[d][1,3]dioxol-5-ilo, y está sustituido con uno o más RM. Más preferiblemente, D es  ,  , y está opcionalmente sustituido con uno o más RM.

Preferiblemente, RM es halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, ciano; o C1-C6alquilo, C2-C6alquenilo o C2-C6alquinilo, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo o ciano; o C3-C6carbociclo o heterociclo de entre 3 y 6 miembros, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C1-C6alquilo, C2-C6alquenilo, C2-C6alquinilo, C1-C6haloalquilo, C2-C6haloalquenilo o C2-

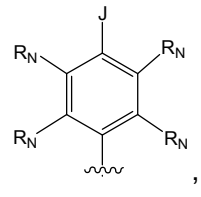
C6haloalquinilo. Más preferiblemente, RM es halógeno, hidroxi, mercapto, amino, carboxi; o C1-C6alquilo, C2-C6alquenilo o C2-C6alquinilo, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino o carboxi. Más preferiblemente, RM es C1-C6alquilo el cual está opcionalmente sustituido con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino o carboxi.

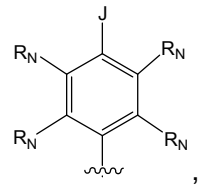
También preferiblemente, RM es halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, o ciano; o RM es –LS–RE, donde LS es una unión o C1-C6alquileno, y RE es –N(RSRS'), –O–RS, –C(O)RS, –C(O)ORS, –C(O)N(RSRS'), –N(RS)C(O)RS', –N(RS)C(O)ORS', –N(RS)SO2RS', –SO2RS, –SRS, o –P(O)(ORS)2, donde RS y RS' pueden seleccionarse en forma independiente entre sí, por ejemplo, entre (1) hidrógeno o (2) C1-C6alquilo opcionalmente sustituido en cada caso con uno o más halógeno, hidroxi, –O–C1-C6alquilo o heterociclo de entre 3 y 6 miembros; o RM es C1-C6alquilo, C2-C6alquenilo o C2-C6alquinilo, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo o ciano; o RM es C3-C6carbociclo o heterociclo de entre 3 y 6 miembros, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C1-C6alquilo, C2-C6alquenilo, C2-C6alquinilo, C1-C6haloalquilo, C2-C6haloalquenilo, C2-C6haloalquinilo, –C(O)ORS, o –N(RSRS'). Más preferiblemente, RM es halógeno (por ejemplo, fluoro, cloro, bromo, yodo), hidroxi, mercapto, amino, carboxi, o C1-C6alquilo (por ejemplo, metilo, isopropilo, tert-butilo), C2-C6alquenilo o C2-C6alquinilo, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, ciano, o carboxi. Por ejemplo RM es CF3, –C(CF3)2–OH, –C(CH3)2–CN, –C(CH3)2–CH2OH, o –

C(CH3)2–CH2NH2. También preferiblemente RM es –LS–RE donde LS es una unión y RE es –N(RSRS'), –O–RS, –N(RS)C(O)ORS', –N(RS)SO2RS', –SO2RS, o –SRS. Por ejemplo donde LS es una unión, RE es –N(C1-C6alquil)2 (por ejemplo, –NMe2); –N(C1-C6alquilen–O–C1-C6alquil)2 (por ejemplo –N(CH2CH2OMe)2); –N(C1-C6alquil)(C1-C6alquilen–O–C1-C6alquilo) (por ejemplo –N(CH3)(CH2CH2OMe)); –O–C1-C6alquilo (por ejemplo, –O–Me, –O–Et, –O–isopropilo, –O–tert-butilo, –O–n-hexilo); –O–C1-C6haloalquilo (por ejemplo, – OCF3, –OCH2CF3); –O–C1-C6alquilen–piperidina (por ejemplo, –O–CH2CH2–1-piperidilo); –N(C1-C6alquil)C(O)OC1-C6alquilo (por ejemplo, –N(CH3)C(O)O–CH2CH(CH3)2), –N(C1-C6alquil)SO2C1-C6alquilo (por ejemplo, –N(CH3)SO2CH3); –SO2C1-C6alquilo (por ejemplo, –SO2Me); –SO2C1-C6haloalquilo (por ejemplo, –SO2CF3); o –S–C1-C6haloalquilo (por ejemplo, SCF3). También preferiblemente RM es –LS–RE donde LS es C1-C6alquileno (por ejemplo, –CH2–, –C(CH3)2–, –C(CH3)2–CH2–) y RE es –O–RS, –C(O)ORS, –N(RS)C(O)ORS', o –P(O)(ORS)2. Por ejemplo RM es –C1-C6alquilen–O–RS (por ejemplo, –C(CH3)2–CH2–OMe); –C1-C6alquilen–C(O)ORS (por ejemplo, –C(CH3)2–C(O)OMe); –C1-C6alquilen–N(RS)C(O)ORS' (por ejemplo, –C(CH3)2–CH2–NHC(O)OCH3); o –C1-C6alquilen–P(O)(ORS)2 (por ejemplo, –CH2–P(O)(OEt)2). También más preferiblemente RM es C3-C6carbociclo o heterociclo de entre 3 y 6 miembros, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C1-C6alquilo, C2-C6alquenilo, C2-C6alquinilo, C1-C6haloalquilo, C2-C6haloalquenilo, C2-C6haloalquinilo, –C(O)ORS, o –N(RSRS'). Por ejemplo RM 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). Más preferiblemente, RM es C1-

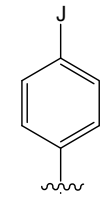
C6alquilo el cual está opcionalmente sustituido con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino o carboxi (por ejemplo, tert-butilo, CF3).

Más preferiblemente, D es C5-C6carbociclo, heterociclo de 5 o 6 miembros o biciclo de entre 6 y 12 miembros y está sustituido con J y opcionalmente sustituido con uno o más RA, donde J es C3-C6carbociclo, heterociclo de entre 3 y 6 miembros o biciclo de entre 6 y 12 miembros y está opcionalmente sustituido con uno o más RA. Preferiblemente, J está sustituido con un C3-C6carbociclo o heterociclo de entre 3 y 6 miembros, donde dicho C3-C6carbociclo o heterociclo de entre 3 y 6 miembros está opcionalmente sustituido en forma independiente con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C1-C6alquilo, C2-C6alquenilo, C2-C6alquinilo, C1-C6haloalquilo, C2-C6haloalquenilo, C2-C6haloalquinilo, C(O)ORS o –N(RSRS'), y J también puede estar opcionalmente sustituido con uno o más RA. También preferiblemente, D es C5-C6carbociclo o heterociclo de 5 o 6 miembros y está sustituido con J y opcionalmente sustituido con uno o más RA, y J es C3-C6carbociclo o heterociclo de entre 3 y 6 miembros y está opcionalmente sustituido con uno o más RA, y preferiblemente, J está sustituido con al menos un C3-C6carbociclo o heterociclo de entre 3 y 6 miembros que está opcionalmente sustituido en forma independiente con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C1-C6alquilo, C2-C6alquenilo, C2-C6alquinilo, C1-C6haloalquilo, C2-C6haloalquenilo, C2-C6haloalquinilo, C(O)ORS o –N(RSRS'). También preferiblemente, D es C5-C6carbociclo o heterociclo de 5 o 6 miembros y está sustituido con J y opcionalmente sustituido con uno o más RA, y J es biciclo de entre 6 y 12 miembros (por ejemplo, un biciclo fusionado, en puente o espiro de entre 7 y 12 miembros que comprende un átomo del anillo nitrógeno a través del cual J se enlaza por unión covalente con D) y está opcionalmente sustituido con uno o más RA. Más

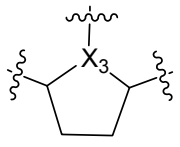
preferiblemente, D es fenilo y está sustituido con J y opcionalmente sustituido con uno o más RA, y J es C3-C6carbociclo, heterociclo de entre 3 y 6 miembros o biciclo de entre 6 y 12 miembros y está opcionalmente sustituido con uno o más RA, y preferiblemente J está sustituido con al menos un C3-C6carbociclo o heterociclo de entre 3 y 6 miembros que está opcionalmente sustituido en forma independiente con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C1-C6alquilo, C2-C6alquenilo, C2-C6alquinilo, C1-C6haloalquilo, C2-C6haloalquenilo, C2-C6haloalquinilo, C(O)ORS o –N(RSRS'). Más preferiblemente, D es 

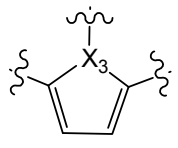
, donde cada RN se selecciona en forma independiente entre RD y preferiblemente es hidrógeno o halógeno, y J es C3-C6carbociclo, heterociclo de entre 3 y 6 miembros o biciclo de entre 6 y 12 miembros y está opcionalmente sustituido con uno o más RA, y preferiblemente J está sustituido con al menos un C3-C6carbociclo o heterociclo de entre 3 y 6 miembros que está opcionalmente sustituido en forma independiente con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C1-C6alquilo, C2-C6alquenilo, C2-C6alquinilo, C1-C6haloalquilo, C2-C6haloalquenilo, C2-C6haloalquinilo, C(O)ORS o –N(RSRS'). También preferiblemente, D es 

, donde cada RN se selecciona en forma independiente entre RD y preferiblemente es hidrógeno o halógeno, y J es C3-C6carbociclo o heterociclo de entre 3 y 6 miembros y está sustituido con un C3-C6carbociclo o heterociclo de entre 3 y 6 miembros que está opcionalmente sustituido en forma independiente con uno o más sustituyentes seleccionados entre halógeno, hidroxi,

mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C1-C6alquilo, C2-C6alquenilo, C2-C6alquinilo, C1-C6haloalquilo, C2-C6haloalquenilo, C2-C6haloalquinilo, C(O)ORS o –N(RSRS'), y J también puede estar opcionalmente sustituido con uno o más RA. También preferiblemente, D es 

, y J es C3-C6carbociclo o heterociclo de entre 3 y 6 miembros y está opcionalmente sustituido con uno o más RA, y preferiblemente J está sustituido con al menos un C3-C6carbociclo o heterociclo de entre 3 y 6 miembros que está opcionalmente sustituido en forma independiente con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C1-C6alquilo, C2-C6alquenilo, C2-C6alquinilo, C1-C6haloalquilo, C2-C6haloalquenilo, C2-C6haloalquinilo, C(O)ORS o –N(RSRS').

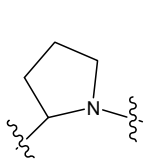
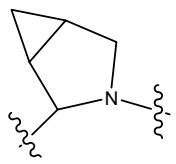
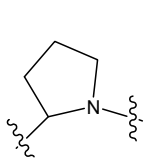
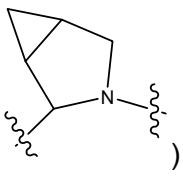
X preferiblemente es C5-C6carbociclo, heterociclo de 5 o 6 miembros, o biciclos de entre 6 y 12 miembros (por ejemplo, 

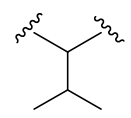
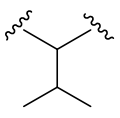
o 

, donde X3 es N y está directamente unido a –L3–D), y está opcionalmente sustituido con uno o más RA o RF. Los ejemplos no limitativos de X se describen precedentemente.

L1 y L2 son preferiblemente en forma independiente un enlace o C1-C6alquileno, L3 preferiblemente se selecciona entre un enlace, C1-C6alquileno o –C(O)–, y L1, L2, y L3 están opcionalmente sustituidos en forma independiente entre sí con uno o más RL. Más preferiblemente, L1, L2 y L3 son en forma independiente entre sí un enlace o C1-C6alquileno (por ejemplo, –CH2– o –CH2CH2–), y están opcionalmente sustituidos en forma independiente entre sí con uno o más RL. Más preferiblemente, L1, L2 y L3 son un enlace.

R2 y R5, tomados junto con los átomos a los cuales están unidos, preferiblemente

forman un heterociclo de 5 o 6 miembros o biciclo de entre 6 y 12 miembros (por ejemplo,  o ) que está opcionalmente sustituido con uno o más RA. R9 y R12, tomados junto con los átomos a los cuales están unidos, preferiblemente forman un heterociclo de 5 o 6 miembros o biciclo de entre 6 y 12 miembros (por ejemplo,  o ) que está opcionalmente sustituido con uno o más RA.

-T-RD' puede seleccionarse en forma independiente en cada caso, sin que esto constituya limitación alguna, entre –C(O)–LY'–RD', –C(O)O–LY'–RD', –C(O)–LY'–N(RB)C(O)–LS''–RD', –C(O)–LY'–N(RB)C(O)O–LS''–RD', –N(RB)C(O)–LY'–N(RB)C(O)–LS''–RD', –N(RB)C(O)–LY'—N(RB)C(O)O–LS''–RD', o –N(RB)C(O)–LY'—N(RB)–LS''–RD', donde LY' es en forma independiente en cada caso LS' y, preferiblemente, es en forma independiente en cada caso C1-C6alquileno (por ejemplo, -CH2- o ) y está opcionalmente sustituido con uno o más sustituyentes seleccionados entre RL. Preferiblemente, -T-RD' se selecciona en forma independiente en cada caso entre –C(O)–LY'–M'–LS''–RD' o –N(RB)C(O)–LY'–M'–LS''–RD'. Más preferiblemente, -T-RD' se selecciona en forma independiente en cada caso entre –C(O)–LY'–N(RB)C(O)–LS''–RD' o –C(O)–LY'–N(RB)C(O)O–LS''–RD'. Más preferiblemente, -T-RD' se selecciona en forma independiente en cada caso entre –C(O)–LY'–N(RB)C(O)–RD' o –C(O)–LY'–N(RB)C(O)O–RD', donde LY' preferiblemente es en forma independiente en cada caso C1-C6alquileno (por ejemplo, -CH2- o ) y está opcionalmente sustituido con uno o más sustituyentes seleccionados entre RL.

RC' es preferiblemente hidrógeno, y RD' preferiblemente se selecciona en forma

independiente en cada caso entre RE. Más preferiblemente, RD' se selecciona en forma independiente en cada caso entre C1-C6alquilo, C2-C6alquenilo o C2-C6alquinilo, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C3-C6carbociclo o heterociclo de entre 3 y 6 miembros; o C3-C6carbociclo o heterociclo de entre 3 y 6 miembros, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C1-C6alquilo, C2-C6alquenilo, C2-C6alquinilo, C1-C6haloalquilo, C2-C6haloalquenilo o C2-C6haloalquinilo.

RA preferiblemente es halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, ciano; o C1-C6alquilo, C2-C6alquenilo o C2-C6alquinilo, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo o ciano; o C3-C6carbociclo o heterociclo de entre 3 y 6 miembros, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C1-C6alquilo, C2-C6alquenilo, C2-C6alquinilo, C1-C6haloalquilo, C2-C6haloalquenilo o C2-C6haloalquinilo; o –LA–O–RS, –LA–S–RS, –LA–C(O)RS, –LA–OC(O)RS, –LA–C(O)ORS, –LA–N(RSRS'), –LA–S(O)RS, –LA–SO2RS, –LA–C(O)N(RSRS'), –LA–N(RS)C(O)RS', –LA–N(RS)C(O)N(RS'RS''), –LA–N(RS)SO2RS', –LA–SO2N(RSRS'), –LA–N(RS)SO2N(RS'RS''), –LA–N(RS)S(O)N(RS'RS''), –LA–OS(O)–RS, –LA–OS(O)2–RS, –LA–S(O)2ORS, –LA–S(O)ORS, –LA–OC(O)ORS, –LA–N(RS)C(O)ORS', –LA–OC(O)N(RSRS'), –LA–N(RS)S(O)–RS', –LA–S(O)N(RSRS') o –LA–C(O)N(RS)C(O)–RS', donde LA es un enlace, C1-C6alquileno, C2-C6alquenileno o C2-C6alquinileno.

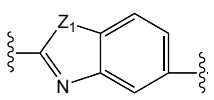
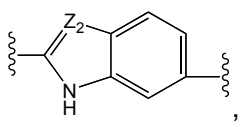
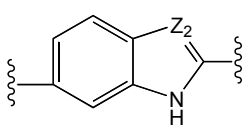
Más preferiblemente, RA es halógeno, hidroxi, mercapto, amino, carboxi, nitro,

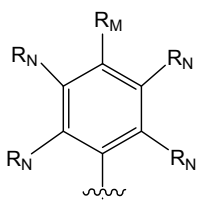
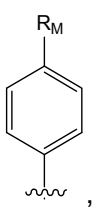
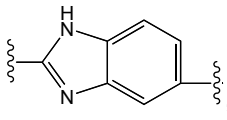
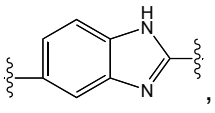
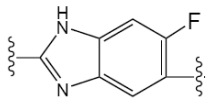
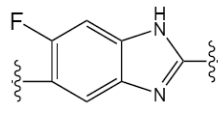
oxo, fosfonoxi, fosfono, tioxo, ciano; o C1-C6alquilo, C2-C6alquenilo o C2-C6alquinilo, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo o ciano; o C3-C6carbociclo o heterociclo de entre 3 y 6 miembros, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C1-C6alquilo, C2-C6alquenilo, C2-C6alquinilo, C1-C6haloalquilo, C2-C6haloalquenilo o C2-C6haloalquinilo.

Más preferiblemente, RA es halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, ciano; o C1-C6alquilo, C2-C6alquenilo o C2-C6alquinilo, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo o ciano.

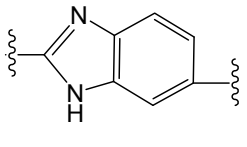
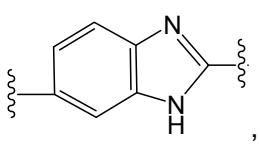
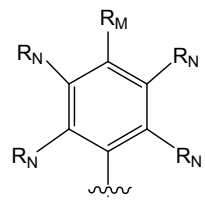
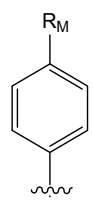
LS, LS' y LS'' preferiblemente se seleccionan en forma independiente entre sí en cada caso entre un enlace; o C1-C6alquileno, C2-C6alquenileno o C2-C6alquinileno.

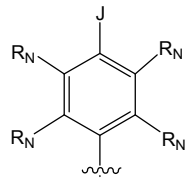
A y B pueden ser iguales o diferentes. De la misma manera, L1 y L2 pueden ser iguales o diferentes.

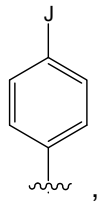
En una forma de realización de este aspecto, A es  o  , y está opcionalmente sustituido con uno o más RA; B es  o  , y está opcionalmente sustituido con uno o más RA; y D es C5-C6carbociclo o heterociclo de 5 o 6 miembros (por ejemplo, fenilo), y está opcionalmente sustituido con uno o más RA, o está sustituido con J y opcionalmente sustituido con uno o más RA, donde J es C3-C6carbociclo, heterociclo de entre 3 y 6

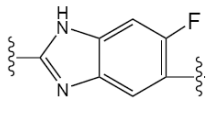
miembros o biciclo de entre 6 y 12 miembros y está opcionalmente sustituido con uno o más RA. Preferiblemente, J está sustituido con un C3-C6carbociclo o heterociclo de entre 3 y 6 miembros que está opcionalmente sustituido en forma independiente con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C1-C6alquilo, C2-C6alquenilo, C2-C6alquinilo, C1-C6haloalquilo, C2-C6haloalquenilo, C2-C6haloalquinilo, C(O)ORS o –N(RSRS'), y J también puede estar opcionalmente sustituido con uno o más RA. Preferiblemente, D es  o  , donde RM y RN son como se definen precedentemente. También preferiblemente, D es o , donde J y RN son como se definen precedentemente. Z1 se selecciona en forma independiente en cada caso entre O, S, NH o CH2; y Z2 se selecciona en forma independiente en cada caso entre N o CH. Preferiblemente, A es  , B es  , y A y B están sustituidos con uno o más halógeno, como por ejemplo F o Cl. Cuando A y/o B son benzimidazol sustituido con halo (por ejemplo, A es  y B es ), los compuestos de esta forma de realización pueden tener propiedades farmacocinéticas significativamente mejoradas así como también una actividad inhibitoria mejorada contra ciertas mutaciones de HCV genotipo 1a, en comparación con los mismos compuestos pero con benzimidazol no sustituido. L1 y L2 son en forma independiente entre sí un enlace o C1-C6alquileno, y L3 es un enlace, C1-C6alquileno o -C(O)-, y L1, L2, y L3 están

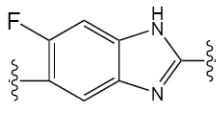
opcionalmente sustituidos en forma independiente entre sí con uno o más RL. Preferiblemente, L1, L2, y L3 son un enlace. –T-RD' se selecciona en forma independiente en cada caso entre –C(O)–LY'–N(RB)C(O)–LS''–RD' o –C(O)–LY'–N(RB)C(O)O–LS''–RD', donde LY' es C1-C6alquileno (por ejemplo, -CH2-) y está opcionalmente sustituido con uno o más sustituyentes seleccionados entre RL, y LS'' preferiblemente es un enlace. –T-RD' también puede seleccionarse, sin que esto constituya limitación alguna, entre –C(O)–LY'–LS''–RD', –C(O)–LY'–O–LS''–RD', –C(O)–LY'–N(RB)–LS''–RD', o –C(O)–LY'–N(RB)S(O)2–LS''–RD'.

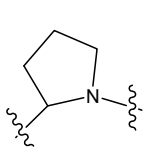
En otra forma de realización de este aspecto, A es  y está opcionalmente sustituido con uno o más RA (por ejemplo, halógeno); B es  , y está opcionalmente sustituido con uno o más RA (por ejemplo, halógeno); y D es C5-C6carbociclo o heterociclo de 5 o 6 miembros (por ejemplo, fenilo), y está opcionalmente sustituido con uno o más RA, o está sustituido con J y opcionalmente sustituido con uno o más RA, donde J es C3-C6carbociclo, heterociclo de entre 3 y 6 miembros o biciclo de entre 6 y 12 miembros y está opcionalmente sustituido con uno o más RA. Preferiblemente, J está sustituido con un C3-C6carbociclo o heterociclo de entre 3 y 6 miembros que está opcionalmente sustituido en forma independiente con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C1-C6alquilo, C2-C6alquenilo, C2-C6alquinilo, C1-C6haloalquilo, C2-C6haloalquenilo, C2-C6haloalquinilo, C(O)ORS o –N(RSRS'), y J también puede estar opcionalmente sustituido con uno o más RA. Preferiblemente, D es  o  , donde RM y

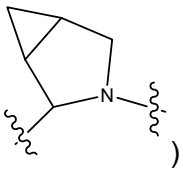
RN son como se definen precedentemente. También preferiblemente, D es 

o 

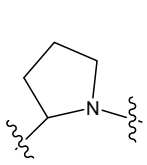
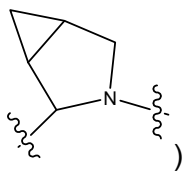
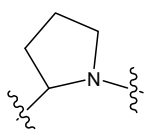
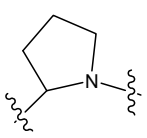
, donde J y RN son como se definen precedentemente. Cuando A y/o B son benzimidazol sustituido con halo (por ejemplo, A es 

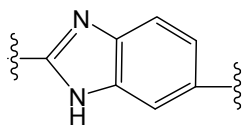
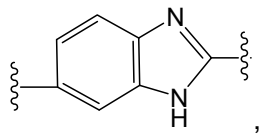
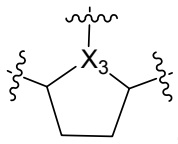
y B es 

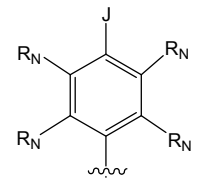
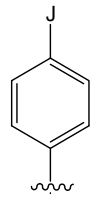
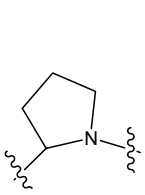
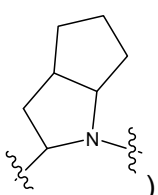
), los compuestos de esta forma de realización pueden tener propiedades farmacocinéticas significativamente mejoradas así como también una actividad inhibitoria mejorada contra ciertas mutaciones de HCV genotipo 1a, en comparación con los mismos compuestos pero con benzimidazol no sustituido. L1 y L2 son en forma independiente entre sí un enlace o C1-C6alquileno, y L3 es un enlace, C1-C6alquileno o -C(O)-, y L1, L2, y L3 están opcionalmente sustituidos en forma independiente entre sí con uno o más RL. Preferiblemente, L1, L2, y L3 son un enlace. –T-RD' se selecciona en forma independiente en cada caso entre –C(O)–LY'–N(RB)C(O)–LS''–RD' o –C(O)–LY'–N(RB)C(O)O–LS''–RD', donde LY' es C1-C6alquileno (por ejemplo, -CH2-) y está opcionalmente sustituido con uno o más sustituyentes seleccionados entre RL, y LS'' preferiblemente es un enlace. –T-RD' también puede seleccionarse, sin que esto constituya limitación alguna, entre –C(O)–LY'–LS''–RD', –C(O)–LY'–O–LS''–RD', –C(O)–LY'–N(RB)–LS''–RD', o –C(O)–LY'–N(RB)S(O)2–LS''–RD'. R2 y R5, tomados junto con los átomos a los cuales están unidos, preferiblemente forman un heterociclo de 5 o 6 miembros o biciclo de entre 6 y 12 miembros (por ejemplo, 

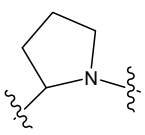
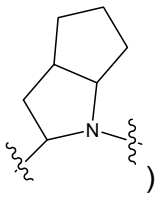
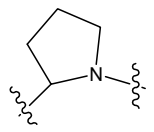
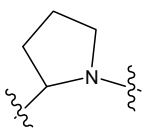
o 

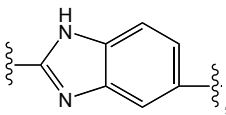
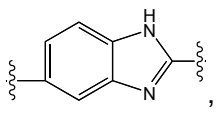
)

que está opcionalmente sustituido con uno o más RA. R9 y R12, tomados junto con los átomos a los cuales están unidos, preferiblemente forman un heterociclo de 5 o 6 miembros o biciclo de entre 6 y 12 miembros (por ejemplo,  o ) que está opcionalmente sustituido con uno o más RA. Más preferiblemente, R2 y R5, tomados junto con los átomos a los cuales están unidos, forman  que está opcionalmente sustituido con uno o más RA; R9 y R12, tomados junto con los átomos a los cuales están unidos, forman  que está opcionalmente sustituido con uno o más RA.

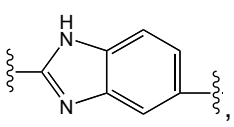
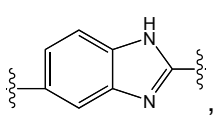
En aun otra forma de realización de este aspecto, A es  y opcionalmente sustituido con uno o más RA (preferiblemente, A está sustituido con al menos un halógeno tal como F); B es  , y está opcionalmente sustituido con uno o más RA (preferiblemente, B está sustituido con al menos un halógeno tal como F). X es  , donde X3 es N y está directamente unido a –L3–D, y X está opcionalmente sustituido con uno o más RA o RF. D es fenilo, y está sustituido con J y opcionalmente sustituido con uno o más RA. J es C3-C6carbociclo, heterociclo de entre 3 y 6 miembros, biciclo de entre 6 y 12 miembros, triciclo de entre 10 y 15 miembros o carbociclo/heterociclo de entre 13 y 15 miembros, y J está opcionalmente sustituido con uno o más RA. Preferiblemente, J está sustituido con un C3-C6carbociclo, heterociclo de

entre 3 y 6 miembros, biciclo de entre 6 y 12 miembros o carbociclo/heterociclo de entre 7 y 12 miembros, que está opcionalmente sustituido en forma independiente con uno o más sustituyentes seleccionados entre (1) halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C1-C6alquilo, C2-C6alquenilo, C2-C6alquinilo, C1-C6haloalquilo, C2-C6haloalquenilo, C2-C6haloalquinilo, –C(O)ORS o –N(RSRS'), o (2) trimetilsililo, –O–RS, –S–RS o –C(O)RS; y J también puede estar opcionalmente sustituido con uno o más RA. Preferiblemente, D es  o  , donde J es como se define precedentemente, y cada RN se selecciona en forma independiente entre RD y preferiblemente es hidrógeno o halo como por ejemplo F. L1 y L2 son en forma independiente entre sí un enlace o C1-C6alquileno, y L3 es un enlace, C1-C6alquileno o -C(O)-, y L1, L2, y L3 están opcionalmente sustituidos en forma independiente entre sí con uno o más RL. Preferiblemente, L1, L2, y L3 son un enlace. –T-RD' se selecciona en forma independiente en cada caso entre –C(O)–LY'–N(RB)C(O)–LS''–RD' o –C(O)–LY'–N(RB)C(O)O–LS''–RD', donde LY' es C1-C6alquileno (por ejemplo, -CH2-) y está opcionalmente sustituido con uno o más sustituyentes seleccionados entre RL, y LS'' preferiblemente es un enlace. –T-RD' también puede seleccionarse, sin que esto constituya limitación alguna, entre –C(O)–LY'–LS''–RD', –C(O)–LY'–O–LS''–RD', –C(O)–LY'–N(RB)–LS''–RD', o –C(O)–LY'–N(RB)S(O)2–LS''–RD'. R2 y R5, tomados junto con los átomos a los cuales están unidos, preferiblemente forman un heterociclo de 5 o 6 miembros o biciclo de entre 6 y 12 miembros (por ejemplo,  o ) que

está opcionalmente sustituido con uno o más RA. R9 y R12, tomados junto con los átomos a los cuales están unidos, preferiblemente forman un heterociclo de 5 o 6 miembros o biciclo de entre 6 y 12 miembros (por ejemplo,  o ) que está opcionalmente sustituido con uno o más RA. Más preferiblemente, R2 y R5, tomados junto con los átomos a los cuales están unidos, forman  que está opcionalmente sustituido con uno o más RA; R9 y R12, tomados junto con los átomos a los cuales están unidos, forman  que está opcionalmente sustituido con uno o más RA.

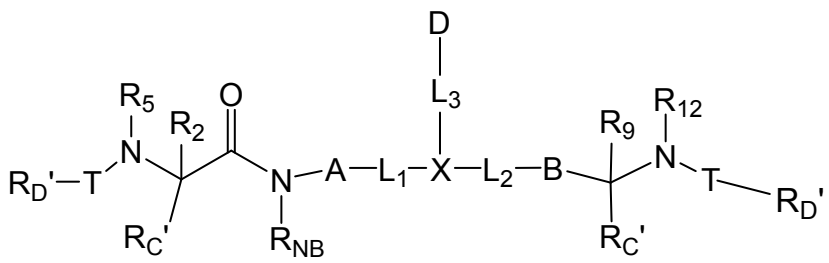
La presente invención en forma inesperada demuestra que un compuesto de acuerdo con este aspecto de la invención (preferiblemente un compuesto de Fórmula IB o una sal aceptable farmacéuticamente del mismo, donde A es  , B es  , y A y B están opcionalmente sustituidos en forma independiente con uno o más RA como por ejemplo uno o más halo) mostró una actividad mejorada significativamente contra distintos genotipos y variantes de HCV. Por ejemplo, cuando se evaluaron contra réplicas de HCV de diferentes genotipos en líneas celulares estables (en presencia de FBS 5%), y en comparación con el Ejemplo 37 de la Solicitud de Patente de los Estados Unidos Nro. 2010/0317568, los valores EC50 de los compuestos de los Ejemplos 3,48, 3,52, 4,38, y 5,1 fueron al menos aproximadamente 6 veces menores que los del Ejemplo 37 contra el genotipo 1a, al menos aproximadamente 3 veces menores

contra el genotipo 3a, al menos aproximadamente 50 veces menores contra el genotipo 6a, y significativamente menores contra el genotipo 2a. Además, cuando se evaluaron contra Réplicas de HCV genotipo 1a que contenían ciertas mutaciones NS5A en ensayos de transfección transitoria, y en comparación con el Ejemplo 37 de la Solicitud de Patente de los Estados Unidos Nro. 2010/0317568, los valores EC50 de los compuestos de los Ejemplos 3,48, 3,52, 4,38, y 5,1 fueron al menos aproximadamente 130 veces menores que los del Ejemplo 37 contra la variante L31V, al menos aproximadamente 7,500 veces menores contra la variante M28T, al menos aproximadamente 80 veces menores contra la variante M28V, al menos aproximadamente 500 veces menores contra la variante Q30E, al menos aproximadamente 300 veces menores contra la variante Q30R, al menos aproximadamente 800 veces menores contra la variante Y93C, al menos aproximadamente 1,500 veces menores contra la variante Y93H, y significativamente menores contra la variante Q30H. De la misma manera, cuando se evaluaron contra réplicas de HCV genotipo 1b que contenían ciertas mutaciones NS5A en ensayos de transfección transitoria, y en comparación con el Ejemplo 37 de la Solicitud de Patente de los Estados Unidos Nro. 2010/0317568, el valor EC50 del compuesto de Ejemplo 5.1 fue al menos aproximadamente 10 veces menor que el del Ejemplo 37 contra la variante Y93H.

De manera acorde, la presente invención presenta métodos para tratar infecciones de distintos genotipos o variantes de HCV. Los métodos comprenden administrar un compuesto de Fórmula IB, o una sal aceptable farmacéuticamente del mismo, a un paciente infectado con HCV genotipo 1a, 1b, 2a, 2b, 3a, 4a, 5a o 6a, o infectado con una de las variantes que se han descrito. Preferiblemente, A es  , B es  , y A y B están opcionalmente sustituidos en forma independiente con uno o más RA como por ejemplo uno o más halo. Otros compuestos descritos en este aspecto

de la invención o cualquier forma de realización bajo la misma, así como también los compuestos del título en los Ejemplos que se describen más adelante, también pueden utilizarse. En una forma de realización, el paciente tratado está infectado con HCV genotipo 1, como por ejemplo 1a. En otra forma de realización, el paciente tratado está infectado con HCV genotipo 2, como por ejemplo 2a. En aun otra forma de realización, el paciente tratado está infectado con HCV genotipo 3, como por ejemplo 3a. En otra forma de realización, el paciente tratado está infectado con HCV genotipo 4, como por ejemplo 4a. En una forma de realización adicional, el paciente tratado está infectado con HCV genotipo 5, como por ejemplo 5a. En aun otra forma de realización, el paciente tratado está infectado con HCV genotipo 6, como por ejemplo 6a.

En aun otro aspecto, la presente invención además presenta compuestos de Fórmula IC y sales aceptables farmacéuticamente del mismo.



IC

donde:

RNB es RB;

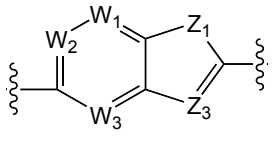
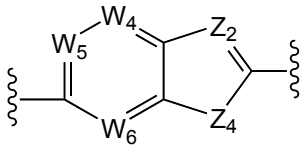
RC’ se selecciona en forma independiente entre RC;

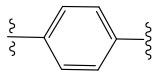
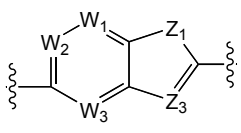
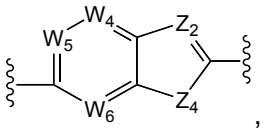
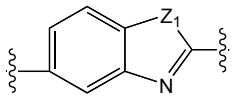
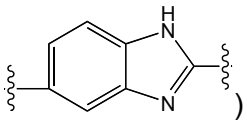
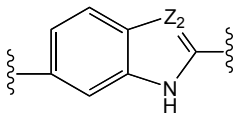
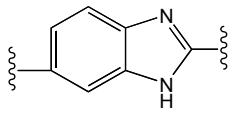
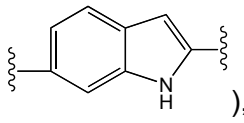
RD’ se selecciona en forma independiente entre RD;

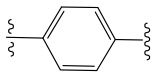
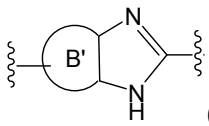
R2 y R5, tomados junto con los átomos a los cuales están unidos, forman un heterociclo de entre 3 y 12 miembros que está opcionalmente sustituido con uno o más RA;

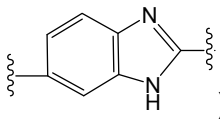
R9 y R12, tomados junto con los átomos a los cuales están unidos, forman un heterociclo de entre 3 y 12 miembros que está opcionalmente sustituido con uno o más RA;

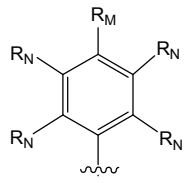
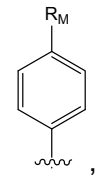
A, B, D, X, L1, L2, L3, T, RA, RB, RC, y RD son como se describe precedentemente en Fórmula I.

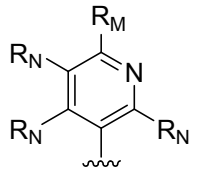
En este aspecto, A preferiblemente es C5-C6carbociclo o heterociclo de 5 o 6 miembros, y está opcionalmente sustituido con uno o más RA; y B preferiblemente es un biciclo de entre 8 y 12 miembros (como por ejemplo  o ), y está opcionalmente sustituido con uno o más RA. Z1 es O, S, NH o CH2; Z2 es N o CH; Z3 es N o CH; Z4 es O, S, NH o CH2; y W1, W2, W3, W4, W5 y W6 se seleccionan en forma independiente entre sí entre CH o N.

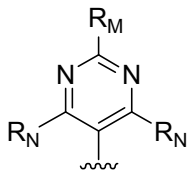
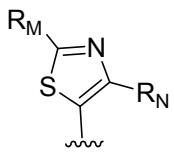
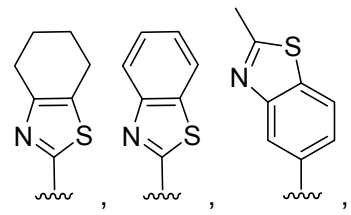
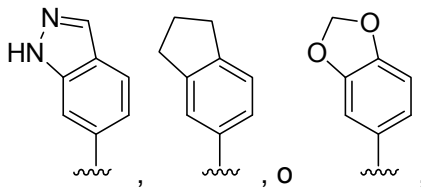
Más preferiblemente, A es fenilo (por ejemplo, ), y está opcionalmente sustituido con uno o más RA; y B es  o  , y está opcionalmente sustituido con uno o más RA, donde Z1, Z2, Z3, Z4, W1, W2, W3, W4, W5, W6 son como se definen precedentemente. Preferiblemente, Z3 es N y Z4 es NH. Por ejemplo, B puede ser  (por ejemplo, ) o  (por ejemplo,  o ), y está opcionalmente sustituido con uno o más RA.

También preferiblemente, A es C5-C6carbociclo (por ejemplo, fenilo como por ejemplo ) o heterociclo de 5 o 6 miembros; y B es  (por ejemplo,


), donde B' se selecciona entre C5-C6carbociclo o heterociclo de 5 o 6 miembros. A y B están opcionalmente sustituidos en forma independiente con uno o más RA.

D preferiblemente se selecciona entre C5-C6carbociclo, heterociclo de 5 o 6 miembros, o biciclos de entre 6 y 12 miembros, y está opcionalmente sustituido con uno o más RA. D también puede seleccionarse preferiblemente entre C1-C6alquilo, C2-C6alquenilo o C2-C6alquinilo, y está opcionalmente sustituido con uno o más sustituyentes seleccionados entre RL. Más preferiblemente, D es C5-C6carbociclo, heterociclo de 5 o 6 miembros, o biciclos de entre 6 y 12 miembros, y está sustituido con uno o más RM, donde RM es halógeno, nitro, oxo, fosfonoxi, fosfono, tioxo, ciano, o –LS–RE. También preferiblemente, D es fenilo, y está opcionalmente sustituido con uno o más RA. Más preferiblemente, D es fenilo, y está sustituido con uno o más RM, donde RM es como se define precedentemente. Más preferiblemente, D es  o  , donde RM es como se define precedentemente, y cada RN se selecciona en forma independiente entre RD y preferiblemente es hidrógeno. Uno o más RN también puede ser preferiblemente halo como por ejemplo F.

D es también preferiblemente piridinilo, pirimidinilo, o tiazolilo, opcionalmente sustituido con uno o más RA. Más preferiblemente D es piridinilo, pirimidinilo, o tiazolilo, y está sustituido con uno o más RM. Más preferiblemente, D es  ,


, o 
, donde RM es como se define precedentemente, y cada RN se selecciona en forma independiente entre RD y preferiblemente es hidrógeno. Uno o más RN también puede ser preferiblemente halo como por ejemplo F. D es también preferiblemente indanilo, 4,5,6,7-tetrahidrobenzo[d]tiazolilo, benzo[d]tiazolilo, o indazolilo, y está opcionalmente sustituido con uno o más RA. Más preferiblemente D es indanilo, 4,5,6,7-tetrahidrobenzo[d]tiazolilo, benzo[d]tiazolilo, indazolilo, o benzo[d][1,3]dioxol-5-ilo, y está sustituido con uno o más RM. Más preferiblemente, D es 
, 
, o
, y está opcionalmente sustituido con uno o más RM.

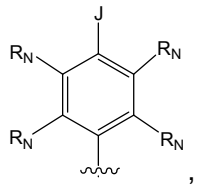
Preferiblemente, RM es halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, ciano; o C1-C6alquilo, C2-C6alquenilo o C2-C6alquinilo, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo o ciano; o C3-C6carbociclo o heterociclo de entre 3 y 6 miembros, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C1-C6alquilo, C2-C6alquenilo, C2-C6alquinilo, C1-C6haloalquilo, C2-C6haloalquenilo o C2-C6haloalquinilo. Más preferiblemente, RM es halógeno, hidroxi, mercapto, amino, carboxi; o C1-C6alquilo, C2-C6alquenilo o C2-C6alquinilo, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más

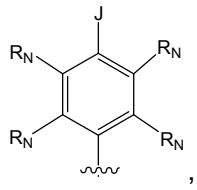
sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino o carboxi. Más preferiblemente, RM es C1-C6alquilo el cual está opcionalmente sustituido con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino o carboxi.

También preferiblemente, RM es halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, o ciano; o RM es –LS–RE, donde LS es una unión o C1-C6alquileno, y RE es –N(RSRS'), –O–RS, –C(O)RS, –C(O)ORS, –C(O)N(RSRS'), –N(RS)C(O)RS', –N(RS)C(O)ORS', –N(RS)SO2RS', –SO2RS, –SRS, o –P(O)(ORS)2, donde RS y RS' pueden seleccionarse en forma independiente entre sí, por ejemplo, entre (1) hidrógeno o (2) C1-C6alquilo opcionalmente sustituido en cada caso con uno o más halógeno, hidroxi, –O–C1-C6alquilo o heterociclo de entre 3 y 6 miembros; o RM es C1-C6alquilo, C2-C6alquenilo o C2-C6alquinilo, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo o ciano; o RM es C3-C6carbociclo o heterociclo de entre 3 y 6 miembros, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C1-C6alquilo, C2-C6alquenilo, C2-C6alquinilo, C1-C6haloalquilo, C2-C6haloalquenilo, C2-C6haloalquinilo, –C(O)ORS, o –N(RSRS'). Más preferiblemente, RM es halógeno (por ejemplo, fluoro, cloro, bromo, yodo), hidroxi, mercapto, amino, carboxi, o C1-C6alquilo (por ejemplo, metilo, isopropilo, tert-butilo), C2-C6alquenilo o C2-C6alquinilo, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, ciano, o carboxi. Por ejemplo RM es CF3, –C(CF3)2–OH, –C(CH3)2–CN, –C(CH3)2–CH2OH, o –C(CH3)2–CH2NH2. También preferiblemente RM es –LS–RE donde LS es una unión y RE es –N(RSRS'), –O–RS, –N(RS)C(O)ORS', –N(RS)SO2RS', –SO2RS, o –SRS. Por ejemplo donde LS es una unión, RE es –N(C1-C6alquil)2 (por ejemplo, –NMe2); –N(C1-

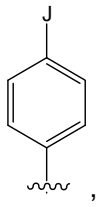
C6alquilen–O–C1-C6alquil)2 (por ejemplo –N(CH2CH2OMe)2); –N(C1-C6alquil)(C1-C6alquilen–O–C1-C6alquilo) (por ejemplo –N(CH3)(CH2CH2OMe)); –O–C1-C6alquilo (por ejemplo, –O–Me, –O–Et, –O–isopropilo, –O–tert-butilo, –O–n-hexilo); –O–C1-C6haloalquilo (por ejemplo, – OCF3, –OCH2CF3); –O–C1-C6alquilen–piperidina (por ejemplo, –O–CH2CH2–1-piperidilo); –N(C1-C6alquil)C(O)OC1-C6alquilo (por ejemplo, –N(CH3)C(O)O–CH2CH(CH3)2), –N(C1-C6alquil)SO2C1-C6alquilo (por ejemplo, –N(CH3)SO2CH3); –SO2C1-C6alquilo (por ejemplo, –SO2Me); –SO2C1-C6haloalquilo (por ejemplo, –SO2CF3); o –S–C1-C6haloalquilo (por ejemplo, SCF3). También preferiblemente RM es –LS–RE donde LS es C1-C6alquileno (por ejemplo, –CH2–, –C(CH3)2–, –C(CH3)2–CH2–) y RE es –O–RS, –C(O)ORS, –N(RS)C(O)ORS', o –P(O)(ORS)2. Por ejemplo RM es –C1-C6alquilen–O–RS (por ejemplo, –C(CH3)2–CH2–OMe); –C1-C6alquilen–C(O)ORS (por ejemplo, –C(CH3)2–C(O)OMe); –C1-C6alquilen–N(RS)C(O)ORS' (por ejemplo, –C(CH3)2–CH2–NHC(O)OCH3); o –C1-C6alquilen–P(O)(ORS)2 (por ejemplo, –CH2–P(O)(OEt)2). También más preferiblemente RM es C3-C6carbociclo o heterociclo de entre 3 y 6 miembros, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C1-C6alquilo, C2-C6alquenilo, C2-C6alquinilo, C1-C6haloalquilo, C2-C6haloalquenilo, C2-C6haloalquinilo, –C(O)ORS, o –N(RSRS'). Por ejemplo RM 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). Más preferiblemente, RM es C1-C6alquilo el cual está opcionalmente sustituido con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino o carboxi (por ejemplo, tert-butilo, CF3).

Más preferiblemente, D es C5-C6carbociclo, heterociclo de 5 o 6 miembros o biciclo de entre 6 y 12 miembros y está sustituido con J y opcionalmente sustituido con uno o más RA, donde J es C3-C6carbociclo, heterociclo de entre 3 y 6 miembros o biciclo de entre 6 y 12 miembros y está opcionalmente sustituido con uno o más RA. Preferiblemente, J está sustituido con un C3-C6carbociclo o heterociclo de entre 3 y 6 miembros, donde dicho C3-C6carbociclo o heterociclo de entre 3 y 6 miembros está opcionalmente sustituido en forma independiente con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C1-C6alquilo, C2-C6alquenilo, C2-C6alquinilo, C1-C6haloalquilo, C2-C6haloalquenilo, C2-C6haloalquinilo, C(O)ORS o –N(RSRS'), y J también puede estar opcionalmente sustituido con uno o más RA. También preferiblemente, D es C5-C6carbociclo o heterociclo de 5 o 6 miembros y está sustituido con J y opcionalmente sustituido con uno o más RA, y J es C3-C6carbociclo o heterociclo de entre 3 y 6 miembros y está opcionalmente sustituido con uno o más RA, y preferiblemente J está sustituido con al menos un C3-C6carbociclo o heterociclo de entre 3 y 6 miembros que está opcionalmente sustituido en forma independiente con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C1-C6alquilo, C2-C6alquenilo, C2-C6alquinilo, C1-C6haloalquilo, C2-C6haloalquenilo, C2-C6haloalquinilo, C(O)ORS o –N(RSRS'). También preferiblemente, D es C5-C6carbociclo o heterociclo de 5 o 6 miembros y está sustituido con J y opcionalmente sustituido con uno o más RA, y J es biciclo de entre 6 y 12 miembros (por ejemplo, un biciclo fusionado, en puente o espiro de entre 7 y 12 miembros que comprende un átomo del anillo nitrógeno a través del cual J se enlaza por unión covalente con D) y está opcionalmente sustituido con uno o más RA. Más preferiblemente, D es fenilo y está sustituido con J y opcionalmente sustituido con uno o más RA, y J es C3-C6carbociclo, heterociclo de entre 3 y 6 miembros o biciclo de entre 6 y 12 miembros y está opcionalmente sustituido con uno o más RA, y preferiblemente J

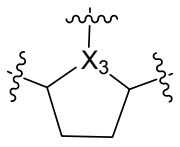
está sustituido con al menos un C3-C6carbociclo o heterociclo de entre 3 y 6 miembros que está opcionalmente sustituido en forma independiente con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C1-C6alquilo, C2-C6alquenilo, C2-C6alquinilo, C1-C6haloalquilo, C2-C6haloalquenilo, C2-C6haloalquinilo, C(O)ORS o –N(RSRS'). Más preferiblemente, D es 

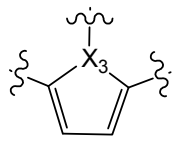
, donde cada RN se selecciona en forma independiente entre RD y preferiblemente es hidrógeno o halógeno, y J es C3-C6carbociclo, heterociclo de entre 3 y 6 miembros o biciclo de entre 6 y 12 miembros y está opcionalmente sustituido con uno o más RA, y preferiblemente J está sustituido con al menos un C3-C6carbociclo o heterociclo de entre 3 y 6 miembros que está opcionalmente sustituido en forma independiente con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C1-C6alquilo, C2-C6alquenilo, C2-C6alquinilo, C1-C6haloalquilo, C2-C6haloalquenilo, C2-C6haloalquinilo, C(O)ORS o –N(RSRS'). También preferiblemente, D es 

, donde cada RN se selecciona en forma independiente entre RD y preferiblemente es hidrógeno o halógeno, y J es C3-C6carbociclo o heterociclo de entre 3 y 6 miembros y está sustituido con un C3-C6carbociclo o heterociclo de entre 3 y 6 miembros que está opcionalmente sustituido en forma independiente con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C1-C6alquilo, C2-C6alquenilo, C2-C6alquinilo, C1-C6haloalquilo, C2-C6haloalquenilo, C2-C6haloalquinilo, C(O)ORS o –N(RSRS'), y J también puede estar opcionalmente

sustituido con uno o más RA. También preferiblemente, D es 

, y J es C3-C6carbociclo o heterociclo de entre 3 y 6 miembros y está opcionalmente sustituido con uno o más RA, y preferiblemente J está sustituido con al menos un C3-C6carbociclo o heterociclo de entre 3 y 6 miembros que está opcionalmente sustituido en forma independiente con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C1-C6alquilo, C2-C6alquenilo, C2-C6alquinilo, C1-C6haloalquilo, C2-C6haloalquenilo, C2-C6haloalquinilo, C(O)ORS o –N(RSRS').

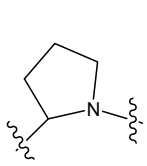
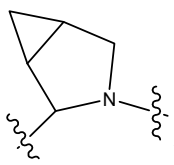
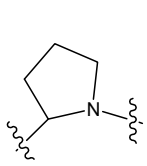
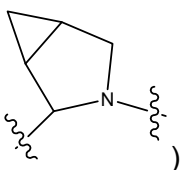
X preferiblemente es C5-C6carbociclo, heterociclo de 5 o 6 miembros, o biciclos de entre 6 y 12 miembros (por ejemplo, 

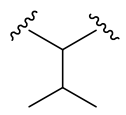
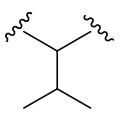
o 

, donde X3 es N y está directamente unido a –L3–D), y está opcionalmente sustituido con uno o más RA o RF. Los ejemplos no limitativos de X se describen precedentemente.

L1 y L2 son preferiblemente en forma independiente un enlace o C1-C6alquileno, L3 preferiblemente se selecciona entre un enlace, C1-C6alquileno o –C(O)–, y L1, L2, y L3 están opcionalmente sustituidos en forma independiente entre sí con uno o más RL. Más preferiblemente, L1, L2 y L3 son en forma independiente entre sí un enlace o C1-C6alquileno (por ejemplo, –CH2– o –CH2CH2–), y están opcionalmente sustituidos en forma independiente entre sí con uno o más RL. Más preferiblemente, L1, L2 y L3 son un enlace. L1 y L2 pueden ser iguales o diferentes.

R2 y R5, tomados junto con los átomos a los cuales están unidos, preferiblemente forman un heterociclo de 5 o 6 miembros o biciclo de entre 6 y 12 miembros (por ejemplo,

 o ) que está opcionalmente sustituido con uno o más RA. R9 y R12, tomados junto con los átomos a los cuales están unidos, preferiblemente forman un heterociclo de 5 o 6 miembros o biciclo de entre 6 y 12 miembros (por ejemplo,  o ) que está opcionalmente sustituido con uno o más RA.

-T-RD' puede seleccionarse en forma independiente en cada caso, sin que esto constituya limitación alguna, entre –C(O)–LY'–RD', –C(O)O–LY'–RD', –C(O)–LY'–N(RB)C(O)–LS''–RD', –C(O)–LY'–N(RB)C(O)O–LS''–RD', –N(RB)C(O)–LY'–N(RB)C(O)–LS''–RD', –N(RB)C(O)–LY'—N(RB)C(O)O–LS''–RD', o –N(RB)C(O)–LY'—N(RB)–LS''–RD', donde LY' es en forma independiente en cada caso LS' y, preferiblemente, es en forma independiente en cada caso C1-C6alquileno (por ejemplo, -CH2- o ) y está opcionalmente sustituido con uno o más sustituyentes seleccionados entre RL. Preferiblemente, -T-RD' se selecciona en forma independiente en cada caso entre –C(O)–LY'–M'–LS''–RD' o –N(RB)C(O)–LY'–M'–LS''–RD'. Más preferiblemente, -T-RD' se selecciona en forma independiente en cada caso entre –C(O)–LY'–N(RB)C(O)–LS''–RD' o –C(O)–LY'–N(RB)C(O)O–LS''–RD'. Más preferiblemente, -T-RD' se selecciona en forma independiente en cada caso entre –C(O)–LY'–N(RB)C(O)–RD' o –C(O)–LY'–N(RB)C(O)O–RD', donde LY' preferiblemente es en forma independiente en cada caso C1-C6alquileno (por ejemplo, -CH2- o ) y está opcionalmente sustituido con uno o más sustituyentes seleccionados entre RL.

RNB y RC' son preferiblemente hidrógeno, y RD' preferiblemente se selecciona en forma independiente en cada caso entre RE. Más preferiblemente, RD' se selecciona en

forma independiente en cada caso entre C1-C6alquilo, C2-C6alquenilo o C2-C6alquinilo, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C3-C6carbociclo o heterociclo de entre 3 y 6 miembros; o C3-C6carbociclo o heterociclo de entre 3 y 6 miembros, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C1-C6alquilo, C2-C6alquenilo, C2-C6alquinilo, C1-C6haloalquilo, C2-C6haloalquenilo o C2-C6haloalquinilo.

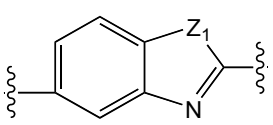
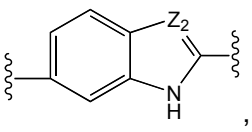
RA preferiblemente es halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, ciano; o C1-C6alquilo, C2-C6alquenilo o C2-C6alquinilo, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo o ciano; o C3-C6carbociclo o heterociclo de entre 3 y 6 miembros, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C1-C6alquilo, C2-C6alquenilo, C2-C6alquinilo, C1-C6haloalquilo, C2-C6haloalquenilo o C2-C6haloalquinilo; o –LA–O–RS, –LA–S–RS, –LA–C(O)RS, –LA–OC(O)RS, –LA–C(O)ORS, –LA–N(RSRS’), –LA–S(O)RS, –LA–SO2RS, –LA–C(O)N(RSRS’), –LA–N(RS)C(O)RS’, –LA–N(RS)C(O)N(RS’RS’’), –LA–N(RS)SO2RS’, –LA–SO2N(RSRS’), –LA–N(RS)SO2N(RS’RS’’), –LA–N(RS)S(O)N(RS’RS’’), –LA–OS(O)–RS, –LA–OS(O)2–RS, –LA–S(O)2ORS, –LA–S(O)ORS, –LA–OC(O)ORS, –LA–N(RS)C(O)ORS’, –LA–OC(O)N(RSRS’), –LA–N(RS)S(O)–RS’, –LA–S(O)N(RSRS’) o –LA–C(O)N(RS)C(O)–RS’, donde LA es un enlace, C1-C6alquileno, C2-C6alquenileno o C2-C6alquinileno.

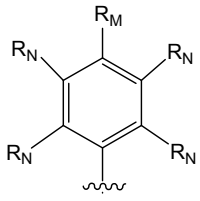
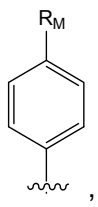
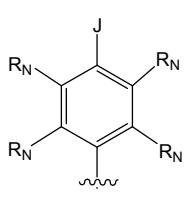
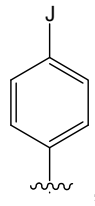
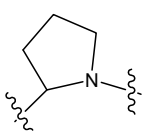
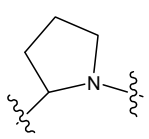
Más preferiblemente, RA es halógeno, hidroxi, mercapto, amino, carboxi, nitro,

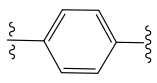
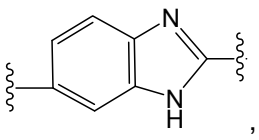
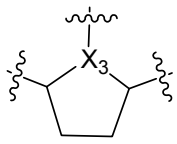
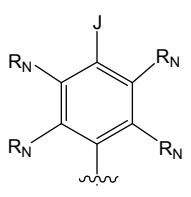
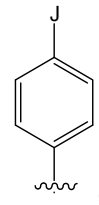
oxo, fosfonoxi, fosfono, tioxo, ciano; o C1-C6alquilo, C2-C6alquenilo o C2-C6alquinilo, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo o ciano; o C3-C6carbociclo o heterociclo de entre 3 y 6 miembros, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C1-C6alquilo, C2-C6alquenilo, C2-C6alquinilo, C1-C6haloalquilo, C2-C6haloalquenilo o C2-C6haloalquinilo.

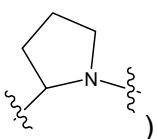
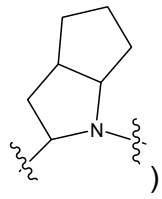
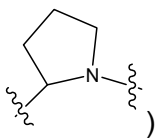
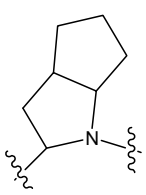
Más preferiblemente, RA es halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, ciano; o C1-C6alquilo, C2-C6alquenilo o C2-C6alquinilo, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo o ciano.

LS, LS' y LS'' preferiblemente se seleccionan en forma independiente entre sí en cada caso entre un enlace; o C1-C6alquileno, C2-C6alquenileno o C2-C6alquinileno.

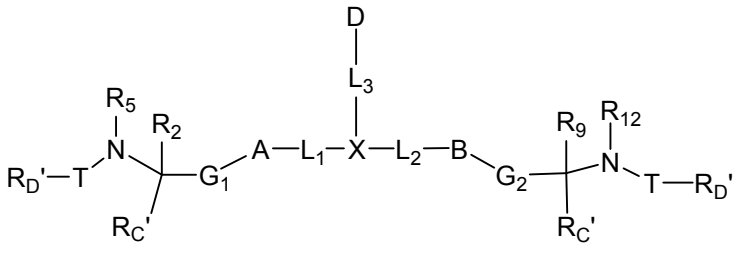
En una forma de realización de este aspecto, A es fenilo, y está opcionalmente sustituido con uno o más RA; y B es  o  , y está opcionalmente sustituido con uno o más RA, donde Z1 es O, S, NH o CH2; y Z2 es N o CH. D es C5-C6carbociclo o heterociclo de 5 o 6 miembros (por ejemplo, fenilo), y está opcionalmente sustituido con uno o más RA, o está sustituido con J y opcionalmente sustituido con uno o más RA, donde J es C3-C6carbociclo, heterociclo de entre 3 y 6 miembros o biciclo de entre 6 y 12 miembros y está opcionalmente sustituido con uno o más RA. Preferiblemente, J está sustituido con un C3-C6carbociclo o heterociclo de entre 3 y 6 miembros que está opcionalmente sustituido en forma independiente con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo,

fosfonoxi, fosfono, tioxo, formilo, ciano, C1-C6alquilo, C2-C6alquenilo, C2-C6alquinilo, C1-C6haloalquilo, C2-C6haloalquenilo, C2-C6haloalquinilo, C(O)ORS o –N(RSRS'), y J también puede estar opcionalmente sustituido con uno o más RA. Preferiblemente, D es  o  , donde RM y RN son como se definen precedentemente. También preferiblemente, D es  o  , donde J y RN son como se definen precedentemente. L1 y L2 son en forma independiente entre sí un enlace o C1-C6alquileno, y L3 es un enlace, C1-C6alquileno o -C(O)-, y L1, L2, y L3 están opcionalmente sustituidos en forma independiente entre sí con uno o más RL. Preferiblemente, L1, L2, y L3 son un enlace. –T-RD' se selecciona en forma independiente en cada caso entre –C(O)–LY'–N(RB)C(O)–LS''–RD' o –C(O)–LY'–N(RB)C(O)O–LS''–RD', donde LY' es C1-C6alquileno (por ejemplo, -CH2-) y está opcionalmente sustituido con uno o más sustituyentes seleccionados entre RL, y LS'' preferiblemente es un enlace. –T-RD' también puede seleccionarse, sin que esto constituya limitación alguna, entre –C(O)–LY'–LS''–RD', –C(O)–LY'–O–LS''–RD', –C(O)–LY'–N(RB)–LS''–RD', o –C(O)–LY'–N(RB)S(O)2–LS''–RD'. Preferiblemente, R2 y R5, tomados junto con los átomos a los cuales están unidos, forman  que está opcionalmente sustituido con uno o más RA; R9 y R12, tomados junto con los átomos a los cuales están unidos, forman  que está opcionalmente sustituido con uno o más RA.

En otra forma de realización de este aspecto, A es fenilo (por ejemplo, ), y está opcionalmente sustituido con uno o más RA (preferiblemente, A está sustituido con al menos un halógeno tal como F); y B es  , y está opcionalmente sustituido con uno o más RA (preferiblemente, B está sustituido con al menos un halógeno tal como F). X es  , donde X3 es N y está directamente unido a –L3–D, y X está opcionalmente sustituido con uno o más RA o RF. D es fenilo, y está sustituido con J y opcionalmente sustituido con uno o más RA. J es C3-C6carbociclo, heterociclo de entre 3 y 6 miembros, biciclo de entre 6 y 12 miembros, triciclo de entre 10 y 15 miembros o carbociclo/heterociclo de entre 13 y 15 miembros, y J está opcionalmente sustituido con uno o más RA. Preferiblemente, J está sustituido con un C3-C6carbociclo, heterociclo de entre 3 y 6 miembros, biciclo de entre 6 y 12 miembros o carbociclo/heterociclo de entre 7 y 12 miembros, que está opcionalmente sustituido en forma independiente con uno o más sustituyentes seleccionados entre (1) halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C1-C6alquilo, C2-C6alquenilo, C2-C6alquinilo, C1-C6haloalquilo, C2-C6haloalquenilo, C2-C6haloalquinilo, –C(O)ORS o –N(RSRS'), o (2) trimetilsililo, –O–RS, –S–RS o –C(O)RS; y J también puede estar opcionalmente sustituido con uno o más RA. Preferiblemente, D es  o  , donde J es como se define precedentemente, y cada RN se selecciona en forma independiente entre RD y preferiblemente es hidrógeno o halo como por ejemplo F. L1 y L2 son en forma independiente entre sí un enlace o C1-C6alquileno, y L3 es un enlace, C1-C6alquileno o -C(O)-, y L1, L2, y L3 están opcionalmente sustituidos

en forma independiente entre sí con uno o más RL. Preferiblemente, L1, L2, y L3 son un enlace. –T-RD' se selecciona en forma independiente en cada caso entre –C(O)–LY'–N(RB)C(O)–LS''–RD' o –C(O)–LY'–N(RB)C(O)O–LS''–RD', donde LY' es C1-C6alquileno (por ejemplo, -CH2-) y está opcionalmente sustituido con uno o más sustituyentes seleccionados entre RL, y LS'' preferiblemente es un enlace. –T-RD' también puede seleccionarse, sin que esto constituya limitación alguna, entre –C(O)–LY'–LS''–RD', –C(O)–LY'–O–LS''–RD', –C(O)–LY'–N(RB)–LS''–RD', o –C(O)–LY'–N(RB)S(O)2–LS''–RD'. Preferiblemente, R2 y R5, tomados junto con los átomos a los cuales están unidos, forman un anillo heterocíclico de 5 o 6 miembros (por ejemplo, ) o biciclo de entre 6 y 12 miembros (por ejemplo, ) que está opcionalmente sustituido con uno o más RA; R9 y R12, tomados junto con los átomos a los cuales están unidos, forman un anillo heterocíclico de 5 o 6 miembros (por ejemplo, ) o biciclo de entre 6 y 12 miembros (por ejemplo, ) que está opcionalmente sustituido con uno o más RA.

En aun otro aspecto, la presente invención presenta compuestos de Fórmula ID y sales aceptables farmacéuticamente del mismo.



ID

donde:

G1 y G2 se seleccionan en forma independiente entre sí entre C5-C6carbociclo o heterociclo de 5 o 6 miembros, y están opcionalmente sustituidos en forma independiente entre sí con uno o más RA;

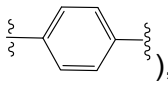
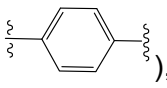
RC' se selecciona en forma independiente entre RC;

RD' se selecciona en forma independiente entre RD;

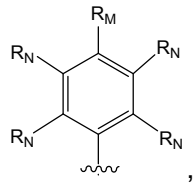
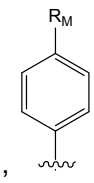
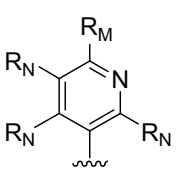
R2 y R5, tomados junto con los átomos a los cuales están unidos, forman un heterociclo de entre 3 y 12 miembros que está opcionalmente sustituido con uno o más RA;

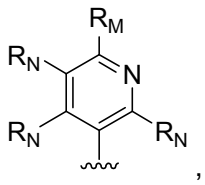
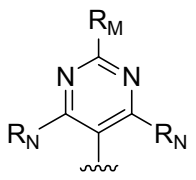
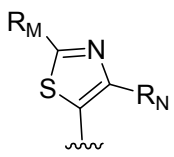
R9 y R12, tomados junto con los átomos a los cuales están unidos, forman un heterociclo de entre 3 y 12 miembros que está opcionalmente sustituido con uno o más RA;

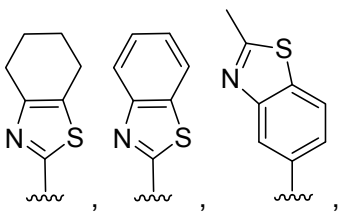
A, B, D, X, L1, L2, L3, T, RA, RC, y RD son como se describe precedentemente en Fórmula I.

En este aspecto, A y B preferiblemente se seleccionan en forma independiente entre C5-C6carbociclo o heterociclo de 5 o 6 miembros, y están opcionalmente sustituidos en forma independiente entre sí con uno o más RA. Más preferiblemente, al menos uno de A y B es fenilo (por ejemplo, ), y está opcionalmente sustituido con uno o más RA. Más preferiblemente, A y B son en forma independiente entre sí fenilo (por ejemplo, ), y están opcionalmente sustituidos en forma independiente entre sí

con uno o más RA.

D preferiblemente se selecciona entre C5-C6carbociclo, heterociclo de 5 o 6 miembros, o biciclos de entre 8 y 12 miembros, y está opcionalmente sustituido con uno o más RA. D también puede seleccionarse preferiblemente entre C1-C6alquilo, C2-C6alquenilo o C2-C6alquinilo, y está opcionalmente sustituido con uno o más RL. Más preferiblemente, D es C5-C6carbociclo, heterociclo de 5 o 6 miembros, o biciclos de entre 6 y 12 miembros, y está sustituido con uno o más RM, donde RM es halógeno, nitro, oxo, fosfonoxi, fosfono, tioxo, ciano, o –LS–RE. También preferiblemente, D es fenilo, y está opcionalmente sustituido con uno o más RA. Más preferiblemente, D es fenilo, y está sustituido con uno o más RM, donde RM es como se define precedentemente. Más preferiblemente, D es  ,  o  , donde RM es como se define precedentemente, y cada RN se selecciona en forma independiente entre RD y preferiblemente es hidrógeno. Uno o más RN también puede ser preferiblemente halo como por ejemplo F.

D es también preferiblemente piridinilo, pirimidinilo, o tiazolilo, opcionalmente sustituido con uno o más RA. Más preferiblemente D es piridinilo, pirimidinilo, o tiazolilo, y está sustituido con uno o más RM. Más preferiblemente, D es  ,  , o  , donde RM es como se define precedentemente, y cada RN se selecciona en forma independiente entre RD y preferiblemente es hidrógeno. Uno o más RN también puede ser preferiblemente halo como por ejemplo F. D es también

preferiblemente indanilo, 4,5,6,7-tetrahidrobenzo[d]tiazolilo, benzo[d]tiazolilo, o indazolilo, y está opcionalmente sustituido con uno o más RA. Más preferiblemente D es indanilo, 4,5,6,7-tetrahidrobenzo[d]tiazolilo, benzo[d]tiazolilo, indazolilo, o benzo[d][1,3]dioxol-5-ilo, y está sustituido con uno o más RM. Más preferiblemente, D es  , y está opcionalmente sustituido con uno o más RM.

Preferiblemente, RM es halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, ciano; o C1-C6alquilo, C2-C6alquenilo o C2-C6alquinilo, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo o ciano; o C3-C6carbociclo o heterociclo de entre 3 y 6 miembros, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C1-C6alquilo, C2-C6alquenilo, C2-C6alquinilo, C1-C6haloalquilo, C2-C6haloalquenilo o C2-C6haloalquinilo. Más preferiblemente, RM es halógeno, hidroxi, mercapto, amino, carboxi; o C1-C6alquilo, C2-C6alquenilo o C2-C6alquinilo, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino o carboxi. Más preferiblemente, RM es C1-C6alquilo el cual está opcionalmente sustituido con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino o carboxi.

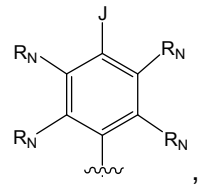
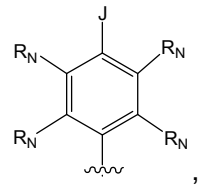
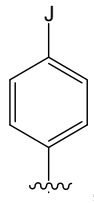
También preferiblemente, RM es halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, o ciano; o RM es –LS–RE, donde LS es una unión o

C1-C6alquileno, y RE es –N(RSRS'), –O–RS, –C(O)RS, –C(O)ORS, –C(O)N(RSRS'), –N(RS)C(O)RS', –N(RS)C(O)ORS', –N(RS)SO2RS', –SO2RS, –SRS, o –P(O)(ORS)2, donde RS y RS' pueden seleccionarse en forma independiente entre sí, por ejemplo, entre (1) hidrógeno o (2) C1-C6alquilo opcionalmente sustituido en cada caso con uno o más halógeno, hidroxi, –O–C1-C6alquilo o heterociclo de entre 3 y 6 miembros; o RM es C1-C6alquilo, C2-C6alquenilo o C2-C6alquinilo, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo o ciano; o RM es C3-C6carbociclo o heterociclo de entre 3 y 6 miembros, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C1-C6alquilo, C2-C6alquenilo, C2-C6alquinilo, C1-C6haloalquilo, C2-C6haloalquenilo, C2-C6haloalquinilo, –C(O)ORS, o –N(RSRS'). Más preferiblemente, RM es halógeno (por ejemplo, fluoro, cloro, bromo, yodo), hidroxi, mercapto, amino, carboxi, o C1-C6alquilo (por ejemplo, metilo, isopropilo, tert-butilo), C2-C6alquenilo o C2-C6alquinilo, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, ciano, o carboxi. Por ejemplo RM es CF3, –C(CF3)2–OH, –C(CH3)2–CN, –C(CH3)2–CH2OH, o –C(CH3)2–CH2NH2. También preferiblemente RM es –LS–RE donde LS es una unión y RE es –N(RSRS'), –O–RS, –N(RS)C(O)ORS', –N(RS)SO2RS', –SO2RS, o –SRS. Por ejemplo donde LS es una unión, RE es –N(C1-C6alquil)2 (por ejemplo, –NMe2); –N(C1-C6alquilen–O–C1-C6alquil)2 (por ejemplo –N(CH2CH2OMe)2); –N(C1-C6alquil)(C1-C6alquilen–O–C1-C6alquilo) (por ejemplo –N(CH3)(CH2CH2OMe)); –O–C1-C6alquilo (por ejemplo, –O–Me, –O–Et, –O–isopropilo, –O–tert-butilo, –O–n-hexilo); –O–C1-C6haloalquilo (por ejemplo, – OCF3, –OCH2CF3); –O–C1-C6alquilen–piperidina (por ejemplo, –O–CH2CH2–1-piperidilo); –N(C1-C6alquil)C(O)OC1-C6alquilo (por ejemplo, –

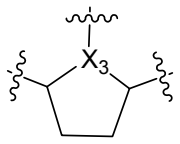
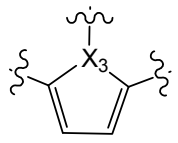
N(CH3)C(O)O–CH2CH(CH3)2), –N(C1-C6alquil)SO2C1-C6alquilo (por ejemplo, –N(CH3)SO2CH3); –SO2C1-C6alquilo (por ejemplo, –SO2Me); –SO2C1-C6haloalquilo (por ejemplo, –SO2CF3); o –S–C1-C6haloalquilo (por ejemplo, SCF3). También preferiblemente RM es –LS–RE donde LS es C1-C6alquileno (por ejemplo, –CH2–, –C(CH3)2–, –C(CH3)2–CH2–) y RE es –O–RS, –C(O)ORS, –N(RS)C(O)ORS', o –P(O)(ORS)2. Por ejemplo RM es –C1-C6alquilen–O–RS (por ejemplo, –C(CH3)2–CH2–OMe); –C1-C6alquilen–C(O)ORS (por ejemplo, –C(CH3)2–C(O)OMe); –C1-C6alquilen–N(RS)C(O)ORS' (por ejemplo, –C(CH3)2–CH2–NHC(O)OCH3); o –C1-C6alquilen–P(O)(ORS)2 (por ejemplo, –CH2–P(O)(OEt)2). También más preferiblemente RM es C3-C6carbociclo o heterociclo de entre 3 y 6 miembros, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C1-C6alquilo, C2-C6alquenilo, C2-C6alquinilo, C1-C6haloalquilo, C2-C6haloalquenilo, C2-C6haloalquinilo, –C(O)ORS, o –N(RSRS'). Por ejemplo RM 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). Más preferiblemente, RM es C1-C6alquilo el cual está opcionalmente sustituido con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino o carboxi (por ejemplo, tert-butilo, CF3).

Más preferiblemente, D es C5-C6carbociclo, heterociclo de 5 o 6 miembros o biciclo de entre 6 y 12 miembros y está sustituido con J y opcionalmente sustituido con uno o más RA, donde J es C3-C6carbociclo, heterociclo de entre 3 y 6 miembros o biciclo de entre 6 y 12 miembros y está opcionalmente sustituido con uno o más RA. Preferiblemente, J está sustituido con un C3-C6carbociclo o heterociclo de entre 3 y 6

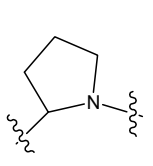
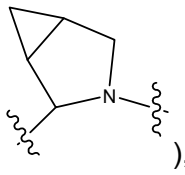
miembros, donde dicho C3-C6carbociclo o heterociclo de entre 3 y 6 miembros está opcionalmente sustituido en forma independiente con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C1-C6alquilo, C2-C6alquenilo, C2-C6alquinilo, C1-C6haloalquilo, C2-C6haloalquenilo, C2-C6haloalquinilo, C(O)ORS o –N(RSRS'), y J también puede estar opcionalmente sustituido con uno o más RA. También preferiblemente, D es C5-C6carbociclo o heterociclo de 5 o 6 miembros y está sustituido con J y opcionalmente sustituido con uno o más RA, y J es C3-C6carbociclo o heterociclo de entre 3 y 6 miembros y está opcionalmente sustituido con uno o más RA, y preferiblemente, J está sustituido con al menos un C3-C6carbociclo o heterociclo de entre 3 y 6 miembros que está opcionalmente sustituido en forma independiente con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C1-C6alquilo, C2-C6alquenilo, C2-C6alquinilo, C1-C6haloalquilo, C2-C6haloalquenilo, C2-C6haloalquinilo, C(O)ORS o –N(RSRS'). También preferiblemente, D es C5-C6carbociclo o heterociclo de 5 o 6 miembros y está sustituido con J y opcionalmente sustituido con uno o más RA, y J es biciclo de entre 6 y 12 miembros (por ejemplo, un biciclo fusionado, en puente o espiro de entre 7 y 12 miembros que comprende un átomo del anillo nitrógeno a través del cual J se enlaza por unión covalente con D) y está opcionalmente sustituido con uno o más RA. Más preferiblemente, D es fenilo y está sustituido con J y opcionalmente sustituido con uno o más RA, y J es C3-C6carbociclo, heterociclo de entre 3 y 6 miembros o biciclo de entre 6 y 12 miembros y está opcionalmente sustituido con uno o más RA, y preferiblemente J está sustituido con al menos un C3-C6carbociclo o heterociclo de entre 3 y 6 miembros que está opcionalmente sustituido en forma independiente con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C1-C6alquilo, C2-C6alquenilo, C2-C6alquinilo, C1-C6haloalquilo, C2-C6haloalquenilo, C2-C6haloalquinilo, C(O)ORS o –N(RSRS'). Más

preferiblemente, D es  , donde cada RN se selecciona en forma independiente entre RD y preferiblemente es hidrógeno o halógeno, y J es C3-C6carbociclo, heterociclo de entre 3 y 6 miembros o biciclo de entre 6 y 12 miembros y está opcionalmente sustituido con uno o más RA, y preferiblemente J está sustituido con al menos un C3-C6carbociclo o heterociclo de entre 3 y 6 miembros que está opcionalmente sustituido en forma independiente con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C1-C6alquilo, C2-C6alquenilo, C2-C6alquinilo, C1-C6haloalquilo, C2-C6haloalquenilo, C2-C6haloalquinilo, C(O)ORS o –N(RSRS'). También preferiblemente, D es  , donde cada RN se selecciona en forma independiente entre RD y preferiblemente es hidrógeno o halógeno, y J es C3-C6carbociclo o heterociclo de entre 3 y 6 miembros y está sustituido con un C3-C6carbociclo o heterociclo de entre 3 y 6 miembros que está opcionalmente sustituido en forma independiente con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C1-C6alquilo, C2-C6alquenilo, C2-C6alquinilo, C1-C6haloalquilo, C2-C6haloalquenilo, C2-C6haloalquinilo, C(O)ORS o –N(RSRS'), y J también puede estar opcionalmente sustituido con uno o más RA. También preferiblemente, D es  , y J es C3-C6carbociclo o heterociclo de entre 3 y 6 miembros y está opcionalmente sustituido con uno o más RA, y preferiblemente J está sustituido con al menos un C3-C6carbociclo o

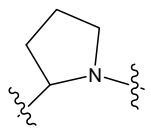
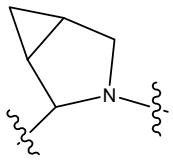
heterociclo de entre 3 y 6 miembros que está opcionalmente sustituido en forma independiente con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C1-C6alquilo, C2-C6alquenilo, C2-C6alquinilo, C1-C6haloalquilo, C2-C6haloalquenilo, C2-C6haloalquinilo, C(O)ORS o –N(RSRS').

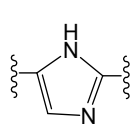
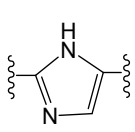
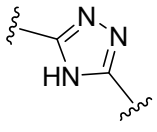
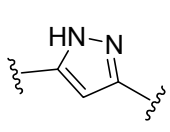
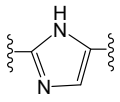
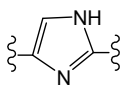
X preferiblemente es C5-C6carbociclo, heterociclo de 5 o 6 miembros, o biciclos de entre 6 y 12 miembros (por ejemplo,  o  , donde X3 es N y está directamente unido a –L3–D), y está opcionalmente sustituido con uno o más RA o RF. Los ejemplos no limitativos de X se describen precedentemente.

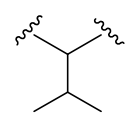
L1 y L2 son preferiblemente en forma independiente un enlace o C1-C6alquileno, L3 preferiblemente se selecciona entre un enlace, C1-C6alquileno o –C(O)–, y L1, L2, y L3 están opcionalmente sustituidos en forma independiente entre sí con uno o más RL. Más preferiblemente, L1, L2 y L3 son en forma independiente entre sí un enlace o C1-C6alquileno (por ejemplo, –CH2– o –CH2CH2–), y están opcionalmente sustituidos en forma independiente entre sí con uno o más RL. Más preferiblemente, L1, L2 y L3 son un enlace.

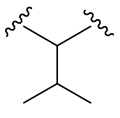
R2 y R5, tomados junto con los átomos a los cuales están unidos, preferiblemente forman un heterociclo de 5 o 6 miembros o biciclo de entre 6 y 12 miembros (por ejemplo,  o ), que está opcionalmente sustituido con uno o más RA.

R9 y R12, tomados junto con los átomos a los cuales están unidos, preferiblemente forman un heterociclo de 5 o 6 miembros o biciclo de entre 6 y 12

miembros (por ejemplo,  o ), que está opcionalmente sustituido con uno o más RA.

G1 y G2 preferiblemente se seleccionan en forma independiente entre sí entre  ,  ,  o  , y están opcionalmente sustituidos en forma independiente entre sí con uno o más RA (por ejemplo, uno o más cloro o bromo). Más preferiblemente, G1 es  (incluyendo cualquier tautómero del mismo), y G2 es  (incluyendo cualquier tautómero del mismo), y cada G1 y G2 está opcionalmente sustituido en forma independiente con uno o más RA (por ejemplo, uno o más cloro o bromo).

-T-RD' puede seleccionarse en forma independiente en cada caso, sin que esto constituya limitación alguna, entre –C(O)–LY'–, –C(O)O–LY'–RD', –C(O)–LY'–N(RB)C(O)–LS''–RD', –C(O)–LY'–N(RB)C(O)O–LS''–RD', –N(RB)C(O)–LY'–N(RB)C(O)–LS''–RD', –N(RB)C(O)–LY'—N(RB)C(O)O–LS''–RD', o –N(RB)C(O)–LY'—N(RB)–LS''–RD', donde LY' es en forma independiente en cada caso LS' y, preferiblemente, es en forma independiente en cada caso C1-C6alquileno (por ejemplo, -CH2- o ) y está opcionalmente sustituido con uno o más sustituyentes seleccionados entre RL. Preferiblemente, -T-RD' se selecciona en forma independiente en cada caso entre –C(O)–LY'–M'–LS''–RD' o –N(RB)C(O)–LY'–M'–LS''–RD'. Más preferiblemente, -T-RD' se selecciona en forma independiente en cada caso entre –C(O)–LY'–N(RB)C(O)–LS''–RD' o –C(O)–LY'–N(RB)C(O)O–LS''–RD'. Más preferiblemente, -T-RD' se selecciona en forma

independiente en cada caso entre –C(O)–LY'–N(RB)C(O)–RD' o –C(O)–LY'–N(RB)C(O)O–RD', donde LY' preferiblemente es en forma independiente en cada caso C1-C6alquileno (por ejemplo, -CH2- o ) y está opcionalmente sustituido con uno o más sustituyentes seleccionados entre RL.

RC' es preferiblemente hidrógeno, y RD' preferiblemente se selecciona en forma independiente en cada caso entre RE. Más preferiblemente, RD' se selecciona en forma independiente en cada caso entre C1-C6alquilo, C2-C6alquenilo o C2-C6alquinilo, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C3-C6carbociclo o heterociclo de entre 3 y 6 miembros; o C3-C6carbociclo o heterociclo de entre 3 y 6 miembros, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C1-C6alquilo, C2-C6alquenilo, C2-C6alquinilo, C1-C6haloalquilo, C2-C6haloalquenilo o C2-C6haloalquinilo.

RA preferiblemente es halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, ciano; o C1-C6alquilo, C2-C6alquenilo o C2-C6alquinilo, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo o ciano; o C3-C6carbociclo o heterociclo de entre 3 y 6 miembros, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C1-C6alquilo, C2-C6alquenilo, C2-C6alquinilo, C1-C6haloalquilo, C2-C6haloalquenilo o C2-C6haloalquinilo; o –LA–O–RS, –LA–S–RS, –LA–C(O)RS, –LA–OC(O)RS, –LA–C(O)ORS, –LA–N(RSRS'), –LA–S(O)RS, –LA–SO2RS, –LA–C(O)N(RSRS'), –LA–N(RS)C(O)RS', –

LA–N(RS)C(O)N(RS’RS’’), –LA–N(RS)SO2RS’, –LA–SO2N(RSRS’), –LA–N(RS)SO2N(RS’RS’’), –LA–N(RS)S(O)N(RS’RS’’), –LA–OS(O)–RS, –LA–OS(O)2–RS, –LA–S(O)2ORS, –LA–S(O)ORS, –LA–OC(O)ORS, –LA–N(RS)C(O)ORS’, –LA–OC(O)N(RSRS’), –LA–N(RS)S(O)–RS’, –LA–S(O)N(RSRS’) o –LA–C(O)N(RS)C(O)–RS’, donde LA es un enlace, C1-C6alquileno, C2-C6alquenileno o C2-C6alquinileno.

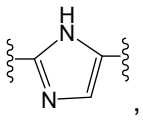
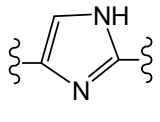
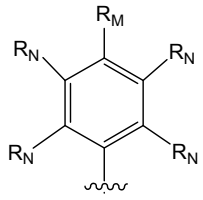
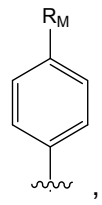
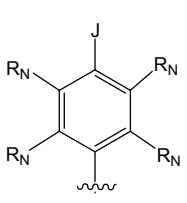
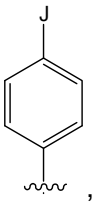
Más preferiblemente, RA es halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, ciano; o C1-C6alquilo, C2-C6alquenilo o C2-C6alquinilo, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo o ciano; o C3-C6carbociclo o heterociclo de entre 3 y 6 miembros, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C1-C6alquilo, C2-C6alquenilo, C2-C6alquinilo, C1-C6haloalquilo, C2-C6haloalquenilo o C2-C6haloalquinilo.

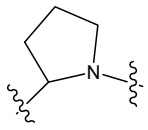
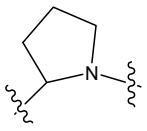
Más preferiblemente, RA es halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, ciano; o C1-C6alquilo, C2-C6alquenilo o C2-C6alquinilo, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo o ciano.

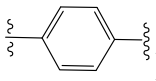
LS, LS’ y LS’’ preferiblemente se seleccionan en forma independiente entre sí en cada caso entre un enlace; o C1-C6alquileno, C2-C6alquenileno o C2-C6alquinileno.

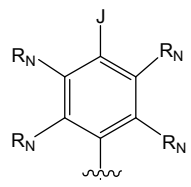
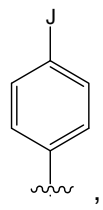
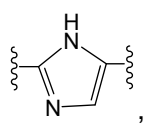
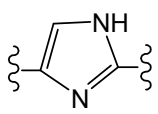
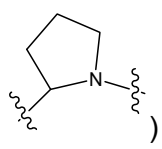
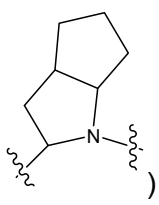
A y B pueden ser iguales o diferentes. De la misma manera, L1 y L2 pueden ser iguales o diferentes.

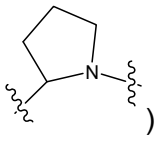
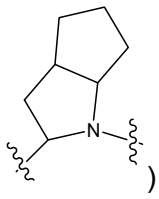
En una forma de realización de este aspecto, A y B son en forma independiente entre sí fenilo, y están opcionalmente sustituidos en forma independiente entre sí con uno o más RA; D es fenilo, y está opcionalmente sustituido en forma independiente con uno o

más RA, o está sustituido con J y opcionalmente sustituido con uno o más RA, donde J es C3-C6carbociclo, heterociclo de entre 3 y 6 miembros o biciclo de entre 6 y 12 miembros y está opcionalmente sustituido con uno o más RA. Preferiblemente, J está sustituido con un C3-C6carbociclo o heterociclo de entre 3 y 6 miembros que está opcionalmente sustituido en forma independiente con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C1-C6alquilo, C2-C6alquenilo, C2-C6alquinilo, C1-C6haloalquilo, C2-C6haloalquenilo, C2-C6haloalquinilo, C(O)ORS o –N(RSRS'), y J también puede estar opcionalmente sustituido con uno o más RA; y G1 es  , G2 es  , y cada G1 y G2 está opcionalmente sustituido en forma independiente con uno o más RA (por ejemplo, uno o más cloro o bromo). Preferiblemente, D es  o  , donde RM y RN son como se definen precedentemente. También preferiblemente, D es  o  , donde J y RN son como se definen precedentemente. L1 y L2 son en forma independiente entre sí un enlace o C1-C6alquileno, y L3 es un enlace, C1-C6alquileno o -C(O)-, y L1, L2, y L3 están opcionalmente sustituidos en forma independiente entre sí con uno o más RL. Preferiblemente, L1, L2, y L3 son un enlace. -T-RD' se selecciona en forma independiente en cada caso entre –C(O)–LY'–N(RB)C(O)–LS''–RD' o –C(O)–LY'–N(RB)C(O)O–LS''–RD', donde LY' es C1-C6alquileno (por ejemplo, -CH2-) y está opcionalmente sustituido con uno o más sustituyentes seleccionados entre RL, y LS'' preferiblemente es un enlace. –T-RD' también puede seleccionarse, sin que esto constituya limitación alguna, entre –C(O)–LY'–LS''–RD', –C(O)–LY'–O–LS''–RD', –

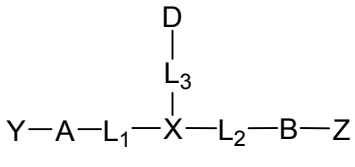
C(O)–LY'–N(RB)–LS''–RD', o –C(O)–LY'–N(RB)S(O)2–LS''–RD'. Preferiblemente, R2 y R5, tomados junto con los átomos a los cuales están unidos, forman  que está opcionalmente sustituido con uno o más RA; R9 y R12, tomados junto con los átomos a los cuales están unidos, forman  que está opcionalmente sustituido con uno o más RA.

En otra forma de realización de este aspecto, A y B son en forma independiente entre sí fenilo (por ejemplo, ), y están opcionalmente sustituidos en forma independiente entre sí con uno o más RA (preferiblemente, A y B están sustituidos en forma independiente entre sí con al menos un halógeno tal como F). X es , donde X3 es N y está directamente unido a –L3–D, y X está opcionalmente sustituido con uno o más RA o RF. D es fenilo, y está sustituido con J y opcionalmente sustituido con uno o más RA. J es C3-C6carbociclo, heterociclo de entre 3 y 6 miembros, biciclo de entre 6 y 12 miembros, triciclo de entre 10 y 15 miembros o carbociclo/heterociclo de entre 13 y 15 miembros, y J está opcionalmente sustituido con uno o más RA. Preferiblemente, J está sustituido con un C3-C6carbociclo, heterociclo de entre 3 y 6 miembros, biciclo de entre 6 y 12 miembros o carbociclo/heterociclo de entre 7 y 12 miembros, que está opcionalmente sustituido en forma independiente con uno o más sustituyentes seleccionados entre (1) halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C1-C6alquilo, C2-C6alquenilo, C2-C6alquinilo, C1-C6haloalquilo, C2-C6haloalquenilo, C2-C6haloalquinilo, –C(O)ORS o –N(RSRS'), o (2) trimetilsililo, –O–RS, –S–RS o –C(O)RS; y J también puede estar opcionalmente

sustituido con uno o más RA. Preferiblemente, D es  o  , donde J es como se define precedentemente, y cada RN se selecciona en forma independiente entre RD y preferiblemente es hidrógeno o halo como por ejemplo F. G1 es  , G2 es  , y cada G1 y G2 está opcionalmente sustituido en forma independiente con uno o más RA (por ejemplo, uno o más cloro o bromo). L1 y L2 son en forma independiente entre sí un enlace o C1-C6alquileno, y L3 es un enlace, C1-C6alquileno o -C(O)-, y L1, L2, y L3 están opcionalmente sustituidos en forma independiente entre sí con uno o más RL. Preferiblemente, L1, L2, y L3 son un enlace. -T-RD' se selecciona en forma independiente en cada caso entre –C(O)–LY'–N(RB)C(O)–LS''–RD' o –C(O)–LY'–N(RB)C(O)O–LS''–RD', donde LY' es C1-C6alquileno (por ejemplo, -CH2-) y está opcionalmente sustituido con uno o más sustituyentes seleccionados entre RL, y LS'' preferiblemente es un enlace. –T-RD' también puede seleccionarse, sin que esto constituya limitación alguna, entre –C(O)–LY'–LS''–RD', –C(O)–LY'–O–LS''–RD', –C(O)–LY'–N(RB)–LS''–RD', o –C(O)–LY'–N(RB)S(O)2–LS''–RD'. Preferiblemente, R2 y R5, tomados junto con los átomos a los cuales están unidos, forman un anillo heterocíclico de 5 o 6 miembros (por ejemplo, ) o biciclo de entre 6 y 12 miembros (por ejemplo, ) que está opcionalmente sustituido con uno o más RA; R9 y R12, tomados junto con los átomos a los cuales están unidos, forman un anillo heterocíclico de 5 o 6

miembros (por ejemplo, ) o biciclo de entre 6 y 12 miembros (por ejemplo, ) que está opcionalmente sustituido con uno o más RA.

En otro aspecto, la presente invención presenta compuestos de Fórmula IE y sales aceptables farmacéuticamente del mismo,



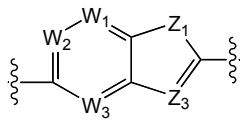
IE

donde:

X es heterociclo de entre 4 y 8 miembros, y está opcionalmente sustituido con uno o más RA;

L1 y L2 se seleccionan en forma independiente entre sí entre un enlace o C1-C6alquileno que está opcionalmente sustituido en forma independiente en cada caso con uno o más halo, hidroxi, –O–C1-C6alquilo, o –O–C1-C6haloalquilo;

L3 es un enlace o C1-C6alquileno;

A y B son en forma independiente entre sí fenilo, piridinilo, tiazolilo, o  donde Z1 se selecciona en forma independiente en cada caso entre O, S, NH o CH2, Z3 se selecciona en forma independiente en cada caso entre N o CH, y W1, W2, y W3 se seleccionan en forma independiente entre sí en cada caso entre CH o N; A y B están opcionalmente sustituidos en forma independiente entre sí con uno o más RA.

D es C6-C10carbociclo o heterociclo de entre 5 y 12 miembros, cada uno de los cuales está opcionalmente sustituido con uno o más RM;

Y es –T'–C(R1R2)N(R5)–T–RD;

Z es –T'–C(R8R9)N(R12)–T–RD;

R1 es hidrógeno, C1-C6alquilo, C1-C6haloalquilo, o carbociclo o heterociclo de entre 3 y 6 miembros, donde cada carbociclo o heterociclo de entre 3 y 6 miembros está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, C1-C6alquilo, C1-C6haloalquilo, –O–C1-C6alquilo o –O–C1-C6haloalquilo;

R2 y R5 son en forma independiente entre sí hidrógeno, C1-C6alquilo, C1-C6haloalquilo, o carbociclo o heterociclo de entre 3 y 6 miembros, donde cada carbociclo o heterociclo de entre 3 y 6 miembros está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, C1-C6alquilo, C1-C6haloalquilo, –O–C1-C6alquilo o –O–C1-C6haloalquilo; o R2 y R5, tomados junto con los átomos a los cuales están unidos, forman un heterociclo de entre 3 y 12 miembros que está opcionalmente sustituido con uno o más RA (por ejemplo, 1, 2, 3, o 4 RA);

R8 es hidrógeno, C1-C6alquilo, C1-C6haloalquilo, o carbociclo o heterociclo de entre 3 y 6 miembros, donde cada carbociclo o heterociclo de entre 3 y 6 miembros está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, C1-C6alquilo, C1-C6haloalquilo, –O–C1-C6alquilo o –O–C1-C6haloalquilo;

R9 y R12 son en forma independiente entre sí hidrógeno, C1-C6alquilo, C1-C6haloalquilo, o carbociclo o heterociclo de entre 3 y 6 miembros, donde cada carbociclo o heterociclo de entre 3 y 6 miembros está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, C1-C6alquilo, C1-C6haloalquilo, –O–C1-

C6alquilo o –O–C1-C6haloalquilo; o R9 y R12, tomados junto con los átomos a los cuales están unidos, forman un heterociclo de entre 3 y 12 miembros que está opcionalmente sustituido con uno o más RA (por ejemplo, 1, 2, 3, o 4 RA);

T se selecciona en forma independiente en cada caso entre un enlace o –C(O)–LS'–;

T' se selecciona en forma independiente en cada caso entre un enlace, –C(O)N(RB)–, –N(RB)C(O)–, o heterociclo de entre 3 y 12 miembros, donde dicho heterociclo de entre 3 y 12 miembros está opcionalmente sustituido en forma independiente en cada caso con uno o más RA;

RD se selecciona en forma independiente en cada caso entre hidrógeno o RA;

RA se selecciona en forma independiente en cada caso entre halógeno, nitro, oxo, fosfonoxi, fosfono, tioxo, ciano, o –LS–RE;

RB y RB' se seleccionan en forma independiente entre sí en cada caso entre hidrógeno; o C1-C6alquilo que está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno o carbociclo o heterociclo de entre 3 y 6 miembros; o carbociclo o heterociclo de entre 3 y 6 miembros; donde cada carbociclo o heterociclo de entre 3 y 6 miembros en RB o RB' está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, C1-C6alquilo, C1-C6haloalquilo, –O–C1-C6alquilo, o –O–C1-C6haloalquilo;

RE se selecciona en forma independiente en cada caso entre –O–RS, –S–RS, –C(O)RS, –OC(O)RS, –C(O)ORS, –N(RSRS'), –S(O)RS, –SO2RS, –C(O)N(RSRS'), –N(RS)C(O)RS', –N(RS)C(O)N(RS'RS''), –N(RS)SO2RS', –SO2N(RSRS'), –N(RS)SO2N(RS'RS''), –N(RS)S(O)N(RS'RS''), –OS(O)–RS, –OS(O)2–RS, –S(O)2ORS, –S(O)ORS, –OC(O)ORS, –N(RS)C(O)ORS', –OC(O)N(RSRS'), –N(RS)S(O)–RS', –S(O)N(RSRS'), –C(O)N(RS)C(O)–RS', o

=C(RSRS'); o C1-C6alquilo, C2-C6alquenilo o C2-C6alquinilo, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo o ciano; o C3-C12carbociclo o heterociclo de entre 3 y 12 miembros, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C1-C6alquilo, C2-C6alquenilo, C2-C6alquinilo, C1-C6haloalquilo, C2-C6haloalquenilo o C2-C6haloalquinilo;

RL se selecciona en forma independiente en cada caso entre halógeno, nitro, oxo, fosfonoxi, fosfono, tioxo, ciano, –O–RS, –S–RS, –C(O)RS, –OC(O)RS, –C(O)ORS, –N(RSRS'), –S(O)RS, –SO2RS, –C(O)N(RSRS'), o –N(RS)C(O)RS'; o C3-C12carbociclo o heterociclo de entre 3 y 12 miembros, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C1-C6alquilo, C2-C6alquenilo, C2-C6alquinilo, C1-C6haloalquilo, C2-C6haloalquenilo o C2-C6haloalquinilo;

LS se selecciona en forma independiente en cada caso entre un enlace; o C1-C6alquileno, C2-C6alquenileno o C2-C6alquinileno, cada opcionalmente sustituido en forma independiente con halógeno;

LS' se selecciona en forma independiente en cada caso entre un enlace; o C1-C6alquileno, C2-C6alquenileno o C2-C6alquinileno, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más RL;

RS, RS' y RS'' se seleccionan en forma independiente entre sí en cada caso entre

hidrógeno; C1-C6alquilo, C2-C6alquenilo o C2-C6alquinilo, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, –O–C1-C6alquilo, –O–C1-C6haloalquilo, o carbociclo o heterociclo de entre 3 y 12 miembros; o carbociclo o heterociclo de entre 3 y 12 miembros; donde cada carbociclo o heterociclo de entre 3 y 12 miembros en RS , RS' o RS'' está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C1-C6alquilo, C2-C6alquenilo, C2-C6alquinilo, C1-C6haloalquilo, C2-C6haloalquenilo o C2-C6haloalquinilo;

RM se selecciona en forma independiente en cada caso entre:

halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, ciano, SF5, –N(RSRS'), –O–RS, –OC(O)RS, –OC(O)ORS, –OC(O)N(RSRS'), –C(O)RS, –C(O)ORS, –C(O)N(RSRS'), –N(RS)C(O)RS', –N(RS)C(O)ORS', –N(RS)SO2RS', –S(O)RS, –SO2RS, –S(O)N(RSRS'), –SRS, –Si(RS)3, o –P(O)(ORS)2;

C1-C6alquilo, C2-C6alquenilo o C2-C6alquinilo, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, –N(RSRS'), –O–RS, –OC(O)RS, –OC(O)ORS, –OC(O)N(RSRS'), –C(O)RS, –C(O)ORS, –C(O)N(RSRS'), –N(RS)C(O)RS', –N(RS)C(O)ORS', –N(RS)SO2RS', –S(O)RS, –SO2RS, –S(O)N(RSRS'), –SRS, o –P(O)(ORS)2; o

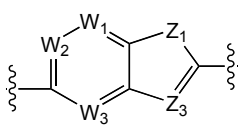
G2, donde G2 es un C3-C12carbociclo o heterociclo de entre 3 y 12 miembros, cada uno de los cuales está opcionalmente sustituido en forma

independiente en cada caso con uno o más RG2, y cada RG2 se selecciona en forma independiente entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C1-C6alquilo, C2-C6alquenilo, C2-C6alquinilo, C1-C6haloalquilo, C2-C6haloalquenilo, C2-C6haloalquinilo, –O–RS, –C(O)ORS, –C(O)RS, –N(RSRS'), o –L4–G3;

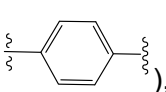
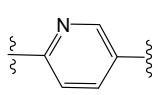
L4 es una unión, C1-C6alquileno, C2-C6alquenileno, C2-C6alquinileno, –O–, –S–, –N(RB)–, –C(O)–, –S(O)2–, –S(O)–, –C(O)O–, –OC(O)–, –OC(O)O–, –C(O)N(RB)–, –N(RB)C(O)–, –N(RB)C(O)O–, –OC(O)N(RB)–, –N(RB)S(O)–, –N(RB)S(O)2–, –S(O)N(RB)–, –S(O)2N(RB)–, –N(RB)C(O)N(RB')–, –N(RB)SO2N(RB')–, o –N(RB)S(O)N(RB')–;

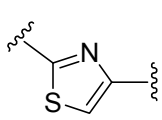
G3 es un C3-C12carbociclo o heterociclo de entre 3 y 12 miembros, y está opcionalmente sustituido con uno o más RG3; y

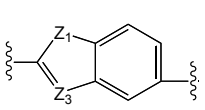
RG3 es cada en forma independiente, en cada caso, halógeno, –C1-C6alquilo, –C(O)C1-C6alquilo, –C1-C6haloalquilo, –O–C1-C6alquilo, –O–C1-C6haloalquilo, C3-C6carbociclo, o heterociclo de entre 3 y 6 miembros.

Como se ha descrito para los compuestos de Fórmula IE A y B son cada uno fenilo, piridinilo, tiazolilo, o 

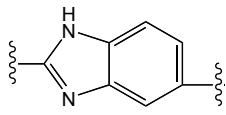
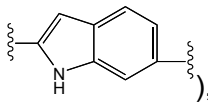
donde Z1 se selecciona en forma independiente en cada caso entre O, S, NH o CH2, Z3 se selecciona en forma independiente en cada caso entre N o CH, y W1, W2, y W3 se seleccionan en forma independiente entre sí en cada caso entre CH o N; A y B están opcionalmente sustituidos en forma independiente entre sí con uno o más RA.

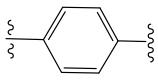
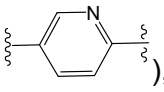
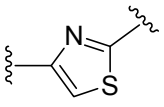
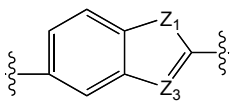
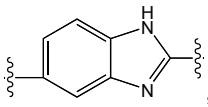
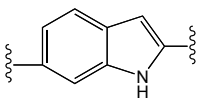
Preferiblemente, A se selecciona entre fenilo (por ejemplo, ), piridinilo (por ejemplo, 

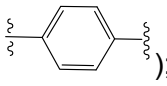
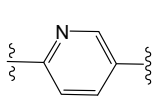
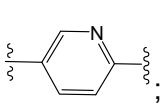
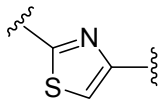
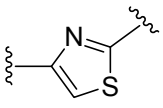
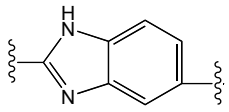
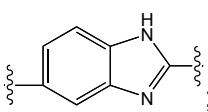
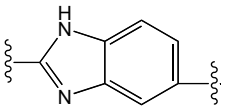
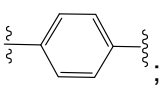
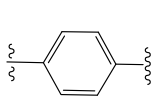
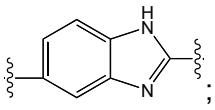
), tiazolilo (por ejemplo, 

), o 

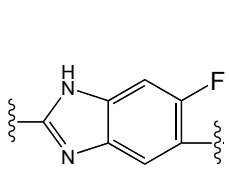
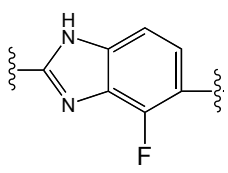
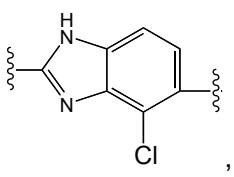
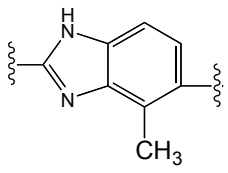
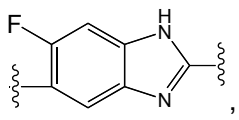
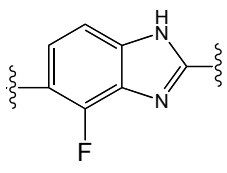
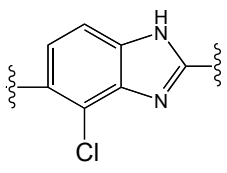
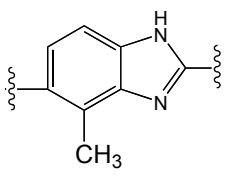
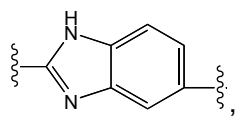
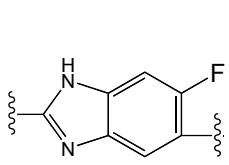
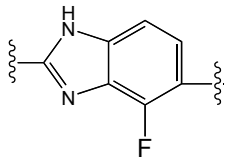
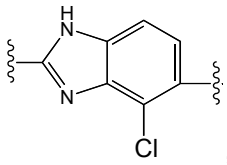
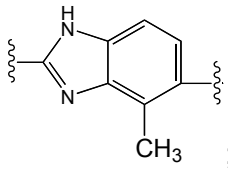
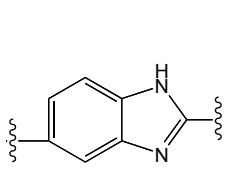
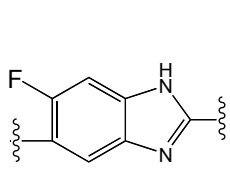
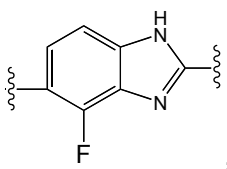
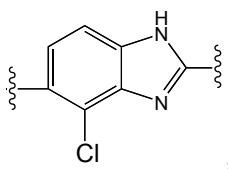
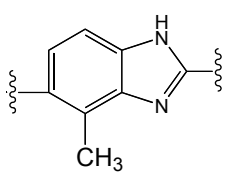
(por

ejemplo,  , ), y está opcionalmente sustituido con uno o más RA.

Preferiblemente, B se selecciona entre fenilo (por ejemplo, ), piridinilo (por ejemplo, ), tiazolilo (por ejemplo, ), o  (por ejemplo,  , ), y está opcionalmente sustituido con uno o más RA.

Más preferiblemente, A y B son fenilo (por ejemplo, A y B son ); o 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 está opcionalmente sustituido en forma independiente con uno o más RA.

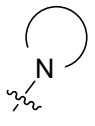
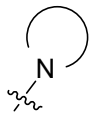
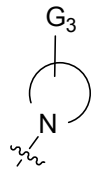
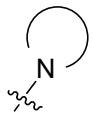
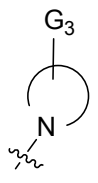
En algunas formas de realización de este aspecto de la invención, A y B se sustituyen con uno o más RA, donde cada RA se selecciona en forma independiente entre halógeno (por ejemplo, fluoro, cloro), LS–RE (donde LS es un enlace y RE es –C1-C6alquilo (por ejemplo, metilo), –O–RS (por ejemplo, –O–C1-C6alquilo, –OCH3), o –C1-C6alquilo opcionalmente sustituido con uno o más halógeno (por ejemplo, –CF3)), o LS–RE (donde LS es C1-C6alquileno y RE es –O–RS (por ejemplo, –C1-C6alquil–O–C1-C6alquilo, –CH2OCH3)). Por ejemplo, en algunas formas de realización A es

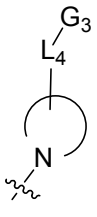
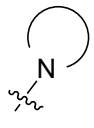
 ,  ,  , o  y B es como se define precedentemente. En algunas otras formas de realización B es  ,  ,  , o  y A es como se define precedentemente. En aun otras formas de realización A es  ,  ,  ,  , o  ; y B es  ,  ,  ,  , o  .

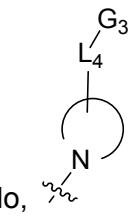
Como se ha descrito para los compuestos de Fórmula IE D es C6-C10carbociclo o heterociclo de entre 3 y 12 miembros opcionalmente sustituido con uno o más RM. Preferiblemente, D es C6-C10arilo (por ejemplo, fenilo, naftilo, indanilo), o heteroarilo de entre 5 y 10 miembros (piridinilo, tiazolilo, 4,5,6,7-tetrahidrobenzo[d]tiazolilo, benzo[d]tiazolilo, indazolilo, benzo[d][1,3]dioxol-5-ilo), y D está sustituido con uno o más RM. Por ejemplo, en algunas formas de realización D es preferiblemente fenilo sustituido con uno o más RM, donde cada RM es en forma independiente halógeno (por ejemplo, fluoro, cloro, bromo); C1-C6alquilo (por ejemplo, tert-butilo); C1-C6alquilo sustituido con

uno o más halógeno (por ejemplo, CF3); –O–RS como por ejemplo –O–C1-C6alquilo (por ejemplo, –O–CH2CH3); o –O–C1-C6alquilo sustituido en cada caso con uno o más halógeno (por ejemplo, –O–CF3, –O–CH2CHF2) o –O–C1-C6alquilo (por ejemplo, –O–CH2CH2OCH3); –O–RS (por ejemplo, –O–C1-C6alquilo, como por ejemplo –O–CH2) sustituido con heterociclo de entre 3 y 12 miembros (por ejemplo, 3-etiloxetan-3-ilo, 1,3-dioxolan-4-ilo); –O–RS donde RS es un carbociclo o heterociclo opcionalmente sustituido de entre 3 y 12 miembros (por ejemplo, ciclopentilo, ciclohexilo, fenilo, 1,3-dioxan-5-ilo); –N(RS)C(O)RS' donde RS y RS' son en forma independiente entre sí C1-C6alquilo (por ejemplo, –N(t-Bu)C(O)Me); SF5; –SO2RS donde RS es C1-C6alquilo (por ejemplo, –SO2Me); o C3-C12carbociclo (por ejemplo, ciclopropilo, ciclohexilo, fenilo).

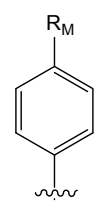
En algunas formas de realización de este aspecto de la invención, D es preferiblemente fenilo o piridilo y está sustituido con uno o más RM donde un RM es G2. En algunas formas de realización donde D es fenilo o piridilo, D está sustituido con G2, G2 es heterociclo de entre 3 y 12 miembros (por ejemplo, piridinilo, piperidinilo, pirrolidinilo, azetidinilo, oxazolilo) y está opcionalmente sustituido con uno o más halógeno (por ejemplo, fluoro, cloro), hidroxi, oxo, ciano, C1-C6alquilo (por ejemplo, metilo), C2-C6alquenilo, C2-C6alquinilo, C1-C6haloalquilo (por ejemplo, CF3), C2-C6haloalquenilo, C2-C6haloalquinilo, –O–C1-C6alquilo (por ejemplo, –O–CH3), –C(O)ORS (por ejemplo, –C(O)OCH3), –C(O)RS (por ejemplo, –C(O)CH3), o –N(RSRS'); y D además está opcionalmente sustituido con uno o más RM donde RM es halógeno (por ejemplo, fluoro, cloro), C1-C6alquilo (por ejemplo, metilo), C1-C6haloalquilo (por ejemplo, CF3), o –O–C1-C6alquilo (por ejemplo, –O–CH3). En algunas otras formas de realización D es fenilo o piridilo y G2 es, por ejemplo, un carbociclo monocíclico de entre 3 y 8 miembros o heterociclo monocíclico de entre 4 y 8 miembros monociclic sustituido con L4–G3 y opcionalmente sustituido con uno o más RG2 donde L4, G3 y RG2 son como se definen en la presente. L4, por ejemplo es una unión, a C1-C6 alquileno (por ejemplo, –CH2–, –CH2CH2–, –CH2CH2CH2–, etc.), –O–, o –S(O)2–. G3 es por ejemplo a C3-C12carbociclo

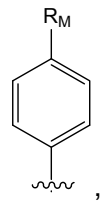
opcionalmente sustituido con uno o más RG3. RG2 y RG3 son en forma independiente entre sí en cada caso halógeno, –C(O)C1-C6alquilo, –C1-C6alquilo, –C1-C6haloalquilo, –O–C1-C6alquilo, o –O–C1-C6haloalquilo. En algunas formas de realización G2 es  , donde  es un heterociclo monocíclico que contiene nitrógeno de entre 4 y 8 miembros (por ejemplo, azetidinilo, pirrolidinilo, piperidinilo, piperazinilo) unido a la porción molecular principal a través de un átomo de nitrógeno y sustituido con uno o dos L4–G3 y opcionalmente sustituido con uno o más RG2. De este modo, en algunas formas de realización donde L4 es una unión G2 es  , donde  está opcionalmente sustituido con RG2 y G3 está opcionalmente sustituido con RG3. De este modo,  puede ser, por ejemplo, 3-fenilazetidin-1-ilo, 3-fenilpirrolidin-1-ilo, 4-fenilpiperazin-1-ilo, 4-fenilpiperidin-1-ilo, 4-fenil-3,6-dihidropiridin-1(2H)-ilo, 4,4-difenilpiperidin-1-ilo, 4-acetil-4-fenilpiperidin-1-ilo, 4-(4-metoxifenil)piperidin-1-ilo, 4-(4-fluorofenil)piperidin-1-ilo, o 3-fenilpiperidin-1-ilo, y donde D además puede estar opcionalmente sustituido con uno o más RM (por ejemplo, fluoro, cloro, metilo, metoxi).

En algunas otras formas de realización de este aspecto de la invención, L4 es un C1-C6 alquileno, –O–, o –S(O)2–, y G2 es  , donde  es como se define precedentemente y está opcionalmente sustituido con RG2 y G3 es como se define

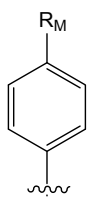
precedentemente y está opcionalmente sustituido con RG3. De este modo,  puede ser, por ejemplo, 4-tosilpiperazin-1-ilo, 4-fenoxipiperidin-1-ilo, 3-fenoxipirrolidin-1-ilo, 4-bencilpiperidin-1-ilo, 4-fenetilpiperidin-1-ilo, o 3-fenilpropil)piperidin-1-ilo.

En algunas otras formas de realización de este aspecto de la invención, D es fenilo o piridilo, D está sustituido con G2 y G2 es un carbociclo o heterociclo bicíclico espiro, en puente o fusionado opcionalmente sustituido con L4–G3 y uno o más RG2, donde D está opcionalmente sustituido con uno o más RM y RM, L4, G3, y RG2 son como se definen en la presente. En algunas formas de realización G2 es  , donde  es un heterociclo bicíclico que contiene nitrógeno espiro, en puente o fusionado (por ejemplo, 3-azabiciclo[3,2,0]hept-3-ilo, 2-azabiciclo[2,2,2]oct-2-ilo, 6-azaespiro[2,5]oct-6-ilo, octahidro-2H-isoindol-2-ilo, 3-azaespiro[5,5]undec-3-ilo, 1,3-dihidro-2H-isoindol-2-ilo, 1,4-dioxa-8-azaespiro[4,5]dec-8-ilo) unido a la porción molecular principal a través de un átomo de nitrógeno y opcionalmente sustituido con G3 y uno o más RG2. De este modo, G2 es 3-azabiciclo[3,2,0]hept-3-ilo, 2-azabiciclo[2,2,2]oct-2-ilo, 6-azaespiro[2,5]oct-6-ilo, octahidro-2H-isoindol-2-ilo, 3-azaespiro[5,5]undec-3-ilo, 1,3-dihidro-2H-isoindol-2-ilo, o 1,4-dioxa-8-azaespiro[4,5]dec-8-ilo; L4 es una unión y D está opcionalmente sustituido con uno o más RM (por ejemplo, fluoro, cloro, metilo, metoxi).

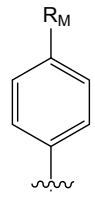
En algunas formas de realización de este aspecto de la invención, D es  donde RM es como se define precedentemente en relación a la Fórmula IE, y D está



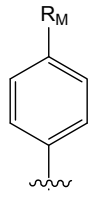
opcionalmente sustituido con uno o más RM adicionales. Por ejemplo, donde D es , RM puede ser fluoro, cloro, tert-butilo, –O–CH2CH3, –O–CF3, –O–CH2CHF2, –O–CH2CH2OCH3, –O–CH2–(3-etiloxetan-3-ilo), –O–CH2–(1,3-dioxolan-4-ilo), –O–ciclopentilo, –O–ciclohexilo, –O–fenilo, –O–(1,3-dioxan-5-ilo), ciclopropilo, ciclohexilo, fenilo, SF5, –SO2Me, o –N(t-Bu)C(O)Me y D puede estar opcionalmente sustituido con uno o más RM adicionales seleccionados entre el grupo que consiste en halógeno (por ejemplo, fluoro, cloro) y C1-C6alquilo (por ejemplo, metilo).



En algunas formas de realización, D es donde RM es fluoro, cloro, tert-butilo, –O–CH2CH3, –O–CF3, –O–CH2CHF2, –O–CH2CH2OCH3, SF5, –SO2Me, o –N(t-Bu)C(O)Me y D está opcionalmente sustituido con uno o más RM adicionales seleccionados entre el grupo que consiste en halógeno (por ejemplo, fluoro, cloro) y C1-C6alquilo (por ejemplo, metilo).

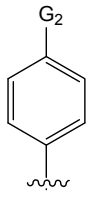


En algunas formas de realización, D es donde RM es ciclopropilo, ciclohexilo, o fenilo y D está opcionalmente sustituido con uno o más RM adicionales seleccionados entre el grupo que consiste en halógeno (por ejemplo, fluoro, cloro) y C1-C6alquilo (por ejemplo, metilo).

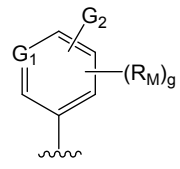


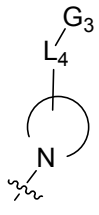
En algunas formas de realización, D es donde RM es –O–CH2–(3-

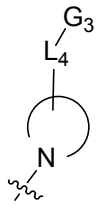
etiloxetan-3-ilo), –O–CH2–(1,3-dioxolan-4-ilo), –O–ciclopentilo, –O–ciclohexilo, –O–fenilo, o –O–(1,3-dioxan-5-ilo) y D está opcionalmente sustituido con uno o más RM adicionales seleccionados entre el grupo que consiste en halógeno (por ejemplo, fluoro, cloro) y C1-C6alquilo (por ejemplo, metilo).

En algunas formas de realización, D es 

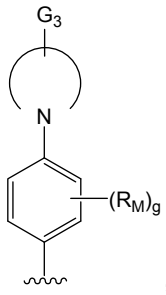
donde G2 es piridinilo (por ejemplo, piridin-2-ilo), piperidin-1-ilo, 4,4-dimetilpiperidin-1-ilo, 4,4-difluoropiperidin-1-ilo, 2,6-dimetilpiperidin-1-ilo, 4-(propan-2-il)piperidin-1-ilo, 4-fluoropiperidin-1-ilo, 3,5-dimetilpiperidin-1-ilo, 4-(trifluorometil)piperidin-1-ilo, 4-metilpiperidin-1-ilo, 4-tert-butilpiperidin-1-ilo, 2-oxopiperidin-1-ilo, 3,3-dimetilazetidin-1-ilo, u oxazolilo (por ejemplo, 1,3-oxazol-2-ilo) y D está opcionalmente sustituido con uno o más RM adicionales seleccionados entre el grupo que consiste en halógeno (por ejemplo, fluoro, cloro) y C1-C6alquilo (por ejemplo, metilo).

En otra forma de realización de este aspecto de la invención, D es 

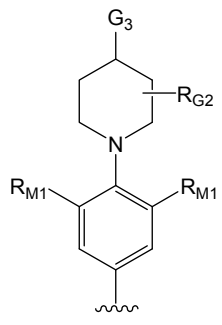
donde G1 es N, C–H, o C–RM; G2 es 

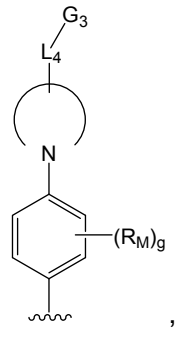
, donde 

es un heterociclo monocíclico que contiene nitrógeno de entre 4 y 8 miembros (por ejemplo, azetidinilo, pirrolidinilo, piperidinilo) unido a la porción molecular principal a través de un átomo de nitrógeno y sustituido con L4–G3 y opcionalmente sustituido con uno o más RG2; L4 es una unión, C1-C6 alquileno, –O–, o –S(O)2–; G3 es arilo (por ejemplo, fenilo), cicloalquilo (por ejemplo, ciclohexilo), o heterociclo (por ejemplo, tienilo) donde cada G3 está opcionalmente sustituido con uno o más RG3; RG2 y RG3 en cada caso son en forma

independiente entre sí halógeno, –C(O)C1-C6alquilo, –C1-C6alquilo, –C1-C6haloalquilo, –O–C1-C6alquilo, o –O–C1-C6haloalquilo; g es 0, 1, 2, o 3; y RM es como se define precedentemente en relación a la Fórmula IE. En un grupo de compuestos de acuerdo con esta forma de realización, D es 

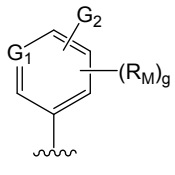
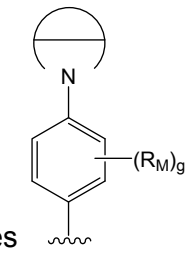
, donde G3 es fenilo opcionalmente sustituido con uno o dos RG3; g es 0, 1, o 2; RM es en forma independiente en cada caso fluoro, cloro, metilo, metoxi, trifluorometilo, o trifluorometoxi; y 

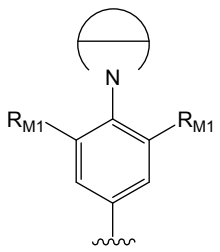
y RG3 son como se definen precedentemente. En otro subgrupo de compuestos de esta forma de realización, D es 

donde G3 es fenilo opcionalmente sustituido con uno o dos RG3; RM1 es en forma independiente en cada caso hidrógeno, fluoro, cloro, o metilo; y RG2 es un sustituyente opcional como se describe aquí. En otro grupo de compuestos de acuerdo con esta forma de realización, D es 

, donde L4 es C1-C6 alquileno, –O–, o –S(O)2–; G3 es fenilo opcionalmente sustituido con uno o dos RG3; g es 0, 1, o 2; RM es en forma independiente en cada caso fluoro, cloro, metilo, metoxi, trifluorometilo, o

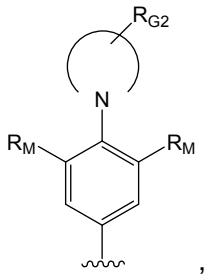
trifluorometoxi; y  y RG3 son como se definen precedentemente.

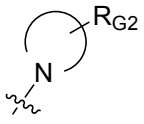
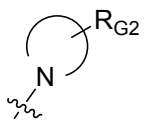
En aun otra forma de realización de este aspecto de la invención, D es  donde G1 es N, C–H, o C–RM; G2 es  , donde  es un heterociclo bicíclico que contiene nitrógeno espiro, en puente o fusionado (por ejemplo, 3-azabiciclo[3,2,0]hept-3-ilo, 2-azabiciclo[2,2,2]oct-2-ilo, 6-azaespiro[2,5]oct-6-ilo, octahidro-2H-isoindol-2-ilo, 3-azaespiro[5,5]undec-3-ilo, 1,3-dihidro-2H-isoindol-2-ilo, 1,4-dioxa-8-azaespiro[4,5]dec-8-ilo) unido a la porción molecular principal a través de un átomo de nitrógeno y opcionalmente sustituido con L4–G3 y uno o más RG2; L4 es una unión, C1-C6 alquileno, –O–, o –S(O)2–; G3 es arilo (por ejemplo, fenilo), cicloalquilo (por ejemplo, ciclohexilo), o heterociclo (por ejemplo, tienilo) donde cada G3 está opcionalmente sustituido con uno o más RG3; RG2 y RG3 en cada caso son en forma independiente entre sí halógeno, –C(O)C1-C6alquilo, –C1-C6alquilo, –C1-C6haloalquilo, –O–C1-C6alquilo, o –O–C1-C6haloalquilo; g es 0, 1, 2, o 3; y RM es como se define precedentemente en relación a la Fórmula IE. En un grupo de compuestos de acuerdo con esta forma de realización, D es  donde g es 0, 1, o 2; RM es en forma independiente en cada caso fluoro, cloro, metilo, metoxi, trifluorometilo, o trifluorometoxi; y  es como se define precedentemente. En otro subgrupo de compuestos D es

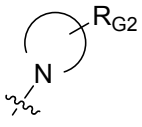


donde RM1 es en forma independiente en cada caso hidrógeno, fluoro, cloro, o metilo, y  es como se define precedentemente (por ejemplo, 3-azabiciclo[3,2,0]hept-3-ilo, octahidro-2H-isoindol-2-ilo, 2-azabiciclo[2,2,2]oct-2-ilo, 6-azaespiro[2,5]oct-6-ilo, 3-azaespiro[5,5]undec-3-ilo, 1,3-dihidro-2H-isoindol-2-ilo, 1,4-dioxa-8-azaespiro[4,5]dec-8-ilo).

En aun otra forma de realización de este aspecto de la invención, D es

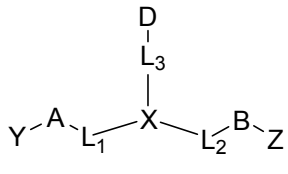


, donde  es un heterociclo monocíclico que contiene nitrógeno de entre 4 y 8 miembros (por ejemplo, azetidinilo, pirrolidinilo, piperidinilo) sustituido con uno o más RG2, donde RG2 en cada caso es en forma independiente en cada caso halógeno, –C(O)C1-C6alquilo, –C1-C6alquilo, –C1-C6haloalquilo, –O–C1-C6alquilo, o –O–C1-C6haloalquilo; y RM es en forma independiente en cada caso halógeno, –C1-C6alquilo, –C1-C6haloalquilo, –O–C1-C6alquilo, o –O–C1-C6haloalquilo. En un grupo de compuestos de acuerdo con esta forma de realización,  es azetidinilo, pirrolidinilo, o piperidinilo sustituido con uno o dos RG2, donde RG2 en cada caso es en forma independiente en cada caso metilo, etilo, isopropilo, tert-butilo, fluoro, cloro, o trifluorometilo; y RM es en forma independiente en cada caso fluoro, cloro, o metilo. Por



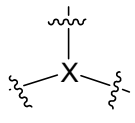
ejemplo es 4,4-dimetilpiperidin-1-ilo, 4,4-difluoropiperidin-1-ilo, 2,6-dimetilpiperidin-1-ilo, 4-(propan-2-il)piperidin-1-ilo, 4-fluoropiperidin-1-ilo, 3,5-dimetilpiperidin-1-ilo, 4-(trifluorometil)piperidin-1-ilo, 4-metilpiperidin-1-ilo, 4-tert-butilpiperidin-1-ilo, 2-oxopiperidin-1-ilo, o 3,3-dimetilazetidin-1-ilo.

Para los compuestos de Fórmula IE



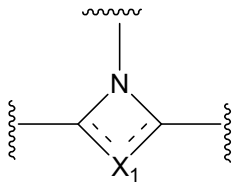
IE

la unión de X al resto de la molécula puede ilustrarse de manera conveniente con la Fórmula estructural abreviada X', donde los grupos unidos a X mantienen la misma orientación espacial relativa que la mostrada en la Fórmula IE Debe comprenderse que en las ilustraciones posteriores del grupo variable X, los sustituyentes de X mantienen las mismas posiciones y orientaciones relativas que en la Fórmula IE y Fórmula X'.

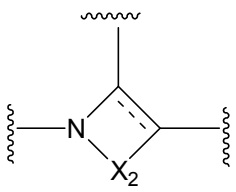


X'

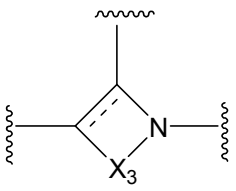
Los compuestos de Fórmula IE incluyen aquellos donde la variable X se selecciona entre el grupo que consiste en X-1, X-2, X-3, y X-4 donde X-1, X-2, X-3, y X-4 mantienen la misma orientación que la estructura X' en relación al resto de la molécula; donde la presencia de ⎓ en X-1, X-2, y X-3 representuna uniones simples o dobles, X1 es C1-C2alquileno o C2alquenileno, X2 y X3 son cada uno C1-C2alquileno o C2alquenileno, y X4 es C1-C2 alquileno.



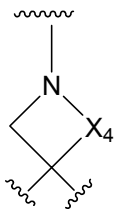
X-1



X-2

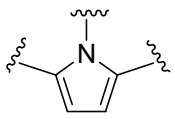


X-3



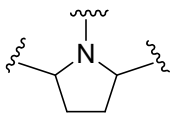
X-4

De acuerdo con la descripción previa, en algunas formas de realización de este aspecto de la invención, X es pirrolilo y se une al resto de la molécula como se muestra en Fórmula XA:



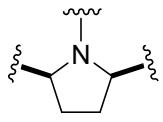
X_A

. En algunas formas de realización, X es pirrolidinilo y se une al resto de la molécula como se muestra en Fórmula XB:

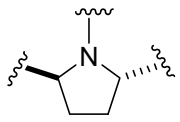


X_B

. Las formas de realización de acuerdo con la Fórmula XB pueden existir en formas cis (XB1) o trans (XB2):



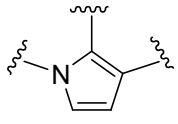
X_{B1}



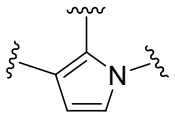
X_{B2}

. Los átomos de carbono quirales en XB, XB1, y XB2 pueden tener estereoquímica absoluta (R) o (S).

En aun otra forma de realización de este aspecto de la invención, X es pirrolilo y se une al resto de la molécula como se muestra en las Fórmulas XC1 o XC2:

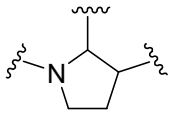


X_{C1}

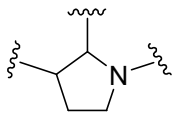


X_{C2}

. En algunas formas de realización, X es pirrolidinilo y se une al resto de la molécula como se muestra en las Fórmulas XD1 o XD2:



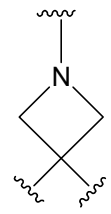
X_{D1}

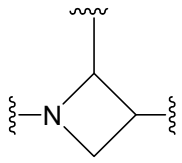


X_{D2}

. Las formas de realización de acuerdo con las

Fórmulas XD1 o XD2 pueden existir en forma cis o trans y los átomos de carbono quirales en XD1 y XD2 pueden tener estereoquímica absoluta (R) o (S). En algunas formas de realización, X es azetidinilo y se une al resto de la molécula como se muestra en las





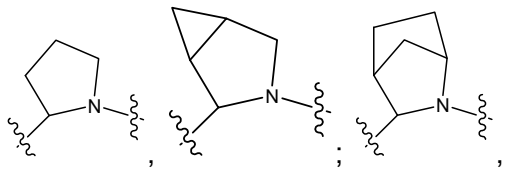
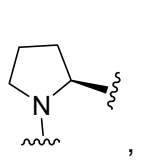
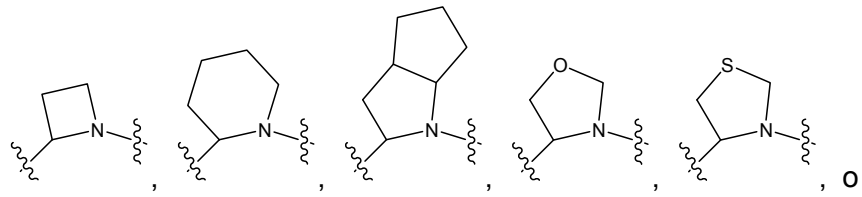
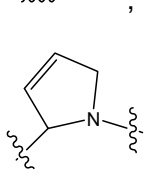
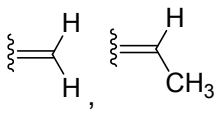
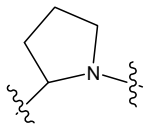
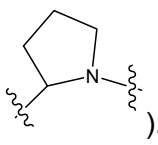
Fórmulas XE1 o XE2: X_{E1} X_{E2} . Los átomos de carbono quirales en XE1 y XE2 pueden tener en forma independiente estereoquímica absoluta (R) o (S).

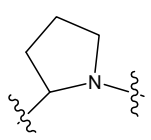
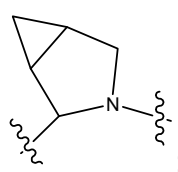
En ciertas formas de realización preferidas de este aspecto de la invención, X es XA, XB, XB1, XB2, XC1, o XC2 y L1, L2, y L3 son cada uno un enlace. En algunas otras formas de realización, X es XD1, XD2, XE1, o XE2 y L1, L2, y L3 son cada uno un enlace. En otra forma de realización, X es XE1 y L1 y L2 son cada uno metileno (por ejemplo –CH2–), y L3 es un enlace.

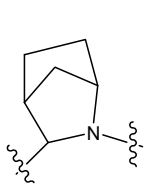
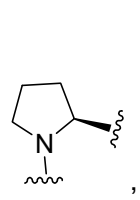
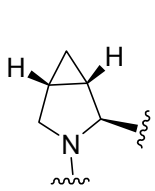
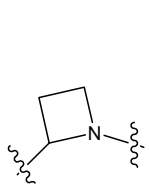
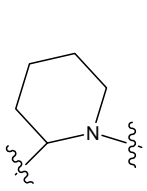
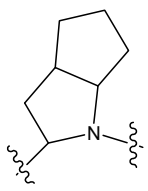
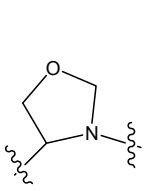
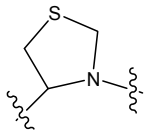
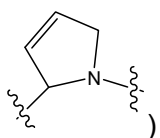
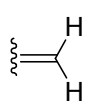
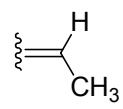
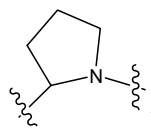
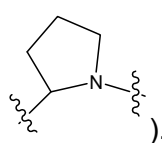
En compuestos de Fórmula IE, Y es–T'–C(R1R2)N(R5)–T–RD y Z es –T'–C(R8R9)N(R12)–T–RD; donde T', R1, R2, R5, R8, R9, R12, T, y RD son como se definen en la presente.

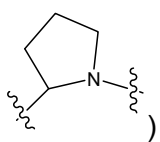
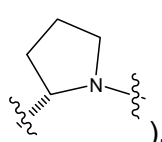
Preferiblemente R1, R2, R5, R8, R9, y R12 son en forma independiente entre sí hidrógeno; C1-C6alquilo; o carbociclo o heterociclo de entre 3 y 6 miembros, donde cada carbociclo o heterociclo de entre 3 y 6 miembros está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno o C1-C6alquilo; donde R2 y R5, tomados junto con los átomos a los cuales están unidos, forman opcionalmente un heterociclo de entre 3 y 12 miembros que está sustituido con 0, 1, 2, 3, o 4 RA, y R9 y R12 tomados junto con los átomos a los cuales están unidos, forman opcionalmente un heterociclo de entre 3 y 12 miembros que está sustituido con 0, 1, 2, 3, o 4 RA donde RA es como se define aquí.

En algunas formas de realización de este aspecto de la invención, R1 es

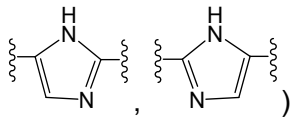
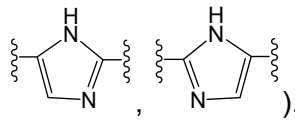
hidrógeno y R2 y R5, tomados junto con los átomos a los cuales están unidos forman un heterociclo de entre 3 y 12 miembros (por ejemplo,  ,  ,  , ) sustituido con 0, 1, 2, 3, o 4 RA donde RA es halógeno (por ejemplo, fluoro, cloro); ciano; LS–RE donde LS es una unión simple y RE es C1-C6alquilo (por ejemplo, metilo, etilo), –O–C1-C6alquilo (por ejemplo, metoxi), o –O–C1-C6haloalquilo (por ejemplo, trifluorometoxi); o LS–RE donde LS es una unión doble y RE es =C(RSRS') (por ejemplo, ). En una forma de realización preferida R2 y R5, tomados junto con los átomos a los cuales están unidos forman un anillo pirrolidina (por ejemplo, ) sustituido con 0 o 1 RA donde RA es fluoro, metoxi, metilo, etilo, o ciano. En otra forma de realización preferida R2 y R5, tomados junto con los átomos a los cuales están unidos forman un anillo pirrolidina (por ejemplo, ).

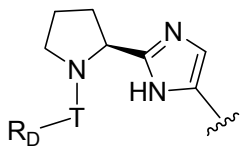
En algunas otras formas de realización de este aspecto de la invención, R8 es hidrógeno y R9 y R12, tomados junto con los átomos a los cuales están unidos forman un heterociclo de entre 3 y 12 miembros (por ejemplo,  o  ; o

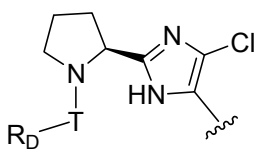
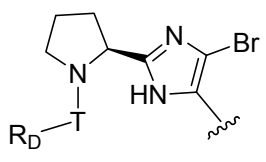
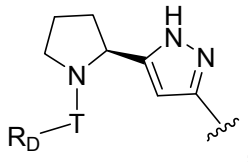
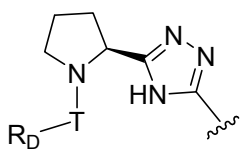



; o 




, o 
) sustituido con 0, 1, 2, 3, o 4 RA donde RA es halógeno (por ejemplo, fluoro, cloro); ciano; LS–RE donde LS es una unión simple y RE es C1-C6alquilo (por ejemplo, metilo, etilo), –O–C1-C6alquilo (por ejemplo, metoxi), o –O–C1-C6haloalquilo (por ejemplo, trifluorometoxi); o LS–RE donde LS es una unión doble y RE es =C(RSRS') (por ejemplo, 
, 
). En una forma de realización preferida, R9 y R12, tomados junto con los átomos a los cuales están unidos forman un anillo pirrolidina (por ejemplo, 
) sustituido con 0 o 1 RA donde RA es fluoro, metoxi, metilo, etilo, o ciano. En otra forma de realización preferida R9 y R12, tomados junto con los átomos a los cuales están unidos forman un anillo pirrolidina (por ejemplo, 
).

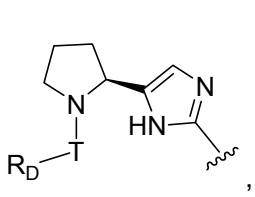
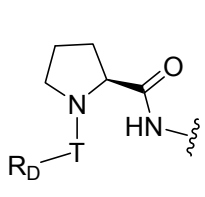
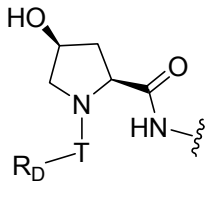
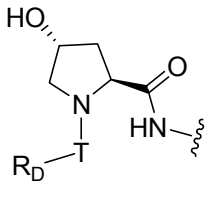
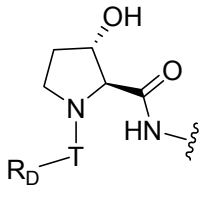
Como se lo utiliza en la presente, un carbono quiral en cualquier anillo formado por la unión de R2 y R5 o R9 y R12 puede tener estereoquímica (R) o (S). Un anillo pirrolidina (por ejemplo, 
) formado a partir de R2 y R5 o R9 y R12 preferiblemente tiene estereoquímica (S) (por ejemplo, 
).

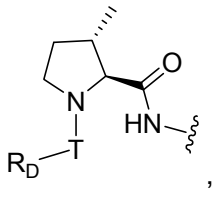
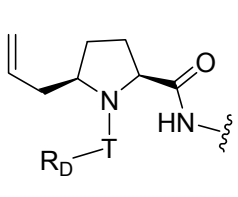
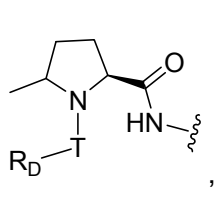
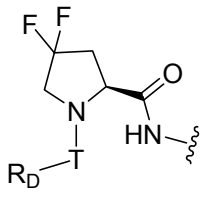
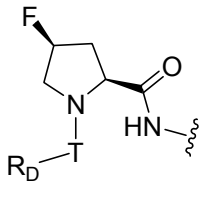
En este aspecto de la invención, T' se selecciona en forma independiente en cada caso entre una unión,–C(O)N(RB)–, –N(RB)C(O)–, o heterociclo de entre 3 y 12

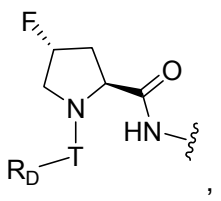
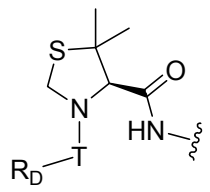
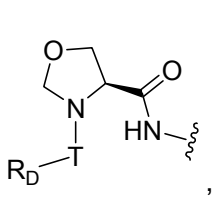
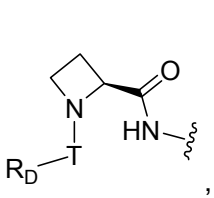
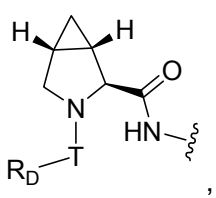
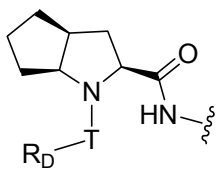
miembros, y donde dicho heterociclo de entre 3 y 12 miembros es en forma independiente en cada caso opcionalmente sustituido en cada caso con uno o más RA, y RA y RB son como se describe aquí. En particular, donde T' es –C(O)N(RB)–, RB puede ser hidrógeno (por ejemplo, T' es –C(O)N(H)–). En algunas formas de realización, T' es imidazolilo (por ejemplo, ) opcionalmente sustituido en cada caso con uno o más RA donde RA es halógeno (por ejemplo, fluoro, cloro), C1-C6alquilo (por ejemplo, metilo, etilo), o C1-C6haloalquilo (por ejemplo, trifluorometilo). En algunas formas de realización, T' es imidazolilo (por ejemplo, ).

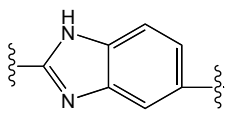
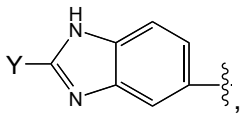
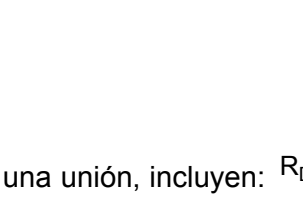
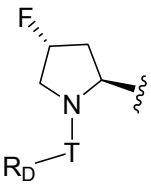
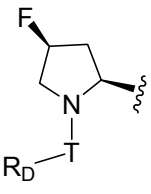
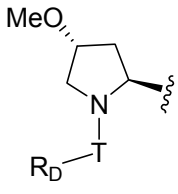
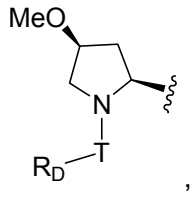
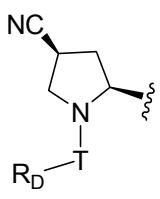
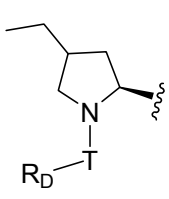
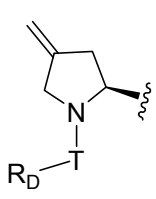
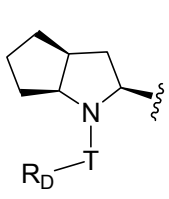
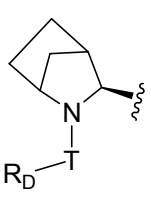
Este aspecto de la invención contempla particular combinaciones de A con Y y B con Z. Los ejemplos no limitativos de los Y preferidos cuando A es C5-C6carbociclo (por ejemplo, fenilo) o heterociclo de 5 o 6 miembros (por ejemplo, piridinilo o tiazolilo) y los Z preferidos cuando B es C5-C6carbociclo (por ejemplo, fenilo) o heterociclo de 5 o 6 miembros (por ejemplo, piridinilo o tiazolilo) incluyen:  ,

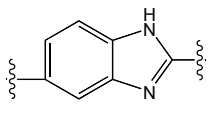
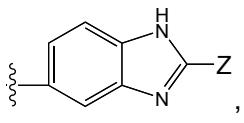
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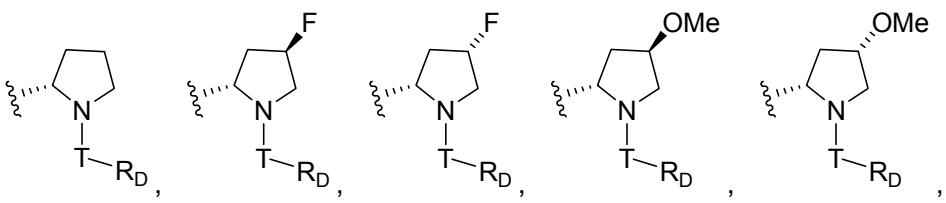
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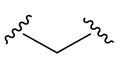
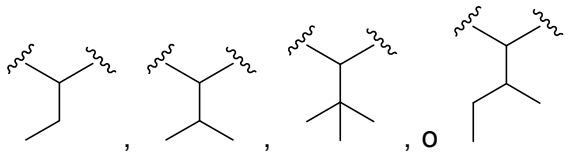
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, o 
donde T y RD son como se definen en la presente.

En algunas formas de realización de este aspecto de la invención, A es 
opcionalmente sustituido con uno o más RA como se describe aquí, o Y–A es 
, y los ejemplos no limitativos de los Y preferidos, donde T' es una 
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donde T y RD son como se definen en la presente.

En algunas formas de realización de este aspecto de la invención, B es 
opcionalmente sustituido con uno o más RA como se describe aquí, o B–Z es 
, y los ejemplos no limitativos de los Z preferidos, donde T' es una

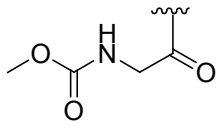
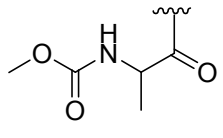
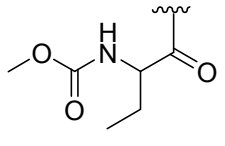
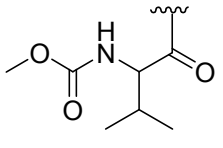
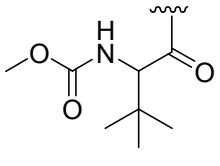
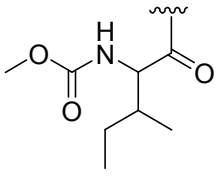
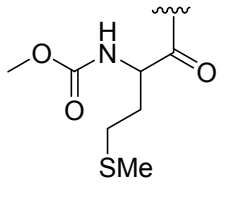
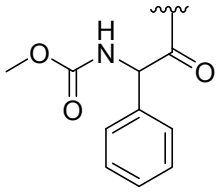
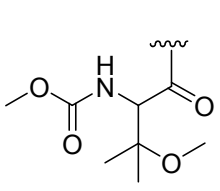
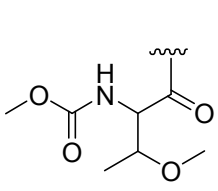
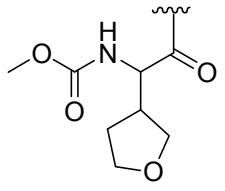
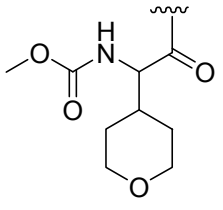
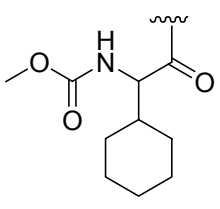
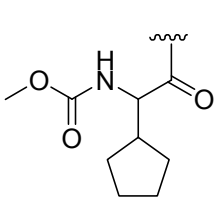
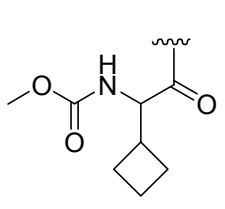
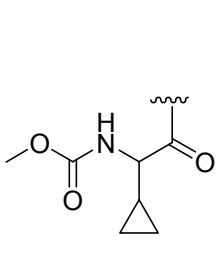
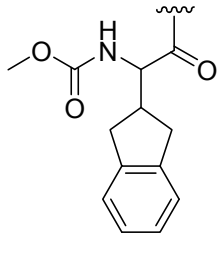
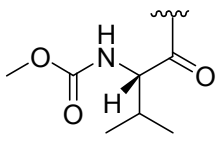
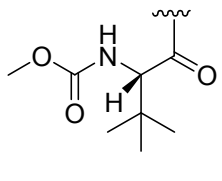
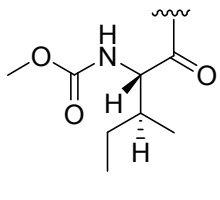
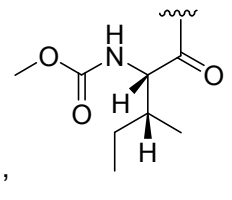
unión, incluyen:  donde T y RD son como se definen en la presente.

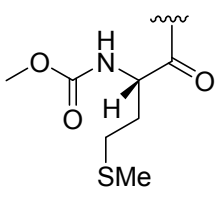
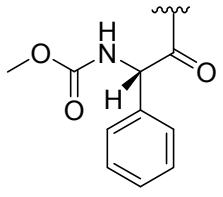
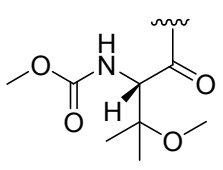
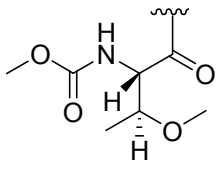
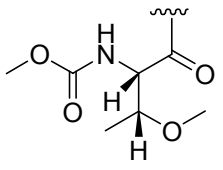
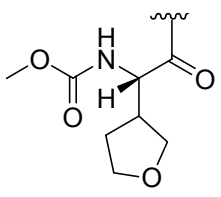
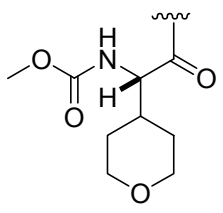
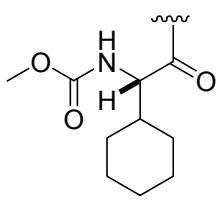
T en cada caso es en forma independiente una unión o –C(O)–LS'–, donde LS' es como se define aquí. LS' incluye, sin que esto constituya limitación alguna,  ,  , donde LS' está opcionalmente sustituido con uno o más RL; y RL es un sustituyente como por ejemplo, sin que esto constituya limitación alguna, carbociclo (por ejemplo, ciclohexilo, ciclopentilo, ciclobutilo, ciclopropilo, fenilo), metoxi, o heterociclo (por ejemplo, tetrahidrofuranilo, tetrahidropiranilo).

RD es hidrógeno o RA donde RA es como se define aquí. por lo tanto RD incluye, sin que esto constituya limitación alguna, RA donde RA es LS-RE, y LS y RE son como se definen en la presente. por lo tanto RD incluye, sin que esto constituya limitación alguna, LS-RE donde LS es una unión y RE es–N(RSRS'), –N(RS)C(O)RS', –N(RS)C(O)N(RS'RS''), –N(RS)SO2RS', —N(RS)SO2N(RS'RS''), –N(RS)S(O)N(RS'RS''), –N(RS)C(O)ORS', o –N(RS)S(O)–RS'; o C3-C12carbociclo o heterociclo de entre 3 y 12 miembros, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, ciano, C1-C6alquilo, C2-C6alquenilo, C2-C6alquinilo, o C1-C6haloalquilo.

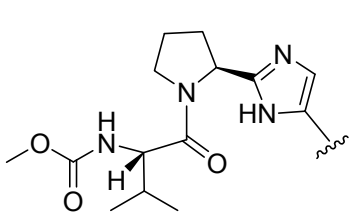
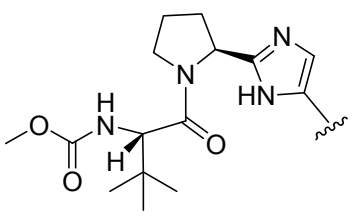
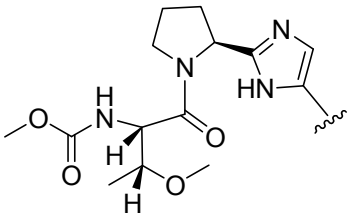
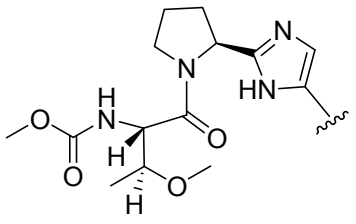
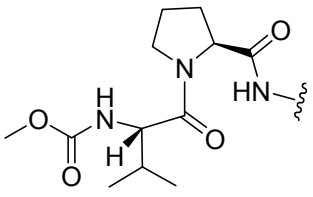
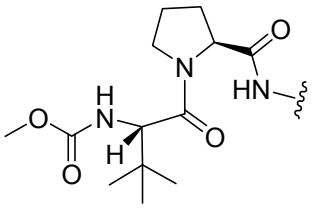
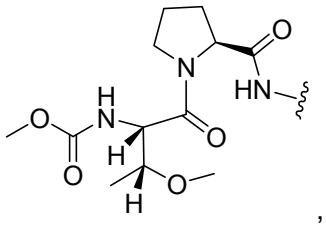
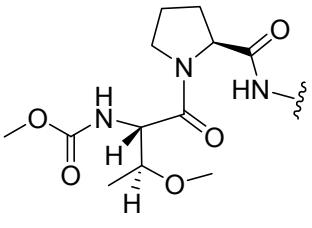
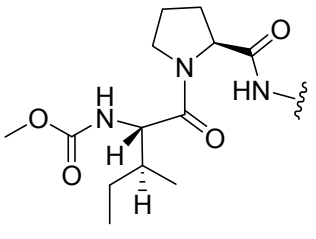
En una forma de realización de este aspecto de la invención, RD es LS-RE donde LS es una unión y RE es –N(RS)C(O)ORS' o heterociclo de entre 3 y 12 miembros (por

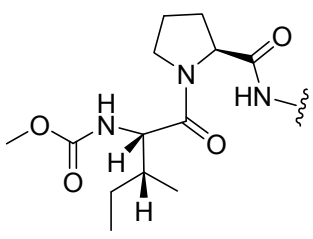
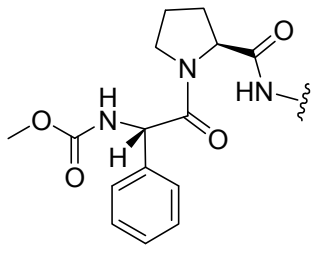
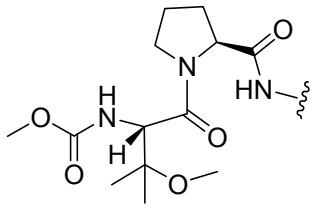
ejemplo, pirrolidina, piperidina, azepanilo) donde RS y RS' son como se definen en la presente. Por ejemplo RD es preferiblemente LS-RE donde LS es una unión y RE es –N(H)C(O)OMe.

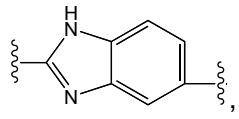
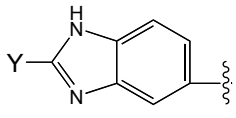
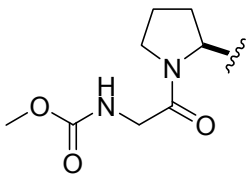
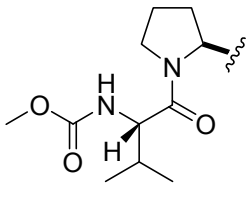
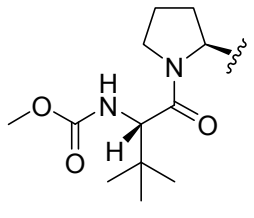
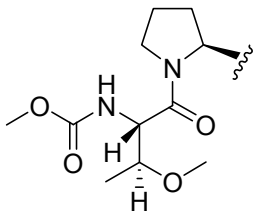
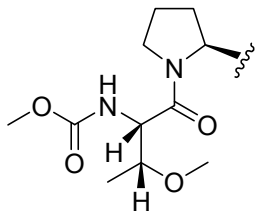
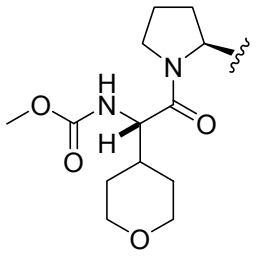
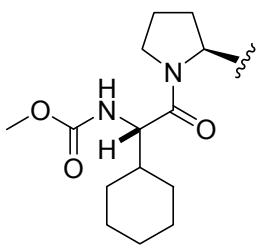
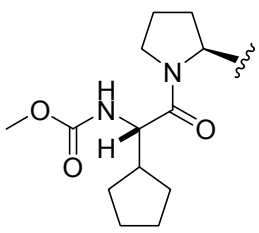
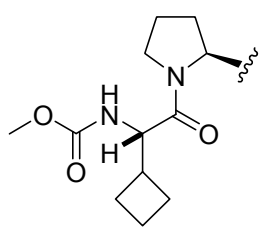
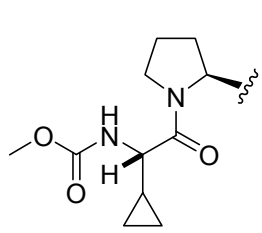
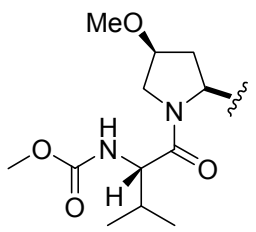
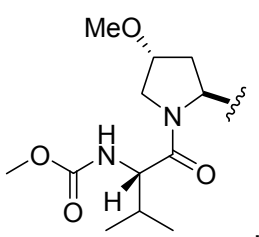
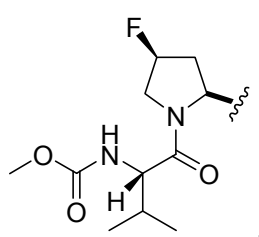
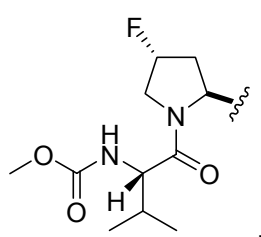
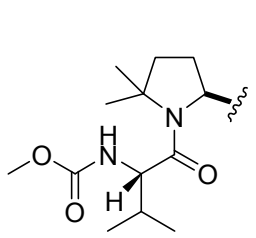
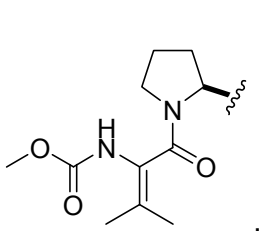
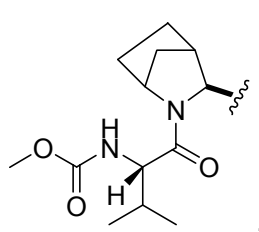
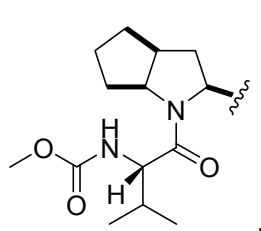
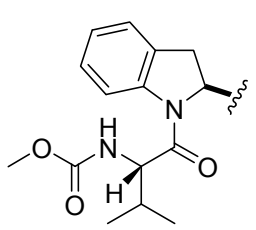
Por lo tanto de acuerdo con la descripción previa T-RD incluye, sin que esto constituya limitación alguna:  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , y  . T-RD también puede incluir configuraciones estereoquímicas particulares; por lo tanto T-RD incluye, sin que esto constituya limitación alguna:  ,  ,  ,  ,

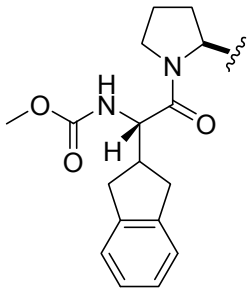
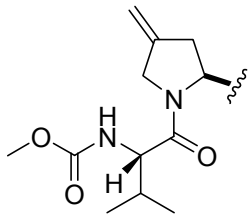
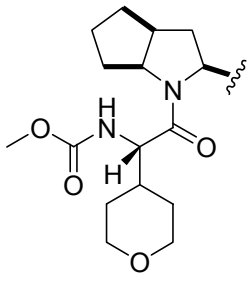
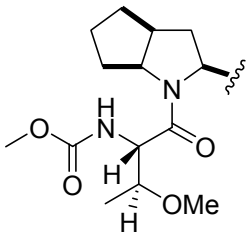
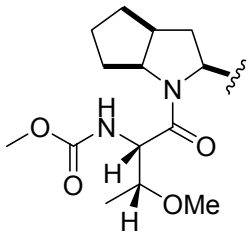








, etc.

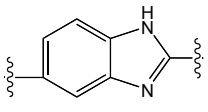
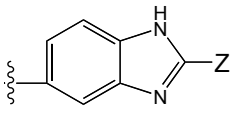
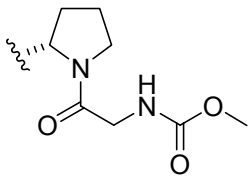
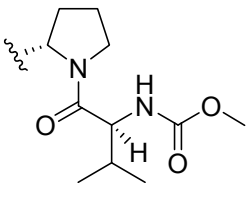
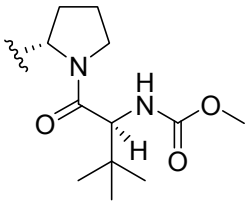
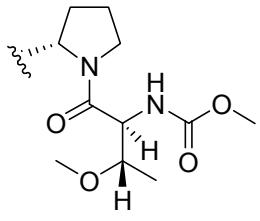
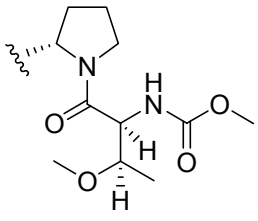
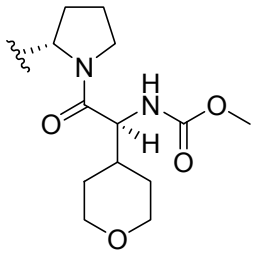
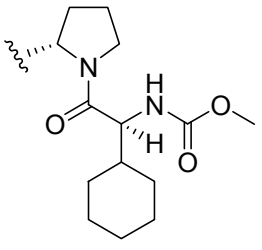
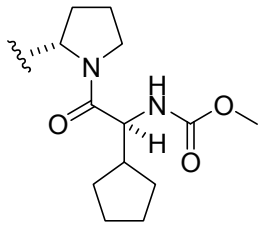
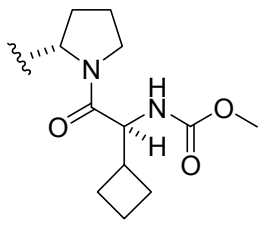
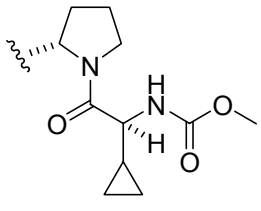
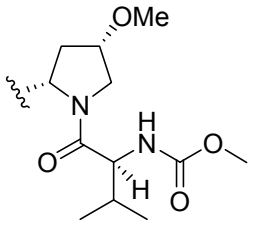
De acuerdo con este aspecto de la invención, los ejemplos no limitativos de los Y preferidos cuando A es C5-C6carbociclo (por ejemplo, fenilo) o heterociclo de 5 o 6 miembros (por ejemplo, piridinilo o tiazolilo) y los Z preferidos cuando B es C5-C6carbociclo (por ejemplo, fenilo) o heterociclo de 5 o 6 miembros (por ejemplo, piridinilo o tiazolilo) incluyen:

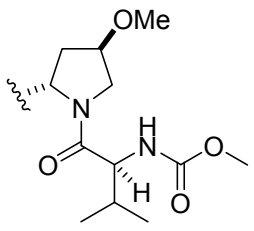
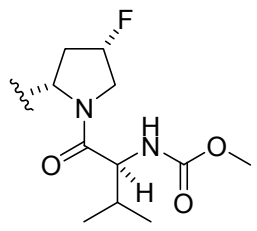
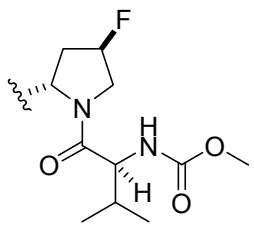
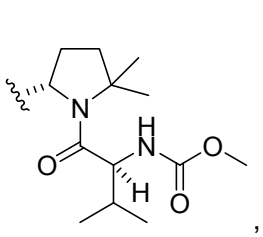
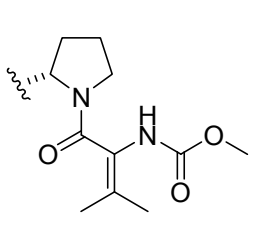
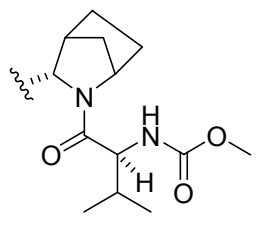
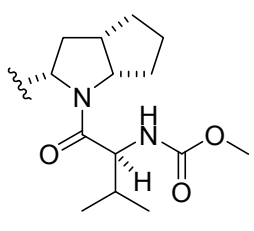
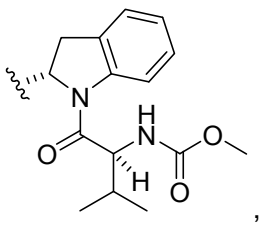
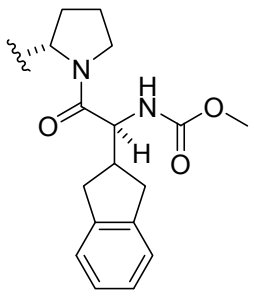
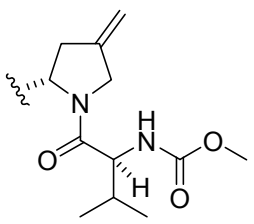
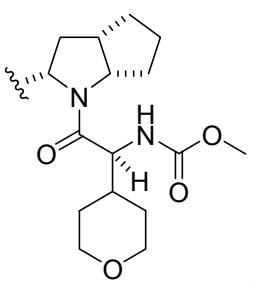
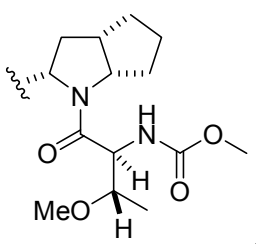
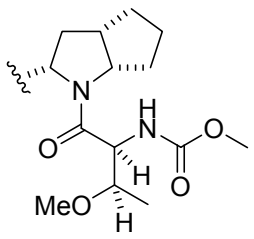











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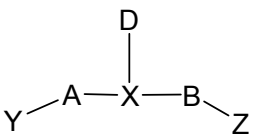
Los ejemplos no limitativos de los Y preferidos cuando A es  , opcionalmente sustituido con uno o más RA como se describe aquí, y Y–A es  incluyen: 
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Los ejemplos no limitativos de los Z preferidos donde B es  opcionalmente sustituido con uno o más RA como se describe aquí, y B–Z es  incluyen: 
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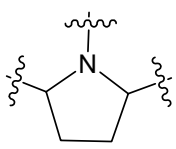
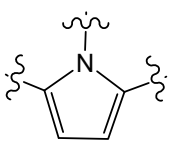

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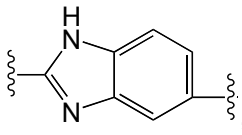
En aun otro aspecto, la presente invención presenta compuestos de Fórmula IF y sales aceptables farmacéuticamente del mismo:

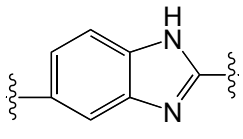
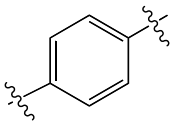


IF

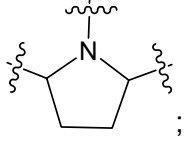
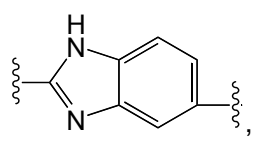
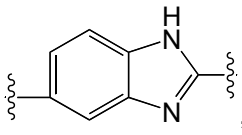
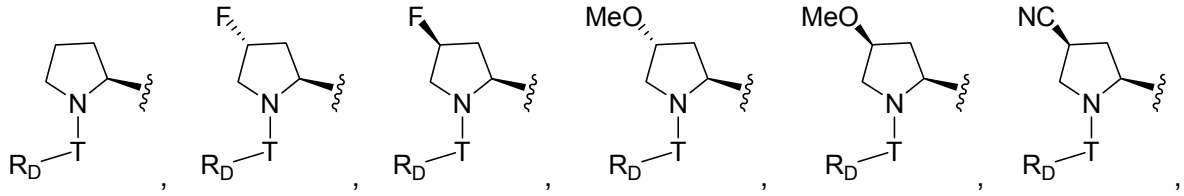
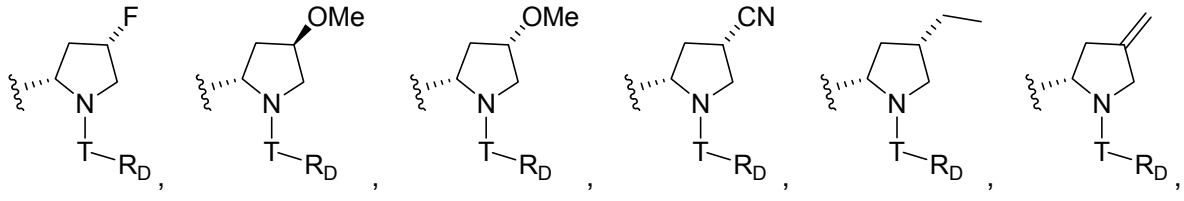
donde:

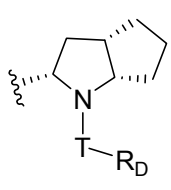
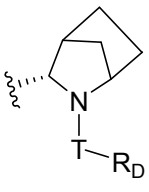
X es  o  , donde X está opcionalmente sustituido con uno o más RA

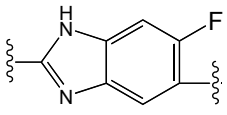
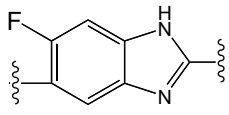
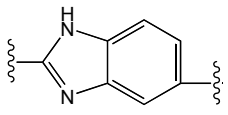
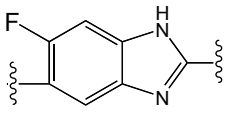
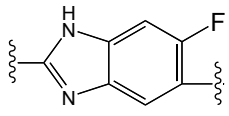
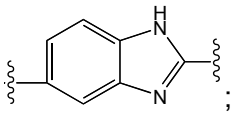
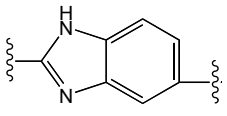
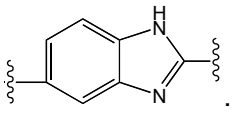
A es  , donde A está opcionalmente sustituido con uno o más RA;

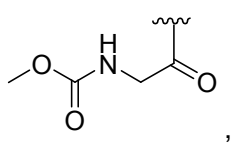
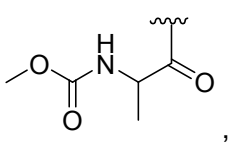
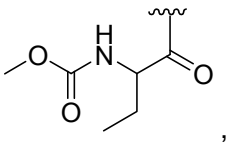
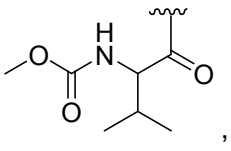
B es  o  , donde B está opcionalmente sustituido con uno o más RA; y

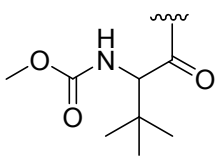
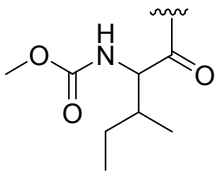
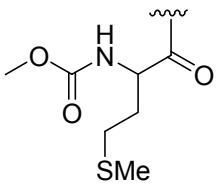
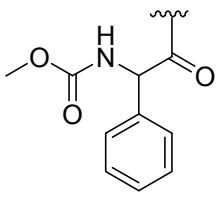
Y, Z, RA, y D son como se describe precedentemente (por ejemplo, Y, Z, RA, y D como se describe para la Fórmula I, IA, IB, IC, ID, o IE, preferiblemente como se describe para la Fórmula IE).

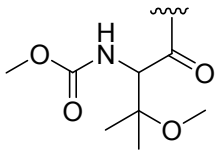
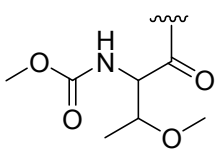
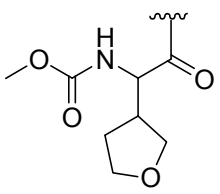
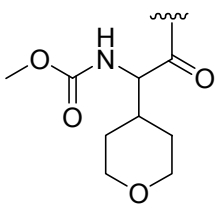
En una forma de realización de este aspecto de la invención, X es  ; A es  , donde A está opcionalmente sustituido con uno o más RA; B es  , donde B está opcionalmente sustituido con uno o más RA; Y es  ; Z es  ;

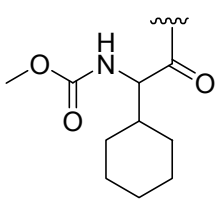
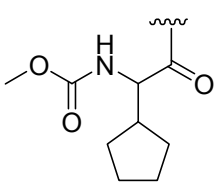
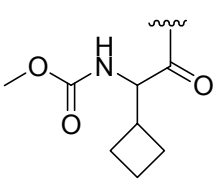
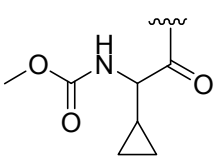
 , o  ; y D, RA, T y RD son como se definen precedentemente (por ejemplo, como se describe para la Fórmula I, IA, IB, IC, ID o IE, preferiblemente como se describe para la Fórmula IE).

En otra forma de realización de acuerdo con este aspecto de la invención, A o B están opcionalmente sustituidos con uno o más sustituyentes seleccionados entre: RA donde RA es en forma independiente en cada caso halógeno (por ejemplo, fluoro, cloro); LS–RE donde LS es una unión simple, y RE es –C1-C6alquilo (por ejemplo, metilo), –O–RS (por ejemplo, –O–C1-C6alquilo, –OCH3), o –C1-C6alquilo opcionalmente sustituido con uno o más halógeno (por ejemplo, –CF3); o LS–RE donde LS es un C1-C6alquileno y RE es –O–RS (por ejemplo, –C1-C6alquil–O–C1-C6alquilo, –CH2OCH3). Esta forma de realización incluye compuestos donde A y B están ambos sustituidos con un RA; compuestos donde A y B están ambos sustituidos con cero RA; compuestos donde A está sustituido con un RA y B está sustituido con cero RA; y compuestos donde A está sustituido con cero RA y B está sustituido con un RA. Preferiblemente, A es  y B es  ; o A es  y B es  ; o A es  y B es  ; o A es  y B es  .

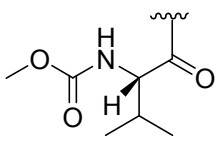
En una forma de realización adicional de este aspecto de la invención, T–RD se selecciona en forma independiente en cada caso entre el grupo que consiste en  ,  ,  ,  ,

 ,  ,  ,  ,

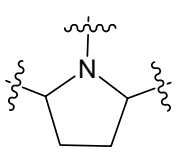
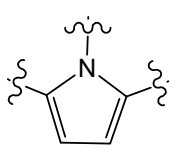
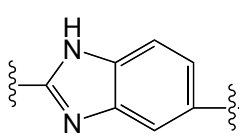
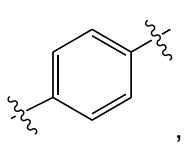
 ,  ,  ,  ,

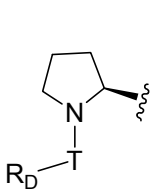
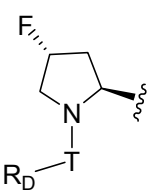
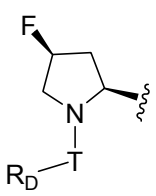
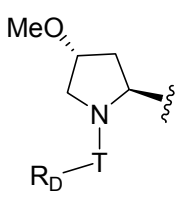
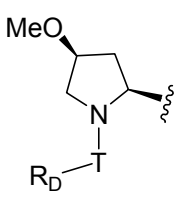
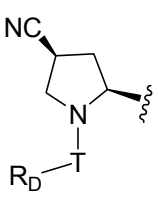
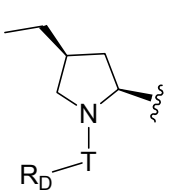
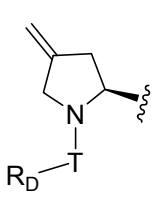
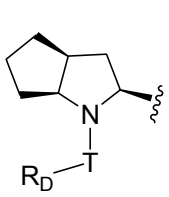
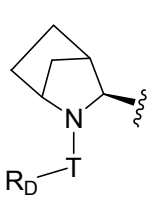
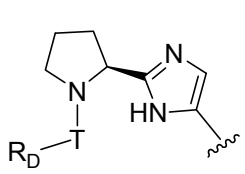
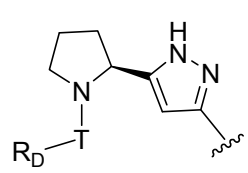
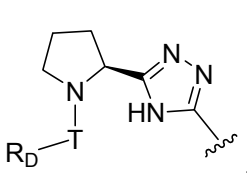
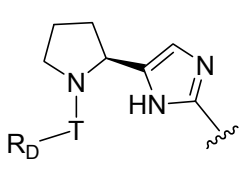
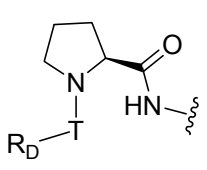
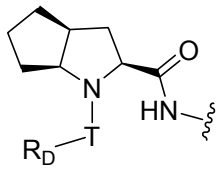
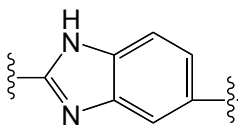
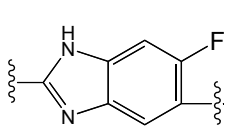
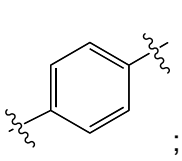
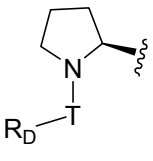
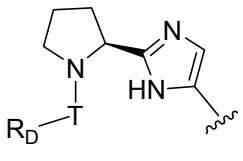
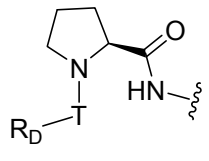
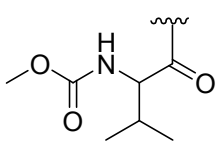
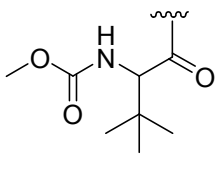
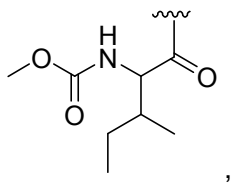
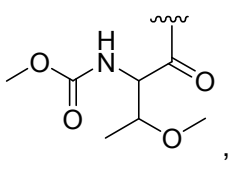
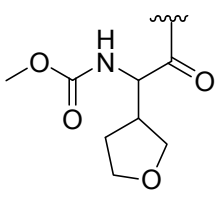
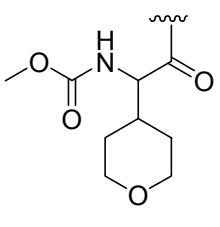
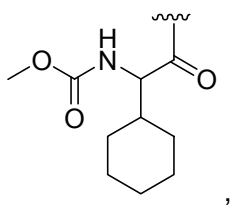
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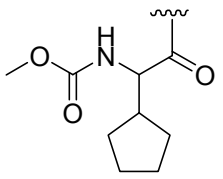
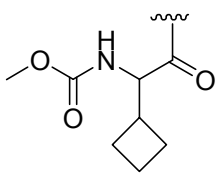
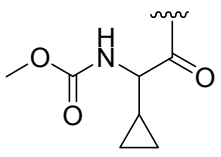
; donde los compuestos con estereoquímica (S) (por ejemplo,

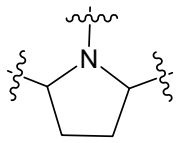
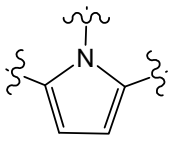
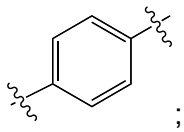
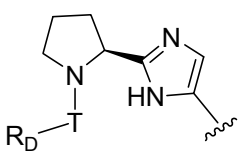
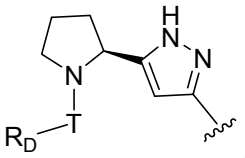
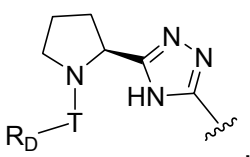
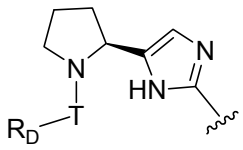
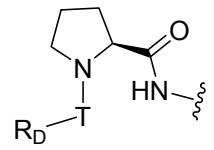
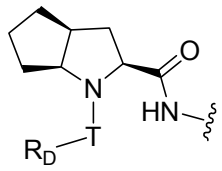
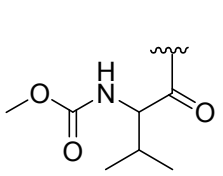
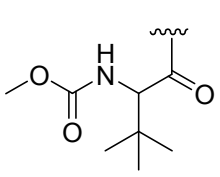
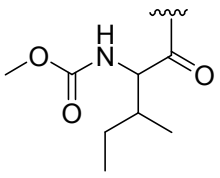
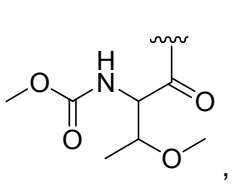
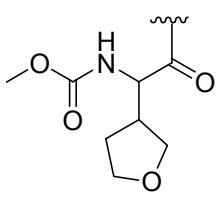
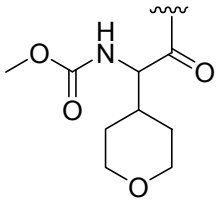
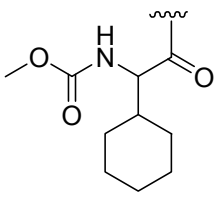
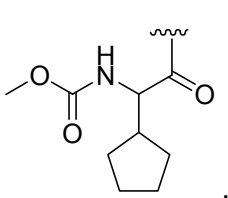
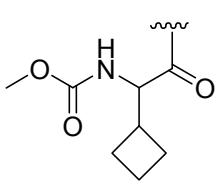
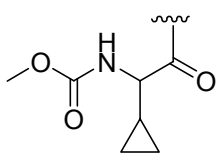
) son los Y preferidos donde D es como se define precedentemente.

En otra forma de realización, este aspecto de la invención presenta compuesto de Fórmula IF y sales aceptables farmacéuticamente del mismo, donde:

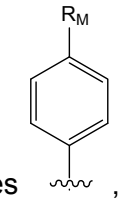
X es  o  ; A es  , donde A está opcionalmente sustituido con uno o más RA; B es  , donde B está

opcionalmente sustituido con uno o más RA; Y es  ,  ,  ,  ,  ,  ,  ,  ,  , o  ; Z es  ,  ,  ,  ,  , o  ; y D, RA, T y RD son como se definen precedentemente. Un subgrupo particular de acuerdo con esta forma de realización incluye compuestos donde A es  o  ; B es  ; Y es  ; Z es  o  ; T–RD es en forma independiente en cada caso  ,  ,  ,  ,  ,  ,  ,

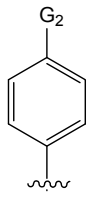

, 
, o 
; y D es como se define precedentemente.

En aun otra forma de realización, este aspecto de la invención presenta compuestos de Fórmula IF y sales aceptables farmacéuticamente del mismo, donde: X es 
o 
; A y B son cada uno 
; Y y Z son en forma independiente entre sí 
, 
, 
, 
, 
, o 
; y D, T y RD son como se definen precedentemente. Un subgrupo particular de acuerdo con esta forma de realización incluye compuestos donde T–RD se selecciona en forma independiente entre 
, 
, 
, 
, 
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, 
, 
, o 
; y D es como se define precedentemente.

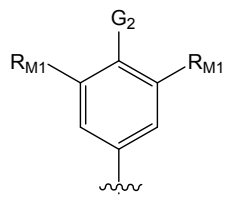
De acuerdo con cada una de las formas de realización y descripción precedentes de este aspecto de la invención de Fórmula IF existen grupos y subgrupos de compuestos con valores particulares para D. En cada una de las formas de realización precedentes existen grupos y subgrupos de compuestos con los siguientes valores particulares para D:

En algunos grupos de compuestos de acuerdo con la Fórmula IF y las formas de realización y descripción precedentes de este aspecto de la invención, D es 

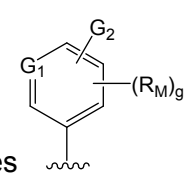
, donde RM es fluoro, cloro, tert-butilo, –O–CH2CH3, –O–CF3, –O–CH2CHF2, –O–CH2CH2OCH3, –O–CH2–(3-etiloxetan-3-ilo), –O–CH2–(1,3-dioxolan-4-ilo), –O–ciclopentilo, –O–ciclohexilo, –O–fenilo, –O–(1,3-dioxan-5-ilo), ciclopropilo, ciclohexilo, fenilo, SF5, –SO2Me, o –N(t-Bu)C(O)Me y D está opcionalmente sustituido con uno o más RM adicionales, seleccionados entre el grupo que consiste en halógeno (por ejemplo, fluoro, cloro) o C1-C6alquilo (por ejemplo, metilo).

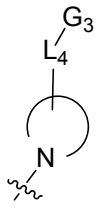
En otros grupos de compuestos de acuerdo con la Fórmula IF y las formas de realización y descripción precedentes de este aspecto de la invención, D es 

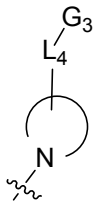
donde G2 es piridinilo (por ejemplo, piridin-2-ilo), piperidin-1-ilo, 4,4-dimetilpiperidin-1-ilo, 4,4-difluoropiperidin-1-ilo, 2,6-dimetilpiperidin-1-ilo, 4-(propan-2-il)piperidin-1-ilo, 4-fluoropiperidin-1-ilo, 3,5-dimetilpiperidin-1-ilo, 4-(trifluorometil)piperidin-1-ilo, 4-metilpiperidin-1-ilo, 4-tert-butilpiperidin-1-ilo, 2-oxopiperidin-1-ilo, 3,3-dimetilazetidin-1-ilo, u oxazolilo (por ejemplo, 1,3-oxazol-2-ilo) y D está opcionalmente sustituido con uno o más RM adicionales seleccionados entre el grupo que consiste en halógeno (por ejemplo, fluoro, cloro), o C1-C6alquilo (por ejemplo, metilo). En particular de acuerdo con estos

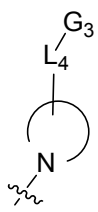
grupos existen compuestos donde D es 

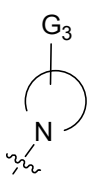
; G2 es piperidin-1-ilo, 4,4-dimetilpiperidin-1-ilo, 4,4-difluoropiperidin-1-ilo, 2,6-dimetilpiperidin-1-ilo, 4-(propan-2-il)piperidin-1-ilo, 4-fluoropiperidin-1-ilo, 3,5-dimetilpiperidin-1-ilo, 4-(trifluorometil)piperidin-1-ilo, 4-metilpiperidin-1-ilo, 4-tert-butilpiperidin-1-ilo, 2-oxopiperidin-1-ilo, o 3,3-dimetilazetidin-1-ilo; y RM1 es en forma independiente en cada caso hidrógeno, fluoro, cloro, o metilo.

En otros grupos de compuestos de acuerdo con la Fórmula IF y las formas de realización y descripción precedentes de este aspecto de la invención, D es 

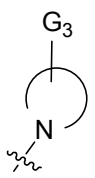
donde G1 es N, C–H, o C–RM; G2 es 

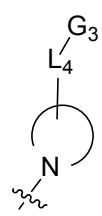
, donde 

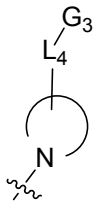
, RM, y g son como se definen precedentemente. En particular de acuerdo con estos grupos, RM es en forma independiente en cada caso fluoro, cloro, metilo, metoxi, trifluorometilo, o trifluorometoxi; g es 0, 1, o 2; y 

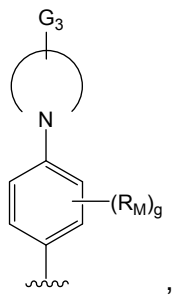
es como se define precedentemente. En otros subgrupos L4 es un enlace; G2 es 

; RM es en forma independiente en cada caso fluoro, cloro, metilo, metoxi, trifluorometilo, o trifluorometoxi; y g es 0, 1, o 2. En subgrupos particulares,



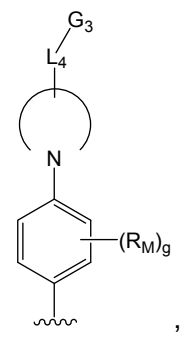
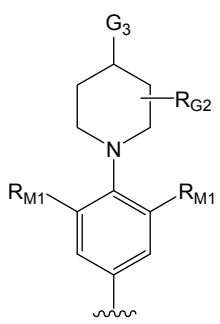
es 3-fenilazetidin-1-ilo, 3-fenilpirrolidin-1-ilo, 4-fenilpiperazin-1-ilo, 4-fenilpiperidin-1-ilo, 4-fenil-3,6-dihidropiridin-1(2H)-ilo, 4,4-difenilpiperidin-1-ilo, 4-acetil-4-fenilpiperidin-1-ilo, 4-(4-metoxifenil)piperidin-1-ilo, 4-(4-fluorofenil)piperidin-1-ilo, o 3-fenilpiperidin-1-ilo; RM es en forma independiente en cada caso fluoro, cloro, metilo, metoxi, trifluorometilo, o trifluorometoxi; y g es 0, 1, o 2. En otros subgrupos L4 es C1-C6 alquileno, –O–, o –S(O)2–; G2 es 

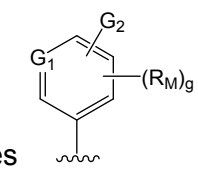
; RM es en forma independiente en cada caso fluoro, cloro, metilo, metoxi, trifluorometilo, o trifluorometoxi; y g es 0, 1, o 2. En subgrupos particulares, 

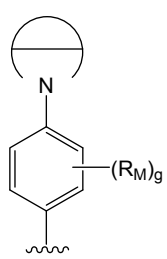
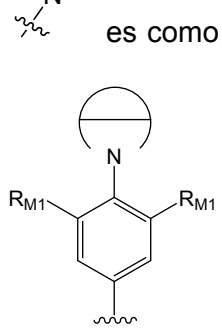
es 4-tosilpiperazin-1-ilo, 4-fenoxipiperidin-1-ilo, 3-fenoxipirrolidin-1-ilo, 4-bencilpiperidin-1-ilo, 4-fenetilpiperidin-1-ilo, o 3-fenilpropil)piperidin-1-ilo; RM es en forma independiente en cada caso fluoro, cloro, metilo, metoxi, trifluorometilo, o trifluorometoxi; y g es 0, 1, o 2. En otros subgrupos de compuestos D es 

, donde G3 es fenilo opcionalmente sustituido con uno o dos RG3; g es 0, 1, o 2; RM es en forma independiente en cada caso fluoro, cloro, metilo, metoxi, trifluorometilo, o trifluorometoxi; y 

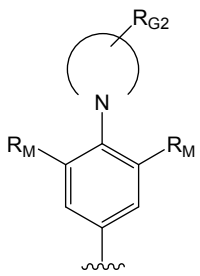
y RG3 son como se definen precedentemente. En otros grupos de compuestos D

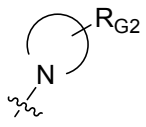
es  , donde L4 es C1-C6 alquileno, –O–, o –S(O)2–; G3 es fenilo opcionalmente sustituido con uno o dos RG3; g es 0, 1, o 2; RM es en forma independiente en cada caso fluoro, cloro, metilo, metoxi, trifluorometilo, o trifluorometoxi; y  y RG3 son como se definen precedentemente. En otros subgrupos de compuestos D es  donde G3 es fenilo opcionalmente sustituido con uno o dos RG3 como se define precedentemente; RM1 es en forma independiente en cada caso hidrógeno, fluoro, cloro, o metilo; y RG2 es un sustituyente opcional, como se describe precedentemente, seleccionado entre el grupo que consiste en –C(O)C1-C6alquilo, –C1-C6alquilo, –C1-C6haloalquilo, –O–C1-C6alquilo, y –O–C1-C6haloalquilo.

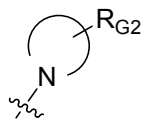
En otros grupos de compuestos de acuerdo con la Fórmula IF y las formas de realización y descripción precedentes de este aspecto de la invención, D es  donde G1 es N, C–H, o C–RM; G2 es  , donde  , RM, y g son como se definen precedentemente. En particular de acuerdo con estos subgrupos, RM es en forma independiente en cada caso fluoro, cloro, metilo, metoxi, trifluorometilo, o trifluorometoxi; g

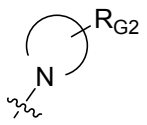
es 0, 1, o 2; y  es 3-azabiciclo[3,2,0]hept-3-ilo, 2-azabiciclo[2,2,2]oct-2-ilo, 6-azaespiro[2,5]oct-6-ilo, octahidro-2H-isoindol-2-ilo, 3-azaespiro[5,5]undec-3-ilo, 1,3-dihidro-2H-isoindol-2-ilo, o 1,4-dioxa-8-azaespiro[4,5]dec-8-ilo. En otros subgrupos de compuestos D es  donde g es 0, 1, o 2; RM es en forma independiente en cada caso fluoro, cloro, metilo, metoxi, trifluorometilo, o trifluorometoxi; y  es como se define precedentemente. En otros subgrupos de compuestos D es  donde RM1 es en forma independiente en cada caso hidrógeno, fluoro, cloro, o metilo y  es como se define precedentemente (por ejemplo, 3-azabiciclo[3,2,0]hept-3-ilo, octahidro-2H-isoindol-2-ilo, 2-azabiciclo[2,2,2]oct-2-ilo, 6-azaespiro[2,5]oct-6-ilo, 3-azaespiro[5,5]undec-3-ilo, 1,3-dihidro-2H-isoindol-2-ilo, 1,4-dioxa-8-azaespiro[4,5]dec-8-ilo).

En otros grupos de compuestos de acuerdo con la Fórmula IF y las formas de realización y descripción precedentes de este aspecto de la invención, D es



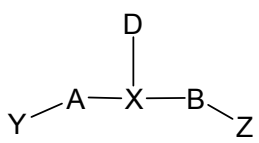
, donde 

es un heterociclo monocíclico que contiene nitrógeno de entre 4 y 8 miembros (por ejemplo, azetidinilo, pirrolidinilo, piperidinilo) sustituido con uno o más RG2, donde RG2 en cada caso es en forma independiente en cada caso halógeno, –C(O)C1-C6alquilo, –C1-C6alquilo, –C1-C6haloalquilo, –O–C1-C6alquilo, o –O–C1-C6haloalquilo; y RM es en forma independiente en cada caso halógeno, –C1-C6alquilo, –C1-C6haloalquilo, –O–C1-C6alquilo, o –O–C1-C6haloalquilo. En cada grupo de compuestos de acuerdo con las formas de realización precedentes 

es azetidinilo, pirrolidinilo, o piperidinilo sustituido con uno o dos RG2, donde RG2 en cada caso es cada metilo, etilo, isopropilo, tert-butilo, fluoro, cloro, o trifluorometilo; y RM es en forma independiente en cada caso fluoro, cloro, o metilo. Por ejemplo 

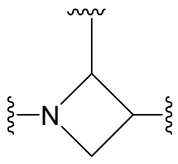
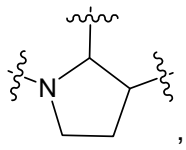
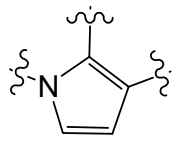
es 4,4-dimetilpiperidin-1-ilo, 4,4-difluoropiperidin-1-ilo, 2,6-dimetilpiperidin-1-ilo, 4-(propan-2-il)piperidin-1-ilo, 4-fluoropiperidin-1-ilo, 3,5-dimetilpiperidin-1-ilo, 4-(trifluorometil)piperidin-1-ilo, 4-metilpiperidin-1-ilo, 4-tert-butilpiperidin-1-ilo, 2-oxopiperidin-1-ilo, o 3,3-dimetilazetidin-1-ilo.

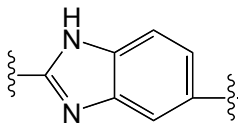
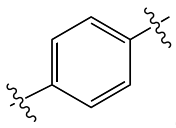
En aun otro aspecto, la presente invención presenta compuestos de Fórmula IG y sales aceptables farmacéuticamente de los mismos,

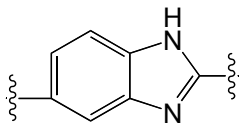
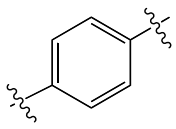


IG

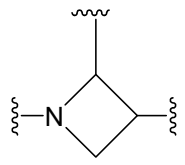
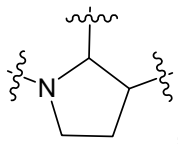
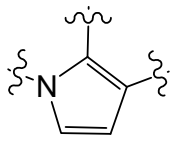
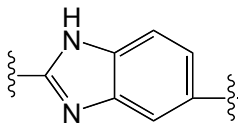
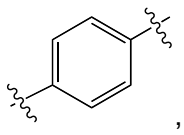
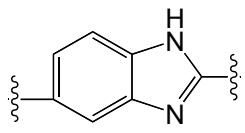
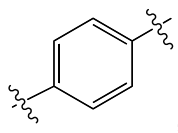
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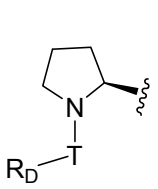
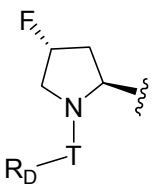
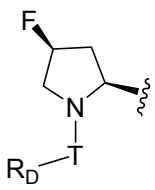
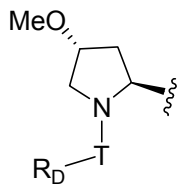
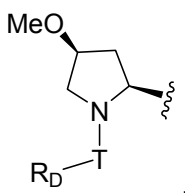
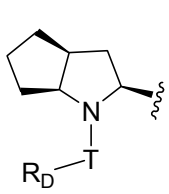
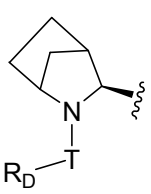
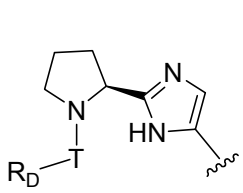
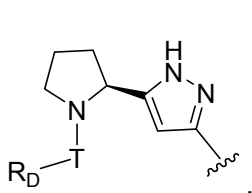
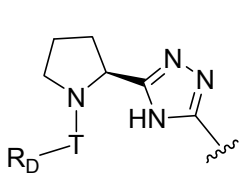
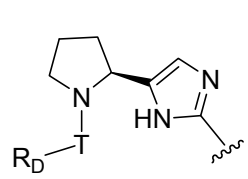
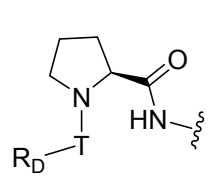
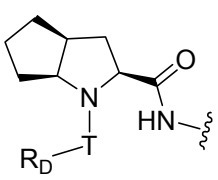
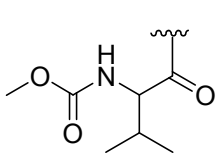
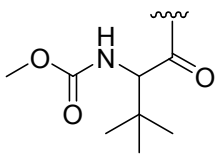
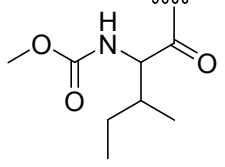
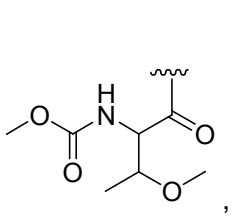
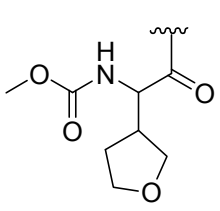
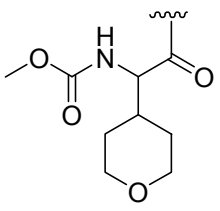
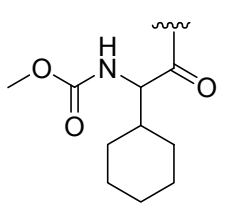
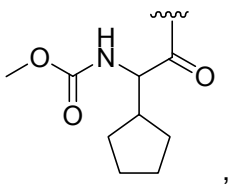
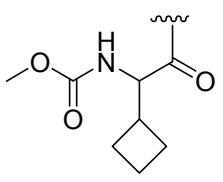
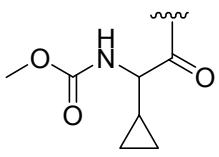
X es  ,  , o  , donde X está opcionalmente sustituido con uno o más RA

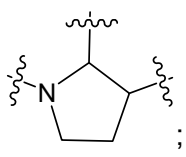
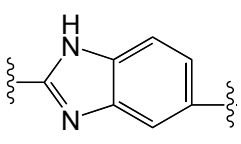
A es  o  , donde A está opcionalmente sustituido con uno o más RA;

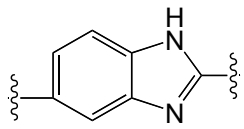
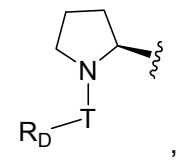
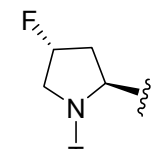
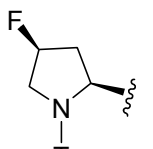
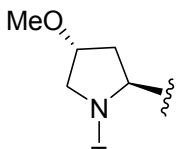
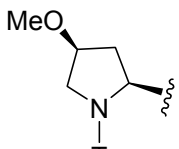
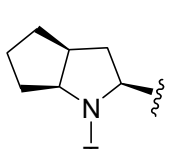
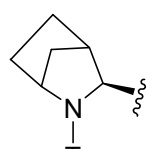
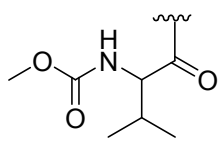
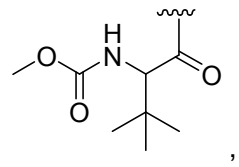
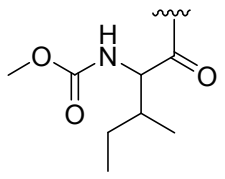
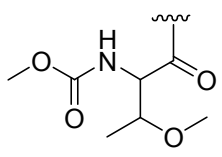
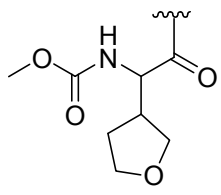
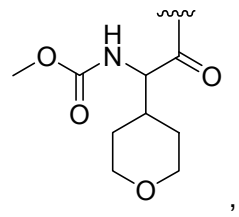
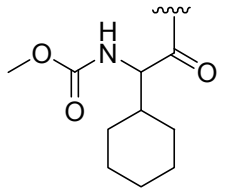
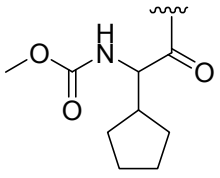
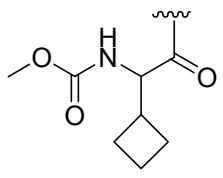
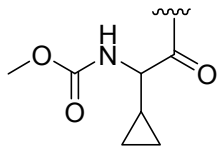
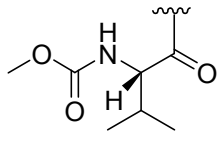
B es  o  , donde B está opcionalmente sustituido con uno o más RA; y

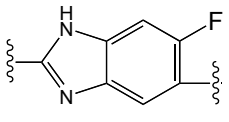
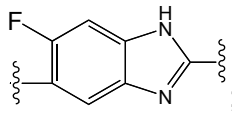
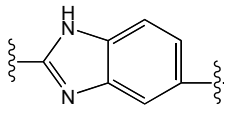
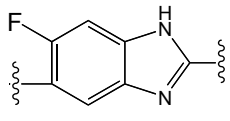
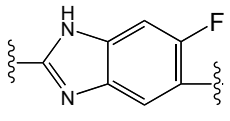
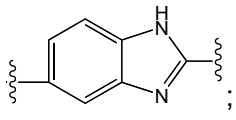
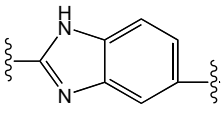
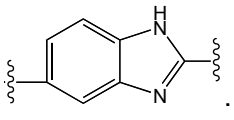
Y, Z, RA, y D son como se describe precedentemente (por ejemplo, como se describe para la Fórmula I, IA, IB, IC, ID, IE o IF, preferiblemente como se describe para la Fórmula IE).

En una forma de realización, este aspecto de la invención presenta compuestos de Fórmula IG y sales aceptables farmacéuticamente del mismo, donde: X es  ,  , o  ; A es  o  , donde A está opcionalmente sustituido con un RA; B es  o  , donde B está opcionalmente sustituido con un RA; RA es halógeno (por ejemplo, fluoro, cloro); LS–RE donde LS es una unión simple y RE es –C1-C6alquilo (por ejemplo, metilo), –O–RS (por ejemplo, –O–C1-C6alquilo, –OCH3), o –C1-C6alquilo opcionalmente sustituido con uno o más halógeno (por ejemplo, –CF3); o LS–RE donde LS es un C1-C6alquileno y RE es –

O–RS (por ejemplo, –C1-C6alquil–O–C1-C6alquilo, –CH2OCH3); Y y Z son en forma independiente entre sí  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , o  ; T–RD es en forma independiente en cada caso  ,  ,  ,  ,  ,  ,  ,  ,  , o  ; y D es como se define precedentemente.

En otra forma de realización, este aspecto de la invención presenta compuestos de Fórmula IG y sales aceptables farmacéuticamente del mismo, donde X es  ; A es  , donde A está opcionalmente sustituido con un RA;

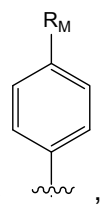
B es  , donde B está opcionalmente sustituido con un RA; RA es halógeno (por ejemplo, fluoro, cloro); LS–RE donde LS es una unión simple y RE es –C1-C6alquilo (por ejemplo, metilo), –O–RS (por ejemplo, –O–C1-C6alquilo, –OCH3), o –C1-C6alquilo opcionalmente sustituido con uno o más halógeno (por ejemplo, –CF3); o LS–RE donde LS es un C1-C6alquileno y RE es –O–RS (por ejemplo, –C1-C6alquil–O–C1-C6alquilo, –CH2OCH3); Y y Z son en forma independiente entre sí  ,  ,  ,  ,  ,  ,  , o , T–RD es en forma independiente en cada caso  ,  ,  ,  ,  ,  ,  ,  ,  , o  , donde se contemplan particularmente los compuestos con estereoquímica (S) (por ejemplo, ); y D es como se define precedentemente. Este subgrupo incluye compuestos donde A y B están ambos sustituidos con un RA; compuestos donde A y B

están ambos sustituidos con cero RA; compuestos donde A está sustituido con un RA y B está sustituido con cero RA; y compuestos donde A está sustituido con cero RA y B está sustituido con un RA. En particular, de acuerdo con este subgrupo se incluyen compuestos donde A es  y B es  ; o A es  y B es  ; o A es  y B es  ; o A es  y B es  .

De acuerdo con cada una de las formas de realización y descripción precedentes de este aspecto de la invención de Fórmula IG existen grupos y subgrupos de compuestos con valores particulares para D. En cada una de las formas de realización precedentes existen grupos y subgrupos de compuestos con los siguientes valores particulares para D:

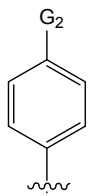
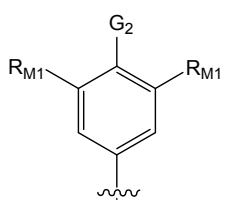
Los grupos de compuestos de acuerdo con este aspecto de la invención incluyen compuestos donde D es C6-C10arilo (por ejemplo, fenilo, naftilo, indanilo), o heteroarilo de entre 5 y 10 miembros (piridinilo, tiazolilo, 4,5,6,7-tetrahidrobenzo[d]tiazolilo, benzo[d]tiazolilo, indazolilo, benzo[d][1,3]dioxol-5-ilo), y D está sustituido con uno o más RM. Los subgrupos particulares de acuerdo con este aspecto y estas formas de realización incluyen compuestos donde RM es halógeno (por ejemplo, fluoro, cloro, bromo); C1-C6alquilo (por ejemplo, tert-butilo); C1-C6alquilo sustituido con uno o más halógeno (por ejemplo, CF3); –O–C1-C6alquilo (por ejemplo, –O–CH2CH3); –O–C1-C6alquilo sustituido en cada caso con uno o más halógeno (por ejemplo, –O–CF3, –O–CH2CHF2) o –O–C1-C6alquilo (–O–CH2CH2OCH3); –O–C1-C6alquilo (por ejemplo, –O–CH2) sustituido con un heterociclo opcionalmente sustituido de entre 3 y 12 miembros (por ejemplo, 3-etiloxetan-3-ilo, 1,3-dioxolan-4-ilo); –O–RS donde RS es un carbociclo o heterociclo opcionalmente sustituido de entre 3 y 12 miembros (por ejemplo, ciclopentilo,

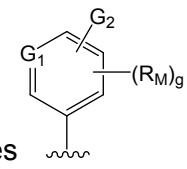
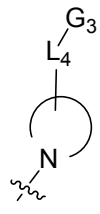
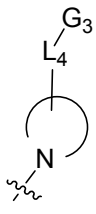
ciclohexilo, fenilo, 1,3-dioxan-5-ilo); –N(RS)C(O)RS' donde RS y RS' son en forma independiente entre sí C1-C6alquilo (por ejemplo, –N(t-Bu)C(O)Me); SF5; –SO2RS donde RS es C1-C6alquilo (por ejemplo, –SO2Me); o C3-C12carbociclo (por ejemplo, ciclopropilo, ciclohexilo, fenilo). Otros subgrupos de acuerdo con esta forma de realización incluyen compuestos donde D es fenilo sustituido con G2 y opcionalmente sustituido con uno o más RM, donde G2 es un heterociclo de entre 3 y 12 miembros (por ejemplo, piridinilo, piperidinilo, pirrolidinilo, azetidinilo, oxazolilo) donde el heterociclo está opcionalmente sustituido con uno o más sustituyentes seleccionados entre halógeno, hidroxi, oxo, ciano, C1-C6alquilo (por ejemplo, metilo), C2-C6alquenilo, C2-C6alquinilo, C1-C6haloalquilo (por ejemplo, CF3), C2-C6haloalquenilo, C2-C6haloalquinilo, –O–C1-C6alquilo (por ejemplo, –O–CH3), –C(O)ORS (por ejemplo, –C(O)OCH3), –C(O)RS (por ejemplo, –C(O)CH3), –N(RSRS'), o L4–G3; RM es halógeno (por ejemplo, fluoro, cloro), alquilo (por ejemplo, metilo), haloalquilo (por ejemplo, CF3), o –O–C1-C6alquilo (por ejemplo, –O–CH3); y L4, G3, RS, y RS' son como se definen precedentemente.

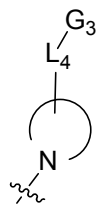
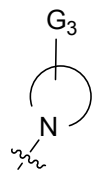
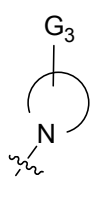
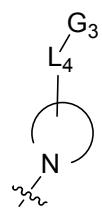
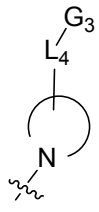
En algunos grupos de compuestos de acuerdo con la Fórmula IG y las formas de realización y descripción precedentes de este aspecto de la invención, D es 

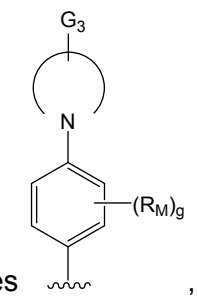
, donde RM es fluoro, cloro, tert-butilo, –O–CH2CH3, –O–CF3, –O–CH2CHF2, –O–CH2CH2OCH3, –O–CH2–(3-etiloxetan-3-ilo), –O–CH2–(1,3-dioxolan-4-ilo), –O–ciclopentilo, –O–ciclohexilo, –O–fenilo, –O–(1,3-dioxan-5-ilo), ciclopropilo, ciclohexilo, fenilo, SF5, –SO2Me, o –N(t-Bu)C(O)Me y D está opcionalmente sustituido con uno o más RM adicionales, seleccionados entre el grupo que consiste en halógeno (por ejemplo, fluoro, cloro) o C1-C6alquilo (por ejemplo, metilo).

En otros grupos de compuestos de acuerdo con la Fórmula IG y las formas de

realización y descripción precedentes de este aspecto de la invención, D es  donde G2 es piridinilo (por ejemplo, piridin-2-ilo), piperidin-1-ilo, 4,4-dimetilpiperidin-1-ilo, 4,4-difluoropiperidin-1-ilo, 2,6-dimetilpiperidin-1-ilo, 4-(propan-2-il)piperidin-1-ilo, 4-fluoropiperidin-1-ilo, 3,5-dimetilpiperidin-1-ilo, 4-(trifluorometil)piperidin-1-ilo, 4-metilpiperidin-1-ilo, 4-tert-butilpiperidin-1-ilo, 2-oxopiperidin-1-ilo, 3,3-dimetilazetidin-1-ilo, u oxazolilo (por ejemplo, 1,3-oxazol-2-ilo) y D está opcionalmente sustituido con uno o más RM adicionales seleccionados entre el grupo que consiste en halógeno (por ejemplo, fluoro, cloro), o C1-C6alquilo (por ejemplo, metilo). En particular de acuerdo con estos grupos existen compuestos donde D es  ; G2 es piperidin-1-ilo, 4,4-dimetilpiperidin-1-ilo, 4,4-difluoropiperidin-1-ilo, 2,6-dimetilpiperidin-1-ilo, 4-(propan-2-il)piperidin-1-ilo, 4-fluoropiperidin-1-ilo, 3,5-dimetilpiperidin-1-ilo, 4-(trifluorometil)piperidin-1-ilo, 4-metilpiperidin-1-ilo, 4-tert-butilpiperidin-1-ilo, 2-oxopiperidin-1-ilo, o 3,3-dimetilazetidin-1-ilo; y RM1 es en forma independiente en cada caso hidrógeno, fluoro, cloro, o metilo.

En otros grupos de compuestos de acuerdo con la Fórmula IG y las formas de realización y descripción precedentes de este aspecto de la invención, D es  donde G1 es N, C–H, o C–RM; G2 es  , donde  , RM, y g son como se

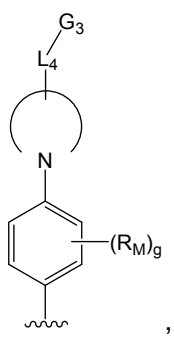
definen precedentemente. En particular de acuerdo con estos grupos, RM es en forma independiente en cada caso fluoro, cloro, metilo, metoxi, trifluorometilo, o trifluorometoxi; g es 0, 1, o 2; y  es como se define precedentemente. En otros subgrupos L4 es un enlace; G2 es  ; RM es en forma independiente en cada caso fluoro, cloro, metilo, metoxi, trifluorometilo, o trifluorometoxi; y g es 0, 1, o 2. En subgrupos particulares,  es 3-fenilazetidin-1-ilo, 3-fenilpirrolidin-1-ilo, 4-fenilpiperazin-1-ilo, 4-fenilpiperidin-1-ilo, 4-fenil-3,6-dihidropiridin-1(2H)-ilo, 4,4-difenilpiperidin-1-ilo, 4-acetil-4-fenilpiperidin-1-ilo, 4-(4-metoxifenil)piperidin-1-ilo, 4-(4-fluorofenil)piperidin-1-ilo, o 3-fenilpiperidin-1-ilo; RM es en forma independiente en cada caso fluoro, cloro, metilo, metoxi, trifluorometilo, o trifluorometoxi; y g es 0, 1, o 2. En otros subgrupos L4 es C1-C6 alquileno, –O–, o –S(O)2–; G2 es  ; RM es en forma independiente en cada caso fluoro, cloro, metilo, metoxi, trifluorometilo, o trifluorometoxi; y g es 0, 1, o 2. En subgrupos particulares,  es 4-tosilpiperazin-1-ilo, 4-fenoxipiperidin-1-ilo, 3-fenoxipirrolidin-1-ilo, 4-bencilpiperidin-1-ilo, 4-fenetilpiperidin-1-ilo, o 3-fenilpropil)piperidin-1-ilo; RM es en forma independiente en cada caso fluoro, cloro, metilo, metoxi, trifluorometilo, o trifluorometoxi; y



g es 0, 1, o 2. En otros subgrupos de compuestos D es , donde G3 es fenilo opcionalmente sustituido con uno o dos RG3; g es 0, 1, o 2; RM es en forma independiente en cada caso fluoro, cloro, metilo, metoxi, trifluorometilo, o trifluorometoxi; y



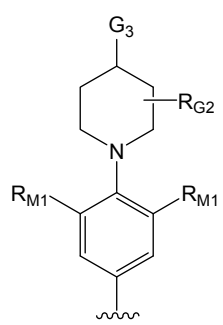
y RG3 son como se definen precedentemente. En otros grupos de compuestos D



es , donde L4 es C1-C6 alquileno, –O–, o –S(O)2–; G3 es fenilo opcionalmente sustituido con uno o dos RG3; g es 0, 1, o 2; RM es en forma independiente en cada caso fluoro, cloro, metilo, metoxi, trifluorometilo, o trifluorometoxi; y

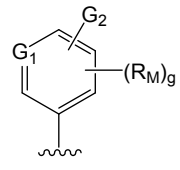


y RG3 son como se definen precedentemente. En otros subgrupos de compuestos D es



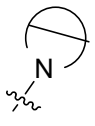
donde G3 es fenilo opcionalmente sustituido con uno o dos RG3 como se define precedentemente; RM1 es en forma independiente en cada caso hidrógeno, fluoro, cloro, o metilo; y RG2 es un sustituyente opcional, como se describe precedentemente, seleccionado entre el grupo que consiste en –C(O)C1-C6alquilo, –C1-

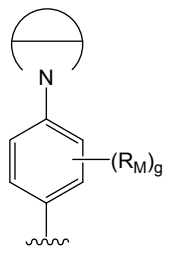
C6alquilo, –C1-C6haloalquilo, –O–C1-C6alquilo, y –O–C1-C6haloalquilo.

En otros grupos de compuestos de acuerdo con la Fórmula IG y las formas de realización y descripción precedentes de este aspecto de la invención, D es 

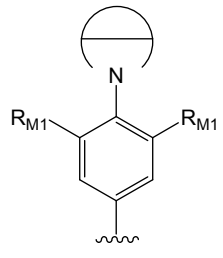
donde G1 es N, C–H, o C–RM; G2 es 

, donde 

, RM, y g son como se definen precedentemente. En particular de acuerdo con estos subgrupos, RM es en forma independiente en cada caso fluoro, cloro, metilo, metoxi, trifluorometilo, o trifluorometoxi; g es 0, 1, o 2; y 

es 3-azabiciclo[3,2,0]hept-3-ilo, 2-azabiciclo[2,2,2]oct-2-ilo, 6-azaespiro[2,5]oct-6-ilo, octahidro-2H-isoindol-2-ilo, 3-azaespiro[5,5]undec-3-ilo, 1,3-dihidro-2H-isoindol-2-ilo, o 1,4-dioxa-8-azaespiro[4,5]dec-8-ilo. En otros subgrupos de compuestos D es 

donde g es 0, 1, o 2; RM es en forma independiente en cada caso fluoro, cloro, metilo, metoxi, trifluorometilo, o trifluorometoxi; y 

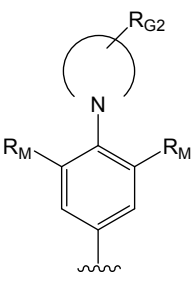
es como se define precedentemente. En otros subgrupos de compuestos D es 

donde RM1 es en forma independiente en cada caso hidrógeno, fluoro, cloro, o metilo y

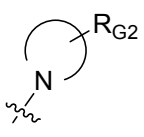


es como se define precedentemente (por ejemplo, 3-azabiciclo[3,2,0]hept-3-ilo, octahidro-2H-isoindol-2-ilo, 2-azabiciclo[2,2,2]oct-2-ilo, 6-azaespiro[2,5]oct-6-ilo, 3-azaespiro[5,5]undec-3-ilo, 1,3-dihidro-2H-isoindol-2-ilo, 1,4-dioxa-8-azaespiro[4,5]dec-8-ilo).

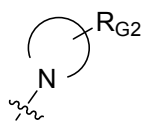
En otros grupos de compuestos de acuerdo con la Fórmula IG y las formas de realización y descripción precedentes de este aspecto de la invención, D es



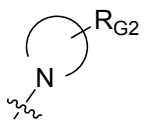
, donde



es un heterociclo monocíclico que contiene nitrógeno de entre 4 y 8 miembros (por ejemplo, azetidinilo, pirrolidinilo, piperidinilo) sustituido con uno o más RG2, donde RG2 en cada caso es en forma independiente en cada caso halógeno, –C(O)C1-C6alquilo, –C1-C6alquilo, –C1-C6haloalquilo, –O–C1-C6alquilo, o –O–C1-C6haloalquilo; y RM es en forma independiente en cada caso halógeno, –C1-C6alquilo, –C1-C6haloalquilo, –O–C1-C6alquilo, o –O–C1-C6haloalquilo. En cada grupo de compuestos de acuerdo con las formas de realización precedentes



es azetidinilo, pirrolidinilo, o piperidinilo sustituido con uno o dos RG2, donde RG2 en cada caso es cada metilo, etilo, isopropilo, tert-butilo, fluoro, cloro, o trifluorometilo; y RM es en forma independiente en cada caso fluoro, cloro, o metilo. Por ejemplo



es 4,4-dimetilpiperidin-1-ilo, 4,4-difluoropiperidin-1-ilo, 2,6-dimetilpiperidin-1-ilo, 4-(propan-2-il)piperidin-1-ilo, 4-fluoropiperidin-1-ilo, 3,5-dimetilpiperidin-1-ilo, 4-(trifluorometil)piperidin-1-ilo, 4-metilpiperidin-1-ilo, 4-tert-butilpiperidin-1-ilo, 2-oxopiperidin-1-ilo, o 3,3-

dimetilazetidin-1-ilo.

La presente invención también presenta compuestos de las Fórmulas IE, IF y IG como se describe aquí (incluyendo cada forma de realización descrita bajo las mismas) y sales aceptables farmacéuticamente de los mismos, donde:

RE se selecciona en forma independiente en cada caso entre –O–RS, –S–RS, –C(O)RS, –OC(O)RS, –C(O)ORS, –N(RSRS'), –S(O)RS, –SO2RS, –C(O)N(RSRS'), –N(RS)C(O)RS', –N(RS)C(O)N(RS'RS''), –N(RS)SO2RS', –SO2N(RSRS'), –N(RS)SO2N(RS'RS''), –N(RS)S(O)N(RS'RS''), –OS(O)–RS, –OS(O)2–RS, –S(O)2ORS, –S(O)ORS, –OC(O)ORS, –N(RS)C(O)ORS', –OC(O)N(RSRS'), –N(RS)S(O)–RS', –S(O)N(RSRS'), –P(O)(ORS)2, =C(RSRS'), o –C(O)N(RS)C(O)–RS'; o C1-C6alquilo, C2-C6alquenilo o C2-C6alquinilo, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo o ciano; o C3-C12carbociclo o heterociclo de entre 3 y 12 miembros, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, trimetilsililo, C1-C6alquilo, C2-C6alquenilo, C2-C6alquinilo, C1-C6haloalquilo, C2-C6haloalquenilo, C2-C6haloalquinilo, –O–RS, –S–RS, –C(O)RS, –C(O)ORS, o –N(RSRS').

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 preferiblemente 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 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;

preferiblemente, al menos un 90% del compuesto en una composición es el estereoisómero descrito; y más preferiblemente, 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 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, L1, L2, L3, Y, Z, T, RA o RB,). 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 “Cx-Cy”, donde x es la cantidad mínima e y es la cantidad máxima de átomos de

carbono en el grupo. Así, por ejemplo, “C1-C6-alquilo” significa un sustituyente alquilo que contiene entre 1 y 6 átomos de carbono. A modo de ilustración adicional, un C3-C6-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, C3-C6carbociclilC1-C6alquilo se refiere a un C3-C6carbociclilo unido a la porción molecular parental a través de un grupo C1-C6alquilo.

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 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 –LS–M–LS’– y M es –N(RB)S(O)–, entonces la estructura química es –LS–N(RB)S(O)–LS’–.

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 –LS–M–LS’– y M se selecciona como un enlace, entonces la estructura química será –LS–LS’–. 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 –LS–M–LS’–M’–LS’’–, y M y LS’ se seleccionan como enlaces, entonces la estructura química será –LS–M’–LS’’–. Asimismo, si una estructura química se representa como –LS–M–LS’–M’–LS’’–, y M, LS’ y M’ son enlaces, entonces la estructura química será –LS–

LS''–.

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.

Cuando un grupo está sustituido con oxo o tioxo, significa que el grupo contiene un átomo de carbono unido covalentemente a por lo menos dos hidrógenos (por ejemplo, CH2), y los dos radicales hidrógeno están sustituidos con oxo o tioxo para formar C=O o C=S, respectivamente.

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)─CH2─, ─C(H)=C(H)─CH2─CH2─, ─CH2─C(H)=C(H)─CH2─, ─C(H)=C(H)─CH(CH3)─ y ─CH2─C(H)=C(H)─CH(CH2CH3)─.

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, -CH2-, -CH2CH2-, -CH2CH2CH2-, -CH2CH2CH2CH2- y -CH2CH(CH3)CH2-.

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─CH2─, ─C≡C─CH2─CH2─, ─CH2─C≡C─CH2─, ─C≡C─CH(CH3)─ y ─CH2─C≡C─CH(CH2CH3)─.

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, C3-C6carbociclilC1-C6alquilo se refiere a un grupo C3-C6carbociclilo unido a la porción molecular parental a través de un C1-C6alquileno.

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, “C1-C6haloalquilo” se refiere a un sustituyente C1-C6alquilo en donde uno o más átomos de hidrógeno son reemplazados de manera independiente con radicales de halógeno seleccionados. Los ejemplos no limitativos de C1-C6haloalquilo 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 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, sin que esto constituya limitación alguna, un monociclo

que contiene un único 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 (also known 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, sin que esto constituya limitación alguna, un biciclo que contiene dos anillos fusionados, como por ejemplo, naftiridinilo (incluyendo [1,8] naftiridinilo, y [1,6] naftiridinilo), tiazolpirimidinilo, tienopirimidinilo, pirimidopirimidinilo, piridopirimidinilo, pirazolopirimidinilo, 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 benzofusionados, como por ejemplo indolilo, isoindolilo, indoleninilo (también conocido como “pseudoindolilo”),

isoindazolilo (también conocido como “benzpirazolilo” o indazolilo), benzazinilo (incluyendo quinolinilo (también conocido como “1-benzazinilo”) y isoquinolinilo (también conocido como “2-benzazinilo”)), benzimidazolilo, ftalazinilo, quinoxalinilo, benzodiazinilo (incluyendo cinnolinilo (también conocido como “1,2-benzodiazinilo”) y quinazolinilo (también conocido como “1,3-benzodiazinilo”)), benzopiranilo (incluyendo “cromenilo” y “isocromenilo”), benzotiopiranilo (también conocido como “tiocromenilo”), benzoxazolilo, indoxazinilo (también conocido como “bencisoxazolilo”), antranililo, benzodioxolilo, benzodioxanilo, benzoxadiazolilo, benzofuranilo (también conocido como “coumaronilo”), isobenzofuranilo, benzotienilo (también conocido como “benzotiofenilo”, “tionaftenilo”, y “benzotiofuranilo”), isobenzotienilo (también conocido como “isobenzotiofenilo”, “isotionaftenilo”, y “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), bencisoxazinilo (incluyendo 1,2-bencisoxazinilo y 1,4-bencisoxazinilo), y tetrahidroisoquinolinilo.

Un heterociclilo también puede ser, sin que esto constituya limitación alguna, un sistema de anillos espiro, como por ejemplo, 1,4-dioxa-8-azaespiro[4,5]decanilo.

Un heterociclilo puede comprender uno o más átomos de azufre como miembros del anillo; y en algunos casos, los átomos de azufre se oxidan a SO o SO2. Los heteroáromos nitrógeno en un heterociclilo pueden estar cuaternizados o no, y pueden estar oxidados a un N-óxido o no. Además, los heteroáromos nitrógeno pueden estar N-protegidos o no.

Un heterociclo o carbociclo puede estar sustituido adicionalmente. Salvo que se especifique lo contrario, el término “sustituido” hace referencia a la sustitución por reemplazo independiente de uno, dos o tres o más de los átomos de hidrógeno con sustituyentes incluyendo, sin que esto constituya limitación alguna, -F, -Cl, -Br, -I, hidroxi, hidroxi protegido, -NO2, -N3, -CN, -NH2, amino protegido, oxo, tioxo, -NH-C1-C12-alquilo,

-NH-C2-C8-alquenilo, -NH-C2-C8-alquinilo, -NH-C3-C12-cicloalquilo, -NH-arilo, -NH-heteroarilo, -NH-heterocicloalquilo, -dialquilamino, -diarilamino, -diheteroarilamino, -O-C1-C12-alquilo, -O-C2-C8-alquenilo, -O-C2-C8-alquinilo, -O-C3-C12-cicloalquilo, -O-arilo, -O-heteroarilo, -O-heterocicloalquilo, -C(O)-C1-C12-alquilo, -C(O)-C2-C8-alquenilo, -C(O)-C2-C8-alquinilo, -C(O)-C3-C12-cicloalquilo, -C(O)-arilo, -C(O)-heteroarilo, -C(O)-heterocicloalquilo, -CONH2, -CONH-C1-C12-alquilo, -CONH-C2-C8-alquenilo, -CONH-C2-C8-alquinilo, -CONH-C3-C12-cicloalquilo, -CONH-arilo, -CONH-heteroarilo, -CONH-heterocicloalquilo, -OCO2-C1-C12-alquilo, -OCO2-C2-C8-alquenilo, -OCO2-C2-C8-alquinilo, -OCO2-C3-C12-cicloalquilo, -OCO2-arilo, -OCO2-heteroarilo, -OCO2-heterocicloalquilo, -OCONH2, -OCONH-C1-C12-alquilo, -OCONH-C2-C8-alquenilo, -OCONH-C2-C8-alquinilo, -OCONH-C3-C12-cicloalquilo, -OCONH-arilo, -OCONH-heteroarilo, -OCONH-heterocicloalquilo, -NHC(O)-C1-C12-alquilo, -NHC(O)-C2-C8-alquenilo, -NHC(O)-C2-C8-alquinilo, -NHC(O)-C3-C12-cicloalquilo, -NHC(O)-arilo, -NHC(O)-heteroarilo, -NHC(O)-heterocicloalquilo, -NHCO2-C1-C12-alquilo, -NHCO2-C2-C8-alquenilo, -NHCO2-C2-C8-alquinynl, -NHCO2-C3-C12-cicloalquilo, -NHCO2-arilo, -NHCO2-heteroarilo, -NHCO2-heterocicloalquilo, -NHC(O)NH2, -NHC(O)NH-C1-C12-alquilo, -NHC(O)NH-C2-C8-alquenilo, -NHC(O)NH-C2-C8-alquinilo, -NHC(O)NH-C3-C12-cicloalquilo, -NHC(O)NH-arilo, -NHC(O)NH-heteroarilo, -NHC(O)NH-heterocicloalquilo, NHC(S)NH2, -NHC(S)NH-C1-C12-alquilo, -NHC(S)NH-C2-C8-alquenilo, -NHC(S)NH-C2-C8-alquinilo, -NHC(S)NH-C3-C12-cicloalquilo, -NHC(S)NH-arilo, -NHC(S)NH-heteroarilo, -NHC(S)NH-heterocicloalquilo, -NHC(NH)NH2, -NHC(NH)NH-C1-C12-alquilo, -NHC(NH)NH-C2-C8-alquenilo, -NHC(NH)NH-C2-C8-alquinilo, -NHC(NH)NH-C3-C12-cicloalquilo, -NHC(NH)NH-arilo, -NHC(NH)NH-heteroarilo, -NHC(NH)NH-heterocicloalquilo, -NHC(NH)-C1-C12-alquilo, -NHC(NH)-C2-C8-alquenilo, -NHC(NH)-C2-C8-alquinilo, -NHC(NH)-C3-C12-cicloalquilo, -NHC(NH)-arilo, -NHC(NH)-heteroarilo, -NHC(NH)-heterocicloalquilo, -C(NH)NH-C1-C12-alquilo, -C(NH)NH-C2-C8-alquenilo, -C(NH)NH-C2-C8-alquinilo, -C(NH)NH-C3-C12-cicloalquilo, -C(NH)NH-arilo, -C(NH)NH-

heteroarilo, -C(NH)NH-heterocicloalquilo, -S(O)-C1-C12-alquilo, -S(O)-C2-C8-alquenilo, -S(O)-C2-C8-alquinilo, -S(O)-C3-C12-cicloalquilo, -S(O)-arilo, -S(O)-heteroarilo, -S(O)-heterocicloalquilo, -SO2NH2, -SO2NH-C1-C12-alquilo, -SO2NH-C2-C8-alquenilo, -SO2NH-C2-C8-alquinilo, -SO2NH-C3-C12-cicloalquilo, -SO2NH-arilo, -SO2NH-heteroarilo, -SO2NH-heterocicloalquilo, -NHSO2-C1-C12-alquilo, -NHSO2-C2-C8-alquenilo, -NHSO2-C2-C8-alquinilo, -NHSO2-C3-C12-cicloalquilo, -NHSO2-arilo, -NHSO2-heteroarilo, -NHSO2-heterocicloalquilo, -CH2NH2, -CH2SO2CH3, -arilo, -arilalquilo, -heteroarilo, -heteroarilalquilo, -heterocicloalquilo, -C3-C12-cicloalquilo, polialcoxialquilo, polialcoxi, -metoximetoxi, -metoxietoxi, -SH, -S-C1-C12-alquilo, -S-C2-C8-alquenilo, -S-C2-C8-alquinilo, -S-C3-C12-cicloalquilo, -S-arilo, -heteroarilo, -S-heterocicloalquilo, o metiltiometilo. Debe comprenderse que los arilos, heteroarilos, alquilos, y similares pueden estar sustituidos adicionalmente.

Un grupo “alifático” es un grupo no aromático compuesto por cualquier combinación de átomos de carbono, átomos de hidrógeno, átomos de halógeno, oxígeno, nitrógeno u otros átomos, y opcionalmente contiene una o más unidades de insaturación, por ejemplo, enlaces dobles y/o triples. Los ejemplos de grupos alifáticos son grupos funcionales, tales como, O, OH, NH, NH2, C(O), S(O)2, C(O)O, C(O)NH, OC(O)O, OC(O)NH, OC(O)NH2, S(O)2NH, S(O)2NH2, NHC(O)NH2, NHC(O)C(O)NH, NHS(O)2NH, NHS(O)2NH2, C(O)NHS(O)2, C(O)NHS(O)2NH o C(O)NHS(O)2NH2, y semejantes, grupos que comprenden uno o más grupos funcionales, hidrocarbonos no aromáticos (opcionalmente sustituidos), y grupos en donde uno o más carbonos de un hidrocarbono no aromático (opcionalmente sustituido) es reemplazado por un grupo funcional. Los átomos de carbono de un grupo alifático opcionalmente pueden estar oxo-sustituidos. El grupo alifático puede ser de cadena lineal, ramificada o cíclica y preferiblemente contiene entre aproximadamente 1 y aproximadamente 24 átomos de carbono, más típicamente entre aproximadamente 1 y aproximadamente 12 átomos de carbono. Además de los grupos de hidrocarbono alifáticos, según se usa en la presente, los grupos alifáticos

incluyen expresamente, por ejemplo, alcoxialquilos, polialcoxialquilos, tales como, por ejemplo, polialquilenglicoles, poliaminas y poliiminas. Los grupos alifáticos pueden estar opcionalmente sustituidos. Un grupo alifático lineal es un grupo alifático no cíclico. Se comprenderá que cuando se dice que un grupo alifático lineal “contiene” o “incluye” o “comprende” uno o más grupos funcionales especificados, el grupo alifático lineal se puede seleccionar entre uno o más de los grupos funcionales especificados o una combinación de los mismos, o un grupo en donde uno o más carbonos de un hidrocarbono no aromático (opcionalmente sustituido) está reemplazado por un grupo funcional especificado. Un ejemplo de un grupo alifático lineal es un alquilo, alquenilo o alquinilo, cada uno opcionalmente sustituido, que fue interrumpido o terminado por un grupo funcional.

------ 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, carboxilo o fosfato). 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, o ésteres de fosfato de 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-

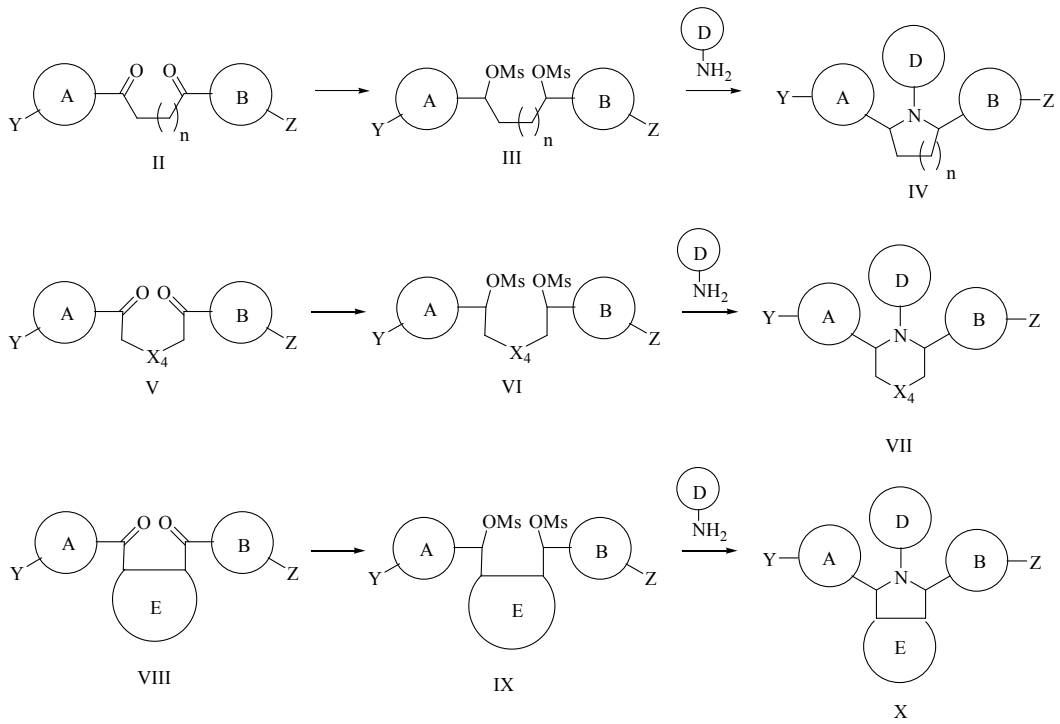
dimetoxibenciloxicarbonilo, 3,4,5-trimetoxibenciloxicarbonilo, 1-(p-bifenililo)-1-metiletoxicarbonilo, dimetil-3,5-dimetoxibenciloxicarbonilo, benzhidriloxicarbonilo, t-butiloxicarbonilo, diisopropilmetoxicarbonilo, isopropiloxicarbonilo, etoxicarbonilo, metoxicarbonilo, aliloxicarbonilo, 2,2,2-tricloro-etoxi-carbonilo, 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).

A continuación se detallan las abreviaturas que se utilizaron en las descripciones de los esquemas, de los intermediarios y de los ejemplos. Ac para acetilo; APCI para ionización química a presión atmosférica; ac o ac. para acuoso; atm para atmósfera; Boc para t-butoxicarbonilo; Bu para butilo; t-Bu o ter-butilo para butilo terciario; Cbz para benciloxicarbonilo; dba para dibencilidinacetona; DCI para ionización química por desorción; DDQ para 2,3-dicloro-5,6-diciano-p-benzoquinona; DEPBT para 3-(dietoxifosforiloxi)-1, 2, 3-benzotriazin-4(3H)-ona; DIBAL para hidruro de diisobutilaluminio; DMA para N,N-dimetilacetamida; DME para 1,2-dimetoxietano; DMF para N,N-dimetilformamida; DMSO para dimetilsulfóxido; DMPU para 1,3-dimetil-3,4,5,6-tetrahidro-2(1H)-pirimidinona; dppf para 1,1′-bis(difenilfosfino)ferroceno; EDC, EDAC o EDCI para clorhidrato de N-(3-dimetilaminopropil)-N'-etilcarbodiimida; e.e. para exceso enantiomérico; ELSD para detector de dispersión de luz evaporativa; ESI para ionización por electroatomización; Et para etilo; Et3N para trietilamina; EtOAc para acetato de etilo; EtOH para etanol; Et2O para éter dietílico; eq o equiv para equivalentes; Fmoc para 9-fluorenilmetoxicarbonilo; HATU para hexafluorofosfato de O-(7-azabenzotriazol-1-il)-N,N,N’,N’-tetrametiluronio; HOBt para 1-hidroxibenzotriazol; HPLC para cromatografía líquida de alta presión; HOBt para 1-hidroxibenzotriazol; LCMS para cromatografía líquida/espectrometría de masa; mCPBA para ácido m-cloroperoxibenzoico; Me para

metilo; MeOH para metanol; OAc para acetato; Ms para metansulfonilo; OTF para triflato o trifluorometansulfonato; PDC para dicromato de piridinio; i-Pr para isopropilo; Ph para fenilo; PPh3 para trifenilfosfina; psi o psig para libras por pulgada cuadrada (gas); PTFE para politetrafluoroetileno; PXPd para [(t-Bu)2PCl]2PdCl2, PyBOP para hexafluorofosfato de (benzotriazol-1-iloxi)tripirrolidinfosfonio; SEM para 2-(trimetilsilil)etoximetilo; T3P para anhídrido del ácido propanfosfónico; Tf para trifluorosulfonilo; TFA para ácido trifluoroacético; THF para tetrahidrofurano; TLC para cromatografía en capa delgada; Troc para 2,2,2-tricloroetoxicarbonilo; v/v para volumen/volumen; %peso para por ciento en peso; p/v para peso/volumen; p/p para peso/peso; XantPhos para 4,5-bis(difenilfosfino)-9,9-dimetilxanteno;

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 (X4 puede ser, por ejemplo, O o NRA, donde RA es como se describió precedentemente y es preferiblemente H o RE como se definió previamente tal como C1-C6alquilo, carbociclo o heterociclo de 3 a 12 miembros, –C(O)RS, –C(O)ORS, –C(O)N(RSRS'), –SO2N(RSRS'), –S(O)2ORS, –S(O)ORS, –S(O)N(RSRS'), 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 RA), en donde A, B, D, Y, Z y RA 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. L1 y L2 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-L3-NH2 en lugar de D-NH2, como podrán apreciar los especialistas en el arte.



Esquema I

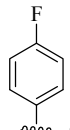
A modo de otro ejemplo no limitativo, los compuestos de la presente invención se pueden preparar comenzando a partir de los compuestos de la fórmula II y de la fórmula III como se muestra en el esquema II. Las 1,4-dicetonas, tal como de la Fórmula IV, se pueden preparar usando métodos conocidos (véase Nevar, et al., Synthesis: 1259-1262 (2000), tal como la reacción de α-bromocetonas, tal como de la Fórmula II, con metil cetonas, tal como de la Fórmula III, en la presencia de un ácido de Lewis adecuado, tales como ZnCl2 o Ti(OiPr)4. Por ejemplo, la reacción de II (1 equivalente) con III (1,5 equivalentes) en la presencia de ZnCl2 (2 equivalentes), dietilamina (1,5 equivalentes) y ter-butanol (1,5 equivalentes) en un solvente, tal como benceno, a temperatura ambiente

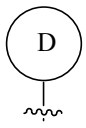
aproximadamente puede proveer las dicetonas IV. Las 1,4-dicetonas IV se pueden reducir en los 1,4-dioles, tal como V, por la acción de NaBH4, LiAlH4 o DIBAL. Como alternativa, la reducción enantioselectiva de 1,4-dicetonas, tal como de la fórmula IV, se puede efectuar por analogía con los métodos informados (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). Las dicetonas IV (1 equivalente) se pueden reducir con NaBH4 (3 equivalentes) en solventes, tal como tetrahidrofurano, con calentamiento a 50 °C aproximadamente. Las dicetonas IV (1 equivalente) se pueden reducir enantioselectivamente mediante su adición a una mezcla de N,N-dietilanilina borano (aproximadamente 2 equivalentes), trimetilborato (aproximadamente 0,2 equivalentes) y ya sea (S) o (R) α,α-difenil-2-pirrolidinmetanol (aproximadamente 0,17 equivalentes) en un solvente, tal como THF, a temperaturas que varían en un rango entre aproximadamente 10 °C y aproximadamente 30 °C (Synthesis 2507-2510 (2003)). Los 1,4-dioles racémicos, enantioméricamente enriquecidos o meso V resultantes se pueden hacer reaccionar con cloruro de metansulfonilo o anhídrido metansulfónico para proveer el dimesilato de la fórmula VI. Por ejemplo, los dioles V (1 equivalente) se pueden hacer reaccionar con anhídrido metansulfónico (aproximadamente 2,5 equivalentes) en la presencia de una base, tal como diisopropiletilamina (aproximadamente 4 equivalentes), en un solvente tal como tetrahidrofurano o 2-metiltetrahidrofurano a temperaturas que comienzan entre aproximadamente -15 °C y -25 °C y aumentando hasta temperatura ambiente aproximadamente. 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 PPh3 en la presencia de CCl4 o CBr4, o por la acción de SOCl2, POCl3 o PBr3. 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 ºC, para dar pirrolidinas tal como de la fórmula VII. El dimesilato VI (1 equivalente) (o, como alternativa, el ditriflato, el ditosilato o el dihaluro) se pueden hacer reaccionar con entre 1 y 20 equiv de una amina D-NH2, tal como, por ejemplo, una anilina sustituida en solventes tales como tetrahidrofurano o 2-metiltetrahidrofurano con o sin un co-solvente tal como DMF, a una temperatura entre aproximadamente temperatura ambiente y aproximadamente 100 ºC, para dar pirrolidinas tales como de la Fórmula VII. Cuando se emplean menos equivalentes de amina D-NH2 (es decir, 1-2 equivalentes), se puede agregar una base, tal como diisopropiletilamina, para promover la reacción. En determinados casos, la amina se puede usar en un gran exceso (es decir, como solvente de reacción). Por ejemplo, la reacción de un dimesilato (1 equivalente) con un exceso de anilina (aproximadamente 6,5 equivalentes) se puede conducir por calentamiento a 65 °C en 2-metiltetrahidrofurano hasta completar la reacción. Se pueden hacer reaccionar numerosas anilinas sustituidas con el dimesilato de la Fórmula VI, incluyendo, pero en un sentido no limitativo, 3-fluoro-4-(piperidin-1-il)anilina, 3,5-difluoro-4-(piperidin-1-il)anilina, 3,5-difluoro-4-(4-fenilpiperidin-1-il)anilina, 3-difluoro-4-(4-fenilpiperidin-1-il)anilina, 4-(4-fenilpiperidin-1-il)anilina, 4-ciclopropilanilina, 4-ciclopropil-2-fluoroanilina, 4-ciclopropil-3,5-difluoroanilina, 4-ciclohexil-3-fluoroanilina, bifenil-4-amina, 4-(piridin-2-il)anilina, 3,5-dicloro-4-(piperidin-1-il)anilina, 4-(4,4-dimetilpiperidin-1-il)-3,5-difluoroanilina, 4-(4,4-fluoropiperidin-1-il)-3,5-difluoroanilina, 3-metil-4-(piperidin-1-il)anilina, 2,5-difluoro-4-(piperidin-1-il)anilina, 4-(3,5-dimetilpiperidin-1-il)-3,5-difluoroanilina, 4-(2,6-dimetilpiperidin-1-il)-3,5-difluoroanilina, 2,3,5-trifluoro-4-(piperidin-1-il)anilina, 3,5-difluoro-4-(4-isopropilpiperidin-1-il)anilina, 3,5-difluoro-4-(4-metilpiperidin-1-il)anilina, 3,5-

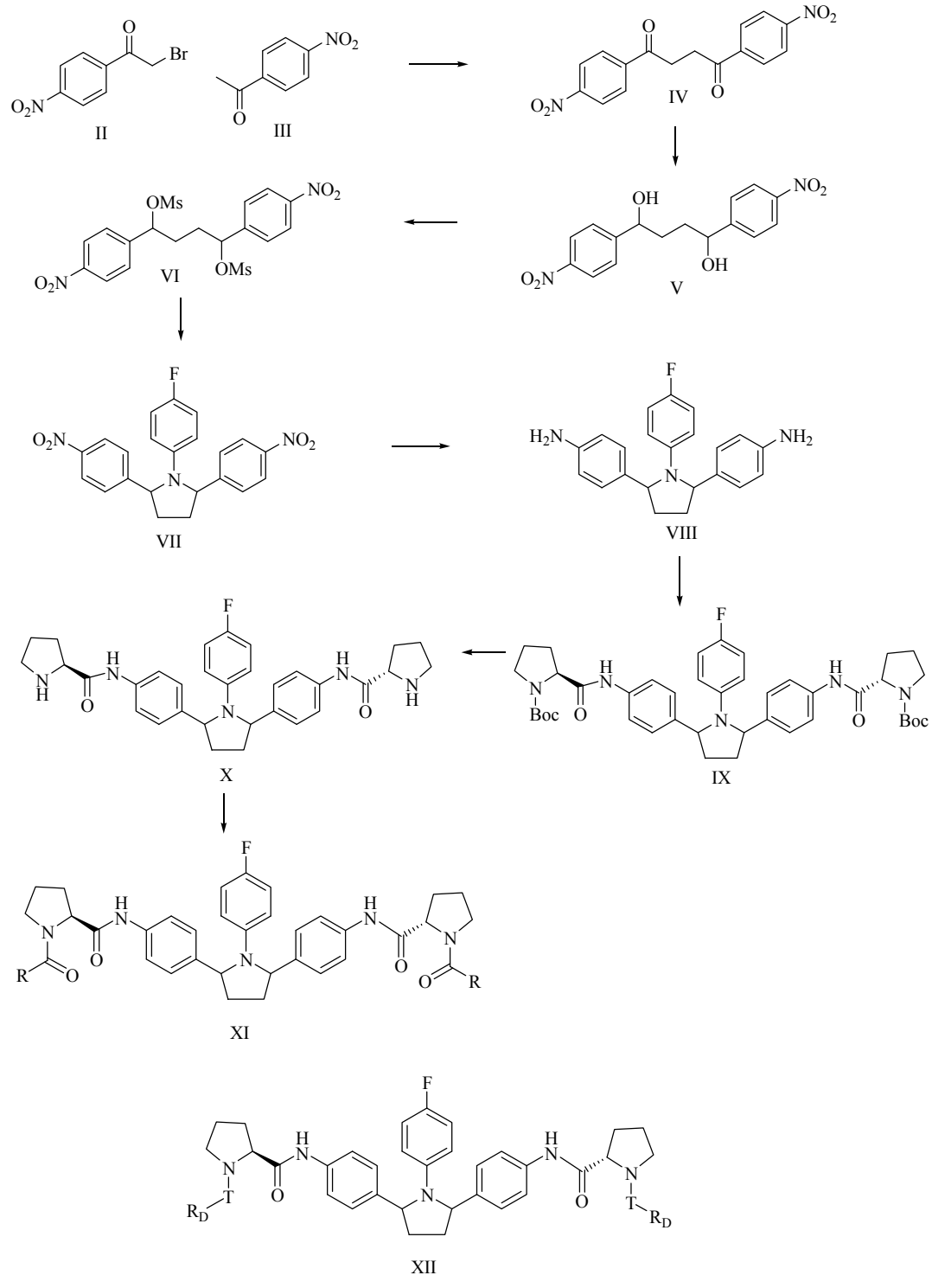
difluoro-4-(4-(trifluorometil)piperidin-1-il)anilina, 4-(4-ter-butilpiperidin-1-il)-3,5-difluoroanilina, 3,5-difluoro-4-(6-azaespiro[2.5]octan-6-il)anilina, 4-(2-azabiciclo[2.2.2]octan-2-il)-3,5-difluoroanilina, 4-(3,3-dimetilazetidin-1-il)-3,5-difluoroanilina, 4-ter-butilanilina, 4-etoxianilina, 4-fenoxianilina, 1-(4-aminofenil)piperidin-2-ona, 4-(ciclopentiloxi)-3-fluoroanilina, 3-cloro-4-(trifluorometoxi)anilina, 2,5-difluoro-4-(trifluorometil)anilina, 4-(2,2-difluoroetoxi)anilina, 4-cloroanilina, 4-(2-metoxietoxi)anilina, 4-(oxazol-2-il)anilina, 4-(2-fluoropiridin-4-il)anilina, 3,4-difluoroanilina, 4-cloro-3-fluoroanilina, 3-fluoro-4-(metilsulfonil)anilina, 4-(3-azabiciclo[3.2.0]heptan-3-il)-3,5-difluoroanilina, 4-((3-etiloxetan-3-il)metoxi)anilina, 4-ciclopropil-3,5-difluoroanilina, 4-(1,3-dioxan-5-iloxi)anilina, 3,5-difluoro-4-(octahidroisoindol-2-il)anilina, 4-((1,3-dioxolan-4-il)metoxi)anilina, 4-((3-etiloxetan-3-il)metoxi)-3,5-difluoroanilina, 4-(pentafluorosulfanil)anilina, N1-ter-butil-2-fluorobencen-1,4-diamina, heteroarilaminas, alquilaminas, cicloalquilaminas, bencilaminas sustituidas, alilamina o las anilinas enumeradas o elaboradas usando los Procedimientos generales 1, 1.1 ó 1.2. El dinitro de la fórmula VII se puede reducir en la diamino de la fórmula VIII usando Fe en la presencia de NH4Cl, 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 BiCl3, SbCl3, NiCl2, Cu2Cl2 o CoCl2) en un solvente, tal como etanol o THF. Por ejemplo, los compuestos VII (1 equivalente) se pueden reducir a VIII mediante reacción con hierro en polvo (aproximadamente 6 equivalentes) y cloruro de amonio en una mezcla 1:1 de THF y etanol con calentamiento a 60-80 °C aproximadamente. Como alternativa, la Fórmula VII se pueden reducir al producto de la Fórmula VIII por hidrogenación en la presencia de un catalizador adecuado, tales como un catalizador de paladio o platino o níquel Raney. Por ejemplo, la reducción de VII a VIII se puede efectuar por exposición a 30 psig de hidrógeno gaseoso en la presencia de níquel Raney Grace 2800 en un solvente, tal como tetrahidrofurano con agitación. 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, T3P o DEBPT, en un solvente tal como THF, DMF, diclorometano, acetato de etilo o DMSO, con o sin la adición de una base de amina, tal como N-metilmorfolina, base de Hunig, piridina, 2,6-lutidina o trietilamina, para dar la fórmula IX. Por ejemplo, la reacción de VIII (1 equivalente) con ácido 1-(ter-butoxicarbonil)pirrolidin-2-carboxílico (2,5 equivalentes) y HATU (2,5 equivalentes) en la presencia de diisopropiletilamina (3 equivalentes) en DMSO a temperatura ambiente aproximadamente puede proveer el producto IX. La eliminación de los grupos protectores Boc para dar X se puede efectuar por tratamiento con un ácido, tal como TFA, HCl o ácido fórmico. Por ejemplo, la reacción de IX (1 equivalente) con TFA:CH2Cl2 (1:1) a temperatura ambiente puede proveer los compuestos X. Los compuestos XI se pueden preparar by acoplamiento de la Fórmula X con un ácido de elección usando los reactivos y las condiciones de acoplamiento de péptidos estándar descritos previamente. Por ejemplo, se puede hacer reaccionar X (1 equivalente) con ácidos (2 equivalentes) tales como, pero en un sentido no limitativo, ácido 2-(metoxicarbonilamino)-3-metilbutanoico, ácido 2-(metoxicarbonilamino)-3,3-dimetilbutanoico, ácido 2-ciclohexil-2-(metoxicarbonilamino)acético, ácido 2-(metoxicarbonilamino)-2-(tetrahidro-2H-piran-4-il)acético, o los ácidos enumerados bajo el Procedimiento general 19. Como alternativa, se puede hacer reaccionar directamente a la diamina VIII con una prolina apropiadamente N-sustituida en la presencia de un reactivo de acoplamiento de péptidos, tales como EDAC/HOBT, PyBOP, HATU, T3P o DEPBT, en un solvente tal como THF, DMF, diclorometano o DMSO, con o sin la adición de una base de amina tal como N-metilmorfolina, base de Hunig, piridina, 2,6-lutidina o trietilamina, para dar directamente los compuestos XI. Por ejemplo, se puede hacer reaccionar directamente VIII (1 equivalente) con ácido 1-(2-(metoxicarbonilamino)-3-metilbutanoil)pirrolidin-2-carboxílico (aproximadamente 2 equivalentes) y T3P (aproximadamente 2,8 equivalentes) en la presencia de diisopropiletilamina (aproximadamente 5,5 equivalentes) en un solvente, tal como acetato de etilo, a

temperaturas entre aproximadamente 0 °C y aproximadamente temperatura ambiente para proveer XI. La secuencia precedente ilustra la síntesis de compuestos particulares XI de la invención que tienen un grupo prolina sustituido en Y y Z (es decir, R2 y R5 tomados juntos con los átomos a los cuales están unidos, y R9 y R12 tomados juntos con los átomos a los cuales están unidos, forman, cada uno, un heterociclo de 5 miembros). Se comprenderá que se pueden usar procedimientos de síntesis análogos para elaborar los compuestos de la invención, donde Y, Z, R2, R5, R9 y R12 son distintos de lo indicado y descrito en el Esquema II. En cada fórmula del Esquema II 

se puede reemplazar por 

, donde D es como se definió previamente, y dichos compuestos se pueden preparar fácilmente de acuerdo con el proceso descrito en el Esquema II (incluyendo la obtención del compuesto XI directamente a partir del compuesto VIII). Asimismo, los compuestos de la Fórmula XII se pueden preparar a partir de los compuestos de la Fórmula X o directamente a partir de los compuestos de la Fórmula VIII.

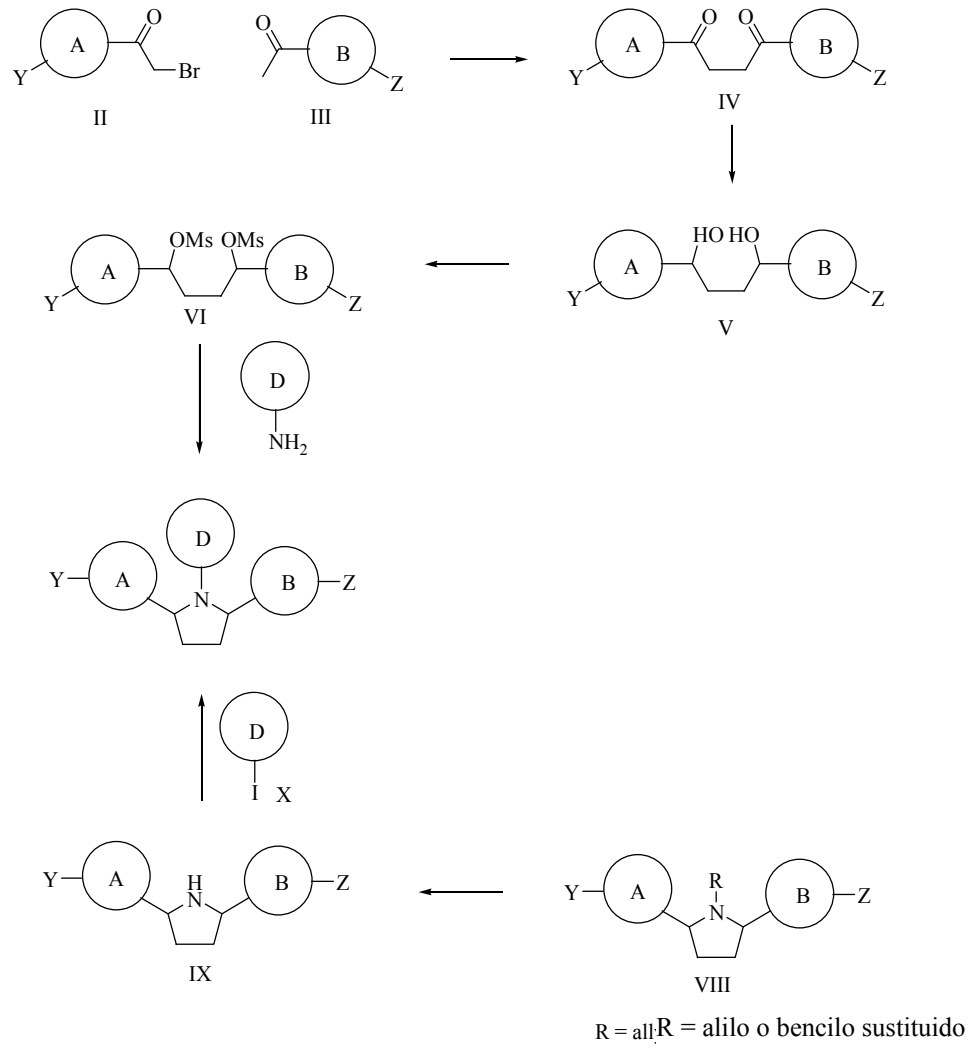


Esquema II

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(Ph3P)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 Pd2(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 K3PO4) 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,

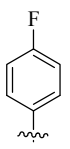
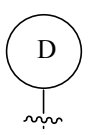
tal como un catalizador de paladio o platino o níquel Raney. Como alternativa, la amina IX puede reaccionar con reactivos electrofílicos, tales como haluros de alquilo, o con electrófilos de arilo (convenientemente haluros y triflatos de arilo y heteroarilo deficientes en electrones) a través de reacciones de sustitución nucleofílica aromática para dar los compuestos de la presente invención.



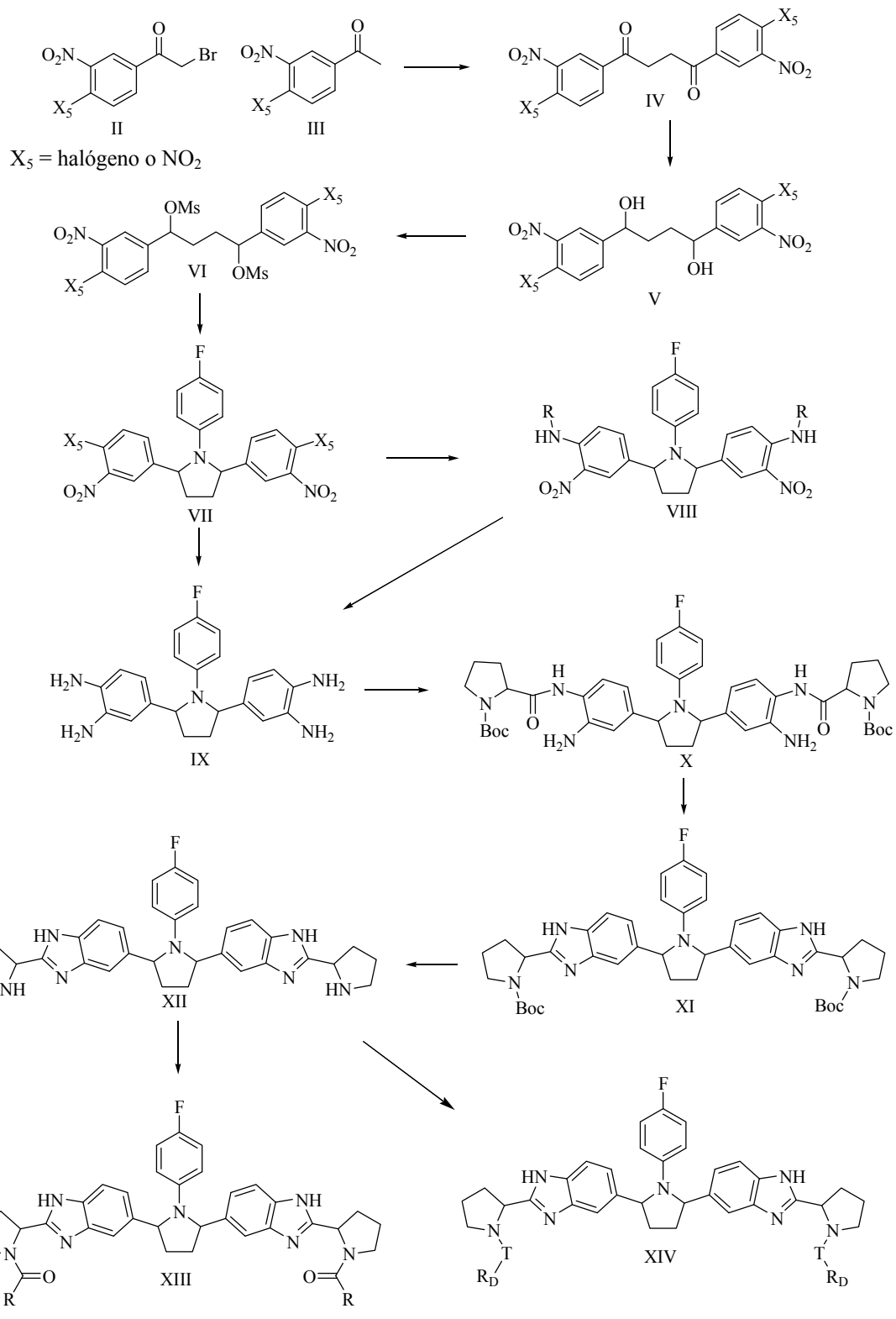
Esquema III

A modo de ejemplo no limitativo adicional, los compuestos de XIII 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 X5 en la fórmula II y la fórmula III representa un halógeno (por ejemplo, Cl, Br o F) o un grupo nitro. Además, cada anillo fenilo puede estar sustituido con X13, en donde X13 es X5, H, alquilo, haloalquilo, alcoxi o haloalcoxi.

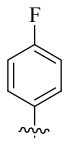
Las 1,4-dicetonas, tal como IV, se pueden preparar usando los métodos conocidos descritos previamente para la preparación de IV en el Esquema II. Las 1,4-dicetonas IV se pueden reducir en los 1,4-dioles, tal como V, por la acción de NaBH4, LiAlH4 o DIBAL. Como alternativa, se puede conducir una reducción enantioselectiva de 1,4-dicetona, tal como IV, mediante los métodos que se describieron previamente para la preparación de V en el esquema II. Según se describió para el Intermediario 20D, la reducción quiral puede proceder con una menor estereoselectividad con un sustituyente X13 adicional sobre el anillo fenilo. Los 1,4-dioles racémicos, enantioméricamente enriquecidos o meso V resultantes se pueden hacer reaccionar con cloruro de metansulfonilo o anhídrido metansulfónico 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, el ditriflato, el ditosilato o el dihaluro pueden reaccionar, de manera análoga al Esquema II, con una amina D–NH2 incluyendo, pero en un sentido no limitativo, las aminas que se describen o a las cuales se hace referencia en el Esquema II para dar VII. Cuando X5 en la fórmula VII es nitro, los grupos nitro se pueden reducir en el producto de tetramina IX usando Fe en la presencia de NH4Cl, 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 BiCl3, SbCl3, NiCl2, Cu2Cl2 o CoCl2) en un solvente, tal como etanol o THF. Como alternativa, VII (X5 = 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 X5 = 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(Ph3P)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

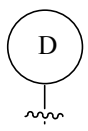
para R = bencilo sustituido) para dar el producto IX. La fórmula IX se puede hacer reaccionar con una prolina ácida adecuadamente protegida (se indica Boc, aunque puede sustituirse por Cbz, Troc o Fmoc) en la presencia de un reactivo de acoplamiento peptídico, tal como EDAC/HOBT, PyBOP, HATU, T3P o DEBPT, en un solvente tal como THF, DMF, diclorometano o DMSO, con o sin la adición de una base de amina, tal como N-metilmorfolina, base de Hunig, piridina, 2,6-lutidina o trietilamina, para dar la fórmula X como una mezcla de los productos de amida. Aunque la fórmula X muestra la reacción en un grupo NH2 específico, la reacción puede tener lugar en cualquier NH2. La conversión en el compuesto benzimidazol XI se puede efectuar por calentamiento de X en ácido acético (50-100 ºC). Como alternativa, XI se puede preparar mediante reacción de IX con un aldehído, seguido por tratamiento con un oxidante, tal como Cu(OAc)2 o MnO2 (véase Penning, et al., Bioorg. Med. Chem. 2008, 16, 6965-6975). Después de eliminar los grupos protectores Boc de XI (mediante tratamiento con un ácido, tales 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 descritos previamente para el Esquema II para dar XIII. En cada Fórmula del Esquema IV  se puede reemplazar por  , donde D es como se definió previamente, y dichos compuestos se pueden preparar fácilmente de acuerdo con el proceso descrito en el Esquema IV. Los compuestos de la Fórmula XIV se pueden preparar de manera similar a partir de los compuestos de la Fórmula XII. Cuando son sometidos a los procesos de síntesis del Esquema IV, los dioles enantioméricamente enriquecidos V pueden producir mezclas que contienen cantidades variables de las pirrolidinas estereoisoméricas cis y trans VII. Las pirrolidinas estereoisoméricas se pueden separar de acuerdo con técnicas de

cromatografía estándar. Como alternativa, dichas separaciones se pueden realizar en una etapa posterior del proceso de síntesis incluyendo los pasos de los Esquemas XIII y XIV, o después del paso final.

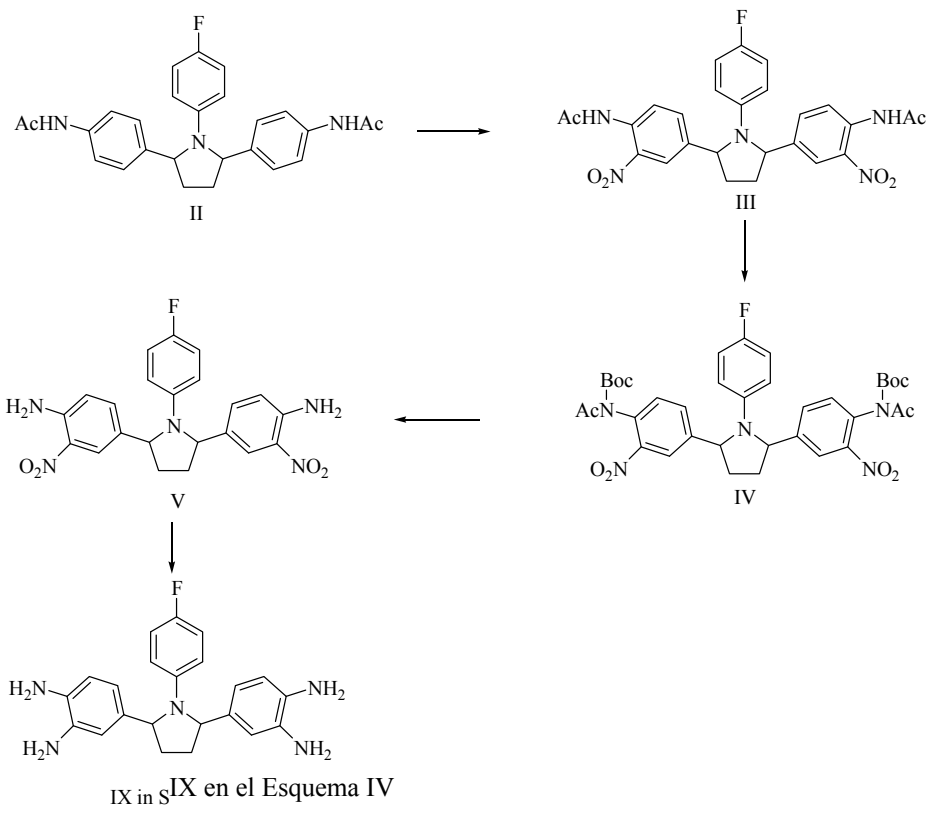


Esquema IV

Como alternativa IX, en el esquema IV, se puede preparar a partir de un compuesto de la fórmula II como se muestra en el esquema V. El compuesto VIII del esquema II se puede tratar con un agente de acilación, 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 NO2BF4. La eliminación del grupo protector de acetamida se puede efectuar mediante 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 eliminar el grupo acetilo y un ácido fuerte, tal como TFA o HCl, para eliminar el grupo protector Boc y proveer V. Los grupos nitro en V se pueden reducir a grupos amino usando los métodos descritos previamente para el Esquema IV y proveer IX. En cada Fórmula del Esquema V 

se puede reemplazar por 

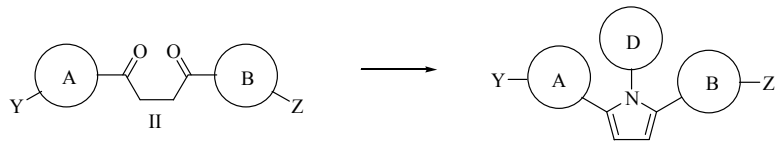
, donde D es como se definió previamente, y dichos compuestos se pueden preparar fácilmente de acuerdo con el proceso descrito en el Esquema V.



IX in S IX en el Esquema IV

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.



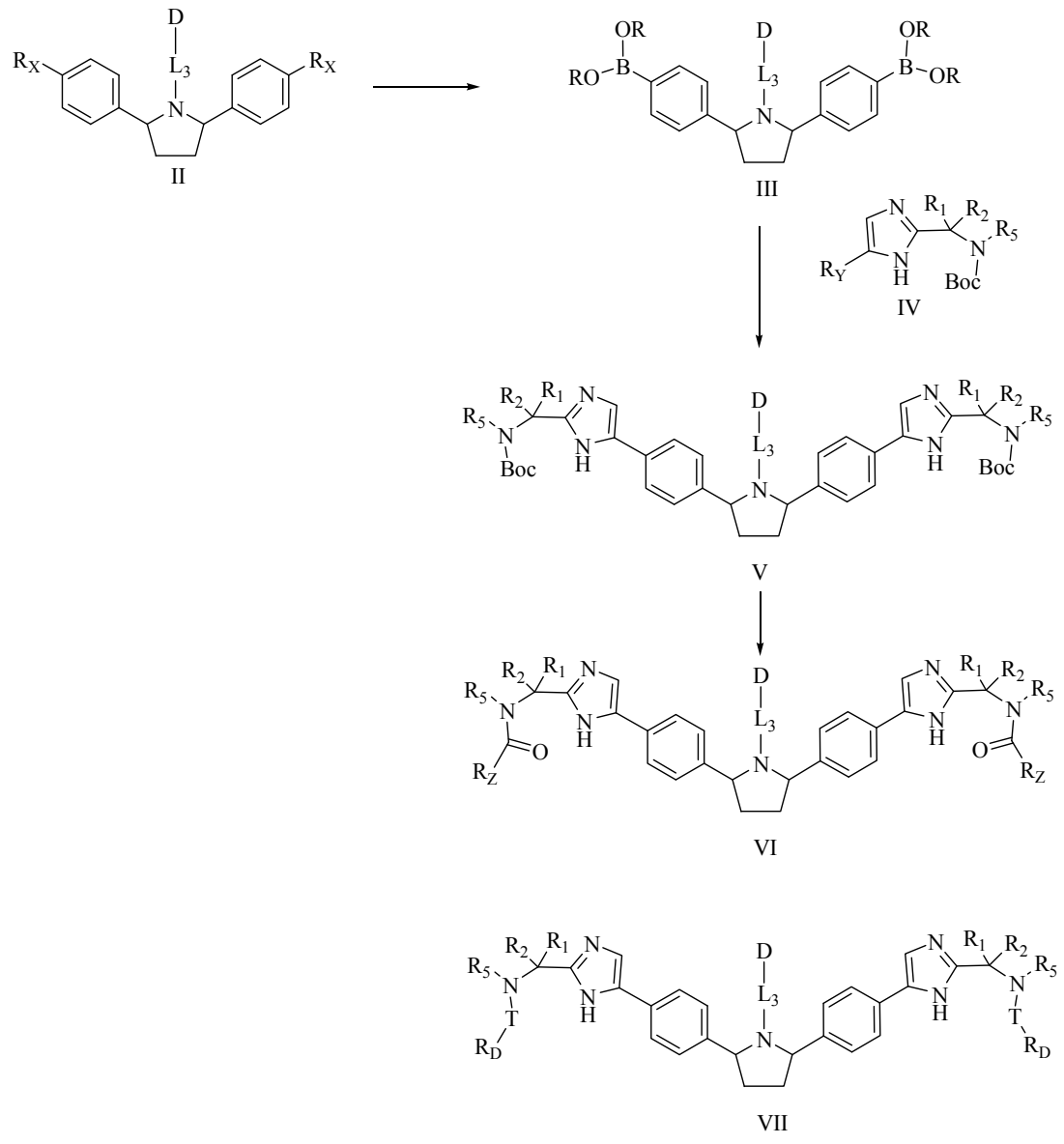
Esquema VI

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 RX 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 de la Fórmula III, usando una química análoga a la del Esquema II para preparar VII (en el Esquema II); por ejemplo, comenzando con 1-(4-bromofenil)etanona y 2-bromo-1-(4-bromofenil)etanona. Un compuesto de la fórmula II, donde RX 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, (por ejemplo, un éster de pinacolato cíclico) donde R es hidrógeno, metilo, etilo o un éster de pinacolato cíclico. Por ejemplo, se puede transformar un compuesto de la Fórmula II 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 temperatura ambiente y aproximadamente 130°C. Como alternativa, el compuesto II se puede hacer reaccionar con bis(pinacolato)diboro en la presencia de un catalizador tal como, por ejemplo, Combiphos-Pd6 (CombiPhos Catalysts, Inc. (NJ, EE.UU.), dicloro[1,1'-bis(difenilfosfino)ferroceno]paladio (II) aducto de diclorometano o acetato de paladio en la 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 dar 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

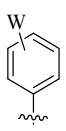
compuesto de la fórmula IV, donde RY es un halógeno, tal como bromo, cloro o iodo, bajo condiciones de reacción de Suzuki para proveer un compuesto de la fórmula V. Dichas condiciones incluyen, por ejemplo, el uso de un catalizador de paladio tal como, por ejemplo, tris(dibencilidinacetona)paladio (0), 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.

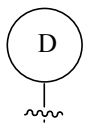
La eliminación de los grupos protectores Boc de V se puede efectuar por tratamiento con un ácido, tal como TFA, HCl o ácido fórmico. Determinados compuestos de la presente invención, tal como VI, se pueden preparar por acoplamiento de los compuestos de amino resultantes con un ácido de elección usando los reactivos de acoplamiento de péptidos estándar, tales 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 N-metilmorfolina, base de Hunig, piridina, 2,6-lutidina o trietilamina. Cada RZ es, de manera independiente, –LY'–M'–RD (por ejemplo, –LY–N(RB'')C(O)–LS–RE), y D, L3, R1, R2, R5 , LY, RB'', LS, RE , LY', M' y RD son como se definieron previamente. Como alternativa, la funcionalidad de T-RD se puede introducir de manera similar después de la eliminación de los grupos protectores Boc en V para dar los compuestos de la Fórmula VII.



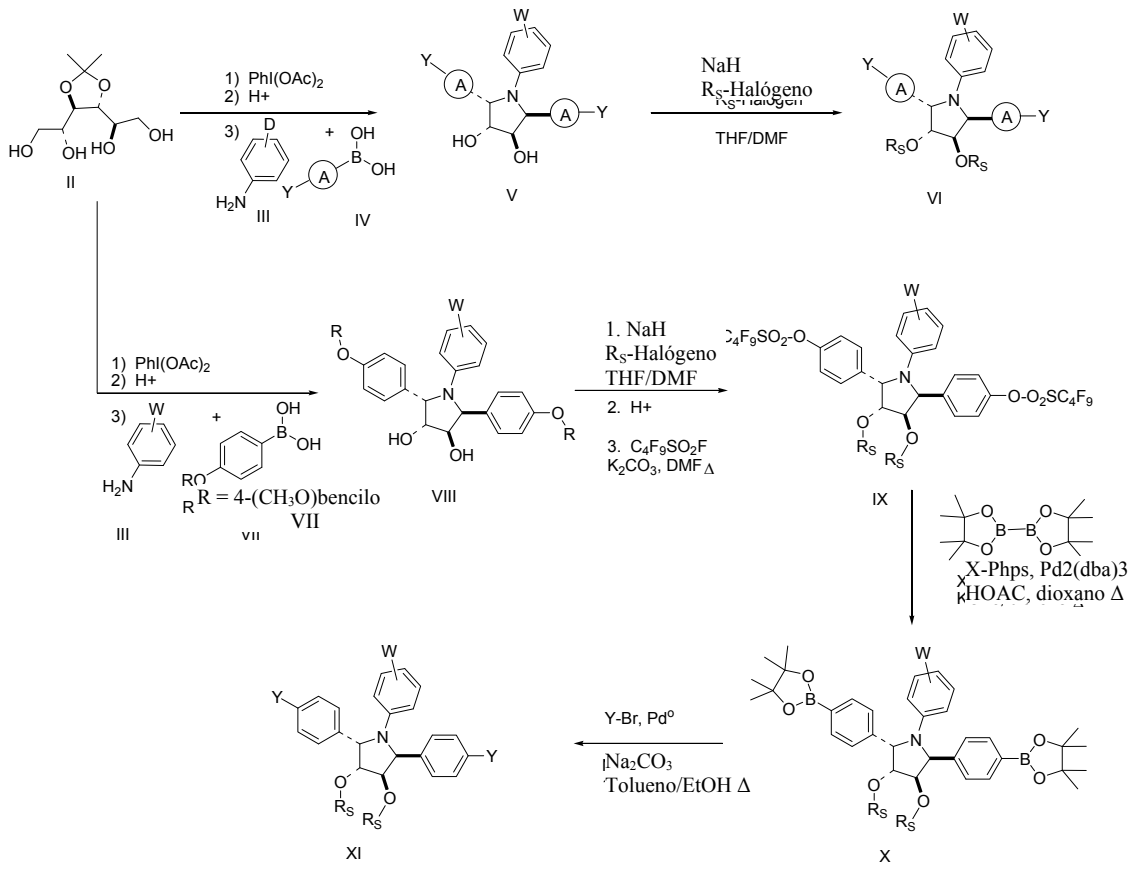
Esquema VII

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 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 RM o J, y RM 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 RS-halógeno. Como alternativa, la fórmula VIII se puede desprotonar con una base fuerte (por ejemplo, hidruro de sodio) y alquilar con RS-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. RS es como se definió previamente. En cada Fórmula del Esquema VIII 

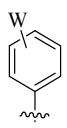
se puede reemplazar por 

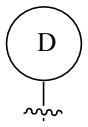
, donde D es como se definió previamente, y dichos compuestos se pueden preparar fácilmente de acuerdo con el proceso descrito en el Esquema VIII.



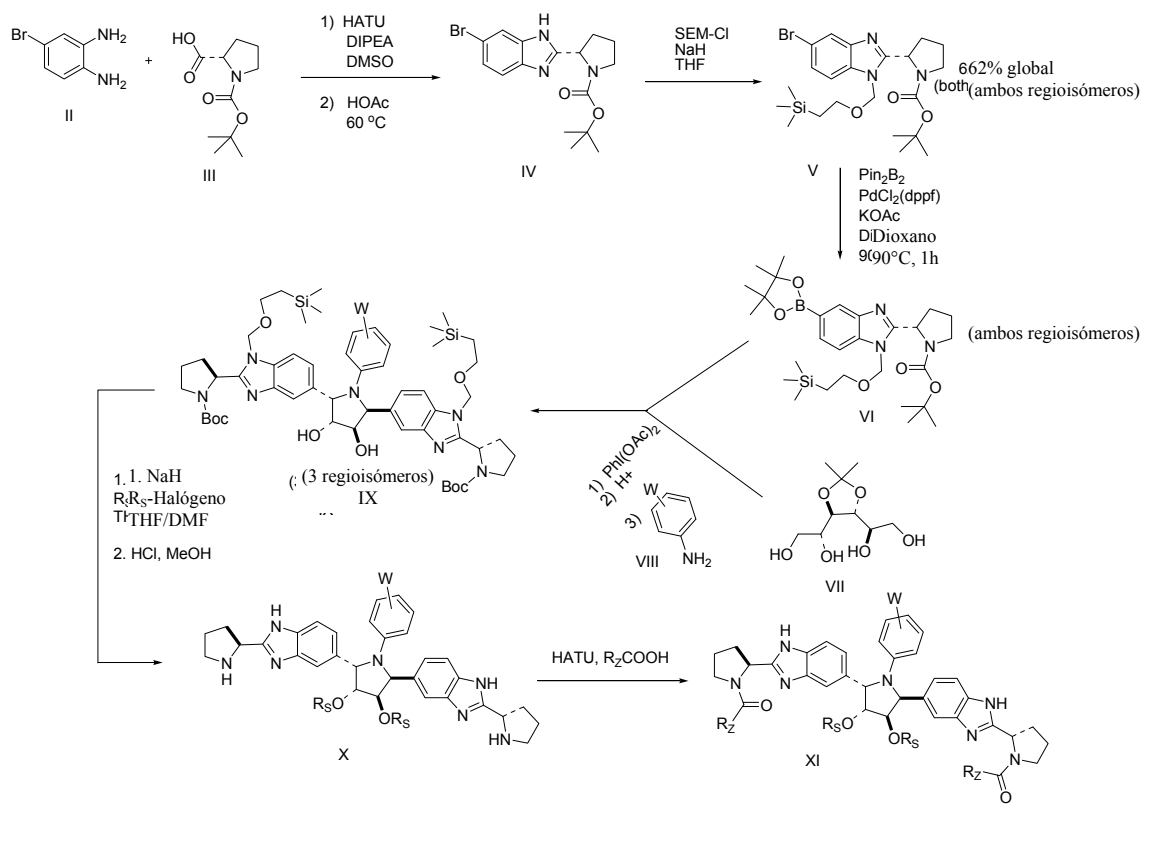
Esquema VIII

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, preferiblemente a 60 oC, 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 RM o J, y RM 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 RS-halógeno, seguido por hidrólisis ácida de la pirrolidina y grupos protectores de benzimidazol, preferiblemente mediante tratamiento con un ácido mineral, tal como ácido clorhídrico en un solvente de alcohol, tal como metanol. El ácido carboxílico RZ-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, la Fórmula X se agrega a la reacción, con el aislamiento de la Fórmula XI. En cada Fórmula del Esquema IX 

se puede reemplazar por 

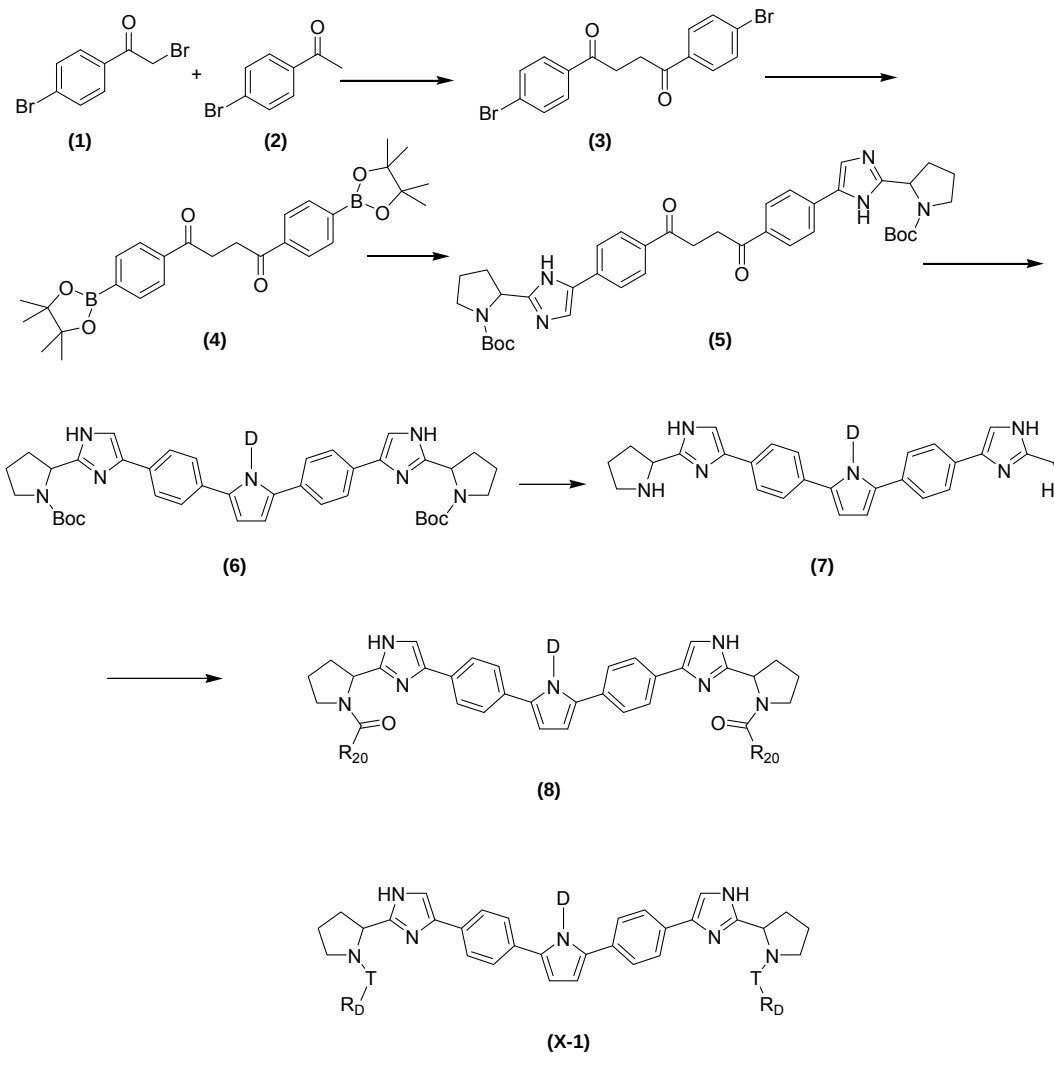
, donde D es como se definió previamente, y dichos compuestos se pueden preparar fácilmente de acuerdo con el proceso descrito en el Esquema IX.



Esquema IX

Determinados compuestos de la invención de la fórmula general (8), donde R20 es –LS'–M'–LS''–RD 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 PdCl2(dppf)-CH2Cl2, 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–NH2 bajo condiciones análogas a las descritas en el esquema VI. Por ejemplo, la reacción de (5) con D–NH2 en la presencia de un ácido tal como, pero

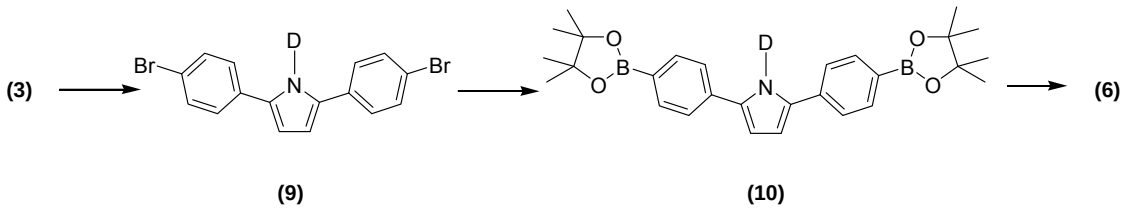
en un sentido no taxativo, TFA, en un solvente tal como, pero en un sentido no taxativo, tolueno y con calentamiento hasta 110 °C puede proporcionar los intermediarios de la estructura general (6). Los compuestos (6) se pueden convertir en los compuestos de las fórmulas generales (7) y luego (8) usando, de manera análoga, los métodos que se describen en el esquema VII. Como alternativa, la funcionalidad de T-RD se puede introducir de manera similar en los compuestos de la Fórmula (7) para dar los compuestos de la Fórmula (X-1).



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–NH2 usando, de manera análoga, las condiciones que se describen en los esquemas VI y X

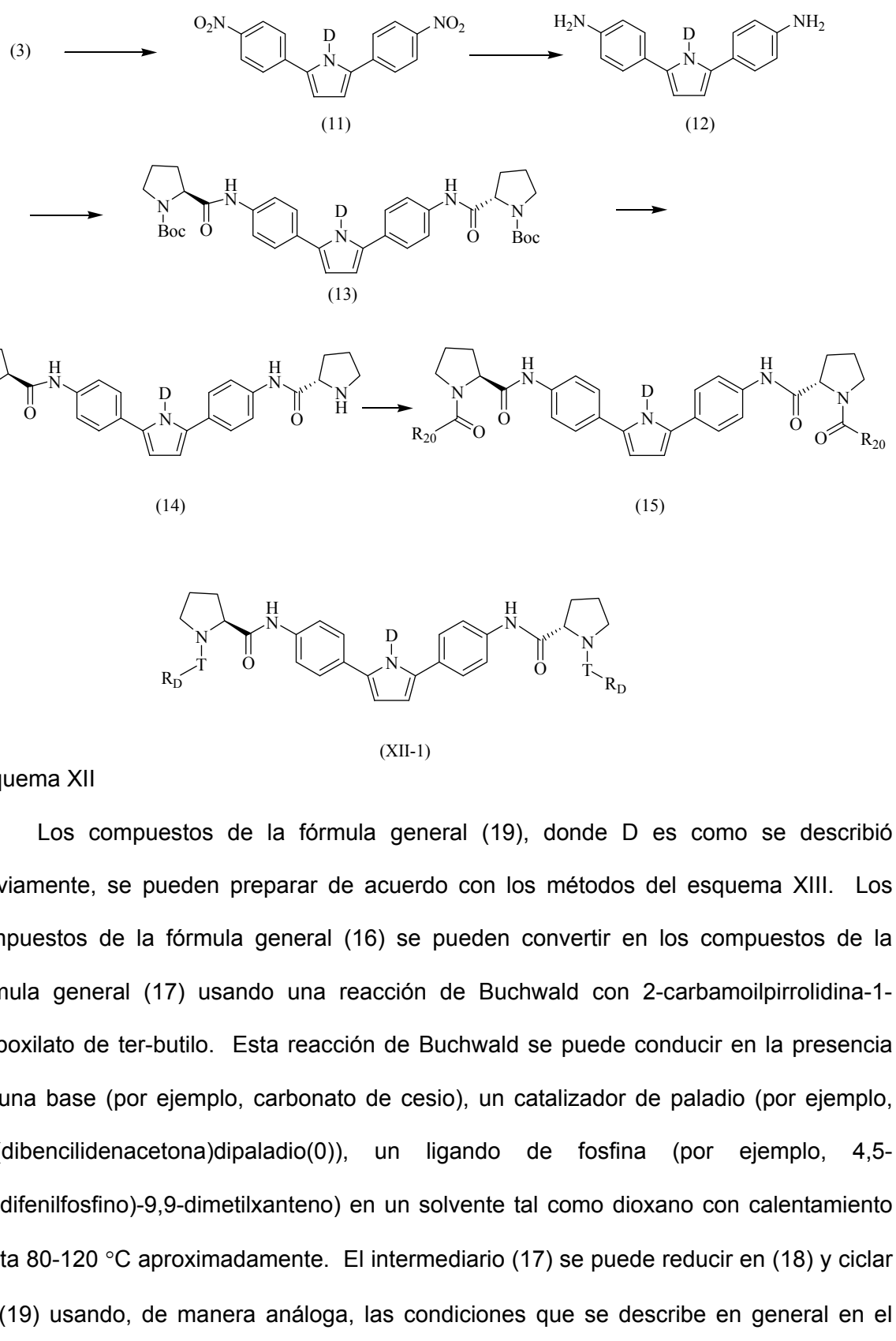
para proveer los intermediarios (9), que se pueden convertir en (10) usando, de manera análoga, las condiciones que se describieron previamente en el esquema X; y, a su vez, (10) se puede convertir en los compuestos (6) usando las condiciones de la reacción de Suzuki que se describen en el esquema VII.



Esquema XI

A modo de otro ejemplo no limitativo, los compuestos de la invención de la fórmula general (15), donde R20 es –LS'–M'–LS''–RD y D es como se describió previamente, se pueden preparar como se muestra en el esquema XII. Se puede hacer reaccionar un compuesto 1,4-dicetona (3) con una amina D-NH2, bajo condiciones catalizadas por ácidos, tales como ácido acético, TFA, ácido fórmico o HCl, para dar los compuestos (11). Por ejemplo, se puede hacer reaccionar una dicetona (3) (1 equivalente) con una anilina (1,2 equivalentes) y TFA (2 equivalentes) en un solvente, tal como tolueno, con calentamiento hasta una temperatura entre 80 y 120 °C aproximadamente para proveer los compuestos (11). Como alternativa, se puede hacer reaccionar una dicetona (3) con una anilina (aproximadamente 10 equivalentes) con calentamiento en ácido acético hasta 70 °C aproximadamente para proveer los compuestos (11). Las aminas que se pueden hacer reaccionar de acuerdo con la descripción precedente incluyen, pero en un sentido no limitativo, las aminas que se describen o a las cuales se hace referencia en el Esquema II como adecuadas para la reacción con el intermediario (5). Los compuestos de la Fórmula (11) se pueden convertir en los compuestos de la Fórmula (12) por reducción con hierro en la presencia de cloruro de amonio. Por ejemplo, la reacción de los compuestos (11) (1 equivalente) con hierro en polvo (aproximadamente 6 equivalentes) en la presencia de cloruro de amonio (aproximadamente 3 equivalentes) en

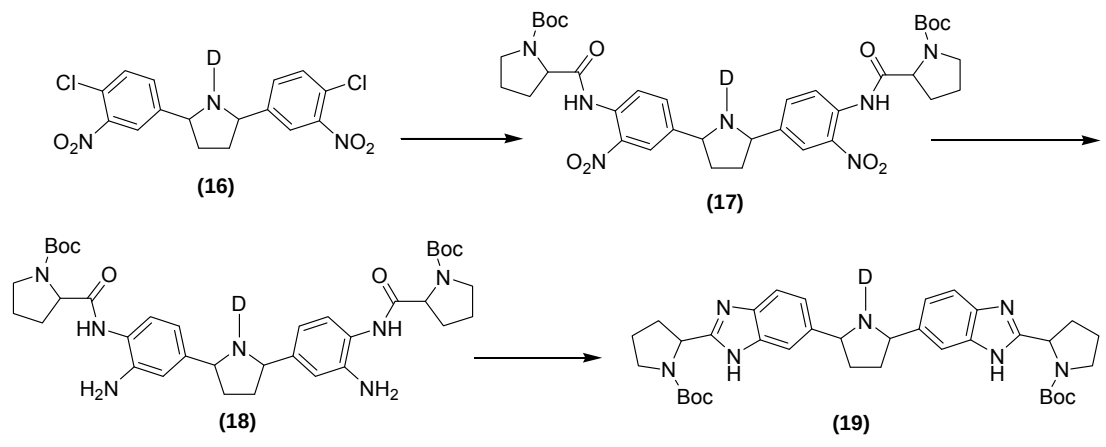
una mezcla de solventes de etanol:THF:agua (1:1:0,25) a reflujo puede proveer los compuestos (12). La conversión de (11) en (12) también puede efectuarse mediante otros métodos descritos previamente en el Esquema II para convertir VII a VIII, por ejemplo por hidrogenación catalítica. Los compuestos (12) (1 equivalente) se pueden convertir en los compuestos (13) usando la condición de acoplamiento de péptidos descrita para la conversión de VIII en IX en el Esquema II, por ejemplo usando EDAC/HOBt (2 equivalentes) y un ácido apropiado en solventes, tal como DMF, a temperatura ambiente aproximadamente. Los compuestos (13) se pueden convertir en los compuestos (14) usando TFA/CH2Cl2 como se describió previamente para la conversión de IX en X en el Esquema II. Los compuestos (14) se pueden convertir en los compuestos (15) usando procedimientos análogos a los del Esquema II para convertir X en XI, tal como el procedimiento de acoplamiento, para convertir (12) en (13). Como alternativa, la funcionalidad de T-RD se puede introducir de manera similar en los compuestos de la Fórmula (14) para dar los compuestos de la Fórmula (XII-1).



Esquema XII

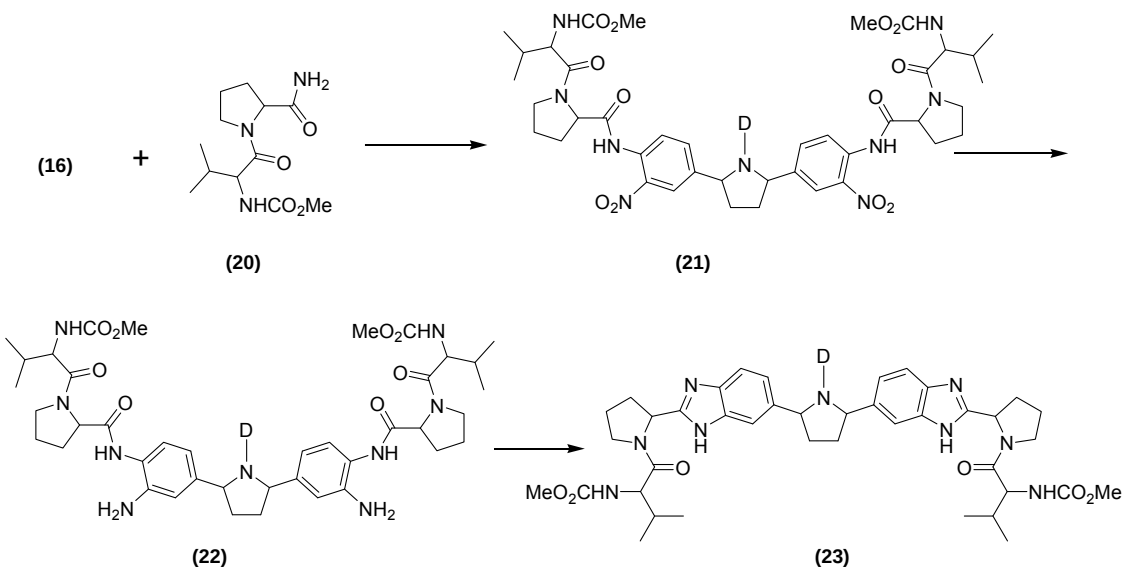
Los compuestos de la fórmula general (19), donde D es como se describió previamente, se pueden preparar de acuerdo con los métodos del esquema XIII. Los compuestos de la fórmula general (16) se pueden convertir en los compuestos de la fórmula general (17) usando una reacción de Buchwald con 2-carbamoilpirrolidina-1-carboxilato 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. Cada anillo fenilo en las

estructuras anteriores puede sustituirse por X13, en donde X13 es H, halógeno, alquilo, haloalquilo, alcoxi o haloalcoxi. Las mezclas de pirrolidinas cis y trans estereoisoméricas en el Esquema XIII se pueden separar en los isómeros cis y trans usando técnicas cromatográficas estándar.



Esquema XIII

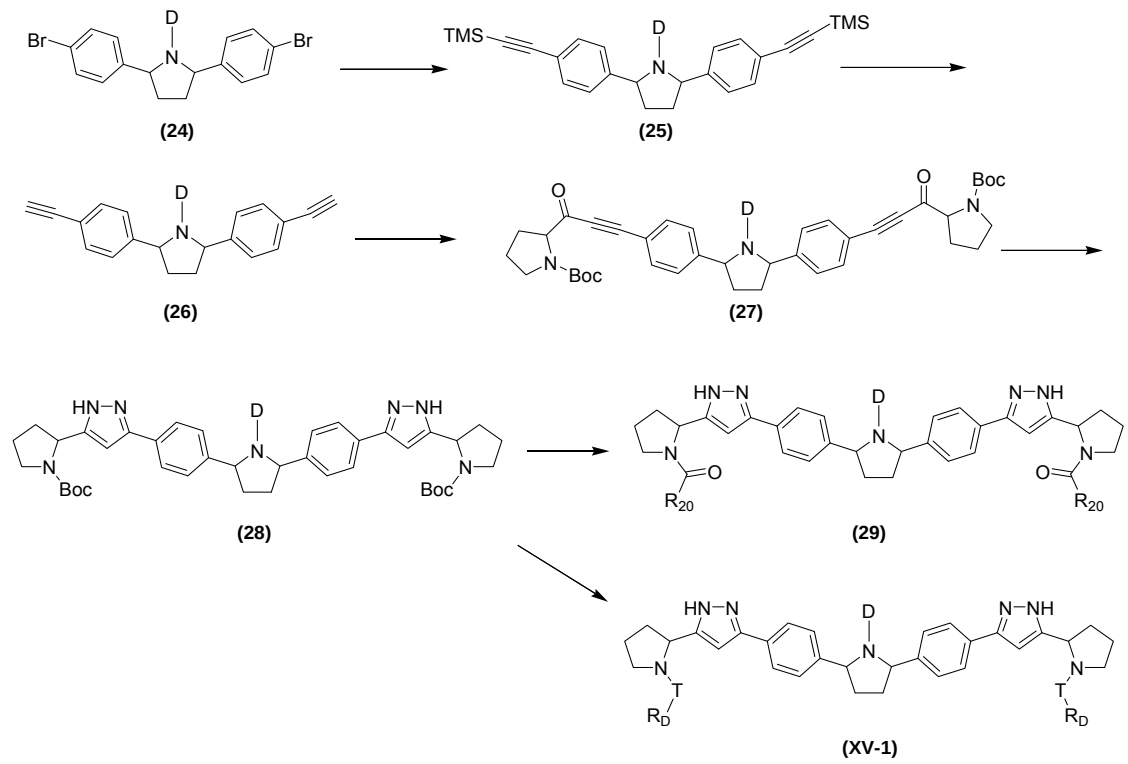
Determinados compuestos de la invención de la fórmula general (23), donde D es como se describió previamente, se pueden preparar de acuerdo con los métodos del esquema XIV. Los compuestos (16) se pueden hacer reaccionar con los compuesto (20) usando una reacción de Buchwald como se describe en general 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.



Esquema XIV

Determinados compuestos de la invención de la fórmula general (29), donde R20 es –LS'–M'–LS''–RD 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. Como alternativa, la funcionalidad de T-RD se puede introducir de manera

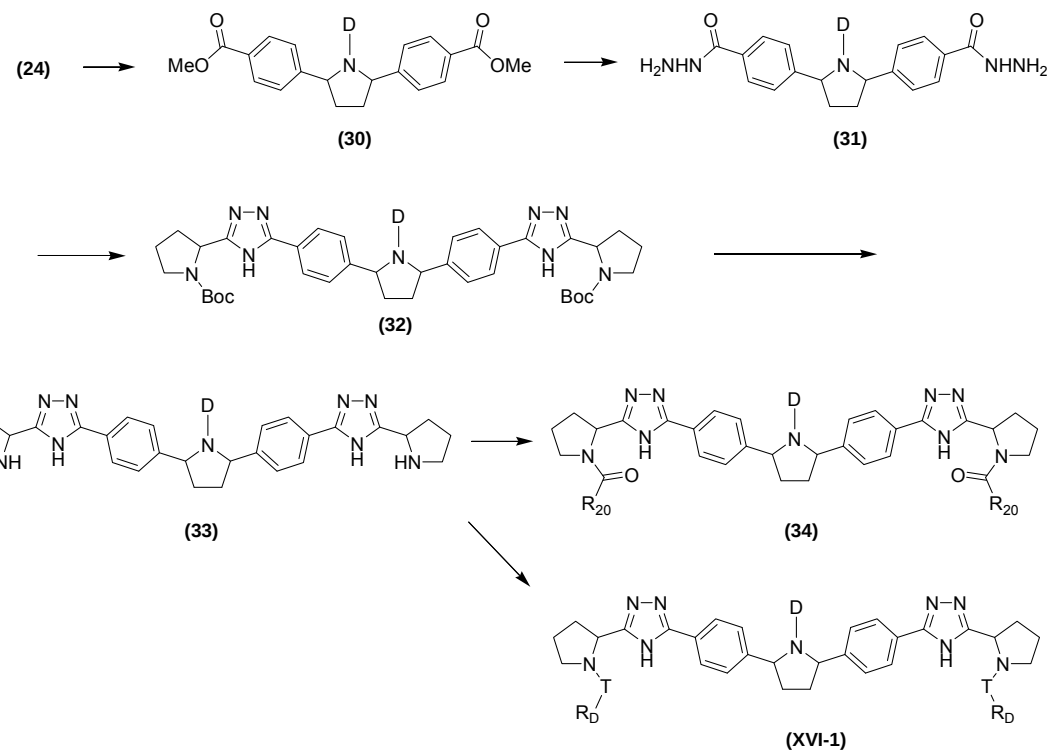
similar en los compuestos de la Fórmula (28) para dar los compuestos de la Fórmula (XV-1).



Esquema XV

Determinados compuestos de la invención de la fórmula general (34), donde R20 es –LS'–M'–LS''–RD 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, PdCl2(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

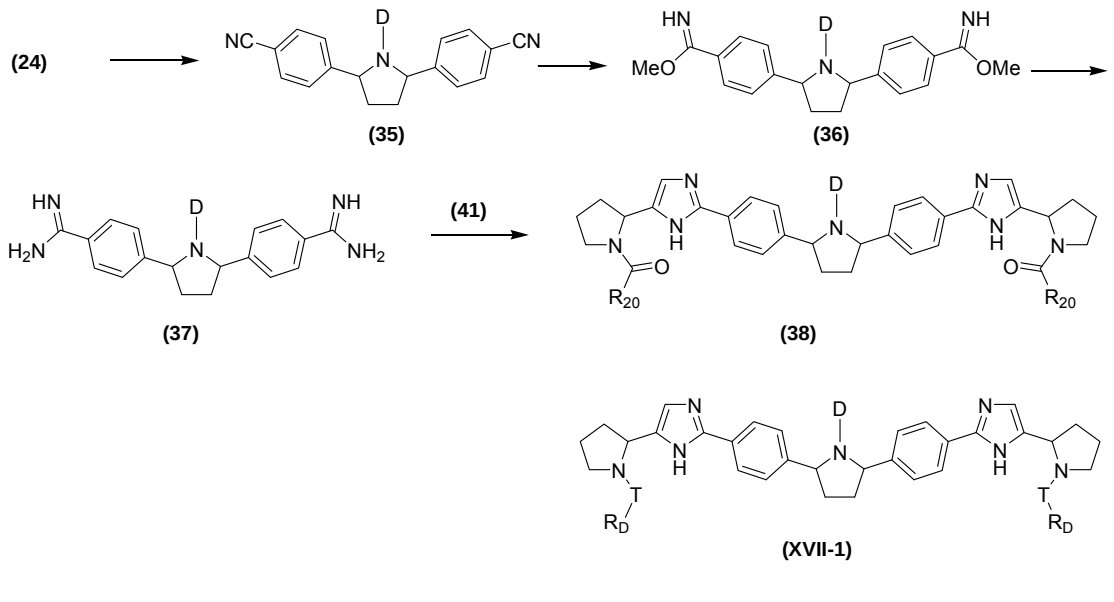
desproteger en los compuestos (33) y acilar en (34) usando, de manera análoga, las condiciones que se describen en general en los esquemas precedentes. Como alternativa, la funcionalidad de T-RD se puede introducir de manera similar en los compuestos de la Fórmula (33) para dar los compuestos de la Fórmula (XVI-1).



Esquema XVI

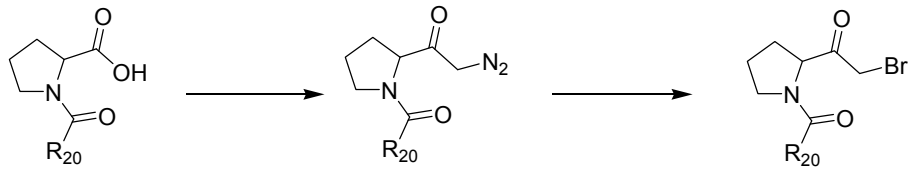
Determinados compuestos de la invención de la fórmula general (38), donde R20 es –LS'–M'–LS''–RD y D es como se describió previamente, se pueden preparar de acuerdo con los métodos del esquema XVII. Los compuestos de la fórmula (24) se pueden convertir en los compuestos (35) por reacción con CuCN en 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 NH3(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

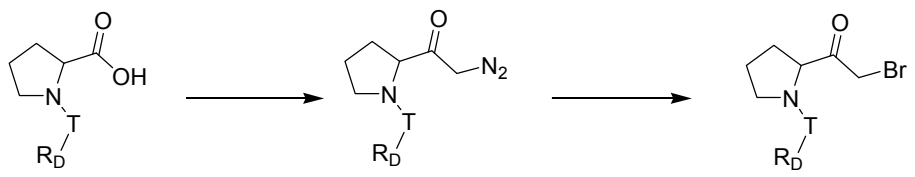
presencia de una base (por ejemplo, carbonato de potasio). Como alternativa, la funcionalidad de T-RD se puede introducir de manera similar en los compuestos de la Fórmula (33) para dar los compuestos de la Fórmula (XVII-1).



Esquema XVII

Los compuestos de la fórmula (41), donde R20 es –LS'–M'–LS''–RD, 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. De manera similar, los compuestos de la Fórmula (XVIII-1) se pueden convertir en los compuestos de la Fórmula (XVIII-2) y luego (XVIII-3), en donde T-RD son como se definieron previamente.

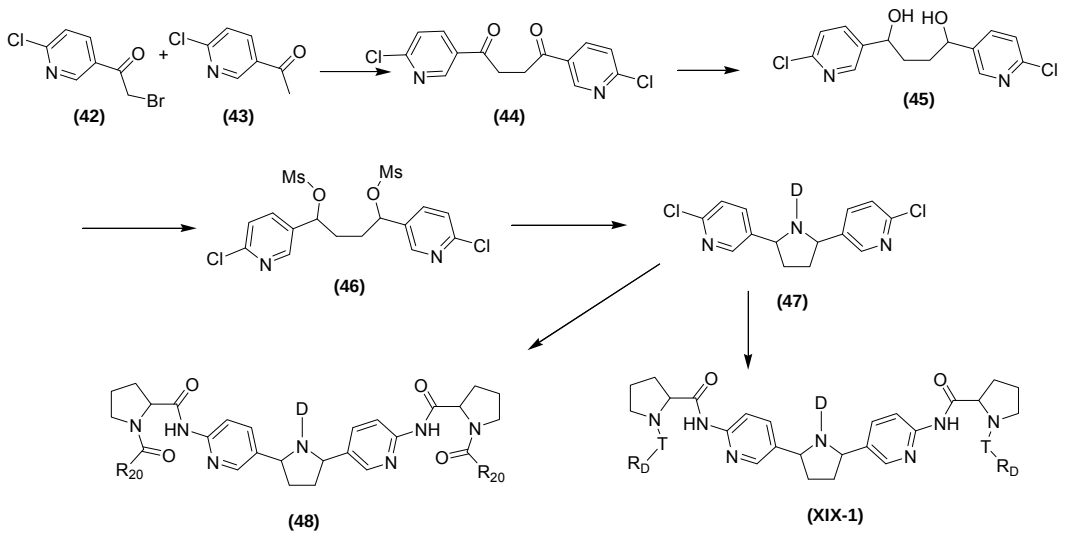




(XVIII-1) **(XVIII-2)** **(XVIII-3)**

Esquema XVIII

Determinados compuestos de la invención de la fórmula general (48), donde R20 es –LS'–M'–LS''–RD 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. Como alternativa, la funcionalidad de T-RD, en donde T y RD son como se definieron previamente, se puede introducir de manera similar en los compuestos de la Fórmula (47) para dar los compuestos de la Fórmula (XIX-1).

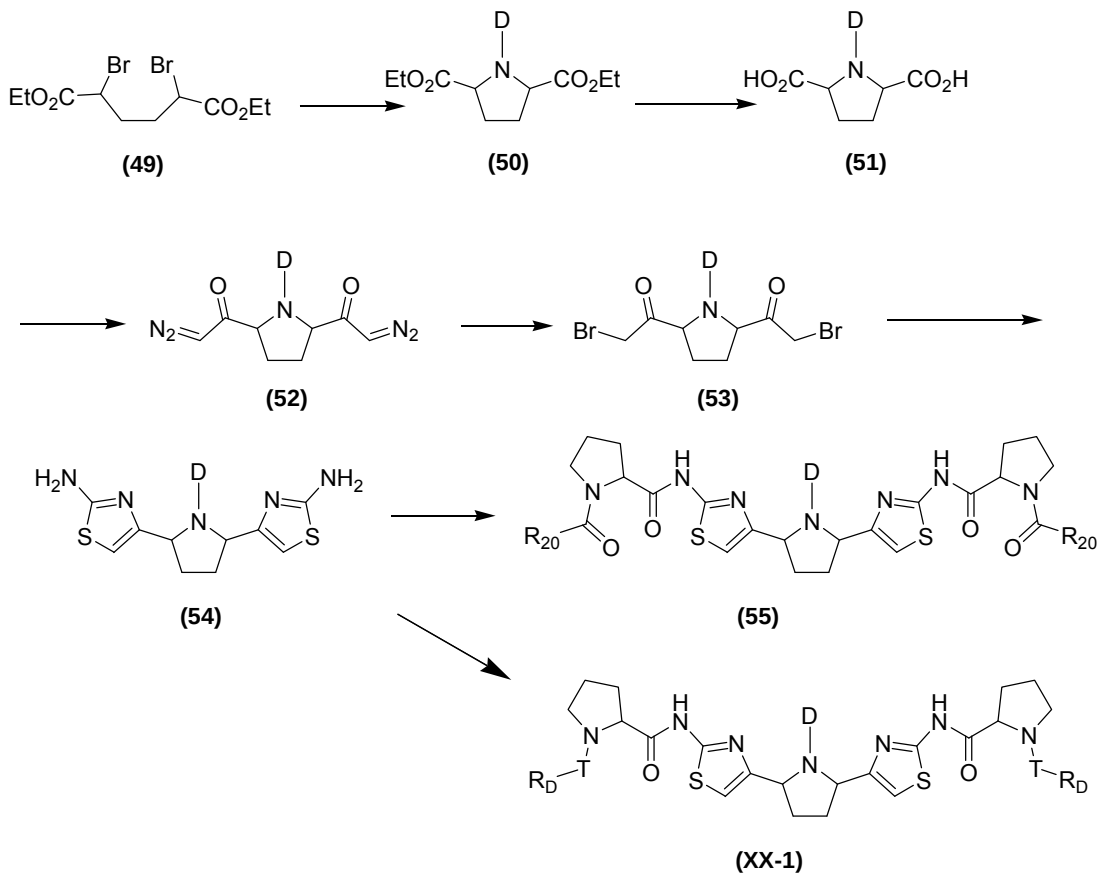


(42) **(43)** **(44)** **(45)** **(46)** **(47)** **(48)** **(XIX-1)**

Esquema XIX

Determinados compuestos de la invención de la fórmula general (55), donde R20

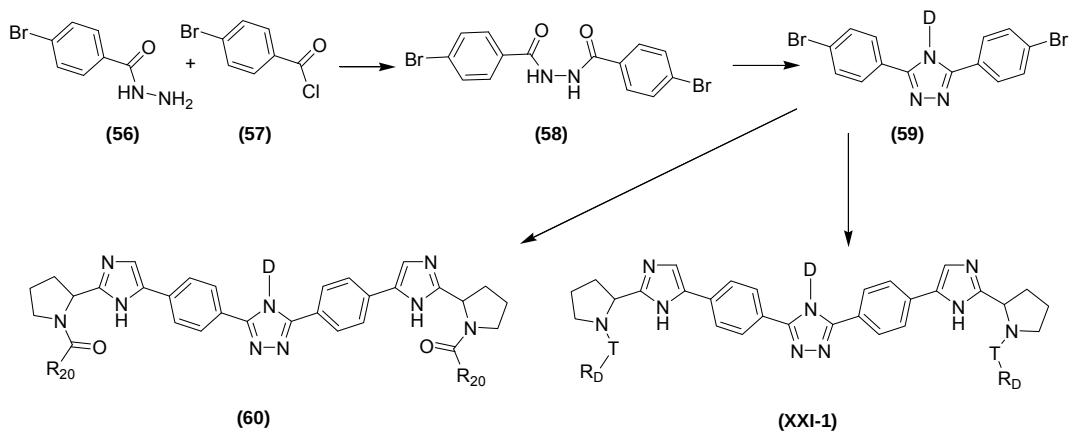
es –LS'–M'–LS''–RD y D es como se describió previamente, se pueden preparar de acuerdo con los métodos del esquema XX. Se puede hacer reaccionar meso-2,5-dibromoadipato de dietilo (49) con una amina D–NH2 en un solvente, tal como THF, dioxano o dimetoxietano, con calentamiento a una temperatura de 50-100 °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. De manera similar, la funcionalidad de T-RD, en donde T y RD son como se definieron previamente, se puede introducir en los compuestos de la Fórmula (54) para dar los compuestos de la Fórmula (XX-1).



(49) (50) (51) (52) (53) (54) (55) (XX-1)

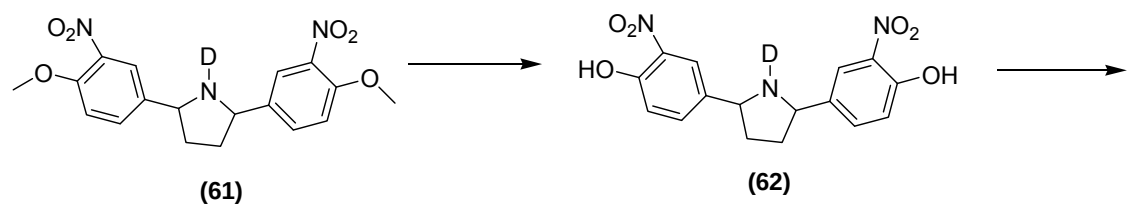
Esquema XX

Determinados compuestos de la invención de la fórmula general (60), donde R20 es –LS'–M'–LS''–RD 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-NH2 con POCl3 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. De manera similar, la funcionalidad de T-RD, en donde T y RD son como se definieron previamente, se puede introducir en los compuestos de la Fórmula (59) para dar los compuestos de la Fórmula (XXI-1).

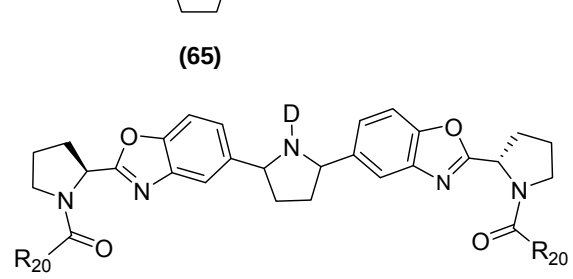


Esquema XXI

Determinados compuestos de la invención de la fórmula general (66), donde R20 es –LS'–M'–LS''–RD 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), que pueden someterse luego a condiciones de hidrogenación 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.



(61) **(62)** **(63)** **(64)** **(65)**

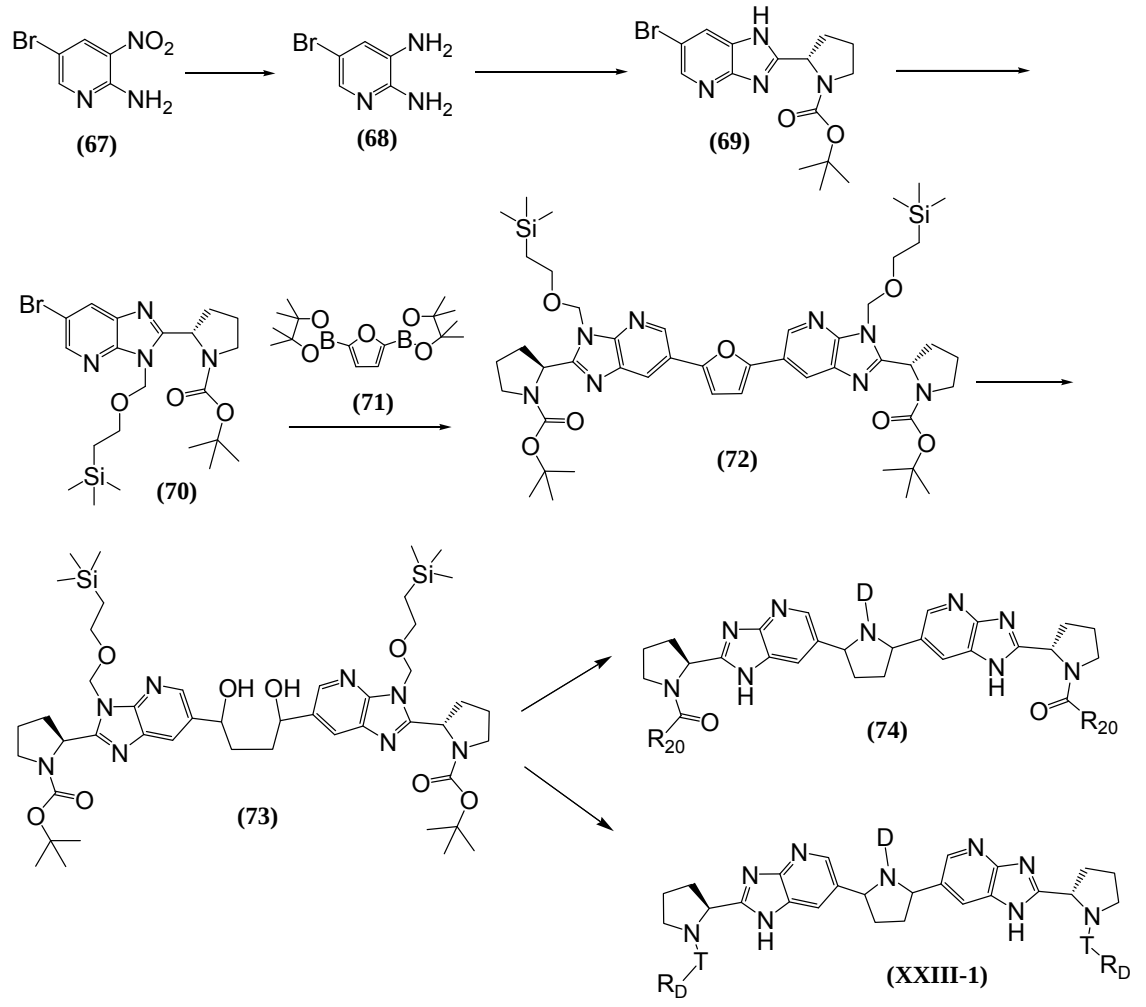


(66)

Esquema XXII

Determinados compuestos de la invención de la fórmula general (74), donde R20 es –LS'–M'–LS''–RD 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) mediante 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

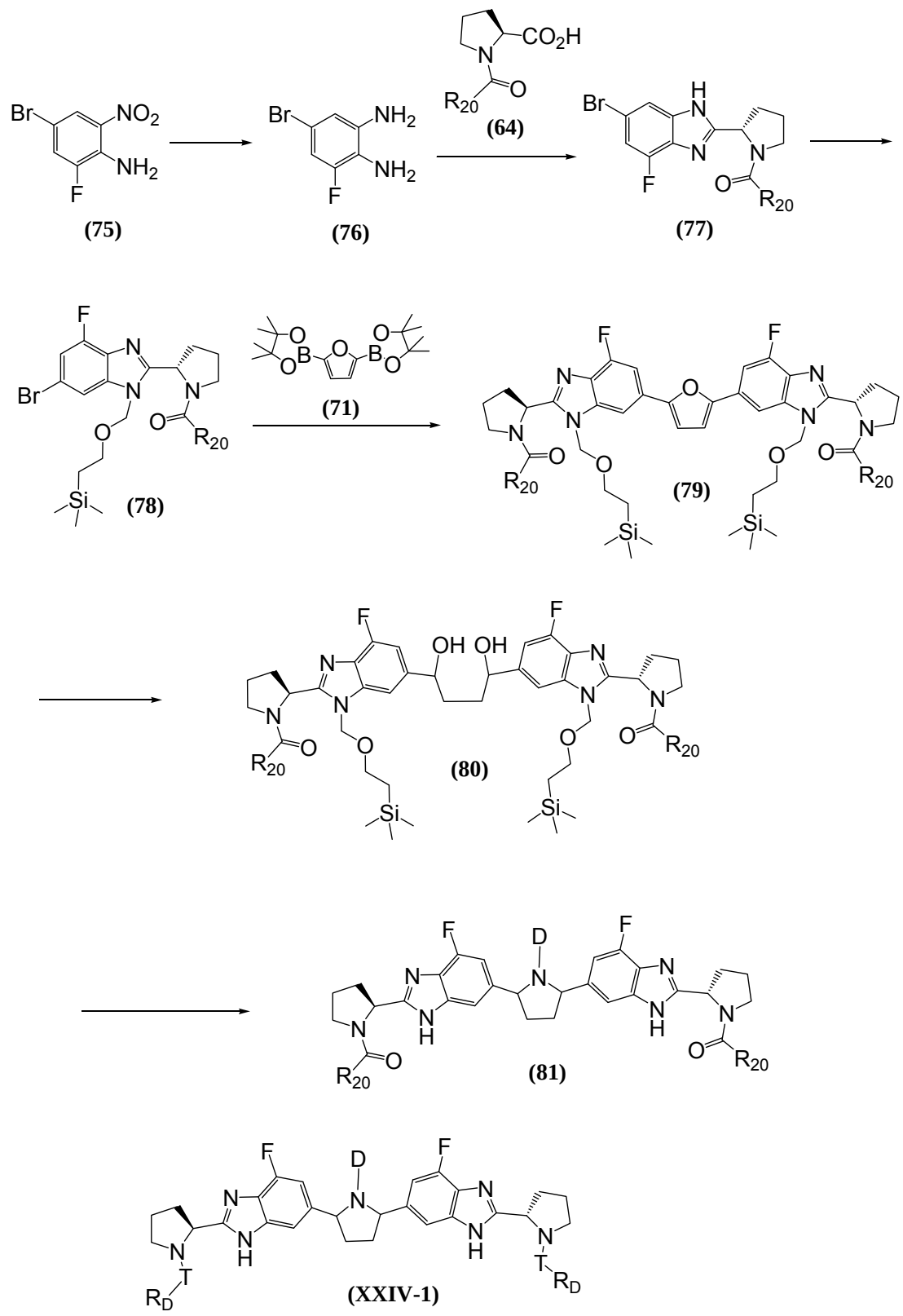
en (73) por reacción con Selectfluor en una mezcla de THF y agua, seguido por hidrogenación usando Pt sobre carbón 3% en acetato de etilo y luego reducción usando borohidruro de sodio en metanol. El compuesto (73) se puede hacer reaccionar con cloruro de metansulfonilo y trietilamina en diclorometano a -10 °C, seguido por adición de una amina (H2N-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 R20CO2H usando los procedimientos de acoplamiento de péptidos que se describieron previamente. De manera similar, la funcionalidad de T-RD, en donde T y RD son como se definieron previamente, se puede introducir en los compuestos de la Fórmula (73) para dar los compuestos de la Fórmula (XXIII-1).



Esquema XXIII

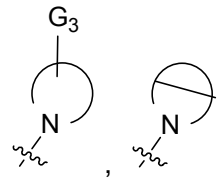
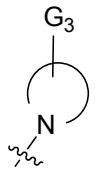
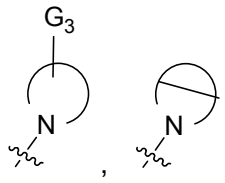
Determinados compuestos de la invención de la fórmula general (81), donde R20

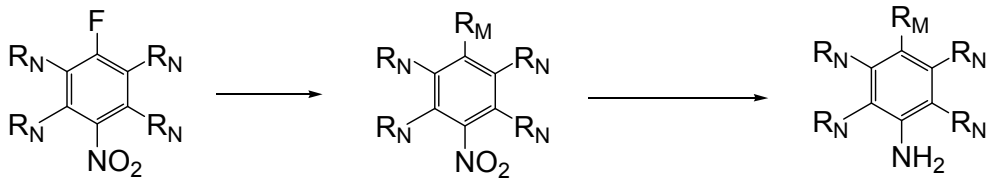
es –LS'–M'–LS''–RD y D es como se describió previamente, se pueden preparar de acuerdo con los métodos del esquema XXIV. El compuesto (75) se puede convertir en (76) usando SnCl2 en etanol. Además, el anillo fenilo del compuesto (75) puede sustituirse con X13 en cualquier posición sustituido por hidrógeno o flúor, en donde X13 es H, alquilo, haloalquilo, alcoxi o haloalcoxi, y dichos compuestos se utilizan en la subsiguiente secuencia. 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). A efectos de una ilustración conveniente, los SEM grupos protectores SEM sobre los benzimidazoles se muestran unidos a nitrógenos particulares del benzimidazol. Las posiciones de substitución reales de los grupos SEM pueden ser en cualquier nitrógeno (es decir, (78) puede ser una mezcla de regioisómeros). En los subsiguientes compuestos (79) a (80), la isomería de posición del grupo SEM da como resultado mezclas de regioisómeros SEM que pueden ser separables o no. En la práctica, los regioisómeros SEM pueden pasar como mezclas. El compuesto (78) 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 o condiciones de reducción quiral con (S) o (R) α,α-difenil-2-pirrolidinmetanol, dietilanilina borano y trimetilborano. 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 H2N-D y desprotección usando HCl 4 N en 1,4-dioxano. De manera similar, la funcionalidad de T-RD, en donde T y RD son como se definieron previamente, se puede introducir en los compuestos de la Fórmula (77) para dar compuestos de la Fórmula (XXIV-1) al final de la secuencia de síntesis.



Esquema XXIV

Determinadas aminas, D–NH2, 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 RN es como se definió previamente (por ejemplo, halógeno, alquilo, haloalquilo) y RM es –N(RSRS') (por ejemplo, –NEt2), heterociclilo (por ejemplo, pirrolidin-1-ilo, piperidin-1-ilo,  , etc.), en donde G3 es como se definió previamente,  es un heterociclo que contiene nitrógeno sustituido con G3, y  es un heterociclo bicíclico, con puente, que contiene nitrógeno) o –ORS (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 RM es –N(RSRS') (por ejemplo, –NEt2) 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 RM es –ORS (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.

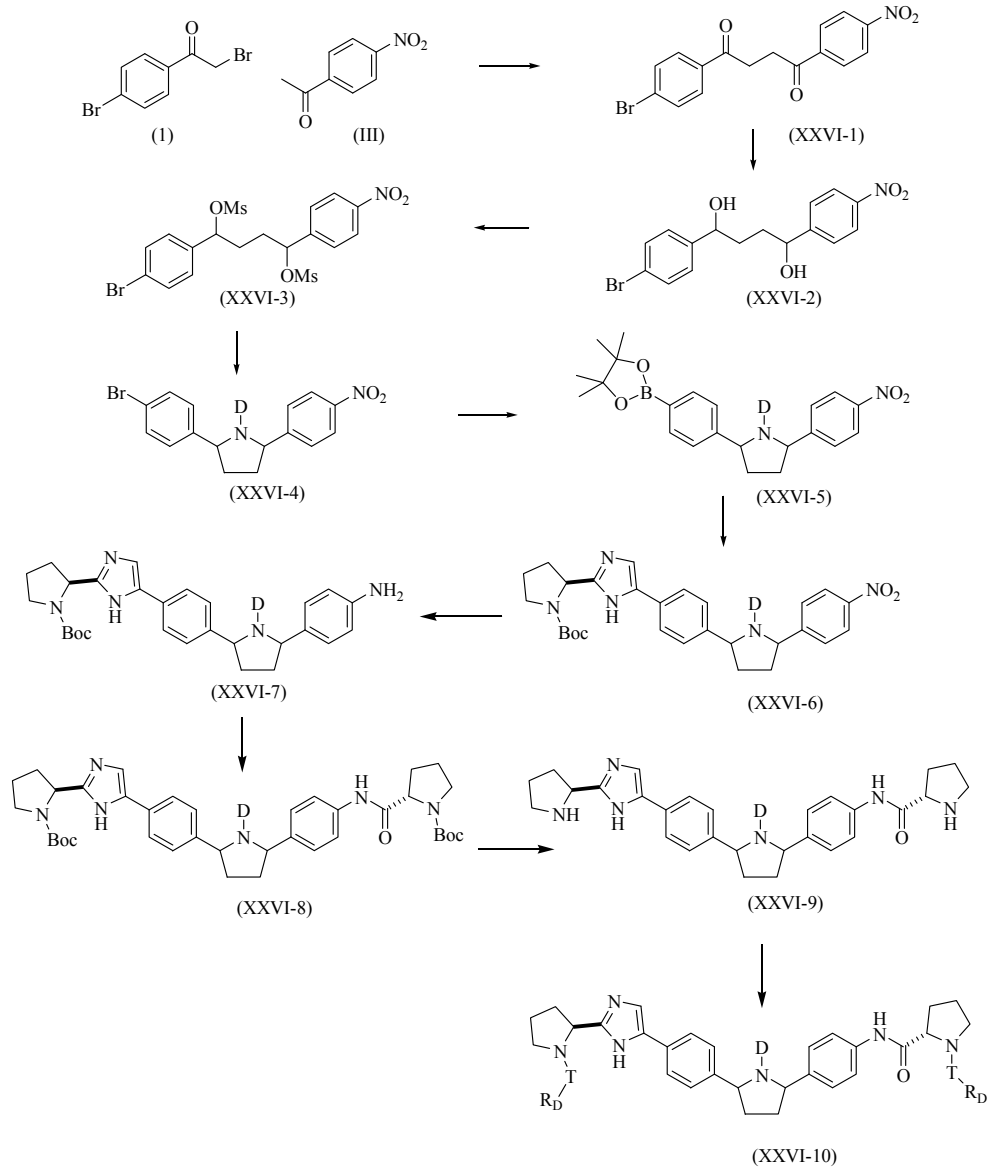


(82) **(83)** **(84)**

Esquema XXV

Determinados compuestos de la presente invención (XXVI-10) se pueden preparar como se muestra en general en el Esquema XXVI, donde D, T y RD son como se describió previamente. La reacción de los compuestos (1) con los compuestos (III), usando las condiciones que se describen en general en el Esquema II para la preparación de los compuestos (IV), puede proveer los compuestos dicetona (XXVI-1). Los compuestos (XXVI-1) se pueden convertir en los compuestos (XXVI-2) usando las condiciones generales del Esquema II para la conversión de (IV) en (V). Los compuestos (XXVI-2) se pueden convertir en los compuestos (XXVI-3) usando las condiciones generales del Esquema II para la conversión de (V) en (VI). Los compuestos (XXVI-3) se pueden convertir en los compuestos (XXVI-4) usando las condiciones generales del Esquema II para la conversión de (VI) en (VII). Los compuestos de la Fórmula (XXVI-4) se pueden convertir en los compuestos (XXVI-5) usando las condiciones generales del Esquema VII para la conversión de (II) en (III). Los compuestos (XXVI-5) se pueden convertir en los compuestos (XXVI-6) usando las condiciones generales del Esquema VII para la conversión de (III) en (IV). Los compuestos (XXVI-6) se pueden convertir en los compuestos (XXVI-7) usando las condiciones generales del Esquema II para la conversión de (VII) en (VIII). Por ejemplo, los compuestos (XXVI-6) (1 equivalente) se pueden reducir con hidrógeno gaseoso (1 atm) en la presencia de PtO2 (aproximadamente 0,2 equivalentes) en un solvente tal como etanol:THF (1:1). Los compuestos (XXVI-7) se pueden convertir en los compuestos (XXVI-8) usando los métodos que se describen en general en el Esquema II para la conversión de (VIII) en (IX). Por ejemplo, la reacción de (XXVI-7) (1 equivalente) con ácido 1-(ter-

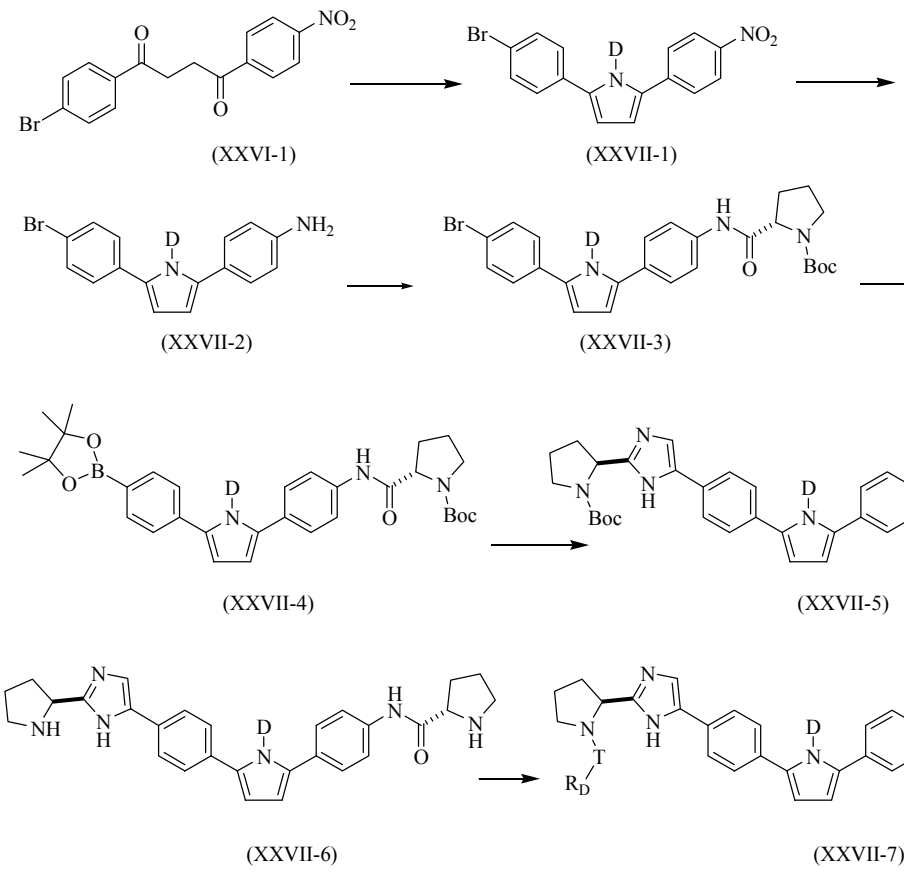
butoxicarbonil)pirrolidin-2-carboxílico (1,5 a 3 equivalentes) y HATU (aproximadamente 1,6 equivalentes) en la presencia de diisopropiletilamina (3 equivalentes) en DMSO a temperatura ambiente aproximadamente puede proveer los compuestos (XXVI-8). Los compuestos (XXVI-8) se pueden convertir en los compuestos (XXVI-9) usando los métodos que se describen en general en el Esquema II para la conversión de (IX) en (X). Por ejemplo, la reacción de (XXVI-8) (1 equivalente) con HCl en dioxano a temperatura ambiente aproximadamente puede proveer los compuestos (XXVI-9). Los compuestos (XXVI-9) se pueden convertir en los compuestos (XXVI-10) mediante reacción con un ácido apropiado usando los métodos que se describen en general en el Esquema II para la conversión de (X) en (XI). Por ejemplo, la reacción de (XXVI-9) (1 equivalente) con ácido 2-(metoxicarbonilamino)-3-metilbutanoico (aproximadamente 2 a 3 equivalentes), HATU (aproximadamente 2,5 a 3,5 equivalentes) y diisopropiletilamina (aproximadamente 10 equivalentes) en un solvente tal como DMSO puede proveer los productos (XXVI-10).



Esquema XXVI

Determinados compuestos de la presente invención (XXVII-7) se pueden preparar como se muestra en general en el Esquema XXVII, donde D, T y RD son como se describió previamente. Los compuestos (XXVI-1) se pueden convertir en los compuestos (XXVII-1) usando las condiciones generales del Esquema XII para la conversión de (3) en (11). Los compuestos (XXVII-1) se pueden convertir en los compuestos (XXVII-2) por reducción usando las condiciones que se describieron en general previamente en el esquema II. Por ejemplo, se puede reducir (XXVII-1) (1 equivalente) con hierro en polvo (aproximadamente 6 equivalentes) y cloruro de amonio (aproximadamente 3 equivalentes)

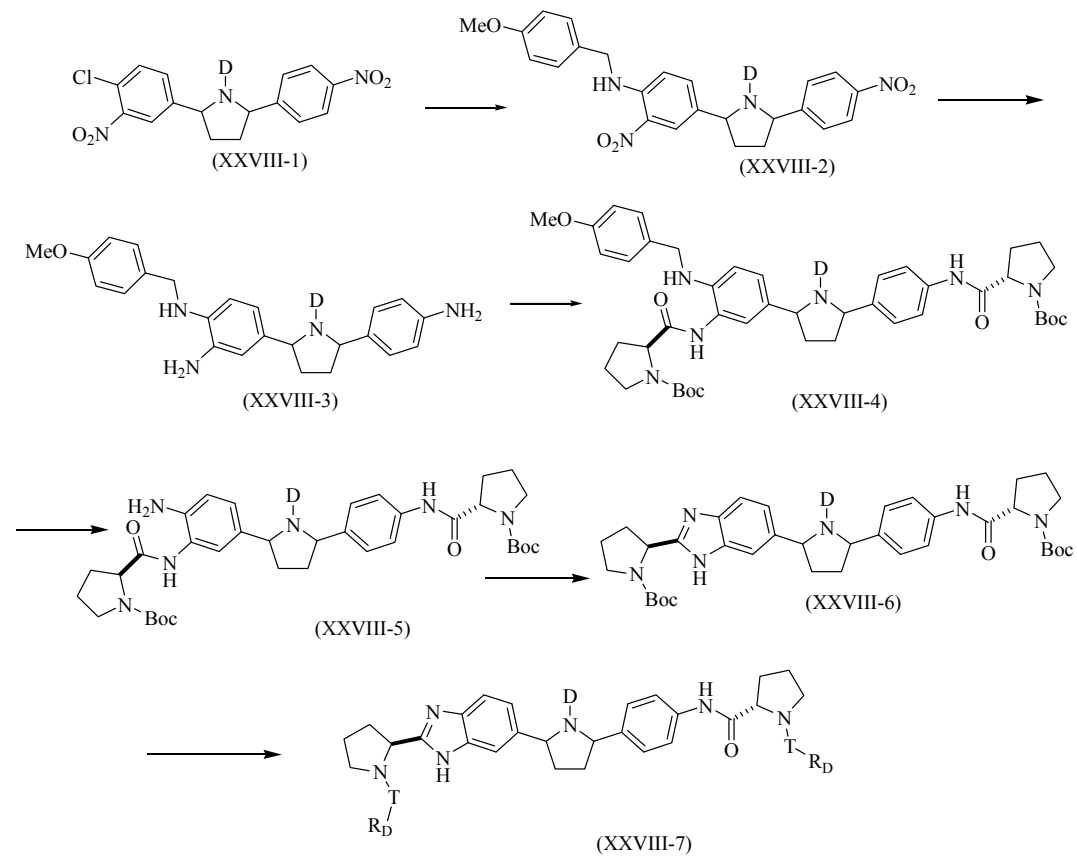
en etanol:THF:agua (1:1:0,25) con calentamiento hasta la temperatura de reflujo para proveer (XXVII-2). Los compuestos (XXVII-2) se pueden convertir en los compuestos (XXVII-3) usando las condiciones descritas previamente para la conversión de VIII en IX en el Esquema II, (12) en (13) en el Esquema XII o bien, (XXVI-7) en (XXVI-8) en el Esquema XXVI. Los compuestos (XXVII-3) se pueden convertir sucesivamente en los compuestos (XXVII-4) y (XXVII-5) usando los métodos y las condiciones que se describen en general en el Esquema VII para la conversión de (II) en (III) en (V). Los compuestos (XXVII-5) se pueden convertir sucesivamente en los compuestos (XXVII-6) y (XXVII-7) usando los métodos y las condiciones que se describen previamente de manera general, por ejemplo usando los métodos para convertir (IX) en (X) en (XI) en el Esquema II.



Esquema XXVII

Determinados compuestos de la invención de la fórmula general (XXVIII-7), donde D, T y RD son como se describió previamente, se pueden preparar de acuerdo con la secuencia del Esquema XXVIII. Los compuestos (XXVIII-1) se pueden preparar a partir

de 2-bromo-1-(4-nitrofenil)etanona, 1-(4-cloro-3-nitrofenil)etanona y una amina D–NH2 de acuerdo con los métodos descritos previamente para preparar los compuestos (VII) en el Esquema II, (XXVI-4) en el Esquema XXVI y (VII) en el Esquema IV. Los compuestos (XXVIII-1) (1 equivalente) se pueden convertir en los compuestos (XXVIII-2) mediante reacción con 4-metoxibencilamina pura (aproximadamente 4-6 equivalentes) con calentamiento hasta 140-150 °C aproximadamente. Los compuestos (XXVIII-2) se pueden convertir en los compuestos (XXVIII-3) mediante reducción de acuerdo con las condiciones que se describen en general en el Esquema II para preparar los compuestos (VIII). Por ejemplo, la reacción de (XXVIII-2) (1 equivalente) con PtO2 (aproximadamente 0,4-0,5 equivalentes) en un solvente tal como etanol:THF (1:1) bajo atmósfera de hidrógeno (1-4 atm) puede proveer los compuestos (XXVIII-3). Los compuestos (XXVIII-3) se pueden convertir en los compuestos (XXVIII-4) de acuerdo con las condiciones que se describen en general en el Esquema II para preparar los compuestos (IX). Por ejemplo, la reacción de (XXVIII-3) (1 equivalente) con ácido 1-(ter-butoxicarbonil)pirrolidin-2-carboxílico (aproximadamente 2-3 equivalentes), HATU (aproximadamente 2-3 equivalentes) y diisopropiletilamina (aproximadamente 3 equivalentes) en un solvente tal como DMSO a temperatura ambiente puede proveer los compuestos (XXVIII-4). Los compuestos (XXVIII-4) (1 equivalente) se pueden convertir en los compuestos (XXVIII-5) mediante reacción con DDQ (aproximadamente 1,2 equivalentes) en una mezcla de solventes de CH2Cl2:agua (20:1) a temperatura ambiente. Los compuestos (XXVIII-5) se pueden convertir en los compuestos (XXVIII-6) de acuerdo con los métodos generales descritos en el Esquema IV para preparar los compuestos (XI) (por ejemplo, calentamiento en ácido acético hasta 60-70 °C aproximadamente). Los compuestos (XXVIII-6) se pueden convertir además en los compuestos (XXVIII-7) usando los métodos de desprotección y acoplamiento estándar a los cuales se hizo referencia en el Esquema IV para preparar los compuestos (XIII) o (XIV).

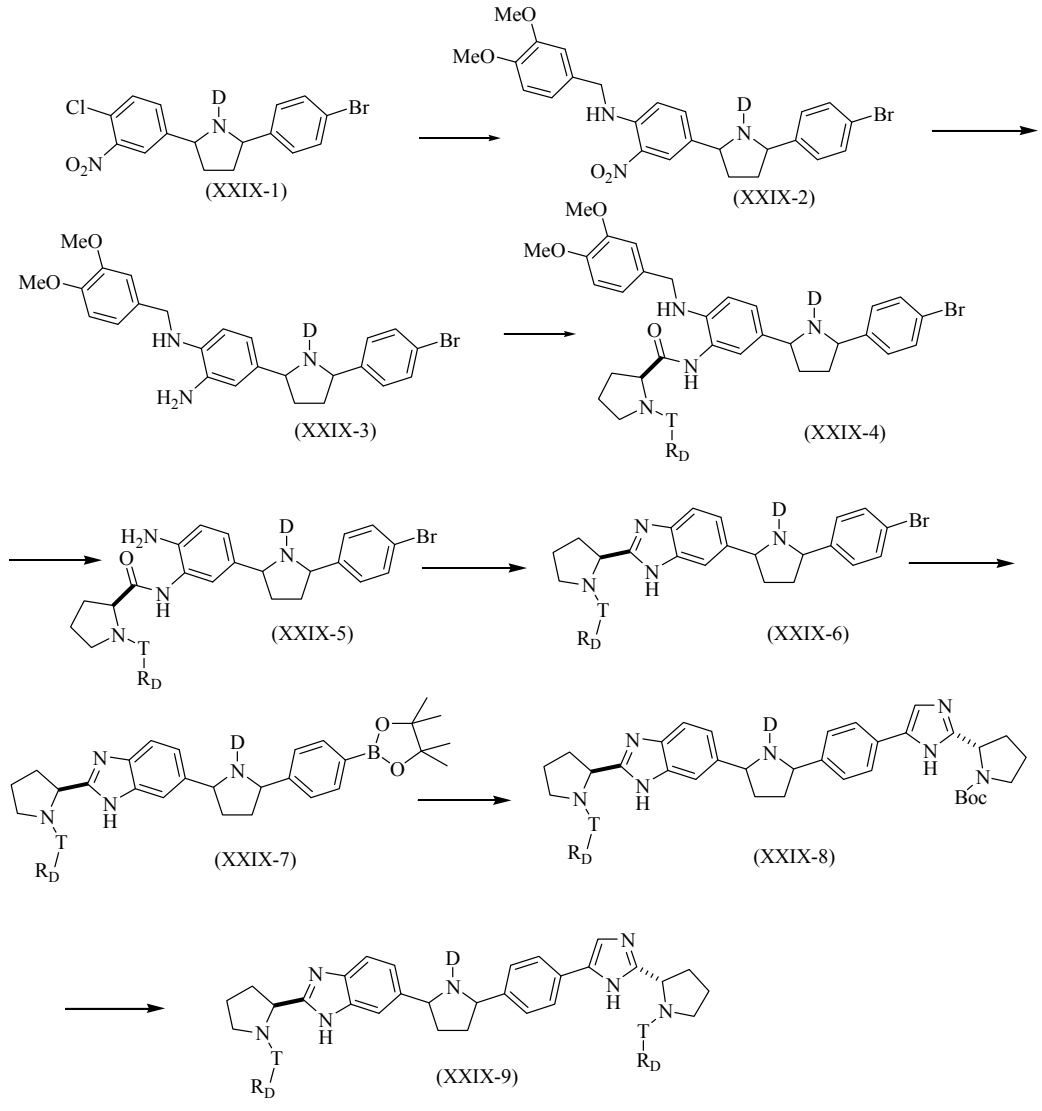


Esquema XXVIII

Determinados compuestos de la invención (XXIX-9), donde D, T y RD son como se describió previamente, se pueden preparar de acuerdo con la secuencia del Esquema XXIX. Los compuestos (XXIX-1) se pueden preparar a partir de 2-bromo-1-(4-bromofenil)etanona, 1-(4-cloro-3-nitrofenil)etanona y una amina D–NH2 de acuerdo con los métodos descritos previamente para preparar los compuestos (VII) en el Esquema II, (XXVI-4) en el Esquema XXVI y (VII) en el Esquema IV. Los compuestos (XXIX-1) (1 equivalente) se pueden convertir en los compuestos (XXIX-2) mediante reacción con 3,4-dimetoxibencilamina pura (aproximadamente 10 equivalentes) con calentamiento hasta aproximadamente 140-150 °C. Los compuestos (XXIX-2) se pueden convertir en los compuestos (XXIX-3) mediante reducción de acuerdo con las condiciones que se describen en general en el Esquema II para preparar los compuestos (VIII). Por ejemplo, la reacción de (XXIX-2) (1 equivalente) con PtO2 (aproximadamente 0,1 equivalente) en un solvente tal como etanol:THF:EtOAc (1:1) bajo atmósfera de hidrógeno (por ejemplo, 1

atm) puede proveer los compuestos (XXIX-3). Los compuestos (XXIX-3) se pueden convertir en los compuestos (XXIX-4) de acuerdo con las condiciones que se describen en general en el Esquema II para preparar los compuestos (IX). Por ejemplo, la reacción de (XXIX-3) (1 equivalente) con una prolina sustituida como ácido (S)-1-((S)-2-(metoxicarbonilamino)-3-metilbutanoil)pirrolidin-2-carboxílico (aproximadamente 1,2-1,5 equivalentes), HOBt (aproximadamente 1,2-1,5 equivalentes), EDAC (aproximadamente 1,2-1,5 equivalentes) y N-metilmorfolina (aproximadamente 5-6 equivalentes) en un solvente tal como DMF a temperatura ambiente puede proveer los compuestos (XXIX-4). Los compuestos (XXIX-4) se pueden desproteger para dar los compuestos (XXIX-5) mediante reacción con un exceso de TFA en solventes, tal como cloruro de metileno, a temperatura ambiente aproximadamente. Los compuestos (XXIX-5) se pueden convertir en los compuestos (XXVIX-6) de acuerdo con los métodos generales descritos en el Esquema IV para preparar los compuestos (XI) (por ejemplo, calentamiento en ácido acético hasta 60-80 °C aproximadamente). Los compuestos (XXIX-6) se pueden convertir en los compuestos (XXIX-7) de acuerdo con las condiciones generales del Esquema VII para preparar los compuestos (III). Por ejemplo, la reacción de (XXIX-6) (1 equivalente) con PdCl2(dppf) (aproximadamente 0,1 equivalente), acetato de potasio (aproximadamente 3-5 equivalentes) y bis(pinacolato)diboro (aproximadamente 3 equivalentes) en un solvente, tal como tolueno, con calentamiento a 80-100 °C puede proveer los compuestos (XXIX-7). Los compuestos (XXIX-7) se pueden convertir en los compuestos (XXIX-8) de acuerdo con las condiciones generales del Esquema VII para preparar los compuestos (V). Por ejemplo, la reacción de los compuestos (XXIX-7) (1 equivalente) con el Intermediario 1D (aproximadamente 2 equivalentes), carbonato de sodio 1 M (aproximadamente 3 equivalentes), y PdCl2(dppf) (aproximadamente 0,1 equivalente) en un solvente tal como tolueno a 80-100 °C aproximadamente puede proveer los compuestos (XXIX-8). Los compuestos (XXIX-8) se pueden convertir además en los compuestos (XXIX-9) usando los métodos de desprotección (por ejemplo,

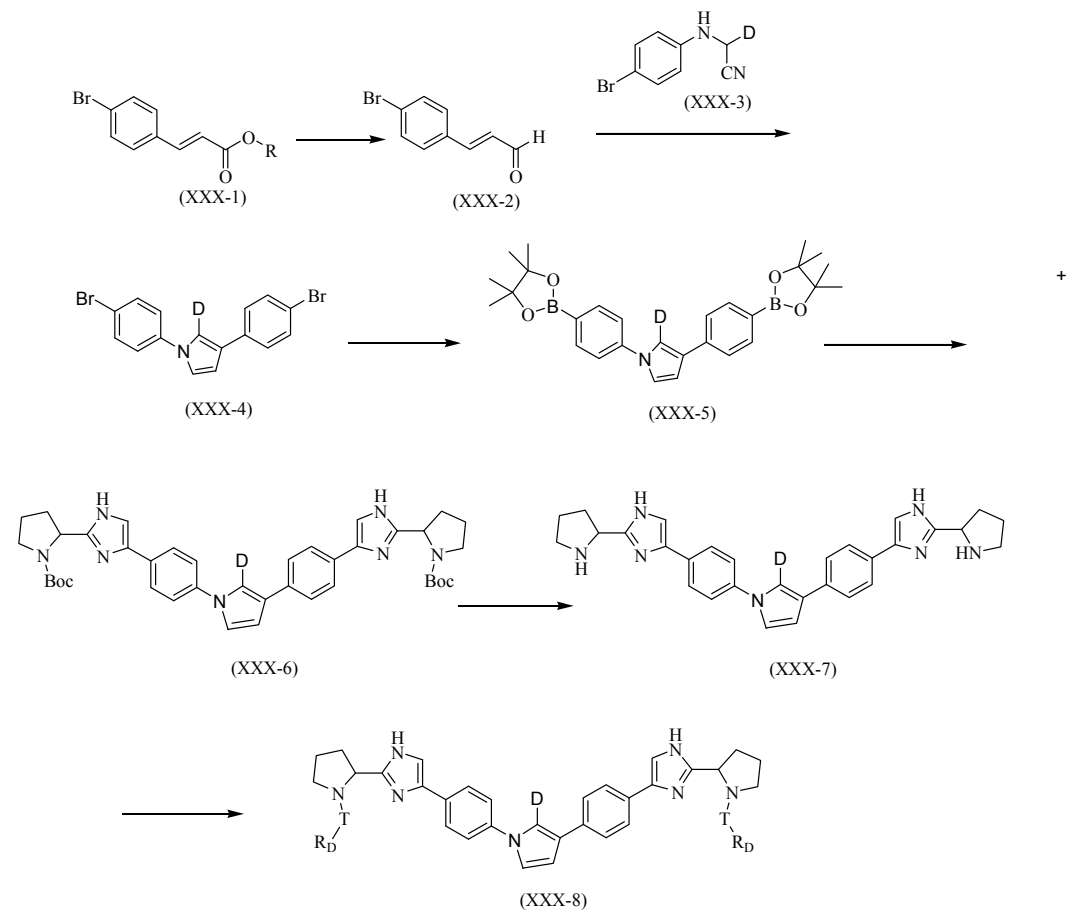
HCl/dioxano) y acoplamiento (por ejemplo, ácido carboxílico, HOBt, EDAC y N-metilmorfolina) estándar a los cuales se hizo referencia en el Esquema IV para preparar los compuestos (XIV).



Esquema XXIX

Determinados compuestos de la presente invención (XXX-8) se pueden preparar como se muestra en el Esquema XXX. Se puede hacer reaccionar un éster (XXX-1) con un agente reductor adecuado, tal como DIBAL-H, en un solvente tal como THF, diclorometano o éter dietílico, para obtener el correspondiente alcohol y luego oxidar en el aldehído (XXX-2) empleando un agente oxidante adecuado tal como PDC en un solvente tal como diclorometano, THF o éter dietílico. Se puede preparar un pirrol de la Fórmula

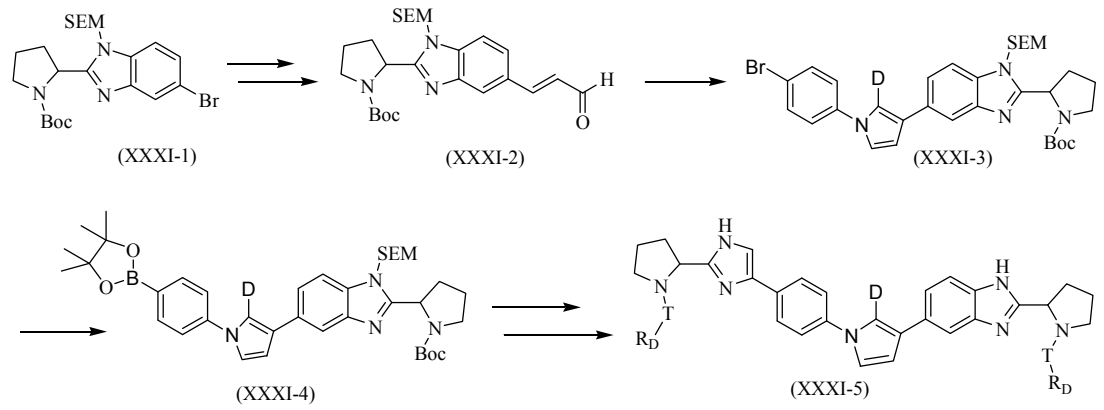
(XXX-4) haciendo reaccionar (XXX-3) (obtenido a partir de una anilina, un aldehído y KCN usando la reacción de Strecker) junto con un aldehído (XXX-2) con una base tal como hidróxido de potasio en un solvente tal como etanol (Synlett, 2003, páginas 1427-1430). Los átomos de bromo en los compuestos pirrol (XXX-4) se pueden convertir en un compuesto bis-borano (XXX-5) usando de catálisis con paladio como se describió previamente en el Esquema VII. Los compuestos pirrol (XXX-5) se pueden hacer reaccionar con bromoimidazoles como el Intermediario 1D usando las condiciones de la reacción de Suzuki para dar el fenilimidazol (XXX-6). Existe una variedad de condiciones de reacción que son bien conocidas por los especialistas en el arte por su eficacia en la reacción de Suzuki. En particular, la reacción para producir (XXX-6) se puede conducir con el catalizador Pd(dppf)Cl2 y carbonato de potasio en una mezcla de tolueno y agua y con calentamiento hasta 100 °C aproximadamente. La eliminación de los grupos protectores Boc para dar (XXX-7) se puede efectuar mediante tratamiento con un ácido, tal como TFA, HCl o ácido fórmico. Determinados compuestos de la presente invención (XXX-8), en donde T, RD y D son como se describió previamente, se pueden preparar mediante acoplamiento de (XXX-7) con un ácido de elección usando los reactivos y las condiciones de acoplamiento de péptidos estándar descritos previamente.



Esquema XXX

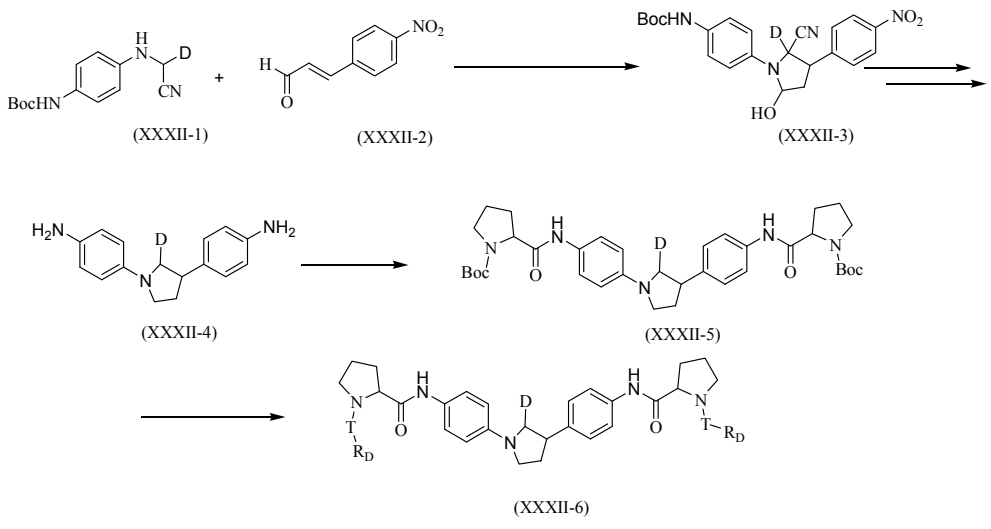
La presente invención también contempla los Esquemas XXXI-XXXIII para obtener un compuesto de la invención. Por ejemplo, los compuestos de la invención (XXXI-5) se pueden preparar usando la secuencia de pasos indicados en general en el Esquema XXXI. Esta secuencia es semejante a la del Esquema XXX. Se puede convertir un compuesto (XXXI-1) en un compuesto (XXXI-2) mediante una reacción de Heck sucesiva con etilacrilato seguido por reducción en un aldehído (XXXI-2). Un aldehído como (XXXI-2) se puede hacer reaccionar con un compuesto (XXX-3) de manera análoga a las condiciones de Esquema XXX para proveer los compuestos (XXXI-3). A su vez, los compuestos (XXXI-3) se pueden convertir en los compuestos boronato (XXXI-4) usando la condición que se describió previamente en general en el Esquema VII. Los compuestos (XXXI-4) se pueden convertir en los compuestos (XXXI-5) sobre varios pasos incluyendo la reacción Suzuki, desprotección y acoplamiento como se describió en general en los

Esquemas precedentes.



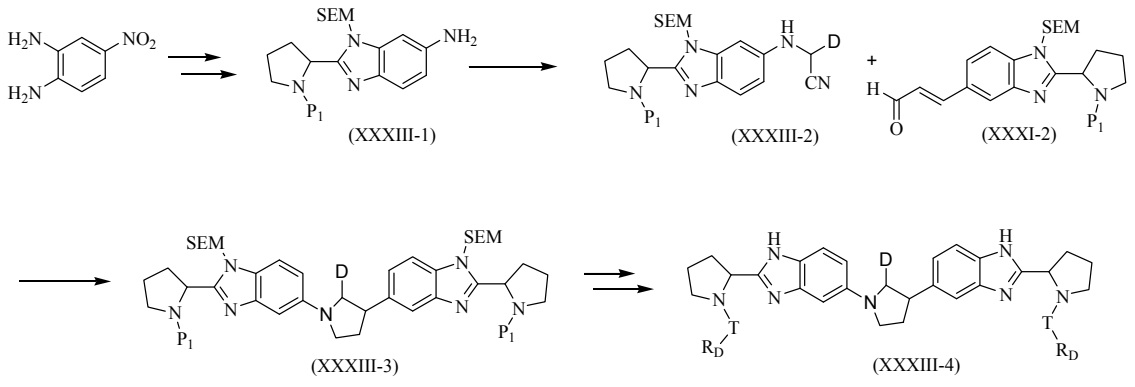
Esquema XXXI

Según se describió en Meyer et al., Synthesis, 2005, páginas 945-956 y Meyer et al Synlett, 2003, páginas 1427-1430, se pueden hacer reaccionar α-aminonitrilos sustituidos con compuestos carbonilo α,β-insaturados para proveer hidroxi-cianopirrolidinas sustituidas. De una manera análoga, se puede hacer reaccionar un compuesto (XXXII-1) con un aldehído α,β-insaturado (XXXII-2) para dar una pirrolidina (XXXII-3). Los grupos hidroxi y ciano de compuestos tales como (XXXII-3) se pueden separar por reducción usando reactivos tales como NaBH3CN o NaBH3CN con FeSO4 como se describe en Synthesis, 2005, páginas 945-956. El grupo nitro de los compuestos tales como (XXXII-3) se puede reducir usando condiciones estándar, tales como hidrogenación catalítica o reducción con hierro polvo y cloruro de amonio. Las típicas condiciones de reducción del nitro se describen en otra parte en la presente. El grupo Boc de los compuestos tales como (XXXII-3) se pueden eliminar usando condiciones estándar tales como con TFA/CH2Cl2 o HCl en dioxano. Los compuestos tales como (XXXII-4) se pueden hacer reaccionar con una prolina N-protegida apropiada bajo condiciones estándar como se describe en otra parte en la presente para dar los compuestos (XXXII-5). Los compuestos tales como (XXXII-5) se pueden desproteger y acoplar con un ácido de elección como se describe en la presente para dar los compuestos (XXXII-6), en donde T, RD, y D son como se describe en la presente.



Esquema XXXII

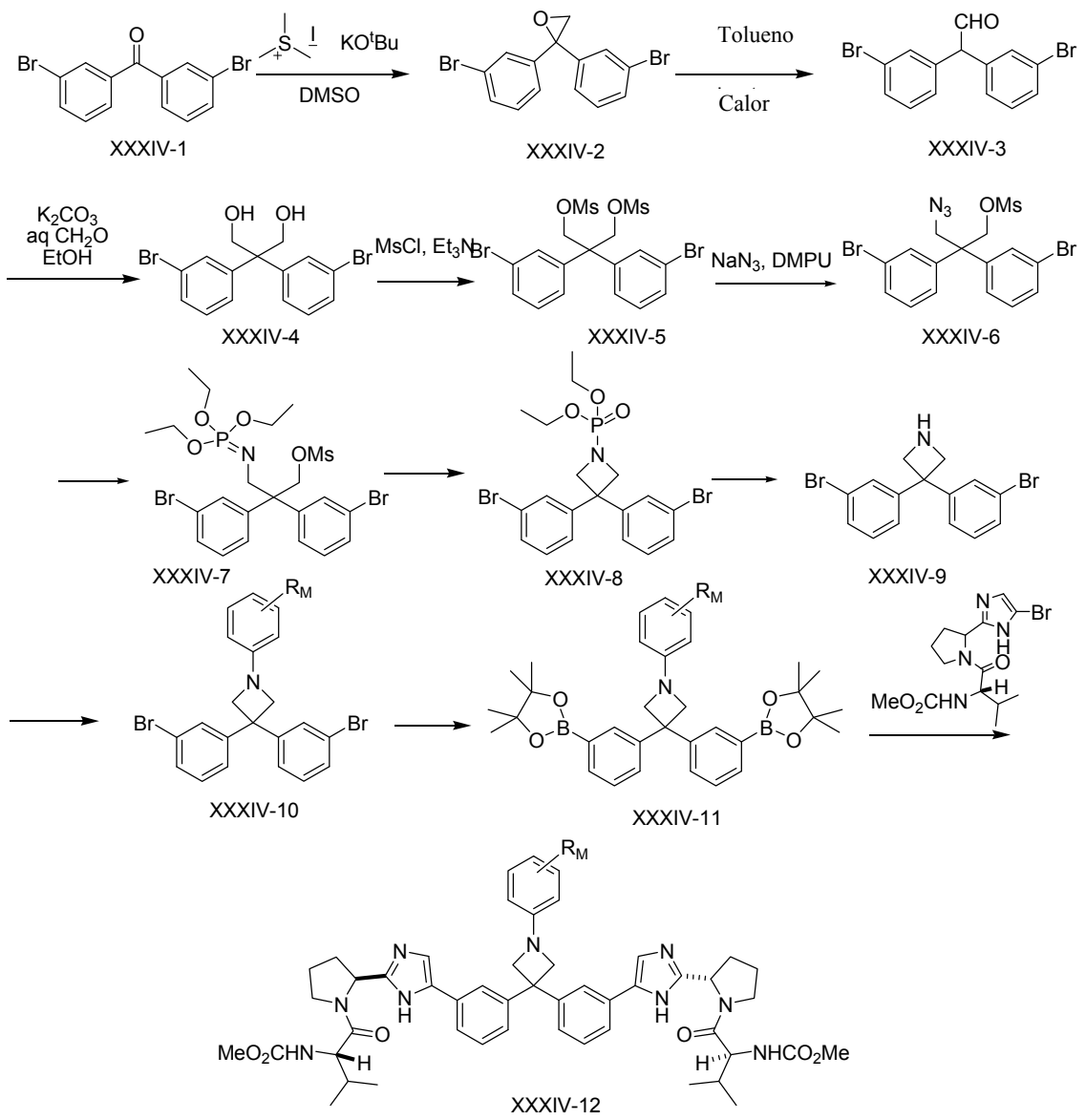
Se pueden preparar otros compuestos de la invención como se describe en general en el Esquema XXXIII. Los compuestos tales como (XXXIII-1) se pueden preparar a partir de 4-nitro-o-fenilendiamina por acilación con una prolina protegida (véase Tetrahedron 2003, páginas 2701-2712), ciclación (véase Tet. Lett. 2003, 5807-5810), protección con SEM y reducción de nitro. Los compuestos tales como (XXXIII-1) se pueden convertir en el producto de Strecker (XXXIII-2) mediante una reacción con un aldehído D–CHO y KCN de manera análoga con el proceso al cual se hizo referencia en el Esquema XXX. Los compuestos tales como (XXXIII-2) se pueden condensar con compuestos tales como (XXXI-2) seguido por reducción para dar compuestos tales como (XXXIII-3) (véase por ejemplo Meyer et al., Synthesis, 2005, páginas 945-956 y Meyer et al Synlett, 2003, páginas 1427-1430). Los compuestos tales como (XXXIII-3) se pueden desproteger usando condiciones estándar para la eliminación de los grupos Boc y SEM (véase el Procedimiento general 23) y el compuesto amino resultante se puede hacer reaccionar con un ácido apropiado bajo condiciones convencionales de formación de enlaces amida para dar los compuestos (XXXIII-4), en donde T, RD y D son como se describe en la presente.



Esquema XXXIII

Determinados compuestos de la invención también se pueden preparar usando los métodos que se muestran en general en el Esquema XXXIV. La cetona XXXIV-1 (Referencia: US20090076076; página 19, [0146]) se puede homologar en dos pasos al aldehído XXXIV-3. En el primer paso, la cetona se puede hacer reaccionar con metiluro de dimetilsulfonio en dimetilsulfóxido para producir el epóxido XXXIV-2. El epóxido se puede reordenar en el aldehído mediante tratamiento con un ácido tal como ácido p-toluensulfónico con calentamiento en tolueno a temperaturas entre aproximadamente 80-110 °C (Referencias: J. Am. Chem. Soc. (1965) 1353, 1358; J. Org. Chem. (1972) 4075, 4076, 4077; Bioorg. Med. Chem. Lett. (2009) 5684, 5686). El aldehído XXXIV-3 se puede convertir en el diol XXXIV-4 con carbonato de potasio y formaldehído en etanol como se describe en general en J. Am. Chem. Soc, 1951, 73, página 5171 y US5095153, Ejemplo 3a. El diol se puede convertir en el bimesilato XXXIV-5 mediante reacción con un exceso de cloruro de metansulfonilo y trietilamina en diclorometano a una temperatura entre 0 °C y temperatura ambiente. El bimesilato se puede convertir en la azida XXXIV-6 mediante reacción con azida sódica (aproximadamente 1 equivalente) en DMPU y calentamiento hasta aproximadamente 110 °C. La azida se puede convertir en el fosforimidato XXXIV-7 mediante reacción con trietilfosfito recién destilado (aproximadamente 1 equivalente) en tolueno/tetrahidrofurano anhidro a temperatura ambiente. El fosforimidato se puede convertir en el azetidin-fosfonato XXXIV-8 mediante calentamiento en o-xileno hasta aproximadamente 150 °C. El azetidin-fosfonato se puede convertir en la azetidina XXXIV-

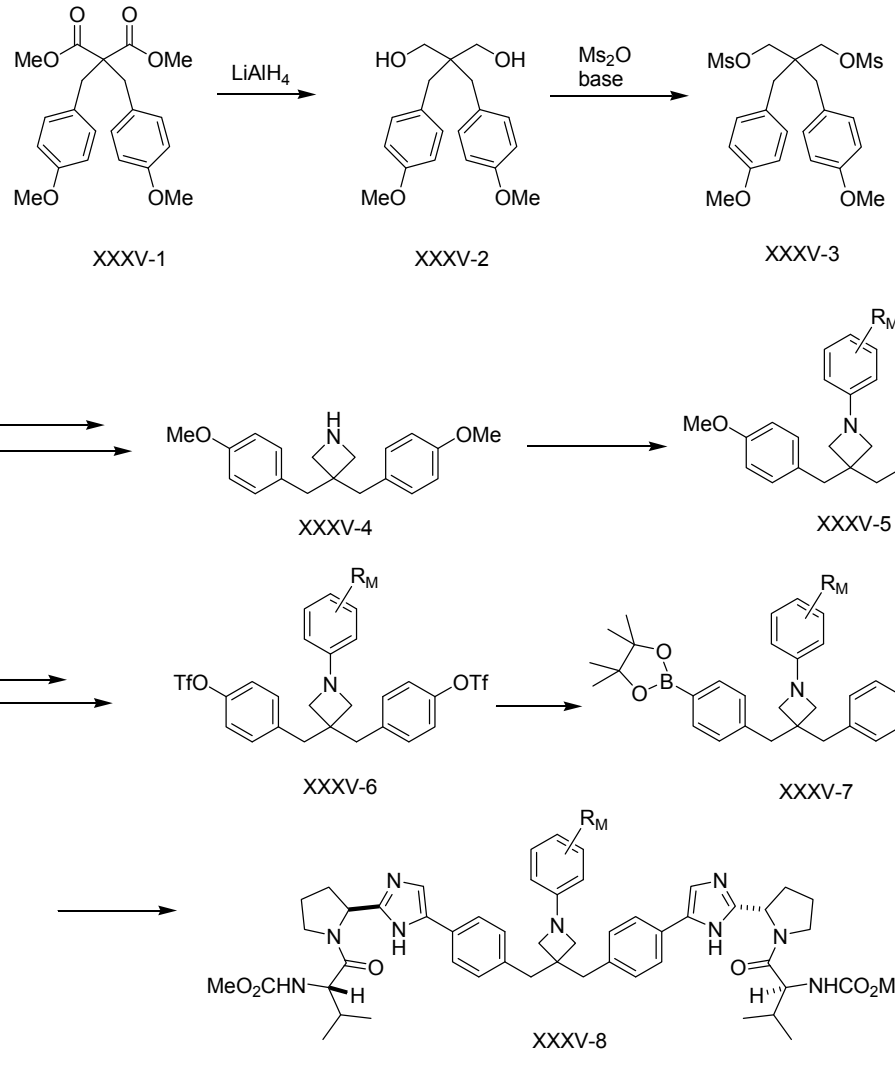
9 mediante reacción con ácido trifluoroacético en diclorometano a temperatura ambiente. La azetidina se puede hacer reaccionar con un haluro de arilo apropiado (por ejemplo, ioduro) usando la reacción de Buchwald para generar una N-arilazetidina XXXIV-10. Las condiciones apropiadas incluyen reacción con un ioduro de arilo (aproximadamente 2 equivalentes), Pd2(dba)3 (aproximadamente 0,025 equivalentes), 4,5-bis(difenilfosfino)-9,9-dimetilxanteno (Xantphos; aproximadamente 0,1 equivalentes) y ter-butóxido de sodio (aproximadamente 1,2 equivalentes) con calentamiento en un solvente tal como dioxano a 80-100 °C, opcionalmente con irradiación de microondas. EL bibromuro se puede convertir en el bisboronato XXXIV-11 mediante reacción con bis(pinacolato)diborano, acetato de potasio y PdCl2(dppf) en un solvente tal como DME, dioxano o DMSO, con calentamiento hasta aproximadamente 85 °C. El bisboronato se puede convertir en los compuestos de la invención XXXIV-12 mediante reacción con un haluro apropiado (es decir, la reacción de Suzuki) tal como (S)-1-((S)-2-(5-bromo-1H-imidazol-2-il)pirrolidin-1-il)-3-metil-1-oxobutan-2ilcarbamato de metilo.



Esquema XXXIV

Determinados compuestos de la invención también se pueden preparar usando los métodos que se muestran en general en el Esquema XXXV. Los compuestos tales como XXXV-1 se pueden preparar usando métodos conocidos mediante alquilación de un éster malonato con un haluro de bencilo. El compuesto XXXV-1 se puede convertir en el compuesto XXXV-2 por reducción con hidruro de litio y aluminio. El compuesto XXXV-2 se puede convertir en el compuesto XXXV-3 mediante reacción con Ms2O y una base tal como diisopropiletilamina. El compuesto XXXV-3 se puede convertir en el compuesto XXXV-4 usando métodos análogos a los usados para convertir XXXIV-5 en XXXIV-9

(véase el Esquema XXXIV). De manera similar, el compuesto XXXV-4 se puede convertir en el compuesto XXXV-5 usando una reacción de Buchwald análoga a la del Esquema XXXIV. A su vez, los compuestos XXXV-5 se pueden convertir en XXXV-6 por desmetilación (por ejemplo, con BBr3) y formación de triflato con Tf2O. Los compuestos XXXV-6 se pueden convertir en los compuestos XXXV-7 por analogía con la conversión de XXXIV-10 en XXXIV-11. Finalmente, los compuestos XXXV-7 se pueden convertir en los compuestos XXXV-8 usando el acoplamiento de Suzuki del Esquema XXXIV.



En los esquemas precedentes (Esquemas I-XXXV), 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

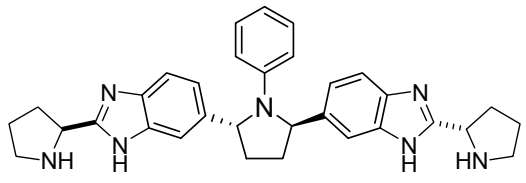
sustitución en para. El especialista en el arte comprenderá que, en los esquemas precedentes, una substitución de un material de partida o de un intermediario con una regioquímica diferente (por ejemplo, meta) proporcionaría un producto final con una regioquímica diferente. Por ejemplo, el reemplazo 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, -NH2 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 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 Intermediarios, Procedimientos generales y Ejemplos, como podrán apreciar los especialistas en el arte. Se comprenderá que las formas de realización y los esquemas descritos precedentemente y los siguientes Intermediarios, Procedimientos generales y 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 ejemplos de compuestos indicados más adelante se nombraron usando ACD Name versión 12 (ACD Name v12). Otros compuestos se nombraron usando ChemDraw versión 9.0 (v9), a menos que se indique de otra manera, es decir, que se nombraron usando ACD Name v12. Ambos programas de nombramiento pueden proporcionar un nombre químico que depende de la estructura tautomérica elegida para nombrar los compuestos. Las estructuras se pueden mostrar o nombrar como cualquier tautómero químicamente distinto.

Por ejemplo, la estructura tautomérica:

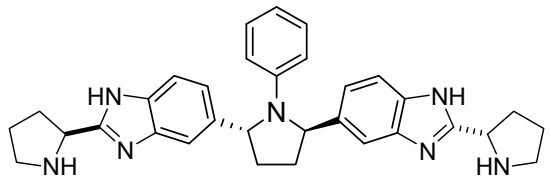


recibe los siguientes nombres:

(S)-6,6'-((2R,5R)-1-fenilpirrolidin-2,5-diil)bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol) (Chemdraw v9);

6,6'-[(2R,5R)-1-fenilpirrolidin-2,5-diil]bis{2-[(2S)-pirrolidin-2-il]-1H-benzimidazol} (ACD Name v12).

La estructura tautomérica:

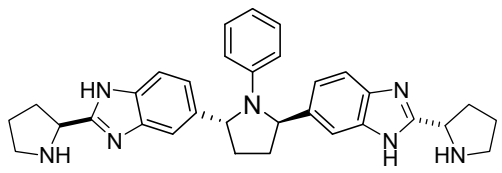


recibe los siguientes nombres:

(S)-5,5'-((2R,5R)-1-fenilpirrolidin-2,5-diil)bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol) (Chemdraw v9);

5,5'-[(2R,5R)-1-fenilpirrolidin-2,5-diil]bis{2-[(2S)-pirrolidin-2-il]-1H-benzimidazol} (ACD Name v12).

La estructura tautomérica:



recibe los siguientes nombres:

(S)-5,5'-((2R,5R)-1-fenilpirrolidin-2,5-diil)bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol) (Chemdraw v9);

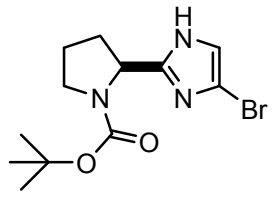
5-[(2R,5R)-1-fenil-5-{2-[(2S)-pirrolidin-2-il]-1H-benzimidazol-6-il}pirrolidin-2-il]-2-[(2S)-pirrolidin-2-il]-1H-benzimidazol (ACD Name v12).

Determinados compuestos en los siguientes ejemplos se pueden purificar usando HPLC de fase reversa. La purificación se puede conducir usando una columna de fase reversa C18 o C8. Los compuestos se pueden eluir 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 pueden purificar 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 compuestos también se pueden purificar mediante TLC-prep.

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, metanol en cloruro de metileno, metanol en cloruro de metileno con NH4OH, acetona en hexanos y cloruro de metileno en hexanos.

Síntesis de Intermediarios



Intermediario 1

(S)- 2-(4-bromo-1H-imidazol-2-il)pirrolidin-1-carboxilato de tert-butilo

Intermediario 1A

(S)- 2-formilpirrolidin-1-carboxilato de tert-butilo

A un recipiente de tres bocas de 500 mL secado al 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 de presión constante a lo largo de un período de 20 minutos. 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 de presión constante a lo largo de un período de 20 minutos, y luego la mezcla de reacción se agitó a -78 °C durante 30 minutos. Se agregó trietilamina (32,6 mL, 234 mmol) por goteo mediante una jeringa a lo largo de un período de 5 minutos y la mezcla espesa blanca se agitó en un baño de agua-hielo durante 30 minutos. La reacción se detuvo con ácido cítrico acuoso 10% (p/v) (30 mL). La mezcla se particionó en un embudo de separación entre Et2O (550 mL) y ácido cítrico acuoso 10% (p/v). Las capas se separaron, y la fase orgánica se lavó con agua y salmuera. La fase orgánica se secó sobre Na2SO4 anhidro, se filtró, y se concentró para dar un aceite amarillo (9,4 g), que se usó directamente en la siguiente reacción.

Intermediario 1B

(S)- 2-(1H-imidazol-2-il)pirrolidin-1-carboxilato de tert-butilo

El producto del Intermediario 1A (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 minutos. 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. La capa orgánica se lavó con salmuera, se secó (Na2SO4) y se concentró hasta dar un sólido color tostado. El sólido se trató con éter y se concentró. El sólido luego se trituró con éter dietílico:hexanos 2:1 (150 mL) para dar 17 g de sólido, que se usó directamente en la siguiente reacción. 1HRMN (400 MHz, DMSO-d6) δ ppm 1,14/1,40 (s, 9H), 1,81-2,12 (m, 4H), 3,32-3,33 (m, 1H), 3,35-3,50 (m, 1H), 4,72-4,81 (m, 1H), 6,84 (s, 1 H), 11,68 (s, 1 H).

Intermediario 1C

(S)- 2-(4,5-dibromo-1H-imidazol-2-il)pirrolidin-1-carboxilato de tert-butilo

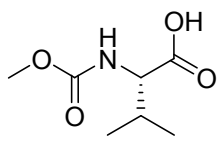
Se agregó N-bromosuccinimida (108 mmol) a una solución fría (0 ºC) del producto del Intermediario 1B (12,05 g, 50,8 mmol) en diclorometano (200 mL). La mezcla se agitó en baño de hielo durante 2 horas y luego se concentró, se disolvió en acetato de etilo (250 mL), se lavó con agua (3×150 mL) y salmuera (1×100 mL), se secó (MgSO4), y se concentró hasta dar un residuo muy oscuro. El residuo se mezcló y se concentró a partir de diclorometano/hexanos (1:1) para dar un sólido marrón (~19 g). El sólido se trituró con éter (~100 mL) y se filtró para aislar un sólido color tostado (13,23 g, 65% de rendimiento). 1H RMN (400 MHz, CDCl3) δ ppm 1,49 (s, 9 H), 1,86 - 2,17 (m, 3 H), 2,80 - 2,95 (m, 1 H), 3,30 - 3,44 (m, 2 H), 4,85 (dd, J=7,54, 2,55 Hz, 1 H), 10,82 (s, 1 H); MS (DCI+) m/z 394/396/398 (M+H)+.

Intermediario 1D

(S)- 2-(4-bromo-1H-imidazol-2-il)pirrolidin-1-carboxilato de tert-butilo

El producto del Intermediario 1C (6,25 g, 15,82 mmol) se disolvió en dioxano (200 mL) y agua (200 mL) en un balón de 1 L equipado con un condensador y tapón de vidrio. Una solución de sulfito de sodio (22,38 g, 174 mmol) en agua (200 mL) se agregó, y la

mezcla se calentó a reflujo durante 16 horas. La mezcla de reacción se enfrió a temperatura ambiente, y se eliminaron el dioxano y parte del agua por evaporación por rotación. El residuo se extrajo con diclorometano. Las fases orgánicas combinadas se lavaron con salmuera (50 mL), se secó sobre Na2SO4 anhidro, se filtró, y se concentró por evaporación por rotación, coevaporando con hexanos/diclorometano (2:1 100 mL) para dar una espuma color beige (4,38 g). La espuma se disolvió en diclorometano (2 mL), se agregaron hexanos (2 mL), y la solución resultante se aplicó a una columna, y se purificó mediante cromatografía flash en gel de sílice eluyendo con acetato de etilo/hexanos 30% a 80% para dar el compuesto del título como un sólido blanco (3,48 g). 1H RMN (400 MHz, CDCl3) δ ppm 1,48 (s, 9 H), 1,83 - 2,33 (m, 3 H), 2,79 - 3,02 (m, 1 H), 3,37 (dd, J=7,10, 5,37 Hz, 2 H), 4,88 (dd, J=7,59, 2,49 Hz, 1 H), 6,92 (s, 1 H), 10,70 (s ancho, 1 H); MS (ESI+) m/z 316/318 (M+H)+.

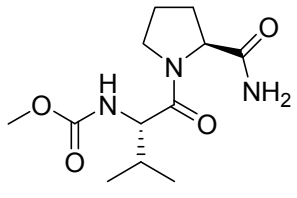


Intermediario 2

Ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico

A ácido (S)-2-amino-3-metilbutanoico (57 g, 487 mmol) disuelto en dioxano (277 mL) se agregó solución acuosa de hidróxido de sodio 2 N (803 mL, 1606 mmol) y luego se agregó por goteo cloroformato de metilo (75 mL, 973 mmol) durante 1 hora lo que causó el calentamiento de la solución. Luego de la adición, la mezcla se calentó a 60 ºC durante 22 horas, luego se enfrió y se extrajo con diclorometano (400 mL). La fase acuosa resultante se enfrió en un baño de hielo, y luego ácido clorhídrico 12 N se agregó por goteo hasta que el pH alcanzó 2. La mezcla resultante se agitó a 0 ºC durante 2 horas, y luego el sólido resultante se recogió mediante filtración al vacío, y se secó en un horno de vacío para dar 80g (94%) del compuesto del título como un sólido incoloro. 1H RMN (400

MHz, DMSO-d6) δ ppm 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).



Intermediario 3

(S)-1-((S)-2-carbamoilpirrolidin-1-il)-3-metil-1-oxobutan-2-ilcarbamato de metilo

Intermediario 3A

sal clorhidrato de (S)-pirrolidin-2-carboxamida

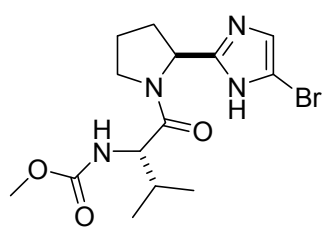
A (S)- 2-carbamoilpirrolidin-1-carboxilato de tert-butilo (29,8 g, 139 mmol) se agregó una solución de HCl 4 N en dioxano (209 mL, 836 mmol), y la mezcla resultante se agitó a temperatura ambiente durante 18 horas. La mezcla luego se concentró y se trituró con éter dietílico y luego se filtró al vacío y se secó bajo vacío para dar 21,6 g (104%) del producto del título como un sólido incoloro.

Intermediario 3B

(S)-1-((S)-2-carbamoilpirrolidin-1-il)-3-metil-1-oxobutan-2-ilcarbamato de metilo

Se disolvieron el Intermediario 3A (21,6 g, 144 mmol), el Intermediario 2 (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) en diclorometano (960 mL) y se agitó a temperatura ambiente durante 18 horas. La solución resultante luego se concentró hasta un residuo, luego se agregó agua y la solución se extrajo con una solución de isopropanol en cloroformo 25% (2×2000 mL). La capa orgánica se lavó con salmuera, y luego el extracto orgánico se secó sobre MgSO4, luego se concentró hasta un aceite amarillo que se purificó mediante cromatografía en columna eluyendo con un gradiente de 0-10% metanol en diclorometano para dar 25 g (64%) del compuesto del título como un sólido incoloro. 1H RMN (400 MHz, DMSO-d6) δ ppm 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).



Intermediario 4

(S)-1-((S)-2-(5-bromo-1H-imidazol-2-il)pirrolidin-1-il)-3-metil-1-oxobutan-2-ilcarbamato de metilo

Intermediario 4A

clorhidrato de (S)-5-bromo-2-(pirrolidin-2-il)-1H-imidazol

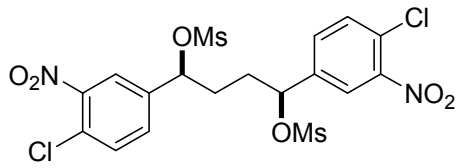
Una mezcla del Intermediario 1D (5,0g, 15,8 mmol) en HCl 4 M/Dioxano (40 mL) se dejó agitar durante una hora. La mezcla se concentró para dar 3,99 g (100%) del compuesto del título. MS (ESI) m/z 217 (M+H)+.

Intermediario 4B

(S)-1-((S)-2-(5-bromo-1H-imidazol-2-il)pirrolidin-1-il)-3-metil-1-oxobutan-2-ilcarbamato de metilo

Una mezcla del Intermediario 4A (3,99g, 15,8 mmol), el Intermediario 2 (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 en agitación durante la noche. La mezcla se diluyó con H2O y se extrajo con EtOAc (3×300 mL). La fase orgánica se lavó con H2O y salmuera. La fase orgánica luego se secó (MgSO4), 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. 1H RMN (400 MHz, DMSO-d6) 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)+.



Intermediario 5

dimetansulfonato de (1S,4S)-1,4-bis(4-cloro-3-nitrofenil)butan-1,4-diilo

Intermediario 5A

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 esta mezcla en agitación se agregó en porciones tribromuro de feniltrimetilamonio (19,78 g, 52,6 mmol) a lo largo de un período de 15 minutos. La mezcla resultante luego se agitó monitoreando cada hora por LCMS. Después de 3 horas, la mezcla se filtró y los sólidos resultantes se lavaron con EtOAc. La solución orgánica luego se concentró, se agregaron H_2O y $NaHCO_3$ acuoso 10%, y la mezcla se lavó con EtOAc (2×300 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 por cristalización. El residuo se disolvió en EtOAc (100 mL) y lentamente se agregaron hexanos hasta que la mezcla se tornó turbia. Después de dejarse en reposo durante algunas horas, se recogió 2-bromo-1-(4-cloro-3-nitrofenil)etanona (9,81 g, 70%) como un producto sólido blancuzco. 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 color rojo intenso. La mezcla se agitó durante 1 hora para dar una solución amarilla que se concentró al vacío para dar un sólido amarillo. Se recristalizó desde hexano/acetato de etilo 9:1 para dar 2-bromo-1-(4-cloro-3-nitrofenil)etanona como agujas amarillas.

Intermediario 5B

1,4-bis(4-cloro-3-nitrofenil)butan-1,4-diona

Se agregó cloruro de zinc (II) (14,68 g, 108 mmol) a tolueno (81 mL) seguido por dietilamina (8,35 mL, 81 mmol) y tert-butanol (7,73 mL, 81 mmol). La solución heterogénea resultante se agitó a temperatura ambiente durante aproximadamente 2 horas. Luego se agregaron el Intermediario 5A (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 durante 42 horas. La reacción luego se neutralizó con ácido sulfúrico acuoso 5% (500 mL) y se agitó enérgicamente para inducir la formación de sólido. El sólido resultante se recogió mediante filtración al vacío, luego se lavó con tolueno, agua, y metanol en forma sucesiva. Luego el sólido se agregó a una solución de acetato de etilo caliente y la solución heterogénea resultante se agitó durante 30 minutos. El sólido luego se recogió y se secó durante la noche en un horno de vacío para dar 16,6 g (78%) del compuesto del título. 1H 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).

Intermediario 5C

(1S,4S)-1,4-bis(4-cloro-3-nitrofenil)butan-1,4-diol

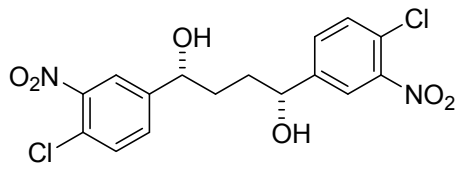
Se disolvió (R)-(+)-α,α-Difenil-2-pirrolidinmetanol (1,08g, 4,28mmol) en 70 mL de THF a temperatura ambiente en un recipiente seco bajo nitrógeno y se agregó borato de trimetilo (650 uL, 5,54 mmol) por goteo. La solución resultante se agitó durante 1 hora. La solución se enfrió en un baño de frío hasta ~ 10 ºC y el borano de N,N-dietilanilina (9,18

mL, 51,6 mmol) se agregó por goteo con algo de burbujeo. Luego de 15 minutos, 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 (Intermediario 5B) (10,0g, 25,2 mmol) suspendida en 200 mL de THF y se enfrió a ~ 10 ºC. Se observó burbujeo. Luego de la adición, la mezcla se agitó a temperatura ambiente durante 4 horas. La mezcla se enfrió en un baño de hielo y se agregaron 30 mL de metanol por goteo hasta detenerse el burbujeo, luego la mezcla se dejó agitar a temperatura ambiente durante 30 minutos. La mezcla se filtró para eliminar las trazas de material de partida insoluble sin reaccionar. El material filtrado se concentró, se volcó sobre HCl 1 M y se extrajo con acetato de etilo, se secó sobre sulfato de sodio, y se concentró para dar el compuesto del título (9,9 g, 99%) como un sólido ceroso amarillo. Chiral HPLC e.e. >99,9% (RR diol was undetectable). 1H RMN (400 MHz, DMSO-d6) δ ppm 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).

Intermediario 5D

Dimetansulfonato de (1S,4S)-1,4-bis(4-cloro-3-nitrofenil)butan-1,4-diilo

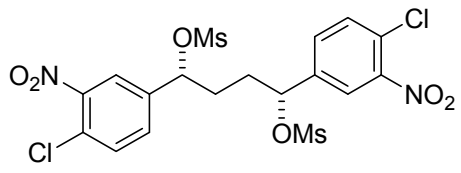
En un balón de 1 L que contenía el Intermediario 5C (20,0 g, 49,9 mmol) se agregaron 310 mL de diclorometano con agitación y enfriamiento en un baño de hielo. A la suspensión se agregó trietilamina (20,84 mL, 150 mmol) y luego de 10 minutos de agitación en el baño de hielo, se agregó una solución de cloruro de metansulfonilo (8,5 mL, 110 mmol) en diclorometano (10 mL) por goteo a la reacción. Luego de completarse la adición, el recipiente se retiró del baño de hielo y se agitó a temperatura ambiente durante 3 horas. A la reacción se agregó agua (400 mL) con agitación vigorosa durante 20 minutos. El sólido se recogió mediante filtración y se lavó cuidadosamente con agua diclorometano y éter dietílico. El sólido se secó durante la noche en un horno de secado al vacío a 60 ºC para dar un sólido blanco (20,49 g, 73,7% de rendimiento). 1H RMN (400 MHz, DMSO-d6) ppm 1,81 - 1,91 (m, 2 H) 2,06 (m, 2 H) 3,18 (s, 6 H) 5,73 - 5,84 (m, 2 H) 7,71 - 7,77 (m, 2 H) 7,80 - 7,85 (m, 2 H) 8,13 (d, J=1,74 Hz, 2 H).



Intermediario 5,1

(1R,4R)-1,4-bis(4-cloro-3-nitrofenil)butan-1,4-diol

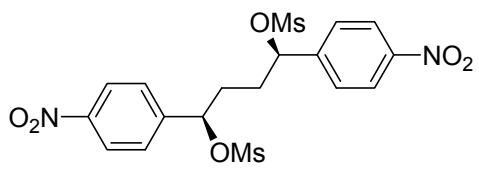
(1R,4R)-1,4-bis(4-cloro-3-nitrofenil)butan-1,4-diol puede prepararse usando (S)-(-)-α,α-difenil-2-pirrolidinmetanol y el método del Intermediario 5C.



Intermediario 5,2

dimetansulfonato de (1R,4R)-1,4-bis(4-cloro-3-nitrofenil)butan-1,4-diilo

Puede transformarse dimetansulfonato de (1R,4R)-1,4-bis(4-cloro-3-nitrofenil)butan-1,4-diol en (1R,4R)-1,4-bis(4-cloro-3-nitrofenil)butan-1,4-diilo como se describe bajo el Intermediario 5D.



Intermediario 6

dimetansulfonato de (1R,4R)-1,4-bis(4-nitrofenil)butan-1,4-diilo

Intermediario 6A

1,4-Bis(4-nitrofenil)butan-1,4-diona

Se agitó cloruro de zinc(II) anhidro (2,73 g, 20,00 mmol) en benceno seco (15 mL) mientras se abregaba 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 durante 90 minutos 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 volcó sobre agua (50 mL) y se extrajo con acetato de etilo (3×50 mL). Las capas orgánicas combinadas se secaron sobre Na2SO4, 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 g, 61% de rendimiento).

Intermediario 6B

(1R,4R)-1,4-bis(4-nitrofenil)butan-1,4-diol

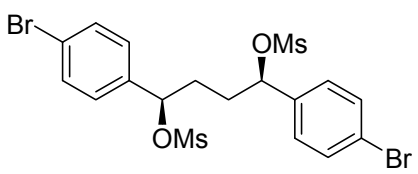
A (S)-(-)-α,α-difenil-2-pirrolidinmetanol (2,71 g, 10,70 mmol) se agregó THF (80 mL) a 23 °C. La suspensión fina se trató con borato de trimetilo (1,44 g, 13,86 mmol) durante 30 segundos, y la solución resultante se mezcló a 23 °C durante 1 hora. La solución se enfrió a 16-19 °C, y se agregó borano de N,N-dietilanilina (21,45 g, 132 mmol) por goteo mediante una jeringa a lo largo de 3-5 minutos (precaución: evolución vigorosa de H2), mientras se mantenía la temperatura interna a 16-19 °C. Luego de 15 minutos, la evolución de H2 había cesado. En un recipiente separado se agregó el producto del Ejemplo 6A (22,04 g, 95 % en peso, 63,8 mmol), seguido por THF (80 mL), para formar una suspensión anaranjada. Luego de enfriar la suspensión a 11 °C, la solución de borano se transfirió mediante cánulas a la suspensión de diona a lo largo de 3-5 minutos. Durante este período, la temperatura interna de la suspensión se elevó a 16 °C. Luego de completarse la adición, la reacción se mantuvo a 20-27 °C durante otras 2,5 horas. Una vez completa 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 minutos, manteniendo una temperatura interna <20 °C (nota: evolución vigorosa de H2). Después de haber cesado la reacción exotérmica (aprox. 10 minutos), la temperatura se ajustó a 23 °C, y la reacción se mezcló hasta la disolución completa de los sólidos. Se agregaron acetato de etilo (300 mL) y HCl 1 M (120 mL), y las fases se separaron. La fase orgánica luego se lavó en forma sucesiva con HCl 1 M (2×120 mL), H2O (65 mL), y NaCl acuoso 10% (65 mL). Los materiales orgánicos se secaron sobre MgSO4, se filtró, y se concentró al vacío. La cristalización del producto

ocurrió durante la concentración. La suspensión se calentó a 50 °C, y se agregó heptano (250 mL) a lo largo de 15 minutos. La suspensión luego se mezcló a 23 °C durante 30 minutos y se filtró. La almohadilla húmeda se lavó con heptano:acetato de etilo 3:1 (75 mL), y los sólidos cristalinos anaranjados se secaron a 45 °C durante 24 horas para dar el compuesto del título (15,35 g, 99,3% ee, 61% de rendimiento), que estaba contaminado con 11% del isómero meso (contra isómero dl).

Intermediario 6C

Dimetansulfonato de (1R,4R)-1,4-bis(4-nitrofenil)butan-1,4-diilo

El producto del Intermediario 6B (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. Por separado, se preparó una solución de anhídrido metansulfónico (6,01 g, 34,5 mmol) en 2-metiltetrahidrofurano (30 mL) y se agregó a la suspensión de diol a lo largo de 3 minutos, manteniendo la temperatura interna entre -15 °C y -25 °C. Después de mezclar durante 5 minutos a -15 °C, el baño de frío se retiró y la reacción se dejó calentar lentamente a 23 °C y se mezcló durante 30 minutos. Una vez completa la reacción, la suspensión cruda se usó directamente sin purificación o aislación.



Intermediario 7

Dimetansulfonato de ((1R,4R)-1,4-bis(4-bromofenil)butan-1,4-diilo

Intermediario 7A

1,4-bis(4-bromofenil)butan-1,4-diona

A una solución de cloruro de zinc(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 durante 2 horas. Se agregaron 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 horas). La mezcla de reacción se detuvo con H2SO4 5% (500 mL) y se agitó enérgicamente para inducir precipitation del producto, el cual se recogió mediante filtración al vacío y se lavó con benceno, agua, metanol, y 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).

Intermediario 7B

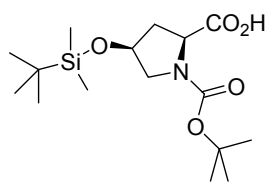
(1R,4R)-1,4-bis(4-bromofenil)butan-1,4-diol

A (S)-(-)-α,α-difenil-2-pirrolidinmetanol (3,81 g, 15,04 mmol) se agregó THF (140 mL) a 23 °C. La suspensión fina se trató con borato de trimetilo (2,189 mL, 19,63 mmol) para formar una solución transparente. Luego de agitar durante 1,5 horas, la solución se enfrió a 10-15 °C, y se agregó borano de N,N-dietilanilina (33,1 mL, 186 mmol) durante 5-10 minutos a través de una jeringa. Se observó una reacción levemente exotérmica y evolución de H2. En un recipiente separado se cargó el Intermediario 7A (35,045 g, 88 mmol), seguido por THF (140 mL), para formar una suspensión. La suspensión se enfrió a 10 °C. La solución de borano enfriada se transfirió mediante cánulas a la suspensión de diona a lo largo de aproximadamente 5 minutos, manteniendo la temperatura interna <25 °C. Una vez completa la transferencia, la suspensión se mantuvo a 15 °C durante 5 minutos y luego la temperatura se mantuvo a 23 °C durante 3 horas. Una vez completa la reacción, la solución se enfrió a 5 °C, y se agregó metanol (31,6 mL, 780 mmol) lentamente para mantener a temperatura <20 °C (nota: evolución vigorosa de hidrógeno). La solución turbia se mezcló durante otra hora con el fin de asegurar la neutralización completa. La solución turbia se diluyó con EtOAc (500 mL) y HCl 1 M (220 mL). Las fases se separaron, y la fase orgánica se lavó en forma sucesiva con HCl 1 M (2×220 mL), H_2O (110 mL), y NaCl acuoso 25% (110 mL). La capa orgánica se concentró al vacío; y luego el residuo se disolvió en EtOAc, se filtró, se concentró y se cristalizó desde EtOAc/hexano para dar el compuesto del título (16,92 g; 100% ee; 47% de rendimiento aislado).

Intermediario 7C

Dimetansulfonato de (1R,4R)-1,4-bis(4-bromofenil)butan-1,4-diilo

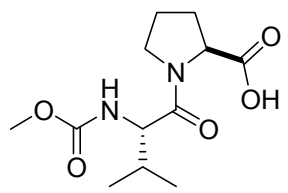
Al Intermediario 7B (0,60 g, 1,500 mmol) en CH2Cl2 anhidro (15 mL) a 0 ºC se agregó Et3N (0,627 mL, 4,50 mmol), y la mezcla resultante se agitó a 0 ºC durante 10 minutos hasta obtenerse una solución homogénea. A la solución enfriada se agregó cloruro de metansulfonilo (0,292 mL, 3,75 mmol) por goteo, y la mezcla resultante se agitó a 0 ºC durante 1,5 horas hasta completarse la reacción según se determinó mediante TLC (EtOAc:hexanos 1:1). El solvente se eliminó al vacío para dar un sólido, que se secó al vacío.



Intermediario 8

Ácido (2S,4S)-1-(tert-butoxicarbonil)-4-(tert-butildimetilsililoxi)pirrolidin-2-carboxílico

Se combinaron 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 agregó tert-butilclorodimetilsilano (7,61 g, 50,5 mmol) en porciones. La mezcla se agitó durante 18 horas y luego se diluyó con agua y se extrajo con acetato de etilo y se concentró para dar el compuesto del título.



Intermediario 9

Ácido (S)-1-((S)-2-(metoxicarbonilamino)-3-metilbutanoil)pirrolidin-2-carboxílico

Se cargaron el Intermediario 2 (150 g, 856 mmol), hidrato de HOBt (138 g, 899 mmol) y DMF (1500 mL) en un recipiente. La mezcla se agitó durante 15 minutos para dar una solución transparente. Se cargó clorhidrato de EDC (172 g, 899 mmol) y se mezcló

durante 20 minutos. La mezcla se enfrió a 13 ºC y se cargó clorhidrato de bencilléster de (L)-prolina (207 g, 856 mmol). Luego se cargó trietilamina (109 g, 1079 mmol) en 30 minutos. La suspensión resultante se mezcló a temperatura ambiente durante 1,5 horas. La mezcla de reacción se enfrió a 15 ºC y se cargaron 1500 mL de NaHCO3 6,7% en 1,5 horas, y luego se agregaron 1200 mL de agua a lo largo de 60 minutos. La mezcla se agitó a temperatura ambiente durante 30 minutos, y luego se filtró y se lavó con una mezcla de agua/DMF (1:2, 250 mL) y luego con agua (1500 mL). La almohadilla húmeda se secó a 55 ºC durante 24 horas para dar 282 g de producto (S)- 1-((S)-2-(metoxicarbonilamino)-3-metilbutanoil)pirrolidin-2-carboxilato de bencilo como un sólido blanco (90%).

Se cargaron (S)- 1-((S)-2-(metoxicarbonilamino)-3-metilbutanoil)pirrolidin-2-carboxilato de bencilo (40 g) y Pd/Alumina 5% en un reactor Parr seguido por THF (160 mL). El reactor se selló y se purgó con nitrógeno (6×20 psig) seguido por una purga de hidrógeno (6×30 psig). El reactor se presurizó a 30 psig con hidrógeno y se agitó a temperatura ambiente durante aproximadamente 15 horas. La suspensión resultante se filtró a través de un filtro GF/F y se concentró hasta aproximadamente 135 g. Se agregó heptano (120 mL), y la solución se agitó hasta haberse formado los sólidos. Después de otras 2–3 horas, se agregó más heptano (240 mL) por goteo, la suspensión se agitó durante aproximadamente 1 hora, luego se filtró. Los sólidos se secaron para dar el compuesto del título ácido (S)-1-((S)-2-(metoxicarbonilamino)-3-metilbutanoil)pirrolidin-2-carboxílico.

Intermediario 10

clorhidrato de 4-ciclohexil-3-fluoroanilina

Intermediario 10A

3-Fluoro-4-yodoanilina

A una suspensión de 3-fluoroanilina (1,0 mL, 1,16 g, 10,39 mmol) y bicarbonato de sodio sólido (1,75 g, 20,79 mmol) en metanol-diclorometano 1:1 (20 mL) a 0 ºC se agregó

una solución de dicloroiodato de benciltrimetilamonio (3,62 g, 10,39 mmol) en diclorometano (15 mL) a lo largo de 30 minutos. La mezcla luego se dejó calentar hasta temperatura ambiente durante 1 hora. La mezcla se detuvo mediante la adición de agua y la capa orgánica se extrajo con agua (2×). El secado (Na2SO4) y la concentración al vacío dieron un aceite, que se cromatografió sobre un cartucho de gel de sílice de 100 g, eluyendo con acetato de etilo en hexanos 10-100%. Se obtuvo el compuesto del título (2,20 g, 89%) como un sólido rosado. 1H RMN (400 MHz, CDCl3) ppm 7,41 (dd, J = 8,3, 7,3 Hz, 1 H), 6,42 (dd, J = 9,9, 2,5 Hz, 1 H), 6,27 (dd, J = 8,5, 2,5 Hz, 1 H), 3,81 (s, 2 H); MS +ESI m/z (abundancia relativa) 238 (100, M+H).

Intermediario 10B

4-(Ciclohexen-1-il)-3-fluoroanilina

El procedimiento para preparar el compuesto del título se describe en el Procedimiento General 1.2A.

Intermediario 10C

clorhidrato de 4-ciclohexil-3-fluoroanilina

Una solución de 4-(ciclohexen-1-il)-3-fluoroanilina (Procedimiento General 1.2A) (1,16 g, 6,07 mmol) en etanol (30 mL) se trató con paladio sobre carbono 10% (300 mg) y luego se hidrogenó a una atmósfera durante 18 horas. La mezcla se filtró a través de tierras diatomeas y se concentró a aproximadamente un cuarto del volumen y se trató con una solución de cloruro de hidrógeno en dioxano (4 N, 10 mL). La mezcla luego se concentró parcialmente al vacío a aproximadamente un cuarto del volumen y se diluyó con éter (aprox. 100 mL) y los sólidos se recogieron mediante filtración. Después del secado en un horno de vacío a 50 ºC durante 3 horas, se obtuvo el compuesto del título (1,13 g, 81%) como un sólido gris claro. 1H RMN (400 MHz, DMSO-d6) ppm 7,35 (t, J = 8,1 Hz, 1 H), 7,03 (d, J = 9,4 Hz, 2 H), 2,76 (dd, J = 15,6, 6,9 Hz, 1 H), 1,74 (m, 5 H), 1,40 (m, 4 H), 1,21 (m, 1 H). MS (DCI+) m/z (abundancia relativa) 194 (100, M+H), 211 (67, M+NH4).

Intermediario 11A

N-(4-bromo-5-fluoro-2-nitrofenil)-2,2,2-trifluoroacetamida

A un recipiente que contenía anhídrido trifluoroacético (10,0 mL, 70,5 mmol) a 0 ºC se agregó 4-bromo-3-fluoroanilina (2,0,g, 10,5 mmol) y la agitación se continuó durante 30 minutos (Charifson, P.S.; et al. J. Med. Chem. 2008, 51, 5243-5263). Se agregó nitrato de potasio (1,3 g, 12,6 mmol) y la solución se dejó calentar a 25 ˚C. La solución se concentró, el residuo se disolvió en EtOAc y se lavó con NaHCO3 10%, salmuera, se secó (Na2SO4), y se filtró. El material filtrado se concentró para dar el compuesto del título (3,5 g, 10,5 mmol, 100%).

Intermediario 11B

4-bromo-5-fluoro-2-nitroanilina

A N-(4-bromo-5-fluoro-2-nitrofenil)-2,2,2-trifluoroacetamida (3,5 g, 10,5 mmol) se agregó CH3OH (30mL) seguido por K2CO3 1,0 M (10,5mL, 10,5 mmol), y la solución se agitó durante 30 minutos (Charifson, P.S.; et al. J. Med. Chem. 2008, 51, 5243-5263). La solución se diluyó con H2O y se agitó durante 1 hora. El sólido anaranjado resultante se recogió mediante filtración y se secó en un horno de vacío para dar el compuesto del título (2,1,g, 8,8 mmol, 84%).

Intermediario 11C

4-bromo-5-fluorobencen-1,2-diamina

A una solución de 4-bromo-5-fluoro-2-nitroanilina (1,0 g, 4,3 mmol) en THF (9,0mL), EtOH (9,0 mL) y H2O (3 mL) se agregó polvo de hierro (1,2 g, 21,3 mmol) y cloruro de amonio (0,34 g, 6,4 mmol), y la mezcla se calentó a 95 ºC durante 4 horas. La mezcla enfriada se diluyó con EtOH, se filtró a través de tierras diatomeas hasta no pasar más color a través del filtro, y se concentró. El residuo se disolvió en EtOAc, se lavó con H2O, salmuera, se secó (Na2SO4), se filtró y se concentró. Se agregó hexano y el sólido resultante se recogió mediante filtración para dar el compuesto del título (710 mg, 3,5 mmol, 81%).

Intermediario 12

4-bromo-3-clorobencen-1,2-diamina

Intermediario 12A

4-bromo-3-cloro-2-nitroanilina

Se disolvió 3-cloro-2-nitroanilina (5,00 g, 29,0 mmol) en ácido acético glacial (258 mL). Se agregó N-bromosuccinimida (5,06 g, 28,4 mmol) y la mezcla resultante se sometió a reflujo durante 1 hora. La reacción se enfrió a temperatura ambiente y se volcó sobre agua para dar un precipitado que se filtró, se enjuagó con agua y se secó a peso constante para dar el compuesto del título (4,78 g, 67%). 1H RMN (400 MHz, CDCL3) δ ppm 7,46 (d, J = 9,0, 1H), 6,64 (d, J = 9,0, 1H), 4,74 (s, 2H).

Intermediario 12B

4-bromo-3-clorobencen-1,2-diamina

Se disolvió 4-bromo-3-cloro-2-nitroanilina (4,78 g, 19,01 mmol) en etanol (112 mL). Se agregó cloruro de estaño (II) (14,42 g, 76 mmol), y la mezcla resultante se agitó a reflujo durante 12 horas. La mezcla se enfrió a temperatura ambiente, se volcó sobre agua, y se ajustó a pH 5 con solución saturada de bicarbonato de sodio. El sólido resultante se filtró y se enjuagó bien con acetato de etilo. El material filtrado se lavó con agua y salmuera, se secó sobre Na2SO4, se filtró y se concentró al vacío. El producto crudo se purificó mediante cromatografía en columna de gel de sílice usando un gradiente de solventes de EtOAc en hexano 0-50% para dar el compuesto del título (3,32 g, 79%). 1H RMN (400 MHz, CDCl3) δ ppm 6,94 (d, 1H), 6,51 (d, J = 7,0, 1H), 3,87 (s ancho, 2H), 3,46 (s ancho, 2H).

Intermediario 13

4-bromo-3-metilbencen-1,2-diamina

Intermediario 13A

N-(3-bromo-2-metil-6-nitrofenil)-2,2,2-trifluoroacetamida

A una solución de 3-bromo-2-metilanilina (1,0 g, 5,37 mmol) en CH2Cl2 (4,0 mL) a 0 ºC se agregó anhídrido trifluoroacético (2,0 mL, 14,2 mmol). La mezcla se agitó a 0 oC durante 30 minutos, y se agregó nitrato de potasio sólido (0,679 g, 6,72 mmol). El baño de frío se retiró, y la mezcla se agitó a temperatura ambiente durante la noche. El análisis por LCMS mostró la formación de un único producto. La mezcla se concentró al vacío, y el residuo se particionó entre agua y CH2Cl2 (2×). Las capas orgánicas se combinaron y se secó sobre Na2SO4. El agente de secado se retiró por filtración y el producto crudo se purificó mediante cristalización desde EtOH acuoso para dar el compuesto del título (1,3 g, 74%).

Intermediario 13B

3-bromo-2-metil-6-nitroanilina

Una solución de N-(3-bromo-2-metil-6-nitrofenil)-2,2,2-trifluoroacetamida (1,3 g, 3,97 mmol) en CH3OH (30 mL) se trató con carbonato de potasio (1,099 g, 7,95 mmol), y la mezcla se agitó a 50 ºC durante la noche. La mezcla se enfrió a temperatura ambiente y se volcó sobre agua, se agregó HCl acuoso 1N para ajustar el pH a 6, y la mezcla se extrajo con CH2Cl2 (3×). Los extractos combinados se secaron sobre Na2SO4, y el agente de secado se retiró por filtración y el solvente se eliminó al vacío para dar el compuesto del título como un sólido amarillo (0,57 g, 62%).

Intermediario 13C

4-bromo-3-metilbencen-1,2-diamina

A una solución de 3-bromo-2-metil-6-nitroanilina (0,45 g, 1,95 mmol) en EtOH (6 mL) se agregó cloruro de estaño (II) (1,48 g, 7,8 mmol), y la solución resultante se agitó a 70 ºC durante 4 horas. La mezcla se enfrió a temperatura ambiente y se volcó sobre agua, y se agregó NaOH acuoso 1 N para alcanzar un pH>7. La mezcla resultante se extrajo con CH2Cl2 (2×), y los extractos combinados se secaron sobre Na2SO4. El agente de secado se retiró por filtración y el solvente se eliminó al vacío para dar el compuesto del título como un aceite (0,34 g, 88%).

Intermediario 14

5-bromo-3-fluorobencen-1,2-diamina

A una solución de 4-bromo-2-fluoro-6-nitroanilina (0,5 g, 2,1 mmol) en THF (4,6 mL), EtOH (4,6 mL) y H2O (1,5 mL) se agregó polvo de hierro (0,6 g, 10,6 mmol) y cloruro de amonio (0,17 g, 3,2 mmol). La mezcla resultante se agitó a 95 ºC durante 22 horas. La mezcla se enfrió a temperatura ambiente y se filtró a través de tierras diatomeas. El sólido se lavó con EtOH hasta no pasar más color a través del filtro. El material filtrado se concentró y el residuo se disolvió en EtOAc, se lavó con H2O y salmuera, se secó sobre Na2SO4, se filtró y se concentró para dar el compuesto del título (0,43 g, 99%) como un sólido ceroso marrón.

Intermediario 15

4-bromo-3-fluorobencen-1,2-diamina

Intermediario 15A

3-fluoro-2-nitroanilina

A un tubo de presión se agregó 1,3-difluoro-2-nitrobenceno (2,8 mL, 26,4 mmol) y NH3 7 N en CH3OH (10 mL, 70 mmol). El tubo se selló y la mezcla se agitó a temperatura ambiente durante 5 días. La solución se diluyó con H2O, se extrajo con CH2Cl2, y los extractos combinados se lavaron con salmuera, se secó sobre Na2SO4, se filtró y se concentró para dar un aceite. El aceite se trituró con hexano y el sólido anaranjado resultante se recogió mediante filtración para dar el compuesto del título (2,1 g, 51%).

Intermediario 15B

4-bromo-3-fluoro-2-nitroanilina

A una solución de 3-fluoro-2-nitroanilina (2,1 g, 13,4 mmol) en DMF (30 mL) a 0 ºC se agregó una solución de N-bromosuccinimida (2,4 g, 13,4 mmol) en DMF (20 mL). La solución resultante se agitó a 0 oC durante 30 minutos y luego se calentó a temperatura ambiente durante 1 hora. La solución se diluyó con EtOAc, se lavó con H2O y salmuera,

se secó sobre MgSO4, se filtró y se concentró para dar el compuesto del título (3,1 g, 97%).

Intermediario 15C

4-bromo-3-fluorobencen-1,2-diamina

A una solución de 4-bromo-3-fluoro-2-nitroanilina (3,0 g, 12,8 mmol) en THF (30 mL) se agregó EtOH (30 mL) y H2O (10 mL) seguido por polvo de hierro (3,6 g, 63,8 mmol) y cloruro de amonio (1,0 g, 19,2 mmol). La mezcla resultante se agitó a 80 ºC durante 16 horas. La mezcla se enfrió a temperatura ambiente y se filtró a través de tierras diatomeas. El sólido se lavó con EtOH hasta no pasar más color a través del filtro. El material filtrado se concentró al vacío y el producto crudo se purificó mediante cromatografía en columna de gel de sílice usando un gradiente de solventes de EtOAc en hexano 0-40% para dar el compuesto del título (2,2 g, 84%).

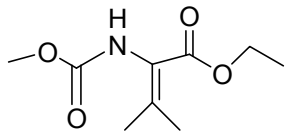
Intermediario 16

4-ciclopropil-2-fluoroanilina

Se disolvió 4-ciclopropil-2-fluoro-1-nitrobenceno (preparado como se describe en el Procedimiento General 1.2C) (2,2 g, 12,14mmol) en 7 mL de una mezcla de etanol:THF:agua 3:3:1 (v/v). A esto se agregó cloruro de amonio (1,02 g, 19,07 mmol) seguido por polvo de hierro (3,50 g, 62,7mmol). La mezcla resultante se calentó en un baño de aceite a 90 ºC bajo una atmósfera de nitrógeno con agitación rápida durante una hora. La mezcla de reacción se filtró al vacío a través de un tapón de arena y tierras diatomeas. El material filtrado se concentró al vacío y el residuo se particionó entre diclorometano y agua. La fase orgánica se lavó con salmuera, se secó (MgSO4) y se concentró al vacío para dar un aceite anaranjado (1,90 g).

Intermediario 17

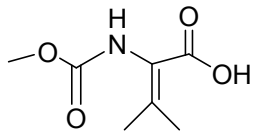
Ácido 2-(metoxicarbonilamino)-3-metilbut-2-enoico



Intermediario 17A

2-(metoxicarbonilamino)-3-metilbut-2-enoato de etilo

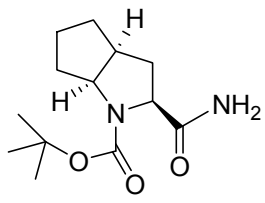
Una solución en benceno (90 mL) de 3-metil-2-oxobutanoato de etilo (4,03 g, 28,0 mmol), carbamato de metilo (2,098g, 28,0 mmol) y 4-metilbencenosulfonato de piridina (0,70 g, 2,80 mmol) se calentó a reflujo en un balón equipado con una trampa Dean-Stark y condensador de reflujo. Después de 44 horas de calentamiento la mezcla se enfrió y luego se particionó entre acetato de etilo (50mL) y salmuera (50 mL). La fase orgánica se lavó con salmuera (2×50 mL) y luego se secó (MgSO4) y se concentró al vacío. El producto crudo se purificó mediante cromatografía sobre gel de sílice (acetato de etilo-hexanos) para dar el compuesto del título como un sólido cristalino blancuzco (1,487 g, 26%).



Intermediario 17B

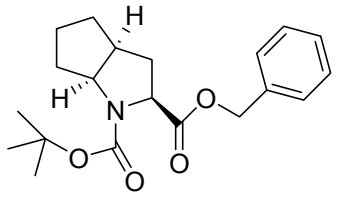
Ácido 2-(metoxicarbonilamino)-3-metilbut-2-enoico

El producto del Intermediario 17A (0,373 g, 1,85 mmol) se disolvió en 2 mL de una mezcla de etanol:agua 1:1(v/v) a temperatura ambiente. A esto se agregó hidróxido de litio (0,095 g, 3,99 mmol) en una porción. Luego de agitar durante la noche, la mezcla de reacción se particionó entre acetato de etilo (25 mL) y HCl 1 N (5 mL) a lo que que se agregó NaCl sólido. La fase acuosa se extrajo con acetato de etilo y los materiales orgánicos combinados se lavaron con salmuera (3×5 mL) y luego se secó (MgSO4) y se concentró para dar el compuesto del título (0,289 g, 90%) como un sólido blanco opaco suficientemente puro para usarse como tal.



Intermediario 18

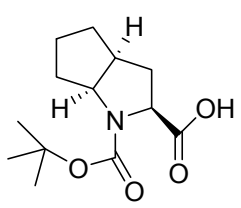
(2S,3aS,6aS)- 2-carbamoilhexahidrociclopenta[b]pirrol-1(2H)-carboxilato de tert-butilo



Intermediario 18A

(2S,3aS,6baS)- hexahidrociclopenta[b]pirrol-1,2(2H)-dicarboxilato de 2-bencilo 1-tert-butilo

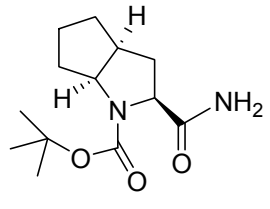
A una suspensión de clorhidrato de (2S,3aS,6aS)- octahidrociclopenta[b]pirrol-2-carboxilato de bencilo (2,0 g, 7,10 mmol) en diclorometano (36 mL) a temperatura ambiente se agregó dicarbonato de di-tert-butilo (1,7 0g, 7,81 mmol) seguido por trietilamina (2,18 mL, 15,62 mmol). La solución rápidamente se tornó homogénea y se observó evolución vigorosa de gas que se detuvo rápidamente. Después de dos horas, la mezcla se diluyó con diclorometano, se lavó con salmuera (3×60 mL), se secó (MgSO4) y se concentró. El producto crudo se purificó mediante cromatografía sobre gel de sílice (acetato de etilo–hexanos) para dar el compuesto del título (2,58 g, cuantitativo) como un aceite traslúcido.



Intermediario 18B

Ácido (2S,3aS,6aS)-1-(tert-butoxicarbonil)octahidrociclopenta[b]pirrol-2-carboxílico

El producto del Intermediario 18A (2,45 g, 7,1mmol) se disolvió en metanol (35 mL) a temperatura ambiente. A esto se agregó catalizador de Pearlman (0,153 g) y luego se desgasificó al vacío (3×) y se agregó hidrógeno (balón). Después de una hora, la mezcla de reacción se filtró al vacío a través de tierras diatomeas y el material filtrado se concentró para dar un aceite espeso transparente (1,89 g, cuantitativo) que resultó suficientemente puro para usarse como tal.



Intermediario 18C

(2S,3aS,6aS)- 2-carbamoilhexahidrociclopenta[b]pirrol-1(2H)-carboxilato de tert-butilo

El producto del Intermediario 18B (1,81 g, 7,1 mmol) se disolvió en THF (40 mL) a temperatura ambiente bajo nitrógeno. A esto se agregó N-metilmorfolina (1,0 mL, 9,09 mmol) y la solución resultante se enfrió a -15 ºC. A la solución fría se agregó cloroformato de isobutilo (1,03 mL, 7,81 mmol) por goteo mediante una jeringa. Se formó un precipitado blanco. Una vez completa la adición, la mezcla se dejó agitar en frío durante 20 minutos. Luego se introdujo gas amoníaco burbujeándose a través de la mezcla durante dos minutos con enfriamiento adicional. Una vez completa la adición, la reacción se dejó calentar a temperatura de baño de hielo y se agitó durante media hora y luego se calentó a temperatura ambiente. Después de 15 minutos a temperatura ambiente, la mezcla se volcó sobre salmuera (450 mL) y se extrajo con diclorometano (6×50 mL). Los extractos combinados se secaron (MgSO4) y se concentró. El producto crudo se purificó mediante cromatografía sobre gel de sílice (acetato de etilo–hexanos) para dar el compuesto del título (1,68 g, 93%) como una espuma blanca pegajosa.

Intermediario 19

(S,E)- 2-(5-(3-oxoprop-1-enil)-1-((2-(trimetilsilil)etoxi)metil)-1H-benzo[d]imidazol-2-il)pirrolidin-1-carboxilato de tert-butilo

Intermediario 19A

(S,E)- 2-(5-(3-etoxi-3-oxoprop-1-enil)-1-((2-(trimetilsilil)etoxi)metil)-1H-benzo[d]imidazol-2-il)pirrolidin-1-carboxilato de tert-butilo

En (S)- 2-(5-bromo-1-((2-(trimetilsilil)etoxi)metil)-1H-benzo[d]imidazol-2-il)pirrolidin-1-carboxilato de tert-butilo (2,973 g, 5,99 mmol), acrilato de etilo (0,714 mL, 6,59 mmol), tetrafluoroborato de tri-tert-butilfosfonio (0,104 g, 0,359 mmol), N,N-diciclohexilmetilamina (1,461 mL, 6,89 mmol), y tris(dibencilidenacetona)dipaladio(0) (0,164 g, 0,18 mmol) disueltos en THF (18 mL) se burbujeó a través de la solución durante 15 minutos para eliminar el oxígeno, y luego la mezcla se calentó a 60 °C durante 2 horas. Luego de enfriar a temperatura ambiente la solución se filtró a través de tierras diatomeas y se lavó con EtOAc. El filtrado luego se concentró hasta un residuo, y luego el residuo se disolvió en diclorometano y se extrajo con agua. La capa orgánica luego se secó y se concentró. El residuo se purificó mediante cromatografía (gel de sílice, hexanos en acetato de etilo) para dar 2,56 g, (83%) del compuesto del título. MS (ESI) m/z 516 (M+H)+.

Intermediario 19B

(S,E)- 2-(5-(3-hidroxiprop-1-enil)-1-((2-(trimetilsilil)etoxi)metil)-1H-benzo[d]imidazol-2-il)pirrolidin-1-carboxilato de tert-butilo

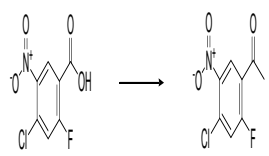
El Intermediario 19A (2,56 g, 4,97 mmol) se disolvió en THF (17 mL), y la mezcla se enfrió a -78 °C en un baño de hielo seco y acetona. Luego se agregó una solución de hidruro de diisobutilaluminio (1,0 N en THF, 22,75 mL, 24,75 mmol) por goteo. La mezcla resultante se dejó calentar lentamente a temperatura ambiente durante la noche, y luego se detuvo con una solución acuosa de hidróxido de sodio 1 N. La mezcla luego se agregó a acetato de etilo y se extrajo con una solución acuosa de sal de Rochelle (tartrato de sodio y potasio). Las capas orgánicas se combinaron y se secó, y luego se concentró.

El residuo se purificó mediante cromatografía (gel de sílice, hexanos en acetato de etilo) para dar 0,93 g, (40%) del compuesto del título. MS (ESI) m/z 474 (M+H)+.

Intermediario 19C

(S,E)- 2-(5-(3-oxoprop-1-enil)-1-((2-(trimetilsilil)etoxi)metil)-1H-benzo[d]imidazol-2-il)pirrolidin-1-carboxilato de tert-butilo

El producto del Intermediario 19B (0,93 g, 1,96 mmol) se disolvió en diclorometano (7,5 mL) y se agregó dicromato de piridinio (1,11 g, 2,95 mmol), y la mezcla resultante se agitó a temperatura ambiente durante la noche. Se agregaron hexanos a la solución, y luego se filtró a través de tierras diatomeas. El material filtrado luego se concentró hasta un residuo que luego se disolvió en diclorometano y se extrajo con agua. La capa orgánica luego se secó, se concentró y el residuo se purificó mediante cromatografía (gel de sílice, hexanos en acetato de etilo) para dar 0,3 g, (32%) del compuesto del título. 1H RMN (400 MHz, DMSO-d6) □ ppm 9,65 (d, J=7,8 Hz, 1H), 8,05 (m, 1H), 7,82 (d, J=15,8 Hz, 1H), 7,70 (m, 2H), 6,87 (dd, J=15,8, 7,8 Hz, 1H), 5,70 (s, 2H), 5,14 (m, 1H), 3,57 (m, 2H), 3,42 (m, 1H), 2,40 (m, 5H), 1,30 (s, 4H), 0,95 (s, 5H), 0,80 (m, 2H), -0,10 (s, 9H); MS (ESI) m/z 472 (M+H)+.



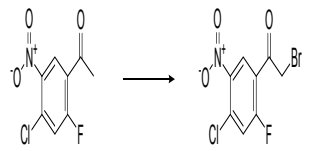
Intermediario 20A

1-(4-cloro-2-fluoro-5-nitrofenil)etanona

A una solución de ácido 4-cloro-2-fluoro-5-nitrobenzoico (16,0 g, 72,9 mmol) en CH2Cl2 anhidro (400 mL) se agregó cloruro de oxalilo (9,57 mL, 109 mmol) y DMF (2 gotas), y la mezcla resultante se agitó a temperatura ambiente hasta haber cesado la evolución de gas. La mezcla se concentró y se secó al vacío. En un recipiente de reacción secado por calor separado se agregó una mezcla de ZnBr2 (24,6 g , 109 mmol) en THF anhidro (300 mL) a -78◦C a una solución de CH3MgBr (29,1 mL, 3,0 M en Et2O, 87 mmol)

por goteo. La mezcla resultante se agitó a -78 ºC durante 15 minutos, y luego la mezcla de reacción se dejó calentar a temperatura ambiente y se agitó durante 30 minutos. La mezcla se enfrió a -78 ºC y se agregó una solución del cloruro de ácido en THF anhidro (100 mL) por goteo, seguida por Pd(PPh3)4 (1,68 g, 1,46 mmol). La mezcla resultante se dejó agitar a -78 ºC durante 10 minutos, y luego se dejó calentar hasta temperatura ambiente y se agitó durante otras 16 horas. La mezcla se detuvo agregando acuoso HCl 1 M, se diluyó con H2O (100 mL), y se extrajo con CH2Cl2 (3×300 mL). Los extractos orgánicos combinados se secaron (MgSO4), se filtró y se concentró. El producto crudo se purificó mediante cromatografía en columna (gel de sílice, EtOAc en hexanos 5%) para dar el compuesto del título (11,79 g, 74%).

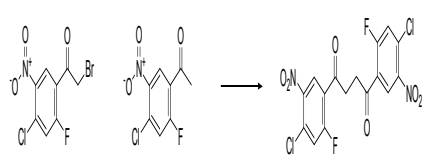
El Intermediario 20A también puede prepararse haciendo reaccionar el intermediario cloruro de ácido con malonato de dimetilo, MgCl2, y trietilamina en cloruro de metileno, sometiéndose luego a hidrólisis ácida y descarboxilación.



Intermediario 20B

2-bromo-1-(4-cloro-2-fluoro-5-nitrofenil)etanona

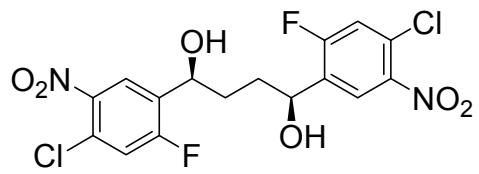
El producto del Intermediario 20A (3,0 g, 13,79 mmol) disuelto en THF (100 mL) se trató con perbromuro de bromuro de piridinio (4,63 g, 14,48 mmol) en porciones a lo largo de varios minutos. La mezcla resultante se agitó a temperatura ambiente durante 2 horas y luego se filtró. Los sólidos filtrados se enjuagaron con EtOAc, y el material filtrado se concentró al vacío. El producto crudo se purificó mediante cromatografía en columna (gel de sílice, EtOAc en hexanos 20%) para dar el compuesto del título (3,8 g, 93%).



Intermediario 20C

1,4-bis(4-cloro-2-fluoro-5-nitrofenil)butan-1,4-diona

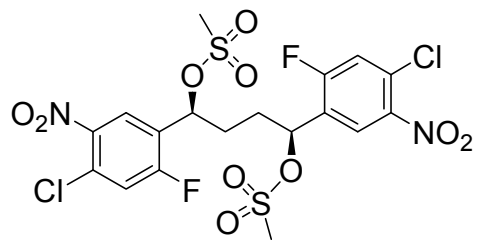
El Intermediario 20A (4,92 g, 22,62 mmol) y el Intermediario 20B (4,47 g, 15,08 mmol) se procesaron usando el método descrito en el Intermediario 5B para dar el compuesto del título (4,74 g, 73%).



Intermediario 20D

(1S,4S)-1,4-bis(4-cloro-2-fluoro-5-nitrofenil)butan-1,4-diol

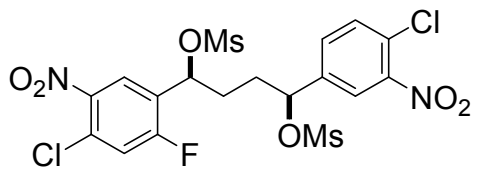
El producto del Intermediario 20C (1,0 g, 2,309 mmol) se procesó usando el método descrito en el Intermediario 5C para dar el compuesto del título (0,96 g, 95%). En la reducción quiral para formar el Intermediario 20D, la reacción procede con menor estereoselectividad que en el caso del Intermediario 5C.



Intermediario 20E

dimetansulfonato de (1S,4S)-1,4-bis(4-cloro-2-fluoro-5-nitrofenil)butan-1,4-diilo

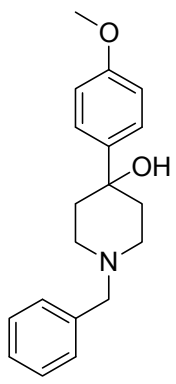
A una solución del Intermediario 20D (0,95 g, 2,17 mmol) en anhidro CH2Cl2 (20 mL) a 0 ºC se agregó cloruro de metansulfonilo (0,42 mL, 5,43 mmol), y luego se agregó por goteo trietilamina (0,91 mL, 6,52 mmol). La mezcla resultante se agitó a temperatura ambiente durante 90 minutos, y luego se concentró al vacío. Se agregaron hexanos, y los sólidos resultantes se recogieron mediante filtración, se lavó con H2O, y se secó al vacío para dar el compuesto del título (1,29 g, 100%).



Intermediario 21

dimetansulfonato de (1S,4S)-1-(4-cloro-2-fluoro-5-nitrofenil)-4-(4-cloro-3-nitrofenil)butan-1,4-diilo

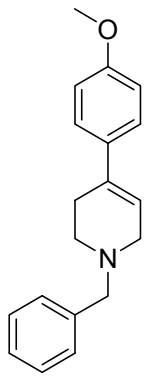
El Intermediario 21 puede prepararse a partir del Intermediario 20B y 1-(4-cloro-3-nitrofenil)etanona (disponible comercialmente en Aldrich) siguiendo los métodos generales para preparar el Intermediario 20E.



Intermediario 22A

1-bencil-4-(4-metoxifenil)piperidin-4-ol

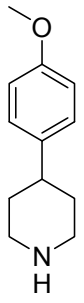
Se agregó bromuro de (4-metoxifenil)magnesio (0,5 M en THF, 90 mL, 45,0 mmol) lentamente (~25 minutos) mediante cánulas a una solución fría (0 ºC) de 1-bencilpiperidin-4-ona (5,4 mL, 30,2 mmol) en THF (60 mL). La reacción se agitó a 0 ºC bajo nitrógeno durante 2 horas. La reacción se detuvo con NH4Cl acuoso saturado y luego se diluyó con éter. La fracción orgánica se lavó con NH4Cl acuoso saturado (2×) salmuera (1×) y se concentró. La purificación usando cromatografía flash (EtOAc /hexano 5 – 100%) dio 4,02 g (44%) del compuesto del título. MS (DCI) m/z 298 (M+H)+.



Intermediario 22B

1-bencil-4-(4-metoxifenil)-1,2,3,6-tetrahidropiridina

Se agregó HCl 6 M (100 mL, acuoso) a una solución de 1-bencil-4-(4-metoxifenil)piperidin-4-ol (12,31 g, 41,36 mmol) en dioxano (50 mL), y la reacción se calentó a reflujo (110 ºC). Luego de 2 horas, la reacción no resultó completa. Se detuvo el calentamiento y la reacción se dejó en agitación a temperatura ambiente durante 2 días. La reacción progresó pero no resultó completa por lo que se calentó a 110 ºC. Luego de 1 hora, la reacción se enfrió y el volumen se redujo a aproximadamente un tercio. La solución luego se enfrió en un baño de hielo y se neutralizó con lentejas de NaOH. La suspensión espesa se filtró. El precipitado se enjuagó con agua y luego se secó bajo vacío a 70ºC para dar 6,2 g (47%) del compuesto del título. ^{1}H RMN (400 MHz, CDCl3) δ ppm 2,74 - 2,62 (m, 1H), 3,30 - 3,06 (m, 2H), 3,50 (d, J = 18,5, 1H), 3,67 - 3,56 (m, 1H), 3,82 (s, 3H), 4,03 - 3,90 (m, 1H), 4,21 (dd, J = 5,7, 13,0, 1H), 4,34 (dd, J = 5,1, 13,0, 1H), 5,88 (s, 1H), 6,88 (d, J = 8,7, 2H), 7,32 (d, J = 8,7, 2H), 7,51 - 7,43 (m, 3H), 7,71 (dd, J = 2,7, 6,3, 2H), 12,85 (s, 1H); MS (ESI) m/z 280 $(M+H)^+$; MS (DCI) m/z 280 $(M+H)^+$.

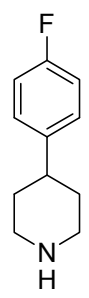


Intermediario 22C

4-(4-metoxifenil)piperidina

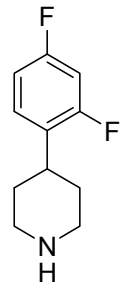
El producto del Intermediario 22B (6,2 g) en trifluoroetanol (60 mL) se agregó a Pd(OH)2-C 20%, húmedo (1,240 g, 8,83 mmol) en una botella de presión de acero inoxidable de 250 mL. La mezcla se agitó bajo 30 psi de hidrógeno a 50 °C durante 23 horas. La mezcla se filtró a través de una membrana PTFE, se concentró y se secó bajo vacío para dar 4,33 g del producto deseado como la sal HCl. (sal de HCl) ^{1}H RMN (400 MHz, CDCl3) δ ppm 2,03 (d, J = 13,1, 2H), 2,28 - 2,11 (m, 2H), 2,72 (t, J = 10,2, 1H), 3,08 - 2,91 (m, 2H), 3,62 (d, J = 8,3, 2H), 3,79 (s, 3H), 6,86 (d, J = 8,3, 2H), 7,16 (d, J = 8,5, 2H), 9,65 (d, J = 83,1, 2H); MS (DCI) m/z 192 $(M+H)^+$.

Los Intermediarios 23, 24, y 25 pueden prepararse usando el método usado para preparar el Intermediario 22C



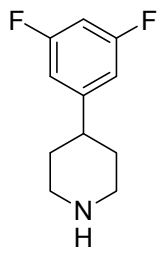
Intermediario 23

4-(4-fluorofenil)piperidina



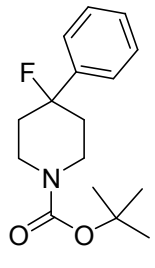
Intermediario 24

4-(2,4-difluorofenil)piperidina



Intermediario 25

4-(3,5-difluorofenil)piperidina

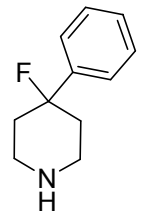


Intermediario 26A

4-fluoro-4-fenilpiperidin-1-carboxilato de tert-butilo

Una solución de trifluoruro de dietilaminoazufre (4 mL, 32,7 mmol) en diclorometano (10 mL) se agregó a una solución fría (-78 ºC; baño de hielo seco/acetona) de 4-hidroxi-4-fenilpiperidin-1-carboxilato de tert-butilo (8,05 g, 29,0 mmol) en diclorometano (100 mL) bajo nitrógeno. La reacción se agitó a -78 ºC durante ~ 1 hora. La reacción se retiró del baño y se calentó a temperatura ambiente y luego se agitó otros 30 minutos. La reacción se detuvo con NaHCO3 acuoso saturado (100 mL). La fracción orgánica se lavó con salmuera (~50 mL). Luego se agregó ácido 3-cloroperoxibenzoico (1,0995 g, 6,37 mmol) a la reacción y se agitó a temperatura ambiente durante 30 minutos. Este paso se detuvo con NaHCO3 acuoso saturado (100 mL). La fracción orgánica se lavó con NaHCO3 acuoso saturado (1×100 mL), agua (1×100 mL), y salmuera (1×100 mL), se secó (MgSO4), se evaluó la presencia peróxido (3 - 10 ppm) y se concentró hasta un aceite amarillo claro. El aceite se secó bajo vacío para dar 8,27 g (100%) del compuesto del título. ^{1}H RMN (400 MHz, DMSO-d6) δ ppm 1,42 (d, J = 5,7, 9H), 1,96 - 1,85 (m, 3,5H), 2,03 (ddd, J = 5,2, 13,3, 17,8, 1,5H), 3,06 (s, 2H), 3,98 (d, J =

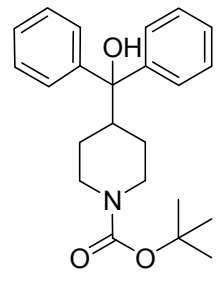
12,0, 2H), 7,33 (d, J = 7,1, 1H), 7,46 - 7,36 (m, 4H); MS (DCI) m/z 280 ($M+H^+$, 60%), 297 ($M+NH_4^+$, 100%).



Intermediario 26B

4-fluoro-4-fenilpiperidina

Se agregó ácido clorhídrico (4 M en dioxano, 20 mL, 80 mmol) a una solución de 4-fluoro-4-fenilpiperidin-1-carboxilato de tert-butilo (8,27 g, 29,6 mmol) en dioxano (10 mL). La reacción se agitó a temperatura ambiente durante 4 horas. La reacción se concentró para dar un aceite. Se agregó éter, y el sólido resultante se sonicó y luego se agitó enérgicamente durante la noche para dar un sólido color tostado. El sólido se filtró, se enjuagó con éter y se secó bajo vacío a 60 ºC durante 3 horas para dar 5,56 g (87%) del producto del título. MS (DCI) m/z 180 $(M+H)^+$.

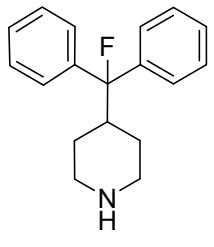


Intermediario 27A

4-(hidroxidifenilmetil)piperidin-1-carboxilato de tert-butilo

Una solución de dicarbonato de di-tert-butilo (8,43 mL, 36,7 mmol) en diclorometano (15 mL) se agregó a una solución de difenil(piperidin-4-il)metanol (8,0721 g, 30,2 mmol) en diclorometano (100 mL); se agregó trietilamina (5,1 mL, 36,6 mmol) y la reacción se agitó a temperatura ambiente durante 2 horas. La reacción se diluyó con diclorometano y luego se lavó con NaHCO3 acuoso saturado (2×), agua (1×), y salmuera

(1×), se secó (MgSO4) y se concentró para dar 11,63 g (105%) del compuesto del título. MS (ESI) m/z 367 $(M+H)^+$, 366 $(M-H)^+$.



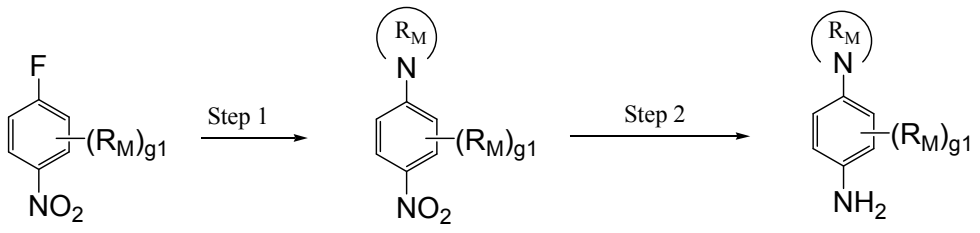
Intermediario 27B

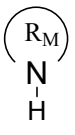
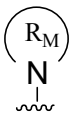
4-(fluorodifenilmetil)piperidina

El compuesto del título se preparó a partir de 4-(hidroxidifenilmetil)piperidin-1-carboxilato de tert-butilo usando los métodos generales de los Intermediarios 26A y 26B. 3,37 g (100%) como sal de HCl, MS (DCI) m/z 270 $(M+H)^+$.

Procedimientos Generales

Procedimiento General 1. Síntesis de anilinas 4-aminosustituidas



Las anilinas intermediarias con un grupo amino en posición para a la anilina pueden prepararse usando los un procedimiento en dos pasos. Puede hacerse reaccionar fluoronitrobencenos, fluoronitropiridinas, o fluoronitropirimidinas en el Paso 1 con una amina apropiada  , donde  representa cualquier grupo amina que está presente en RM y se une a través de nitrógeno, en presencia de fosfato de potasio dibásico (equivalentes) o carbonato de potasio en un solvente como por ejemplo DMSO opcionalmente con calentamiento e irradiación opcional de microondas. El Paso 2 puede

realizarse bajo condiciones de reducción de nitro estándar como por ejemplo hidrogenación catalítica usando paladio sobre carbono o níquel-Raney. De manera alternativa, la reducción puede efectuarse con hierro/cloruro de amonio en THF/metanol/agua como solvente. Donde el grupo  es una amina cíclica opcionalmente sustituida (por ejemplo, piperidina, pirrolidina), las aminas cíclicas opcionalmente sustituidas pueden obtenerse como se describe aquí o usando métodos conocidos en la especialidad. Véase por ejemplo los métodos mostrados en Patel et al. J Medicinal Chemistry 49(25) 7450 (2006).

Ilustración del Procedimiento General 1: Procedimiento General 1A

Paso 1

1-(2,6-difluoro-4-nitrofenil)-4-fenilpiperidina

En un balón de 100 mL se mezcló 3,4,5-trifluoronitrobenceno (1,751 mL, 15 mmol) y fosfato de potasio dibásico (5,23 g, 30,0 mmol) en DMSO (15,00 mL) para dar una suspensión amarilla. Se agregó 4-fenilpiperidina (2,419 g, 15,00 mmol) en porciones como un sólido a lo largo de 10 minutos para dar una suspensión color amarillo intenso y una reacción levemente exotérmica. La mezcla se agitó durante 1 hora y se particionó entre EtOAc y agua. La capa de EtOAc se lavó 2× con 50 mL con agua y salmuera, se secó (Na2SO4), se filtró y se concentró para dar el compuesto del título como un sólido amarillo (4,53 g, 95% de rendimiento).

Paso 2

3,5-difluoro-4-(4-fenilpiperidin-1-il)anilina

En un balón de 500 mL se agregó 1-(2,6-difluoro-4-nitrofenil)-4-fenilpiperidina (4,53 g, 14,23 mmol), hierro (3,97 g, 71,2 mmol), y cloruro de amonio (1,142 g, 21,35 mmol) en una mezcla de solventes de EtOH (60 mL)/THF (60 mL)/agua (20 mL). La mezcla se sometió a reflujo durante 3 horas con agitación vigorosa, se enfrió, se filtró a través de

tierras diatomeas y el material filtrado se concentró. El residuo se particionó entre acetato de etilo y agua. La capa orgánica se lavó con salmuera, se secó (Na2SO4), se filtró y se evaporó para dar el compuesto del título como un sólido amarillo (3,93 g, 96% de rendimiento). 1H RMN (400 MHz, DMSO-d6) ppm 1,63 - 1,81 (m, 4 H) 2,54 - 2,64 (m, 1 H) 2,95 - 3,03 (m, 2 H) 3,09 (t, J=10,57 Hz, 2 H) 5,42 (s, 2 H) 6,10 - 6,21 (m, 2 H) 7,15 - 7,22 (m, 1 H) 7,25 - 7,34 (m, 4 H); MS (ESI+) m/z 289 (M+H)+.

Ilustración del Procedimiento General 1: Procedimiento General 1B

Paso 1

5-nitro-2-(pirrolidin-1-il)piridina

A una suspensión 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 ºC durante 18 horas. La solución enfriada se concentró al vacío y el residuo se particionó entre CH2Cl2 y NaOH 1 M. La capa orgánica se secó (Na2SO4), se filtró y el solvente se eliminó al vacío para dar el compuesto del título (9,52 g, 78%). MS (ESI) m/z 194 (M+H)+.

Paso 2

6-(pirrolidin-1-il)piridin-3-amina

Se disolvió 5-nitro-2-(pirrolidin-1-il)piridina (9,52 g, 49,3 mmol) en THF (50 mL) y DMF (40 mL) y se agregó a un recipiente para presión que contenía níquel-Raney 2800 en suspensión acuosa (45%) (9,52 g, 162 mmol). La mezcla se agitó durante 2 horas a 30 psi bajo gas H2. La solución se filtró a través de una membrana de Nylon, se lavó con CH3OH y el material filtrado se concentró al vacío para dar el compuesto del título (7,78 g, 97%). 1H 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)+.

Ilustración del Procedimiento General 1. paso 2: Procedimiento General 1C

4-(3,5-dimetilpiperidin-1-il)-3,5-difluoroanilina

Se agregaron 1-(2,6-difluoro-4-nitrofenil)-3,5-dimetilpiperidina (14,01 g, 51,8 mmol) y THF (240 mL) a níquel-Raney 2800 en suspensión acuosa (14,01 g, 239 mmol) en una botella de presión de acero inoxidable de 500 mL. La mezcla se agitó durante 8 horas a 30 psi y temperatura ambiente. La mezcla se filtró a través de una membrana de Nylon y se concentró para dar el compuesto del título.

Ilustración del Procedimiento General 1. paso 2: Procedimiento General 1D

3-metil-4-(piperidin-1-il)anilina

A una solución de 1-(2-metil-4-nitrofenil)piperidina (6,75 g, 30,6 mmol) en acetato de etilo (50 mL) se agregó paladio sobre carbono 10% (0,033 g, 0,306 mmol) y la mezcla se hidrogenó (balón de hidrógeno) a temperatura ambiente durante 20 horas. La mezcla luego se filtró a través de tierras diatomeas y se lavó con acetato de etilo; el material filtrado luego se concentró para dar 5,5 g (94%) del compuesto del título. MS (ESI) m/z 191 (M+H)+.

Ilustración del Procedimiento General 1. paso 1: Procedimiento General 1E

1-(4-nitrofenil)-4-fenilpiperidina

Un tubo para microondas secado al horno de 20 mL se cargó con 4-fluoronitrobenceno (0,752 mL, 7,02 mmol), 4-fenilpiperidina (1,166 g, 7,02 mmol), y carbonato de potasio (0,970 g, 7,02 mmol) bajo nitrógeno, se agregó DMSO anhidro (7 mL), el tubo se selló con tapón de aluminio, y se calentó en un reactor de microondas (Personal Chemistry, 300 W, 2,4 bar) a 190 °C durante 10 minutos. El análisis por TLC (SiO_2, 5% EtOAc/hexanos) mostró que la reacción se había completado. La reacción se volcó sobre agua (50 mL), se agitó durante 5 minutos, y se filtró al vacío en un embudo Büchner. Los sólido amarillos que se recogieron se lavaron con agua (2×10 mL) y Et_2O (5 mL), y el sólido amarillo intenso se secó al vacío para dar el compuesto del título (1,712 g, 6,06 mmol, 86%). 1H RMN (400 MHz, $CDCl_3$) δ ppm 1,73 - 1,90 (m, 2 H), 2,00 (d, J=13,34 Hz, 2 H), 2,73 - 2,86 (m, 1 H), 3,02 - 3,17 (m, 2 H), 4,10 (d, J=13,23 Hz, 2 H),

6,87 (d, J=9,43 Hz, 2 H), 7,23 (t, J=7,75 Hz, 3 H), 7,33 (t, J=7,43 Hz, 2 H), 8,14 (d, J=9,33 Hz, 2 H); MS (ESI+) m/z 283 (M+H)+.

Las siguientes aminas pueden prepararse usando los métodos mostrados en el recién mencionado Procedimiento General 1:

4-(4,4-dimetilpiperidin-1-il)-3,5-difluoroanilina;

4-(2-azabiciclo[2,2,2]octan-2-il)-3,5-difluoroanilina;

3,5-difluoro-4-(4-isopropilpiperidin-1-il)anilina;

3,5-difluoro-4-(4-(trifluorometil)piperidin-1-il)anilina;

4-(4-tert-butilpiperidin-1-il)-3,5-difluoroanilina;

3,5-difluoro-4-(6-azaespiro[2,5]octan-6-il)anilina;

4-(3,3-dimetilazetidin-1-il)-3,5-difluoroanilina;

4-(4,4-difluoropiperidin-1-il)-3,5-difluoroanilina;

3,5-difluoro-4-(4-fluoropiperidin-1-il)anilina;

3,5-difluoro-4-(piperidin-1-il)anilina;

2,3,5,6-tetrafluoro-4-(piperidin-1-il)anilina;

3-metil-4-(piperidin-1-il)anilina;

3,5-difluoro-4-((3aR,7aS)-1H-isoindol-2(3H,3aH,4H,5H,6H,7H,7aH)-il)anilina;

N1-tert-butil-2-fluorobencen-1,4-diamina;

3,5-difluoro-4-(4-metilpiperidin-1-il)anilina;

3,5-dicloro-4-(piperidin-1-il)anilina;

2,5-difluoro-4-(piperidin-1-il)anilina;

4-((2R,6S)-2,6-dimetilpiperidin-1-il)-3,5-difluoroanilina;

2,3,5-trifluoro-4-(piperidin-1-il)anilina;

4-((1R,5S)-3-azabiciclo[3.2.0]heptan-3-il)-3,5-difluoroanilina;

3-fluoro-4-(piperidin-1-il)anilina;

3,5-difluoro-4-(3-azaespiro[5,5]undecan-3-il)anilina;

3,5-difluoro-4-(isoindolin-2-il)anilina;

3,5-difluoro-4-(1,4-dioxa-8-azaespiro[4,5]decan-8-il)anilina;

4-(4-fenil-5,6-dihidropiridin-1(2H)-il)anilina;

3-fluoro-4-(4-fenilpiperidin-1-il)anilina;

4-(4,4-difenilpiperidin-1-il)-3,5-difluoroanilina;

4-(4-fenilpiperidin-1-il)anilina;

1-(1-(4-amino-2,6-difluorofenil)-4-fenilpiperidin-4-il)etanona;

3,5-difluoro-4-(4-(3-fenilpropil)piperidin-1-il)anilina;

3,5-difluoro-4-(8-azaespiro[4,5]decan-8-il)anilina;

3,5-difluoro-4-(3-fenilpiperidin-1-il)anilina;

3,5-difluoro-4-(3-fenilpirrolidin-1-il)anilina;

3,5-difluoro-4-(4-(4-(trifluorometil)fenil)piperazin-1-il)anilina;

3,5-difluoro-4-(4-fenilpiperazin-1-il)anilina;

4-(4-(2,6-difluorofenil)piperazin-1-il)-3,5-difluoroanilina;

3,5-difluoro-4-(4-(pirimidin-2-il)piperazin-1-il)anilina;

3,5-difluoro-4-(2-fenilmorfolino)anilina;

(S)-3,5-difluoro-4-(2-fenilmorfolino)anilina

3,5-difluoro-4-(2-fenilpiperidin-1-il)anilina;

4-((2S,6R)-2,6-dimetilmorfolino)-3,5-difluoroanilina;

4-(4-ciclohexilpiperidin-1-il)-3,5-difluoroanilina;

4-(4-bencilpiperidin-1-il)-3,5-difluoroanilina;

3,5-difluoro-4-(4-(4-metoxifenil)piperidin-1-il)anilina;

3,5-difluoro-4-(4-(4-fluorofenil)piperidin-1-il)anilina;

4-(4-(3,4-difluorofenil)piperidin-1-il)-3,5-difluoroanilina;

4-(4-(3,5-difluorofenil)piperidin-1-il)-3,5-difluoroanilina;

3,5-difluoro-4-(4-fluoro-4-fenilpiperidin-1-il)anilina;

3,5-difluoro-4-(4-(fluorodifenilmetil)piperidin-1-il)anilina;

4-(4-fluoro-4-fenilpiperidin-1-il)anilina;

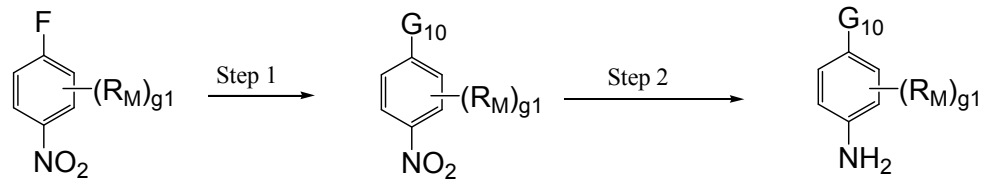
3,5-difluoro-4-(4-(piridin-2-il)piperidin-1-il)anilina;

3,5-difluoro-4-(4-(naftalen-2-il)piperidin-1-il)anilina;

3,5-difluoro-4-(4-(naftalen-1-il)piperidin-1-il)anilina; y

3,5-difluoro-4-(4-(4-(trimetilsilil)fenil)piperidin-1-il)anilina.

Procedimiento General 1.1. anilina4-alcoxi-sustituida



Las anilinas intermediarias con un sustituyente alcoxi en posición para a la anilina pueden prepararse a través de un procedimiento en dos pasos donde G10 es –ORS (por ejemplo, –O–t-butilo, –O–isopropilo, –O–CH2–(3-etiloxetan-3-ilo), –O–CH2–(1,3-dioxolan-4-ilo), –O–ciclopentilo, –O–ciclohexilo, –O–(1,3-dioxan-5-ilo)). En el Paso 1, los fluoronitrobencenos pueden hacerse reaccionar con un alcohol y una base apropiados (por ejemplo, Cs2CO3, tert-butóxido de potasio) en DMSO o un solvente similar con calentamiento a entre 50-100 ºC. El Paso 2 puede realizarse bajo condiciones de reducción de nitro estándar como por ejemplo hidrogenación catalítica usando paladio sobre carbono o níquel de Raney como se describe en la presente. De manera alternativa, la reducción puede efectuarse con hierro/cloruro de amonio en THF/metanol/agua como solvente.

Ilustración del Procedimiento General 1.1: Procedimiento General 1.1A

Paso 1

3-etil-3-((4-nitrofenoxi)metil)oxetano

A una solución de 4-fluoronitrobenceno (3,76 mL, 35,4 mmol) en DMSO (35 mL) a temperatura ambiente se agregó carbonato de cesio (7,09 mL, 89,0 mmol) seguido por 3-etil-3-oxetanometanol (4,48 mL, 42,5 mmol). La mezcla se calentó a 70 ºC durante 2 horas. Luego de enfriar se agregó agua y el precipitado resultante se filtró, se lavó con

agua, y se secó en un horno de vacío para dar el compuesto del título (8,28 g, 98% de rendimiento).

Paso 2

4-((3-etiloxetan-3-il)metoxi)anilina

A una solución de 3-etil-3-((4-nitrofenoxi)metil)oxetano (8,28 g, 34,9 mmol) en una mezcla de THF:EtOH:agua 3:3:1 (140 mL) a temperatura ambiente se agregó cloruro de amonio (2,80 g, 52,3 mmol) seguido por polvo de hierro (9,74 g, 174 mmol). La mezcla se calentó a 90 ºC durante 1 hora, luego se filtró en caliente a través de tierras diatomeas y se lavó con THF para completar la transferencia. El material filtrado se concentró bajo presión reducida, y el residuo se recogió en acetato de etilo y luego se lavó con salmuera, se secó (Na2SO4), y se concentró para dar el compuesto del título (7,12 g, 98% de rendimiento) sin purificación adicional.

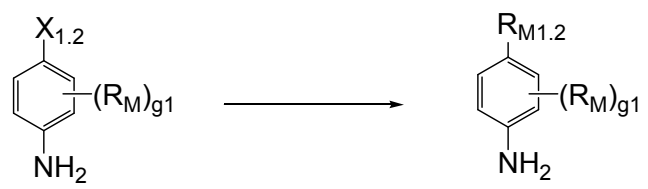
Las siguientes aminas pueden prepararse usando los métodos mostrados en el recién mencionado Procedimiento General 1:

4-((3-etiloxetan-3-il)metoxi)-3,5-difluoroanilina;

4-((1,3-dioxolan-4-il)metoxi)anilina;

4-(1,3-dioxan-5-iloxi)anilina.

Procedimiento General 1.2. Formación de anilina a través de una reacción de tipo Suzuki



Ciertas anilinas intermediarias pueden prepararse a partir de un bromuro, ioduro, o triflato (por ejemplo, X1,2 = Br, I, o OTf) a través de una reacción de Suzuki, Stille, u otra reacción de formación de enlace carbono-carbono mediada por un metal de transición para formar productos donde RM1.,2 es cicloalquilo, arilo, heteroarilo, o cicloalquenilo. Precedentemente se ilustra el proceso que se lleva a cabo sobre la anilina, sin embargo,

el proceso tambien puede llevarse a cabo usando otra funcionalidad que pueda convertirse a una anilina (por ejemplo, un grupo nitro).

Ilustración del Procedimiento General 1.2. Procedimiento General 1.2A.

4-(ciclohexen-1-il)-3-fluoroanilina

En un tubo para presión, una solución de 3-fluoro-4-yodoanilina (2,29 g, 9,66 mmol) y carbonato de potasio (1,74 g, 12,58 mmol) en dimetoxietano-agua 4:1 (33 mL) se desgasificó por burbujeo de nitrógeno durante 40 minutos, y luego se agregó pinacoléster de ácido 1-ciclohexenilborónico (2,7 mL, 2,61 g, 12,56 mmol). Luego se agregó complejo cloruro de 1,1'-bis(difenilfosfino)ferrocenpaladio (II) diclorometano (237 mg, 0,29 mmol) y luego se desgasificó durante otros 5 minutos. El tubo de presión se selló y se calentó a 100 ºC durante 18 horas. La mezcla se enfrió y se diluyó con acetato de etilo, y luego se extrajo con agua y solución saturada de cloruro de sodio. La solución se secó (Na2SO4) y se agitó con gel de 3-(mercaptopropil)sílice durante 1 hora. La concentración al vacío dio un aceite marrón, que se cromatografió sobre un cartucho de gel de sílice de 340 g, eluyendo con acetato de etilo en hexanos 10-100%. Se obtuvo el compuesto del título (1,16 g, 63%) como un aceite marrón claro. 1H RMN (400 MHz, CDCl3) □ ppm 7,00 (m, 1 H), 6,37 (m, 2 H), 5,84 (s, 1 H), 3,71 (s ancho, 2 H), 2,32 (m, 2 H), 2,17 (m, 2 H), 1,73 (m, 2 H), 1,65 (m, 2 H); MS (+DCI) m/z (abundancia relativa) 192 (100, M+H).

Ilustración del Procedimiento General 1.2. Procedimiento General 1.2B.

4-ciclopropil-3,5-difluoroanilina

A un tubo de presión se agregó 4-bromo-3,5-difluoroanilina (1,0g, 4,8 mmol), carbonato de cesio (4,7g, 14,4 mmol), tolueno (10mL) y agua (1mL). La solución se desgasificó con gas N2 durante 30 minutos, y luego se agregó ciclopropiltrifluoroborato, sal de potasio (0,8g, 5,3 mmol), iodhidrato de di(1-adamantil)-n-butilfosfina (0,07g, 0,14 mmol) y acetato de paladio(II) (0,02g, 0,096 mmol). Se continuó la desgasificación durante 5 minutos, el tubo se selló y se calentó a 100 ˚C durante 18 horas. La solución enfriada se diluyó con EtOAc, se lavó con H2O y salmuera, se secó (Na2SO4), y se filtró. El material

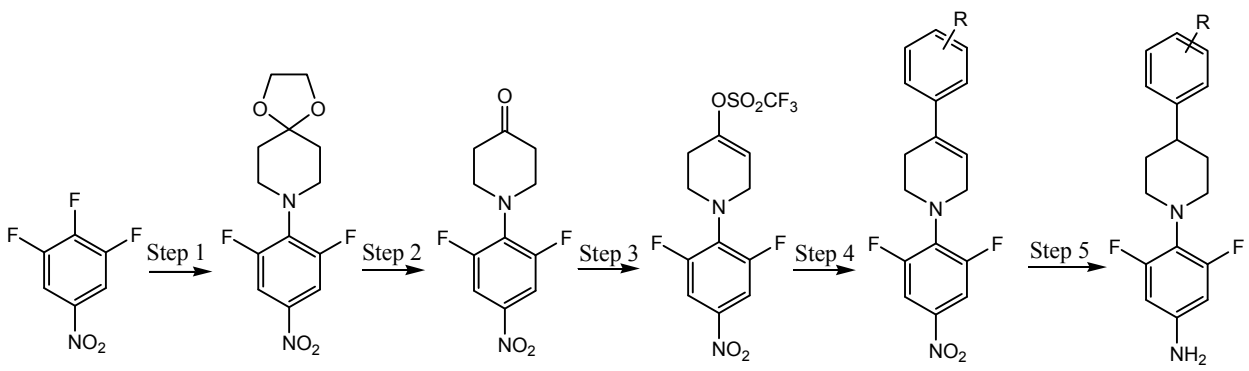
filtrado se trató con gel de 3-mercaptopropilsílice durante 1 hora. La mezcla se filtró y se concentró para dar el producto crudo el cual se purificó mediante cromatografía flash (EtOAc/hexano 0-30%) para dar el compuesto del título (0,67 g, 4,0 mmol, 82%).

Ilustración del Procedimiento General 1.2. Procedimiento General 1.2C.

4-ciclopropil-2-fluoro-1-nitrobenceno

Una solución de 4-bromo-2-fluoronitrobenceno (0,5g, 2,27mmol), ácido ciclopropilborónico (0,293g, 3,41mmol), fosfato de potasio tribásico (0,965g, 4,55mmol), tetrafluoroborato de triciclohexilfosfonio (0,021g, 0,057mmol) y acetato de paladio (II) (6,12mg 0,027mmol) en 11 mL de una mezcla de tolueno–agua 10:1 (v/v) se purgó con nitrógeno y se desgasificó al vacío tres veces. La mezcla de reacción luego se calentó en un baño de aceite a 85ºC durante cuatro horas. La mezcla de reacción se particionó con acetato de etilo y la fase orgánica se lavó con agua y luego se secó (Na2SO4) y se concentró. La mezcla de reacción se particionó entre acetato de etilo y agua. La fase orgánica se lavó con agua, se secó (Na2SO4) y se concentró. El producto crudo se purificó mediante cromatografía sobre gel de sílice (acetato de etilo–hexano) para dar el compuesto del título (0,382g, 88%) como un aceite amarillo.

Procedimiento General 1.3



Ciertas anilinas intermediarias pueden prepararse usando la secuencia general que se ha expuesto y que se ilustra más adelante. La secuencia consiste en la reacción de un fluoronitrobenceno con una porción amina cíclica (Paso 1); la conversion a un compuesto capaz de someterse a acoplamiento vinílico (Pasos 2 y 3); el acoplamiento del

compuesto capaz de someterse a acoplamiento vinílico con otro compuesto adecuado (Paso 4); y la reducción del grupo nitro y la olefina (Paso 5). De manera alternativa, esta ruta puede adaptarse para preparar anilinas donde la olefina se mantiene intacta a lo largo de la reducción selectiva del grupo nitro. Las reacciones de formación de unlace carbono-carbono que pueden ser adecuadas para el Paso 4 incluyen, por ejemplo, la reacción de Suzuki, la reacción de Stille, o la reacción de Negishi.

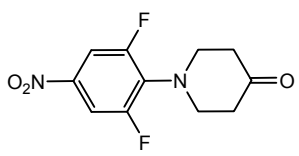
Ilustración del Procedimiento General 1.3: Procedimiento General 1.3A

Paso 1

8-(2,6-difluoro-4-nitrofenil)-1,4-dioxa-8-azaespiro[4,5]decano

Una mezcla de 1,2,3-trifluoro-5-nitrobenceno (4,0 mL, 34,3 mmol), 1,4-dioxa-8-azaespiro[4,5]decano (6,59 mL, 51,4 mmol) y carbonato de potasio (5,68 g, 41,1 mmol) en DMSO (35 mL) se calentó a 100 ºC durante 3 horas y luego se enfrió a temperatura ambiente. La mezcla se particionó entre agua y EtOAc, y la capa orgánica se secó sobre Na2SO4, se filtró y se concentró al vacío. El producto crudo se purificó mediante cromatografía en columna de gel de sílice usando un gradiente de solventes de EtOAc en hexanos 0-20% para dar un aceite amarillo.

Paso 2

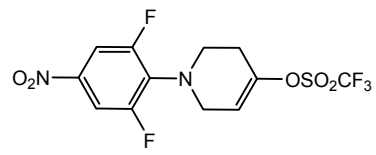


1-(2,6-difluoro-4-nitrofenil)piperidin-4-ona

El 8-(2,6-difluoro-4-nitrofenil)-1,4-dioxa-8-azaespiro[4,5]decano crudo del procedimiento anterior se disolvió en acetona:agua 4:1 (100 mL). Se agregó HCl concentrado (5 mL), y la mezcla resultante se agitó a 50 ºC durante 8 horas y luego se enfrió a temperatura ambiente. La mezcla se concentró al vacío para dar aproximadamente 20 mL, que se agregó cuidadosamente a NaHCO3 acuoso concentrado (100 mL) y se extrajo con EtOAc (2 x 100 mL). Los extractos orgánicos combinados se

secaron sobre Na2SO4, se filtró y se concentró al vacío. El producto crudo se trituró con Et2O y hexanos para dar un sólido amarillo intenso que se recogió y se secó para dar el compuesto del título (7,13 g, 81%).

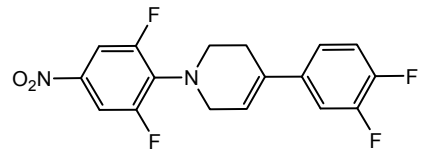
Paso 3



trifluorometansulfonato de 1-(2,6-difluoro-4-nitrofenil)-1,2,3,6-tetrahidropiridin-4-ilo

A una solución de 1-(2,6-difluoro-4-nitrofenil)piperidin-4-ona (5,0 g, 19,52 mmol) en THF anhidro (50 mL) a -78 ºC bajo una atmósfera de N2 seco se agregó una solución de THF 1 M de bis(trietilsilil)amida de litio (29,3 ml, 29,3 mmol) en THF por goteo a lo largo de 10 minutos. La solución color rojo intenso resultante se agitó a -78 ºC durante 5 minutos y se agregó 1,1,1-trifluoro-N-fenil-N-(trifluorometilsulfonil)metansulfonamida (7,67 g, 21,47 mmol). La mezcla resultante se agitó a - 78 ºC durante 1 hora, y luego la mezcla se dejó calentar a temperatura ambiente. La mezcla se diluyó con EtOAc (100 mL) y se lavó con NaOH acuoso 1 N (50 mL) y agua (50 mL), y se secó sobre Na2SO4. El agente de secado se retiró por filtración, y el solvente se eliminó al vacío para dar un producto crudo que se purificó mediante cromatografía en columna de gel de sílice usando un gradiente de solventes de EtOAc en hexanos 0-40%. El compuesto del título se obtuvo como un aceite amarillo que cristalizó al vacío (6,12 g, 81%).

Paso 4 (Reacción de Suzuki)

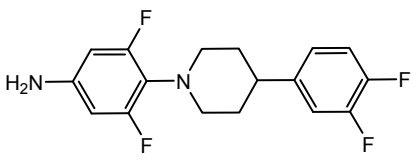


1-(2,6-difluoro-4-nitrofenil)-4-(3,4-difluorofenil)-1,2,3,6-tetrahidropiridina

Una mezcla de trifluorometansulfonato de 1-(2,6-difluoro-4-nitrofenil)-1,2,3,6-tetrahidropiridin-4-ilo (1,18 g, 3,04 mmol), 2-(3,4-difluorofenil)-4,4,5,5-tetrametil-1,3,2-

dioxaborolano (1,02 g, 4,25 mmol), cloruro de litio (0,387 g, 9,12 mmol) y una solución acuosa de carbonato de sodio 2,0 M (4,56 mL, 9,12 mmol) en DME anhidro (15 mL) se agitó enérgicamente burbujeando con gas N2 durante 20 minutos. Se agregó tetrakis(trifenilfosfin)paladio(0) (0,176 g, 0,152 mmol), y la mezcla resultante se desgasificó durante 5 minutos más. El recipiente de la reacción se equipó con un condensador y se colocó en un baño de aceite de 100 ºC. La mezcla oscura se agitó a 100 ºC bajo una atmósfera de N2 seco durante 16 horas, y luego se enfrió a temperatura ambiente y se particionó entre agua (50 mL) y EtOAc (2×50 mL). Las capas orgánicas combinadas se secaron sobre Na2SO4, se filtró y se concentró al vacío, y el producto crudo se purificó mediante cromatografía en columna de gel de sílice usando un gradiente de solventes de EtOAc en hexanos 0-40% para dar un aceite amarillo que solidificó al dejarse en reposo. El sólido se trituró con Et2O y hexanos, se filtró y se secó para dar el compuesto del título (0,67 g, 63%).

Paso 5



(4-(4-(3,4-difluorofenil)piperidin-1-il)-3,5-difluoroanilina

A una solución de 1-(2,6-difluoro-4-nitrofenil)-4-(3,4-difluorofenil)-1,2,3,6-tetrahidropiridina (0,67 g, 1,90 mmol) en THF (20 mL) se agregó Pd sobre carbono al 10% (50 mg). El recipiente de la reacción se purgó con gas N2, y la mezcla resultante se agitó enérgicamente bajo 1 atm de gas H2 durante 24 horas. La mezcla se filtró a través de tierras diatomeas y se concentró al vacío para dar el compuesto del título como un sólido (0,62 g, 100%).

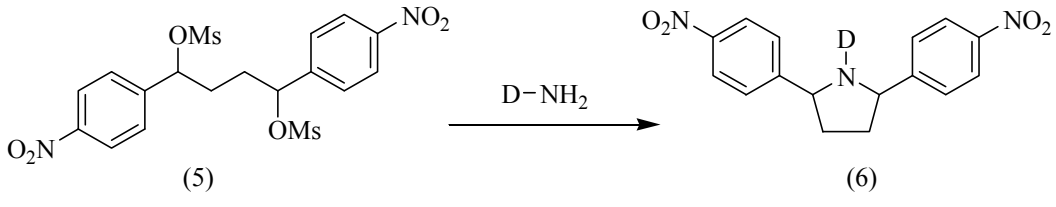
Las siguientes aminas pueden prepararse usando los métodos mostrados en el recién mencionado Procedimiento General 1.3:

3,5-difluoro-4-(4-(4-fluorofenil)piperidin-1-il)anilina;

3,5-difluoro-4-(4-(3-(trimetilsilil)fenil)piperidin-1-il)anilina; y

3,5-difluoro-4-(4-(5-metiltiofen-2-il)piperidin-1-il)anilina.

Procedimiento General 2. Formación de pirrolidina a partir de amina y dimesilato (5)



(5) (6)

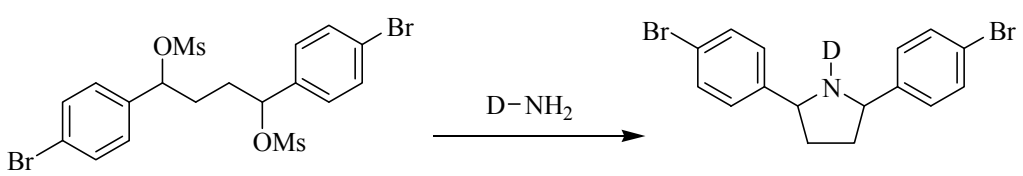
Un dimesilato (5) (1 equivalente), como estereoisómero aislado o mezcla de isómeros, puede hacerse reaccionar con entre 1 y 20 equivalentes de una amina,.D-NH2, puro, o en solventes como por ejemplo tetrahidrofurano o 2-metiltetrahidrofurano con o sin un cosolvente como por ejemplo DMF, a entre aproximadamente temperatura ambiente y aproximadamente 100 ºC, para dar las pirrolidinas como por ejemplo la Fórmula (6). Cuando se utilizan menos equivalentes de amina, D-NH2, (por ejemplo, 1-2 equivalentes), puede agregarse una base como por ejemplo diisopropiletilamina para promover la reacción. Por ejemplo, la reacción de un dimesilato (1 equivalente) con un exceso de una anilina, D-NH2, (aproximadamente 5-10 equivalentes) puede llevarse a cabo por calentamiento a entre 50 y 65 ºC en 2-metiltetrahidrofurano o DMF hasta completarse la reacción. También el dimesilato (1 equivalente) pueden hacerse reaccionar en forma pura con un exceso de una anilina, D-NH2, (aproximadamente 15-20 equivalentes) a temperatura ambiente o con calentamiento a aproximadamente 65 ºC. La reacción puede particionarse entre un solvente orgánico (por ejemplo, acetato de etilo) y HCl acuoso diluido, y luego puede separarse la capa orgánica, opcionalmente lavarse el material orgánico con agua, secarse la capa orgánica con un agente de secado (por ejemplo, MgSO4, Na2SO4), filtrarse y evaporarse el solvente. El producto puede purificarse mediante cromatografía en columna de gel de sílice, eluyendo con solventes estándar como por ejemplo mezclas de acetato de etilo y hexano; o de manera alternativa el producto puede purificarse por trituración o recristalización.

Ilustración del Procedimiento General 2: Procedimiento General 2A

(2S,5S)-1-(4-tert-butilfenil)-2,5-bis(4-nitrofenil)pirrolidina

A la solución de producto crudo del Intermediario 6C (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 durante 2 horas. Una vez completa la reacción, la mezcla de reacción se enfrió a 23 °C y se diluyó con 2-metiltetrahidrofurano (100 mL) y HCl 1 M (150 mL). Después de particionar las fases, la fase orgánica se trató con HCl 1 M (140 mL), 2-metiltetrahidrofurano (50 mL), y NaCl acuoso 25 % en peso (100 mL), y las fases se particionaron. La fase orgánica se lavó con NaCl acuoso 25 % en peso (50 mL), se secó sobre MgSO4, se filtró, y se concentró al vacío para dar aproximadamente 20 mL. Se agregaron heptano (30 mL) y más 2-metiltetrahidrofurano para inducir cristalización. La suspensión se concentró adicionalmente, y se agregó más heptano (40 mL) lentamente y la suspensión se filtró, lavando con 2-metiltetrahidrofuran:heptano (1:4, 20 mL). Los sólidos se suspendieron en CH3OH (46 mL) durante 3 horas, se filtró, y el sólido húmedo se lavó con más CH3OH (18 mL). El sólido se secó a 45 °C en un horno de vacío durante 16 horas para dar el compuesto del título (3,08 g).

Procedimiento General 3. Formación de pirrolidina a partir de amina y bisbromofenildimesilato



El Procedimiento General 3 puede llevarse a cabo usando condiciones sustancialmente similares a las condiciones del Procedimiento General 2.

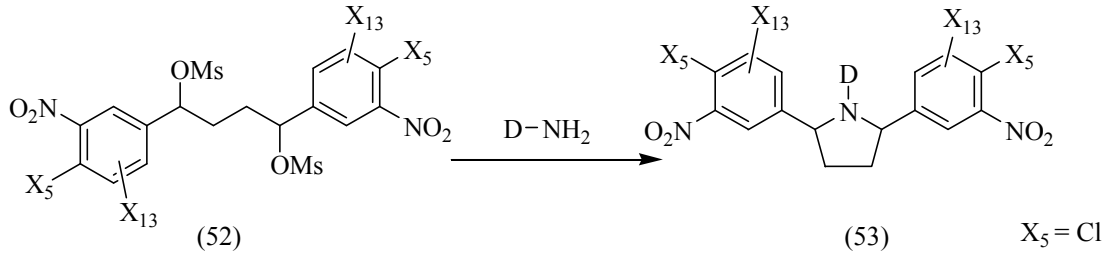
Ilustración del Procedimiento General 3: Procedimiento General 3A

(2S,5S)-2,5-bis(4-bromofenil)-1-(4-tert-butilfenil)pirrolidina

El Intermediario 7C 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 ºC durante 4 horas, y

luego se particionó entre HCl acuoso 1 N (30 mL) y EtOAc (30 mL). La capa orgánica se lavó con H2O y se secó sobre Na2SO4. El agente de secado se retiró por filtración, el solvente se eliminó al vacío, y el producto crudo se purificó mediante cromatografía en columna de gel de sílice usando un gradiente de solventes de EtOAc en hexanos 0-20%. El compuesto del título se obtuvo como un sólido incoloro (0,71 g, 92%). El análisis por 1H RMN indicó que este material era una mezcla 87:13 de isómeros trans:cis de pirrolidina.

Procedimiento General 4. Formación de pirrolidina a partir de amina y dimesilato (52)



El Procedimiento General 4 puede llevarse a cabo usando condiciones sustancialmente similares a las condiciones del Procedimiento General 2. Por ejemplo, un dimesilato (52) (1 equivalente), como estereoisómero aislado o mezcla de isómeros, pueden hacerse reaccionar con entre 1 y 20 equivalentes de una amina D-NH2 pura, o en solventes o mezclas de solventes incluyendo etanol, acetonitrilo, cloruro de metileno, tetrahidrofurano , 2-metiltetrahidrofurano, DMF, o DMA, a entre aproximadamente temperatura ambiente y aproximadamente 100 ºC, para dar las pirrolidinas como por ejemplo las de la Fórmula (53). De manera alternativa, un dimesilato (52) (1 equivalente) puede hacerse reaccionar con una amina D–NH2 (1-4 equivalentes) en presencia de una base como diisopropiletilamina (3-10 equivalentes) en solventes o mezclas de solventes incluyendo cloruro de metileno, tetrahidrofurano, 2-metiltetrahidrofurano, DMF, o DMA a temperaturas desde aproximadamente temperatura ambiente hasta aproximadamente 70 ºC. Cuando se utilizan menos equivalentes de amina D-NH2 (por ejemplo, 1-2 equivalentes), puede agregarse una mayor cantidad de una base (aproximadamente 8-10 equivalentes) como por ejemplo diisopropiletilamina para promover la reacción. Para las aminas menos reactivas (por ejemplo, 2,5-difluoro-4-(trifluorometil)anilina, 2-fluoropiridin-

4-amina), puede ser necesario un tiempo de reacción de varios días. La reacción puede particionarse entre un solvente orgánico (por ejemplo, acetato de etilo) y agua o HCl acuoso diluido, luego puede separarse la capa orgánica, opcionalmente lavarse el material orgánico con agua y/o salmuera, secarse la capa orgánica con un agente de secado (por ejemplo, MgSO4, Na2SO4), filtrarse y evaporarse el solvente. El producto (53) puede purificarse mediante cromatografía en columna de gel de sílice, eluyendo con solventes estándar como por ejemplo mezclas de acetato de etilo y hexano o cloruro de metileno en hexano. El sistema cloruro de metileno/hexano puede utilizarse para eliminar la amina residual en los casos donde la reacción se detiene en agua en lugar de HCl acuoso. En dichos casos puede ser necesaria una segunda cromatografía usando un sistema de acetato de etilo/hexano para separar los productos pirrolidina cis y trans. De manera alternativa, el producto puede purificarse por trituración o recristalización.

Ilustración del Procedimiento General 4: Procedimiento General 4A

(2R,5R)-2,5-bis(4-cloro-3-nitrofenil)-1-(4-ciclohexilfenil)pirrolidina

Al Intermediario 5D (4,99 mmol) en dimetilformamida (8 mL) se agregó 4-ciclohexilanilina (5,24 g, 29,9 mmol), y la solución se calentó a 65 ºC durante 2 horas. La mezcla de reacción luego se volcó sobre HCl 1 M y se extrajo con diclorometano. La fase orgánica se concentró y se purificó con una columna de sílice CombiFlash® de 80g eluyendo con acetato de etilo en hexanos 0-20% para dar 1,38 g (51%) del compuesto del título.

Ilustración del Procedimiento General 4: Procedimiento General 4B

1-(4-((2R,5R)-2,5-bis(4-cloro-3-nitrofenil)pirrolidin-1-il)-2,6-difluorofenil)-4-fenilpiperidina

Un recipiente de 250 mL se cargó con 3,5-difluoro-4-(4-fenilpiperidin-1-il)anilina (3,1 g, 10,76 mmol), el Intermediario 5D (5,0 g, 8,97 mmol), DMF (15 mL) y diisopropiletilamina (15,7 mL, 90 mmol). La suspensión resultante se colocó en un baño de aceite a 60 ºC y se calentó bajo N2 durante 18 horas. La solución ámbar se enfrió, se diluyó con 300 mL de acetato de etilo, se lavó 2×100 mL de agua, 2×100 mL de HCl 1 N,

salmuera, se secó (Na2SO4), se filtró y se concentró. El material crudo se sometió a cromatografía en un cartucho de sílice de 330 g eluyendo con diclorometano en hexano 50-80% para eliminar la anilina sin reaccionar. Las fracciones de la columna que contenían el producto se combinaron y se concentró para dar un sólido anaranjado que se disolvió en 20 mL de acetato de etilo caliente, se trató con 15 mL de hexano, y se dejó agitar a temperatura ambiente durante la noche para producir un precipitado (pirrolidina cis) que se retiró mediante filtración. El material filtrado se concentró y se sometió a cromatografía nuevamente en un cartucho de sílice de 330 g eluyendo con cloruro de metileno en hexano 40-70% para dar 1-(4-((2R,5R)-2,5-bis(4-cloro-3-nitrofenil)pirrolidin-1-il)-2,6-difluorofenil)-4-fenilpiperidina como una espuma anaranjada (2,26 g, 36%). MS (ESI+) m/z 653 (M+H)+.

Ilustración del Procedimiento General 4: Procedimiento General 4C

1-(4-((2R,5R)-2,5-bis(4-cloro-3-nitrofenil)pirrolidin-1-il)-2-fluorofenil)-4-fenilpiperidina

El Intermediario 5D (6,0 g, 10,76 mmol), 3-fluoro-4-(4-fenilpiperidin-1-il)anilina (4,37 g, 16,15 mmol), y diisopropiletilamina (15,04 mL, 86 mmol) se combinaron en N,N-dimetilacetamida (15 mL) y se calentó a 60 ºC durante 3 horas. La solución se diluyó con agua, se extrajo con diclorometano y se lavó con salmuera. Los materiales orgánicos se concentraron y se purificó mediante cromatografía, eluyendo con diclorometano en hexanos 30-100% para dar 5,05 g (74%) de un sólido amarillo.

Ilustración del Procedimiento General 4: Procedimiento General 4D

(2R,5R)-2,5-bis(4-cloro-3-nitrofenil)-1-(4-etoxifenil)pirrolidina

El Intermediario 5D (2,5805 g, 4,63 mmol) y 4-etoxianilina (2,4 mL, 18,60 mmol) se combinaron en DMF (30 mL) y se agitó a temperatura ambiente durante la noche. La reacción se diluyó con EtOAc/éter y se lavó con agua (2×), salmuera (1×) y se concentró. El residuo se purificó mediante cromatografía sobre gel de sílice (hexano/EtOAc) para dar 1,8 g del compuesto del título (77%).

Ilustración del Procedimiento General 4: Procedimiento General 4E

1-(4-((2R,5R)-2,5-bis(4-cloro-2-fluoro-5-nitrofenil)pirrolidin-1-il)-2,6-difluorofenil)piperidina

A una solución de dimetansulfonato de (1S,4S)-1,4-bis(4-cloro-2-fluoro-5-nitrofenil)butan-1,4-diilo (500 mg, 0,843 mmol) en CH3CN (4,5 ml) se agregó 3,5-difluoro-4-(piperidin-1-il)anilina (358 mg, 1,685 mmol) y base de Hunig (0,736 mL, 4,21 mmol). La suspensión se calentó a 75 ºC durante 24 horas. El solvente se eliminó por evaporación por rotación y el residuo se disolvió en EtOAc, se lavó con HCl 1 N, H_2O, salmuera, se secó ($MgSO_4$), se filtró y se concentró. El producto crudo se cromatografió sobre un cartucho de gel de sílice ISCO de 24g eluyendo con CH_2Cl_2/hexano 20-70% para dar el compuesto del título con algo del isómero cis de pirrolidina correspondiente.

Las siguientes pirrolidinas sustituidas pueden prepararse usando los los métodos generales precedentes:

1-(4-((2R,5R)-2,5-bis(4-cloro-3-nitrofenil)pirrolidin-1-il)-2,6-difluorofenil)-4,4-dimetilpiperidina;

2-(4-((2R,5R)-2,5-bis(4-cloro-3-nitrofenil)pirrolidin-1-il)-2,6-difluorofenil)-2-azabiciclo[2,2,2]octano;

1-(4-((2R,5R)-2,5-bis(4-cloro-3-nitrofenil)pirrolidin-1-il)-2,6-difluorofenil)-4-isopropilpiperidina;

1-(4-((2R,5R)-2,5-bis(4-cloro-3-nitrofenil)pirrolidin-1-il)-2,6-difluorofenil)-4-(trifluorometil)piperidina;

1-(4-((2R,5R)-2,5-bis(4-cloro-3-nitrofenil)pirrolidin-1-il)-2,6-difluorofenil)-4-tert-butilpiperidina;

6-(4-((2R,5R)-2,5-bis(4-cloro-3-nitrofenil)pirrolidin-1-il)-2,6-difluorofenil)-6-azaespiro[2,5]octano;

1-(4-((2R,5R)-2,5-bis(4-cloro-3-nitrofenil)pirrolidin-1-il)-2,6-difluorofenil)-4,4-dimetilpiperidina;

(2R,5R)-2,5-bis(4-cloro-3-nitrofenil)-1-(4-(3,3-dimetilazetidin-1-il)-3,5-difluorofenil)pirrolidina;

(2R,5R)-2,5-bis(4-cloro-3-nitrofenil)-1-(4-fenoxifenil)pirrolidina;

1-(4-((2R,5R)-2,5-bis(4-cloro-3-nitrofenil)pirrolidin-1-il)fenil)piridin-2(1H)-ona;

(2R,5R)-2,5-bis(4-cloro-3-nitrofenil)-1-(2,5-difluoro-4-(trifluorometil)fenil)pirrolidina;

2-(4-((2R,5R)-2,5-bis(4-cloro-3-nitrofenil)pirrolidin-1-il)fenil)oxazol;

4-((2R,5R)-2,5-bis(4-cloro-3-nitrofenil)pirrolidin-1-il)-2-fluoropiridina;

(2R,5R)-1-(4-cloro-3-fluorofenil)-2,5-bis(4-cloro-3-nitrofenil)pirrolidina;

1-(4-((2R,5R)-2,5-bis(4-cloro-3-nitrofenil)pirrolidin-1-il)-2,6-difluorofenil)-4,4-difluoropiperidina;

1-(4-((2R,5R)-2,5-bis(4-cloro-3-nitrofenil)pirrolidin-1-il)-2,6-difluorofenil)-4-fluoropiperidina;

1-(4-((2R,5R)-2,5-bis(4-cloro-3-nitrofenil)pirrolidin-1-il)-2,6-difluorofenil)piperidina;

(2R,5R)-2,5-bis(4-cloro-3-nitrofenil)-1-(4-fluorofenil)pirrolidina;

(2R,5R)-1-(4-tert-butilfenil)-2,5-bis(4-cloro-3-nitrofenil)pirrolidina;

(2R,5R)-2,5-bis(4-cloro-3-nitrofenil)-1-(4-ciclopropil-3,5-difluorofenil)pirrolidina;

(2R,5R)-2,5-bis(4-cloro-3-nitrofenil)-1-(4-ciclohexil-3-fluorofenil)pirrolidina;

(2R,5R)-2,5-bis(4-cloro-3-nitrofenil)-1-(3,4-difluorofenil)pirrolidina;

(2R,5R)-2,5-bis(4-cloro-3-nitrofenil)-1-(4-(2,2-difluoroetoxi)fenil)pirrolidina;

1-(4-((2R,5R)-2,5-bis(4-cloro-3-nitrofenil)pirrolidin-1-il)-2,6-difluorofenil)-3,5-dimetilpiperidina;

(2R,5R)-2,5-bis(4-cloro-3-nitrofenil)-1-[4-(pentafluoro-λ6-sulfanil)fenil]pirrolidina (Nomenclatura ACD v12);

2-(4-((2R,5R)-2,5-bis(4-cloro-3-nitrofenil)pirrolidin-1-il)fenil)piridina;

(2R,5R)-2,5-bis(4-cloro-3-nitrofenil)-1-(3-cloro-4-(trifluorometoxi)fenil)pirrolidina;

(2R,5R)-2,5-bis(4-cloro-3-nitrofenil)-1-(4-(2-metoxietoxi)-3-metilfenil)pirrolidina;

(2R,5R)-2,5-bis(4-cloro-3-nitrofenil)-1-(4-clorofenil)pirrolidina;

(2R,5R)-2,5-bis(4-cloro-3-nitrofenil)-1-(4-((3-etiloxetan-3-il)metoxi)fenil)pirrolidina;

(2R,5R)-1-(bifenil-4-il)-2,5-bis(4-cloro-3-nitrofenil)pirrolidina;

(2R,5R)-1-(4-(1,3-dioxan-5-iloxi)fenil)-2,5-bis(4-cloro-3-nitrofenil)pirrolidina;

(2R,5R)-1-(4-((1,3-dioxolan-4-il)metoxi)fenil)-2,5-bis(4-cloro-3-nitrofenil)pirrolidina;

(2R,5R)-2,5-bis(4-cloro-3-nitrofenil)-1-(4-((3-etiloxetan-3-il)metoxi)-3,5-difluorofenil)pirrolidina;

1-(4-((2R,5R)-2,5-bis(4-cloro-3-nitrofenil)pirrolidin-1-il)-2,3,5,6-tetrafluorofenil)piperidina;

1-(4-((2R,5R)-2,5-bis(4-cloro-3-nitrofenil)pirrolidin-1-il)-2-metilfenil)piperidina;

(3aR,7aS)-2-(4-((2R,5R)-2,5-bis(4-cloro-3-nitrofenil)pirrolidin-1-il)-2,6-difluorofenil)octahidro-1H-isoindol;

4-((2R,5R)-2,5-bis(4-cloro-3-nitrofenil)pirrolidin-1-il)-N-tert-butil-2-fluoroanilina;

1-(4-((2R,5R)-2,5-bis(4-cloro-3-nitrofenil)pirrolidin-1-il)-2,6-difluorofenil)-4-metilpiperidina;

(2R,5R)-2,5-bis(4-cloro-3-nitrofenil)-1-(4-(ciclopentiloxi)-3-fluorofenil)pirrolidina;

(2R,5R)-2,5-bis(4-cloro-3-nitrofenil)-1-(3-fluoro-4-(metiltio)fenil)pirrolidina

1-(4-((2R,5R)-2,5-bis(4-cloro-3-nitrofenil)pirrolidin-1-il)-2,6-diclorofenil)piperidina;

1-(4-((2R,5R)-2,5-bis(4-cloro-3-nitrofenil)pirrolidin-1-il)-2,5-difluorofenil)piperidina;

(2R,6S)-1-(4-((2R,5R)-2,5-bis(4-cloro-3-nitrofenil)pirrolidin-1-il)-2,6-difluorofenil)-2,6-dimetilpiperidina;

1-(4-((2R,5R)-2,5-bis(4-cloro-3-nitrofenil)pirrolidin-1-il)-2,3,6-trifluorofenil)piperidina;

(2R,5R)-2,5-bis(4-cloro-3-nitrofenil)-1-(4-ciclopropilfenil)pirrolidina;

(1R,5S)-3-(4-((2R,5R)-2,5-bis(4-cloro-3-nitrofenil)pirrolidin-1-il)-2,6-difluorofenil)-3-azabiciclo[3.2.0]heptano;

(2R,5R)-2,5-bis(4-cloro-3-nitrofenil)-1-(4-ciclopropil-2-fluorofenil)pirrolidina;

1-(4-((2R,5R)-2,5-bis(4-cloro-3-nitrofenil)pirrolidin-1-il)-2-fluorofenil)piperidina;

1-(4-((2R,5R)-2,5-bis(4-cloro-3-nitrofenil)pirrolidin-1-il)fenil)-4-fenilpiperidina;

3-(4-((2R,5R)-2,5-bis(4-cloro-3-nitrofenil)pirrolidin-1-il)-2,6-difluorofenil)-3-azaespiro[5,5]undecano;

2-(4-((2R,5R)-2,5-bis(4-cloro-3-nitrofenil)pirrolidin-1-il)-2,6-difluorofenil)isoindolina;

8-(4-((2R,5R)-2,5-bis(4-cloro-3-nitrofenil)pirrolidin-1-il)-2,6-difluorofenil)-1,4-dioxa-8-azaespiro[4,5]decano;

1-(4-((2R,5R)-2,5-bis(4-cloro-3-nitrofenil)pirrolidin-1-il)-2,6-difluorofenil)-4-fenil-1,2,3,6-tetrahidropiridina;

1-(4-((2R,5R)-2,5-bis(4-cloro-3-nitrofenil)pirrolidin-1-il)-2,6-difluorofenil)-4,4-difenilpiperidina;

1-(1-(4-((2R,5R)-2,5-bis(4-cloro-3-nitrofenil)pirrolidin-1-il)-2,6-difluorofenil)-4-fenilpiperidin-4-il)etanona;

1-(4-((2R,5R)-2,5-bis(4-cloro-2-fluoro-5-nitrofenil)pirrolidin-1-il)-2,6-difluorofenil)piperidina;

1-(4-(2,5-bis(4-cloro-2-fluoro-5-nitrofenil)pirrolidin-1-il)-2,6-difluorofenil)piperidina;

1-(4-((2R,5R)-2,5-bis(4-cloro-3-nitrofenil)pirrolidin-1-il)-2,6-difluorofenil)-4-(3-fenilpropil)piperidina;

8-(4-((2R,5R)-2,5-bis(4-cloro-3-nitrofenil)pirrolidin-1-il)-2,6-difluorofenil)-8-azaespiro[4,5]decano;

1-(4-((2R,5R)-2,5-bis(4-cloro-3-nitrofenil)pirrolidin-1-il)-2,6-difluorofenil)-4-(naftalen-2-il)piperidina;

2-(1-(4-((2R,5R)-2,5-bis(4-cloro-3-nitrofenil)pirrolidin-1-il)-2,6-difluorofenil)piperidin-4-il)piridina;

1-(4-((2R,5R)-2,5-bis(4-cloro-3-nitrofenil)pirrolidin-1-il)-2,6-difluorofenil)-4-(4-(trimetilsilil)fenil)piperidina;

1-(4-((2R,5R)-2,5-bis(4-cloro-3-nitrofenil)pirrolidin-1-il)-2,6-difluorofenil)-4-(naftalen-1-il)piperidina;

1-(4-((2R,5R)-2,5-bis(4-cloro-2-fluoro-5-nitrofenil)pirrolidin-1-il)-2,6-difluorofenil)-4-(3-fenilpropil)piperidina;

6-(4-((2R,5R)-2,5-bis(4-cloro-2-fluoro-5-nitrofenil)pirrolidin-1-il)-2,6-difluorofenil)-6-azaespiro[2,5]octano;

1-(4-((2R,5R)-2,5-bis(4-cloro-2-fluoro-5-nitrofenil)pirrolidin-1-il)-2,6-difluorofenil)-4-tert-butilpiperidina;

1-(4-((2R,5R)-2,5-bis(4-cloro-2-fluoro-5-nitrofenil)pirrolidin-1-il)-2,6-difluorofenil)-4-(naftalen-2-il)piperidina;

1-(4-((2R,5R)-2,5-bis(4-cloro-2-fluoro-5-nitrofenil)pirrolidin-1-il)-2,6-difluorofenil)-3,5-dimetilpiperidina;

1'-(4-((2R,5R)-2,5-bis(4-cloro-2-fluoro-5-nitrofenil)pirrolidin-1-il)-2,6-difluorofenil)-2,3-dihidroespiro[inden-1,4'-piperidina];

1-(4-((2R,5R)-2,5-bis(4-cloro-3-nitrofenil)pirrolidin-1-il)-2,6-difluorofenil)-3-fenilpiperidina;

(2R,5R)-2,5-bis(4-cloro-3-nitrofenil)-1-(3,5-difluoro-4-(3-fenilpirrolidin-1-il)fenil)pirrolidina;

1-(4-((2R,5R)-2,5-bis(4-cloro-3-nitrofenil)pirrolidin-1-il)-2,6-difluorofenil)-4-(4-metoxifenil)piperidina;

1-(4-((2R,5R)-2,5-bis(4-cloro-3-nitrofenil)pirrolidin-1-il)-2,6-difluorofenil)-4-fluoro-4-fenilpiperidina;

1-(4-((2R,5R)-2,5-bis(4-cloro-3-nitrofenil)pirrolidin-1-il)fenil)-4-fluoro-4-fenilpiperidina;

1-(4-((2R,5R)-2,5-bis(4-cloro-2-fluoro-5-nitrofenil)pirrolidin-1-il)-2,6-difluorofenil)-4-(fluorodifenilmetil)piperidina;

1-(4-((2R,5R)-2,5-bis(4-cloro-2-fluoro-5-nitrofenil)pirrolidin-1-il)-2,6-difluorofenil)-4-fenilpiperidina;

1-(4-((2R,5R)-2,5-bis(4-cloro-3-nitrofenil)pirrolidin-1-il)-2,6-difluorofenil)-4-(4-fluorofenil)piperidina;

1-(4-((2R,5R)-2,5-bis(4-cloro-3-nitrofenil)pirrolidin-1-il)-2,6-difluorofenil)-4-(3,4-difluorofenil)piperidina;

1-(4-((2R,5R)-2,5-bis(4-cloro-3-nitrofenil)pirrolidin-1-il)-2,6-difluorofenil)-4-(3,5-difluorofenil)piperidina;

1-(4-((2R,5R)-2,5-bis(4-cloro-3-nitrofenil)pirrolidin-1-il)-2,6-difluorofenil)-4-(3-(trimetilsilil)fenil)piperidina;

(2R,5R)-1-(4-(benciloxi)fenil)-2,5-bis(4-cloro-3-nitrofenil)pirrolidina;

1-(4-((2R,5R)-2,5-bis(4-cloro-2-fluoro-5-nitrofenil)pirrolidin-1-il)-2,6-difluorofenil)-4-(4-(trifluorometil)fenil)piperazina;

1-(4-((2R,5R)-2-(4-cloro-2-fluoro-5-nitrofenil)-5-(4-cloro-3-nitrofenil)pirrolidin-1-il)-2,6-difluorofenil)piperidina;

4-bencil-1-(4-((2R,5R)-2,5-bis(4-cloro-2-fluoro-5-nitrofenil)pirrolidin-1-il)-2,6-difluorofenil)piperidina;

4-(4-((2R,5R)-2,5-bis(4-cloro-3-nitrofenil)pirrolidin-1-il)-2,6-difluorofenil)-2-fenilmorfolina;

1-(4-((2R,5R)-2,5-bis(4-cloro-3-nitrofenil)pirrolidin-1-il)-2,6-difluorofenil)-2-fenilpiperidina;

(2S,6R)-4-(4-((2R,5R)-2,5-bis(4-cloro-2-fluoro-5-nitrofenil)pirrolidin-1-il)-2,6-difluorofenil)-2,6-dimetilmorfolina;

3-(4-((2R,5R)-2,5-bis(4-cloro-2-fluoro-5-nitrofenil)pirrolidin-1-il)-2,6-difluorofenil)-3-azaespiro[5,5]undecano;

1-(4-((2R,5R)-2,5-bis(4-cloro-2-fluoro-5-nitrofenil)pirrolidin-1-il)-2,6-difluorofenil)-4-ciclohexilpiperidina;

(S)-4-(4-((2R,5R)-2,5-bis(4-cloro-3-nitrofenil)pirrolidin-1-il)-2,6-difluorofenil)-2-fenilmorfolina;

1-(4-((2R,5R)-2,5-bis(4-cloro-2-fluoro-5-nitrofenil)pirrolidin-1-il)-2,6-difluorofenil)-4-(2,4-difluorofenil)piperidina;

1-(4-((2R,5R)-2,5-bis(4-cloro-2-fluoro-5-nitrofenil)pirrolidin-1-il)-2,6-difluorofenil)-4-(4-fluorofenil)piperidina;

1-(4-((2R,5R)-2,5-bis(4-cloro-3-nitrofenil)pirrolidin-1-il)-2,6-difluorofenil)-4-fenilpiperazina;

1-(4-((2R,5R)-2,5-bis(4-cloro-3-nitrofenil)pirrolidin-1-il)-2,6-difluorofenil)-4-(4-(trifluorometil)fenil)piperazina;

1-(4-((2R,5R)-2,5-bis(4-cloro-2-fluoro-5-nitrofenil)pirrolidin-1-il)-2,6-difluorofenil)-4-(2,6-difluorofenil)piperazina;

2-(4-(4-((2R,5R)-2,5-bis(4-cloro-2-fluoro-5-nitrofenil)pirrolidin-1-il)-2,6-difluorofenil)piperazin-1-il)pirimidina;

5-((2S,5R)-2,5-bis(4-cloro-2-fluoro-5-nitrofenil)pirrolidin-1-il)-2-(4-fenilpiperidin-1-il)pirimidina;

5-((2S,5R)-2,5-bis(4-cloro-2-fluoro-5-nitrofenil)pirrolidin-1-il)-2-(piperidin-1-il)pirimidina;

1-(4-((2S,5S)-2,5-bis(4-cloro-2-fluoro-5-nitrofenil)pirrolidin-1-il)-2,6-difluorofenil)-4-(2,6-difluorofenil)piperazina;

1-(4-((2R,5R)-2,5-bis(4-cloro-2-fluoro-5-nitrofenil)pirrolidin-1-il)-2,6-difluorofenil)-4-(5-metiltiofen-2-il)piperidina; y

1-(4-((2R,5R)-2,5-bis(4-cloro-2-fluoro-5-nitrofenil)pirrolidin-1-il)-2,6-difluorofenil)-4-fluoro-4-fenilpiperidina.

Procedimiento General 5. Reducción de nitro

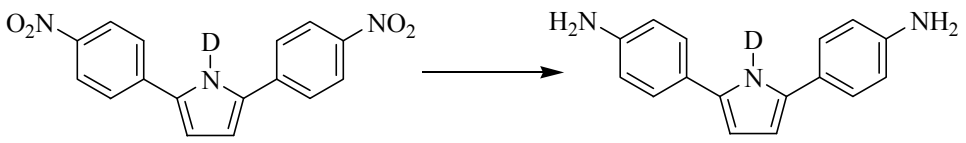


(6) (7)

Los compuestos (6) (1 equivalente) pueden reducirse a (7) por reacción con polvo de hierro (aproximadamente 6 equivalentes) y cloruro de amonio (aproximadamente 3 equivalentes) en un solvente de THF:etanol:agua (1:1:0,2) con calentamiento a aproximadamente 60-80 ºC. La reacción puede someterse a tratamiento posterior por enfriamiento, filtración a través de tierras diatomeas, lavado con etanol y concentración al vacío. De manera alternativa, (6) (1 equivalente) puede reducirse a (7) por hidrogenación(30 psi de H2) en presencia de PtO2 (aproximadamente 0,4 equivalentes) en un solvente de etanol:THF (aproximadamente 1:1). La reacción puede someterse a tratamiento posterior mediante filtración y evaporación de solvente. De manera alternativa, la reducción de (6) (1 equivalente) a (7) puede efectuarse por exposición a 30 psig de gas hidrógeno en presencia de níquel-Raney Grace 2800 (50% en peso de reactivo) en un solvente como por ejemplo tetrahidrofurano con agitación. La reacción puede someterse a tratamiento posterior mediante filtración y evaporación de solvente. El producto (7) puede

purificarse mediante cromatografía en gel de sílice usando solventes orgánicos típicos incluyendo mezclas de acetato de etilo y hexano.

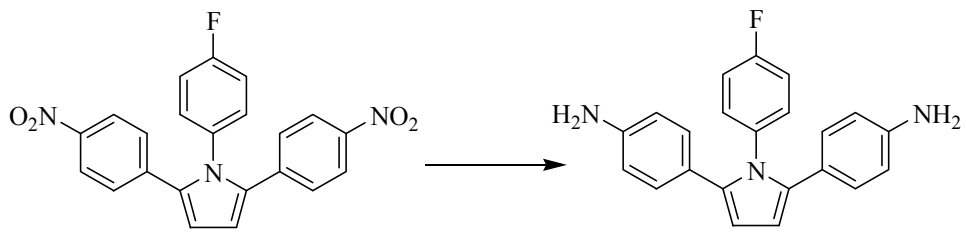
Procedimiento General 5.1. Reducción de nitro a pirrol



(11) (12)

Los compuestos (11) pueden convertirse a (12) usando las condiciones descritas en forma general para el Procedimiento General 5, en particular a través del método de reducción con hierro.

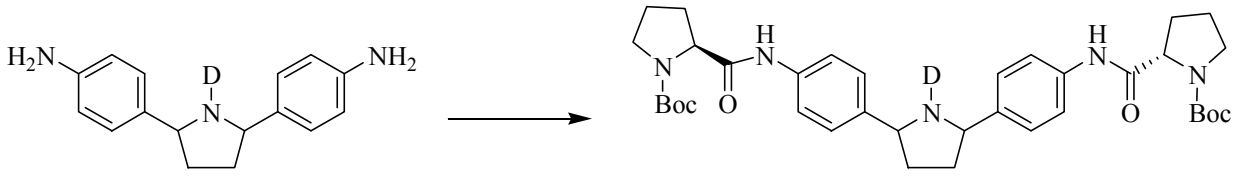
Ilustración del Procedimiento General 5.1: Procedimiento General 5.1A



4,4'-(1-(4-Fluorofenil)-1H-pirrol-2,5-diil)dianilina

A una solución de 1-(4-fluorofenil)-2,5-bis(4-nitrofenil)-1H-pirrol (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 durante 45 minutos. La mezcla de reacción se filtró a través de tierras diatomeas y se lavó con etanol. Los materiales filtrados combinados se concentraron, y el residuo se purificó mediante cromatografía en columna (gradiente de elución EtOAc:hexanos desde 30% hasta 50%) para dar 1,09 g (77%) del compuesto del título.

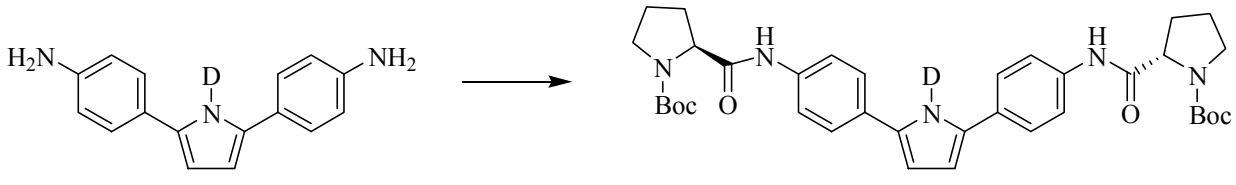
Procedimiento General 6. Acoplamiento de amida



(7) (8)

Los compuestos (7) (1 equivalente) pueden convertirse a compuestos (8) por reacción con ácido 1-(tert-butoxicarbonil)pirrolidin-2-carboxílico (aproximadamente 2,5 equivalentes) y HATU (aproximadamente 2 a 3 equivalentes) en presencia de diisopropiletilamina (3-4 equivalentes) en DMSO a aproximadamente temperatura ambiente. De manera alternativa a la utilización de HATU, esta reacción puede promoverse usando T3P o 1-etil-3-(3-dimetilaminopropilo) carbodiimida/1-hidroxibenzotriazol. La reacción también puede llevarse a cabo en solventes como por ejemplo tetrahidrofurano, acetato de etilo, o DMF. La reacción puede someterse a tratamiento posterior particionándose entre un solvente orgánico (por ejemplo, acetato de etilo) y agua o HCl acuoso diluido, luego puede separarse la capa orgánica, opcionalmente lavarse el material orgánico con agua y/o salmuera, secarse la capa orgánica con un agente de secado (por ejemplo, MgSO4, Na2SO4), filtrarse y evaporarse el solvente. El producto (8) puede purificarse mediante cromatografía en columna de gel de sílice, eluyendo con solventes orgánicos estándar incluyendo mezclas de acetato de etilo y hexano.

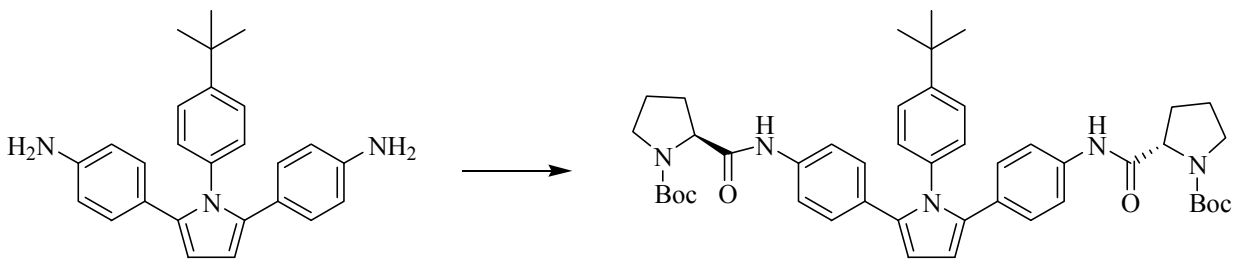
Procedimiento General 6.1. Acoplamiento de amida para dar pirroles



(12) (13)

Los compuestos anilina (12) pueden convertirse a amidas (13) usando las condiciones que se han descrito de manera general en el Procedimiento General 6.

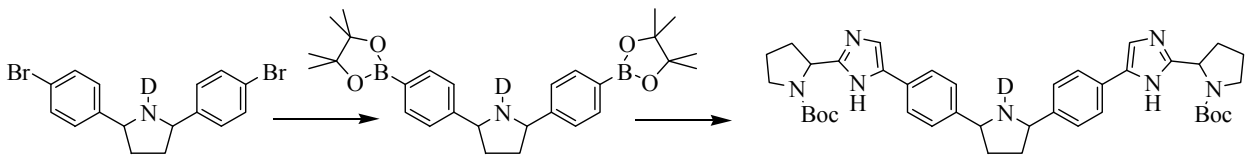
Ilustración del Procedimiento General 6.1: Procedimiento General 6.1A



(2S,2'S)- 2,2'-(4,4'-(1-(4-tert-butilfenil)-1H-pirrol-2,5-diil)bis(4,1-fenilen)bis(azanodiil)bis(oxometilen))dipirrolidin-1-carboxilato de tert-butilo

A una solución de 4,4'-(1-(4-tert-butilfenil)-1H-pirrol-2,5-diil)dianilina (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 volcó sobre agua y se extrajo con CH2Cl2. El extracto orgánico se secó (Na2SO4), se filtró y se concentró para dar un producto crudo que se purificó por trituración con éter para dar 325 mg (51%) del compuesto del título. 1H RMN (400 MHz, DMSO-d6) δ ppm 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).

Procedimiento General 7. Acoplamiento de Suzuki

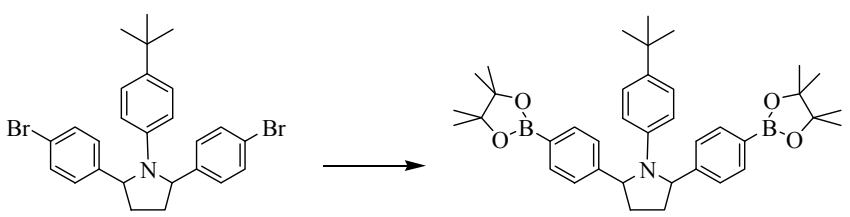


(34.1) (35.1) (36.1)

Los compuestos dibromo (34,1) (1 equivalente) pueden convertirse a compuestos diboronato (35,1) mezclando con bis(pinacolato)diborano (aproximadamente 2 a 4 equivalentes), acetato de potasio (aproximadamente 4-8 equivalentes), y complejo cloruro de 1,1'-bis(difenilfosfino)ferrocen-paladio(II) diclorometano (PdCl2(dppf)) (aproximadamente 0,1 a 0,2 equivalentes) en un solvente como por ejemplo DME, dioxano, o DMSO, desgasificando la mezcla y calentando a aproximadamente 85 ºC. La

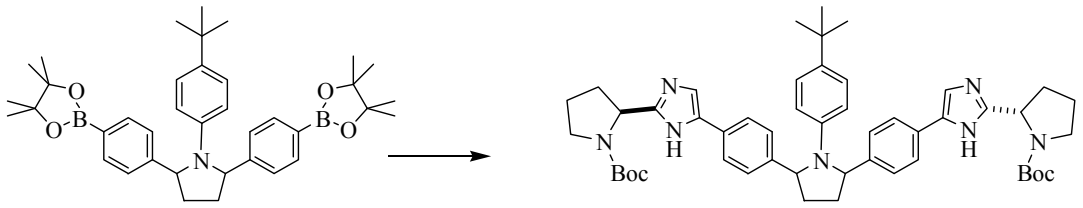
reacción puede someterse a tratamiento posterior por enfriamiento a temperatura ambiente, dilución con cloruro de metileno, opcionalmente lavado de los materiales orgánicos con agua y/o salmuera, secado de los materiales orgánicos con un agente de secado (por ejemplo, MgSO4, Na2SO4), filtración y evaporación del solvente. Los compuestos (35,1) pueden convertirse a compuestos (36,1) mezclando con el Intermediario 1D (aproximadamente 1 a 2 equivalentes), solución acuosa de carbonato de sodio (aproximadamente 1 a 3,5 equivalentes), y PdCl2(dppf) (aproximadamente 0,03 a 0,2 equivalentes) en un solvente como dimetoxietano o tolueno:etanol (1:1), desgasificando, y calentando la reacción a aproximadamente 80-100 ºC. La reacción puede someterse a tratamiento posterior por enfriamiento a temperatura ambiente, particionarse entre un solvente orgánico (por ejemplo, acetato de etilo) y agua, opcionalmente pueden lavarse los materiales orgánicos con agua y/o salmuera, secarse los materiales orgánicos con un agente de secado (por ejemplo, MgSO4, Na2SO4), filtrarse y evaporarse el solvente. De manera alternativa, la reacción puede someterse a tratamiento posterior por concentración al vacío, luego particionarse entre isopropilalcohol/cloroformo 25%, secarse los materiales orgánicos (por ejemplo, Na2SO4), filtrarse, y evaporarse el solvente. Los compuestos (35.1) y (36.1) pueden purificarse mediante cromatografía en columna de gel de sílice, eluyendo con solventes orgánicos estándar incluyendo mezclas de acetato de etilo y hexano; o por trituración o recristalización.

Ilustración del Procedimiento General 7: Procedimiento General 7A



trans-1-(4-tert-butilfenil)-2,5-bis(4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)pirrolidina racémica

Se combinaron trans-2,5-bis(4-bromofenil)-1-(4-tert-butilfenil)pirrolidina racémica (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 gas nitrógeno a través de la solución durante 10 minutos. La mezcla de reacción luego se calentó a 85 ºC durante 1 hora. La solución de la reacción se enfrió a temperatura ambiente, se filtró a través de tierras diatomeas y se lavó con acetato de etilo (20 mL). El material filtrado se secó y se concentró, y el residuo se purificó mediante cromatografía en columna de gel de sílice, eluyendo con un gradiente de solventes de acetato de etilo en hexano 0-10% y luego se trituró el sólido resultante con éter dietílico para dar el compuesto del título (1,14 g, 25%) como una mezcla 1/1 de estereoisómeros trans.

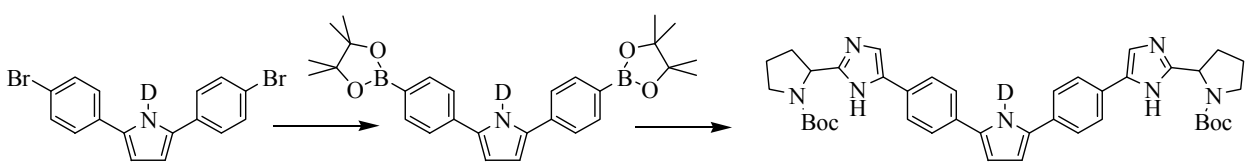


(2S,2'S)- 2,2'-(5,5'-(4,4'-(1-(4-tert-butilfenil)pirrolidin-2,5-diil)bis(4,1-fenilen))bis(1H-imidazol-5,2-diil))dipirrolidin-1-carboxilato de tert-butilo

Se disolvieron trans-1-(4-tert-butilfenil)-2,5-bis(4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)pirrolidina racémica (0,915 g, 1,506 mmol), el Intermediario 1D (1,429 g, 4,52 mmol), y [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 de bicarbonato de sodio 2 N (2,64 mL, 5,28 mmol). Se burbujeó gas nitrógeno a través de la solución durante 10 minutos, y luego la mezcla de reacción se calentó a 100 ºC durante 3 horas. La solución de la reacción se enfrió a temperatura ambiente y se agregó agua (20 mL). Luego la mezcla de reacción se extrajo con diclorometano (50 mL), se secó, y se concentró. El residuo se purificó mediante cromatografía en columna de gel de sílice

eluyendo con un gradiente de solventes de acetato de etilo en hexano 0-80% para dar el compuesto del título (0,93 g, 75%) como una mezcla 1/1 de estereoisómeros trans.

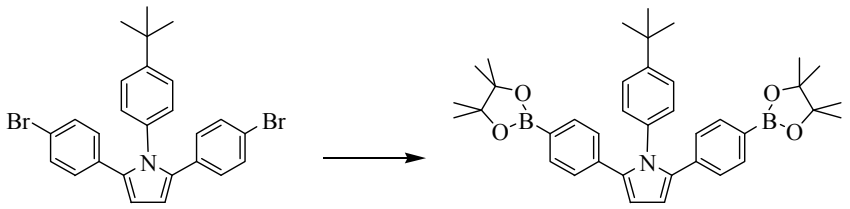
Procedimiento General 7.1. Acoplamiento de Suzuki para dar pirroles



(46) (47) (43)

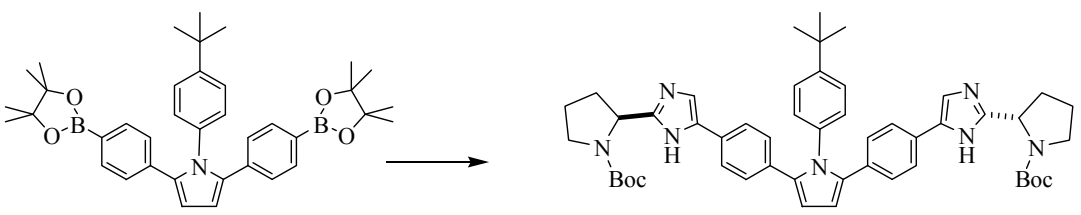
Los compuestos dibromo (46) pueden convertirse en forma secuencial a compuestos (47) y (43) usando las condiciones que se han descrito de manera general en el Procedimiento General 7.

Ilustración del Procedimiento General 7.1: Procedimiento General 7.1B



1-(4-tert-butilfenil)-2,5-bis(4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)-1H-pirrol

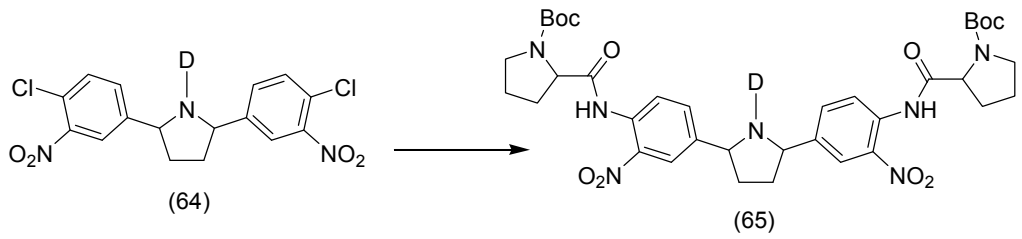
A una solución de 2,5-bis(4-bromofenil)-1-(4-tert-butilfenil)-1H-pirrol (2,32 g, 4,56 mmol) en DMSO (26 mL) a temperatura ambiente se agregaron bis(pinacolato)diborano (2,54 g, 10,02 mmol), acetato de potasio (5,00 g, 36,4 mmol) y PdCl2(dppf) (744 mg, 0,91 mmol). La mezcla se desgasificó y se calentó a 85 °C. Después de 4 horas, la mezcla se enfrió a temperatura ambiente, se diluyó con diclorometano y se lavó con agua seguida por salmuera. La fase orgánica se secó (Na2SO4) y se concentró. El residuo se recogió en acetato de etilo/hexanos 20% y se filtró a través de un tapón corto de gel de sílice (elución con acetato de etilo:hexanos 20%) y se concentró para dar el compuesto del título como un sólido amarillo claro (1,62 g; 59% de rendimiento).



(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

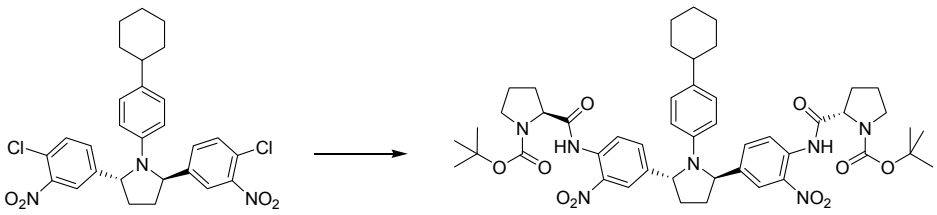
Una mezcla del Intermediario 1D (664 mg, 2,10 mmol), 1-(4-tert-butilfenil)-2,5-bis(4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)-1H-pirrol (1,48 g, 2,45 mmol), carbonato de sodio 2 M (1400 µL, 2,80 mmol), y Pd(dppf)Cl2 (51,2 mg, 0,070 mmol) en DME (2800 µL) se sometió a irradiación de microondas a 140 °C durante 20 minutos. La mezcla se diluyó con acetato de etilo, luego se lavó con agua y salmuera, y se secó sobre Na2SO4. El producto se purificó sobre gel de sílice eluyendo con acetato de etilo:hexanos 30 a 70% para dar el compuesto del título (140 mg; 24% de rendimiento).

Procedimiento General 8. Reacción de Buchwald



Los compuestos (64) (1 equivalente) pueden convertirse a compuestos (65) mezclando con 2-carbamoilpirrolidin-1-carboxilato de tert-butilo (aproximadamente 3 equivalentes), carbonato de cesio (aproximadamente 3 equivalentes), 4,5-bis(difenilfosfino)-9,9-dimetilxanteno (aproximadamente 0,05 a 0,3 equivalentes), y tris(dibencilidenacetona)dipaladio(0) (aproximadamente 0,05 a 0,2 equivalentes) en dioxano, desgasificando la mezcla, y calentamiento a aproximadamente 100 ºC durante entre aproximadamente 1 a 8 horas. De manera alternativa, la reacción puede llevarse a cabo usando carbonato de potasio (aproximadamente 3 equivalentes), Pd(OAc)2 (aproximadamente 0,02 equivalentes), y 4,5-bis(difenilfosfino)-9,9-dimetilxanteno (aproximadamente 0,04 equivalentes). La reacción puede llevarse a cabo en un recipiente con un condensador de reflujo bajo una atmósfera inerte o en un tubo sellado. El producto (65) puede purificarse mediante cromatografía sobre gel de sílice eluyendo con solventes estándar incluyendo acetato de etilo y cloruro de metileno.

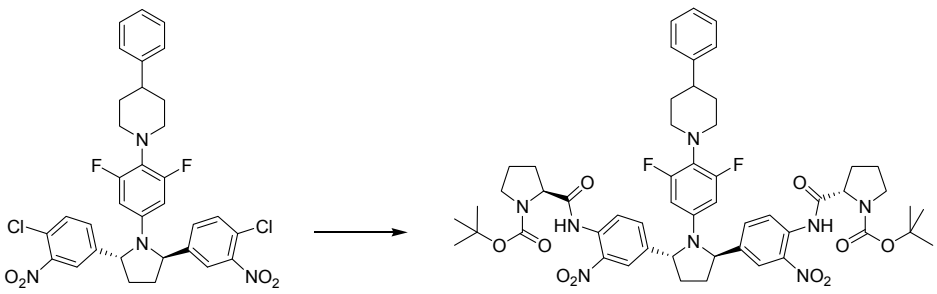
Ilustración del Procedimiento General 8: Procedimiento General 8A



(2S,2'S)- 2,2'-(4,4'-((2R,5R)-1-(4-ciclohexilfenil)pirrolidin-2,5-diil)bis(2-nitro-4,1-fenilen))bis(azanodiil)bis(oxometilen)dipirrolidin-1-carboxilato de tert-butilo

Se combinaron (2R,5R)-2,5-Bis(4-cloro-3-nitrofenil)-1-(4-ciclohexilfenil)pirrolidina (Procedimiento General 4A) (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 tris(dibencilidenacetona)dipaladio(0) (0,328 g, 0,358 mmol) en dioxano (18 mL) y se burbujeó nitrógeno a través de la solución durante 15 minutos. Luego el recipiente se tapó con un condensador de reflujo y la solución se calentó a 100 ºC durante 8 horas. Después del filtrar a través de tierras diatomeas y concentrar, el residuo se purificó con una columna de sílice CombiFlash® de 80g, eluyendo con acetato de etilo en diclorometano 0-20% para dar 1,71 g (80%) del compuesto del título.

Ilustración del Procedimiento General 8: Procedimiento General 8B, Ejemplo 1A



(2S,2'S)- 2,2'-(4,4'-((2R,5R)-1-(3,5-difluoro-4-(4-fenilpiperidin-1-il)fenil)pirrolidin-2,5-diil)bis(2-nitro-4,1-fenilen))bis(azanodiil)bis(oxometilen)dipirrolidin-1-carboxilato de tert-butilo

A un balón de 100 mL se agregó 1-(4-((2R,5R)-2,5-bis(4-cloro-3-nitrofenil)pirrolidin-1-il)-2,6-difluorofenil)-4-fenilpiperidina (2,26 g, 3,46 mmol), (S)- 2-carbamoilpirrolidin-1-

carboxilato de tert-butilo (2,223 g, 10,37 mmol), carbonato de cesio (3,38 g, 10,37 mmol), tris(dibencilidenacetona)dipaladio(0) (0,190 g, 0,207 mmol) y (9,9-dimetil-9H-xanten-4,5-diil)bis(difenilfosfina) (0,300 g, 0,519 mmol) en dioxano (34,6 mL) para dar una suspension violeta. La mezcla se burbujeó con N2 durante 20 minutos, se calentó bajo N2 a 100 ºC durante 3 horas, se enfrió y se volcó sobre EtOAc. La capa de EtOAc se lavó 2×50 mL con H2O y luego con NaCl saturado. La capa de EtOAc se trató simultáneamente durante 1 hora con 3-mercaptopropilsílice y Na2SO4, se filtró y se concentró. La purificación usando cromatografía en un cartucho de sílice de 120 g eluyendo con metanol en cloruro de metileno 1-3 % dio un material que resultó tener un 90% de pureza según HPLC. Una segunda columna en un cartucho de sílice de 120 g eluyendo con EtOAc en hexano 15-50% dio el compuesto del título como una espuma anaranjada (2,6 g, 72%, 97% de pureza según HPLC). MS (ESI+) m/z 1009 (M+H)+.

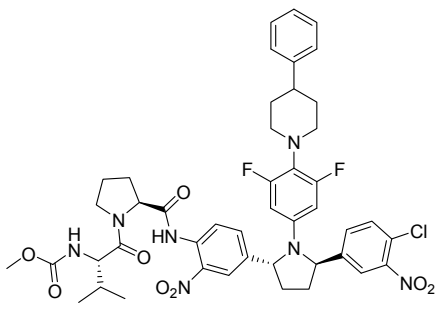


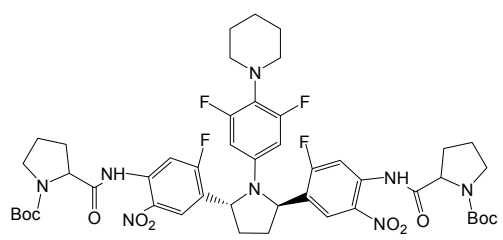
Ilustración del Procedimiento General 8: Procedimiento General 8B, Ejemplo 1B (monodesplazamiento)

(S)-1-((S)-2-(4-((2R,5R)-5-(4-cloro-3-nitrofenil)-1-(3,5-difluoro-4-(4-fenilpiperidin-1-il)fenil)pirrolidin-2-il)-2-nitrofenilcarbamoil)pirrolidin-1-il)-3-metil-1-oxobutan-2-ilcarbamato de metilo

Se disolvió 1-(4-((2R,5R)-2,5-Bis(4-cloro-3-nitrofenil)pirrolidin-1-il)-2,6-difluorofenil)-4-fenilpiperidina (0,745 g, 1,14 mmol) en dioxano (12 mL) en un tubo y se trató con (S)-1-((S)-2-carbamoilpirrolidin-1-il)-3-metil-1-oxobutan-2-ilcarbamato de metilo (0,309 g, 1,14 mmol), carbonato de cesio (0,409 g, 1,25 mmol), Xantphos (0,066 g, 0,11 mmol), y tris(dibencilidenacetona)dipaladio(0) (0,052 g, 0,057mmol). Se burbujeó nitrógeno a través

de esta mezcla durante 15 minutos, luego el tubo se selló y se calentó a 100 ºC durante 2 horas. La mezcla se diluyó con agua, se extrajo con diclorometano, se concentró, y se purificó mediante cromatografía, eluyendo con metanol en diclorometano 0-5% para dar 0,44 g (43%) de un sólido amarillo oscuro.

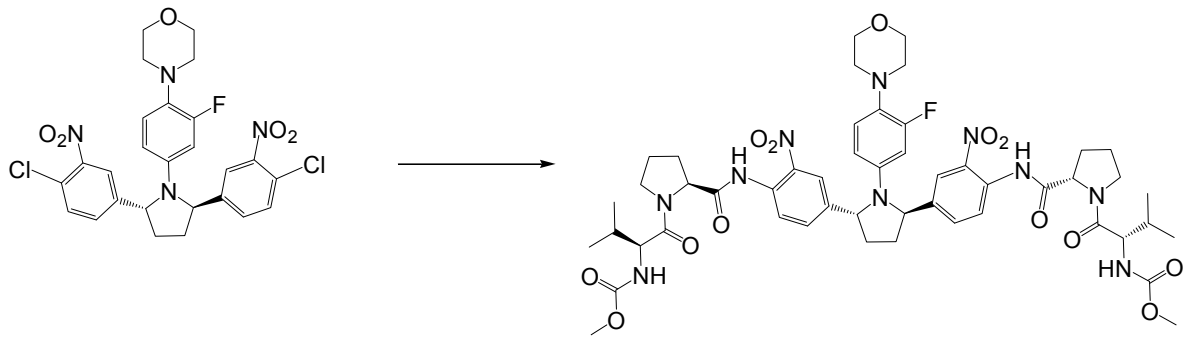
Ilustración del Procedimiento General 8: Procedimiento General 8B, Ejemplo 2



2,2'-(4,4'-((2R,5R)-1-(3,5-difluoro-4-(piperidin-1-il)fenil)pirrolidin-2,5-diil)bis(5-fluoro-2-nitro-4,1-fenilen))bis(azanodiil)bis(oxometilen)dipirrolidin-1-carboxilato de tert-butilo

En un balón se combinó 1-(4-((2R,5R)-2,5-bis(4-cloro-2-fluoro-5-nitrofenil)pirrolidin-1-il)-2,6-difluorofenil)piperidina (4,1 g, 6,68 mmol), (S)- 2-carbamoilpirrolidin-1-carboxilato de tert-butilo (4,30 g, 20,05 mmol), carbonato de cesio (6,1 g, 18,72 mmol), y XantPhos (0,696 g, 1,203 mmol) seguidos por dioxano (30 ml) y la solución se desgasificó con gas N2 durante 30 minutos. La solución se agitó enérgicamente para mantener los sólidos en agitación y mantener la velocidad de flujo del gas N2 a un nivel alto para asegurar la desgasificación completa de la mezcla. Se agregó tris(dibencilidenacetona)dipaladio (0,367 g, 0,401 mmol) y la solución se calentó a 100 ºC durante 2 horas bajo gas N2. La solución se enfrió y se diluyó con EtOAc, se filtró a través de tierras diatomeas, se lavó con H2O y salmuera, se secó (Na2SO4), se filtró, se trató durante 30 minutos con gel de sílice funcionarizado con 3-mercaptopropilo, se filtró y se concentró para dar el producto crudo. La purificación se llevó a cabo en un cartucho de gel de sílice ISCO de 120g eluyendo con EtOAc/hexano 0-40% a lo largo de 30 minutos para dar el compuesto del título (4,52 g, 4,66 mmol, 69,8%).

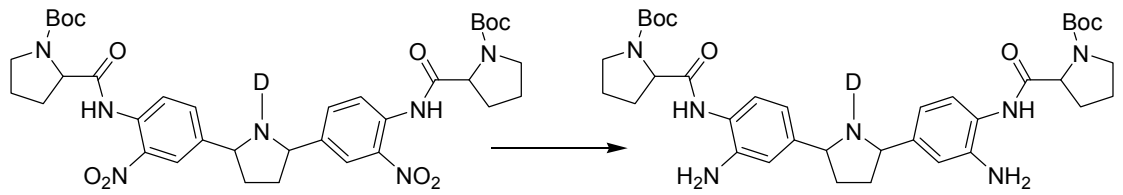
Procedimiento General 8.1. Buchwald con dipéptido



(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(azanodiil)bis(oxometilen)bis(pirrolidin-2,1-diil))bis(3-metil-1-oxobutan-2,1-diil)dicarbamato de dimetilo

En un tubo de microondas, una suspensión de 4-(4-((2R,5R)-2,5-bis(4-cloro-3-nitrofenil)pirrolidin-1-il)-2-fluorofenil)morfolina (1,39 g, 2,48 mmoL), el Intermediario 3B (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 por burbujeo de nitrógeno durante 30 minutos. La mezcla se trató con tris(dibencilidenacetona)dipaladio (0) (68 mg, 0,074 mmol) y luego se desgasificó durante otros 5 minutos. El tubo para microondas se selló y la mezcla se calentó a 100 ºC durante 2 horas. La mezcla se enfrió y se diluyó con acetato de etilo y se extrajo con agua (3×) y solución saturada de cloruro de sodio. La solución se secó (Na2SO4) y se agitó durante la noche con gel de 3-(mercaptopropil)sílice. La filtración y la concentración al vacío dieron un sólido que se cromatografió sobre un cartucho de gel de sílice de 340 g, eluyendo con metanol en diclorometano 0-10%. Se obtuvo el compuesto del título como un sólido anaranjado. 1H RMN (400 MHz, DMSO-d6) δ ppm 0,80-0,90 (m, 12H) 1,74 (s ancho, 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) 6,74f6,81 (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)+.

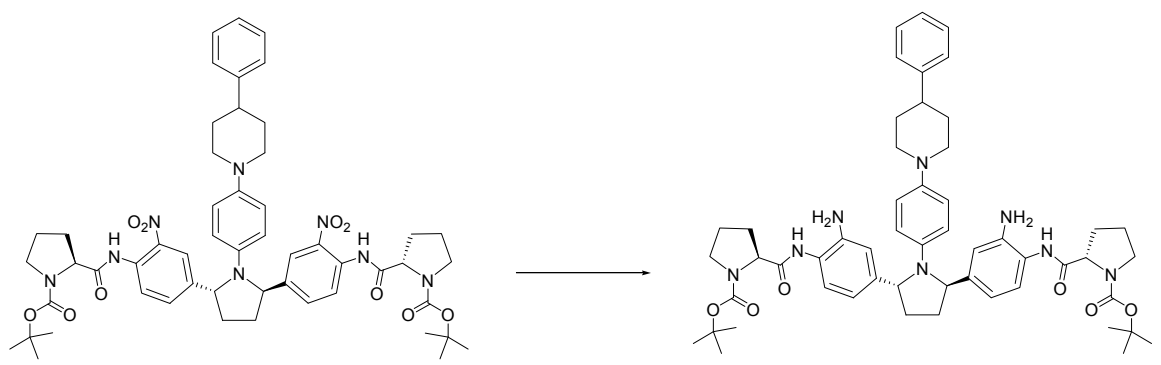
Procedimiento General 9. Reducción de nitro



(65) (66)

Los compuestos (65) (1 equivalente) pueden convertirse a compuestos (66) por hidrogenación con gas hidrógeno (1-4 atm) con un catalizador como por ejemplo PtO2 (aproximadamente 0,2 a 0,3 equivalentes) o níquel-Raney (por ejemplo, acuoso 50%; 1 equivalente en peso) en solventes como por ejemplo tetrahidrofurano, etanol, o mezclas de los mismos. La reacción puede someterse a tratamiento posterior mediante filtración a través de tierras diatomeas o gel de sílice, y el material filtrado se concentró para dar los compuestos (66). La reducción de (65) (1 equivalente) también puede efectuarse por reacción con polvo de hierro (aproximadamente 6 equivalentes) y cloruro de amonio (aproximadamente 3 equivalentes) en un solvente de THF:etanol:agua (1:1:0,2) con calentamiento a aproximadamente 60-100 ºC.

Ilustración del Procedimiento General 9: Procedimiento General 9A, Ejemplo 1



(2S,2'S)- 2,2'-(4,4'-((2R,5R)-1-(4-(4-fenilpiperidin-1-il)fenil)pirrolidin-2,5-diil)bis(2-amino-4,1-fenilen))bis(azanodiil)bis(oxometilen)dipirrolidin-1-carboxilato de tert-butilo

Una solución de (2S,2'S)- 2,2'-(4,4'-((2R,5R)-1-(4-(4-fenilpiperidin-1-il)fenil)pirrolidin-2,5-diil)bis(2-nitro-4,1-fenilen))bis(azanodiil)bis(oxometilen)dipirrolidin-1-carboxilato de tert-butilo (2,287 g, 2,350 mmol) en THF (60 mL) se agregó a PtO2 (0,457 g, 2,014 mmol) en una botella de presión de acero inoxidable de 250 mL y se agitó

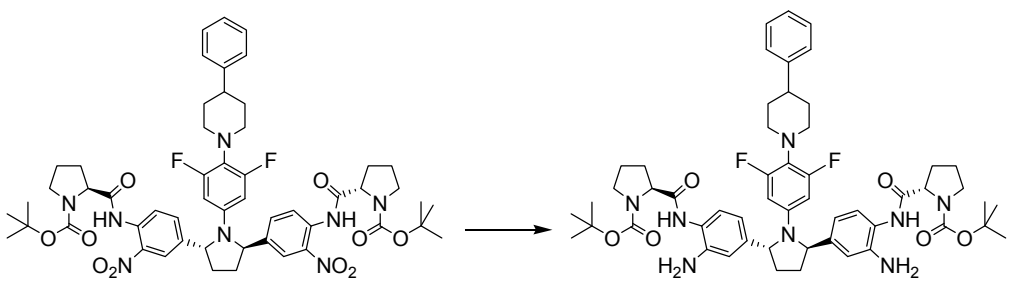
durante 4 horas a temperatura ambiente bajo 30 psi de presión de hidrógeno. La mezcla luego se filtró a través de una membrana de Nylon y el material filtrado se concentró por evaporación por rotación y se secó al vacío para dar el compuesto del título como un sólido marrón (2,02 g, 94%). 1H RMN (400 MHz, DMSO-d6) δ ppm 1,30 - 1,44 (m, 18 H), 1,53 - 1,98 (m, 11 H), 2,08 - 2,29 (m, 1 H), 2,43 - 2,60 (m, 3 H), 3,35 - 3,50 (m, 4 H), 4,16 - 4,29 (m, 2 H), 4,79 (d, J=35,46 Hz, 4 H), 4,97 (s, 2 H), 6,21 (d, J=8,89 Hz, 2 H), 6,41 (dd, J=20,66, 7,86 Hz, 2 H), 6,53 - 6,61 (m, 2 H), 6,66 (d, J=8,89 Hz, 2 H), 6,93 - 7,06 (m, 2 H), 7,17 (t, J=6,89 Hz, 1 H), 7,21 - 7,32 (m, 4 H), 9,18 (d, J=39,25 Hz, 2 H); MS (ESI+) m/z 913 (M+H)+; MS (ESI-) m/z 911 (M-H)-.

Ilustración del Procedimiento General 9: Procedimiento General 9A, Ejemplo 2

2,2'-(4,4'-((2R,5R)-1-(3,5-difluoro-4-(piperidin-1-il)fenil)pirrolidin-2,5-diil)bis(2-amino-5-fluoro-4,1-fenilen))bis(azanodiil)bis(oxometilen)dipirrolidin-1-carboxilato de tert-butilo

Se agregaron 2,2'-(4,4'-((2R,5R)-1-(3,5-difluoro-4-(piperidin-1-il)fenil)pirrolidin-2,5-diil)bis(5-fluoro-2-nitro-4,1-fenilen))bis(azanodiil)bis(oxometilen)dipirrolidin-1-carboxilato de tert-butilo (4,5 g, 4,64 mmol) y THF (100 ml) a PtO2 (0,900 g, 3,96 mmol) en una botella de presión de acero inoxidable de 250 mL y se agitó durante 22 horas bajo una atmósfera de hidrógeno (30 psi) a temperatura ambiente. La mezcla se filtró a través de una membrana de Nylon y se concentró para dar una espuma colo amarillo anaranjado.

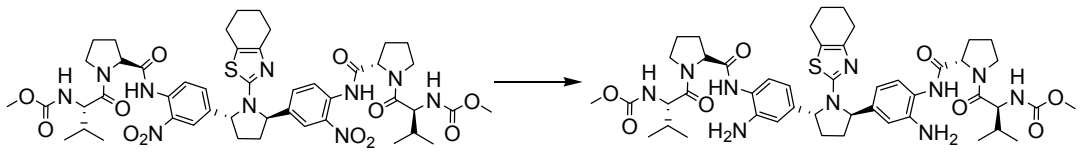
Ilustración del Procedimiento General 9: Procedimiento General 9B



(2S,2'S)- 2,2'-(4,4'-((2R,5R)-1-(3,5-difluoro-4-(4-fenilpiperidin-1-il)fenil)pirrolidin-2,5-diil)bis(2-amino-4,1-fenilen))bis(azanodiil)bis(oxometilen)dipirrolidin-1-carboxilato de tert-butilo

En una botella de presión de 250 mL se combinaron (2S,2'S)- 2,2'-(4,4'-((2R,5R)-1-(3,5-difluoro-4-(4-fenilpiperidin-1-il)fenil)pirrolidin-2,5-diil)bis(2-nitro-4,1-fenilen))bis(azanodiil)bis(oxometilen)dipirrolidin-1-carboxilato de tert-butilo (Procedimiento General 8B) (2,6 g, 2,58 mmol) y níquel-Raney 2800 (45% p/p en agua, 2,6 g, 44 mmol) en THF (40 mL). El recipiente se selló y se agitó bajo 30 psi de H2 durante 5 horas. La solución se filtró a través de una membrana de Nylon y el material filtrado se concentró para dar el compuesto del título como una espuma color tostado (2,44 g, rendimiento cuantitativo) que se usó sin purificación. MS (ESI+) m/z 949 (M+H)+.

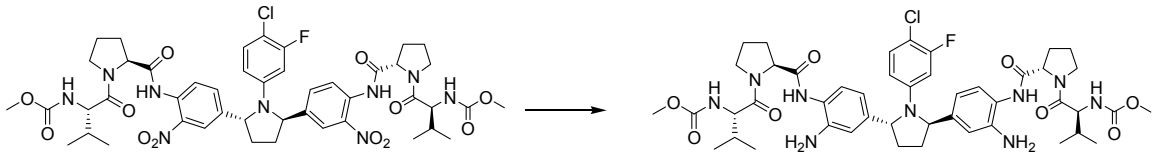
Ilustración del Procedimiento General 9: Procedimiento General 9C



([(2R,5R)-1-(4,5,6,7-tetrahidro-1,3-benzotiazol-2-il)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 (Nomenclatura ACD v12))

Se disolvió ([(2R,5R)-1-(4,5,6,7-tetrahidro-1,3-benzotiazol-2-il)pirrolidin-2,5-diil]bis{(2-nitrobencen-4,1-diil)carbamoil(2S)pirrolidin-2,1-diil[(2S)-3-metil-1-oxobutan-1,2-diil]})biscarbamato de dimetilo (Nomenclatura ACD v12)) (0,59 g, 0,596 mmol) en tetrahidrofurano (15 mL) y se trató con níquel-Raney en agua (0,25 mL). El recipiente se evacuó y se conectó a un balón de hidrógeno y se agitó a temperatura ambiente durante 1 hora. La solución se filtró a través de un tapón de sílice y se concentró hasta secar para dar el compuesto del título.

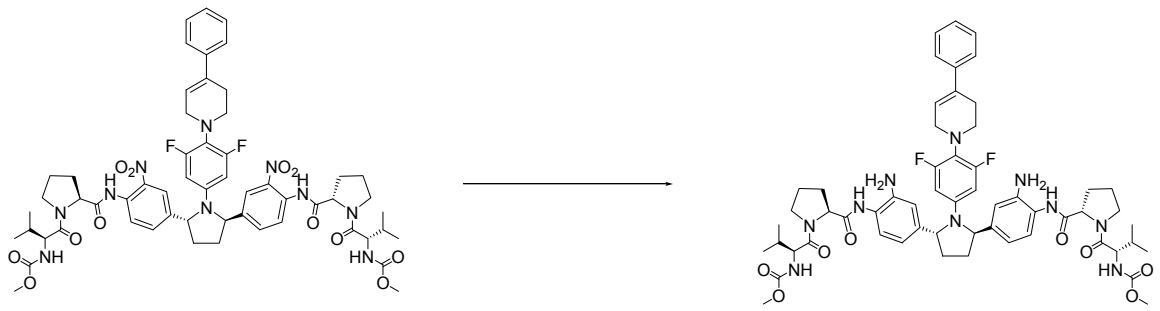
Ilustración del Procedimiento General 9: Procedimiento General 9D



(2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-((2R,5R)-1-(4-cloro-3-fluorofenil)pirrolidin-2,5-diil)bis(2-amino-4,1-fenilen))bis(azanodiil)bis(oxometilen)bis(pirrolidin-2,1-diil))bis(3-metil-1-oxobutan-2,1-diil)dicarbamato de dimetilo

Se agregaron (2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-((2R,5R)-1-(4-cloro-3-fluorofenil)pirrolidin-2,5-diil)bis(2-nitro-4,1-fenilen))bis(azanodiil)bis(oxometilen)bis(pirrolidin-2,1-diil))bis(3-metil-1-oxobutan-2,1-diil)dicarbamato de dimetilo (1,0g, 1,02 mmol) y tetrahidrofurano (25 mL) a óxido de platino (0,20 g, 0,88 mmol) en un recipiente para presión y se agitó a temperatura ambiente bajo hidrógeno a 30 psi durante 1,5 horas. La solución se filtró a través de una membrana de Nylon y se concentró hasta secar para dar 100% de rendimiento de un residuo marrón que se usó sin purificación.

Ilustración del Procedimiento General 9: Procedimiento General 9E

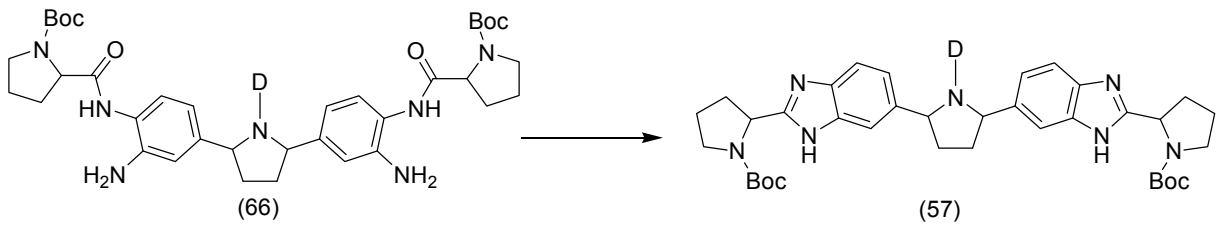


(2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-((2R,5R)-1-(3,5-difluoro-4-(4-fenil-5,6-dihidropiridin-1(2H)-il)fenil)pirrolidin-2,5-diil)bis(2-amino-4,1-fenilen))bis(azanodiil)bis(oxometilen)bis(pirrolidin-2,1-diil))bis(3-metil-1-oxobutan-2,1-diil)dicarbamato de dimetilo

Se disolvió (2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-((2R,5R)-1-(3,5-difluoro-4-(4-fenil-5,6-dihidropiridin-1(2H)-il)fenil)pirrolidin-2,5-diil)bis(2-nitro-4,1-fenilen))bis(azanodiil)bis(oxometilen)bis(pirrolidin-2,1-diil))bis(3-metil-1-oxobutan-2,1-diil)dicarbamato de dimetilo (150 mg, 0,134 mmol) en una mezcla de THF (1 mL) y EtOH absoluto (1 mL) bajo nitrógeno. Se agregó una solución de cloruro de amonio (10,73 mg, 0,201 mmol) en agua (0,333 mL), seguida por polvo de hierro (37,4 mg, 0,669 mmol), y la mezcla se calentó bajo un condensador de reflujo en un baño de aceite a 90 °C. Luego de

1 hora, la mezcla de reacción se enfrió a temperatura ambiente, se filtró al vacío a través de un lecho de Celite 545, y se lavó cuidadosamente con EtOAc. El material filtrado se concentró por evaporación por rotación para eliminar los solventes orgánicos. El residuo se disolvió en EtOAc (50 mL), se lavó con agua (2×25 mL) y salmuera (25 mL), se secó sobre MgSO4 anhidro, se filtró, y se concentró por evaporación por rotación. El residuo se purificó mediante cromatografía flash en SiO2 (columna Alltech Extract-Clean, lecho de 10 g) eluyendo con un gradiente en pasos de metanol/CH2Cl2 3% a 4% para dar el producto como un sólido amarillo (77 mg, 0,073 mmol, 54%). 1H RMN (400 MHz, DMSO-d6) δ ppm 0,92 (dd, J=13,07, 6,56 Hz, 12 H), 1,58 - 1,75 (m, 2 H), 1,83 - 2,09 (m, 8 H), 2,13 - 2,28 (m, 1 H), 3,17 (s, 2 H), 3,38 - 3,68 (m, 8 H), 3,55 (s, 6 H), 3,84 (s, 2 H), 4,05 (t, J=8,35 Hz, 2 H), 4,37 - 4,47 (m, 2 H), 4,93 (s, 4 H), 5,01 (d, J=5,10 Hz, 2 H), 5,85 - 6,00 (m, 2 H), 6,14 (s, 1 H), 6,44 (d, J=8,02 Hz, 2 H), 6,55 - 6,66 (m, 2 H), 7,02 (d, J=7,81 Hz, 2 H), 7,21 - 7,49 (m, 8 H), 9,28 (s, 2 H); MS (ESI+) m/z 1061 (M+H)+; MS (ESI-) m/z 1059 (M-H)-.

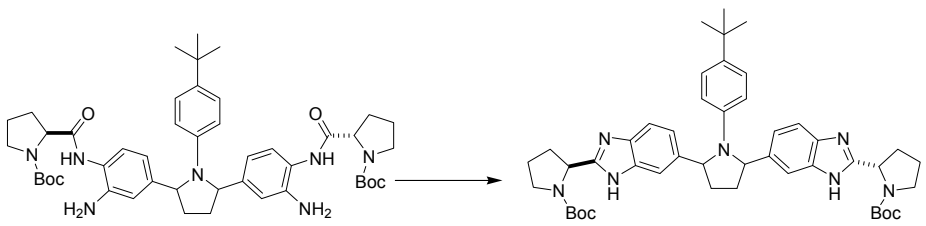
Procedimiento General 10. Formación de benzimidazol



Los compuestos (66) pueden convertirse a compuestos (57) por calentamiento de la forma pura en ácido acético o con ácido acético en tolueno o dioxano a 50-80 ºC. La reacción puede someterse a tratamiento posterior concentrando la solución, neutralizando con solución acuosa de bicarbonato de sodio, extrayendo con un solvente orgánico (por ejemplo, diclorometano), secando la mezcla de solventes orgánicos (por ejemplo, MgSO4, Na2SO4), filtrando y concentrando al vacío. La reacción también puede llevarse a cabo en tolueno como solvente agregando ácido acético (aproximadamente 3 a 5 equivalentes) también con calentamiento a 50-80 ºC. El tratamiento posterior puede consistir simplemente en la evaporación del solvente y la eliminación del ácido acético residual por

adición y evaporación de tolueno. Los compuestos (57) pueden purificarse mediante cromatografía en gel de sílice eluyendo con acetato de etilo/diclorometano o metanol/diclorometano. A pesar de que la ciclización ilustrada se muestra con un grupo t-butoxicarbonilo (Boc) unido, la reacción también puede llevarse a cabo con los grupos –T–RD unidos, donde T y RD son como se definen en la presente.

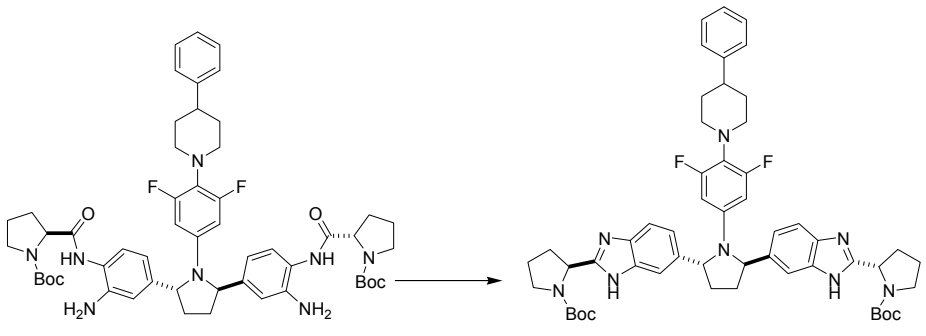
Ilustración del Procedimiento General 10: Procedimiento General 10A; Ejemplo 1



(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

Como una mezcla de diastereómeros trans, se disolvió (2S,2'S)- 2,2'-(5,5'-(1-(4-tert-butilfenil)pirrolidin-2,5-diil)bis(2-amino-5,1-fenilen)bis(azanodiil)bis(oxometilen))dipirrolidin-1-carboxilato de tert-butilo (0,355 g) en ácido acético puro (3 mL) y se calentó a 72 ºC durante 2 horas. La solución se concentró y luego se volcó sobre agua y el pH se ajustó 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 40 g, eluyendo con metanol/diclorometano 0-5% para dar 0,185 g (55%) del compuesto del título como un sólido amarillo claro.

Ilustración del Procedimiento General 10: Procedimiento General 10A; Ejemplo 2



(2S,2'S)- 2,2'-(6,6'-((2R,5R)-1-(3,5-difluoro-4-(4-fenilpiperidin-1-il)fenil)pirrolidin-2,5-diil)bis(1H-benzo[d]imidazol-6,2-diil))dipirrolidin-1-carboxilato de tert-butilo

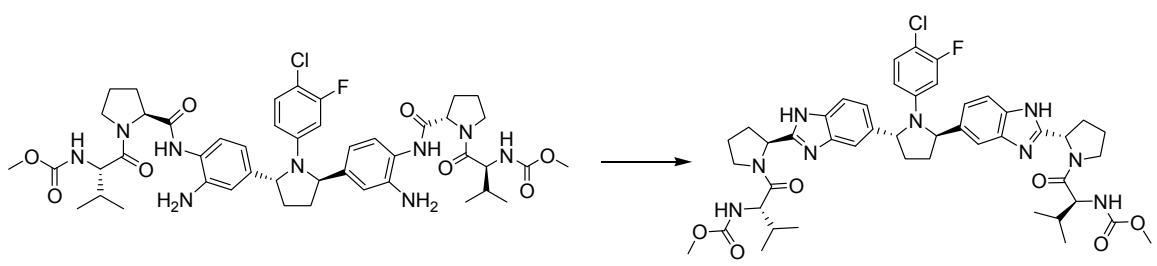
Una solución de (2S,2'S)- 2,2'-(4,4'-((2R,5R)-1-(3,5-difluoro-4-(4-fenilpiperidin-1-il)fenil)pirrolidin-2,5-diil)bis(2-amino-4,1-fenilen))bis(azanodiil)bis(oxometilen)dipirrolidin-1-carboxilato de tert-butilo (2,4 g, 2,57 mmol) y ácido acético (1,54 g, 25,7 mmol) en tolueno (50 mL) se calentó a 70 ºC durante 2 horas, se enfrió y se concentró. El residuo se incluyó en una mezcla azeotrópica 3×15 mL con tolueno y se secó bajo vacío para dar una espuma blanca (2,34 g, rendimiento cuantitativo) que se usó sin purificación. MS (ESI+) m/z 913 (M+H)+.

Ilustración del Procedimiento General 10: Procedimiento General 10A; Ejemplo 3

(2S,2'S)- 2,2'-(6,6'-((2R,5R)-1-(3,5-difluoro-4-(piperidin-1-il)fenil)pirrolidin-2,5-diil)bis(5-fluoro-1H-benzo[d]imidazol-6,2-diil))dipirrolidin-1-carboxilato de tert-butilo

A 2,2'-(4,4'-((2R,5R)-1-(3,5-difluoro-4-(piperidin-1-il)fenil)pirrolidin-2,5-diil)bis(2-amino-5-fluoro-4,1-fenilen))bis(azanodiil)bis(oxometilen)dipirrolidin-1-carboxilato de tert-butilo crudo (del Procedimiento General 9A, Ejemplo 2) se agregó tolueno (45 ml) seguido por ácido acético (2,66 ml, 46,4 mmol) y la solución se agitó a 50 ºC durante 16 horas. La solución enfriada se concentró , se incluyó en una mezcla azeotrópica dos veces con tolueno, y el residuo crudo se purificó en un cartucho de gel de sílice ISCO de 40 g eluyendo con CH3OH/CH2Cl2 0-5% para dar el compuesto del título (2,85 g).

Ilustración del Procedimiento General 10: Procedimiento General 10B, Ejemplo 1

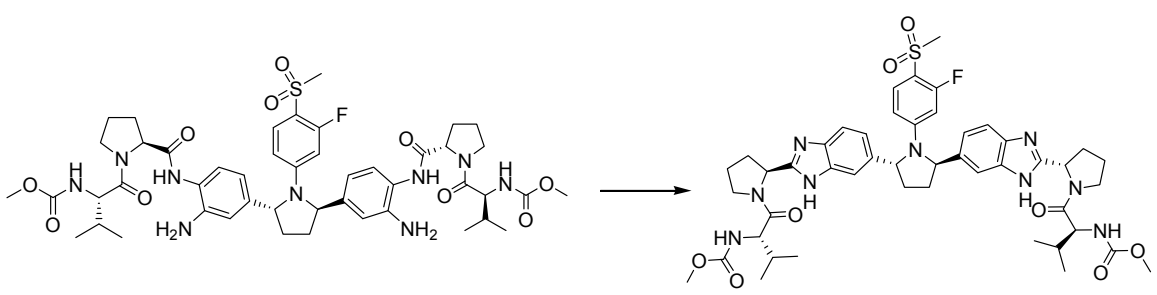


{(2S)-1-[(2S)-2-{5-[(2R,5R)-1-(4-cloro-3-fluorofenil)-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-benzimidazol-5-il}pirrolidin-2-il]-

1H-benzimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo (Nomenclatura ACD v12)

Se disolvió (2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-((2R,5R)-1-(4-cloro-3-fluorofenil)pirrolidin-2,5-diil)bis(2-amino-4,1-fenilen))bis(azanodiil)bis(oxometilen)bis(pirrolidin-2,1-diil))bis(3-metil-1-oxobutan-2,1-diil)dicarbamato de dimetilo (Procedimiento General 9D) (0,98 g, 1,01 mmol) en tolueno (12 mL) y se trató con ácido acético glacial (1,16 mL, 20,2 mmol) y se calentó a 65 ºC durante 1,5 horas. La mezcla se concentró, se disolvió en diclorometano, y se lavó con solución de bicarbonato de sodio. La mezcla de reacción orgánica se concentró y se purificó mediante cromatografía, eluyendo con metanol en diclorometano 0-6% para dar 0,17 g (19%) del compuesto del título como un sólido amarillo oscuro. 1H RMN (400 MHz, DMSO-d6) ppm 0,77 - 0,90 (m, 12 H) 1,66 - 1,78 (m, 2 H) 1,88 - 1,95 (m, 2 H) 1,96 - 2,06 (m, 4 H) 2,15 - 2,24 (m, 4 H) 2,54 - 2,60 (m, 2 H) 3,54 (s, 6 H) 3,79 - 3,86 (m, 4 H) 4,06 (t, J=8,46 Hz, 2 H) 5,10 - 5,18 (m, 2 H) 5,37 - 5,45 (m, 2 H) 6,16 (dd, J=9,49, 2,01 Hz, 1 H) 6,22 (dd, J=13,55, 2,06 Hz, 1 H) 7,00 - 7,11 (m, 3 H) 7,22 (s, 1 H) 7,28 (d, J=8,57 Hz, 2 H) 7,32 (s, 1 H) 7,40 (d, J=8,24 Hz, 1 H) 7,47 (d, J=8,13 Hz, 1 H) 12,07 (d, J=2,93 Hz, 2 H); MS (APCI+) m/z 884 (M+H)+.

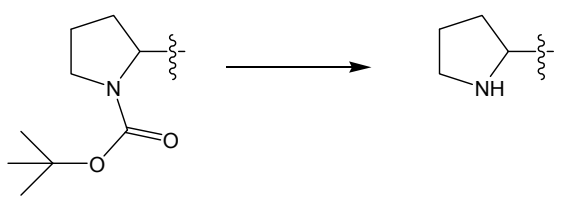
Ilustración del Procedimiento General 10: Procedimiento General 10B; Ejemplo 2



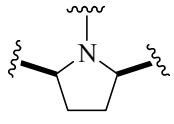
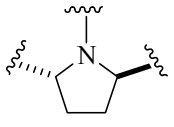
{(2S)-1-[(2S)-2-{6-[(2R,5R)-1-[3-fluoro-4-(metilsulfonil)fenil]-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-benzimidazol-6-il}pirrolidin-2-il]-1H-benzimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo (Nomenclatura ACD v12)

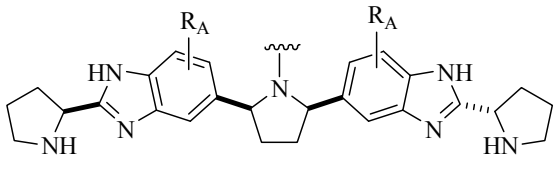
A una suspensión de (2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-((2R,5R)-1-(3-fluoro-4-(metilsulfonil)fenil)pirrolidin-2,5-diil)bis(2-amino-4,1-fenilen))bis(azanodiil)bis(oxometilen)bis(pirrolidin-2,1-diil))bis(3-metil-1-oxobutan-2,1-diil)dicarbamato de dimetilo (0,190 g, 0,197 mmol) en tolueno (2 mL) se agregó ácido acético (1 mL, 17,48 mmol), y la mezcla de reacción se agitó a 60 ºC durante la noche. El análisis por LCMS moestró que la reacción se había completado. La mezcla de reacción se diluyó con acetato de etilo y se lavó con una solución saturada de NaHCO3. El extracto orgánico se separó, se secó sobre sulfato de sodio anhidro, se filtró, se concentró en un rotovap y se purificó mediante HPLC en fase reversa usando acetonitrilo/ agua(TFA) 5-100%. Las fracciones puras se combinaron, se neutralizó con solución saturada de NaHCO3, y se concentró. El residuo se extrajo con CH2Cl2. El extracto orgánico se separó, se secó sobre sulfato de sodio anhidro, se filtró, y se concentró para dar el compuesto del título (30 mg) como un sólido blanco.

Procedimiento General 11. Procedimiento para eliminar Grupos Protectores t-Butoxicarbonilo

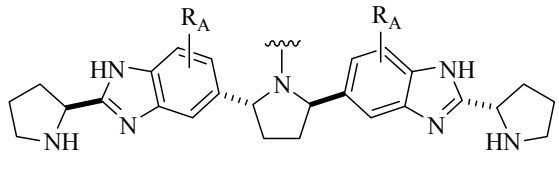


La eliminación de un grupo protector t-butoxicarbonilo (Boc), de acuerdo con la descripción precedente puede efectuarse usando condiciones estándar como por ejemplo por tratamiento con un ácido, como por ejemplo TFA, HCl, o ácido fórmico. Por ejemplo, la reacción con TFA/CH2Cl2 o HCl en dioxano a temperatura ambiente puede eliminar el grupo protector Boc. Los compuestos pueden utilizarse o aislarse como la sal o la base libre.

Luego de la eliminación de los grupos protectores Boc y en los casos donde los compuestos se procesaron como mezclas de pirrolidinas cis,  , y trans,  , donde los diastereómeros cis y trans pueden someterse a separación usando métodos cromatográficos estándar (por ejemplo, gel de sílice en fase normal o fase reversa). Por ejemplo, los compuestos de tipo general 11-1 y 11-2 pueden separarse de esta manera.

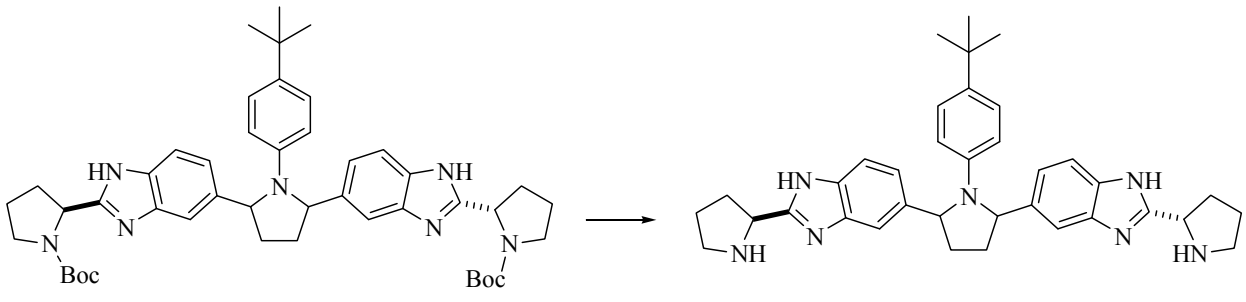


11-1



11-2

Ilustración del Procedimiento General 11. Procedimiento General 11A (HCl-Dioxano), Ejemplo 1



(S)-5,5'-(1-(4-tert-butilfenil)pirrolidin-2,5-diil)bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol)

Se disolvió (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 (0,204 g, 0,264 mmol) en THF (2 mL) a temperatura ambiente y se trató con HCl 4 M en dioxano (2 mL). Una vez

completa la reacción de la reacción, la mezcla se concentró hasta secar para dar el compuesto crudo del título.

Ilustración del Procedimiento General 11. Procedimiento General 11A (HCl-Dioxano), Ejemplo 2

(S)-6,6'-((2R,5R)-1-(3,5-difluoro-4-(4-fenilpiperidin-1-il)fenil)pirrolidin-2,5-diil)bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol)

Una solución de (2S,2'S)- 2,2'-(6,6'-((2R,5R)-1-(3,5-difluoro-4-(4-fenilpiperidin-1-il)fenil)pirrolidin-2,5-diil)bis(1H-benzo[d]imidazol-6,2-diil))dipirrolidin-1-carboxilato de tert-butilo (2,34 g, 2,57 mmol) en dioxano (25 mL) se trató con cloruro de hidrógeno en dioxano 4 M (16,06 mL, 64,3 mmol) para dar una suspensión color tostado. La mezcla se sonicó durante 10 minutos para dispersar los sólidos en una fina suspensión, se agitó durante 2 horas y se concentró. El residuo se incluyó en una mezcla azeotrópica 3×30 mL con tolueno y se secó para dar la sal de HCl del compuesto del título como un polvo color tostado que se usó sin purificación (suponiéndose rendimiento cuantitativo, 2,57 mmol). MS (ESI+) m/z 713 (M+H)+.

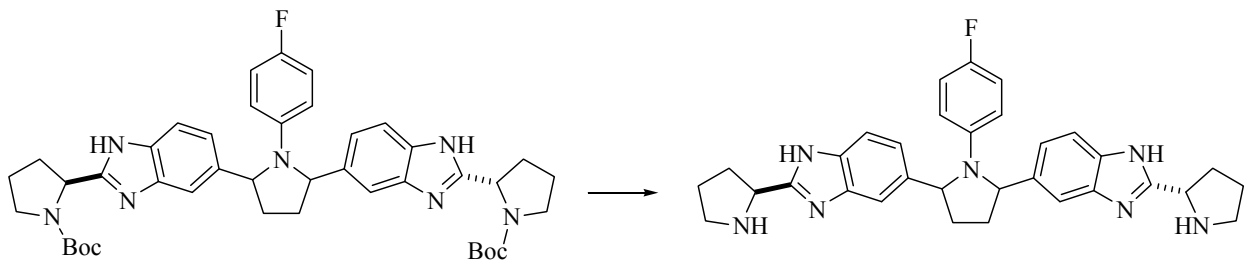
Ilustración del Procedimiento General 11. Procedimiento General 11A (HCl-Dioxano), Ejemplo 3

6,6'-{(2R,5R)-1-[3,5-difluoro-4-(piperidin-1-il)fenil]pirrolidin-2,5-diil}bis{5-fluoro-2-[(2S)-pirrolidin-2-il]-1H-benzimidazol} (Nomenclatura ACD v12)

A una solución de (2S,2'S)- 2,2'-(6,6'-((2R,5R)-1-(3,5-difluoro-4-(piperidin-1-il)fenil)pirrolidin-2,5-diil)bis(5-fluoro-1H-benzo[d]imidazol-6,2-diil))dipirrolidin-1-carboxilato de tert-butilo (2,85 g, 3,26 mmol) en dioxano (10 ml) se agregó HCl 4 M/dioxano (10,0 mL, 40,0 mmol) y la solución se agitó enérgicamente a temperatura ambiente durante 1 hora. La solución se concentró, se disolvió en una cantidad mínima de H2O y se aplicó a un cartucho ISCO C18 de 130 g y se eluyó con CH3CN/(0,1% TFA/H2O) 0-100%. Las fracciones deseadas se combinaron, se basificó con solución de NaHCO3 10%, y se

extrajo con EtOAc. Los extractos combinados se secaron (MgSO4), se filtró y se concentró para dar el compuesto del título (932,5 mg, 1,386 mmol, 42,5%).

Ilustración del Procedimiento General 11. Procedimiento General 11B (TFA-CH2Cl2)



(S)-5,5'-(1-(4-fluorofenil)pirrolidin-2,5-diil)bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol)

Se disolvió (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 (0,120 g, 0,163 mmol) en diclorometano (2 mL) a temperatura ambiente y se trató con TFA (1 mL). La mezcla se concentró hasta secar, se disolvió en isopropanol/diclorometano 25% y se lavó con solución de bicarbonato de sodio. Los sólidos resultantes se retiraron por filtración y se secó. El material orgánico filtrate se concentró y se secó para dar más compuesto del título. Los lotes de sólido blanco opaco se combinaron para dar el compuesto del título (0,062 g 72% de rendimiento).

Los siguientes compuestos pueden prepararse como base libre o sal usando el Procedimiento General 8, Procedimiento General 9A (PtO2), Procedimiento General 10/10A, y Procedimiento General 11/11A:

(S)-6,6'-((2R,5R)-1-(4-(piridin-2-il)fenil)pirrolidin-2,5-diil)bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol);

(S)-6,6'-((2R,5R)-1-(3-cloro-4-(trifluorometoxi)fenil)pirrolidin-2,5-diil)bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol);

(S)-6,6'-((2R,5R)-1-(4-(2-metoxietoxi)fenil)pirrolidin-2,5-diil)bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol);

(S)-6,6'-((2R,5R)-1-(4-clorofenil)pirrolidin-2,5-diil)bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol);

(S)-6,6'-((2R,5R)-1-(3-metil-4-(piperidin-1-il)fenil)pirrolidin-2,5-diil)bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol);

(S)-6,6'-((2S,5S)-1-(4-ciclopropil-3,5-difluorofenil)pirrolidin-2,5-diil)bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol);

(S)-6,6'-((2S,5S)-1-(4-ciclopropil-2-fluorofenil)pirrolidin-2,5-diil)bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol);

(S)-6,6'-((2R,5R)-1-(3-fluoro-4-(piperidin-1-il)fenil)pirrolidin-2,5-diil)bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol);

(S)-6,6'-((2R,5R)-1-(3,5-difluoro-4-(4-(trifluorometil)piperidin-1-il)fenil)pirrolidin-2,5-diil)bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol);

(S)-6,6'-((2R,5R)-1-(4-(4-tert-butilpiperidin-1-il)-3,5-difluorofenil)pirrolidin-2,5-diil)bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol);

(S)-6,6'-((2R,5R)-1-(4-(4,4-dimetilpiperidin-1-il)-3,5-difluorofenil)pirrolidin-2,5-diil)bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol);

(S)-6,6'-((2R,5R)-1-(3,5-difluoro-4-(6-azaespiro[2,5]octan-6-il)fenil)pirrolidin-2,5-diil)bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol);

(S)-6,6'-((2R,5R)-1-(3,5-difluoro-4-(isoindolin-2-il)fenil)pirrolidin-2,5-diil)bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol);

2-(4-((2R,5R)-2,5-bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol-6-il)pirrolidin-1-il)-2,6-difluorofenil)-2-azabiciclo[2,2,2]octano;

(S)-6,6'-((2R,5R)-1-(3,5-difluoro-4-(4-isopropilpiperidin-1-il)fenil)pirrolidin-2,5-diil)bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol);

(S)-6,6'-((2R,5R)-1-(4-(3,3-dimetilazetidin-1-il)-3,5-difluorofenil)pirrolidin-2,5-diil)bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol);

(S)-6,6'-((2R,5R)-1-(4-(4-fenilpiperidin-1-il)fenil)pirrolidin-2,5-diil)bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol);

6,6'-{(2R,5R)-1-[3,5-difluoro-4-(piperidin-1-il)fenil]pirrolidin-2,5-diil}bis{5-fluoro-2-[(2S)-pirrolidin-2-il]-1H-benzimidazol} (Nomenclatura ACD v12);

(S)-6,6'-((2S,5R)-1-(3,5-difluoro-4-(piperidin-1-il)fenil)pirrolidin-2,5-diil)bis(5-fluoro-2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol)

(S,S,S)-6,6'-((2R,5R)-1-(3,5-difluoro-4-(piperidin-1-il)fenil)pirrolidin-2,5-diil)bis(5-fluoro-2-((2S,3aS,6aS)-octahidrociclopenta[b]pirrol-2-il)-1H-benzo[d]imidazol);

(S,S,S)-6,6'-((2R,5R)-1-(3,5-difluoro-4-(piperidin-1-il)fenil)pirrolidin-2,5-diil)bis(2-((2S,3aS,6aS)-octahidrociclopenta[b]pirrol-2-il)-1H-benzo[d]imidazol);

(S)-6,6'-((2R,5R)-1-(4-(2,3-dihidroespiro[inden-1,4'-piperidin]-1'-il)-3,5-difluorofenil)pirrolidin-2,5-diil)bis(5-fluoro-2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol);

(S)-6,6'-((2R,5R)-1-(3,5-difluoro-4-(4-(4-metoxifenil)piperidin-1-il)fenil)pirrolidin-2,5-diil)bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol);

(S)-6,6'-((2R,5R)-1-(3,5-difluoro-4-(4-fluoro-4-fenilpiperidin-1-il)fenil)pirrolidin-2,5-diil)bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol);

(S)-6,6'-((2R,5R)-1-(4-(4-fluoro-4-fenilpiperidin-1-il)fenil)pirrolidin-2,5-diil)bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol);

(S)-6,6'-((2R,5R)-1-(3,5-difluoro-4-(4-(fluorodifenilmetil)piperidin-1-il)fenil)pirrolidin-2,5-diil)bis(5-fluoro-2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol);

(S)-6,6'-((2R,5R)-1-(3,5-difluoro-4-(4-fenilpiperidin-1-il)fenil)pirrolidin-2,5-diil)bis(5-fluoro-2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol);

(S)-6,6'-((2R,5R)-1-(3,5-difluoro-4-(4-(4-fluorofenil)piperidin-1-il)fenil)pirrolidin-2,5-diil)bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol);

(S)-6,6'-((2R,5R)-1-(3,5-difluoro-4-(4-(3-(trimetilsilil)fenil)piperidin-1-il)fenil)pirrolidin-2,5-diil)bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol);

(S)-6,6'-((2R,5R)-1-(4-(4-(3,4-difluorofenil)piperidin-1-il)-3,5-difluorofenil)pirrolidin-2,5-diil)bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol);

(S)-6,6'-((2R,5R)-1-(4-(4-(3,5-difluorofenil)piperidin-1-il)-3,5-difluorofenil)pirrolidin-2,5-diil)bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol);

(S)-6,6'-((2R,5R)-1-(3,5-difluoro-4-(4-(4-(trifluorometil)fenil)piperazin-1-il)fenil)pirrolidin-2,5-diil)bis(5-fluoro-2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol);

6-((2R,5R)-1-(3,5-difluoro-4-(piperidin-1-il)fenil)-5-(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol-6-il)pirrolidin-2-il)-5-fluoro-2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol;

(S)-6,6'-((2R,5R)-1-(4-(4-bencilpiperidin-1-il)-3,5-difluorofenil)pirrolidin-2,5-diil)bis(5-fluoro-2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol);

(S)-6,6'-((2R,5R)-1-(4-(4-bencilpiperidin-1-il)-3,5-difluorofenil)pirrolidin-2,5-diil)bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol);

(S)-6,6'-((2S,5R)-1-(3,5-difluoro-4-(4-fenilpiperidin-1-il)fenil)pirrolidin-2,5-diil)bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol);

4-(4-((2R,5R)-2,5-bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol-6-il)pirrolidin-1-il)-2,6-difluorofenil)-2-fenilmorfolina;

(S)-6,6'-((2R,5R)-1-(3,5-difluoro-4-(2-fenilpiperidin-1-il)fenil)pirrolidin-2,5-diil)bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol);

(2S,6R)-4-(4-((2R,5R)-2,5-bis(5-fluoro-2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol-6-il)pirrolidin-1-il)-2,6-difluorofenil)-2,6-dimetilmorfolina;

(S)-6,6'-((2R,5R)-1-(3,5-difluoro-4-(3-azaespiro[5,5]undecan-3-il)fenil)pirrolidin-2,5-diil)bis(5-fluoro-2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol);

(S)-6,6'-((2R,5R)-1-(4-(4-ciclohexilpiperidin-1-il)-3,5-difluorofenil)pirrolidin-2,5-diil)bis(5-fluoro-2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol);

(S)-4-(4-((2R,5R)-2,5-bis(5-fluoro-2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol-6-il)pirrolidin-1-il)-2,6-difluorofenil)-2-fenilmorfolina;

(S)-6,6'-((2R,5R)-1-(3,5-difluoro-4-(4-fenilpiperazin-1-il)fenil)pirrolidin-2,5-diil)bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol);

(S,R)-6,6'-((2R,5R)-1-(3,5-difluoro-4-(piperidin-1-il)fenil)pirrolidin-2,5-diil)bis(2-((2S,4R)-4-fluoropirrolidin-2-il)-1H-benzo[d]imidazol);

(S)-6,6'-((2R,5R)-1-(4-(4-(2,6-difluorofenil)piperazin-1-il)-3,5-difluorofenil)pirrolidin-2,5-diil)bis(5-fluoro-2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol);

(S)-6,6'-((2R,5R)-1-(4-(4-(2,4-difluorofenil)piperidin-1-il)-3,5-difluorofenil)pirrolidin-2,5-diil)bis(5-fluoro-2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol);

(S)-6,6'-((2R,5R)-1-(3,5-difluoro-4-(4-(4-fluorofenil)piperidin-1-il)fenil)pirrolidin-2,5-diil)bis(5-fluoro-2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol);

(S)-6,6'-((2S,5S)-1-(4-(4-(2,6-difluorofenil)piperazin-1-il)-3,5-difluorofenil)pirrolidin-2,5-diil)bis(5-fluoro-2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol);

(S)-6,6'-((2R,5R)-1-(3,5-difluoro-4-(4-(5-metiltiofen-2-il)piperidin-1-il)fenil)pirrolidin-2,5-diil)bis(5-fluoro-2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol); y

(S)-6,6'-((2R,5R)-1-(3,5-difluoro-4-(4-fluoro-4-fenilpiperidin-1-il)fenil)pirrolidin-2,5-diil)bis(5-fluoro-2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol).

Los siguientes compuestos pueden prepararse como base libre o sal usando el Procedimiento General 8, Procedimiento General 9B (níquel-Raney), Procedimiento General 10/10A, y Procedimiento General 11/11A:

(S)-6,6'-((2R,5R)-1-(bifenil-4-il)pirrolidin-2,5-diil)bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol);

(S)-6,6'-((2R,5R)-1-(4-(ciclopentiloxi)-3-fluorofenil)pirrolidin-2,5-diil)bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol);

(S)-6,6'-((2R,5R)-1-(3,5-difluoro-4-((3aR,7aS)-1H-isoindol-2(3H,3aH,4H,5H,6H,7H,7aH)-il)fenil)pirrolidin-2,5-diil)bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol);

(S)-6,6'-((2R,5R)-1-(3,5-dicloro-4-(piperidin-1-il)fenil)pirrolidin-2,5-diil)bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol);

(S)-6,6'-((2R,5R)-1-(2,5-difluoro-4-(piperidin-1-il)fenil)pirrolidin-2,5-diil)bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol);

(S)-6,6'-((2R,5R)-1-(4-((2R,6S)-2,6-dimetilpiperidin-1-il)-3,5-difluorofenil)pirrolidin-2,5-diil)bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol);

(S)-6,6'-((2R,5R)-1-(2,3,5-trifluoro-4-(piperidin-1-il)fenil)pirrolidin-2,5-diil)bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol);

(S)-6,6'-((2R,5R)-1-(4-ciclohexil-3-fluorofenil)pirrolidin-2,5-diil)bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol);

(S)-6,6'-((2R,5R)-1-(3,4-difluorofenil)pirrolidin-2,5-diil)bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol);

(S)-6,6'-((2R,5R)-1-(4-etoxifenil)pirrolidin-2,5-diil)bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol);

(S)-6,6'-((2R,5R)-1-(4-(2,2-difluoroetoxi)fenil)pirrolidin-2,5-diil)bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol);

(S)-6,6'-((2R,5R)-1-(4-(3,5-dimetilpiperidin-1-il)-3,5-difluorofenil)pirrolidin-2,5-diil)bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol);

6,6'-{(2R,5R)-1-[4-(pentafluoro-λ6-sulfanil)fenil]pirrolidin-2,5-diil}bis{2-[(2S)-pirrolidin-2-il]-1H-benzimidazol} (Nomenclatura ACD v12);

(S)-6,6'-((2S,5S)-1-(4-ciclopropilfenil)pirrolidin-2,5-diil)bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol);

(S)-6,6'-((2R,5R)-1-(4-tert-butilfenil)pirrolidin-2,5-diil)bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol);

(S,S)-6,6'-((2R,5R)-1-(3,5-difluoro-4-(piperidin-1-il)fenil)pirrolidin-2,5-diil)bis(2-((2S,4S)-4-metoxipirrolidin-2-il)-1H-benzo[d]imidazol);

(S,S)-6,6'-((2R,5R)-1-(3,5-difluoro-4-(piperidin-1-il)fenil)pirrolidin-2,5-diil)bis(2-((2S,4S)-4-fluoropirrolidin-2-il)-1H-benzo[d]imidazol);

(S,S)-6,6'-((2R,5R)-1-(4-fluorofenil)pirrolidin-2,5-diil)bis(2-((2S,4S)-4-fluoropirrolidin-2-il)-1H-benzo[d]imidazol);

(S,S)-6,6'-((2R,5R)-1-(4-fluorofenil)pirrolidin-2,5-diil)bis(2-((2S,4S)-4-metoxipirrolidin-2-il)-1H-benzo[d]imidazol);

(S)-6,6'-((2R,5R)-1-(4-tert-butilfenil)pirrolidin-2,5-diil)bis(2-((S)-5,5-dimetilpirrolidin-2-il)-1H-benzo[d]imidazol);

(S,S)-6,6'-((2R,5R)-1-(4-tert-butilfenil)pirrolidin-2,5-diil)bis(2-((2S,4S)-4-fluoropirrolidin-2-il)-1H-benzo[d]imidazol);

(S)-6,6'-((2R,5R)-1-(3,5-difluoro-4-(piperidin-1-il)fenil)pirrolidin-2,5-diil)bis(2-((3S)-2-azabiciclo[2,2,1]heptan-3-il)-1H-benzo[d]imidazol);

(S)-6,6'-((2R,5R)-1-(3,5-difluoro-4-(piperidin-1-il)fenil)pirrolidin-2,5-diil)bis(2-((S)-indolin-2-il)-1H-benzo[d]imidazol);

(S,R)-6,6'-((2R,5R)-1-(3,5-difluoro-4-(piperidin-1-il)fenil)pirrolidin-2,5-diil)bis(2-((2S,4R)-4-metoxipirrolidin-2-il)-1H-benzo[d]imidazol);

(S)-6,6'-((2R,5R)-1-(4-tert-butilfenil)pirrolidin-2,5-diil)bis(2-((S)-4-metilenepirrolidin-2-il)-1H-benzo[d]imidazol);

(S)-6,6'-((2R,5R)-1-(4-(4,4-difenilpiperidin-1-il)-3,5-difluorofenil)pirrolidin-2,5-diil)bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol);

1-(1-(4-((2R,5R)-2,5-bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol-6-il)pirrolidin-1-il)-2,6-difluorofenil)-4-fenilpiperidin-4-il)etanona;

(S)-6,6'-((2R,5R)-1-(3,5-difluoro-4-(piperidin-1-il)fenil)pirrolidin-2,5-diil)bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol);

(S,S,S)-6,6'-((2R,5R)-1-(3,5-difluoro-4-(piperidin-1-il)fenil)pirrolidin-2,5-diil)bis(2-((2S,3aS,6aS)-octahidrociclopenta[b]pirrol-2-il)-1H-benzo[d]imidazol);

(S,S,S)-6,6'-((2R,5R)-1-(4-tert-butilfenil)pirrolidin-2,5-diil)bis(2-((2S,3aS,6aS)-octahidrociclopenta[b]pirrol-2-il)-1H-benzo[d]imidazol);

(S)-6,6'-((2R,5R)-1-(3,5-difluoro-4-(3-azaespiro[5,5]undecan-3-il)fenil)pirrolidin-2,5-diil)bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol);

(S)-6,6'-((2R,5R)-1-(3-fluoro-4-(4-fenilpiperidin-1-il)fenil)pirrolidin-2,5-diil)bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol);

(S,S,S)-6,6'-((2R,5R)-1-(3,5-difluoro-4-(4-fenilpiperidin-1-il)fenil)pirrolidin-2,5-diil)bis(2-((2S,3aS,6aS)-octahidrociclopenta[b]pirrol-2-il)-1H-benzo[d]imidazol);

(S)-6,6'-((2R,5R)-1-(3,5-difluoro-4-(3-fenilpiperidin-1-il)fenil)pirrolidin-2,5-diil)bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol);

(S)-6,6'-((2R,5R)-1-(3,5-difluoro-4-(3-fenilpirrolidin-1-il)fenil)pirrolidin-2,5-diil)bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol);

(S)-6,6'-((2R,5R)-1-(3,5-difluoro-4-(4-(pirimidin-2-il)piperazin-1-il)fenil)pirrolidin-2,5-diil)bis(5-fluoro-2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol);

(S)-6,6'-((2S,5R)-1-(2-(4-fenilpiperidin-1-il)pirimidin-5-il)pirrolidin-2,5-diil)bis(5-fluoro-2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol); y

(S)-6,6'-((2S,5R)-1-(2-(piperidin-1-il)pirimidin-5-il)pirrolidin-2,5-diil)bis(5-fluoro-2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol).

Los siguientes compuestos pueden prepararse como base libre o sal usando el Procedimiento General 8, Procedimiento General 9E (Fe/NH4Cl), Procedimiento General 10/10A, y Procedimiento General 11/11A:

(S)-6,6'-((2R,5R)-1-(3,5-difluoro-4-(4-(3-fenilpropil)piperidin-1-il)fenil)pirrolidin-2,5-diil)bis(5-fluoro-2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol);

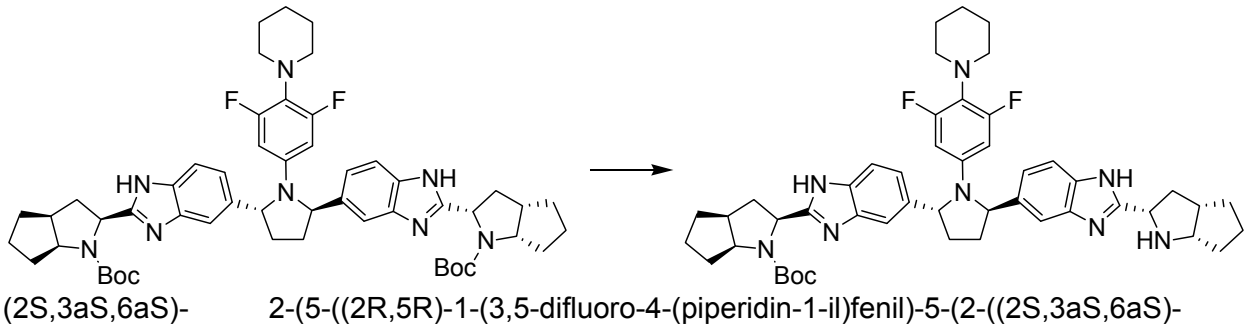
(S)-6,6'-((2R,5R)-1-(3,5-difluoro-4-(6-azaespiro[2,5]octan-6-il)fenil)pirrolidin-2,5-diil)bis(5-fluoro-2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol);

(S)-6,6'-((2R,5R)-1-(4-(4-tert-butilpiperidin-1-il)-3,5-difluorofenil)pirrolidin-2,5-diil)bis(5-fluoro-2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol);

(S)-6,6'-((2R,5R)-1-(3,5-difluoro-4-(4-(naftalen-2-il)piperidin-1-il)fenil)pirrolidin-2,5-diil)bis(5-fluoro-2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol); y

(S)-6,6'-((2R,5R)-1-(4-(benciloxi)fenil)pirrolidin-2,5-diil)bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol).

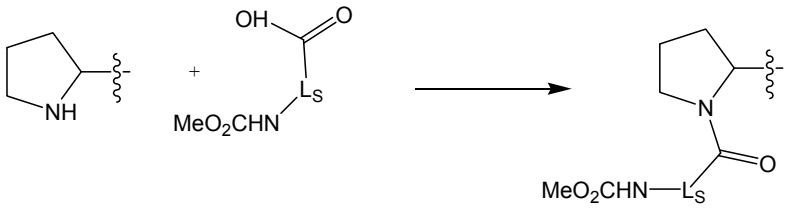
Ilustración del Procedimiento General 11. Procedimiento General 11C (monodesprotección)



(2S,3aS,6aS)-2-(5-((2R,5R)-1-(3,5-difluoro-4-(piperidin-1-il)fenil)-5-(2-((2S,3aS,6aS)-octahidrociclopenta[b]pirrol-2-il)-1H-benzo[d]imidazol-5-il)pirrolidin-2-il)-1H-benzo[d]imidazol-2-il)hexahidrociclopenta[b]pirrol-1(2H)-carboxilato de tert-butilo

La amina de partida protegida con di-Boc (1,24 g, 1,36 mmol) se disolvió en diclorometano (12 mL) a temperatura ambiente y se trató con alícuotas de ácido trifluoroacético (0,10 mL, 1,35 mmol) cada 30 minutos durante 1,5 horas. La solución se concentró hasta secar y luego se redisolvió en diclorometano y se lavó con solución de bicarbonato de sodio. Después de la concentración, el residuo se purificó mediante cromatografía, eluyendo con metanol en diclorometano 0-20% para dar 425 mg (38%) de la amina del título monodesprotegida como un polvo amarillo.

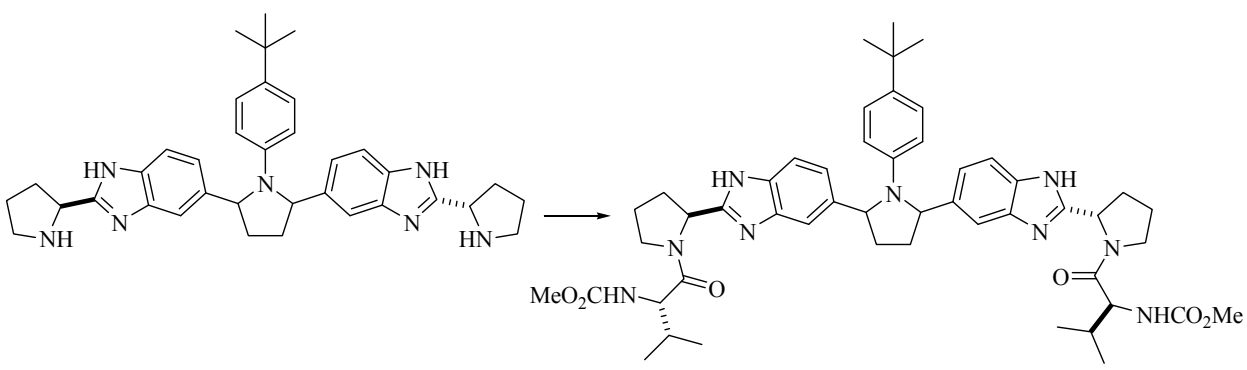
Procedimiento General 12. Protección de extremos terminales



La reacción de una amina con un ácido para formar una amida como se ilustra precedentemente puede efectuarse como se describe de manera general en el Esquema

1 y otros Esquemas descritos. La reacción puede favorecerse con un reactivo de acoplamiento de péptidos, como por ejemplo EDAC/HOBT, PyBOP, HATU, T3P o DEPBT, en un solvente como por ejemplo THF, DMF, diclorometano, acetato de etilo, o DMSO, con o sin la adición de una base amina como por ejemplo base de Hunig, N-metilmorfolina, piridina, 2,6-lutidina, o trietilamina, para dar productos amida. Por ejemplo, una amina (1 equivalente) puede hacerse reaccionar con ácidos (2 equivalentes) como por ejemplo, sin que esto constituya limitación alguna, ácido 2-(metoxicarbonilamino)-3-metilbutanoico, ácido 2-(metoxicarbonilamino)-3,3-dimetilbutanoico, ácido 2-ciclohexil-2-(metoxicarbonilamino)acético, ácido 2-(metoxicarbonilamino)-2-(tetrahidro-2H-piran-4-il)acético, o los que se enumeran más adelante bajo el Procedimiento General 19. Los productos finales de acoplamiento pueden contener distintas cantidades de estereoisómeros con respecto al anillo pirrolidina. En el caso de productos que contienen benzimidazol sustituido con fluoro (por ejemplo el Ejemplo 6.1, Ejemplo 6.12, Ejemplo 6.16), la purificación final para eliminar cantidades residuales de otro estereoisómero puede requerir cromatografía como se describe más adelante en el Procedimiento General 12C.

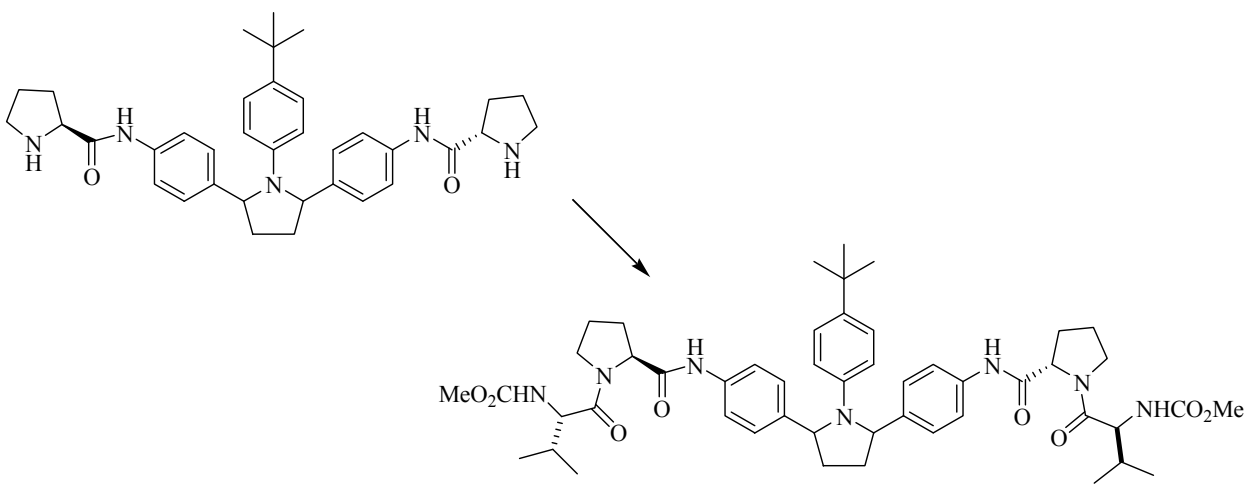
Ilustración del Procedimiento General 12. Procedimiento General 12A



(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

Se disolvieron (S)-5,5'-(1-(4-tert-butilfenil)pirrolidin-2,5-diil)bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol) (0,150 g, 0,261 mmol) y diisopropiletilamina (0,365 mL, 2,09 mmol) 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 durante 1 hora a temperatura ambiente y luego se diluyó con agua. El sólido producto se retiró por filtración y se purificó mediante cromatografía sobre gel de sílice con una columna de 12 g, eluyendo con metanol en diclorometano 0-8% para dar 0,143 g (60%) de un sólido amarillo como una mezcla de diastereómeros trans. 1H 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).

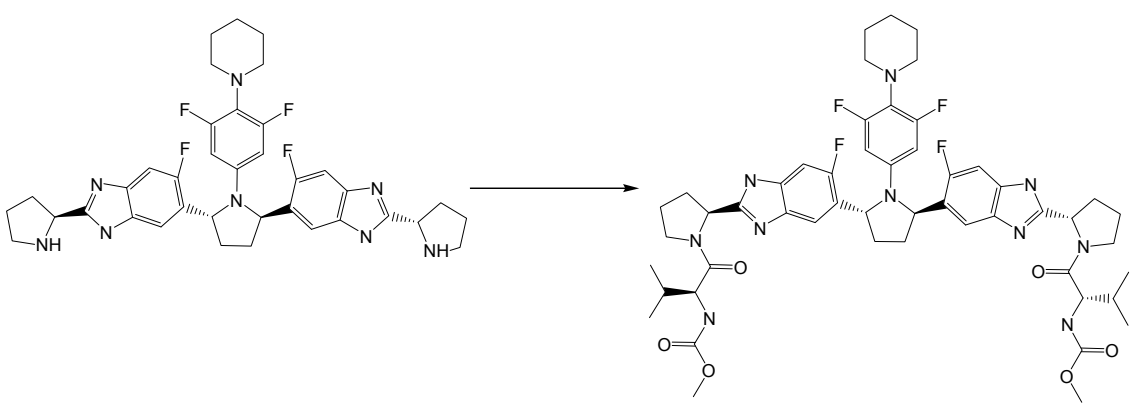
Ilustración del Procedimiento General 12. Procedimiento General 12B



(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(azanodiil)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(azanodiil)bis(oxometilen)bis(pirrolidin-2,1-diil))bis(3-metil-1-oxobutan-2,1-diil)dicarbamato de dimetilo

Se combinaron (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 (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) en DMF (2 mL). La mezcla de reacción se agitó a temperatura ambiente durante 3 horas. La mezcla 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 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%) como una mezcla de diastereómeros trans. 1H 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); MS (ESI+) m/z 895 (M+H)+.

Ilustración del Procedimiento General 12. Procedimiento General 12C



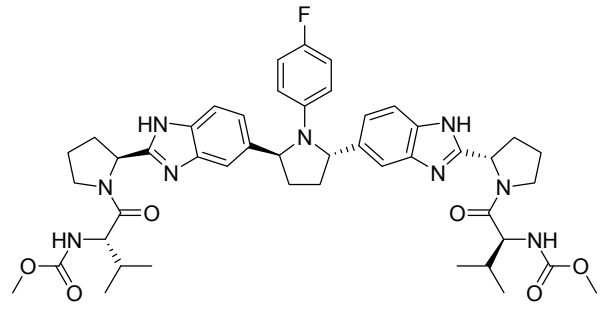
{(2S)-1-[(2S)-2-{5-[(2R,5R)-1-[3,5-difluoro-4-(piperidin-1-il)fenil]-5-{6-fluoro-2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-benzimidazol-5-il}pirrolidin-2-il]-6-fluoro-1H-benzimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

A una solución de ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico (116 mg, 0,660 mmol) en CH2Cl2 (1,0 mL) se agregó EDC (127 mg, 0,660 mmol) y la solución se agitó a temperatura ambiente durante 20 minutos. Esta solución luego se agregó a través de una cánula a una solución de 6,6'-{(2R,5R)-1-[3,5-difluoro-4-(piperidin-1-il)fenil]pirrolidin-2,5-diil}bis{5-fluoro-2-[(2S)-pirrolidin-2-il]-1H-benzimidazol} (Nomenclatura ACD v12) (148 mg, 0,220 mmol) y base de Hunig (0,231 ml, 1,320 mmol) en CH2Cl2 (1,000 mL) y luego se agregó HOBT (101 mg, 0,660 mmol), y la solución luego se agitó a temperatura ambiente durante 1 hora. La solución se diluyó con CH2Cl2, se lavó con H2O, se secó (Na2SO4), se filtró y se concentró. El producto puede someterse a purificación adicional.

En un experimento separado usando el procedimiento de acoplamiento descrito, el producto crudo (aproximadamente 4 mmol) se purificó on en un sistema Teledyne/ISCO Combiflash® Rf usando un cartucho C18 eluyendo con CH3CN/(0,1%TFA/H2O) 0-30% a lo largo de 30 minutos. Las fracciones deseadas se basificaron con solución de NaHCO3 10% y se extrajo con EtOAc. Los extractos combinados se secaron (Na2SO4), se filtró y se concentró para dar un sólido blanco (545 mg). Este material luego volvió a purificarse en un sistema de HPLC preparativa Waters usando una columna C18 eluyendo con CH3CN/(0,1% TFA/H2O) 0-95% a lo largo de 40 minutos para dar un material (195 mg) que contenía principalmente el compuesto del título y una cantidad residual de un producto diasteromérico. Para eliminar la cantidad restante del diasterómero, esta muestra se sometió a cromatografía quiral usando una columna Chiralpak® IA (5 cm×15 cm, 20 mL/minuto) y eluyendo con hexano/THF/[CH3OH/EtOH 8:2]55/30/15 para dar el compuesto del título (116 mg, 0,118 mmol). 1H RMN (400 MHz, CDCl3) δ ppm 10,51-10,60 (m, 1H) 10,33-10,41 (m, 1H) 7,43-7,50 (m, 1H) 7,32 (t, 1H) 7,13 (d, 1H) 6,93 (t, 1H)

5,82 (d, 2H) 5,28-5,48 (m, 6H) 4,26-4,39 (m, 2H) 3,78-3,90 (m, 2H) 3,70-3,71 (d, 6H) 3,57-3,67 (m, 2H) 3,44-3,57 (m, 1H) 2,99-3,12 (m, 2H) 2,79-2,98 (m, 4H) 1,78-2,58 (m, 12H) 1,41-1,51 (m, 2H) 0,80-0,95 (m, 12H); MS (ESI) m/z 987 (M+H)+.

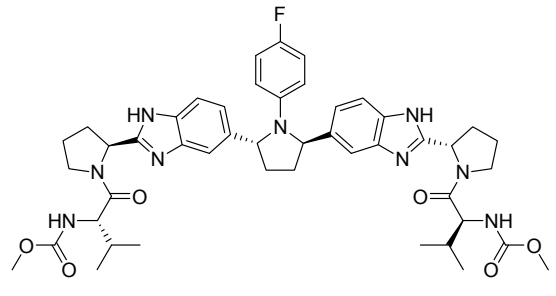
Procedimiento General 14. Separación quiral



(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

La mezcla de diastereómeros trans se cromatografió mediante cromatografía quiral en una columna Chiralpak IA eluyendo con una mezcla de hexano/EtOH/CH3OH/1,2-dicloroetano/dietilamina (25/25/25/25/0,1) para dar dos isómeros separados. 1H 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).

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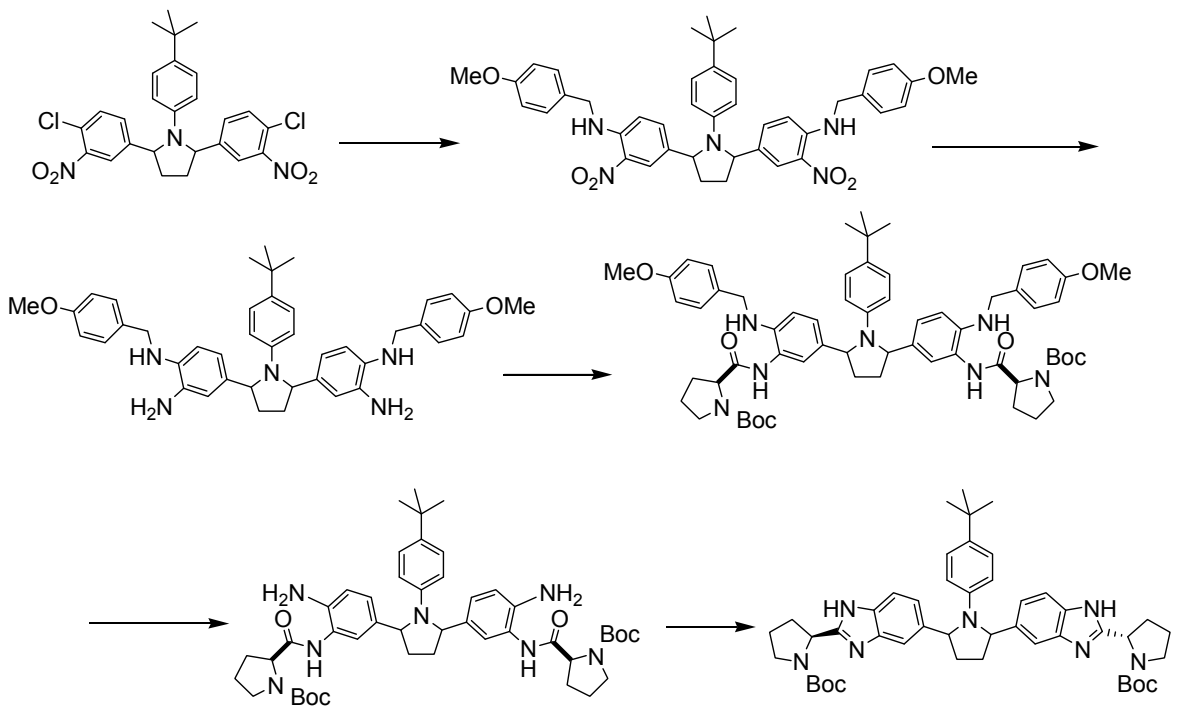
(2S,2'S)-1,1'-((2S,2'S)-2,2'-(5,5'-((2R,5R)-1-(4-fluorofenil)pirrolidin-2,5-diil)bis(1H-benzo[d]imidazol-5,2-diil))bis(pirrolidin-2,1-diil))bis(3-metil-1-oxobutan-2,1-diil)dicarbamato de dimetilo

1H 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).

Procedimiento General 15. Síntesis de benzimidazol por desplazamiento de metoxibencilamina ruta I

Se describe en forma general en el Esquema VIII un método para preparar ciertos compuestos (57) y (59). A continuación en el Procedimiento General 15A se ilustra una síntesis representativa de (57) donde D es 4-tert-butilfenilo.

Ilustración del Procedimiento General 15. Procedimiento General 15A



Los cinco pasos que se han ilustrado se describen por medio de los siguientes procedimientos experimentales:

4,4'-(1-(4-tert-butilfenil)pirrolidin-2,5-diil)bis(N-(4-metoxibencil)-2-nitroanilina)

Se combinó 1-(4-tert-butilfenil)-2,5-bis(4-cloro-3-nitrofenil)pirrolidina (4,41 g, 8,57 mmol), puro, con p-metoxibencilamina (8,93 mL, 68,6 mmol) y se calentó a 145 ºC durante 1 hora. La mezcla se diluyó con diclorometano y se filtró. El material filtrado se lavó con HCl 0,5 M, solución de NaHCO3, y luego salmuera. La fase orgánica se concentró y se purificó mediante cromatografía sobre gel de sílice con una columna de 80 g, eluyendo con acetato de etilo /hexanos 0- 50%para dar 4,13g (67%) de un sólido espumoso anaranjado.

4,4'-(1-(4-tert-butilfenil)pirrolidin-2,5-diil)bis(N1-(4-metoxibencil)bencen-1,2-diamina)

Se disolvió 4,4'-(1-(4-tert-Butilfenil)pirrolidin-2,5-diil)bis(N-(4-metoxibencil)-2-nitroanilina) (2 g, 2,79 mmol) 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) como una suspensión en THF. El recipiente se evacuó y se purgó con nitrógeno dos veces, luego se evacuó y se conectó con un balón de hidrógeno. La mezcla se agitó a temperatura ambiente durante 20 horas, luego se filtró a través de tierras diatomeas, se concentró, y se purificó mediante cromatografía sobre gel de sílice con una columna de 80 g, eluyendo con acetato de etilo /diclorometano 0- 40%para dar el primer pico de producto trans (0,508 g, 28%).

(2S,2'S)- 2,2'-(5,5'-(1-(4-tert-butilfenil)pirrolidin-2,5-diil)bis(2-(4-metoxibencilamino)-5,1-fenilen)bis(azanodiil)bis(oxometilen))dipirrolidin-1-carboxilato de tert-butilo

Se disolvieron 4,4'-(1-(4-tert-Butilfenil)pirrolidin-2,5-diil)bis(N1-(4-metoxibencil)bencen-1,2-diamina) (0,422 g, 0,643 mmol) y diisopropiletilamina (0,674 mL, 3,86 mmol) en DMSO (6 mL) a temperatura ambiente y se trató con S-Boc-prolina (0,319 g, 1,48 mmol) seguida por HATU (0,514 g, 1,35 mmol). La solución se agitó durante 1 hora a temperatura ambiente y luego se diluyó con agua. El sólido producto se retiró por filtración y se purificó mediante cromatografía sobre gel de sílice con una columna de 40 g, eluyendo con acetato de etilo en diclorometano 0- 50% para dar el compuesto del título

(0,565 g, 84%) como un sólido amarillo.

(2S,2'S)- 2,2'-(5,5'-(1-(4-tert-butilfenil)pirrolidin-2,5-diil)bis(2-amino-5,1-fenilen)bis(azanodiil)bis(oxometilen))dipirrolidin-1-carboxilato de tert-butilo

Se disolvió (2S,2'S)- 2,2'-(5,5'-(1-(4-tert-butilfenil)pirrolidin-2,5-diil)bis(2-(4-metoxibencilamino)-5,1-fenilen)bis(azanodiil)bis(oxometilen))dipirrolidin-1-carboxilato de tert-butilo (0,565 g, 0,538 mmol) en diclorometano (5 mL) y agua (0,25 mL) a temperatura ambiente y se trató con DDQ (0,244 g, 1,076 mmol) en 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 40 g, eluyendo con metanol/diclorometano 0-15% para dar el compuesto del título (0,355 g, 81%) como un sólido amarillo.

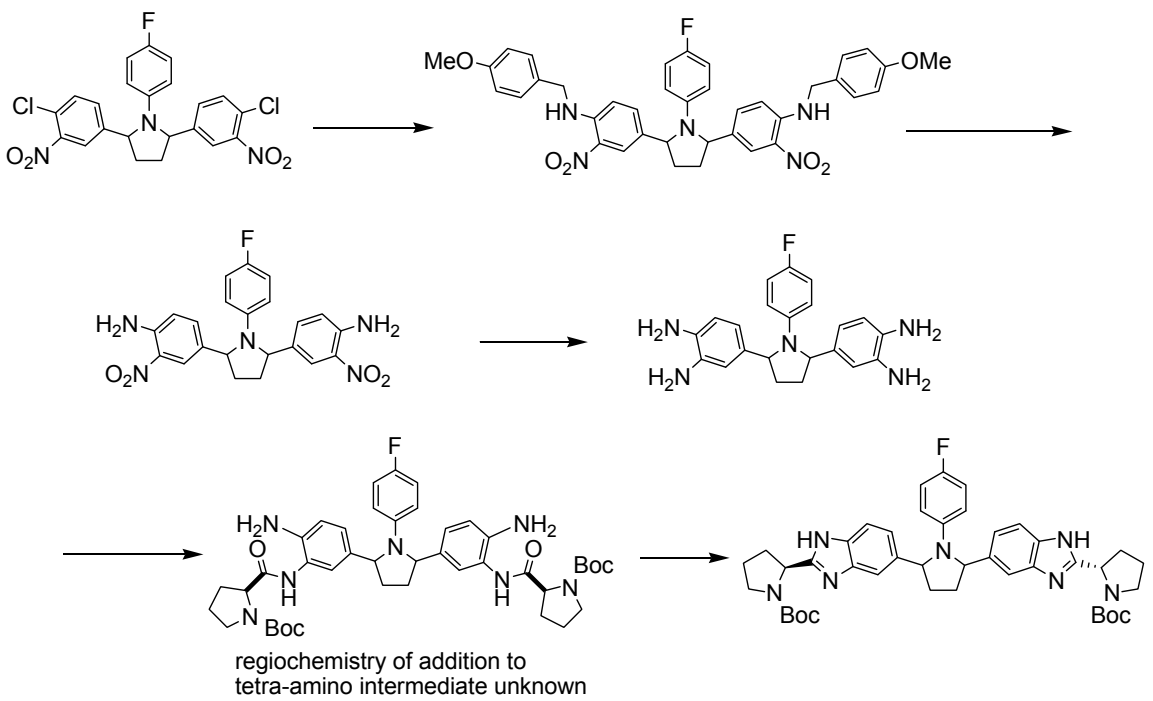
(2S,2'S)- 2,2'-(5,5'-(1-(4-tert-butilfenil)pirrolidin-2,5-diil)bis(1H-benzo[d]imidazol-5,2-diil))dipirrolidin-1-carboxilato de tert-butilo

Se disolvió (2S,2'S)- 2,2'-(5,5'-(1-(4-tert-butilfenil)pirrolidin-2,5-diil)bis(2-amino-5,1-fenilen)bis(azanodiil)bis(oxometilen))dipirrolidin-1-carboxilato de tert-butilo en ácido acético puro (3 mL) y se calentó a 72 ºC durante 2 horas. La solución se concentró y luego se volcó sobre agua. El pH se ajustó 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 40 g, eluyendo con metanol/diclorometano 0-5% para dar el compuesto del título (0,185 g, 55%) como un sólido amarillo claro.

Procedimiento General 16. Síntesis de benzimidazol por desplazamiento de metoxibencilamina ruta II

Se describe en forma general en el Esquema VIII un método para preparar ciertos compuestos (57) y (59). A continuación se ilustra en el Procedimiento General 16A una síntesis representativa de (57) donde D es 4-fluorofenilo.

Ilustración del Procedimiento General 16. Procedimiento General 16A



Los cinco pasos que se han ilustrado se describen con los siguientes procedimientos experimentales:

4,4'-(1-(4-fluorofenil)pirrolidin-2,5-diil)bis(N-(4-metoxibencil)-2-nitroanilina)

Se combinó 2,5-bis(4-cloro-3-nitrofenil)-1-(4-fluorofenil)pirrolidina (0,88 g, 1,86 mmol) con 4-metoxibencilamina (3,64 mL, 28,0 mmol) y se calentó a 145 ºC durante 1 hora 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 330 g, eluyendo con acetato de etilo /hexanos 0-60%para dar 0,79g (62%) de un sólido espumoso anaranjado.

4,4'-(1-(4-fluorofenil)pirrolidin-2,5-diil)bis(2-nitroanilina)

Se disolvió 4,4'-(1-(4-fluorofenil)pirrolidin-2,5-diil)bis(N-(4-metoxibencil)-2-nitroanilina) (0,78 g, 1,15 mmol) en diclorometano (10 mL) a temperatura ambiente y se trató con TFA (1,8 mL, 23,0 mmol) durante 3 horas. El residuo se concentró y se particionó entre diclorometano y solución de bicarbonato de sodio. Los materiales orgánicos se concentraron y se purificó mediante cromatografía sobre gel de sílice con

una columna de 40 g, eluyendo con diclorometano para dar 0,218 g (43%) del isómero trans.

4,4'-(1-(4-fluorofenil)pirrolidin-2,5-diil)dibencen-1,2-diamina

Se disolvió 4,4'-(1-(4-fluorofenil)pirrolidin-2,5-diil)bis(2-nitroanilina) (0,218 g, 0,50 mmol) en DMF (5 mL) y luego se agregó óxido de platino (0,226 g, 0,99 mmol) como una suspensión en THF. El recipiente se evacuó y se purgó con nitrógeno dos veces, luego se evacuó y se concentó a un balón de hidrógeno. La mezcla se agitó a temperatura ambiente durante 20 horas. La solución se utilizó en el siguiente paso sin purificación.

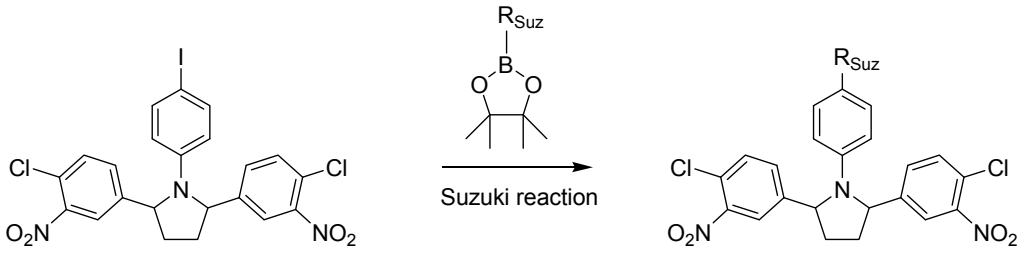
(2S,2'S)- 2,2'-(5,5'-(1-(4-fluorofenil)pirrolidin-2,5-diil)bis(2-amino-5,1-fenilen))bis(azanodiil)bis(oxometilen)dipirrolidin-1-carboxilato de tert-butilo

La solución en DMF cruda de 4,4'-(1-(4-fluorofenil)pirrolidin-2,5-diil)dibencen-1,2-diamina se trató con diisopropiletilamina (0,296 mL, 1,70 mmol) y S-Boc-prolina (0,192 g, 0,89 mmol) seguidas por HATU (0,322 g, 0,85 mmol). La solución se agitó durante 1,5 horas a temperatura ambiente, y luego la mezcla de reacción se diluyó con agua. El sólido producto se retiró por filtración y se purificó mediante cromatografía sobre gel de sílice con una columna de 12 g, eluyendo con metanol en diclorometano 0-3% para dar 0,235 g (72%) de un sólido amarillo, para el cual la regioquímica de acilación se asignó arbitrariamente en el grupo amino meta.

(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

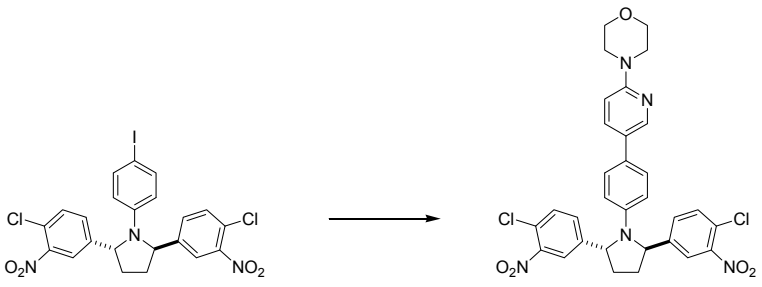
Se disolvió (2S,2'S)- 2,2'-(5,5'-(1-(4-fluorofenil)pirrolidin-2,5-diil)bis(2-amino-5,1-fenilen))bis(azanodiil)bis(oxometilen)dipirrolidin-1-carboxilato de tert-butilo en ácido acético puro (2 mL) y se calentó a 60 ºC durante 1 hora. La solución se concentró y luego se volcó sobre agua y se ajustó el 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 12 g, eluyendo con acetato de etilo en diclorometano 0-20% para dar el compuesto del título (0,124 g, 55%) como un sólido amarillo claro.

Procedimiento General 17. Acoplamientos de Suzuki de un grupo N-Arilo



Los compuestos intermediarios como por ejemplo 2.5-bis(4-cloro-3-nitrofenil)-1-(4-yodofenil)pirrolidina (o el triflato, nonaflato o bromuro correspondiente) puede prepararse además a través de una reacción de Suzuki como se muestra con un ácido o éster borónico apropiado donde RSuz representa un grupo cicloalquilo, arilo, cicloalquenilo, o heteroarilo adecuado. Las condiciones adecuadas para llevar a cabo esta reacción de Suzuki incluyen las descritas en el Esquema V para la síntesis de compuestos (37).

Ilustración del Procedimiento General 17: Procedimiento General 17A



4-(5-(4-((2R,5R)-2,5-bis(4-cloro-3-nitrofenil)pirrolidin-1-il)fenil)piridin-2-il)morfolina

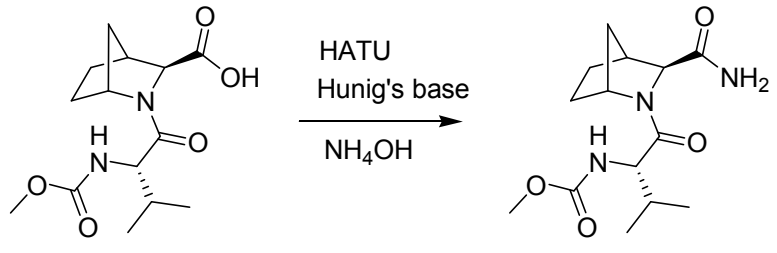
Se combinaron (2R,5R)-2,5-Bis(4-cloro-3-nitrofenil)-1-(4-yodofenil)pirrolidina (1,869 g, 3,2 mmol), 4-(5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)piridin-2-il)morfolina (0,929 g, 3,20 mmol), fosfato de potasio (1,359 g, 6,40 mmol), tris(dibencilidenacetona)dipaladio(0) (0,029 g, 0,032 mmol) y 1,3,5,7-tetrametil-6-fenil-2,4,8-trioxa-6-fosfaadamantano (0,028 g, 0,096 mmol) en THF (18 mL)/agua (6 mL). La mezcla se purgó con nitrógeno durante 15 minutos y se agitó a temperatura ambiente durante 24 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 acetato de etilo/hexano (20% a 40%) para dar el compuesto del título (1,01 g, 51%) como un sólido.

Procedimiento General 18. Síntesis de prolinamida

Pueden prepararse prolinamidas sustituidas particulares usando los métodos como por ejemplo los mostrados en los Procedimientos Generales 18A-18C.

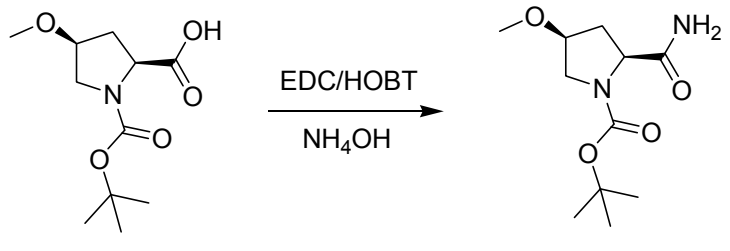
Ilustración del Procedimiento General 18. Procedimiento General 18A



(2S)-1-((3S)-3-carbamoil-2-azabiciclo[2,2,1]heptan-2-il)-3-metil-1-oxobutan-2-ilcarbamato de metilo

Se disolvieron ácido (3S)-2-((S)-2-(Metoxicarbonilamino)-3-metilbutanoil)-2-azabiciclo[2,2,1]heptan-3-carboxílico (1,78 g, 5,97 mmol), hexafluorofosfato de 2-(3H-[1,2,3]triazolo[4,5-b]piridin-3-il)-1,1,3,3-tetrametilisouronio (2,49 g, 5,56 mmol), y diisopropiletilamina (2,61 mL, 14,92 mmol) en acetonitrilo (30 mL) a temperatura ambiente y se trató por adición por goteo de solución de hidróxido de amonio 28% (2,49 g, 17,98 mmol). La mezcla resultante se agitó durante 1 hora y luego se diluyó con agua y se extrajo con diclorometano. La capa orgánica se lavó con salmuera, se secó sobre sulfato de sodio, se filtró, y se concentró para dar (2S)-1-((3S)-3-carbamoil-2-azabiciclo[2,2,1]heptan-2-il)-3-metil-1-oxobutan-2-ilcarbamato de metilo como un sólido ceroso blanco.

Ilustración del Procedimiento General 18. Procedimiento General 18B



(2S,4S)- 2-carbamoil-4-metoxipirrolidin-1-carboxilato de tert-butilo

Se disolvió ácido (2S,4S)-1-(tert-butoxicarbonil)-4-metoxipirrolidin-2-carboxílico (2,9 g, 11,82 mmol) en acetonitrilo (150 mL) y se enfrió en un baño de hielo. Se agregaron clorhidrato de N1-((Etilimino)metilen)-N3,N3-dimetilpropan-1,3-diamina (2,72 g, 14,19 mmol) e hidrato de 1H-benzo[d][1,2,3]triazol-1-ol (2,17 g, 14,19 mmol), y la mezcla se agitó a temperatura ambiente durante 15 horas, tornándose transparente. Se agregó hidróxido de amonio 28% (4,93 mL, 35,5 mmol) por goteo para dar un precipitado. Luego de agitar durante 2 horas, la mezcla se concentró, se diluyó con agua y se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera, se secó sobre sulfato de sodio, se filtró, y se concentró para dar 100% de rendimiento de (2S,4S)- 2-carbamoil-4-metoxipirrolidin-1-carboxilato tert-butilo de cómo un sólido ceroso blanco.

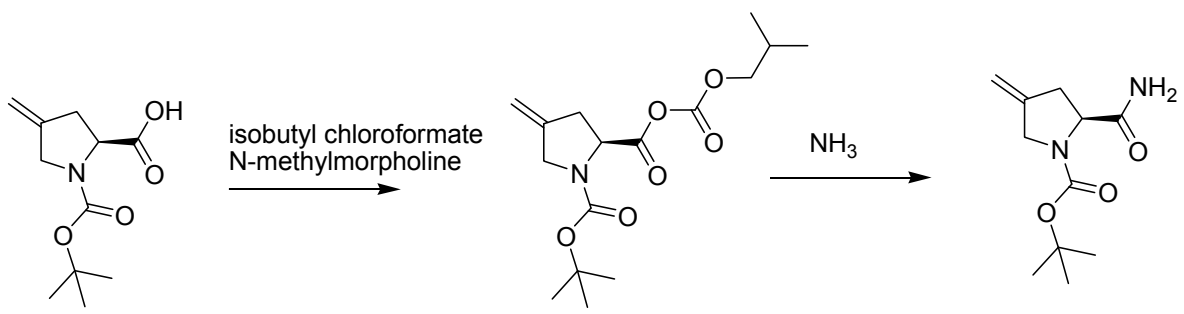
Otras amidas que pueden prepararse usando el Procedimiento General 18B incluyen:

(2S,4R)- 2-carbamoil-4-metoxipirrolidin-1-carboxilato de tert-butilo;

(2S,4S)- 2-carbamoil-4-fluoropirrolidin-1-carboxilato de tert-butilo; y

(S)- 5-carbamoil-2,2-dimetilpirrolidin-1-carboxilato de tert-butilo.

Ilustración del Procedimiento General 18. Procedimiento General 18C

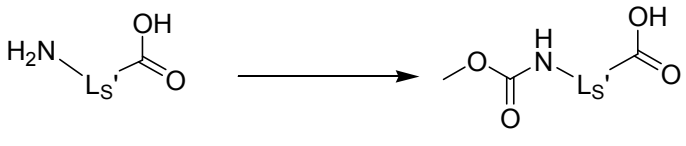


(S)- 2-carbamoil-4-metilenepirrolidin-1-carboxilato de tert-butilo

Se disolvieron ácido (S)-1-(tert-Butoxicarbonil)-4-metilenepirrolidin-2-carboxílico (1,05 g, 4,48 mmol) y N-metilmorfolina (0,64 mL, 5,83 mmol) en tetrahidrofurano (25 mL) y se enfrió a –15 ºC en un baño de hielo seco/acetona. Se agregó cloroformato de isobutilo (0,65 mL, 4,93 mmol) por goteo y la solución se agitó durante 15 minutos. La temperatura

interna se levó a –25 ºC y se burbujeó amoníaco (g) a través de la solución durante 2 minutos, luego el recipiente se transfirió a un baño de hielo y se agitó durante otros 20 minutos. La solución se volcó sobre salmuera y se extrajo con acetato de etilo, se secó sobre sulfato de magnesio, se filtró y se concentró. Este residuo se trituró con éter/hexanos, se filtró, y se secó para dar 0,97 g (81%) de (S)- 2-carbamoil-4-metilenepirrolidin-1-carboxilato de tert-butilo como un sólido blanco.

Procedimiento General 19



Los carbamatos de aminoácido de los Intermediarios pueden prepararse usando el método y la ilustración general que se ha provisto para preparar el Intermediario 2.

Los siguientes compuestos pueden prepararse siguiendo el Procedimiento General 19 comenzando con el aminoácido apropiado:

ácido (S)-2-(metoxicarbonilamino)-2-(tetrahidro-2H-piran-4-il)acético;

ácido (S)-2-ciclohexil-2-(metoxicarbonilamino)acético;

ácido (S)-2-ciclopentil-2-(metoxicarbonilamino)acético;

ácido (S)-2-ciclobutil-2-(metoxicarbonilamino)acético;

ácido (S)-2-ciclopropil-2-(metoxicarbonilamino)acético;

ácido (S)-2-(metoxicarbonilamino)-3,3-dimetilbutanoico;

ácido (2S,3R)-3-metoxi-2-(metoxicarbonilamino)butanoico;

ácido (2S,3S)-3-metoxi-2-(metoxicarbonilamino)butanoico;

ácido (S)-2-(metoxicarbonilamino)-2-((R)-tetrahidrofurano-3-il)acético;

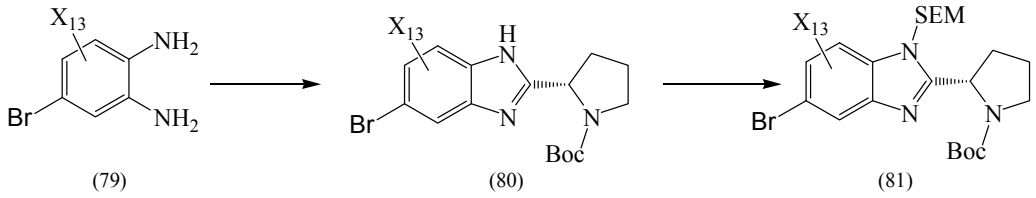
ácido (S)-2-(metoxicarbonilamino)-2-((S)-tetrahidrofurano-3-il)acético;

ácido (S)-2-(2,3-dihidro-1H-inden-2-il)-2-(metoxicarbonilamino)acético.

ácido (S)-3-etil-2-(metoxicarbonilamino)pentanoico; y

ácido (S)-2-(etoxicarbonilamino)-3-metilbutanoico.

Procedimiento General 20



Como se describe precedentemente en forma general en el Esquema XIII, las diaminas (79) pueden convertirse a benzimidazoles (81) en dos pasos.

Ilustración del Procedimiento General 20. Procedimiento General 20A

(S)- 2-(6-bromo-5-fluoro-1H-benzo[d]imidazol-2-il)pirrolidin-1-carboxilato de tert-butilo

A una solución de 4-bromo-5-fluorobencen-1,2-diamina (1,7 g, 8,4 mmol) en DMSO (42 mL) se agregó ácido (S)-1-(tert-butoxicarbonil)pirrolidin-2-carboxílico (1,8 g, 8,4 mmol) seguido por HATU (3,5 g, 9,3 mmol) y N,N-diisopropil-N-etilamina (3,7 mL, 21,1 mmol), y la solución se agitó durante 16 horas. La mezcla de reacción se diluyó con EtOAc, se lavó con H2O y salmuera, se secó (Na2SO4), se filtró y se concentró. Se agregó ácido acético (40 mL), y la mezcla se agitó a 60 ºC durante 4 horas. Luego, la mezcla de reacción se enfrió y se concentró. El residuo se incluyó en una mezcla azeotrópica 2 veces con tolueno para dar el producto crudo el cual se purificó mediante cromatografía flash (EtOAc /hexano 0-50%) para dar el compuesto del título (2,5g, 6,4 mmol, 77%).

(S)- 2-(5-bromo-6-fluoro-1-((2-(trimetilsilil)etoxi)metil)-1H-benzo[d]imidazol-2-il)pirrolidin-1-carboxilato de tert-butilo

A una solución de (S)- 2-(6-bromo-5-fluoro-1H-benzo[d]imidazol-2-il)pirrolidin-1-carboxilato de tert-butilo (2,5 g, 6,4 mmol) en THF (32 mL) se agregó hidruro de sodio (0,27 g, 6,8 mmol) y la agitación se continuó durante 30 minutos. Se agregó cloruro de 2-(trimetilsilil)-etoximetilo (1,2 mL, 6,8 mmol) y la agitación se continuó durante 30 minutos. Se agregó agua para detener la reacción. La mezcla se diluyó con EtOAc, se lavó con HCl 1N, H2O, y salmuera, se secó (Na2SO4), se filtró y se concentró para dar un aceite. El

aceite se purificó mediante cromatografía flash (EtOAc/hexano 0-30%) para dar el compuesto del título (2,9 g, 5,7 mmol, 89%).

Los siguientes compuestos de Fórmula general (81) pueden prepararse siguiendo el Procedimiento General 20 comenzando con la amina apropiada:

(S)- 2-(5-bromo-1-((2-(trimetilsilil)etoxi)metil)-1H-benzo[d]imidazol-2-il)pirrolidin-1-carboxilato de tert-butilo;

(S)- 2-(5-bromo-4-metil-1-((2-(trimetilsilil)etoxi)metil)-1H-benzo[d]imidazol-2-il)pirrolidin-1-carboxilato de tert-butilo;

(S)- 2-(5-bromo-4-cloro-1-((2-(trimetilsilil)etoxi)metil)-1H-benzo[d]imidazol-2-il)pirrolidin-1-carboxilato de tert-butilo;

(S)- 2-(5-bromo-4-fluoro-1-((2-(trimetilsilil)etoxi)metil)-1H-benzo[d]imidazol-2-il)pirrolidin-1-carboxilato de tert-butilo;

(S)- 2-(6-bromo-3-((2-(trimetilsilil)etoxi)metil)-3H-imidazo[4,5-b]piridin-2-il)pirrolidin-1-carboxilato de tert-butilo;

(S)- 2-(5-bromo-7-metil-1-((2-(trimetilsilil)etoxi)metil)-1H-benzo[d]imidazol-2-il)pirrolidin-1-carboxilato de tert-butilo;

(S)- 2-(5-bromo-6-metil-1-((2-(trimetilsilil)etoxi)metil)-1H-benzo[d]imidazol-2-il)pirrolidin-1-carboxilato de tert-butilo;

(S)- 2-(5-bromo-6-(trifluorometil)-1-((2-(trimetilsilil)etoxi)metil)-1H-benzo[d]imidazol-2-il)pirrolidin-1-carboxilato de tert-butilo;

(S)- 2-(5-bromo-7-(trifluorometil)-1-((2-(trimetilsilil)etoxi)metil)-1H-benzo[d]imidazol-2-il)pirrolidin-1-carboxilato de tert-butilo;

(S)- 2-(5-bromo-6-metoxi-1-((2-(trimetilsilil)etoxi)metil)-1H-benzo[d]imidazol-2-il)pirrolidin-1-carboxilato de tert-butilo;

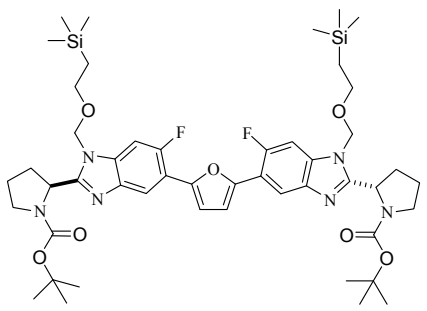
(S)- 2-(5-bromo-7-metoxi-1-((2-(trimetilsilil)etoxi)metil)-1H-benzo[d]imidazol-2-il)pirrolidin-1-carboxilato de tert-butilo; y

(S)- 5-bromo-2-(1-(tert-butoxicarbonil)pirrolidin-2-il)-1-((2-(trimetilsilil)etoxi)metil)-1H-benzo[d]imidazol-7-carboxilato de metilo.

Procedimiento General 21

Como se describe precedentemente en forma general en el Esquema XIII, los compuestos (81) pueden convertirse a compuestos (82,2). A continuación se ilustra en el Procedimiento General 21A es una síntesis representativa de compuestos (82,2) donde X13 es fluoro en la posición 6 de la porción benzimidazol. En una ilustración conveniente, los grupos protectores SEM en los benzimidazoles se muestran unidos a átomos de nitrógeno particulares del benzimidazol. En los Procedimientos Generales 21A y 22A, las posiciones de sustitución reales de los grupos SEM no se determinaron y puede ser sobre el nitrógeno.

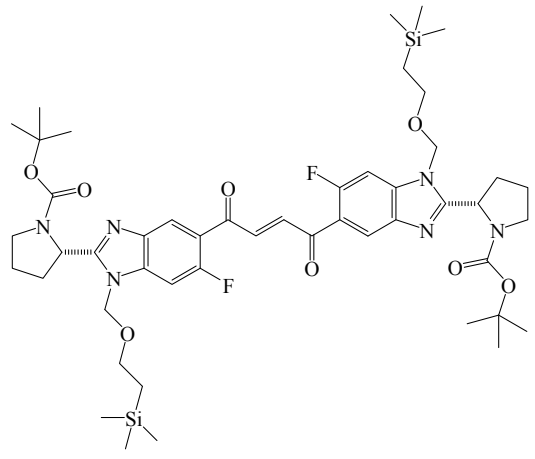
Ilustración del Procedimiento General 21. Procedimiento General 21A.



(2S,2'S)- 2,2'-(5,5'-(furan-2,5-diil)bis(6-fluoro-1-((2-(trimetilsilil)etoxi)metil)-1H-benzo[d]imidazol-5,2-diil))dipirrolidin-1-carboxilato de tert-butilo

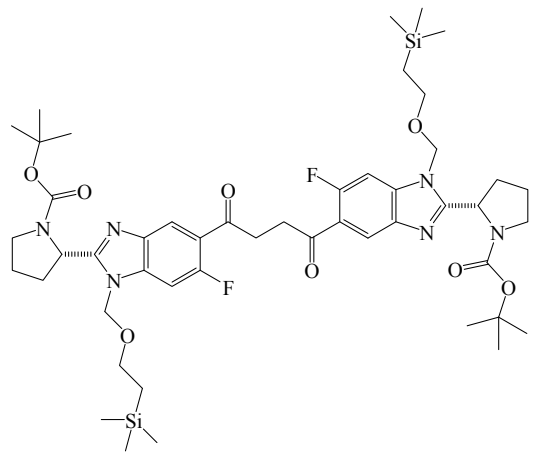
En un tubo de presión se combinaron (S)- 2-(5-bromo-6-fluoro-1-((2-(trimetilsilil)etoxi)metil)-1H-benzo[d]imidazol-2-il)pirrolidin-1-carboxilato de tert-butilo (600 mg, 1,2 mmol), 2,5-bis(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)furano (186 mg, 0,6 mmol), fluoruro de cesio (353 mg, 2,3 mmol) y DMF (4 mL), y la mezcla se desgasificó con gas N2 durante 30 minutos. A esta mezcla se agregó [(t-Bu)2PCl]2PdCl2 (PXPd) (15,7 mg, 0,03 mmol) y el tubo se selló y se calentó a 100 ºC durante 18 horas. La solución enfriada se diluyó con EtOAc, se filtró a través de tierras diatomeas. El material filtrado se lavó con H2O y salmuera, se secó (Na2SO4), se filtró y se trató con gel de 3-

mercaptopropilsílice durante 30 minutos. La mezcla se filtró, y el material filtrado se concentró para dar el producto crudo el cual se purificó mediante cromatografía flash (EtOAc /hexano 0-50%) para dar el compuesto del título (269mg, 0,29 mmol, 50%).



(2S,2'S)-2,2'-{[(2E)-1,4-dioxobut-2-en-1,4-diil]bis(6-fluoro-1-{[2-(trimetilsilil)etoxi]metil}-1H-benzimidazol-5,2-diil)}dipirrolidin-1-carboxilato de di-tert-butilo (Nomenclatura ACD v12)

A una solución de (2S,2'S)- 2,2'-(5,5'-(furan-2,5-diil)bis(6-fluoro-1-((2-(trimetilsilil)etoxi)metil)-1H-benzo[d]imidazol-5,2-diil)dipirrolidin-1-carboxilato de tert-butilo (340 mg, ,36 mmol) en THF (8 mL) se agregó Selectfluor® (bis(tetrafluoroborato) de 1-clorometil-4-fluoro-1,4-diazoniabiciclo[2,2,2]octano) (258 mg, 0,73 mmol) seguido por H2O (1 mL). La solución se agitó durante 1 hora, se diluyó con EtOAc, se lavó con H2O y salmuera, se secó (Na2SO4), se filtró y se concentró para dar el compuesto del título.



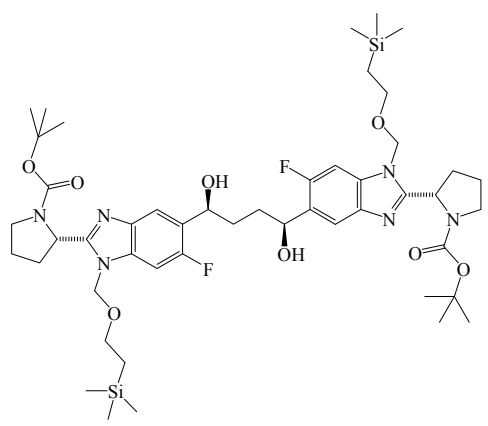
(2S,2'S)-2,2'-[(1,4-dioxobutan-1,4-diil)bis(6-fluoro-1-{[2-(trimetilsilil)etoxi]metil}-1H-benzimidazol-5,2-diil)]dipirrolidin-1-carboxilato de di-tert-butilo (Nomenclatura ACD v12)

A una solución de (2S,2'S)-2,2'-{[(2E)-1,4-dioxobut-2-en-1,4-diil]bis(6-fluoro-1-{[2-(trimetilsilil)etoxi]metil}-1H-benzimidazol-5,2-diil)}dipirrolidin-1-carboxilato de di-tert-butilo (346 mg, 0,36 mmol) en EtOAc (7 mL) se agregó platino (3% sobre carbono) (71 mg, 0,36 mmol) y la solución se agitó bajo gas H2 a 1 atm durante 2 horas. La solución se filtró, se lavó con EtOAc y el material filtrado se concentró para dar un residuo que se purificó mediante cromatografía flash (EtOAc /hexano 0-50%) para dar el compuesto del título (269 mg, 0,28 mmol, 78%).

Procedimiento General 22

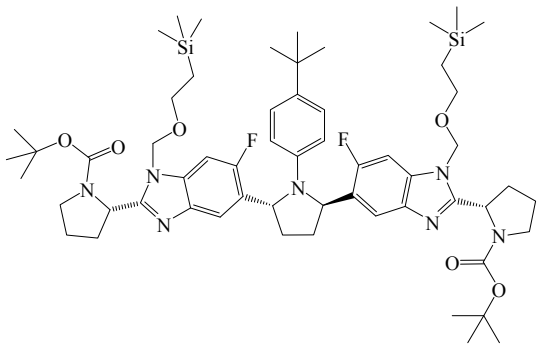
Como se describe precedentemente en forma general en el Esquema XIII, los compuestos (82,2) pueden convertirse a compuestos (84). A continuación se ilustra en el Procedimiento General 22A una síntesis representativa de compuestos (84) donde D es 4-tert-butilfenilo, las estereoquímicas de los alcoholes en el grupo butan-1,4-diilo son ambas (S), y X13 es 6-fluoro. La ciclización para formar la pirrolidina puede formar la trans-pirrolidina junto con diversas cantidades de cis-pirrolidina. La cis-pirrolidina puede separarse después de la desprotección (véase el Procedimiento General 23) o luego de culquier paso posterior a la desprotección.

Ilustración del Procedimiento General 22. Procedimiento General 22A



(2S,2'S)-2,2'-{[(1S,4S)-1,4-dihidroxibutan-1,4-diil]bis(6-fluoro-1-{[2-(trimetilsilil)etoxi]metil}-1H-benzimidazol-5,2-diil)}dipirrolidin-1-carboxilato de di-tert-butilo (Nomenclatura ACD v12)

A una solución de (R)-(+)-α,α-difenil-2-pirrolidinmetanol (59,9 mg, 0,24 mmol) en THF (2,8 mL) se agregó trimetilborato (0,034 mL, 0,31 mmol), y la solución resultante se agitó durante 90 minutos. La solución se enfrió a 0 ºC y se agregó borano de N,N-dietilanilina (0,4 mL, 2,2 mmol) en porciones durante 30 minutos con agitación continua a 0 ºC. Esta solución se agregó mediante cánulas a una solución a 0˚C de (2S,2'S)-2,2'-[(1,4-dioxobutan-1,4-diil)bis(6-fluoro-1-{[2-(trimetilsilil)etoxi]metil}-1H-benzimidazol-5,2-diil)]dipirrolidin-1-carboxilato de di-tert-butilo (265 mg, ,28 mmol) en THF (2,8 mL) y luego se calentó a temperatura ambiente y se agitó durante 16 horas. La solución se enfrió a 0 ºC y se agregó CH3OH (0,09 mL, 2,2 mmol), y la solución se calentó a temperatura ambiente y se agitó durante 2 horas. Se agregó HCl 1N, y la solución acuosa se extrajo con EtOAc. Los extractos combinados se lavaron con salmuera, se secó (Na2SO4), se filtró y se concentró. La purificación se llevó a cabo mediante cromatografía flash (0-3% CH3OH/CH2Cl2) para dar el compuesto del título (248 mg, 0,26 mmol, 93%).

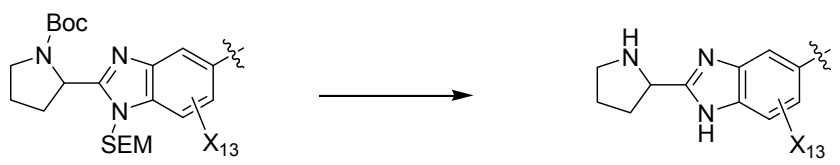


(2S,2'S)-2,2'-{[(2R,5R)-1-(4-tert-butilfenil)pirrolidin-2,5-diil]bis(6-fluoro-1-{[2-(trimetilsilil)etoxi]metil}-1H-benzimidazol-5,2-diil)}dipirrolidin-1-carboxilato de di-tert-butilo (Nomenclatura ACD v12)

A una solución de (2S,2'S)-2,2'-{[(1S,4S)-1,4-dihidroxibutan-1,4-diil]bis(6-fluoro-1-{[2-(trimetilsilil)etoxi]metil}-1H-benzimidazol-5,2-diil)}dipirrolidin-1-carboxilato de di-tert-butilo (100 mg, ,10 mmol) en CH2Cl2 (1 mL) a -20 ºC se agregó trietilamina (0,044 mL, 0,31 mmol) seguida por cloruro de mesilo (0,018 mL, 0,23 mmol) y la solución se agitó a -20 ºC durante 1 hora. Se agregó 4-tert-butilanilina (0,083 mL, 0,52 mmol) en una porción,

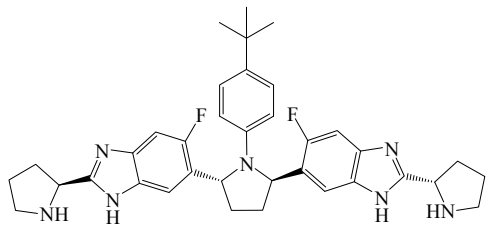
y la solución se dejó calentar a temperatura ambiente durante la noche, con agitación. La solución se diluyó con EtOAc, se lavó con HCl 1N, H2O, y salmuera, se secó (Na2SO4), se filtró y se concentró. La purificación mediante cromatografía flash (EtOAc /hexano 0-50%) dio el compuesto del título (46 mg, 0,04 mmol, 41%).

Procedimiento General 23. Procedimiento de separación de Boc/SEM



La eliminación simultánea de los grupos protectores Boc y SEM de acuerdo con la descripción precedente puede efectuarse usando condiciones estándar como por ejemplo por tratamiento con un ácido, como por ejemplo HCl, en solventes como por ejemplo dioxano o metanol o mezclas de los mismos a una temperatura entre aproximadamente temperatura ambiente y aproximadamente 60 ºC. Los compuestos obtenidos de la desprotección pueden consistir en una mezcla de estereoisómeros que puede separarse por HPLC en fase reversa. Los compuestos desprotegidos obtenidos pueden aislarse como sal directamente de la reacción o de HPLC en fase reversa o como base libre luego de la neutralización, extracción con solvente orgánico y aislación estándar.

Ilustración del Procedimiento General 23. Procedimiento General 23A



6,6'-[(2R,5R)-1-(4-tert-butilfenil)pirrolidin-2,5-diil]bis{5-fluoro-2-[(2S)-pirrolidin-2-il]-1H-benzimidazol} (Nomenclatura ACD v12)

A una solución de (2S,2'R)-2,2'-{[(2R,5R)-1-(4-tert-butilfenil)pirrolidin-2,5-diil]bis(6-fluoro-1-{[2-(trimetilsilil)etoxi]metil}-1H-benzimidazol-5,2-diil)}dipirrolidin-1-carboxilato de di-tert-butilo (44 mg, 0,04 mmol) en dioxano (1 mL) se agregó HCl 4 M/dioxano (1 mL, 4,0

mmol) y la solución se agitó a 50 ºC durante 2 horas. La solución enfriada se concentró y se colocó bajo vacío durante 1 hora para dar el compuesto del título crudo que se usó sin purificación.

Las siguientes diaminas

4-bromo-3-metilbencen-1,2-diamina;

5-bromo-3-fluorobencen-1,2-diamina;

4-bromo-3-fluorobencen-1,2-diamina;

4-bromo-3-clorobencen-1,2-diamina; y

4-bromo-5-fluorobencen-1,2-diamina.

puede someterse a una secuencia de los Procedimientos Generales 20/20A, 21/21A, 22/22A, 23/23A para dar los siguientes compuestos:

6,6'-[1-(4-tert-butilfenil)pirrolidin-2,5-diil]bis{4-fluoro-2-[(2S)-pirrolidin-2-il]-1H-benzimidazol} (Nomenclatura ACD v12);

6,6'-[(2R,5R)-1-(4-tert-butilfenil)pirrolidin-2,5-diil]bis{7-fluoro-2-[(2S)-pirrolidin-2-il]-1H-benzimidazol} (Nomenclatura ACD v12);

6,6'-[(2R,5S)-1-(4-tert-butilfenil)pirrolidin-2,5-diil]bis{7-fluoro-2-[(2S)-pirrolidin-2-il]-1H-benzimidazol} (Nomenclatura ACD v12);

6,6'-[(2R,5R)-1-(4-tert-butilfenil)pirrolidin-2,5-diil]bis{7-cloro-2-[(2S)-pirrolidin-2-il]-1H-benzimidazol} (Nomenclatura ACD v12);

6,6'-[(2R,5S)-1-(4-tert-butilfenil)pirrolidin-2,5-diil]bis{7-cloro-2-[(2S)-pirrolidin-2-il]-1H-benzimidazol} (Nomenclatura ACD v12);

6,6'-[(2R,5R)-1-(4-tert-butilfenil)pirrolidin-2,5-diil]bis{7-metil-2-[(2S)-pirrolidin-2-il]-1H-benzimidazol} (Nomenclatura ACD v12);

6,6'-[(2R,5S)-1-(4-tert-butilfenil)pirrolidin-2,5-diil]bis{7-metil-2-[(2S)-pirrolidin-2-il]-1H-benzimidazol} (Nomenclatura ACD v12);

6,6'-{(2R,5R)-1-[3-fluoro-4-(piperidin-1-il)fenil]pirrolidin-2,5-diil}bis{5-fluoro-2-[(2S)-pirrolidin-2-il]-1H-benzimidazol} (Nomenclatura ACD v12);

6,6'-{(2R,5R)-1-[3,5-difluoro-4-(piperidin-1-il)fenil]pirrolidin-2,5-diil}bis{5-fluoro-2-[(2S)-pirrolidin-2-il]-1H-benzimidazol} (Nomenclatura ACD v12); y

6,6'-{(2R,5R)-1-[3,5-difluoro-4-(4-fenilpiperidin-1-il)fenil]pirrolidin-2,5-diil}bis{5-fluoro-2-[(2S)-pirrolidin-2-il]-1H-benzimidazol} (Nomenclatura ACD v12).

Ejemplos

Los siguientes ejemplos de compuestos 1.1-1.8 pueden prepararse a partir de la pirrolidina sustituida apropiada siguiendo los métodos del Procedimiento General 8.1, Procedimiento General 9C (níquel-Raney), y Procedimiento General 10B.

Pirrolidinas:

(2R,5R)-2,5-bis(4-cloro-3-nitrofenil)-1-(4-fenoxifenil)pirrolidina;

1-(4-((2R,5R)-2,5-bis(4-cloro-3-nitrofenil)pirrolidin-1-il)fenil)piridin-2(1H)-ona;

(2R,5R)-2,5-bis(4-cloro-3-nitrofenil)-1-(2,5-difluoro-4-(trifluorometil)fenil)pirrolidina;

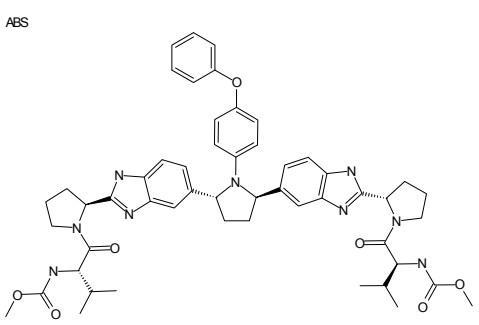
4-((2R,5R)-2,5-bis(4-cloro-3-nitrofenil)pirrolidin-1-il)-2-fluoropiridina;

1-(4-((2R,5R)-2,5-bis(4-cloro-3-nitrofenil)pirrolidin-1-il)-2,6-difluorofenil)-4,4-difluoropiperidina;

1-(4-((2R,5R)-2,5-bis(4-cloro-3-nitrofenil)pirrolidin-1-il)-2,6-difluorofenil)-4-fluoropiperidina;

(2R,5R)-2,5-bis(4-cloro-3-nitrofenil)-1-(4-((3-etiloxetan-3-il)metoxi)fenil)pirrolidina; y

(1R,5S)-3-(4-((2R,5R)-2,5-bis(4-cloro-3-nitrofenil)pirrolidin-1-il)-2,6-difluorofenil)-3-azabiciclo[3.2.0]heptano.

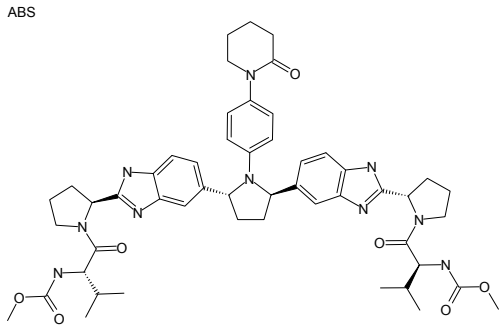


Ejemplo 1.1

{(2S)-1-[(2S)-2-{5-[(2R,5R)-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-benzimidazol-5-il}-1-(4-fenoxifenil)pirrolidin-2-il]-1H-benzimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

1H RMN (400 MHz, DMSO-d6) □ ppm 0,78 - 0,91 (m, 12 H) 1,70 (d, J=6,83 Hz, 2 H) 1,86 - 1,96 (m, 2 H) 1,99 (d, J=2,17 Hz, 4 H) 2,15 - 2,25 (m, 4 H) 2,55 - 2,61 (m, 2 H) 3,54 (s, 6 H) 3,82 (s, 4 H) 4,06 (t, J=8,40 Hz, 2 H) 5,13 (t, J=7,26 Hz, 2 H) 5,35 - 5,43 (m, 2 H) 6,35 (d, J=9,11 Hz, 2 H) 6,62 - 6,69 (m, 2 H) 6,71 (d, J=8,02 Hz, 2 H) 6,93 (t, J=7,43 Hz, 1 H) 7,08 (t, J=9,43 Hz, 2 H) 7,18 - 7,25 (m, 3 H) 7,27 - 7,34 (m, 3 H) 7,39 (d, J=8,13 Hz, 1 H) 7,47 (d, J=8,02 Hz, 1 H) 12,05 (d, J=12,04 Hz, 2 H); MS (ESI+) m/z 924,4 (M+H)+.

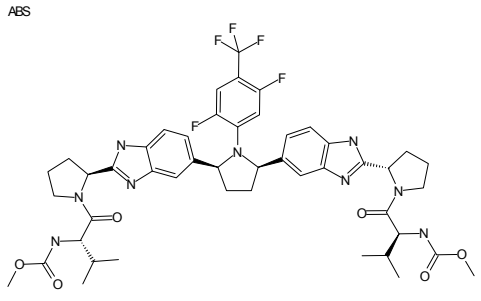
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Ejemplo 1.2

{(2S)-1-[(2S)-2-(5-{(2R,5R)-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-benzimidazol-5-il}-1-[4-(2-oxopiperidin-1-il)fenil]pirrolidin-2-il}-1H-benzimidazol-2-il)pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

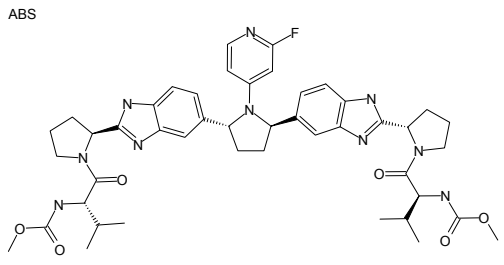
1H RMN (400 MHz, DMSO-d6) □ ppm 0,76 - 0,92 (m, 12 H) 1,66 - 1,76 (m, 6 H) 1,91 (dd, J=13,61, 7,54 Hz, 2 H) 1,95 - 2,04 (m, 4 H) 2,20 (dd, J=16,26, 3,80 Hz, 6 H) 2,58 - 2,64 (m, 2 H) 3,39 - 3,45 (m, 2 H) 3,54 (s, 6 H) 3,82 (s, 4 H) 4,02 - 4,09 (m, 2 H) 5,09 - 5,19 (m, 2 H) 5,35 - 5,43 (m, 2 H) 6,29 (d, J=8,89 Hz, 2 H) 6,70 - 6,78 (m, 2 H) 7,07 (d, J=8,13 Hz, 2 H) 7,22 (s, 1 H) 7,29 (d, J=8,35 Hz, 2 H) 7,33 (s, 1 H) 7,38 (d, J=8,35 Hz, 1 H) 7,47 (d, J=8,13 Hz, 1 H) 12,04 (s, 2 H); MS (ESI+) m/z 929,5 (M+H)+.



Ejemplo 1.3

{(2S)-1-[(2S)-2-{5-[(2S,5R)-1-[2,5-difluoro-4-(trifluorometil)fenil]-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-benzimidazol-5-il}pirrolidin-2-il]-1H-benzimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

1H RMN (400 MHz, DMSO-d6) ppm 0,76 - 0,94 (m, 12 H) 1,83 - 2,07 (m, 8 H) 2,14 - 2,28 (m, 4 H) 2,35 - 2,45 (m, 2 H) 3,54 (s, 6 H) 3,75 - 3,94 (m, 4 H) 4,07 (dd, J=8,19, 4,93 Hz, 2 H) 5,19 (dd, J=31,50, 3,74 Hz, 4 H) 6,48 - 6,61 (m, 1 H) 7,20 - 7,35 (m, 5 H) 7,40 - 7,46 (m, 1 H) 7,49 - 7,56 (m, 2 H) 7,58 - 7,65 (m, 1 H) 12,12 (d, J=4,66 Hz, 2 H); MS (APCI+) m/z 936,24 (M+H)+.

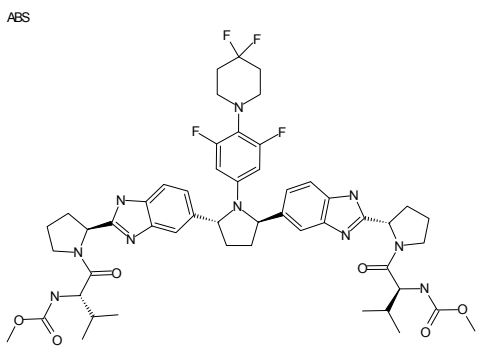


Ejemplo 1.4

{(2S)-1-[(2S)-2-{5-[(2R,5R)-1-(2-fluoropiridin-4-il)-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-benzimidazol-5-il}pirrolidin-2-il]-1H-benzimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

1H RMN (400 MHz, DMSO-d6) ppm 0,77 - 0,91 (m, 12 H) 1,32 (td, J=14,99, 7,43 Hz, 1 H) 1,53 (dt, J=21,23, 6,63 Hz, 1 H) 1,74 (dd, J=11,93, 6,07 Hz, 2 H) 1,86 - 2,05 (m, 6 H) 2,14 - 2,23 (m, 4 H) 3,54 (s, 6 H) 3,77 - 3,86 (m, 4 H) 4,05 - 4,10 (m, 2 H) 5,11 - 5,18 (m, 2 H) 5,45 - 5,59 (m, 2 H) 5,79 (s, 1 H) 6,18 - 6,23 (m, 1 H) 7,03 - 7,13 (m, 2 H) 7,23 (s, 1 H)

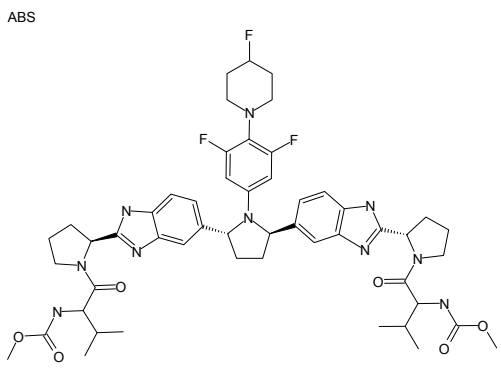
7,29 (d, J=8,35 Hz, 2 H) 7,34 (d, J=1,52 Hz, 1 H) 7,42 (d, J=8,35 Hz, 1 H) 7,47 - 7,56 (m, 2 H) 12,11 (s, 2 H); MS (ESI+) m/z 851,3 (M+H)+.



Ejemplo 1.5

{(2S)-1-[(2S)-2-{5-[(2R,5R)-1-[4-(4,4-difluoropiperidin-1-il)-3,5-difluorofenil]-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-benzimidazol-5-il}pirrolidin-2-il]-1H-benzimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

1H RMN (400 MHz, DMSO-d6) □ ppm 0,74 - 0,93 (m, 12 H) 1,63 - 1,74 (m, 2 H) 1,85 - 2,06 (m, 12 H) 2,19 (dd, J=9,49, 5,37 Hz, 4 H) 2,86 - 2,96 (m, 4 H) 3,54 (s, 6 H) 3,76 - 3,86 (m, 4 H) 4,07 (t, J=8,24 Hz, 2 H) 5,09 - 5,20 (m, 2 H) 5,33 - 5,42 (m, 2 H) 5,92 (d, J=12,90 Hz, 2 H) 7,07 (t, J=7,37 Hz, 2 H) 7,21 (s, 1 H) 7,26 - 7,33 (m, 3 H) 7,41 (d, J=8,13 Hz, 1 H) 7,49 (d, J=8,13 Hz, 1 H) 12,08 (d, J=12,90 Hz, 2 H); MS (ESI+) m/z 987,5 (M+H)+.

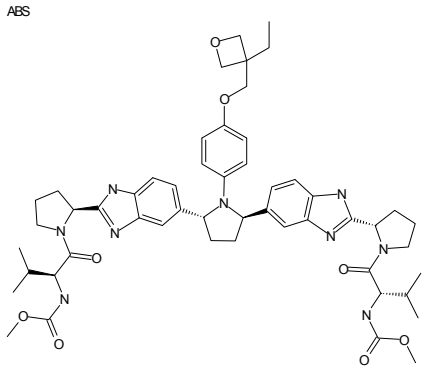


Ejemplo 1.6

{1-[(2S)-2-{5-[(2R,5R)-1-[3,5-difluoro-4-(4-fluoropiperidin-1-il)fenil]-5-{2-[(2S)-1-{2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-benzimidazol-5-il}pirrolidin-2-il]-1H-benzimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

1H RMN (400 MHz, DMSO-d6) ppm 0,74 - 0,91 (m, 12 H) 1,63 - 1,71 (m, 6 H) 1,76 - 1,97 (m, 4 H) 1,98 - 2,07 (m, 4 H) 2,14 - 2,23 (m, 4 H) 2,71 - 2,78 (m, 2 H) 2,90 - 3,00 (m, 2 H) 3,54 (s, 6 H) 3,82 (s, 4 H) 4,06 (t, J=8,73 Hz, 2 H) 4,58 - 4,78 (m, 1 H) 5,11 - 5,18 (m, 2 H) 5,33 - 5,43 (m, 2 H) 5,90 (d, J=12,69 Hz, 2 H) 7,07 (t, J=7,37 Hz, 2 H) 7,20 (s, 1 H) 7,26 - 7,32 (m, 3 H) 7,41 (d, J=8,24 Hz, 1 H) 7,49 (d, J=8,24 Hz, 1 H) 12,07 (d, J=16,48 Hz, 2 H); MS (ESI+) m/z 969,5 (M+H)+.

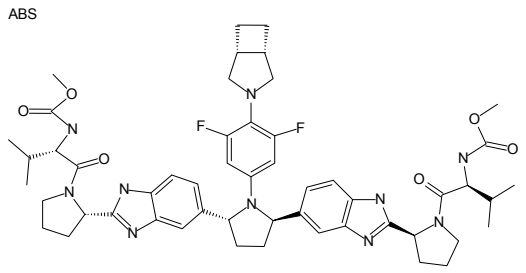
ABS



Ejemplo 1.7

{(2S)-1-[(2S)-2-{5-[(2R,5R)-1-{4-[(3-etiloxetan-3-il)metoxi]fenil}-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-benzimidazol-5-il}pirrolidin-2-il]-1H-benzimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

1H RMN (400 MHz, DMSO-d6) δ 12,26 – 11,98 (m, 2H), 7,44 (d, J = 8,2, 1H), 7,37 (d, J = 8,2, 1H), 7,33 – 7,18 (m, 4H), 7,05 (t, J = 8,1, 2H), 6,62 – 6,53 (m, 2H), 6,26 (d, J = 8,8, 2H), 5,40 – 5,30 (m, 2H), 5,17 – 5,08 (m, 2H), 4,29 (d, J = 5,7, 2H), 4,22 (d, J = 5,8, 2H), 4,06 (t, J = 8,3, 2H), 3,86 – 3,75 (m, 6H), 3,53 (s, 6H), 2,54 (s, 2H), 2,24 – 2,12 (m, 4H), 2,06 – 1,83 (m, 6H), 1,75 – 1,62 (m, 4H), 0,91 – 0,74 (m, 15H); MS (ESI+) m/z 946,5 (M+H)+.



Ejemplo 1.8

{(2S)-1-[(2S)-2-{5-[(2R,5R)-1-{4-[(1R,5S)-3-azabiciclo[3.2.0]hept-3-il]-3,5-difluorofenil}-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-benzimidazol-5-il}pirrolidin-2-il]-1H-benzimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

1H RMN (400 MHz, DMSO-d6) □ ppm 0,82 (s, 12 H) 1,61 (s, 3 H) 1,71 (d, 2 H) 1,97 (m, 9 H) 2,20 (s, 2 H) 2,74 - 2,78 (m, 2 H) 2,85 (s, 5 H) 3,53 (s, 6 H) 3,82 (s, 3 H) 4,06 (s, 2 H) 5,14 (s, 2 H) 5,38 (s, 2 H) 5,91 (s, 2 H) 7,09 (s, 1 H) 7,37 (m, 6 H) 7,63 (s, 1 H) 7,88 (s, 1 H) 12,05 (s, 2 H); MS (ESI+) m/z 963,5 (M+H)+, (ESI-) m/z 961,4 (M-H)-.

Los siguientes ejemplos de compuestos 2.1-2.17 pueden prepararse a partir de la pirrolidina sustituida apropiada siguiendo los métodos del Procedimiento General 8.1, Procedimiento General 9D (PtO2), y Procedimiento General 10B.

Pirrolidinas:

2-(4-((2R,5R)-2,5-bis(4-cloro-3-nitrofenil)pirrolidin-1-il)fenil)oxazol;

(2R,5R)-1-(4-cloro-3-fluorofenil)-2,5-bis(4-cloro-3-nitrofenil)pirrolidina;

(2R,5R)-1-(4-(1,3-dioxan-5-iloxi)fenil)-2,5-bis(4-cloro-3-nitrofenil)pirrolidina;

(2R,5R)-1-(4-((1,3-dioxolan-4-il)metoxi)fenil)-2,5-bis(4-cloro-3-nitrofenil)pirrolidina;

(2R,5R)-2,5-bis(4-cloro-3-nitrofenil)-1-(4-((3-etiloxetan-3-il)metoxi)-3,5-difluorofenil)pirrolidina;

1-(4-((2R,5R)-2,5-bis(4-cloro-3-nitrofenil)pirrolidin-1-il)-2,3,5,6-tetrafluorofenil)piperidina;

(2R,5R)-2,5-bis(4-cloro-3-nitrofenil)-1-(3-fluoro-4-(metilsulfonil)fenil)pirrolidina (obtenida por oxidación con mCPBA de (2R,5R)-2,5-bis(4-cloro-3-nitrofenil)-1-(3-fluoro-4-(metiltio)fenil)pirrolidina);

4-((2R,5R)-2,5-bis(4-cloro-3-nitrofenil)pirrolidin-1-il)-N-tert-butil-2-fluoroanilina;

1-(4-((2R,5R)-2,5-bis(4-cloro-3-nitrofenil)pirrolidin-1-il)-2,6-difluorofenil)-4-metilpiperidina;

1-(4-((2R,5R)-2,5-bis(4-cloro-3-nitrofenil)pirrolidin-1-il)-2,6-difluorofenil)-4-(3-fenilpropil)piperidina;

8-(4-((2R,5R)-2,5-bis(4-cloro-3-nitrofenil)pirrolidin-1-il)-2,6-difluorofenil)-8-azaespiro[4,5]decano;

1-(4-((2R,5R)-2,5-bis(4-cloro-3-nitrofenil)pirrolidin-1-il)-2,6-difluorofenil)-4-(naftalen-2-il)piperidina;

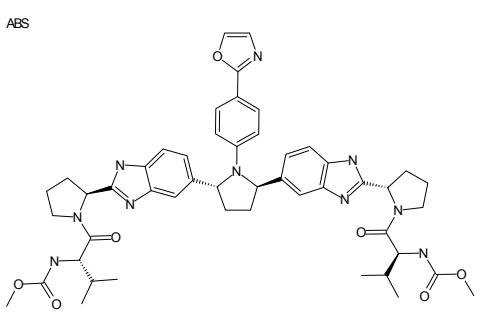
2-(1-(4-((2R,5R)-2,5-bis(4-cloro-3-nitrofenil)pirrolidin-1-il)-2,6-difluorofenil)piperidin-4-il)piridina;

1-(4-((2R,5R)-2,5-bis(4-cloro-3-nitrofenil)pirrolidin-1-il)-2,6-difluorofenil)-4-(4-(trimetilsilil)fenil)piperidina;

1-(4-((2R,5R)-2,5-bis(4-cloro-3-nitrofenil)pirrolidin-1-il)-2,6-difluorofenil)-4-(naftalen-1-il)piperidina;

1-(4-((2R,5R)-2,5-bis(4-cloro-2-fluoro-5-nitrofenil)pirrolidin-1-il)-2,6-difluorofenil)-3,5-dimetilpiperidina; y

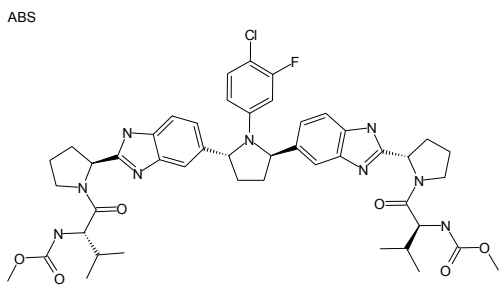
1-(4-((2R,5R)-2,5-bis(4-cloro-3-nitrofenil)pirrolidin-1-il)-2,6-difluorofenil)-4-(4-(trifluorometil)fenil)piperazina.



Ejemplo 2.1

{(2S)-1-[(2S)-2-(5-{(2R,5R)-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-benzimidazol-5-il}-1-[4-(1,3-oxazol-2-il)fenil]pirrolidin-2-il}-1H-benzimidazol-2-il)pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

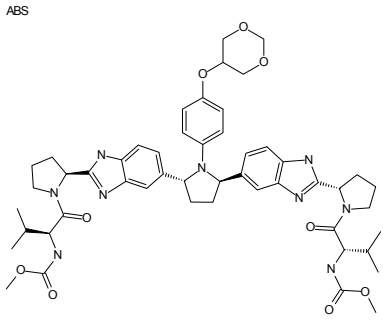
1H RMN (400 MHz, DMSO-d6) □ ppm 0,74 - 0,91 (m, 12 H) 1,70 - 1,79 (m, 2 H) 1,89 (ddd, J=14,20, 7,05, 6,94 Hz, 2 H) 1,95 - 2,04 (m, 4 H) 2,13 - 2,23 (m, 4 H) 2,55 - 2,61 (m, 2 H) 3,53 (s, 6 H) 3,77 - 3,84 (m, 4 H) 4,05 (t, J=8,67 Hz, 2 H) 5,09 - 5,18 (m, 2 H) 5,46 - 5,54 (m, 2 H) 6,45 (d, J=8,89 Hz, 2 H) 7,08 (t, J=7,75 Hz, 2 H) 7,13 (s, 1 H) 7,23 (s, 1 H) 7,28 (d, J=8,24 Hz, 2 H) 7,33 (s, 1 H) 7,39 (d, J=8,13 Hz, 1 H) 7,45 - 7,56 (m, 3 H) 7,94 (s, 1 H) 12,06 (s, 2 H); MS (ESI+) m/z 899,4 (M+H)+.



Ejemplo 2.2

{(2S)-1-[(2S)-2-{5-[(2R,5R)-1-(4-cloro-3-fluorofenil)-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-benzimidazol-5-il}pirrolidin-2-il]-1H-benzimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

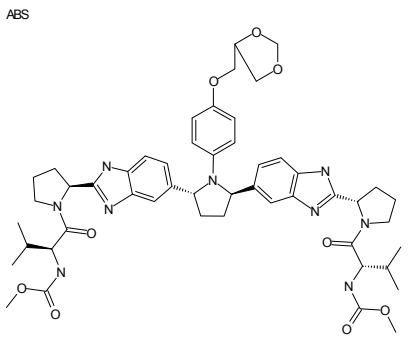
1H RMN (400 MHz, DMSO-d6) □ ppm 0,77 - 0,90 (m, 12 H) 1,66 - 1,78 (m, 2 H) 1,88 - 1,95 (m, 2 H) 1,96 - 2,06 (m, 4 H) 2,15 - 2,24 (m, 4 H) 2,54 - 2,60 (m, 2 H) 3,54 (s, 6 H) 3,79 - 3,86 (m, 4 H) 4,06 (t, J=8,46 Hz, 2 H) 5,10 - 5,18 (m, 2 H) 5,37 - 5,45 (m, 2 H) 6,16 (dd, J=9,49, 2,01 Hz, 1 H) 6,22 (dd, J=13,55, 2,06 Hz, 1 H) 7,00 - 7,11 (m, 3 H) 7,22 (s, 1 H) 7,28 (d, J=8,57 Hz, 2 H) 7,32 (s, 1 H) 7,40 (d, J=8,24 Hz, 1 H) 7,47 (d, J=8,13 Hz, 1 H) 12,07 (d, J=2,93 Hz, 2 H); MS (APCI+) m/z 884 (M+H)+.



Ejemplo 2.3

{(2S)-1-[(2S)-2-{5-[(2R,5R)-1-[4-(1,3-dioxan-5-iloxi)fenil]-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-benzimidazol-5-il}pirrolidin-2-il]-1H-benzimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

1H RMN (400 MHz, DMSO-d6) δ ppm 12,28 – 11,98 (m, 2H), 7,45 (d, J = 8,1, 1H), 7,37 (d, J = 8,2, 1H), 7,32 – 7,23 (m, 3H), 7,21 (s, 1H), 7,12 – 7,01 (m, 2H), 6,62 – 6,51 (m, 2H), 6,24 (d, J = 8,9, 2H), 5,40 – 5,27 (m, 2H), 5,18 – 5,09 (m, 2H), 4,72 (d, J = 6,1, 1H), 4,67 (d, J = 6,2, 1H), 4,06 (t, J = 8,4, 2H), 4,01 – 3,75 (m, 7H), 3,68 – 3,58 (m, 2H), 3,52 (d, J = 15,9, 6H), 2,28 – 1,83 (m, 12H), 1,74 – 1,62 (m, 2H), 0,93 – 0,73 (m, 12H); MS (ESI+) m/z 934,5 (M+H)+.

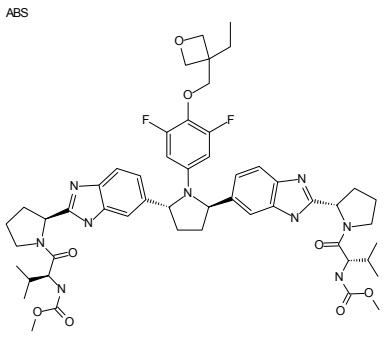


Ejemplo 2.4

{(2S)-1-[(2S)-2-{5-[(2R,5R)-1-[4-(1,3-dioxolan-4-ilmetoxi)fenil]-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-benzimidazol-5-il}pirrolidin-2-il]-1H-benzimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

1H RMN (400 MHz, DMSO-d6) δ ppm 12,27 – 11,95 (m, 2H), 7,43 (d, J = 8,1, 1H), 7,35 (d, J = 8,2, 1H), 7,32 – 7,22 (m, 3H), 7,19 (s, 1H), 7,03 (t, J = 7,4, 2H), 6,59 – 6,47 (m,

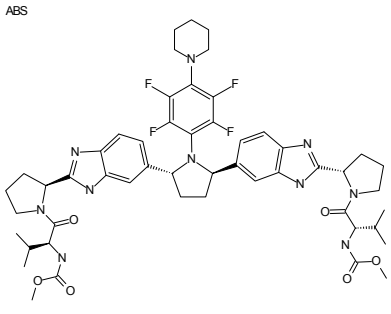
2H), 6,23 (d, J = 8,8, 2H), 5,39 – 5,27 (m, 2H), 5,16 – 5,04 (m, 2H), 4,83 (d, J = 2,6, 1H), 4,74 (s, 1H), 4,22 – 4,12 (m, 1H), 4,04 (t, J = 8,3, 2H), 3,88 (t, J = 7,5, 1H), 3,83 – 3,67 (m, 6H), 3,57 – 3,47 (m, 7H), 2,29 – 1,80 (m, 12H), 1,74 – 1,60 (m, 2H), 0,93 – 0,71 (m, 12H); MS (ESI+) m/z 934,4 (M+H)+.



Ejemplo 2.5

{(2S)-1-[(2S)-2-{6-[(2R,5R)-1-{4-[(3-etiloxetan-3-il)metoxi]-3,5-difluorofenil}-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-benzimidazol-6-il}pirrolidin-2-il]-1H-benzimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

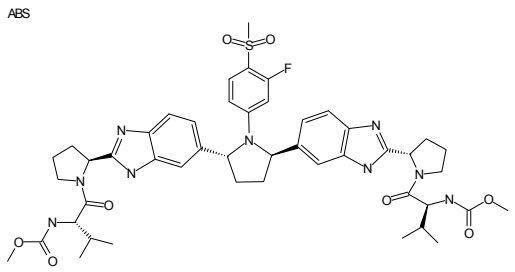
1H RMN (400 MHz, DMSO-d6) δ 12,30 – 12,02 (m, 2H), 7,47 (d, J = 8,3, 1H), 7,40 (d, J = 8,3, 1H), 7,34 – 7,16 (m, 4H), 7,06 (t, J = 7,0, 2H), 5,98 (d, J = 12,3, 2H), 5,46 – 5,30 (m, 2H), 5,24 – 5,05 (m, 2H), 4,29 (d, J = 5,5, 2H), 4,21 (d, J = 5,8, 2H), 4,05 (t, J = 8,2, 2H), 3,90 – 3,72 (m, 6H), 3,52 (s, 6H), 2,27 – 1,81 (m, 12H), 1,73 – 1,60 (m, 4H), 0,91 – 0,69 (m, 15H); MS (ESI+) m/z 982,4 (M+H)+.



Ejemplo 2.6

{(2S)-1-[(2S)-2-(6-{(2R,5R)-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-benzimidazol-6-il}-1-[2,3,5,6-tetrafluoro-4-(piperidin-1-il)fenil]pirrolidin-2-il}-1H-benzimidazol-2-il)pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

1H RMN (400 MHz, DMSO-d6) δ 12,10 (dd, J = 58,0, 37,7, 2H), 7,52 – 7,21 (m, 6H), 7,07 (t, J = 8,1, 2H), 5,52 – 5,29 (m, 2H), 5,17 – 5,03 (m, 2H), 4,12 – 3,93 (m, 2H), 3,88 – 3,66 (m, 4H), 3,53 (s, 6H), 2,87 – 2,71 (m, 4H), 2,27 – 1,76 (m, 14H), 1,50 – 1,32 (m, 6H), 0,93 – 0,70 (m, 12H); MS (ESI+) m/z 987,3 (M+H)+.

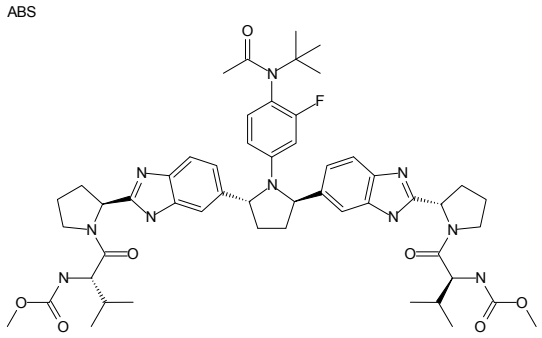


Ejemplo 2.7

{(2S)-1-[(2S)-2-{6-[(2R,5R)-1-[3-fluoro-4-(metilsulfonil)fenil]-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-benzimidazol-6-il}pirrolidin-2-il]-1H-benzimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

1H RMN (400 MHz, DMSO-d6) □ ppm 0,81 - 0,97 (m, 12 H), 1,30 (s, 2 H), 1,82 (d, J=4,2 Hz, 2 H), 1,90 - 2,35 (m, 12 H), 3,60 (s, 6 H), 3,88 (s, 3 H), 4,13 (t, J=8,3 Hz, 2 H), 5,20 (t, J=7,3 Hz, 2 H), 5,62 (s, 2 H), 6,26 - 6,40 (m, J=9,5 Hz, 2 H), 7,15 (d, J=7,0 Hz, 2 H), 7,30 (s, 1 H), 7,32 - 7,45 (m, 4 H), 7,49 (d, J=8,2 Hz, 1 H), 7,56 (d, J=8,1 Hz, 1 H), 12,16 (s, 2 H); MS (ESI+) m/z 928,4 (M+H)+, (ESI-) m/z 926,3 (M-H)-.

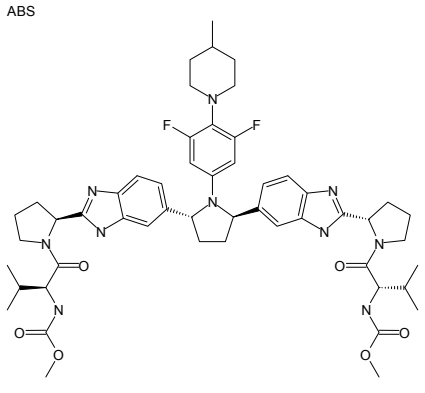
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Ejemplo 2.8

{(2S)-1-[(2S)-2-{6-[(2R,5R)-1-{4-[acetil(tert-butil)amino]-3-fluorofenil}-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-benzimidazol-6-il}pirrolidin-2-il]-1H-benzimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

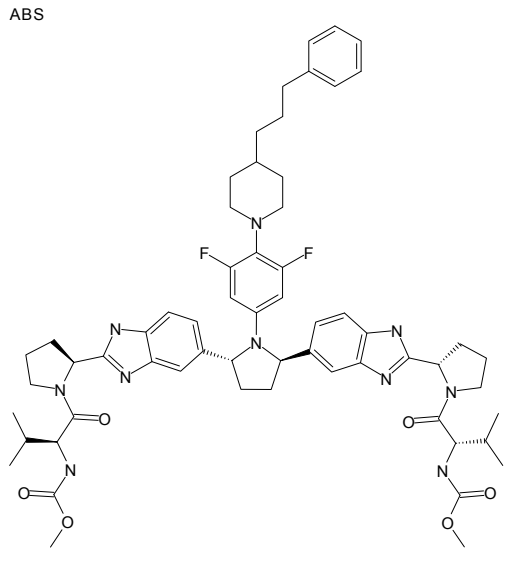
Comenzando con 4-((2R,5R)-2,5-bis(4-cloro-3-nitrofenil)pirrolidin-1-il)-N-tert-butil-2-fluoroanilina, el producto inicial de la secuencia que se ha descrito fue {(2S)-1-[(2S)-2-{6-[(2R,5R)-1-[4-(tert-butilamino)-3-fluorofenil]-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-benzimidazol-6-il}pirrolidin-2-il]-1H-benzimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo (Nomenclatura ACD v12). El grupo N-acetilo se agregó por reacción con anhídrido acético/piridina para dar el compuesto del título. 1H RMN (400 MHz, DMSO-d6) δ ppm 0,73 - 0,90 (m, 12 H), 1,13 (d, J=5,20 Hz, 9 H), 1,37 - 1,44 (m, 4 H), 1,62 - 1,72 (m, 2 H), 1,92 - 2,02 (m, 9 H), 2,10 - 2,26 (m, 5 H), 2,51 - 2,58 (m, 2 H), 3,52 (s, 6 H), 3,73 - 3,85 (m, 4 H), 3,98 - 4,12 (m, 2 H), 5,09 - 5,17 (m, 2 H), 5,36 - 5,48 (m, 3 H), 6,08 - 6,18 (m, 3 H), 6,74 - 6,87 (m, 1 H), 7,08 (dd, J=13,72, 8,29 Hz, 3 H), 7,20 (s, 1 H), 7,24 - 7,31 (m, 4 H), 7,40 (d, J=8,24 Hz, 1 H), 7,48 (d, J=8,13 Hz, 1 H), 12,01 (s, 1 H), 12,17 (s, 1 H); MS (ESI+) m/z 964 (M+H)+.



Ejemplo 2.9

{(2S)-1-[(2S)-2-{6-[(2R,5R)-1-[3,5-difluoro-4-(4-metilpiperidin-1-il)fenil]-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-benzimidazol-6-il}pirrolidin-2-il]-1H-benzimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

1H RMN (400 MHz, DMSO-d6) δ ppm 0,75 - 0,90 (m, 12 H), 1,05 - 1,18 (m, 2 H), 1,24 - 1,37 (m, 2 H), 1,45 - 1,54 (m, 2 H), 1,62 - 1,73 (m, 2 H), 1,84 - 2,05 (m, 7 H), 2,12 - 2,25 (m, 5 H), 2,69 - 2,81 (m, 4 H), 3,52 (s, 6 H), 3,77 - 3,86 (m, 4 H), 4,05 (t, J=8,35 Hz, 2 H), 5,10 - 5,18 (m, 2 H), 5,35 (q, J=7,34 Hz, 2 H), 5,87 (d, J=12,69 Hz, 2 H), 7,02 - 7,10 (m, 2 H), 7,19 (s, 1 H), 7,24 - 7,32 (m, 3 H), 7,39 (d, J=8,24 Hz, 1 H), 7,47 (d, J=8,13 Hz, 1 H), 12,06 (d, J=20,93 Hz, 2 H); MS (ESI+) m/z 966 (M+H)+.

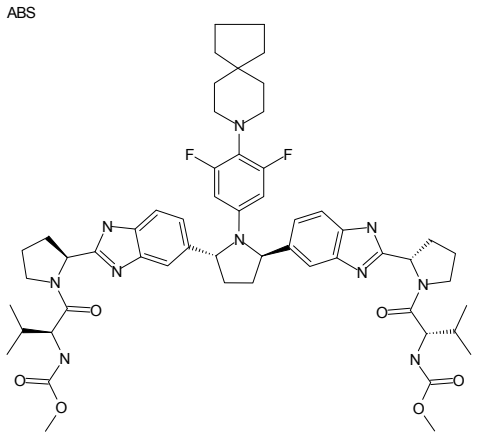


Ejemplo 2.10

{(2S)-1-[(2S)-2-{5-[(2R,5R)-1-{3,5-difluoro-4-[4-(3-fenilpropil)piperidin-1-il]fenil}-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-benzimidazol-5-il}pirrolidin-2-il]-1H-benzimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

1H RMN (400 MHz, DMSO-d6) δ ppm 0,72 - 0,95 (m, 12 H), 1,00 - 1,31 (m, 9 H), 1,46 - 1,59 (m, 4 H), 1,61 - 1,79 (m, 2 H), 1,83 - 2,08 (m, 6 H), 2,11 - 2,27 (m, 4 H), 2,77 (s, 4 H), 3,54 (s, 6 H), 3,82 (s, 4 H), 4,06 (t, J=8,46 Hz, 2 H), 5,08 - 5,19 (m, 2 H), 5,28 - 5,46 (m, 2 H), 5,88 (d, J=12,79 Hz, 2 H), 7,01 - 7,10 (m, 2 H), 7,10 - 7,33 (m, 9 H), 7,40 (d, J=8,13 Hz, 1 H), 7,48 (d, J=8,13 Hz, 1 H), 11,71 - 12,51 (m, 2 H); MS (ESI+) m/z 1069 (M+H)+; MS (ESI-) m/z 1067 (M-H)-.

ABS

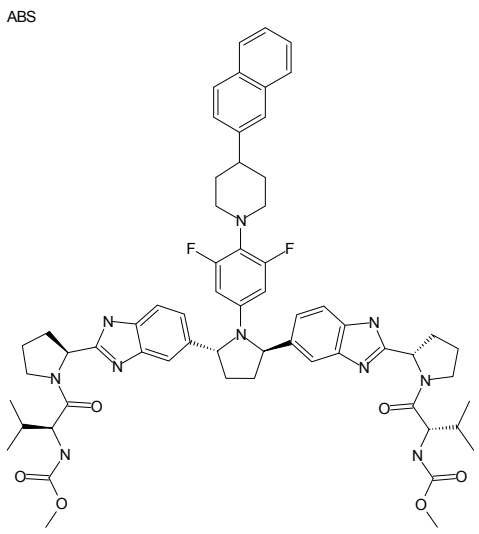


Ejemplo 2.11

{(2S)-1-[(2S)-2-{5-[(2R,5R)-1-[4-(8-azaespiro[4,5]dec-8-il)-3,5-difluorofenil]-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-benzimidazol-5-il}pirrolidin-2-il]-1H-benzimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

1H RMN (400 MHz, DMSO-d6) δ ppm 0,73 - 0,93 (m, 12 H), 1,29 - 1,43 (m, 9 H), 1,52 (t, J=6,83 Hz, 5 H), 1,68 (s, 2 H), 1,81 - 2,08 (m, 6 H), 2,10 - 2,26 (m, 4 H), 2,75 (s, 4 H), 3,54 (s, 6 H), 3,82 (s, 4 H), 4,06 (t, J=8,40 Hz, 2 H), 5,09 - 5,19 (m, 2 H), 5,29 - 5,46 (m, 2 H), 5,88 (d, J=12,58 Hz, 2 H), 7,03 - 7,11 (m, 2 H), 7,20 (s, 1 H), 7,25 - 7,33 (m, 3 H), 7,40 (d,

J=8,24 Hz, 1 H), 7,49 (d, J=8,24 Hz, 1 H), 11,63 - 12,57 (m, 2 H); MS (ESI+) m/z 1005 (M+H)+; MS (ESI-) m/z 1003 (M-H)-.

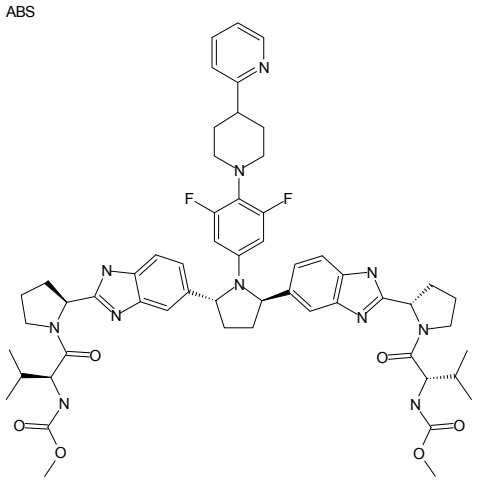


Ejemplo 2.12

{(2S)-1-[(2S)-2-{5-[(2R,5R)-1-{3,5-difluoro-4-[4-(2-naftil)piperidin-1-il]fenil}-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-benzimidazol-5-il}pirrolidin-2-il]-1H-benzimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

1H RMN (400 MHz, DMSO-d6) δ ppm 0,76 - 0,91 (m, 12 H), 1,24 (d, J=2,28 Hz, 2 H), 1,63 - 2,08 (m, 12 H), 2,20 (s, 4 H), 2,86 - 3,19 (m, 5 H), 3,53 (s, 6 H), 3,82 (s, 4 H), 4,06 (t, J=8,29 Hz, 2 H), 5,10 - 5,22 (m, 2 H), 5,32 - 5,48 (m, 2 H), 5,93 (d, J=12,90 Hz, 2 H), 7,03 - 7,16 (m, 2 H), 7,19 - 7,36 (m, 4 H), 7,39 - 7,55 (m, 5 H), 7,69 - 7,89 (m, 4 H), 11,71 - 12,63 (m, 2 H); MS (ESI+) m/z 1077 (M+H)+; MS (ESI-) m/z 1075 (M-H)-.

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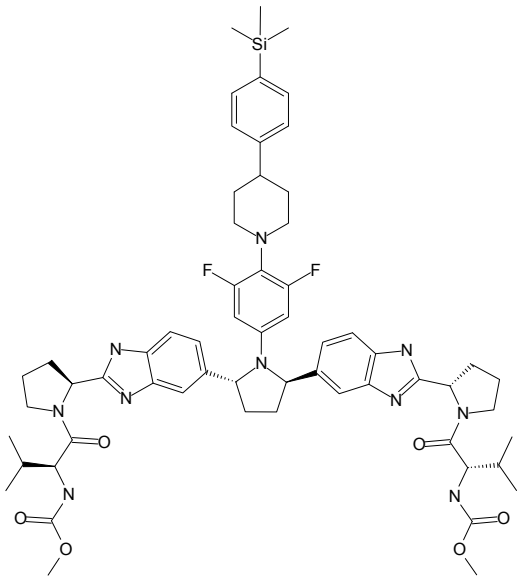


Ejemplo 2.13

{(2S)-1-[(2S)-2-{5-[(2R,5R)-1-{3,5-difluoro-4-[4-(piridin-2-il)piperidin-1-il]fenil}-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-benzimidazol-5-il}pirrolidin-2-il]-1H-benzimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

1H RMN (400 MHz, DMSO-d6) δ ppm 0,71 - 1,02 (m, 12 H), 1,62 - 1,83 (m, 6 H), 1,81 - 2,08 (m, 7 H), 2,10 - 2,29 (m, 4 H), 2,47 - 2,63 (m, 2 H), 2,81 - 3,07 (m, 4 H), 3,53 (s, 6 H), 3,82 (s, 4 H), 4,06 (t, J=8,89 Hz, 2 H), 5,10 - 5,21 (m, 2 H), 5,31 - 5,47 (m, 2 H), 5,91 (d, J=12,69 Hz, 2 H), 7,04 - 7,13 (m, 2 H), 7,14 - 7,20 (m, 1 H), 7,20 - 7,34 (m, 5 H), 7,41 (d, J=8,24 Hz, 1 H), 7,49 (d, J=8,35 Hz, 1 H), 7,62 - 7,72 (m, 1 H), 8,45 (d, J=4,55 Hz, 1 H), 11,74 - 12,57 (m, 2 H); MS (ESI+) m/z 1028 (M+H)+; MS (ESI-) m/z 1026 (M-H)-.

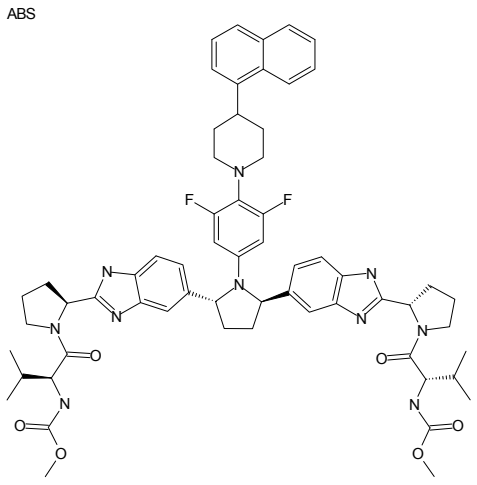
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Ejemplo 2.14

{(2S)-1-[(2S)-2-{5-[(2R,5R)-1-(3,5-difluoro-4-{4-[4-(trimetilsilil)fenil]piperidin-1-il}fenil)-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-benzimidazol-5-il}pirrolidin-2-il]-1H-benzimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

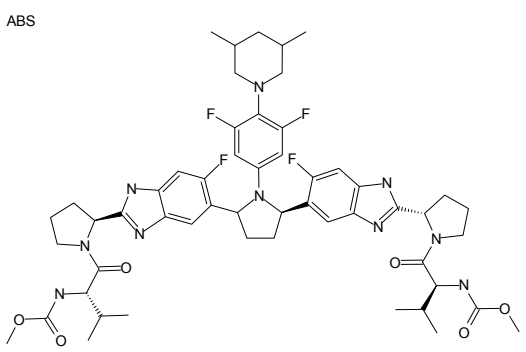
1H RMN (400 MHz, DMSO-d6) δ ppm 0,20 (s, 9 H), 0,74 - 0,94 (m, 12 H), 1,59 - 1,75 (m, 6 H), 1,83 - 2,09 (m, 7 H), 2,13 - 2,29 (m, 4 H), 2,44 - 2,59 (m, 2 H), 2,84 - 3,15 (m, 4 H), 3,53 (s, 6 H), 3,82 (s, 4 H), 4,06 (t, J=8,46 Hz, 2 H), 5,15 (d, J=3,04 Hz, 2 H), 5,31 - 5,47 (m, 2 H), 5,92 (d, J=12,79 Hz, 2 H), 7,04 - 7,14 (m, 2 H), 7,21 (d, J=7,92 Hz, 3 H), 7,27 - 7,37 (m, 3 H), 7,37 - 7,45 (m, 3 H), 7,50 (d, J=8,02 Hz, 1 H), 12,10 (d, J=17,57 Hz, 2 H); MS (ESI+) m/z 1099 (M+H)+; MS (ESI-) m/z 1097 (M-H)-.



Ejemplo 2.15

{(2S)-1-[(2S)-2-{5-[(2R,5R)-1-{3,5-difluoro-4-[4-(1-naftil)piperidin-1-il]fenil}-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-benzimidazol-5-il}pirrolidin-2-il]-1H-benzimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

1H RMN (400 MHz, DMSO-d6) δ ppm 0,74 - 0,94 (m, 12 H), 1,64 - 2,05 (m, 12 H), 2,13 - 2,29 (m, 3 H), 2,45 - 2,62 (m, 2 H), 2,90 - 3,01 (m, J=11,06 Hz, 2 H), 3,08 - 3,25 (m, 2 H), 3,53 (s, 6 H), 3,82 (s, 4 H), 4,06 (t, J=8,29 Hz, 2 H), 5,08 - 5,23 (m, 2 H), 5,32 - 5,52 (m, 2 H), 5,94 (d, J=12,69 Hz, 2 H), 7,04 - 7,17 (m, 2 H), 7,20 - 7,37 (m, 4 H), 7,38 - 7,59 (m, 6 H), 7,75 (d, J=8,35 Hz, 1 H), 7,86 - 7,95 (m, 1 H), 8,14 (d, J=8,24 Hz, 1 H), 11,61 - 12,69 (m, 2 H); MS (ESI+) m/z 1077 (M+H)+; (ESI-) m/z 1075 (M-H)-.

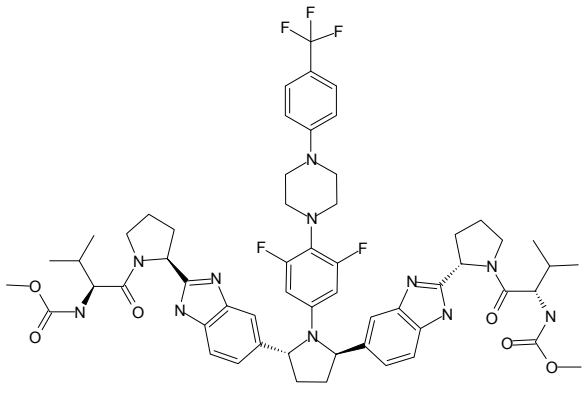


Ejemplo 2.16

{(2S)-1-[(2S)-2-{5-[(5R)-1-[4-(3,5-dimetilpiperidin-1-il)-3,5-difluorofenil]-5-{6-fluoro-2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-benzimidazol-5-il}pirrolidin-2-il]-6-fluoro-1H-benzimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

1H RMN (400 MHz, DMSO-d6) ppm 0,64 - 0,94 (m, 18 H) 1,56 - 1,73 (m, 4 H) 1,75 - 1,93 (m, 6 H) 1,95 - 2,06 (m, 6 H) 2,12 - 2,26 (m, 4 H) 2,69 - 2,79 (m, 1 H) 3,20 - 3,29 (m, 1 H) 3,53 (s, 6 H) 3,74 - 3,89 (m, 4 H) 3,97 - 4,10 (m, 2 H) 5,05 - 5,19 (m, 2 H) 5,48 - 5,62 (m, 2 H) 5,87 (dd, J=11,49, 7,92 Hz, 2 H) 7,02 (dd, J=3,90, 1,95 Hz, 1 H) 7,12 (d, J=6,83 Hz, 1 H) 7,26 - 7,37 (m, 3 H) 7,40 (dd, J=11,11, 6,02 Hz, 1 H) 12,08 - 12,16 (m, 1 H) 12,23 - 12,31 (m, 1 H); MS (APCI+) m/z 1016 (M+H)+.

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Ejemplo 2.17

{(2S)-1-[(2S)-2-{5-[(2R,5R)-1-(3,5-difluoro-4-{4-[4-(trifluorometil)fenil]piperazin-1-il}fenil)-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-benzimidazol-5-il}pirrolidin-2-il]-1H-benzimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

1H RMN (400 MHz, DMSO-d6) ppm 0,69 - 0,96 (m, 14 H) 1,10 - 1,29 (m, 2 H) 1,69 (m, 2 H) 1,99 (m, 4 H) 2,20 (m, 2 H) 2,99 (m, 6 H) 3,22 - 3,26 (m, 6 H) 3,54 (s, 6 H) 3,82 (m, 6 H) 5,15 (m, 2 H) 5,39 (m, 2 H) 5,95 (m, 2 H) 7,03 (d, J=8,78 Hz, 2 H) 7,22 (m, 2 H) 7,24 - 7,36 (m, 2 H) 7,40 - 7,56 (m, 4 H) 12,06 (s, 2 H); MS (ESI+) m/z 1096,4, (ESI-) m/z 1094,3.

Los siguientes ejemplos de compuestos 3.1-3.51 pueden prepararse a partir de los intermediarios apropiados siguiendo los métodos de los Procedimientos Generales 12/12A.

Aminas intermediarias:

(S)-6,6'-((2R,5R)-1-(4-(piridin-2-il)fenil)pirrolidin-2,5-diil)bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol);

(S)-6,6'-((2R,5R)-1-(3-cloro-4-(trifluorometoxi)fenil)pirrolidin-2,5-diil)bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol);

(S)-6,6'-((2R,5R)-1-(4-(2-metoxietoxi)fenil)pirrolidin-2,5-diil)bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol);

(S)-6,6'-((2R,5R)-1-(4-clorofenil)pirrolidin-2,5-diil)bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol);

(S)-6,6'-((2R,5R)-1-(bifenil-4-il)pirrolidin-2,5-diil)bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol);

(S)-6,6'-((2R,5R)-1-(4-tert-butilfenil)pirrolidin-2,5-diil)bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol);

(S,S)-6,6'-((2R,5R)-1-(3,5-difluoro-4-(piperidin-1-il)fenil)pirrolidin-2,5-diil)bis(2-((2S,4S)-4-metoxipirrolidin-2-il)-1H-benzo[d]imidazol);

(S,S)-6,6'-((2R,5R)-1-(3,5-difluoro-4-(piperidin-1-il)fenil)pirrolidin-2,5-diil)bis(2-((2S,4S)-4-fluoropirrolidin-2-il)-1H-benzo[d]imidazol);

(S,S)-6,6'-((2R,5R)-1-(4-fluorofenil)pirrolidin-2,5-diil)bis(2-((2S,4S)-4-fluoropirrolidin-2-il)-1H-benzo[d]imidazol);

(S,S)-6,6'-((2R,5R)-1-(4-fluorofenil)pirrolidin-2,5-diil)bis(2-((2S,4S)-4-metoxipirrolidin-2-il)-1H-benzo[d]imidazol);

(S)-6,6'-((2R,5R)-1-(4-tert-butilfenil)pirrolidin-2,5-diil)bis(2-((S)-5,5-dimetilpirrolidin-2-il)-1H-benzo[d]imidazol);

(S,S)-6,6'-((2R,5R)-1-(4-tert-butilfenil)pirrolidin-2,5-diil)bis(2-((2S,4S)-4-fluoropirrolidin-2-il)-1H-benzo[d]imidazol);

(S)-6,6'-((2S,5S)-1-(4-ciclopropil-2-fluorofenil)pirrolidin-2,5-diil)bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol);

(S)-6,6'-((2R,5R)-1-(3-fluoro-4-(piperidin-1-il)fenil)pirrolidin-2,5-diil)bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol);

(S)-6,6'-((2R,5R)-1-(3,5-difluoro-4-(piperidin-1-il)fenil)pirrolidin-2,5-diil)bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol);

(S)-6,6'-((2R,5R)-1-(3-fluoro-4-(4-fenilpiperidin-1-il)fenil)pirrolidin-2,5-diil)bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol);

(S)-6,6'-((2R,5R)-1-(3,5-difluoro-4-(4-fenilpiperidin-1-il)fenil)pirrolidin-2,5-diil)bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol);

(S)-6,6'-((2R,5R)-1-(3,5-difluoro-4-(piperidin-1-il)fenil)pirrolidin-2,5-diil)bis(2-((3S)-2-azabiciclo[2,2,1]heptan-3-il)-1H-benzo[d]imidazol);

(S)-6,6'-((2R,5R)-1-(3,5-difluoro-4-(piperidin-1-il)fenil)pirrolidin-2,5-diil)bis(2-((S)-indolin-2-il)-1H-benzo[d]imidazol);

(S)-6,6'-((2R,5R)-1-(4-tert-butilfenil)pirrolidin-2,5-diil)bis(2-((S)-4-metilenepirrolidin-2-il)-1H-benzo[d]imidazol);

(S,S,S)-6,6'-((2R,5R)-1-(3,5-difluoro-4-(4-fenilpiperidin-1-il)fenil)pirrolidin-2,5-diil)bis(2-((2S,3aS,6aS)-octahidrociclopenta[b]pirrol-2-il)-1H-benzo[d]imidazol);

(S,S,S)-6,6'-((2R,5R)-1-(3,5-difluoro-4-(piperidin-1-il)fenil)pirrolidin-2,5-diil)bis(2-((2S,3aS,6aS)-octahidrociclopenta[b]pirrol-2-il)-1H-benzo[d]imidazol);

(S)-6,6'-((2R,5R)-1-(3,5-difluoro-4-(4-fenilpiperidin-1-il)fenil)pirrolidin-2,5-diil)bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol);

6,6'-{(2R,5R)-1-[3,5-difluoro-4-(piperidin-1-il)fenil]pirrolidin-2,5-diil}bis{5-fluoro-2-[(2S)-pirrolidin-2-il]-1H-benzimidazol} (Nomenclatura ACD v12);

(S,S,S)-6,6'-((2R,5R)-1-(3,5-difluoro-4-(piperidin-1-il)fenil)pirrolidin-2,5-diil)bis(5-fluoro-2-((2S,3aS,6aS)-octahidrociclopenta[b]pirrol-2-il)-1H-benzo[d]imidazol);

(S)-6,6'-((2R,5R)-1-(3,5-difluoro-4-(4-(4-fluorofenil)piperidin-1-il)fenil)pirrolidin-2,5-diil)bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol);

(S)-6,6'-((2R,5R)-1-(3,5-difluoro-4-(4-(3-(trimetilsilil)fenil)piperidin-1-il)fenil)pirrolidin-2,5-diil)bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol);

(S)-6,6'-((2R,5R)-1-(4-(4-(3,4-difluorofenil)piperidin-1-il)-3,5-difluorofenil)pirrolidin-2,5-diil)bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol);

(S)-6,6'-((2R,5R)-1-(4-(4-(3,5-difluorofenil)piperidin-1-il)-3,5-difluorofenil)pirrolidin-2,5-diil)bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol);

(S)-6,6'-((2S,5R)-1-(2-(4-fenilpiperidin-1-il)pirimidin-5-il)pirrolidin-2,5-diil)bis(5-fluoro-2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol);

(S)-6,6'-((2S,5R)-1-(2-(piperidin-1-il)pirimidin-5-il)pirrolidin-2,5-diil)bis(5-fluoro-2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol);

(S)-6,6'-((2R,5R)-1-(4-(4-(2,6-difluorofenil)piperazin-1-il)-3,5-difluorofenil)pirrolidin-2,5-diil)bis(5-fluoro-2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol);

(S)-6,6'-((2S,5S)-1-(4-(4-(2,6-difluorofenil)piperazin-1-il)-3,5-difluorofenil)pirrolidin-2,5-diil)bis(5-fluoro-2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol); y

(S)-6,6'-((2R,5R)-1-(3,5-difluoro-4-(4-(4-fluorofenil)piperidin-1-il)fenil)pirrolidin-2,5-diil)bis(5-fluoro-2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol).

Ácidos intermediarios:

ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico;

ácido (S)-2-(metoxicarbonilamino)-2-(tetrahidro-2H-piran-4-il)acético;

ácido (S)-2-ciclohexil-2-(metoxicarbonilamino)acético;

ácido (S)-2-ciclopentil-2-(metoxicarbonilamino)acético;

ácido (S)-2-(metoxicarbonilamino)-3,3-dimetilbutanoico;

ácido (2S,3R)-3-metoxi-2-(metoxicarbonilamino)butanoico;

ácido (2S,3S)-3-metoxi-2-(metoxicarbonilamino)butanoico;

ácido (S)-2-(metoxicarbonilamino)-2-((R)-tetrahidrofurano-3-il)acético;

ácido (S)-2-(metoxicarbonilamino)-2-((S)-tetrahidrofurano-3-il)acético;

ácido (S)-2-(2,3-dihidro-1H-inden-2-il)-2-(metoxicarbonilamino)acético;

ácido 2-(tert-butoxicarbonilamino)acético;

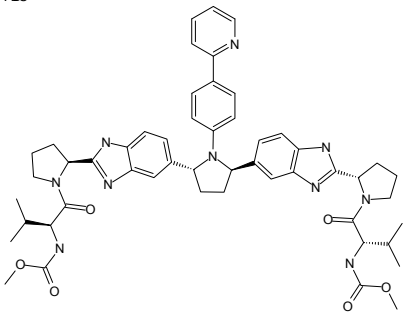
ácido 2-(metoxicarbonilamino)-3-metilbut-2-enoico;

carboxílico (S)-tetrahidrofurano-2- ácido

ácido (S)-3-etil-2-(metoxicarbonilamino)pentanoico; y

ácido (S)-2-(etoxicarbonilamino)-3-metilbutanoico.

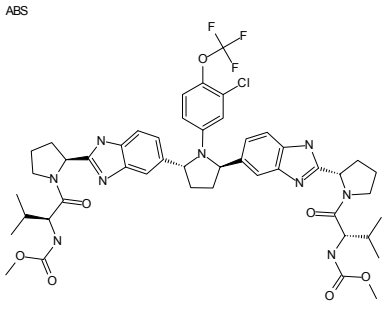
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Ejemplo 3.1

{(2S)-1-[(2S)-2-(5-{(2R,5R)-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-benzimidazol-5-il}-1-[4-(piridin-2-il)fenil]pirrolidin-2-il}-1H-benzimidazol-2-il)pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

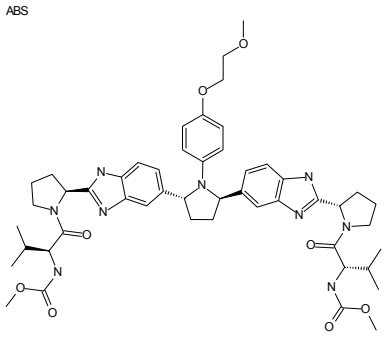
1H RMN (400 MHz, DMSO-d6) δ ppm 12,28 – 11,98 (m, 2H), 8,42 (d, J = 4,4, 1H), 7,70 – 7,56 (m, 4H), 7,46 (d, J = 8,2, 1H), 7,38 (d, J = 8,2, 1H), 7,34 (s, 1H), 7,30 – 7,20 (m, 3H), 7,16 – 7,02 (m, 3H), 6,42 (d, J = 8,7, 2H), 5,56 – 5,42 (m, 2H), 5,18 – 5,06 (m, 2H), 4,03 (t, J = 9,3, 2H), 3,88 – 3,73 (m, 4H), 3,52 (s, 6H), 2,25 – 1,62 (m, 14H), 0,92 – 0,67 (m, 12H); MS (ESI+) m/z 909,5 (M+H)+.



Ejemplo 3.2

{(2S)-1-[(2S)-2-{5-[(2R,5R)-1-[3-cloro-4-(trifluorometoxi)fenil]-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-benzimidazol-5-il}pirrolidin-2-il]-1H-benzimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

1H RMN (400 MHz, DMSO-d6) δ ppm 12,31 – 12,01 (m, 2H), 7,48 (d, J = 7,9, 1H), 7,40 (d, J = 8,2, 1H), 7,34 – 7,17 (m, 4H), 7,15 – 6,99 (m, 3H), 6,44 (s, 1H), 6,30 (d, J = 8,9, 1H), 5,55 – 5,37 (m, 2H), 5,19 – 5,04 (m, 2H), 4,04 (t, J = 7,8, 2H), 3,89 – 3,73 (m, 4H), 3,52 (s, 6H), 2,28 – 1,79 (m, 12H), 1,77 – 1,59 (m, 2H), 0,92 – 0,64 (m, 12H); MS (ESI+) m/z 950,4 (M+H)+.

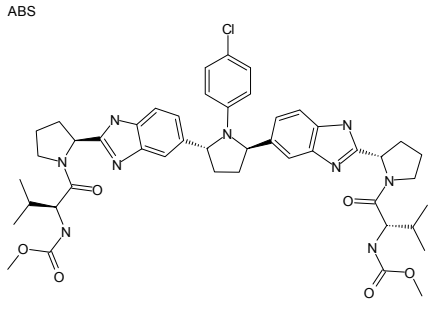


Ejemplo 3.3

{(2S)-1-[(2S)-2-(5-{(2R,5R)-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-benzimidazol-5-il}-1-[4-(2-metoxietoxi)fenil]pirrolidin-2-il}-1H-benzimidazol-2-il)pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

1H RMN (400 MHz, DMSO-d6) δ ppm 12,27 – 11,97 (m, 2H), 7,44 (d, J = 8,4, 1H), 7,36 (d, J = 7,7, 1H), 7,33 – 7,25 (m, 3H), 7,20 (s, 1H), 7,12 – 7,00 (m, 2H), 6,58 – 6,47 (m, 2H), 6,24 (d, J = 9,0, 2H), 5,40 – 5,27 (m, 2H), 5,19 – 5,08 (m, 2H), 4,06 (t, J = 8,3, 2H),

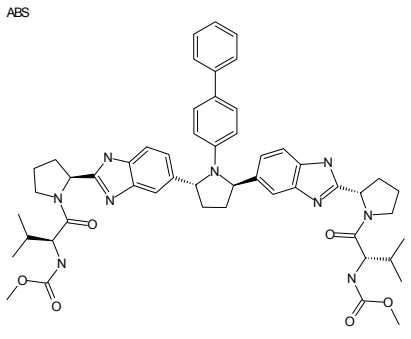
3,88 – 3,76 (m, 6H), 3,54 (s, 6H), 3,51 – 3,45 (m, 2H), 3,21 (s, 3H), 2,26 – 1,83 (m, 12H), 1,75 – 1,64 (m, 2H), 0,93 – 0,74 (m, 12H); MS (ESI+) m/z 906,4 (M+H)+.



Ejemplo 3.4

{(2S)-1-[(2S)-2-{5-[(2R,5R)-1-(4-clorofenil)-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-benzimidazol-5-il}pirrolidin-2-il]-1H-benzimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

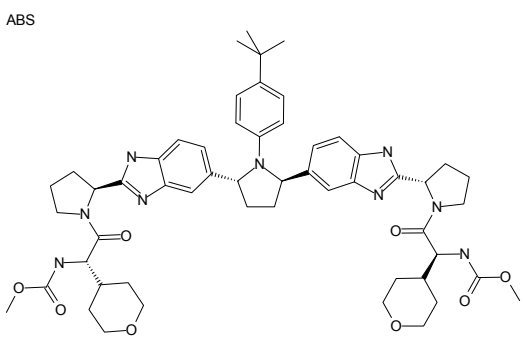
1H RMN (400 MHz, DMSO-d6) δ ppm 12,05 (s, 2H), 7,44 (d, J = 8,2, 1H), 7,36 (d, J = 8,1, 1H), 7,31 – 7,22 (m, 3H), 7,19 (s, 1H), 7,03 (t, J = 8,2, 2H), 6,94 – 6,83 (m, 2H), 6,29 (d, J = 9,1, 2H), 5,42 – 5,32 (m, 2H), 5,16 – 5,04 (m, 2H), 4,04 (t, J = 8,4, 2H), 3,85 – 3,75 (m, 4H), 3,51 (s, 6H), 2,25 – 1,58 (m, 14H), 0,90 – 0,73 (m, 12H); MS (ESI+) m/z 866,4 (M+H)+.



Ejemplo 3.5

{(2S)-1-[(2S)-2-{5-[(2R,5R)-1-(bifenil-4-il)-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-benzimidazol-5-il}pirrolidin-2-il]-1H-benzimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

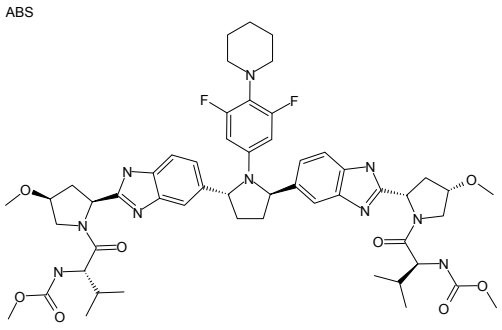
1H RMN (400 MHz, DMSO-d6) δ 12,11 – 11,66 (m, 2H), 7,47 (d, J = 8,3, 1H), 7,43 – 7,33 (m, 4H), 7,32 – 7,19 (m, 7H), 7,17 – 7,06 (m, 3H), 6,43 (d, J = 8,8, 2H), 5,52 – 5,41 (m, 2H), 5,18 – 5,09 (m, 2H), 4,05 (t, J = 8,2, 2H), 3,87 – 3,76 (m, 4H), 3,53 (s, 6H), 2,25 – 2,11 (m, 4H), 2,05 – 1,62 (m, 10H), 0,91 – 0,74 (m, 12H); MS (ESI+) m/z 908,5 (M+H)+.



Ejemplo 3.6

([(2R,5R)-1-(4-tert-butilfenil)pirrolidin-2,5-diil]bis{1H-benzimidazol-5,2-diil(2S)pirrolidin-2,1-diil[(1S)-2-oxo-1-(tetrahidro-2H-piran-4-il)etano-2,1-diil]})biscarbamato de dimetilo

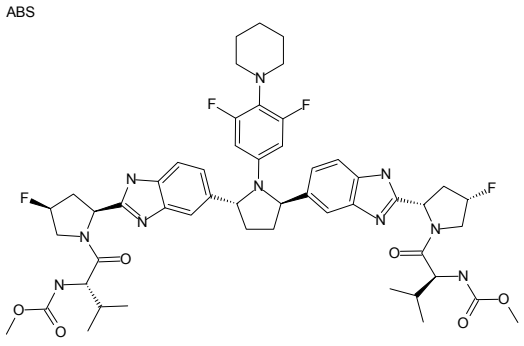
1H RMN (400 MHz, DMSO-d6) □ ppm 1,07 (s, 9 H) 1,22 - 1,32 (m, 2 H) 1,42 - 1,57 (m, 4 H) 1,64 - 1,72 (m, 2 H) 1,82 (dd, J=21,90, 10,63 Hz, 4 H) 1,92 - 2,02 (m, 4 H) 2,10 - 2,25 (m, 4 H) 2,90 - 2,99 (m, 1 H) 3,04 - 3,19 (m, 4 H) 3,53 (s, 6 H) 3,56 - 3,63 (m, 1 H) 3,66 - 3,79 (m, 4 H) 3,83 (d, J=3,04 Hz, 4 H) 4,14 (q, J=8,10 Hz, 2 H) 5,07 - 5,15 (m, 2 H) 5,33 - 5,40 (m, 2 H) 6,24 (d, J=8,89 Hz, 2 H) 6,85 - 6,94 (m, 2 H) 7,09 (dd, J=14,10, 8,46 Hz, 2 H) 7,16 - 7,22 (m, 2 H) 7,30 - 7,41 (m, 3 H) 7,44 (d, J=9,43 Hz, 1 H) 11,99 - 12,12 (m, 2 H); MS (ESI+) m/z 972,5 (M+H)+.



Ejemplo 3.7

{(2S)-1-[(2S,4S)-2-{5-[(2R,5R)-1-[3,5-difluoro-4-(piperidin-1-il)fenil]-5-{2-[(2S,4S)-4-metoxi-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-benzimidazol-5-il}pirrolidin-2-il]-1H-benzimidazol-2-il}-4-metoxipirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

1H RMN (500 MHz, DMSO-d6) □ ppm 0,76 - 0,87 (m, 12 H) 1,35 - 1,40 (m, 2 H) 1,45 (s, 4 H) 1,66 - 1,72 (m, 2 H) 1,95 (dd, J=13,28, 7,17 Hz, 2 H) 2,14 (td, J=12,32, 5,87 Hz, 2 H) 2,41 - 2,46 (m, 2 H) 2,76 (s, 4 H) 3,03 - 3,18 (m, 2 H) 3,25 (d, J=3,66 Hz, 6 H) 3,54 (s, 6 H) 3,64 (td, J=11,14, 5,65 Hz, 2 H) 4,05 - 4,13 (m, 4 H) 4,19 - 4,27 (m, 2 H) 5,10 - 5,16 (m, 2 H) 5,31 - 5,39 (m, 2 H) 5,88 (d, J=12,66 Hz, 2 H) 7,06 (t, J=8,47 Hz, 2 H) 7,21 - 7,31 (m, 4 H) 7,41 (d, J=8,09 Hz, 1 H) 7,48 (dd, J=8,39, 1,83 Hz, 1 H) 11,81 - 11,91 (m, 2 H); MS (ESI+) m/z 1011,6 (M+H)+.

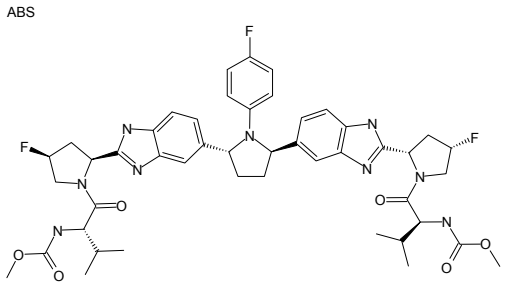


Ejemplo 3.8

{(2S)-1-[(2S,4S)-2-{5-[(2R,5R)-1-[3,5-difluoro-4-(piperidin-1-il)fenil]-5-{2-[(2S,4S)-4-fluoro-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-benzimidazol-5-il}pirrolidin-2-il]-1H-benzimidazol-2-il}-4-fluoropirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

1H RMN (500 MHz, DMSO-d6) □ ppm 0,80 - 0,99 (m, 12 H) 1,38 (d, J=4,73 Hz, 2 H) 1,45 (s, 4 H) 1,64 - 1,74 (m, 2 H) 2,00 - 2,08 (m, 2 H) 2,37 - 2,45 (m, 2 H) 2,76 (s, 4 H) 3,08 - 3,19 (m, 2 H) 3,55 (s, 6 H) 3,99 - 4,26 (m, 6 H) 5,30 - 5,39 (m, 4 H) 5,47 (d, J=53,41 Hz, 4 H) 5,89 (d, J=12,66 Hz, 2 H) 7,02 - 7,11 (m, 2 H) 7,27 (d, J=25,02 Hz, 2 H) 7,41 (d, J=8,09

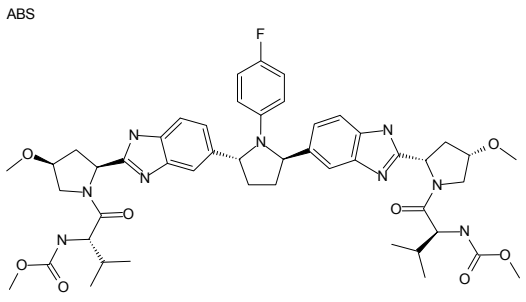
Hz, 3 H) 7,47 (d, J=7,93 Hz, 1 H) 11,85 (d, J=31,74 Hz, 2 H); MS (ESI+) m/z 987,5 (M+H)+.



Ejemplo 3.9

{(2S)-1-[(2S,4S)-4-fluoro-2-{5-[(2R,5R)-5-{2-[(2S,4S)-4-fluoro-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-benzimidazol-5-il}-1-(4-fluorofenil)pirrolidin-2-il]-1H-benzimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

1H RMN (400 MHz, DMSO-d6) ppm 0,82 - 0,98 (m, 12 H) 1,68 - 1,77 (m, 2 H) 1,91 - 2,09 (m, 4 H) 2,36 - 2,44 (m, 2 H) 2,59 - 2,66 (m, 2 H) 3,52 - 3,57 (m, 6 H) 3,72 - 3,98 (m, 2 H) 4,07 - 4,18 (m, 4 H) 5,19 (t, J=8,08 Hz, 1 H) 5,31 - 5,44 (m, 4 H) 5,48 - 5,57 (m, 1 H) 6,24 - 6,31 (m, 2 H) 6,70 - 6,78 (m, 2 H) 7,02 - 7,12 (m, 2 H) 7,17 (s, 1 H) 7,24 - 7,34 (m, 2 H) 7,39 (t, J=7,92 Hz, 2 H) 7,47 (dd, J=20,38, 8,35 Hz, 1 H) 11,78 - 12,06 (m, 2 H); MS (ESI+) m/z 886,4 (M+H)+.

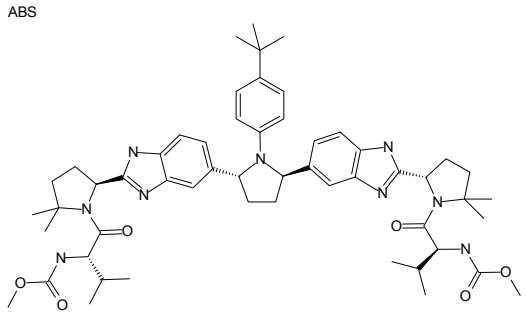


Ejemplo 3.10

{(2S)-1-[(2S,4S)-2-{5-[(2R,5R)-1-(4-fluorofenil)-5-{2-[(2S,4S)-4-metoxi-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-benzimidazol-5-il}pirrolidin-2-il]-1H-benzimidazol-2-il}-4-metoxipirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

1H RMN (400 MHz, DMSO-d6) ppm 0,77 - 0,90 (m, 12 H) 1,66 - 1,76 (m, 2 H) 1,88 - 2,01 (m, 2 H) 2,06 - 2,19 (m, 2 H) 2,54 - 2,62 (m, 2 H) 3,25 (d, J=5,86 Hz, 6 H) 3,54 (s, 6 H) 3,59 - 3,72 (m, 2 H) 3,97 - 4,14 (m, 6 H) 4,16 - 4,30 (m, 2 H) 5,05 - 5,19 (m, 2 H) 5,36 (d, J=3,25 Hz, 2 H) 6,28 (dd, J=7,26, 4,34 Hz, 2 H) 6,69 - 6,79 (m, 2 H) 7,04 (d, J=8,57 Hz, 2 H) 7,22 - 7,33 (m, 4 H) 7,38 (d, J=8,02 Hz, 1 H) 7,45 (d, J=8,24 Hz, 1 H) 11,81 (s, 2 H); MS (ESI+) m/z 910,4 (M+H)+.

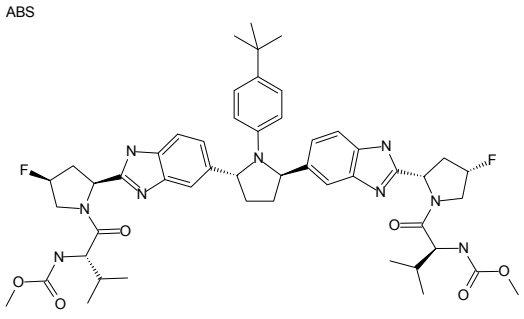
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Ejemplo 3.11

{(2S)-1-[(5S)-5-{5-[(2R,5R)-1-(4-tert-butilfenil)-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}-5,5-dimetilpirrolidin-2-il]-1H-benzimidazol-5-il}pirrolidin-2-il]-1H-benzimidazol-2-il}-2,2-dimetilpirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

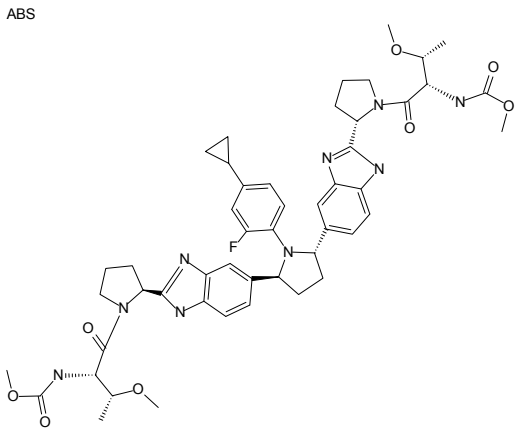
1H RMN (400 MHz, DMSO-d6) ppm 0,81 (d, J=6,61 Hz, 6 H) 0,89 (d, J=6,72 Hz, 6 H) 1,07 (s, 9 H) 1,38 (s, 6 H) 1,62 (s, 6 H) 1,68 - 1,77 (m, 4 H) 1,82 (s, 2 H) 1,94 (dd, J=13,61, 6,78 Hz, 2 H) 2,10 - 2,18 (m, 2 H) 2,27 (dd, J=4,12, 2,60 Hz, 2 H) 3,15 (d, J=3,36 Hz, 6 H) 3,96 - 4,03 (m, 2 H) 5,30 - 5,43 (m, 6 H) 6,24 - 6,31 (m, 2 H) 6,70 (t, J=6,67 Hz, 2 H) 6,84 - 6,91 (m, 2 H) 7,05 - 7,13 (m, 2 H) 7,24 (s, 1 H) 7,36 (d, J=1,08 Hz, 1 H) 7,40 (d, J=7,59 Hz, 1 H) 7,49 (d, J=8,78 Hz, 1 H) 12,16 (d, J=29,28 Hz, 2 H); MS (ESI+) m/z 944,5 (M+H)+.



Ejemplo 3.12

{(2S)-1-[(2S,4S)-2-{5-[(2R,5R)-1-(4-tert-butilfenil)-5-{2-[(2S,4S)-4-fluoro-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-benzimidazol-5-il}pirrolidin-2-il]-1H-benzimidazol-2-il}-4-fluoropirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

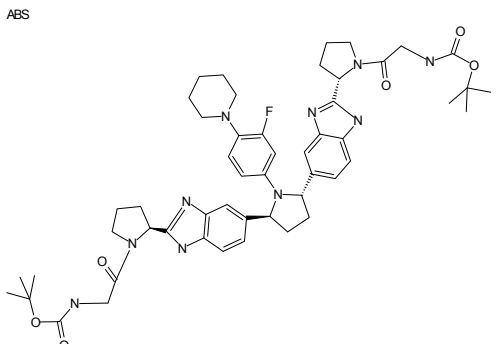
1H RMN (400 MHz, DMSO-d6) □ ppm 0,79 - 0,97 (m, 12 H) 1,07 (s, 9 H) 1,66 - 1,75 (m, 2 H) 1,99 - 2,08 (m, 2 H) 2,40 (dd, J=17,02, 3,04 Hz, 2 H) 3,09 - 3,21 (m, 4 H) 3,55 (s, 6 H) 4,05 - 4,13 (m, 4 H) 4,16 - 4,27 (m, 2 H) 5,35 (dd, J=8,51, 3,09 Hz, 4 H) 5,46 (d, J=53,24 Hz, 2 H) 6,23 - 6,29 (m, 2 H) 6,91 (d, J=8,89 Hz, 2 H) 7,03 - 7,11 (m, 2 H) 7,23 (d, J=3,47 Hz, 1 H) 7,28 (s, 1 H) 7,39 (dd, J=8,08, 4,72 Hz, 3 H) 7,44 (d, J=8,57 Hz, 1 H) 11,80 (d, J=20,06 Hz, 2 H); MS (ESI+) m/z 924,4 (M+H)+.



Ejemplo 3.13

{(2S,3R)-1-[(2S)-2-{5-[(2S,5S)-1-(4-ciclopropil-2-fluorofenil)-5-(2-{(2S)-1-[N-(metoxicarbonil)-O-metil-L-treonil]pirrolidin-2-il}-1H-benzimidazol-5-il)pirrolidin-2-il]-1H-benzimidazol-2-il}pirrolidin-1-il]-3-metoxi-1-oxobutan-2-il}carbamato de metilo

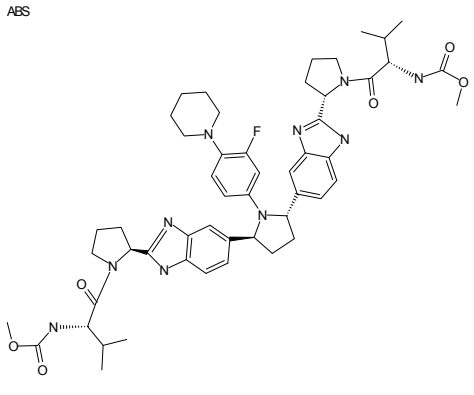
1H RMN (500 MHz, DMSO-d6) ppm 0,35 - 0,57 (m, 2 H) 0,66 - 0,85 (m, 2 H) 1,07 - 1,17 (m, 7 H) 1,59 - 1,69 (m, 1 H) 1,82 (s, 2 H) 1,95 - 2,12 (m, 5 H) 2,13 - 2,33 (m, 5 H) 3,17 - 3,35 (m, 6 H) 3,48 - 3,65 (m, 6 H) 3,85 - 3,95 (m, 4 H) 4,29 - 4,38 (m, 2 H) 5,11 - 5,25 (m, 2 H) 5,58 (s, 2 H) 6,44 - 6,57 (m, 2 H) 6,59 - 6,70 (m, 1 H) 7,07 - 7,19 (m, 2 H) 7,25 - 7,32 (m, 2 H) 7,35 - 7,41 (m, 2 H) 7,45 (d, J=8,24 Hz, 2 H) 12,05 (d, J=16,63 Hz, 2 H); MS (ESI+) m/z 922,4 (M+H)+, (ESI-) m/z 920,3 (M-H)-.



Ejemplo 3.14

{2-[(2S)-2-(5-{(2S,5S)-5-{2-[(2S)-1-{[(tert-butoxicarbonil)amino]acetil}pirrolidin-2-il]-1H-benzimidazol-5-il}-1-[3-fluoro-4-(piperidin-1-il)fenil]pirrolidin-2-il}-1H-benzimidazol-2-il)pirrolidin-1-il]-2-oxoetil}carbamato de tert-butilo

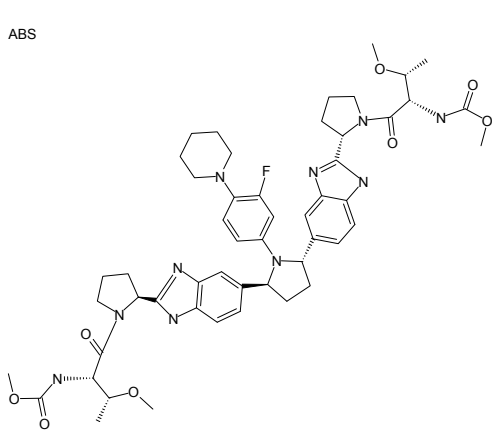
1H RMN (400 MHz, DMSO-d6) ppm 1,16 - 1,43 (m, 18 H) 1,42 - 2,27 (m, 14 H) 2,58 - 2,70 (m, 5 H) 3,38 - 4,02 (m, 9 H) 5,14 (s, 2 H) 5,33 (s, 3 H) 6,04 (s, 2 H) 6,74 (s, 3 H) 7,04 - 7,60 (m, 7 H) 11,83 - 12,43 (m, 2 H); MS (ESI+) m/z 933,4 (M+H)+, (ESI-) m/z 931,4 (M-H)-.



Ejemplo 3.15

{(2S)-1-[(2S)-2-{5-[(2S,5S)-1-[3-fluoro-4-(piperidin-1-il)fenil]-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-benzimidazol-5-il}pirrolidin-2-il]-1H-benzimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

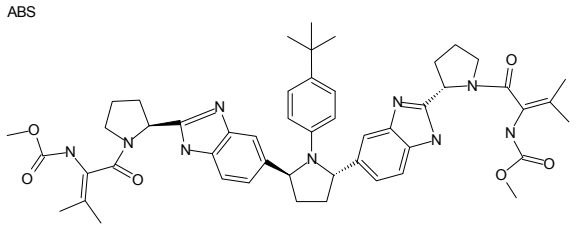
1H RMN (400 MHz, DMSO-d6) ppm 0,73 - 0,93 (m, 12 H) 1,32 - 1,57 (m, 6 H) 1,58 - 2,06 (m, 14 H) 2,18 (s, 4 H) 2,67 (dd, J=3,69, 1,95 Hz, 4 H) 3,75 - 3,87 (m, 6 H) 4,07 (t, 2 H) 5,13 (s, 2 H) 5,37 (dd, J=6,02, 2,11 Hz, 2 H) 6,04 (s, 2 H) 6,65 (s, 1 H) 7,09 (s, 2 H) 7,16 - 7,23 (m, 1 H) 7,23 - 7,48 (m, 5 H) 12,01 (s, 2 H); MS (ESI+) m/z 933,5 (M+H)+, (ESI-) m/z 931,4 (M-H)-.



Ejemplo 3.16

{(2S,3R)-1-[(2S)-2-{5-[(2S,5S)-1-[3-fluoro-4-(piperidin-1-il)fenil]-5-(2-{(2S)-1-[N-(metoxicarbonil)-O-metil-L-threonil]pirrolidin-2-il}-1H-benzimidazol-5-il)pirrolidin-2-il]-1H-benzimidazol-2-il}pirrolidin-1-il]-3-metoxi-1-oxobutan-2-il}carbamato de metilo

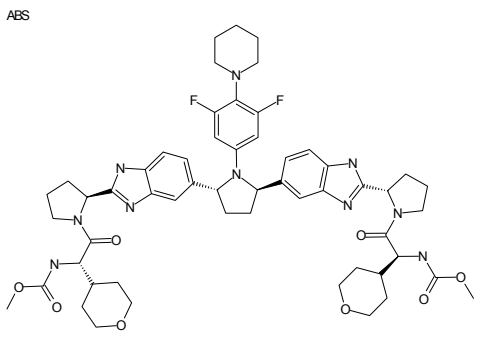
1H RMN (400 MHz, DMSO-d6) ppm 1,00 - 1,14 (m, 6 H) 1,33 - 1,55 (m, 6 H) 1,59 - 2,28 (m, 14 H) 2,58 - 2,71 (m, 4 H) 3,10 - 3,27 (m, 6 H) 3,54 (d, J=1,41 Hz, 6 H) 3,71 - 3,90 (m, 6 H) 4,21 - 4,33 (m, 2 H) 5,02 - 5,22 (m, 2 H) 5,37 (dd, J=6,02, 2,01 Hz, 2 H) 6,04 (s, 2 H) 6,58 - 6,84 (m, 1 H) 7,06 (d, J=22,88 Hz, 2 H) 7,16 - 7,32 (m, 2 H) 7,39 (d, J=8,13 Hz, 2 H) 11,90 - 12,34 (m, 2 H); MS (ESI+) m/z 965,5 (M+H)+, (ESI-) m/z 963,3 (M-H)-.



Ejemplo 3.17

{[(2S,5S)-1-(4-tert-butilfenil)pirrolidin-2,5-diil]bis[1H-benzimidazol-5,2-diil(2S)pirrolidin-2,1-diil(3-metil-1-oxobut-2-en-1,2-diil)]}biscarbamato de dimetilo

1H RMN (400 MHz, DMSO-d6) ppm 0,87 - 1,20 (m, 9 H) 1,60 - 1,77 (m, 14 H) 1,80 - 2,35 (m, 10 H) 3,16 - 3,79 (m, 10 H) 5,14 (s, 2 H) 5,37 (s, 2 H) 6,24 (d, J=3,04 Hz, 2 H) 6,92 (dd, J=8,57, 6,29 Hz, 2 H) 7,11 (s, 3 H) 7,31 (s, 1 H) 7,39 (d, J=8,13 Hz, 1 H) 7,50 (d, J=8,24 Hz, 1 H) 8,89 (d, 2 H) 11,64 - 12,14 (m, 2 H); MS (ESI+) m/z 884,5 (M+H)+, 918,4 (M+NH3+NH4)+.

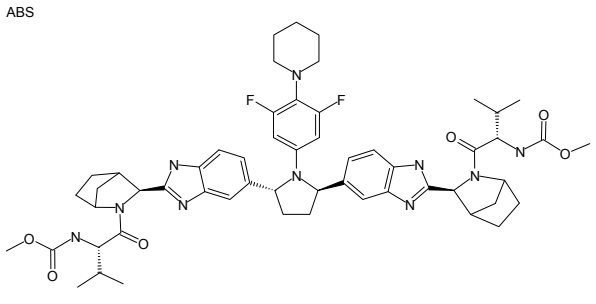


Ejemplo 3.18

({(2R,5R)-1-[3,5-difluoro-4-(piperidin-1-il)fenil]pirrolidin-2,5-diil}bis{1H-benzimidazol-5,2-diil(2S)pirrolidin-2,1-diil[(1S)-2-oxo-1-(tetrahidro-2H-piran-4-il)etano-2,1-diil]})biscarbamato de dimetilo

1H RMN (400 MHz, DMSO-d6) ppm 1,13 - 1,33 (m, 4 H) 1,36 - 1,57 (m, 10 H) 1,65 - 1,71 (m, 2 H) 1,79 - 1,90 (m, 2 H) 1,96 - 2,03 (m, 4 H) 2,13 - 2,26 (m, 4 H) 2,76 (s, 4 H) 2,93 - 3,15 (m, 4 H) 3,53 (s, 6 H) 3,62 (dd, J=10,03, 2,01 Hz, 2 H) 3,68 - 3,80 (m, 4 H) 3,81 - 3,88 (m, 4 H) 4,11 - 4,18 (m, 2 H) 5,10 - 5,18 (m, 2 H) 5,33 - 5,40 (m, 2 H) 5,82 - 5,92 (m, 2 H) 7,09 (dd, J=12,52, 8,29 Hz, 2 H) 7,17 - 7,24 (m, 2 H) 7,35 (t, J=8,35 Hz, 2 H) 7,41 (d,

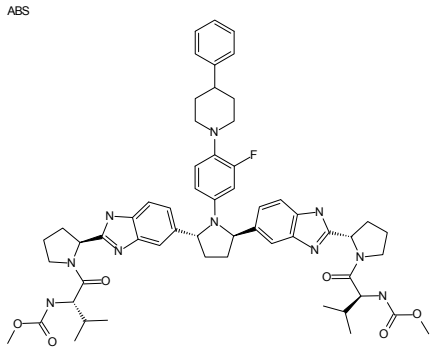
J=7,92 Hz, 1 H) 7,47 (d, J=6,94 Hz, 1 H) 12,05 (d, J=1,73 Hz, 1 H) 12,15 (d, J=2,17 Hz, 1 H); MS (ESI+) m/z 1035,5 (M+H)+.



Ejemplo 3.19

{(2S)-1-[(3S)-3-{5-[(2R,5R)-1-[3,5-difluoro-4-(piperidin-1-il)fenil]-5-{2-[(3S)-2-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}-2-azabiciclo[2,2,1]hept-3-il]-1H-benzimidazol-5-il}pirrolidin-2-il]-1H-benzimidazol-2-il}-2-azabiciclo[2,2,1]hept-2-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

1H RMN (400 MHz, DMSO-d6) □ ppm 0,80 - 0,87 (m, 6 H) 0,93 (t, J=7,05 Hz, 6 H) 1,36 - 1,48 (m, 10 H) 1,49 - 1,57 (m, 2 H) 1,64 - 1,70 (m, 4 H) 1,72 - 1,79 (m, 4 H) 1,84 - 1,90 (m, 2 H) 1,92 - 1,98 (m, 2 H) 2,61 (s, 2 H) 2,72 - 2,78 (m, 4 H) 3,54 (s, 6 H) 4,10 - 4,17 (m, 2 H) 4,50 (s, 2 H) 4,59 (d, J=7,48 Hz, 2 H) 5,32 - 5,41 (m, 2 H) 5,89 (d, J=12,58 Hz, 2 H) 7,07 (d, J=7,70 Hz, 2 H) 7,18 (d, J=9,65 Hz, 2 H) 7,21 (s, 1 H) 7,32 (s, 1 H) 7,40 (d, J=8,13 Hz, 1 H) 7,49 (d, J=8,02 Hz, 1 H) 12,01 (dd, J=12,58, 1,08 Hz, 2 H); MS (ESI+) m/z 1003,4 (M+H)+.



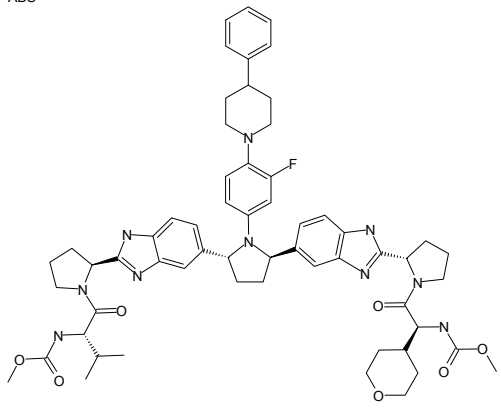
Ejemplo 3.20

{(2S)-1-[(2S)-2-{5-[(2R,5R)-1-[3-fluoro-4-(4-fenilpiperidin-1-il)fenil]-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-benzimidazol-5-il}pirrolidin-2-il]-1H-benzimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

1H RMN (400 MHz, DMSO-d6) ppm 0,77 - 0,90 (m, 12 H) 1,66 - 1,75 (m, 8 H) 1,86 - 1,95 (m, 2 H) 1,96 - 2,05 (m, 4 H) 2,14 - 2,24 (m, 4 H) 3,04 - 3,14 (m, 4 H) 3,53 (s, 6 H) 3,77 - 3,86 (m, 4 H) 4,06 (t, J=8,40 Hz, 2 H) 5,11 - 5,17 (m, 2 H) 5,35 (q, J=6,83 Hz, 2 H) 6,05 - 6,12 (m, 2 H) 6,71 (ddd, J=13,99, 9,22, 4,34 Hz, 1 H) 7,07 (t, J=7,05 Hz, 2 H) 7,16 (t, J=6,94 Hz, 2 H) 7,20 - 7,32 (m, 8 H)

7,39 (d, J=8,13 Hz, 1 H) 7,47 (d, J=8,46 Hz, 1 H) 12,05 (d, J=5,64 Hz, 2 H); MS (ESI+) m/z 1009,4 (M+H)+.

ABS

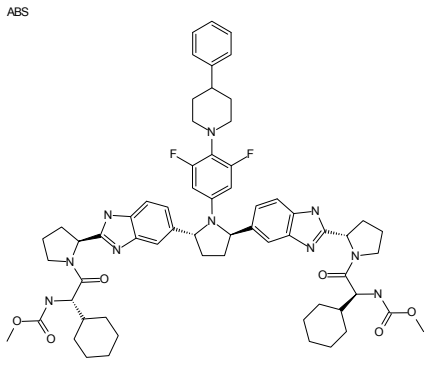


Ejemplo 3.21

[(1S)-2-[(2S)-2-{5-[(2R,5R)-1-[3-fluoro-4-(4-fenilpiperidin-1-il)fenil]-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-benzimidazol-5-il}pirrolidin-2-il]-1H-benzimidazol-2-il}pirrolidin-1-il]-2-oxo-1-(tetrahidro-2H-piran-4-il)etil]carbamato de metilo

1H RMN (400 MHz, DMSO-d6) ppm 0,76 - 0,92 (m, 6 H) 1,47 - 1,57 (m, 2 H) 1,65 - 1,76 (m, 8 H) 1,81 - 1,94 (m, 2 H) 1,94 - 2,04 (m, 4 H) 2,15 - 2,23 (m, 4 H) 3,03 - 3,15 (m, 4 H) 3,53 (s, 6 H) 3,57 - 3,67 (m, 2 H) 3,70 - 3,79 (m, 2 H) 3,79 - 3,89 (m, 4 H) 4,07 - 4,20 (m, 2 H) 5,10 - 5,19 (m, 2 H) 5,32 - 5,41 (m, 2 H) 6,04 - 6,11 (m, 2 H) 6,66 - 6,75 (m, 1 H) 7,03 -

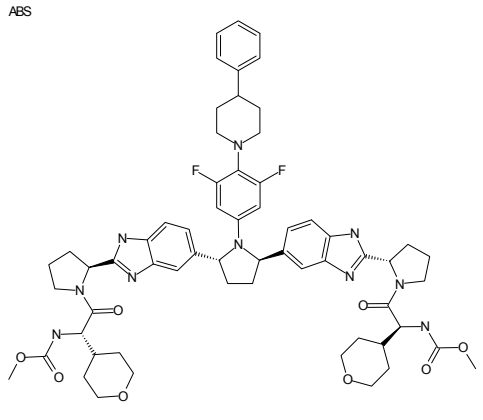
7,36 (m, 12 H) 7,39 (dd, J=8,78, 1,63 Hz, 1 H) 7,46 (t, J=8,78 Hz, 1 H) 12,02 - 12,14 (m, 2 H); MS (APCI+) m/z 1051 (M+H)+.



Ejemplo 3.22

({(2R,5R)-1-[3,5-difluoro-4-(4-fenilpiperidin-1-il)fenil]pirrolidin-2,5-diil}bis{1H-benzimidazol-5,2-diil(2S)pirrolidin-2,1-diil[(1S)-1-ciclohexil-2-oxoetano-2,1-diil]})biscarbamato de dimetilo

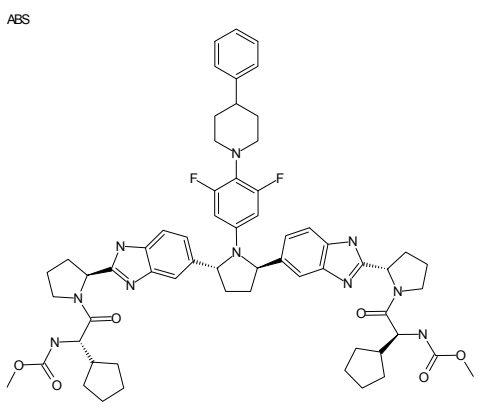
1H RMN (400 MHz, DMSO-d6) □ ppm 0,81 - 1,14 (m, 11 H) 1,40 - 1,71 (m, 20 H) 1,94 - 2,05 (m, 4 H) 2,14 - 2,26 (m, 4 H) 2,83 - 2,91 (m, 2 H) 2,93 - 3,02 (m, 2 H) 3,52 (d, J=3,80 Hz, 6 H) 3,76 - 3,87 (m, 4 H) 4,08 (q, J=8,53 Hz, 2 H) 5,14 (d, J=5,86 Hz, 2 H) 5,33 - 5,45 (m, 2 H) 5,85 - 5,98 (m, 2 H) 7,05 - 7,31 (m, 11 H) 7,42 (d, J=9,76 Hz, 1 H) 7,49 (d, J=8,24 Hz, 1 H) 12,00 (s, 1 H) 12,16 (d, J=3,58 Hz, 1 H); MS (ESI+) m/z 1107,5 (M+H)+.



Ejemplo 3.23

({(2R,5R)-1-[3,5-difluoro-4-(4-fenilpiperidin-1-il)fenil]pirrolidin-2,5-diil}bis{1H-benzimidazol-5,2-diil(2S)pirrolidin-2,1-diil[(1S)-2-oxo-1-(tetrahidro-2H-piran-4-il)etano-2,1-diil]})biscarbamato de dimetilo

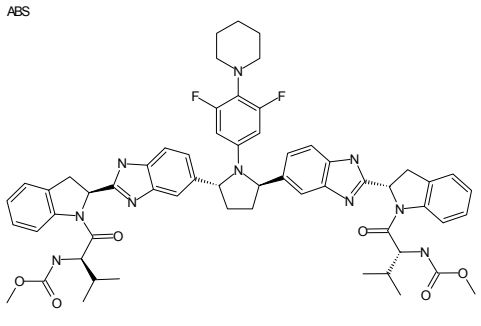
1H RMN (400 MHz, DMSO-d6) ppm 1,14 - 1,37 (m, 4 H) 1,43 - 1,57 (m, 4 H) 1,61 - 1,72 (m, 6 H) 1,77 - 1,91 (m, 2 H) 1,96 - 2,05 (m, 4 H) 2,14 - 2,25 (m, 4 H) 2,87 - 3,02 (m, 6 H) 3,06 - 3,22 (m, 2 H) 3,53 (s, 6 H) 3,58 - 3,67 (m, 2 H) 3,68 - 3,79 (m, 5 H) 3,81 - 3,89 (m, 4 H) 4,11 - 4,19 (m, 2 H) 5,14 (dd, J=7,32, 2,98 Hz, 2 H) 5,34 - 5,42 (m, 2 H) 5,85 - 5,95 (m, 2 H) 7,06 - 7,17 (m, 3 H) 7,19 - 7,29 (m, 6 H) 7,35 (t, J=9,05 Hz, 2 H) 7,42 (d, J=8,57 Hz, 1 H) 7,47 (d, J=8,78 Hz, 1 H) 12,05 (s, 1 H) 12,16 (d, J=1,41 Hz, 1 H); MS (ESI+) m/z 1111,5 (M+H)+.



Ejemplo 3.24

({(2R,5R)-1-[3,5-difluoro-4-(4-fenilpiperidin-1-il)fenil]pirrolidin-2,5-diil}bis{1H-benzimidazol-5,2-diil(2S)pirrolidin-2,1-diil[(1S)-1-ciclopentil-2-oxoetano-2,1-diil]})biscarbamato de dimetilo

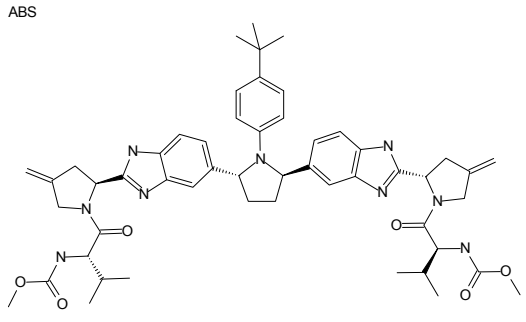
1H RMN (400 MHz, DMSO-d6) ppm 1,16 - 1,28 (m, 4 H) 1,31 - 1,54 (m, 10 H) 1,55 - 1,73 (m, 10 H) 1,95 - 2,06 (m, 4 H) 2,09 - 2,24 (m, 7 H) 2,85 - 3,07 (m, 4 H) 3,53 (s, 6 H) 3,82 (s, 4 H) 4,15 (t, J=8,51 Hz, 2 H) 5,11 - 5,18 (m, 2 H) 5,34 - 5,43 (m, 2 H) 5,92 (d, J=12,69 Hz, 2 H) 7,06 - 7,18 (m, 3 H) 7,19 - 7,31 (m, 6 H) 7,37 - 7,45 (m, 3 H) 7,50 (d, J=8,35 Hz, 1 H) 12,01 (s, 1 H) 12,08 (s, 1 H); MS (ESI+) m/z 1079,4 (M+H)+.



Ejemplo 3.25

{(2R)-1-[(2S)-2-{5-[(2R,5R)-1-[3,5-difluoro-4-(piperidin-1-il)fenil]-5-{2-[(2S)-1-{(2R)-2-[(metoxicarbonil)amino]-3-metilbutanoil}-2,3-dihidro-1H-indol-2-il]-1H-benzimidazol-5-il}pirrolidin-2-il]-1H-benzimidazol-2-il}-2,3-dihidro-1H-indol-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

1H RMN (400 MHz, DMSO-d6) □ ppm 0,90 (dd, J=31,72, 6,23 Hz, 12 H) 1,31 - 1,51 (m, 7 H) 1,52 - 1,70 (m, 2 H) 2,06 - 2,29 (m, 4 H) 2,74 (s, 6 H) 3,08 (d, J=15,40 Hz, 6 H) 3,69 - 3,89 (m, 2 H) 4,27 (s, 1 H) 5,26 - 5,39 (m, 2 H) 5,77 - 6,01 (m, 4 H) 7,01 - 7,33 (m, 12 H) 7,37 - 7,53 (m, 2 H) 8,12 - 8,25 (m, 2 H) 12,34 (d, J=42,07 Hz, 2 H); MS (ESI+) m/z 1047,4 (M+H)+.

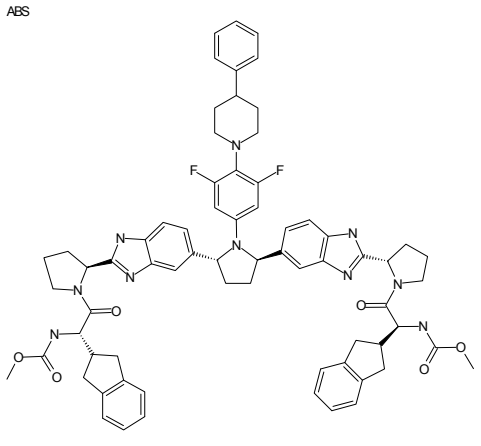


Ejemplo 3.26

{(2S)-1-[(2S)-2-{5-[(2R,5R)-1-(4-tert-butilfenil)-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}-4-metilidenepirrolidin-2-il]-1H-benzimidazol-5-il}pirrolidin-2-il]-1H-benzimidazol-2-il}-4-metilidenepirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

1H RMN (400 MHz, DMSO-d6) □ ppm 0,74 - 0,92 (m, 12 H) 1,07 (s, 9 H) 1,68 (s, 2 H) 1,91 (ddd, J=14,64, 7,64, 7,43 Hz, 2 H) 2,61 - 2,75 (m, 2 H) 2,97 - 3,09 (m, 2 H) 3,13 (s, 1

H) 3,54 (s, 6 H) 3,94 - 4,08 (m, 2 H) 4,46 (d, J=12,36 Hz, 2 H) 4,60 (d, J=14,20 Hz, 2 H) 5,02 (s, 3 H) 5,10 (s, 2 H) 5,31 - 5,45 (m, 4 H) 6,24 (d, J=8,67 Hz, 2 H) 6,86 - 6,94 (m, 2 H) 7,07 (t, J=8,51 Hz, 2 H) 7,20 (s, 1 H) 7,26 (s, 1 H) 7,34 - 7,50 (m, 4 H) 12,05 (d, J=15,72 Hz, 2 H); MS (ESI+) m/z 912,4 (M+H)+.

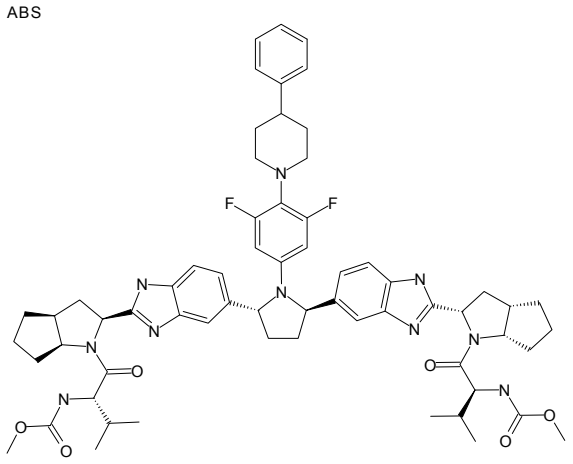


Ejemplo 3.27

({(2R,5R)-1-[3,5-difluoro-4-(4-fenilpiperidin-1-il)fenil]pirrolidin-2,5-diil}bis{1H-benzimidazol-5,2-diil(2S)pirrolidin-2,1-diil[(1S)-1-(2,3-dihidro-1H-inden-2-il)-2-oxoetano-2,1-diil]})biscarbamato de dimetilo

1H RMN (400 MHz, DMSO-d6) □ ppm 1,51 - 1,76 (m, 6 H) 1,94 - 2,06 (m, 4 H) 2,12 - 2,28 (m, 8 H) 2,69 - 2,89 (m, 12 H) 2,92 - 3,05 (m, 1 H) 3,55 (s, 6 H) 3,77 - 3,86 (m, 4 H) 4,36 - 4,43 (m, 2 H) 5,16 - 5,24 (m, 2 H) 5,35 - 5,48 (m, 2 H) 5,97 (d, J=12,90 Hz, 2 H) 7,01 - 7,30 (m, 17 H) 7,34 (s, 1 H) 7,46 (d, J=8,35 Hz, 1 H) 7,54 - 7,60 (m, 2 H) 12,07 (s, 1 H) 12,18 (s, 1 H); MS (ESI+) m/z 1175,5 (M+H)+.

ABS

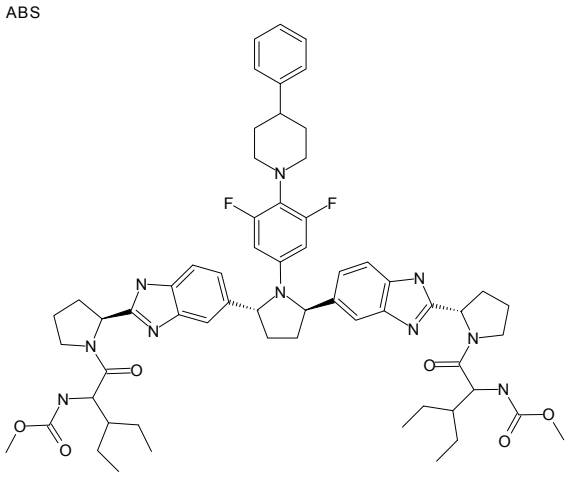


Ejemplo 3.28

{(2S)-1-[(2S,3aS,6aS)-2-{5-[(2R,5R)-1-[3,5-difluoro-4-(4-fenilpiperidin-1-il)fenil]-5-{2-[(2S,3aS,6aS)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}octahidrociclopenta[b]pirrol-2-il]-1H-benzimidazol-5-il}pirrolidin-2-il]-1H-benzimidazol-2-il}hexahidrociclopenta[b]pirrol-1(2H)-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

1H RMN (400 MHz, DMSO-d6) ppm 0,72 - 0,92 (m, 12 H) 1,50 - 1,59 (m, 4 H) 1,62 - 1,72 (m, 8 H) 1,73 - 1,81 (m, 2 H) 1,83 - 1,92 (m, 4 H) 1,95 - 2,03 (m, 2 H) 2,06 - 2,15 (m, 4 H) 2,38 - 2,46 (m, 2 H) 2,75 - 2,83 (m, 1 H) 2,86 - 3,01 (m, 4 H) 3,54 (s, 6 H) 4,01 (td, J=13,28, 6,83 Hz, 4 H) 4,78 (dd, J=7,70, 4,23 Hz, 2 H) 5,13 (t, J=8,24 Hz, 2 H) 5,33 - 5,45 (m, 2 H) 5,92 (dd, J=12,90, 2,82 Hz, 2 H) 7,07 (d, J=8,67 Hz, 2 H) 7,15 (t, J=6,94 Hz, 1 H) 7,20 - 7,29 (m, 5 H) 7,34 (d, J=4,01 Hz, 1 H) 7,39 - 7,47 (m, 3 H) 7,50 (d, J=8,02 Hz, 1 H) 11,97 (s, 1 H) 12,06 (s, 1 H);MS (ESI+) m/z 1107,4 (M+H)+.

ABS

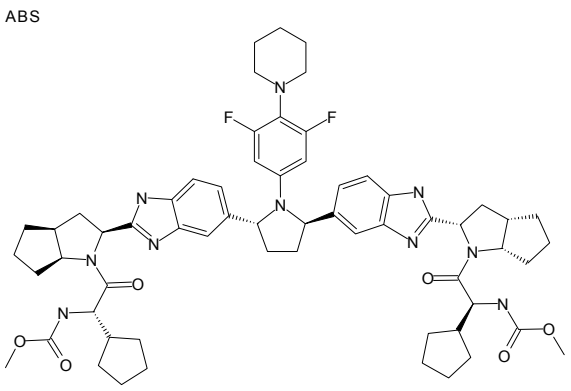


Ejemplo 3.29

{1-[(2S)-2-{5-[(2R,5R)-1-[3,5-difluoro-4-(4-fenilpiperidin-1-il)fenil]-5-{2-[(2S)-1-{3-etil-2-[(metoxicarbonil)amino]pentanoil}pirrolidin-2-il]-1H-benzimidazol-5-il}pirrolidin-2-il]-1H-benzimidazol-2-il}pirrolidin-1-il]-3-etil-1-oxopentan-2-il}carbamato de metilo

1H RMN (400 MHz, DMSO-d6) □ ppm 0,16 (t, J=6,02 Hz, 1 H) 0,34 (t, J=6,89 Hz, 1 H) 0,56 - 0,99 (m, 10 H) 1,16 - 1,36 (m, 4 H) 1,53 - 1,80 (m, 8 H) 1,93 - 2,09 (m, 4 H) 2,14 - 2,30 (m, 4 H) 2,80 - 3,13 (m, 11 H) 3,53 (s, 6 H) 3,73 - 3,95 (m, 4 H) 4,24 - 4,41 (m, 2 H) 5,09 - 5,20 (m, 2 H) 5,30 - 5,44 (m, 2 H) 5,83 - 5,96 (m, 2 H) 7,03 - 7,36 (m, 11 H) 7,39 - 7,62 (m, 2 H) 12,00 (s, 1 H) 12,13 - 12,20 (m, 1 H); MS (ESI+) m/z 1083,5 (M+H)+.

ABS

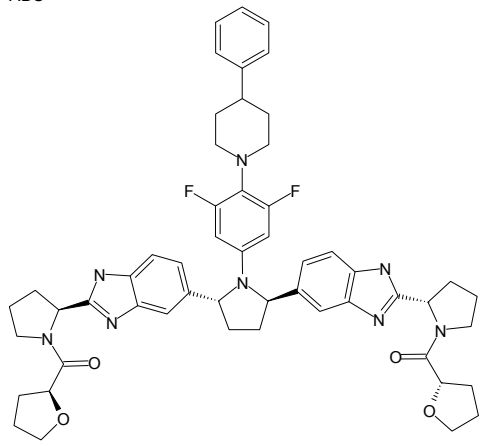


Ejemplo 3.30

({(2R,5R)-1-[3,5-difluoro-4-(piperidin-1-il)fenil]pirrolidin-2,5-diil}bis{1H-benzimidazol-5,2-diil(2S,3aS,6aS)hexahidrociclopenta[b]pirrol-2,1(2H)-diil[(1S)-1-ciclopentil-2-oxoetano-2,1-diil]})biscarbamato de dimetilo

1H RMN (400 MHz, DMSO-d6) ppm 1,17 - 1,32 (m, 10 H) 1,36 - 1,49 (m, 10 H) 1,51 - 1,79 (m, 10 H) 1,87 (dd, J=15,83, 7,26 Hz, 2 H) 1,98 (dd, J=13,07, 8,40 Hz, 2 H) 2,05 - 2,16 (m, 6 H) 2,36 - 2,46 (m, 4 H) 2,72 - 2,81 (m, 6 H) 3,54 (s, 6 H) 4,11 (q, J=9,40 Hz, 2 H) 4,75 - 4,85 (m, 2 H) 5,08 - 5,18 (m, 2 H) 5,36 (dt, J=13,66, 6,83 Hz, 2 H) 5,88 (ddd, J=12,69, 3,52, 3,42 Hz, 2 H) 7,07 (d, J=8,35 Hz, 2 H) 7,21 (s, 1 H) 7,31 (d, J=4,01 Hz, 1 H) 7,41 (d, J=8,24 Hz, 1 H) 7,46 - 7,56 (m, 3 H) 11,88 (d, J=2,49 Hz, 1 H) 12,01 (d, J=3,36 Hz, 1 H); MS (ESI+) m/z 1083,5 (M+H)+.

ABS

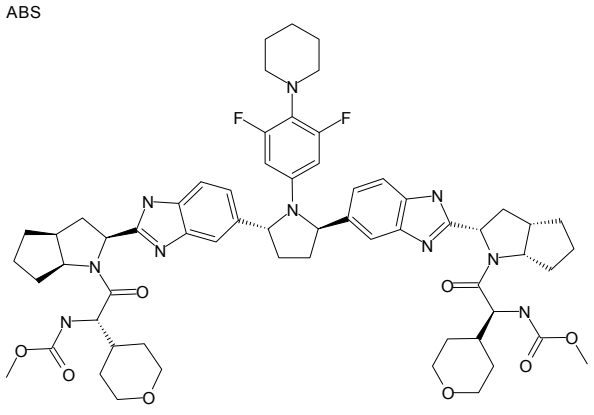


Ejemplo 3.31

({(2R,5R)-1-[3,5-difluoro-4-(4-fenilpiperidin-1-il)fenil]pirrolidin-2,5-diil}bis[1H-benzimidazol-5,2-diil(2S)pirrolidin-2,1-diil])bis[(2S)-tetrahidrofurano-2-ilmetanona]

1H RMN (400 MHz, DMSO-d6) ppm 1,36 - 1,49 (m, J=15,83 Hz, 2 H) 1,60 - 1,75 (m, 8 H) 1,77 - 1,91 (m, 6 H) 1,94 - 2,12 (m, 8 H) 2,16 - 2,27 (m, 2 H) 2,86 - 3,08 (m, 5 H) 3,74 (t, J=6,99 Hz, 6 H) 4,57 - 4,63 (m, 2 H) 5,13 (dd, J=9,00, 1,30 Hz, 2 H) 5,33 - 5,43 (m, 2 H) 5,93 (d, J=13,34 Hz, 2 H) 7,06 - 7,16 (m, 3 H) 7,20 - 7,29 (m, 5 H) 7,32 (s, 1 H) 7,42 (d, J=8,57 Hz, 1 H) 7,52 (d, J=8,13 Hz, 1 H) 12,00 (s, 1 H) 12,08 (s, 1 H); MS (ESI+) m/z 909,4 (M+H)+.

ABS

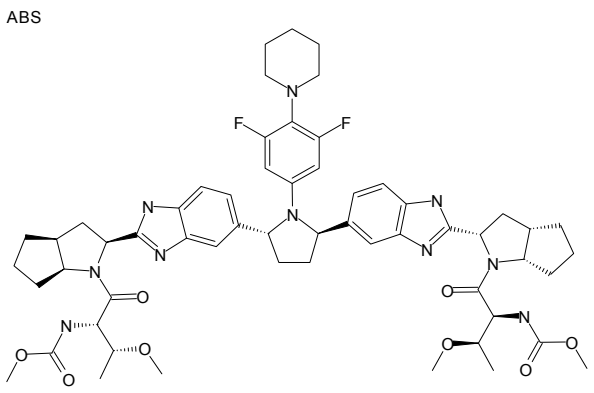


Ejemplo 3.32

({(2R,5R)-1-[3,5-difluoro-4-(piperidin-1-il)fenil]pirrolidin-2,5-diil}bis{1H-benzimidazol-5,2-diil(2S,3aS,6aS)hexahidrociclopenta[b]pirrol-2,1(2H)-diil[(1S)-2-oxo-1-(tetrahidro-2H-piran-4-il)etano-2,1-diil]})biscarbamato de dimetilo

1H RMN (400 MHz, DMSO-d6) □ ppm 1,10 - 1,27 (m, 4 H) 1,33 - 1,51 (m, 12 H) 1,51 - 1,65 (m, 6 H) 1,67 - 1,80 (m, 4 H) 1,83 - 2,00 (m, 6 H) 2,08 - 2,17 (m, 4 H) 2,39 - 2,45 (m, 2 H) 2,73 - 2,85 (m, 8 H) 3,03 - 3,12 (m, 2 H) 3,53 (s, 6 H) 3,70 - 3,87 (m, 2 H) 4,04 - 4,17 (m, 2 H) 4,74 - 4,83 (m, 2 H) 5,08 - 5,17 (m, 2 H) 5,31 - 5,42 (m, 2 H) 5,83 - 5,93 (m, 2 H) 7,04 - 7,11 (m, 2 H) 7,21 (d, J=15,83 Hz, 2 H) 7,41 (d, J=8,02 Hz, 1 H) 7,46 - 7,55 (m, 3 H) 11,96 (d, J=4,12 Hz, 1 H) 12,11 (d, J=4,55 Hz, 1 H); MS (ESI+) m/z 1115,4 (M+H)+.

ABS



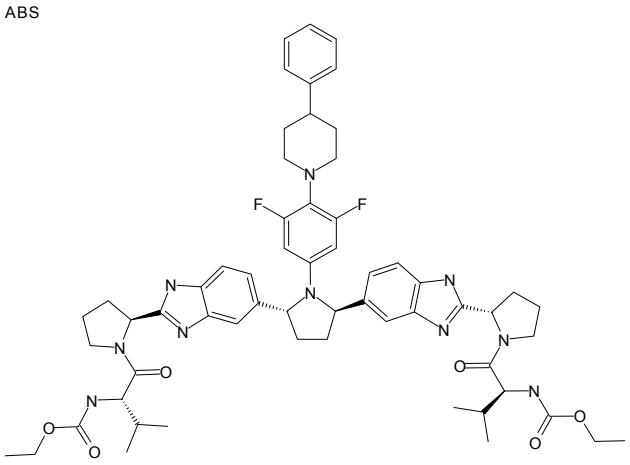
Ejemplo 3.33

{(2S,3R)-1-[(2S,3aS,6aS)-2-{5-[(2R,5R)-1-[3,5-difluoro-4-(piperidin-1-il)fenil]-5-(2-{(2S,3aS,6aS)-1-[N-(metoxicarbonil)-O-metil-L-threonil]octahidrociclopenta[b]pirrol-2-il}-

1H-benzimidazol-5-il)pirrolidin-2-il]-1H-benzimidazol-2-il}hexahidrociclopenta[b]pirrol-1(2H)-il]-3-metoxi-1-oxobutan-2-il}carbamato de metilo

1H RMN (400 MHz, DMSO-d6) □ ppm 0,95 (d, J=6,18 Hz, 3 H) 1,03 (d, J=5,75 Hz, 3 H) 1,35 - 1,49 (m, 8 H) 1,50 - 1,64 (m, 4 H) 1,66 - 1,81 (m, 6 H) 1,84 - 2,01 (m, 6 H) 2,07 - 2,16 (m, 4 H) 2,73 - 2,84 (m, 6 H) 3,13 (s, 3 H) 3,17 (s, 3 H) 3,54 (s, 6 H) 4,20 - 4,29 (m, 2 H) 4,76 - 4,84 (m, 2 H) 5,12 (t, J=8,19 Hz, 2 H) 5,37 (dd, J=6,51, 4,88 Hz, 2 H) 5,88 (d, J=13,45 Hz, 2 H) 7,05 (d, J=8,13 Hz, 2 H) 7,20 (s, 1 H) 7,30 (s, 1 H) 7,40 (d, J=7,81 Hz, 1 H) 7,47 - 7,57 (m, 3 H) 11,98 - 12,15 (m, 2 H); MS (APCI+) m/z 1063,4 (M+H)+.

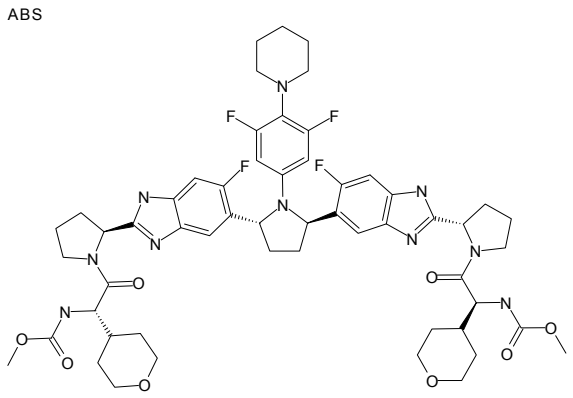
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Ejemplo 3.34

{(2S)-1-[(2S)-2-{5-[(2R,5R)-1-[3,5-difluoro-4-(4-fenilpiperidin-1-il)fenil]-5-{2-[(2S)-1-{(2S)-2-[(etoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-benzimidazol-5-il}pirrolidin-2-il]-1H-benzimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de etilo

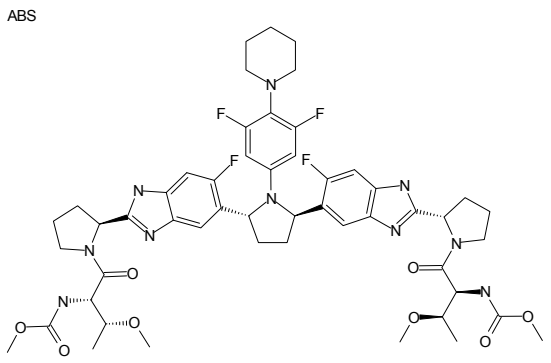
1H RMN (400 MHz, DMSO-d6) □ ppm 0,75 - 0,91 (m, 12 H) 1,15 (t, J=7,43 Hz, 6 H) 1,60 - 1,74 (m, 6 H) 1,85 - 2,07 (m, 8 H) 2,16 - 2,27 (m, 4 H) 2,86 - 3,04 (m, 4 H) 3,40 - 3,48 (m, 1 H) 3,76 - 3,85 (m, 4 H) 3,98 (q, J=7,08 Hz, 4 H) 4,05 (t, J=8,29 Hz, 2 H) 5,11 - 5,19 (m, 2 H) 5,34 - 5,44 (m, 2 H) 5,92 (d, J=12,69 Hz, 2 H) 7,05 - 7,11 (m, 2 H) 7,15 (t, J=6,94 Hz, 1 H) 7,20 - 7,27 (m, 7 H) 7,31 (s, 1 H) 7,42 (d, J=8,24 Hz, 1 H) 7,50 (d, J=7,92 Hz, 1 H) 12,07 (s, 1 H) 12,12 (s, 1 H); MS (ESI+) m/z 1055,4 (M+H)+.



Ejemplo 3.35

({(2R,5R)-1-[3,5-difluoro-4-(piperidin-1-il)fenil]pirrolidin-2,5-diil}bis{(6-fluoro-1H-benzimidazol-5,2-diil)(2S)pirrolidin-2,1-diil[(1S)-2-oxo-1-(tetrahidro-2H-piran-4-il)etano-2,1-diil]})biscarbamato de dimetilo

1H RMN (400 MHz, DMSO-d6) □ ppm 1,12 - 1,33 (m, 4 H) 1,38 - 1,55 (m, 10 H) 1,66 - 1,90 (m, 6 H) 1,94 - 2,04 (m, 4 H) 2,11 - 2,24 (m, 2 H) 2,75 - 2,85 (m, 6 H) 3,01 - 3,19 (m, 2 H) 3,52 (s, 6 H) 3,63 - 3,77 (m, 4 H) 3,78 - 3,89 (m, 6 H) 4,08 - 4,18 (m, 2 H) 5,07 - 5,16 (m, 2 H) 5,46 - 5,63 (m, 2 H) 5,81 - 5,93 (m, 2 H) 6,99 - 7,12 (m, 2 H) 7,31 - 7,44 (m, 4 H) 12,04 - 12,15 (m, 1 H) 12,28 - 12,35 (m, 1 H); MS (APCI+) m/z 1071,2 (M+H)+.

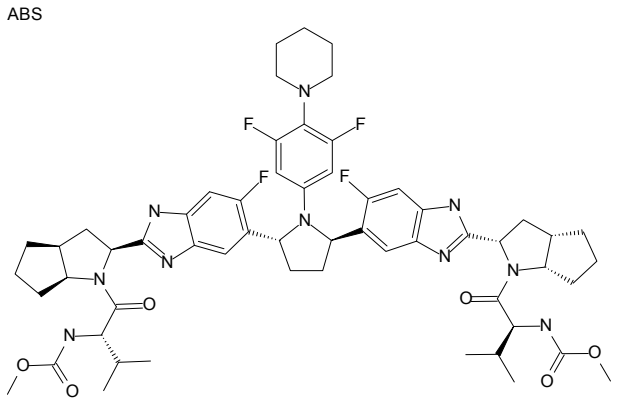


Ejemplo 3.36

{(2S,3R)-1-[(2S)-2-{5-[(2R,5R)-1-[3,5-difluoro-4-(piperidin-1-il)fenil]-5-(6-fluoro-2-{(2S)-1-[N-(metoxicarbonil)-O-metil-L-threonil]pirrolidin-2-il}-1H-benzimidazol-5-il)pirrolidin-2-il]-6-fluoro-1H-benzimidazol-2-il}pirrolidin-1-il]-3-metoxi-1-oxobutan-2-il}carbamato de metilo

1H RMN (400 MHz, DMSO-d6) ppm 0,87 - 1,11 (m, 8 H) 1,35 - 1,52 (m, 6 H) 1,71 - 1,84 (m, 2 H) 1,91 - 2,07 (m, 4 H) 2,12 - 2,26 (m, 4 H) 2,79 (s, 4 H) 3,08 (d, J=37,41 Hz, 6 H) 3,41 - 3,48 (m, 2 H) 3,53 (s, 6 H) 3,82 (d, J=4,88 Hz, 4 H) 4,18 - 4,30 (m, 2 H) 5,11 (s, 2 H) 5,47 - 5,63 (m, 2 H) 5,81 - 5,97 (m, 2 H) 6,99 - 7,28 (m, 4 H) 7,37 (dd, J=25,54, 9,60 Hz, 2 H) 12,10 (s, 1 H) 12,22 - 12,35 (m, 1 H); MS (ESI+) m/z 1019,4 (M+H)+.

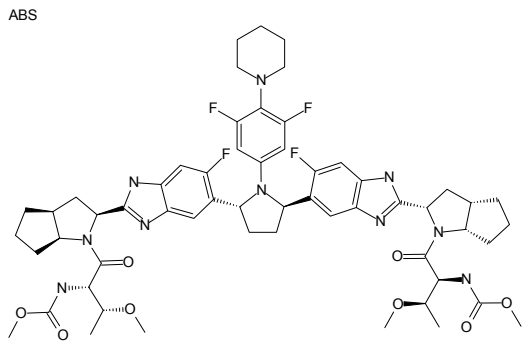
ABS



Ejemplo 3.37

{(2S)-1-[(2S,3aS,6aS)-2-{5-[(2R,5R)-1-[3,5-difluoro-4-(piperidin-1-il)fenil]-5-{6-fluoro-2-[(2S,3aS,6aS)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}octahidrociclopenta[b]pirrol-2-il]-1H-benzimidazol-5-il}pirrolidin-2-il]-6-fluoro-1H-benzimidazol-2-il}hexahidrociclopenta[b]pirrol-1(2H)-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

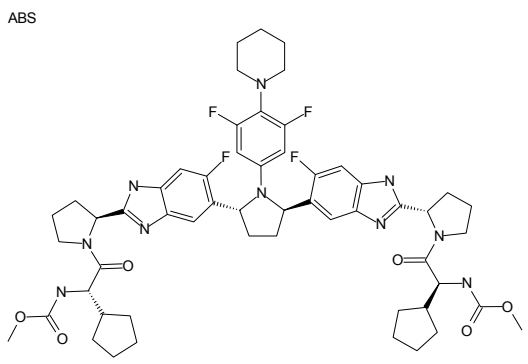
1H RMN (400 MHz, DMSO-d6) ppm 0,80 (dd, J=24,13, 6,45 Hz, 12 H) 1,36 - 1,67 (m, 10 H) 1,69 - 1,87 (m, 8 H) 1,92 - 2,17 (m, 6 H) 2,37 - 2,47 (m, 2 H) 2,78 (s, 6 H) 3,53 (s, 6 H) 3,92 - 4,07 (m, 2 H) 4,69 - 4,84 (m, 2 H) 5,08 (t, J=8,29 Hz, 2 H) 5,36 - 5,68 (m, 4 H) 5,86 (dd, J=11,71, 8,67 Hz, 2 H) 7,10 (dd, J=31,39, 6,89 Hz, 2 H) 7,28 - 7,51 (m, 4 H) 12,02 (s, 1 H) 12,21 (d, J=7,27 Hz, 1 H); MS (ESI+) m/z 1067,4 (M+H)+.



Ejemplo 3.38

{(2S,3R)-1-[(2S,3aS,6aS)-2-{5-[(2R,5R)-1-[3,5-difluoro-4-(piperidin-1-il)fenil]-5-(6-fluoro-2-{(2S,3aS,6aS)-1-[N-(metoxicarbonil)-O-metil-L-threonil]octahidrociclopenta[b]pirrol-2-il}-1H-benzimidazol-5-il)pirrolidin-2-il]-6-fluoro-1H-benzimidazol-2-il}hexahidrociclopenta[b]pirrol-1(2H)-il]-3-metoxi-1-oxobutan-2-il}carbamato de metilo

1H RMN (400 MHz, DMSO-d6) ppm 0,78 - 1,07 (m, 8 H) 1,36 - 1,51 (m, 8 H) 1,51 - 1,67 (m, 4 H) 1,75 (dd, J=12,20, 6,56 Hz, 4 H) 1,90 (dd, J=20,22, 8,95 Hz, 4 H) 2,00 - 2,14 (m, 4 H) 2,37 - 2,47 (m, 2 H) 2,79 (s, 6 H) 3,04 - 3,20 (m, 6 H) 3,54 (s, 6 H) 4,14 - 4,29 (m, 2 H) 4,77 (dd, J=18,00, 7,48 Hz, 2 H) 5,07 (t, J=8,24 Hz, 2 H) 5,47 - 5,65 (m, 2 H) 5,80 - 5,94 (m, 2 H) 7,08 (dd, J=27,27, 6,78 Hz, 2 H) 7,28 - 7,57 (m, 4 H) 12,04 (s, 1 H) 12,26 (s, 1 H); MS (ESI+) m/z 1099,4 (M+H)+.

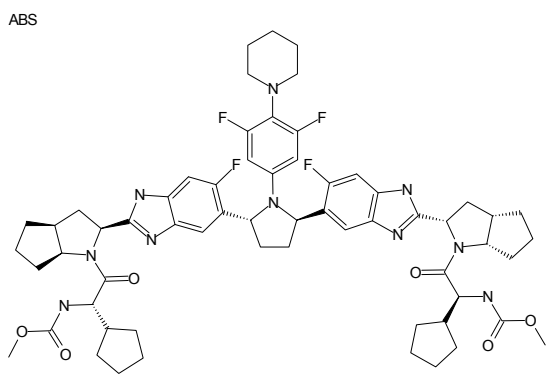


Ejemplo 3.39

({(2R,5R)-1-[3,5-difluoro-4-(piperidin-1-il)fenil]pirrolidin-2,5-diil}bis{(6-fluoro-1H-benzimidazol-5,2-diil)(2S)pirrolidin-2,1-diil[(1S)-1-ciclopentil-2-oxoetano-2,1-diil]})biscarbamato de dimetilo

1H RMN (400 MHz, DMSO-d6) ppm 1,10 - 1,29 (m, 6 H) 1,34 - 1,62 (m, 18 H) 1,71 - 1,86 (m, 2 H) 1,94 - 2,10 (m, 4 H) 2,11 - 2,24 (m, 4 H) 2,74 - 2,84 (m, 4 H) 2,94 - 3,12 (m, 2 H) 3,53 (s, 6 H) 3,73 - 3,87 (m, 4 H) 4,06 - 4,17 (m, 2 H) 5,07 - 5,18 (m, 2 H) 5,47 - 5,63 (m, 2 H) 5,82 - 5,95 (m, 2 H) 7,03 (d, J=6,40 Hz, 1 H) 7,13 (d, J=7,37 Hz, 1 H) 7,30 - 7,46 (m, 4 H) 12,07 (s, 1 H) 12,23 (s, 1 H); MS (APCI+) m/z 1040,3 (M+H)+.

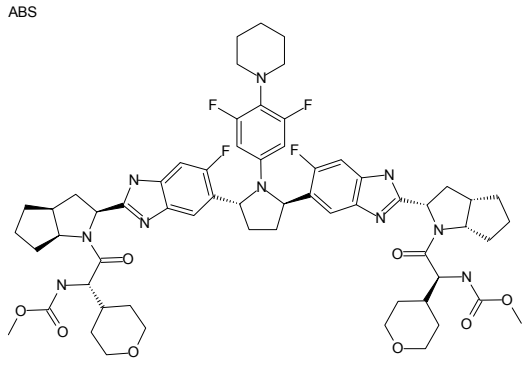
ABS



Ejemplo 3.40

({(2R,5R)-1-[3,5-difluoro-4-(piperidin-1-il)fenil]pirrolidin-2,5-diil}bis{(6-fluoro-1H-benzimidazol-5,2-diil)(2S,3aS,6aS)hexahidrociclopenta[b]pirrol-2,1(2H)-diil[(1S)-1-ciclopentil-2-oxoetano-2,1-diil]})biscarbamato de dimetilo

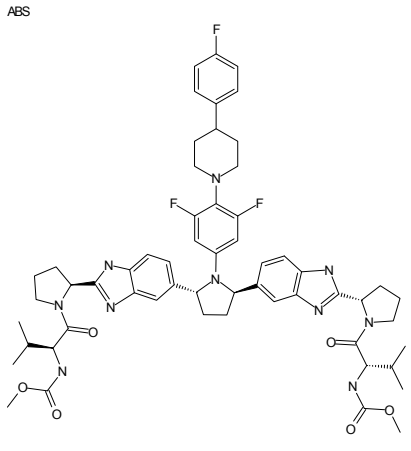
1H RMN (400 MHz, DMSO-d6) ppm 1,12 - 1,25 (m, 8 H) 1,35 - 1,64 (m, 18 H) 1,70 - 1,88 (m, 6 H) 1,92 - 2,15 (m, 8 H) 2,36 - 2,46 (m, 4 H) 2,78 (s, 6 H) 3,53 (s, 6 H) 4,07 (dt, J=18,38, 9,24 Hz, 2 H) 4,72 - 4,83 (m, 2 H) 5,07 (t, J=8,08 Hz, 2 H) 5,46 - 5,65 (m, 2 H) 5,81 - 5,91 (m, 2 H) 7,06 (d, J=6,07 Hz, 1 H) 7,11 - 7,19 (m, 1 H) 7,34 (dd, J=10,63, 4,88 Hz, 1 H) 7,43 (dd, J=11,22, 7,21 Hz, 1 H) 7,51 (dd, J=13,99, 7,92 Hz, 2 H) 11,95 (s, 1 H) 12,20 (s, 1 H); MS (ESI+) m/z 1119,4 (M+H)+.



Ejemplo 3.41

({(2R,5R)-1-[3,5-difluoro-4-(piperidin-1-il)fenil]pirrolidin-2,5-diil}bis{(6-fluoro-1H-benzimidazol-5,2-diil)(2S,3aS,6aS)hexahidrociclopenta[b]pirrol-2,1(2H)-diil[(1S)-2-oxo-1-(tetrahidro-2H-piran-4-il)etano-2,1-diil]})biscarbamato de dimetilo

1H RMN (400 MHz, DMSO-d6) □ ppm 1,30 - 1,65 (m, 18 H) 1,69 - 1,94 (m, 12 H) 2,05 - 2,15 (m, 4 H) 2,37 - 2,45 (m, 4 H) 2,73 - 2,87 (m, 6 H) 2,97 - 3,11 (m, 3 H) 3,53 (s, 6 H) 3,77 (dd, J=27,65, 10,08 Hz, 4 H) 4,06 - 4,14 (m, 2 H) 4,71 - 4,81 (m, 2 H) 5,07 (t, J=8,35 Hz, 2 H) 5,43 - 5,65 (m, 2 H) 5,78 - 5,92 (m, 2 H) 6,99 - 7,05 (m, 1 H) 7,09 (t, J=6,94 Hz, 1 H) 7,33 (dd, J=10,03, 6,13 Hz, 1 H) 7,50 (dd, J=18,16, 7,86 Hz, 2 H) 11,99 (s, 1 H) 12,29 (d, J=5,75 Hz, 1 H); MS (ESI+) m/z 1151,4 (M+H)+.



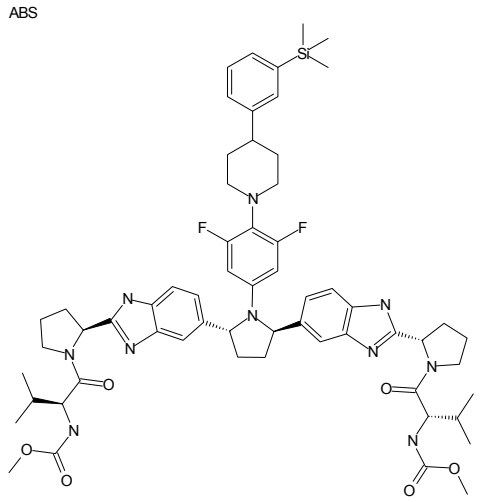
Ejemplo 3.42

{(2S)-1-[(2S)-2-{5-[(2R,5R)-1-{3,5-difluoro-4-[4-(4-fluorofenil)piperidin-1-il]fenil}-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-benzimidazol-5-

il}pirrolidin-2-il]-1H-benzimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

1H RMN (400 MHz, DMSO-d6) δ ppm 12,08 (d, J = 18,9, 2H), 7,50 (d, J = 8,0, 1H), 7,41 (d, J = 8,3, 1H), 7,33 – 7,18 (m, 6H), 7,13 – 7,01 (m, 4H), 5,91 (d, J = 13,1, 2H), 5,42 – 5,33 (m, 2H), 5,19 – 5,10 (m, 2H), 4,06 (t, J = 8,6, 2H), 3,86 – 3,77 (m, 4H), 3,53 (s, 6H), 3,03 – 2,83 (m, 5H), 2,28 – 1,54 (m, 18H), 0,91 – 0,73 (m, 12H); MS (ESI+) m/z 1045,4 (M+H)+.

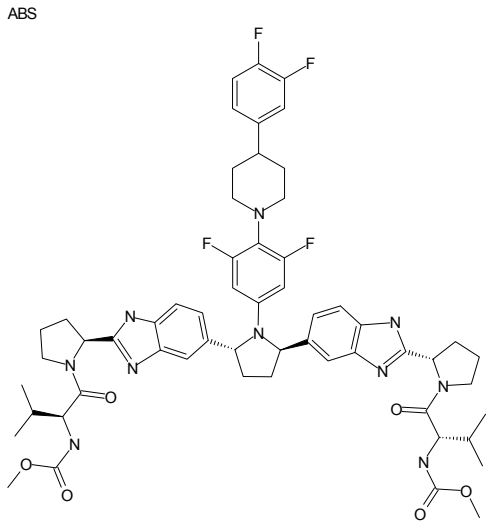
ABS



Ejemplo 3.43

{(2S)-1-[(2S)-2-{5-[(2R,5R)-1-(3,5-difluoro-4-{4-[3-(trimetilsilil)fenil]piperidin-1-il}fenil)-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-benzimidazol-5-il}pirrolidin-2-il]-1H-benzimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

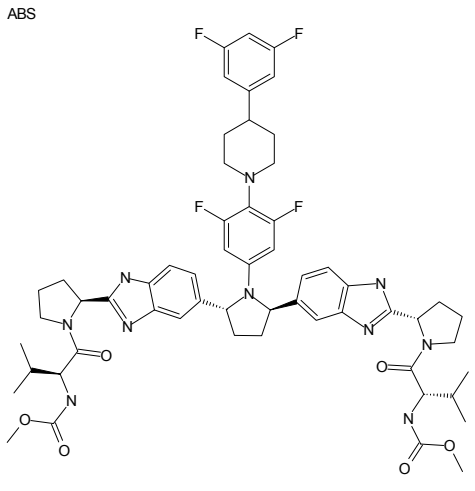
1H RMN (400 MHz, DMSO-d6) δ ppm 12,31 – 12,04 (m, 2H), 7,49 (d, J = 8,4, 1H), 7,40 (d, J = 8,2, 1H), 7,34 – 7,17 (m, 8H), 7,11 – 7,04 (m, 2H), 5,95 – 5,86 (m, 2H), 5,43 – 5,31 (m, 2H), 5,18 – 5,09 (m, 2H), 4,05 (t, J = 8,3, 2H), 3,86 – 3,76 (m, 4H), 3,52 (s, 6H), 3,12 – 2,82 (m, 4H), 2,58 – 2,52 (m, 2H), 2,26 – 1,83 (m, 11H), 1,72 – 1,58 (m, 6H), 0,90 – 0,73 (m, 12H), 0,20 (s, 9H); MS (ESI+) m/z 1099,4 (M+H)+.



Ejemplo 3.44

{(2S)-1-[(2S)-2-{5-[(2R,5R)-1-{4-[4-(3,4-difluorofenil)piperidin-1-il]-3,5-difluorofenil}-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-benzimidazol-5-il}pirrolidin-2-il]-1H-benzimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

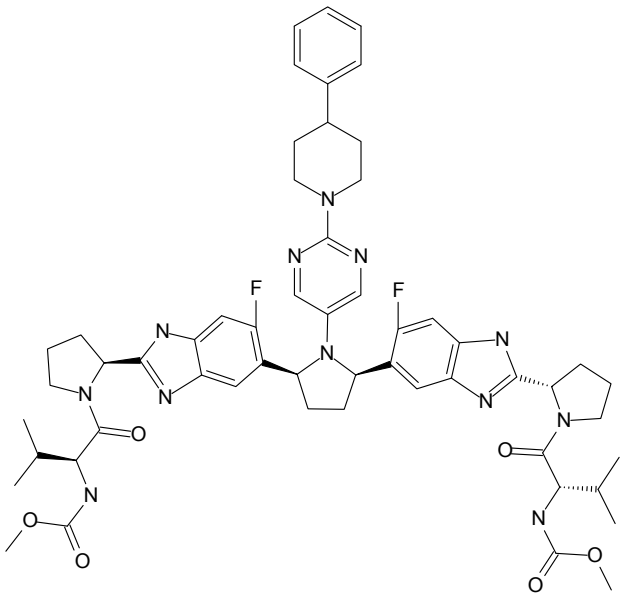
1H RMN (400 MHz, DMSO-d6) δ ppm 12,32 – 12,04 (m, 2H), 7,50 (d, J = 8,5, 1H), 7,41 (d, J = 8,3, 1H), 7,36 – 7,25 (m, 5H), 7,21 (s, 1H), 7,12 – 7,05 (m, 3H), 5,91 (d, J = 12,8, 2H), 5,37 (dd, J = 6,0, 2,1, 2H), 5,18 – 5,11 (m, 2H), 4,06 (t, J = 8,3, 2H), 3,86 – 3,79 (m, 4H), 3,53 (s, 6H), 3,12 – 2,83 (m, 4H), 2,27 – 2,10 (m, 4H), 2,08 – 1,49 (m, 15H), 0,93 – 0,67 (m, 12H); MS (ESI+) m/z 1063,3 (M+H)+.



Ejemplo 3.45

{(2S)-1-[(2S)-2-{5-[(2R,5R)-1-{4-[4-(3,5-difluorofenil)piperidin-1-il]-3,5-difluorofenil}-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-benzimidazol-5-il}pirrolidin-2-il]-1H-benzimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

1H RMN (400 MHz, DMSO-d6) δ ppm 12,47 – 11,91 (m, 2H), 7,52 – 7,40 (m, 2H), 7,36 – 7,19 (m, 4H), 7,10 (d, J = 7,9, 2H), 7,04 – 6,92 (m, 3H), 5,92 (d, J = 12,7, 2H), 5,46 – 5,32 (m, 2H), 5,20 – 5,10 (m, 2H), 4,06 (t, J = 8,3, 2H), 3,89 – 3,75 (m, 4H), 3,53 (s, 6H), 3,13 – 2,82 (m, 4H), 2,63 – 2,54 (m, 3H), 2,28 – 2,12 (m, 4H), 2,08 – 1,84 (m, 6H), 1,77 – 1,56 (m, 6H), 0,91 – 0,71 (m, 12H); MS (ESI+) m/z 1063,4 (M+H)+.

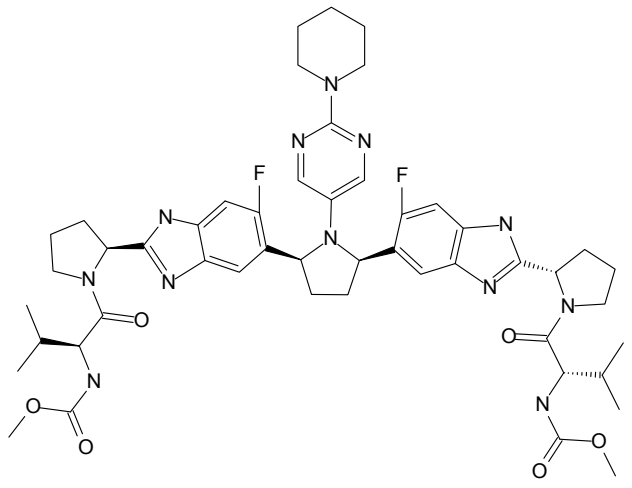


Ejemplo 3.46

{(2S)-1-[(2S)-2-(6-fluoro-5-{(2R,5S)-5-{6-fluoro-2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-benzimidazol-5-il}-1-[2-(4-fenilpiperidin-1-il)pirimidin-5-il]pirrolidin-2-il}-1H-benzimidazol-2-il)pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

1H RMN (400 MHz, DMSO) δ = 12,42 – 12,16 (m, 2H), 7,81 – 7,55 (m, 4H), 7,45 – 7,12 (m, 9H), 5,23 – 5,06 (m, 2H), 5,02 – 4,86 (m, 2H), 4,57 – 4,45 (m, 2H), 4,13 – 3,96 (m, 2H), 3,92 – 3,70 (m, 4H), 3,53 (s, 6H), 2,75 (t, J=12,8, 2H), 2,62 – 2,54 (m, J=8,1, 2H),

2,28 – 1,59 (m, 15H), 1,53 – 1,36 (m, 2H), 0,98 – 0,66 (m, 12H). MS (ESI; M+H) m/z = 1029,4.

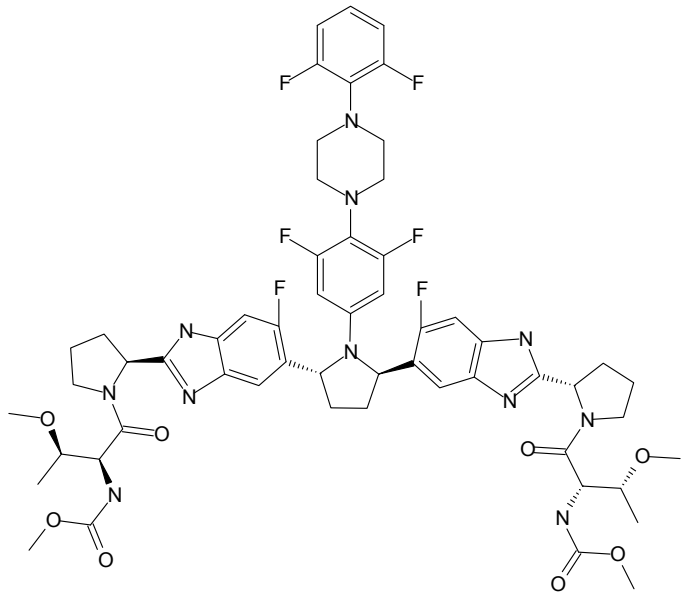


Ejemplo 3.47

{(2S)-1-[(2S)-2-(6-fluoro-5-{(2R,5S)-5-{6-fluoro-2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-benzimidazol-5-il}-1-[2-(piperidin-1-il)pirimidin-5-il]pirrolidin-2-il}-1H-benzimidazol-2-il)pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

1H RMN (400 MHz, DMSO) δ 12,41 – 12,15 (m, 2H), 7,79 – 7,54 (m, 4H), 7,45 – 7,24 (m, 4H), 5,20 – 5,06 (m, 2H), 5,01 – 4,85 (m, 2H), 4,12 – 4,01 (m, 2H), 3,88 – 3,73 (m, 4H), 3,52 (s, 6H), 3,50 – 3,42 (m, 4H), 2,55 (s, 2H), 2,27 – 1,77 (m, 12H), 1,51 (s, 2H), 1,38 (s, 4H), 0,93 – 0,73 (m, 12H). MS (ESI; M+H) m/z = 953,4.

ABS



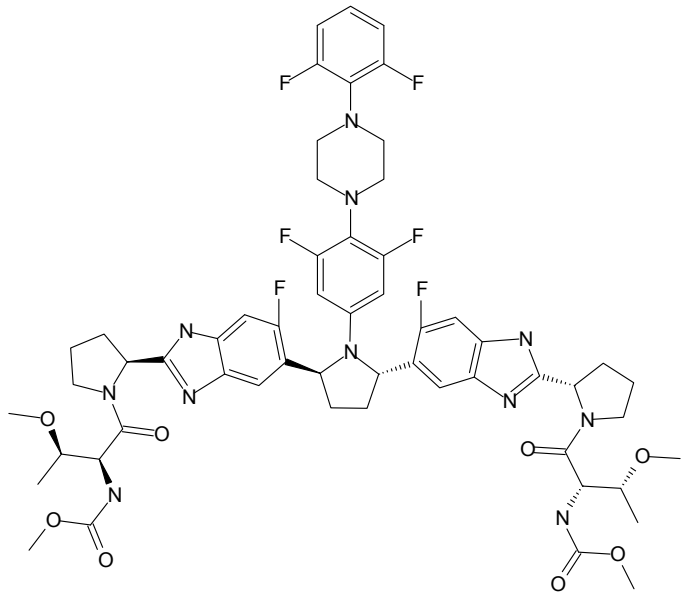
Ejemplo 3.48

{(2S,3R)-1-[(2S)-2-{5-[(2R,5R)-1-{4-[4-(2,6-difluorofenil)piperazin-1-il]-3,5-difluorofenil}-5-(6-fluoro-2-{(2S)-1-[N-(metoxicarbonil)-O-metil-L-threonil]pirrolidin-2-il}-1H-benzimidazol-5-il)pirrolidin-2-il]-6-fluoro-1H-benzimidazol-2-il}pirrolidin-1-il]-3-metoxi-1-oxobutan-2-il}carbamato de metilo

1H RMN (400 MHz, DMSO) δ 12,37 – 12,08 (m, 2H), 7,41 (dd, J = 11,2, 6,3, 1H), 7,34 (dd, J = 10,4, 4,7, 1H), 7,24 (d, J = 8,3, 1H), 7,18 – 6,97 (m, 6H), 5,90 (dd, J = 22,3, 9,7, 2H), 5,57 (s, 2H), 5,16 – 5,06 (m, 2H), 4,25 (dd, J = 15,5, 8,2, 2H), 3,87 – 3,76 (m, 3H), 3,53 (s, 6H), 3,50 – 3,40 (m, 2H), 3,25 (d, J = 3,5, 1H), 3,13 (d, J = 1,1, 3H), 3,09 (s, 4H), 3,04 (d, J = 2,6, 3H), 2,96 (s, 4H), 2,55 – 2,47 (m, 2H), 2,26 – 1,71 (m, 10H), 1,08 – 0,89 (m, 6H).

MS (ESI; M+H) m/z = 1132,4.

ABS

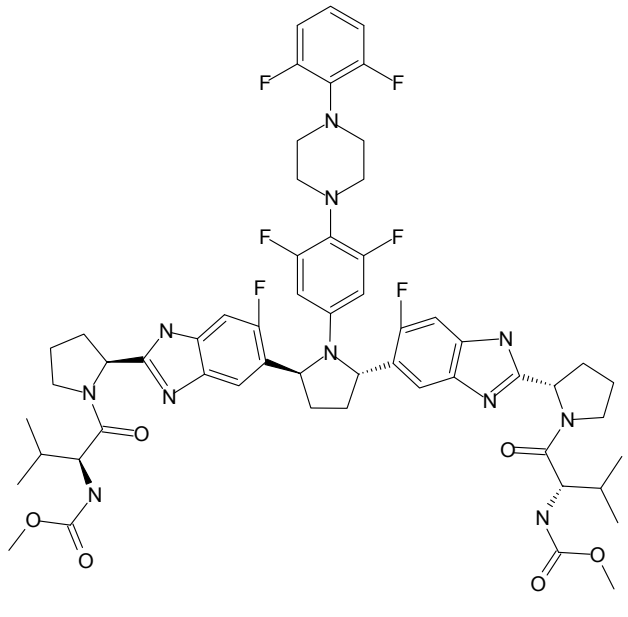


Ejemplo 3.49

{(2S,3R)-1-[(2S)-2-{5-[(2S,5S)-1-{4-[4-(2,6-difluorofenil)piperazin-1-il]-3,5-difluorofenil}-5-(6-fluoro-2-{(2S)-1-[N-(metoxicarbonil)-O-metil-L-threonil]pirrolidin-2-il}-1H-benzimidazol-5-il)pirrolidin-2-il]-6-fluoro-1H-benzimidazol-2-il}pirrolidin-1-il]-3-metoxi-1-oxobutan-2-il}carbamato de metilo

1H RMN (400 MHz, DMSO) δ 12,33 – 12,04 (m, 2H), 7,41 (dd, J = 11,3, 4,7, 1H), 7,36 (dd, J = 10,5, 3,0, 1H), 7,28 (d, J = 7,9, 1H), 7,21 (d, J = 8,1, 1H), 7,16 (t, J = 7,8, 1H), 7,10 – 6,96 (m, 4H), 5,92 (q, J = 10,7, 2H), 5,69 – 5,49 (m, 2H), 5,12 (dd, J = 7,6, 4,1, 2H), 4,27 (t, J = 7,6, 2H), 3,82 (s, 3H), 3,53 (d, J = 3,1, 6H), 3,47 (d, J = 6,3, 2H), 3,24 (d, J = 2,3, 1H), 3,19 (s, 3H), 3,13 (s, 3H), 3,09 (s, 4H), 2,96 (s, 4H), 2,46 (s, 2H), 2,28 – 1,71 (m, 10H), 1,09 – 1,00 (m, 6H). MS (ESI; M+H) m/z = 1132,4.

ABS

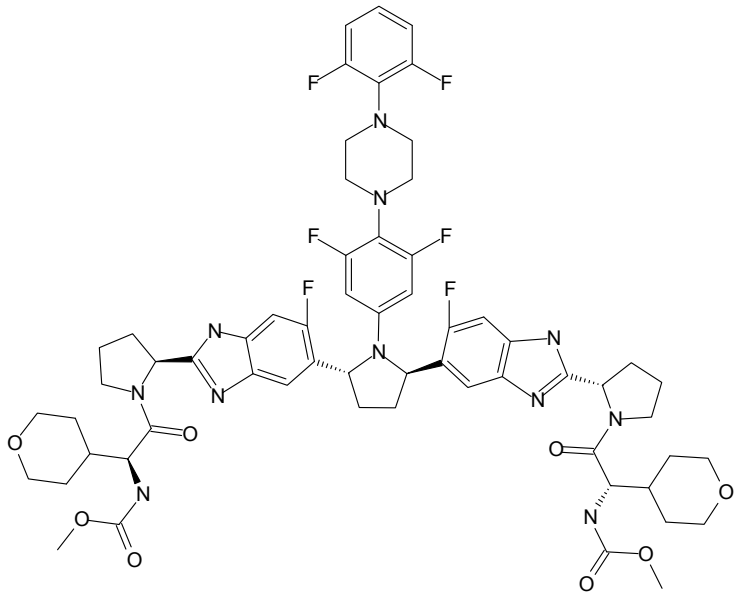


Ejemplo 3.50

{(2S)-1-[(2S)-2-{5-[(2S,5S)-1-{4-[4-(2,6-difluorofenil)piperazin-1-il]-3,5-difluorofenil}-5-{6-fluoro-2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-benzimidazol-5-il}pirrolidin-2-il]-6-fluoro-1H-benzimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

1H RMN (400 MHz, DMSO) δ 12,47 – 11,97 (m, 2H), 7,44 – 7,26 (m, 4H), 7,19 – 6,96 (m, 5H), 5,93 (q, J = 12,0, 2H), 5,67 – 5,48 (m, 2H), 5,18 – 5,07 (m, 2H), 4,05 (dd, J = 14,8, 8,3, 2H), 3,87 – 3,71 (m, 4H), 3,53 (d, J = 3,1, 6H), 3,09 (s, 4H), 2,96 (s, 4H), 2,46 (s, 2H), 2,25 – 1,70 (m, 12H), 0,89 – 0,76 (m, 12H). MS (ESI; M+H) m/z = 1100,4.

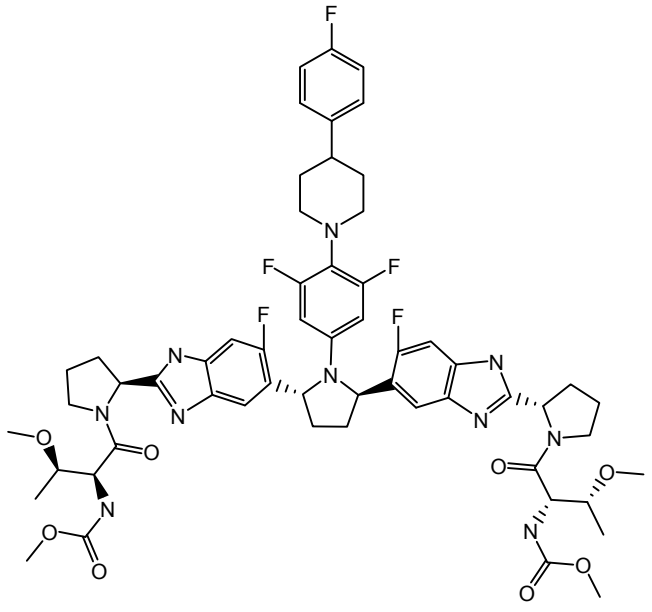
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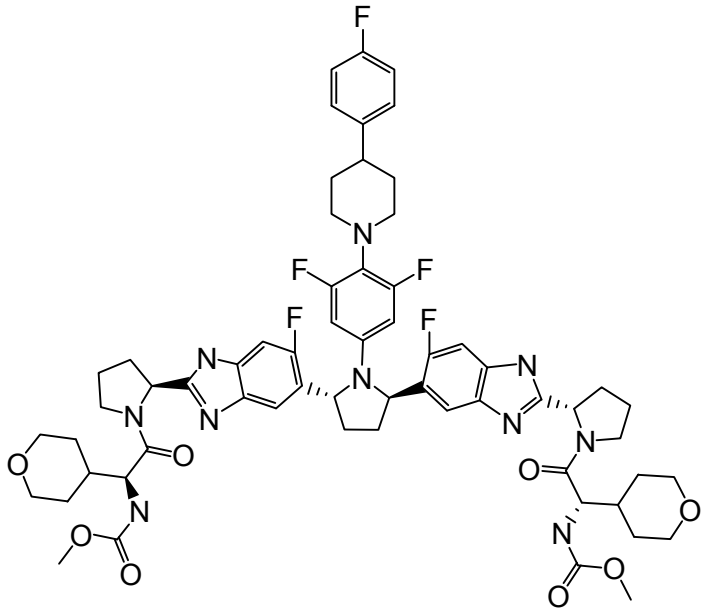
Ejemplo 3.51

([(2R,5R)-1-{4-[4-(2,6-difluorofenil)piperazin-1-il]-3,5-difluorofenil}pirrolidin-2,5-diil]bis{(6-fluoro-1H-benzimidazol-5,2-diil)(2S)pirrolidin-2,1-diil[(1S)-2-oxo-1-(tetrahidro-2H-piran-4-il)etano-2,1-diil]})biscarbamato de dimetilo

1H RMN (400 MHz, DMSO) δ 12,37 – 12,08 (m, 2H), 7,44 – 7,30 (m, 4H), 7,12 – 6,95 (m, 5H), 5,90 (q, J = 11,6, 2H), 5,66 – 5,47 (m, 2H), 5,16 – 5,05 (m, 2H), 4,17 – 4,04 (m, 2H), 3,88 – 3,61 (m, 7H), 3,52 (d, J = 3,1, 6H), 3,23 – 2,80 (m, 13H), 2,26 – 1,67 (m, 12H), 1,55 – 1,05 (m, 10H). MS (ESI; M+H) m/z = 1184,4



Ejemplo 3.52 {(2S,3R)-1-[(2S)-2-{5-[(2R,5R)-1-{3,5-difluoro-4-[4-(4-fluorofenil)piperidin-1-il]fenil}-5-(6-fluoro-2-{(2S)-1-[N-(metoxicarbonil)-O-metil-L-threonil]pirrolidin-2-il}-1H-benzimidazol-5-il)pirrolidin-2-il]-6-fluoro-1H-benzimidazol-2-il}pirrolidin-1-il]-3-metoxi-1-oxobutan-2-il}carbamato de metilo1H RMN (400 MHz, DMSO) δ 12,36 – 12,06 (m, 2H), 7,41 (dd, J = 11,2, 6,3, 1H), 7,34 (dd, J = 10,4, 4,8, 1H), 7,30 – 7,20 (m, 3H), 7,17 – 6,98 (m, 5H), 5,98 – 5,82 (m, 2H), 5,65 – 5,47 (m, 2H), 5,17 – 5,06 (m, 2H), 4,25 (dd, J = 15,6, 8,1, 2H), 3,88 – 3,74 (m, 3H), 3,53 (d, J = 1,3, 6H), 3,49 – 3,38 (m, 2H), 3,31 (d, 1H), 3,25 (d, J = 3,7, 1H), 3,13 (d, J = 1,3, 3H), 3,03 (d, J = 2,3, 3H), 3,00 – 2,84 (m, 3H), 2,60 – 2,53 (m, J = 2,5, 2H), 2,26 – 1,55 (m, 14H), 1,28 – 1,13 (m, 1H), 1,10 – 0,88 (m, 6H). MS (ESI; M+H) m/z = 1113,4.



Ejemplo 3.53 ([(2R,5R)-1-{3,5-difluoro-4-[4-(4-fluorofenil)piperidin-1-il]fenil}pirrolidin-2,5-diil]bis{(6-fluoro-1H-benzimidazol-5,2-diil)(2S)pirrolidin-2,1-diil[(1S)-2-oxo-1-(tetrahidro-2H-piran-4-il)etano-2,1-diil]})biscarbamato de dimetilo1H RMN (400 MHz, DMSO) δ 12,36 – 12,07 (m, 2H), 7,44 – 7,22 (m, 6H), 7,12 – 6,99 (m, 4H), 5,88 (dd, J = 23,6, 11,2, 2H), 5,64 – 5,47 (m, 2H), 5,15 – 5,06 (m, 2H), 4,17 – 4,06 (m, 2H), 3,89 – 3,61 (m, 7H), 3,52 (d, J =

3,3, 6H), 3,25 – 2,82 (m, 9H), 2,26 – 2,08 (m, 4H), 2,05 – 1,92 (m, 4H), 1,91 – 1,57 (m, 9H), 1,54 – 1,38 (m, 4H), 1,38 – 1,02 (m, 6H). MS (ESI; M+H) m/z = 1165,5.

Los siguientes ejemplos de compuestos 4.1-4.62 pueden prepararse a partir de los intermediarios apropiados siguiendo los métodos de los Procedimientos Generales 12/12B.

Aminas intermediarias:

(S)-6,6'-((2R,5R)-1-(4-(ciclopentiloxi)-3-fluorofenil)pirrolidin-2,5-diil)bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol);

(S)-6,6'-((2R,5R)-1-(3-metil-4-(piperidin-1-il)fenil)pirrolidin-2,5-diil)bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol);

(S)-6,6'-((2R,5R)-1-(3,5-difluoro-4-((3aR,7aS)-1H-isoindol-2(3H,3aH,4H,5H,6H,7H,7aH)-il)fenil)pirrolidin-2,5-diil)bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol);

(S)-6,6'-((2R,5R)-1-(3,5-dicloro-4-(piperidin-1-il)fenil)pirrolidin-2,5-diil)bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol);

(S)-6,6'-((2R,5R)-1-(2,5-difluoro-4-(piperidin-1-il)fenil)pirrolidin-2,5-diil)bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol);

(S)-6,6'-((2R,5R)-1-(4-((2R,6S)-2,6-dimetilpiperidin-1-il)-3,5-difluorofenil)pirrolidin-2,5-diil)bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol);

(S)-6,6'-((2R,5R)-1-(2,3,5-trifluoro-4-(piperidin-1-il)fenil)pirrolidin-2,5-diil)bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol);

(S)-6,6'-((2R,5R)-1-(4-ciclohexil-3-fluorofenil)pirrolidin-2,5-diil)bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol);

(S)-6,6'-((2R,5R)-1-(3,4-difluorofenil)pirrolidin-2,5-diil)bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol);

(S)-6,6'-((2R,5R)-1-(4-etoxifenil)pirrolidin-2,5-diil)bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol);

(S)-6,6'-((2R,5R)-1-(4-(2,2-difluoroetoxi)fenil)pirrolidin-2,5-diil)bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol);

(S)-6,6'-((2R,5R)-1-(4-(3,5-dimetilpiperidin-1-il)-3,5-difluorofenil)pirrolidin-2,5-diil)bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol);

6,6'-{(2R,5R)-1-[4-(pentafluoro-λ6-sulfanil)fenil]pirrolidin-2,5-diil}bis{2-[(2S)-pirrolidin-2-il]-1H-benzimidazol} (Nomenclatura ACD v12);

(S)-6,6'-((2S,5S)-1-(4-ciclopropilfenil)pirrolidin-2,5-diil)bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol);

(S)-6,6'-((2S,5S)-1-(4-ciclopropil-3,5-difluorofenil)pirrolidin-2,5-diil)bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol);

(S)-6,6'-((2R,5R)-1-(4-tert-butilfenil)pirrolidin-2,5-diil)bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol);

1-(1-(4-((2R,5R)-2,5-bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol-6-il)pirrolidin-1-il)-2,6-difluorofenil)-4-fenilpiperidin-4-il)etanona;

(S,S,S)-6,6'-((2R,5R)-1-(3,5-difluoro-4-(piperidin-1-il)fenil)pirrolidin-2,5-diil)bis(2-((2S,3aS,6aS)-octahidrociclopenta[b]pirrol-2-il)-1H-benzo[d]imidazol);

(S,S,S)-6,6'-((2R,5R)-1-(4-tert-butilfenil)pirrolidin-2,5-diil)bis(2-((2S,3aS,6aS)-octahidrociclopenta[b]pirrol-2-il)-1H-benzo[d]imidazol);

2-(4-((2R,5R)-2,5-bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol-6-il)pirrolidin-1-il)-2,6-difluorofenil)-2-azabiciclo[2,2,2]octano;

(S)-6,6'-((2R,5R)-1-(3,5-difluoro-4-(4-isopropilpiperidin-1-il)fenil)pirrolidin-2,5-diil)bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol);

(S)-6,6'-((2R,5R)-1-(4-(4,4-dimetilpiperidin-1-il)-3,5-difluorofenil)pirrolidin-2,5-diil)bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol);

(S)-6,6'-((2R,5R)-1-(4-(3,3-dimetilazetidin-1-il)-3,5-difluorofenil)pirrolidin-2,5-diil)bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol);

(S)-6,6'-((2R,5R)-1-(4-(4-fenilpiperidin-1-il)fenil)pirrolidin-2,5-diil)bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol);

(S)-6,6'-((2R,5R)-1-(3,5-difluoro-4-(4-(3-fenilpropil)piperidin-1-il)fenil)pirrolidin-2,5-diil)bis(5-fluoro-2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol);

(S)-6,6'-((2R,5R)-1-(4-(4-tert-butilpiperidin-1-il)-3,5-difluorofenil)pirrolidin-2,5-diil)bis(5-fluoro-2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol);

(S)-6,6'-((2R,5R)-1-(3,5-difluoro-4-(4-(naftalen-2-il)piperidin-1-il)fenil)pirrolidin-2,5-diil)bis(5-fluoro-2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol);

(S)-6,6'-((2R,5R)-1-(4-(2,3-dihidroespiro[inden-1,4'-piperidin]-1'-il)-3,5-difluorofenil)pirrolidin-2,5-diil)bis(5-fluoro-2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol);

(S)-6,6'-((2R,5R)-1-(3,5-difluoro-4-(3-fenilpiperidin-1-il)fenil)pirrolidin-2,5-diil)bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol);

(S)-6,6'-((2R,5R)-1-(3,5-difluoro-4-(3-fenilpirrolidin-1-il)fenil)pirrolidin-2,5-diil)bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol);

(S)-6,6'-((2R,5R)-1-(3,5-difluoro-4-(4-(4-metoxifenil)piperidin-1-il)fenil)pirrolidin-2,5-diil)bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol);

(S)-6,6'-((2R,5R)-1-(3,5-difluoro-4-(4-fluoro-4-fenilpiperidin-1-il)fenil)pirrolidin-2,5-diil)bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol);

(S)-6,6'-((2R,5R)-1-(4-(4-fluoro-4-fenilpiperidin-1-il)fenil)pirrolidin-2,5-diil)bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol);

(S)-6,6'-((2R,5R)-1-(3,5-difluoro-4-(4-(fluorodifenilmetil)piperidin-1-il)fenil)pirrolidin-2,5-diil)bis(5-fluoro-2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol);

(S)-6,6'-((2R,5R)-1-(3,5-difluoro-4-(4-fenilpiperidin-1-il)fenil)pirrolidin-2,5-diil)bis(5-fluoro-2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol);

(S)-6,6'-((2R,5R)-1-(4-(benciloxi)fenil)pirrolidin-2,5-diil)bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol);

(S)-6,6'-((2R,5R)-1-(3,5-difluoro-4-(4-(4-(trifluorometil)fenil)piperazin-1-il)fenil)pirrolidin-2,5-diil)bis(5-fluoro-2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol);

6-((2R,5R)-1-(3,5-difluoro-4-(piperidin-1-il)fenil)-5-(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol-6-il)pirrolidin-2-il)-5-fluoro-2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol;

(S)-6,6'-((2R,5R)-1-(4-(4-bencilpiperidin-1-il)-3,5-difluorofenil)pirrolidin-2,5-diil)bis(5-fluoro-2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol);

(S)-6,6'-((2R,5R)-1-(4-(4-bencilpiperidin-1-il)-3,5-difluorofenil)pirrolidin-2,5-diil)bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol);

(S)-6,6'-((2S,5R)-1-(3,5-difluoro-4-(4-fenilpiperidin-1-il)fenil)pirrolidin-2,5-diil)bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol);

4-(4-((2R,5R)-2,5-bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol-6-il)pirrolidin-1-il)-2,6-difluorofenil)-2-fenilmorfolina;

(S)-6,6'-((2R,5R)-1-(3,5-difluoro-4-(2-fenilpiperidin-1-il)fenil)pirrolidin-2,5-diil)bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol);

(2S,6R)-4-(4-((2R,5R)-2,5-bis(5-fluoro-2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol-6-il)pirrolidin-1-il)-2,6-difluorofenil)-2,6-dimetilmorfolina;

(S)-6,6'-((2R,5R)-1-(3,5-difluoro-4-(3-azaespiro[5,5]undecan-3-il)fenil)pirrolidin-2,5-diil)bis(5-fluoro-2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol);

(S)-6,6'-((2R,5R)-1-(4-(4-ciclohexilpiperidin-1-il)-3,5-difluorofenil)pirrolidin-2,5-diil)bis(5-fluoro-2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol);

(S)-4-(4-((2R,5R)-2,5-bis(5-fluoro-2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol-6-il)pirrolidin-1-il)-2,6-difluorofenil)-2-fenilmorfolina;

(S)-6,6'-((2S,5R)-1-(3,5-difluoro-4-(piperidin-1-il)fenil)pirrolidin-2,5-diil)bis(5-fluoro-2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol);

(S)-6,6'-((2R,5R)-1-(3,5-difluoro-4-(4-fenilpiperazin-1-il)fenil)pirrolidin-2,5-diil)bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol);

(S,R)-6,6'-((2R,5R)-1-(3,5-difluoro-4-(piperidin-1-il)fenil)pirrolidin-2,5-diil)bis(2-((2S,4R)-4-fluoropirrolidin-2-il)-1H-benzo[d]imidazol);

(S)-6,6'-((2R,5R)-1-(3,5-difluoro-4-(4-(pirimidin-2-il)piperazin-1-il)fenil)pirrolidin-2,5-diil)bis(5-fluoro-2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol);

(S)-6,6'-((2R,5R)-1-(4-(4-(2,4-difluorofenil)piperidin-1-il)-3,5-difluorofenil)pirrolidin-2,5-diil)bis(5-fluoro-2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol);

(S)-6,6'-((2R,5R)-1-(3,5-difluoro-4-(4-(4-fluorofenil)piperidin-1-il)fenil)pirrolidin-2,5-diil)bis(5-fluoro-2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol).

(S)-6,6'-((2R,5R)-1-(3,5-difluoro-4-(4-(5-metiltiofen-2-il)piperidin-1-il)fenil)pirrolidin-2,5-diil)bis(5-fluoro-2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol); y

(S)-6,6'-((2R,5R)-1-(3,5-difluoro-4-(4-fluoro-4-fenilpiperidin-1-il)fenil)pirrolidin-2,5-diil)bis(5-fluoro-2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol).

Ácidos intermediarios:

ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico;

ácido (S)-2-(metoxicarbonilamino)-2-(tetrahidro-2H-piran-4-il)acético;

ácido (2S,3R)-3-metoxi-2-(metoxicarbonilamino)butanoico;

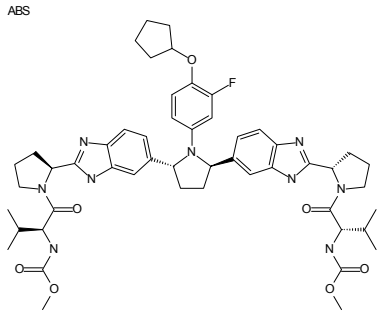
ácido (S)-2-ciclopropil-2-(metoxicarbonilamino)acético;

ácido (2S,3R)-3-tert-butoxi-2-(metoxicarbonilamino)butanoico;

ácido (S)-2-(metoxicarbonilamino)-2-(tetrahidro-2H-piran-4-il)acético;

ácido (S)-2-ciclopentil-2-(metoxicarbonilamino)acético; y

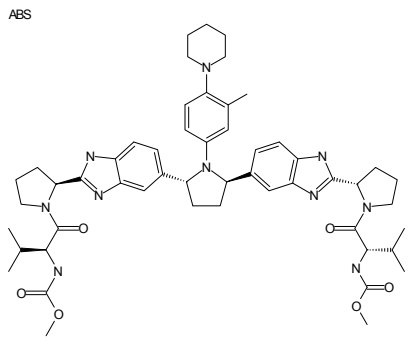
ácido (2S,3R)-3-metoxi-2-(metoxicarbonilamino)butanoico.



Ejemplo 4.1

{(2S)-1-[(2S)-2-{6-[(2R,5R)-1-[4-(ciclopentiloxi)-3-fluorofenil]-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-benzimidazol-6-il}pirrolidin-2-il]-1H-benzimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

1H RMN (400 MHz, DMSO-d6) □ ppm 0,74 - 0,89 (m, 12 H), 1,37 - 1,77 (m, 12 H), 1,81 - 2,06 (m, 6 H), 2,11 - 2,29 (m, 4 H), 3,54 (s, 6 H), 3,72 - 3,92 (m, 4 H), 3,95 - 4,16 (m, 2 H), 4,40 - 4,52 (m, 1 H), 5,07 - 5,23 (m, 2 H), 5,26 - 5,44 (m, 2 H), 5,96 - 6,17 (m, 2 H), 6,63 - 6,98 (m, 2 H), 7,00 - 7,16 (m, 2 H), 7,16 - 7,35 (m, 4 H), 7,35 - 7,54 (m, J=31,23 Hz, 2 H), 11,93 - 12,32 (m, 2 H); MS (ESI) m/z = 934,5 (M+H)+.

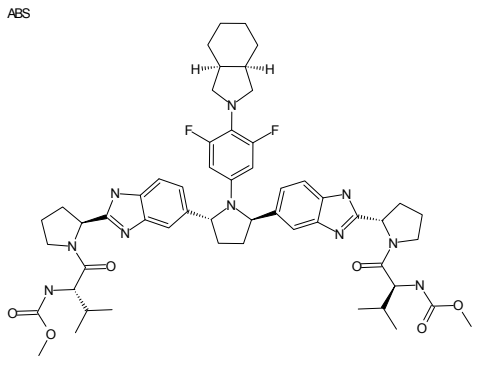


Ejemplo 4.2

{(2S)-1-[(2S)-2-(5-{(2R,5R)-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-benzimidazol-5-il}-1-[3-metil-4-(piperidin-1-il)fenil]pirrolidin-2-il}-1H-benzimidazol-2-il)pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

1H RMN (400 MHz, DMSO-d6) □ ppm 0,74 - 0,89 (m, 12 H) 1,35 - 1,41 (m, 2 H) 1,44 - 1,52 (m, 4 H) 1,62 - 1,67 (m, 2 H) 1,86 - 1,93 (m, 5 H) 1,94 - 2,03 (m, 4 H) 2,15 - 2,24 (m, 4 H) 2,48 - 2,54 (m, 6 H) 3,52 (s, 6 H) 3,74 - 3,84 (m, 4 H) 4,00 - 4,09 (m, 2 H) 5,06 - 5,18

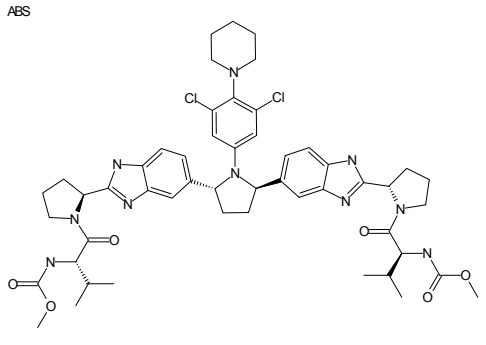
(m, 2 H) 5,28 - 5,37 (m, 2 H) 6,07 - 6,12 (m, 1 H) 6,17 - 6,21 (m, 1 H) 6,56 - 6,62 (m, 1 H) 6,99 - 7,30 (m, 6 H) 7,35 (d, J=8,24 Hz, 1 H) 7,44 (d, J=8,24 Hz, 1 H) 11,94 - 12,04 (m, 2 H); MS (ESI+) m/z 929,5 (M+H)+.



Ejemplo 4.3

{(2S)-1-[(2S)-2-{5-[(2R,5R)-1-{3,5-difluoro-4-[(3aR,7aS)-octahidro-2H-isoindol-2-il]fenil}-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-benzimidazol-5-il}pirrolidin-2-il]-1H-benzimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

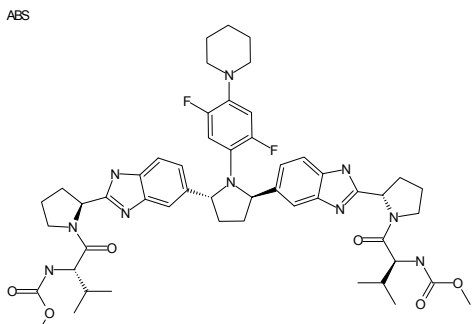
1H RMN (400 MHz, DMSO-d6) ppm 0,71 - 0,94 (m, 12 H) 1,22 - 1,31 (m, 2 H) 1,35 - 1,53 (m, 6 H) 1,66 - 1,74 (m, 2 H) 1,86 - 2,24 (m, 12 H) 2,90 - 2,97 (m, 2 H) 3,05 - 3,15 (m, 2 H) 3,36 - 3,42 (m, 2 H) 3,54 (s, 6 H) 3,77 - 3,86 (m, 4 H) 4,06 (t, J=8,29 Hz, 2 H) 5,09 - 5,20 (m, 2 H) 5,29 - 5,40 (m, 2 H) 5,89 (d, J=12,25 Hz, 2 H) 7,03 - 7,13 (m, 2 H) 7,18 - 7,33 (m, 4 H) 7,40 (d, J=8,13 Hz, 1 H) 7,48 (d, J=8,24 Hz, 1 H) 11,95 - 12,25 (m, 2 H); MS (ESI+) m/z 991,5 (M+H)+.



Ejemplo 4.4

{(2S)-1-[(2S)-2-{5-[(2R,5R)-1-[3,5-dicloro-4-(piperidin-1-il)fenil]-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-benzimidazol-5-il}pirrolidin-2-il]-1H-benzimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

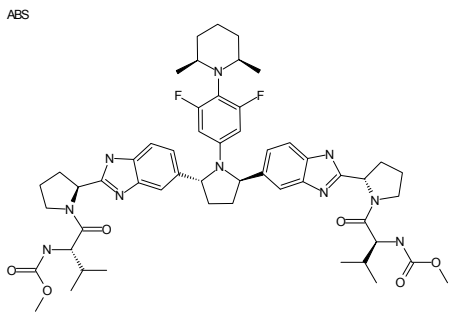
1H RMN (400 MHz, DMSO-d6) ppm 0,68 - 0,94 (m, 12 H) 1,36 - 2,28 (m, 20 H) 2,84 (s, 4 H) 3,54 (s, 6 H) 3,82 (s, 4 H) 4,04 - 4,09 (m, 2 H) 5,09 - 5,19 (m, 2 H) 5,33 - 5,50 (m, 2 H) 6,30 (t, J=2,49 Hz, 2 H) 6,99 - 7,57 (m, 8 H) 12,04 (s, 1 H) 12,09 (s, 1 H); MS (ESI+) m/z 983 (M+H)+.



Ejemplo 4.5

{(2S)-1-[(2S)-2-{5-[(2R,5R)-1-[2,5-difluoro-4-(piperidin-1-il)fenil]-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-benzimidazol-5-il}pirrolidin-2-il]-1H-benzimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

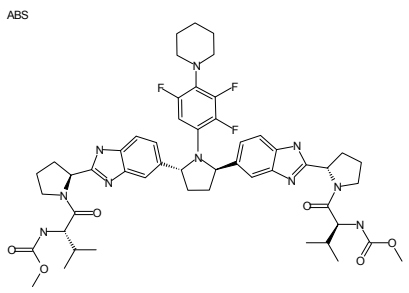
1H RMN (400 MHz, DMSO-d6) ppm 0,80 (s, 12 H) 1,08 - 2,71 (m, 24 H) 3,53 (s, 6 H) 3,81 (s, 4 H) 3,97 - 4,11 (m, 2 H) 5,13 (s, 2 H) 5,51 (s, 2 H) 6,34 - 6,70 (m, 2 H) 7,00 - 7,60 (m, 8 H) 11,87 - 12,30 (m, 2 H); MS (ESI+) m/z 952 (M+H)+.



Ejemplo 4.6

{(2S)-1-[(2S)-2-{5-[(2R,5R)-1-{4-[(2R,6S)-2,6-dimetilpiperidin-1-il]-3,5-difluorofenil}-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-benzimidazol-5-il}pirrolidin-2-il]-1H-benzimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

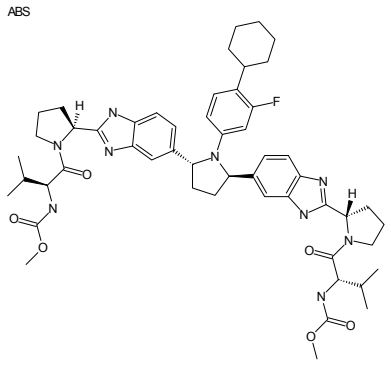
1H RMN (400 MHz, DMSO-d6) □ ppm 0,58 (s, 6 H) 0,73 - 0,92 (m, 12 H) 1,08 - 2,37 (m, 20 H) 3,53 (s, 6 H) 3,82 (s, 4 H) 4,06 (q, J=7,92 Hz, 2 H) 5,15 (s, 2 H) 5,39 (s, 2 H) 5,88 (d, J=13,01 Hz, 2 H) 7,02 - 7,58 (m, 10 H) 12,01 (s, 1 H) 12,18 (s, 1 H); MS (ESI+) m/z 979 (M+H)+.



Ejemplo 4.7

{(2S)-1-[(2S)-2-(5-{(2R,5R)-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-benzimidazol-5-il}-1-[2,3,5-trifluoro-4-(piperidin-1-il)fenil]pirrolidin-2-il}-1H-benzimidazol-2-il)pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

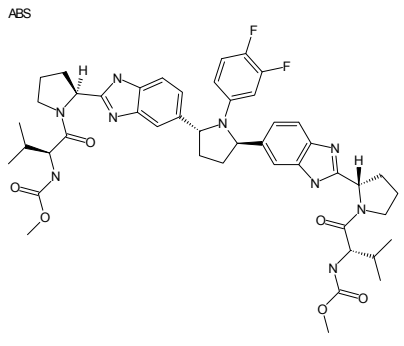
1H RMN (400 MHz, DMSO-d6) □ ppm 0,72 - 0,93 (m, 12 H) 1,34 - 2,38 (m, 20 H) 2,77 (s, 4 H) 3,53 (s, 6 H) 3,82 (s, 4 H) 4,00 - 4,13 (m, 2 H) 5,14 (s, 2 H) 5,56 (s, 2 H) 6,27 - 6,47 (m, 1 H) 6,97 - 7,49 (m, 8 H) 12,01 (s, 1 H) 12,08 (d, J=1,84 Hz, 1 H); MS (ESI+) m/z 970 (M+H)+.



Ejemplo 4.8

{(2S)-1-[(2S)-2-{5-[(2R,5R)-1-(4-ciclohexil-3-fluorofenil)-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-benzimidazol-6-il}pirrolidin-2-il]-1H-benzimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

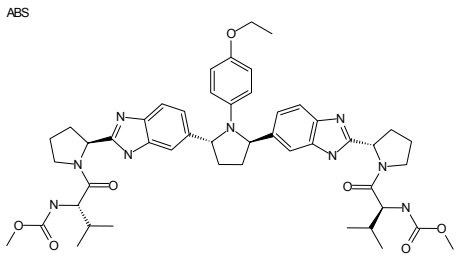
1H RMN (400 MHz, CDCl3) □ ppm 10,48 (m, 1 H), 10,32 (s, 1 H), 7,70 (d, J = 8,0 Hz, 1 H), 7,53 (s, 1 H), 7,34 (d, J = 8,1 Hz, 1 H), 7,13 (d, J = 5,5 Hz, 3 H), 6,72 (s, 1 H), 6,03 (m, 2 H), 5,40 (m, 5 H), 5,26 (d, J = 1,7 Hz, 3 H), 4,34 (dd, J = 8,7, 7,0 Hz, 2 H), 3,84 (d, J = 7,6 Hz, 2 H), 3,70 (s, 6 H), 3,62 (m, 3 H), 3,09 (m, 2 H), 2,57 (m, 4 H), 2,33 (m, 2 H), 2,17 (m, 5 H), 1,97 (m, 3 H), 1,73 (m, 8 H), 1,17 (m, 8 H), 0,89 (t, J = 6,4, 12 H); MS (ESI+) m/z (abundancia relativa) 933 (100, M+H), 934 (53).



Ejemplo 4.9

{(2S)-1-[(2S)-2-{5-[(2R,5R)-1-(3,4-difluorofenil)-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-benzimidazol-6-il}pirrolidin-2-il]-1H-benzimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

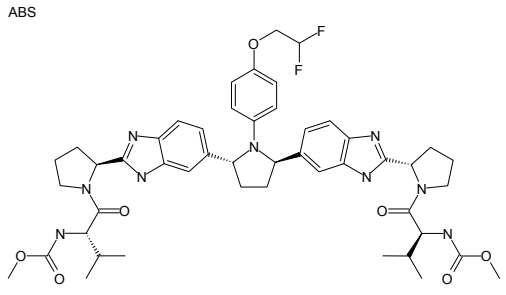
1H RMN (400 MHz, CDCl3) □ ppm 10,49 (d, J = 9,0 Hz, 1 H), 10,38 (s, 1 H), 7,70 (d, J = 8,1 Hz, 1 H), 7,51 (s, 1 H), 7,35 (d, J = 8,3 Hz, 1 H), 7,12 (dd, J = 10,9, 6,3 Hz, 3 H), 6,69 (dd, J = 9,4, 5,7 Hz, 1 H), 6,13 (d, J = 7,2 Hz, 1 H), 6,00 (s, 1 H), 5,41 (m, 4 H), 5,27 (m, 2 H), 4,34 (m, 2 H), 4,06 (d, J = 6,6 Hz, 1 H), 3,85 (m, 2 H), 3,73 (s, 6 H), 3,64 (m, 2 H), 3,08 (m, 2 H), 2,61 (m, 2 H), 2,34 (m, 2 H), 2,19 (m, 4 H), 1,96 (m, 2 H), 1,79 (m, 2 H), 1,64 (m, 4 H), 0,92 (m, 12 H); MS (ESI+) m/z (abundancia relativa) 868 (100, M+H), 869 (43).



Ejemplo 4.10

{(2S)-1-[(2S)-2-{6-[(2R,5R)-1-(4-etoxifenil)-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-benzimidazol-6-il}pirrolidin-2-il]-1H-benzimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

^{1}H RMN (400 MHz, DMSO-d6) δ ppm 0,92 - 0,75 (m, 12H), 1,21 - 1,10 (m, 3H), 1,33 - 1,21 (m, 1H), 1,76 - 1,64 (m, 2H), 2,06 - 1,85 (m, 7H), 2,28 - 2,08 (m, 4H), 3,54 (s, 6H), 3,73 (q, J = 7,0, 2H), 3,81 (s, 4H), 4,11 - 3,99 (m, 2H), 5,18 - 5,06 (m, 2H), 5,33 (s, 2H), 6,24 (d, J = 8,9, 2H), 6,51 (dt, J = 4,9, 9,4, 2H), 7,04 (t, J = 7,7, 2H), 7,34 - 7,18 (m, 4H), 7,36 (d, J = 8,2, 1H), 7,44 (d, J = 8,2, 1H), 12,02 (s, 2H); MS (ESI) m/z 876 $(M+H)^+$, 874 $(M-H)^-$.

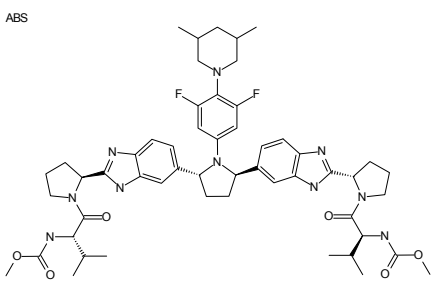


Ejemplo 4.11

{(2S)-1-[(2S)-2-{6-[(2R,5R)-1-[4-(2,2-difluoroetoxi)fenil]-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-benzimidazol-6-il}pirrolidin-2-il]-1H-benzimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

^{1}H RMN (400 MHz, metanol-d4) δ ppm 0,85 (dd, J = 6,7, 20,0, 12H), 1,88 - 1,75 (m, 2H), 2,06 - 1,95 (m, 3H), 2,22 - 2,06 (m, 3H), 2,34 - 2,23 (m, 2H), 2,49 - 2,34 (m, 2H), 2,71 - 2,56 (m, 2H), 3,64 (s, 6H), 4,13 - 3,76 (m, 6H), 4,22 (dd, J = 5,4, 10,3, 1H), 5,28 - 5,17 (m, 2H), 5,37 (t, J = 6,4, 2H), 5,96 (tt, J = 3,9, 55,2, 1H), 6,31 (t, J = 9,7, 2H), 6,60 - 6,51 (m, 2H), 6,98 (d, J = 8,4, 1H), 7,23 (d, J = 8,3, 2H), 7,35 (d, J = 17,8, 2H), 7,50 (d, J = 8,3, 2H); MS (ESI) m/z 912 $(M+H)^+$, 910 $(M-H)^-$.

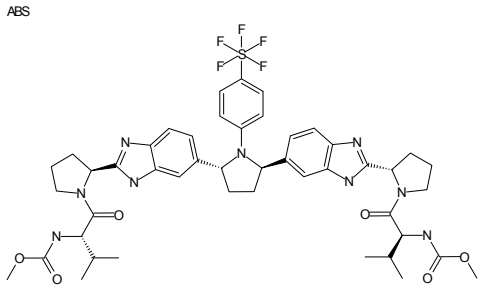
ABS



Ejemplo 4.12

{(2S)-1-[(2S)-2-{6-[(2R,5R)-1-[4-(3,5-dimetilpiperidin-1-il)-3,5-difluorofenil]-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-benzimidazol-6-il}pirrolidin-2-il]-1H-benzimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

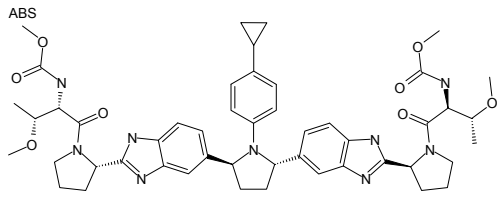
^{1}H RMN (400 MHz, DMSO-d6) δ ppm 0,50 (q, J = 11,9, 1H), 0,97 - 0,64 (m, 18H), 1,32 - 1,20 (m, 2H), 1,81 - 1,46 (m, 5H), 2,09 - 1,80 (m, 6H), 2,32 - 2,13 (m, 5H), 2,75 (dd, J = 10,0, 40,2, 2H), 3,18 - 3,05 (m, 1H), 3,54 (s, 6H), 3,82 (s, 4H), 4,14 - 3,95 (m, 2H), 5,14 (s, 2H), 5,36 (d, J = 7,2, 2H), 5,88 (d, J = 12,8, 2H), 7,14 - 7,02 (m, 2H), 7,19 (s, 1H), 7,33 - 7,23 (m, 3H), 7,41 (d, J = 8,2, 1H), 7,49 (d, J = 8,2, 1H), 12,37 - 11,98 (m, 2H); MS (ESI) m/z 979 $(M+H)^+$.



Ejemplo 4.13

{(2S)-1-[(2S)-2-(6-{(2R,5R)-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-benzimidazol-6-il}-1-[4-(pentafluoro-lambda~6~-sulfanil)fenil]pirrolidin-2-il}-1H-benzimidazol-2-il)pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

^{1}H RMN (400 MHz, DMSO-d6) ppm 0,92 - 0,69 (m, 12H), 2,08 - 1,61 (m, 8H), 2,20 (s, 4H), 3,53 (s, 6H), 3,82 (s, 4H), 4,05 (t, J = 8,0, 2H), 5,13 (dt, J = 4,9, 9,8, 2H), 5,49 (dd, J = 10,8, 15,8, 2H), 6,37 (d, J = 8,6, 2H), 7,13 - 6,81 (m, 3H), 7,20 (d, J = 8,8, 1H), 7,28 (dd, J = 4,6, 9,9, 3H), 7,45 - 7,34 (m, 4H), 7,48 (d, J = 8,2, 1H), 12,16 (dd, J = 22,6, 68,2, 2H); MS (ESI) m/z 958 $(M+H)^+$, 956 $(M-H)^-$.

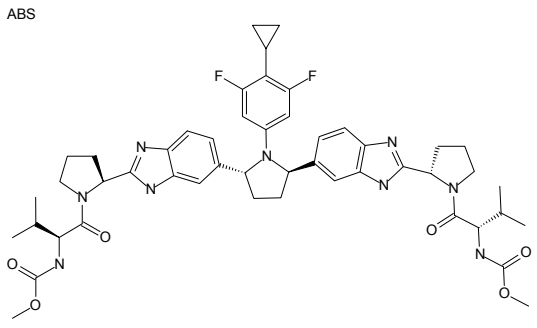


Ejemplo 4.14

{(2S,3R)-1-[(2S)-2-{5-[(2S,5S)-1-(4-ciclopropilfenil)-5-(2-{(2S)-1-[N-(metoxicarbonil)-O-metil-L-threonil]pirrolidin-2-il}-1H-benzimidazol-5-il)pirrolidin-2-il]-1H-benzimidazol-2-il}pirrolidin-1-il]-3-metoxi-1-oxobutan-2-il}carbamato de metilo

1H RMN (400 MHz, DMSO- d6) ppm 0,37 (m, 2 H) 0,68, (s, 2 H) 1,08 (d, 6 H) 1,54 -1,64 (m, 2 H) 1,69 (s, 2 H) 1,99 (s, 4 H) 2,17 (s, 7 H) 3,18 (s, 6 H) 3,42 - 3,53 (m, 2 H) 3,54 (s, J=1,41 Hz, 6 H) 3,84 (s, 3 H) 4,28 (s, 2 H) 5,12 (s, 2 H) 5,34 (s, 2 H) 6,22 (s, 2 H) 6,61 (s,

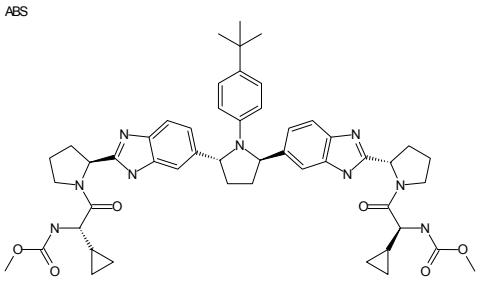
2 H) 7,05 (s, 2 H) 7,16 (s, 2 H) 7,36 (s, 2 H) 11,97 (s, 1 H),12,08 (s, 1H); MS (ESI+) m/z 904,5 (M+H)+, (ESI-) m/z 902,3 (M-H)-.



Ejemplo 4.15

{(2S)-1-[(2S)-2-{6-[(2R,5R)-1-(4-ciclopropil-3,5-difluorofenil)-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-benzimidazol-6-il}pirrolidin-2-il]-1H-benzimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

1H RMN (400 MHz, CDCl3) δ ppm 10,47 (s ancho, 1H) 10,30-10,41 (s ancho, 1H) 7,69 (s ancho, 1H) 7,49 (s, 1H) 7,30-7,43 (s ancho, 1H) 7,04-7,20 (m, 3H) 5,75-5,89 (m, 2H) 5,37 (m, 4H) 5,23 (s, 2H) 4,34 (t, 2H) 3,83 (m, 2H) 3,71 (s, 6H) 3,56-3,67 (m, 2H) 3,11 (m, 2H) 2,58 (s ancho, 2H) 2,33 (m, 2H) 2,08-2,27 (m, 4H) 2,01 (m, 2H) 1,78 (s ancho, 2H) 0,82-0,96 (m, 12H) 0,71 (m, 4H).

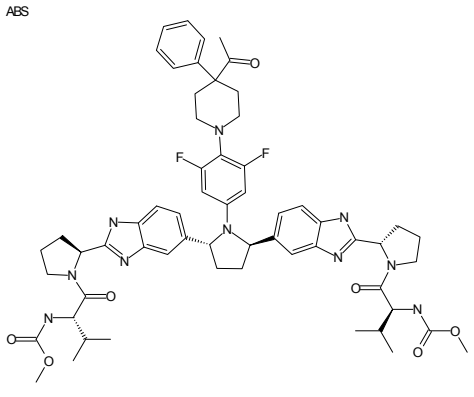


Ejemplo 4.16

([(2R,5R)-1-(4-tert-butilfenil)pirrolidin-2,5-diil]bis{1H-benzimidazol-6,2-diil(2S)pirrolidin-2,1-diil[(1S)-1-ciclopropil-2-oxoetano-2,1-diil]})biscarbamato de dimetilo

^{1}H RMN (500 MHz, DMSO-d6) δ ppm 0,48 - 0,24 (m, 7H), 0,89 - 0,81 (m, 1H), 1,01 (s, 3H), 1,07 (s, 6H), 1,14 (dd, J = 8,7, 16,6, 1H), 1,32 - 1,17 (m, 4H), 1,75 - 1,64 (m, 1H),

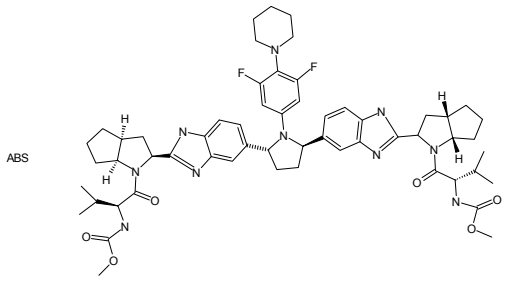
2,05 - 1,78 (m, 4H), 2,24 - 2,09 (m, 3H), 2,45 - 2,39 (m, 2H), 3,21 - 3,12 (m, 1H), 3,53 (s, 6H), 3,72 - 3,63 (m, 2H), 3,76 (s, 2H), 4,03 - 3,85 (m, 2H), 5,17 - 5,04 (m, 1H), 5,44 - 5,26 (m, 2H), 6,26 (d, J = 8,8, 1H), 6,95 - 6,81 (m, 2H), 7,06 - 6,95 (m, 1H), 7,09 (t, J = 8,3, 1H), 7,20 (d, J = 4,3, 1H), 7,35 - 7,25 (m, 1H), 7,55 - 7,36 (m, 4H), 12,28 - 11,84 (m, 2H); MS (ESI+) m/z 884 $(M+H)^+$, (ESI-) m/z 882 $(M-H)^-$.



Ejemplo 4.17

{(2S)-1-[(2S)-2-{5-[(2R,5R)-1-[4-(4-acetil-4-fenilpiperidin-1-il)-3,5-difluorofenil]-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-benzimidazol-5-il}pirrolidin-2-il]-1H-benzimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

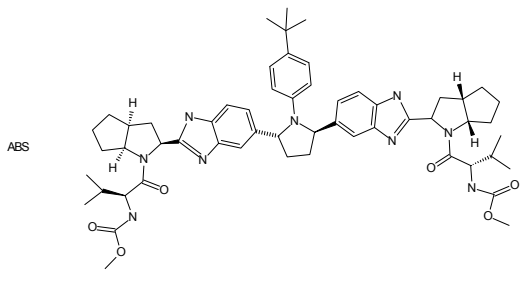
1H RMN (400 MHz, DMSO-d6) □ ppm 0,75 - 0,91 (m, 12 H) 1,68 (d, J=4,66 Hz, 2 H) 1,83 (s, 3 H) 1,87 - 2,38 (m, 16 H) 2,78 - 2,90 (m, 4 H) 3,54 (s, 6 H) 3,82 (s, 4 H) 4,06 (t, J=8,35 Hz, 2 H) 5,09 - 5,18 (m, 2 H) 5,27 - 5,41 (m, 2 H) 5,88 (d, J=12,90 Hz, 2 H) 7,02 - 7,51 (m, 13 H) 12,07 (d, J=16,91 Hz, 2 H); MS (ESI+) m/z 1070 (M+H)+.



Ejemplo 4.18

{(2S)-1-[(2S,3aS,6aS)-2-{5-[(2R,5R)-1-[3,5-difluoro-4-(piperidin-1-il)fenil]-5-{2-[(3aS,6aS)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}octahidrociclopenta[b]pirrol-2-il]-1H-benzimidazol-5-il}pirrolidin-2-il]-1H-benzimidazol-2-il}hexahidrociclopenta[b]pirrol-1(2H)-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

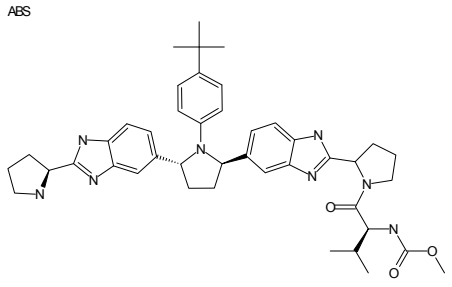
1H RMN (400 MHz, DMSO-d6) □ ppm 0,64 - 0,96 (m, 13 H) 1,31 - 2,18 (m, 21 H) 3,50 - 3,57 (m, 6 H) 3,93 - 4,07 (m, 2 H) 4,72 - 4,85 (m, 1 H) 5,13 (t, 1 H) 5,37 (s, 2 H) 5,90 (dd, 2 H) 7,06 (d, 2 H) 7,21 (s, 1 H) 7,33 (d, 1 H) 7,36 - 7,56 (m, J=8,13 Hz, 4 H) 11,96 (s, 1 H) 12,03 - 12,08 (m, 1 H) 12,24 (none, 1 H); MS (ESI+) m/z 1031,5 (M+H)+, (ESI-) m/z 1029,4 (M-H)-.



Ejemplo 4.19

{(2S)-1-[(2S,3aS,6aS)-2-{5-[(2R,5R)-1-(4-tert-butilfenil)-5-{2-[(3aS,6aS)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}octahidrociclopenta[b]pirrol-2-il]-1H-benzimidazol-5-il}pirrolidin-2-il]-1H-benzimidazol-2-il}hexahidrociclopenta[b]pirrol-1(2H)-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

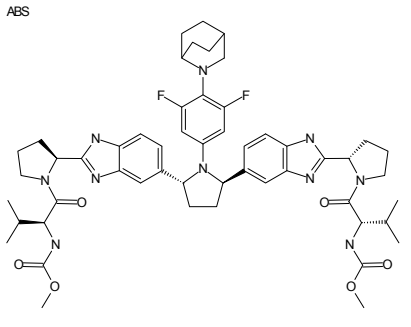
1H RMN (400 MHz, DMSO-d6) □ ppm 0,62 - 0,93 (m, 13 H) 1,42 - 2,16 (m, 25 H) 2,78 (s, 1 H) 3,54 (s, 6 H) 4,01 (s, 2 H) 4,77 (s, 1 H) 5,11 (t, J=8,08 Hz, 2 H) 5,35 (s, 2 H) 6,26 (d, J=8,67 Hz, 2 H) 6,83 - 6,97 (m, 2 H) 7,05 (s, 2 H) 7,21 (s, 1 H) 7,27 - 7,32 (m, 1 H) 7,34 - 7,55 (m, 4 H) 11,92 (s, 1 H) 12,01 (s, 1 H); MS (ESI+) m/z 968,5 (M+H)+, (ESI-) m/z 966,4 (M-H)-, 1011,7 (M+COOH-H)-.



Ejemplo 4.20

[(2S)-1-(2-{5-[(2R,5R)-1-(4-tert-butilfenil)-5-{2-[(2S)-pirrolidin-2-il]-1H-benzimidazol-5-il}pirrolidin-2-il]-1H-benzimidazol-2-il}pirrolidin-1-il)-3-metil-1-oxobutan-2-il]carbamato de metilo

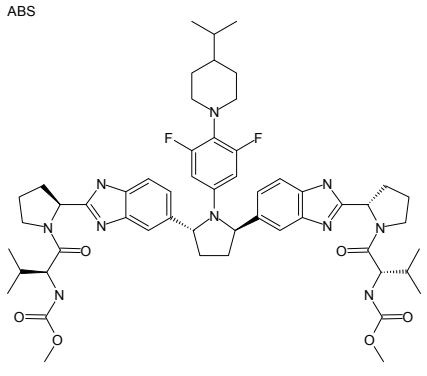
El compuesto del título puede prepararse haciendo reaccionar la amina con un equivalente de un ácido en lugar de dos. 1H RMN (400 MHz, DMSO-d6) □ ppm 0,67 - 0,90 (m, 6 H) 0,97 - 1,17 (m, 9 H) 1,53 - 2,46 (m, 13 H) 3,26 - 3,42 (m, J=11,39 Hz, 2 H) 3,54 (s, 3 H) 3,85 (d, J=4,34 Hz, 2 H) 4,07 - 4,13 (m, 1 H) 4,88 - 4,98 (m, 1 H) 5,15 - 5,23 (m, 1 H) 5,45 (d, J=7,16 Hz, 1 H) 5,50 (d, J=6,94 Hz, 1 H) 6,26 (d, J=8,78 Hz, 2 H) 6,92 (d, J=8,78 Hz, 2 H) 7,19 - 7,77 (m, 7 H) 9,15 (s, 1 H) 9,66 (s, 1 H); MS (ESI+) m/z 731 (M+H)+.



Ejemplo 4.21

{(2S)-1-[(2S)-2-{5-[(2R,5R)-1-[4-(2-azabiciclo[2,2,2]oct-2-il)-3,5-difluorofenil]-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-benzimidazol-5-il}pirrolidin-2-il]-1H-benzimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

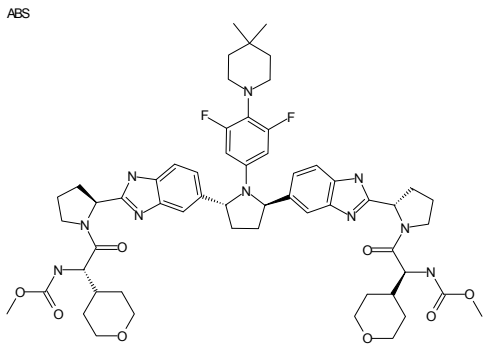
1H RMN (400 MHz, DMSO-d6) δ ppm 0,74 - 1,02 (m, 12 H), 1,41 - 2,27 (m, 26 H), 2,65 (s, 1 H), 3,05 - 3,26 (m, 3 H), 3,54 (s, 6 H), 4,06 (t, J=8,35 Hz, 2 H), 5,07 - 5,20 (m, 2 H), 5,26 - 5,45 (m, 2 H), 5,89 (d, J=12,36 Hz, 2 H), 7,00 - 7,14 (m, 2 H), 7,16 - 7,33 (m, 4 H), 7,44 (dd, J=32,42, 8,24 Hz, 2 H), 12,06 (dos s, 2 H); MS (ESI+) m/z 977 (M+H)+, (ESI-) m/z 975 (M-H)-.



Ejemplo 4.22

{(2S)-1-[(2S)-2-{5-[(2R,5R)-1-{3,5-difluoro-4-[4-(propan-2-il)piperidin-1-il]fenil}-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-benzimidazol-5-il}pirrolidin-2-il]-1H-benzimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

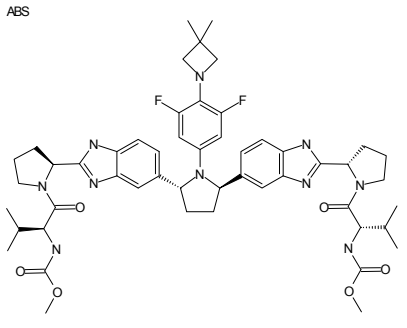
1H RMN (400 MHz, DMSO-d6) ppm 0,74 - 0,91 (m, 18 H), 0,91 - 1,05 (m, 1 H), 1,07 - 1,21 (m, 3 H), 1,31 - 1,43 (m, 1 H), 1,51 (d, J=11,17 Hz, 2 H), 1,63 - 1,77 (m, 2 H), 1,84 - 2,26 (m, 11 H), 2,72 - 2,88 (m, 4 H), 3,54 (s, 6 H) 3,82 (s ancho, 4 H), 4,06 (t, J=8,35 Hz, 2 H), 5,07 - 5,23 (m, 2 H), 5,29 - 5,45 (m, 2 H), 5,88 (d, J=12,79 Hz, 2 H), 7,02 - 7,12 (m, 2 H), 7,16 - 7,32 (m, 4 H), 7,41 (d, J=8,13 Hz, 1 H), 7,49 (d, J=8,13 Hz, 1 H), 12,07 (dos s, 2 H); MS (ESI+) m/z 994 (M+H)+.



Ejemplo 4.23

({(2R,5R)-1-[4-(4,4-dimetilpiperidin-1-il)-3,5-difluorofenil]pirrolidin-2,5-diil}bis{1H-benzimidazol-5,2-diil(2S)pirrolidin-2,1-diil[(1S)-2-oxo-1-(tetrahidro-2H-piran-4-il)etano-2,1-diil]})biscarbamato de dimetilo

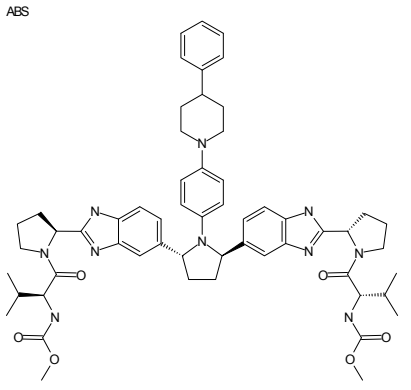
1H RMN (400 MHz, DMSO-d6) δ ppm 0,87 (s, 6 H), 1,18 - 1,34 (m, 9 H), 1,34 - 1,59 (m, 4 H), 1,61 - 1,93 (m, 5 H), 1,93 - 2,06 (m, 4 H), 2,09 - 2,27 (m, 4 H), 2,77 (s, 4 H), 2,90 - 3,27 (m, 4 H), 3,53 (s, 6 H), 3,62 (d, J=11,71 Hz, 1 H), 3,67 - 3,89 (m, 7 H), 4,14 (q, J=8,10 Hz, 2 H), 5,08 - 5,20 (m, 2 H), 5,30 - 5,43 (m, 2 H), 5,81 - 5,94 (m, 2 H), 7,03 - 7,52 (m, 8 H), 12,10 (dos s, 2 H); MS (ESI+) m/z 1063 (M+H)+, (ESI-) m/z 1061 (M-H)-.



Ejemplo 4.24

{(2S)-1-[(2S)-2-{5-[(2R,5R)-1-[4-(3,3-dimetilazetidin-1-il)-3,5-difluorofenil]-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-benzimidazol-5-il}pirrolidin-2-il]-1H-benzimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

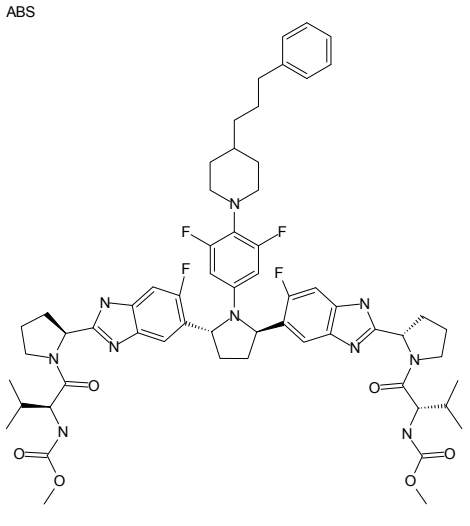
1H RMN (400 MHz, DMSO-d6) δ ppm 0,76-0,94 (m, 12 H), 1,13 (s, 6 H), 1,61-1,74 (m, 2 H), 1,81-2,28 (m, 9 H), 3,07-3,18 (m, 1 H), 3,49 (s, 4 H), 3,54 (s, 6 H), 3,82 (s ancho, 4 H), 4,07 (t, J=8,24 Hz, 2 H), 5,14 (t, J=7,54 Hz, 2 H), 5,25-5,40 (m, 2 H), 5,79-5,94 (m, 2 H), 7,01-7,07 (m, 2 H), 7,08-7,34 (m, 4 H), 7,39 (d, J=8,13 Hz, 1 H), 7,47 (d, J=8,24 Hz, 1 H), 12,05 (dos s, 2 H); MS (ESI+) m/z 951 (M+H)+.



Ejemplo 4.25

{(2S)-1-[(2S)-2-(5-{(2R,5R)-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-benzimidazol-5-il}-1-[4-(4-fenilpiperidin-1-il)fenil]pirrolidin-2-il}-1H-benzimidazol-2-il)pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

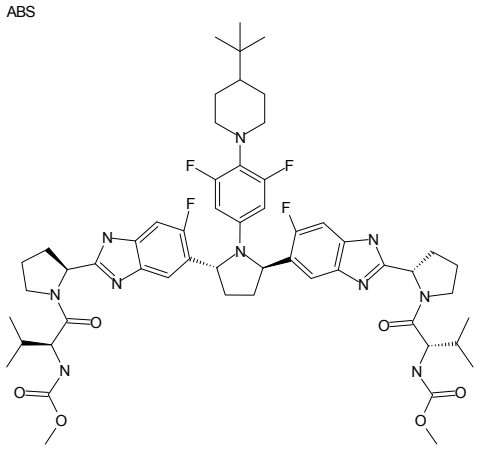
1H RMN (400 MHz, DMSO-d6) δ ppm 0,74 - 0,93 (m, 12 H), 1,61 - 1,79 (m, 6 H), 1,84 - 2,09 (m, 6 H), 2,11 - 2,27 (m, 4 H), 2,40 - 2,60 (m, 4 H), 3,35 (s, 3 H), 3,53 (s, 6 H), 3,82 (s, 4 H), 4,06 (t, J=8,29 Hz, 2 H), 5,08 - 5,19 (m, 2 H), 5,28 - 5,46 (m, 2 H), 6,26 (d, J=8,67 Hz, 2 H), 6,55 - 6,67 (m, 2 H), 7,06 (t, J=7,32 Hz, 2 H), 7,13 - 7,32 (m, 9 H), 7,37 (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 991 (M+H)+, (ESI-) m/z 989 (M-H)-.



Ejemplo 4.26

{(2S)-1-[(2S)-2-{5-[(2R,5R)-1-{3,5-difluoro-4-[4-(3-fenilpropil)piperidin-1-il]fenil}-5-{6-fluoro-2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-benzimidazol-5-il}pirrolidin-2-il]-6-fluoro-1H-benzimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

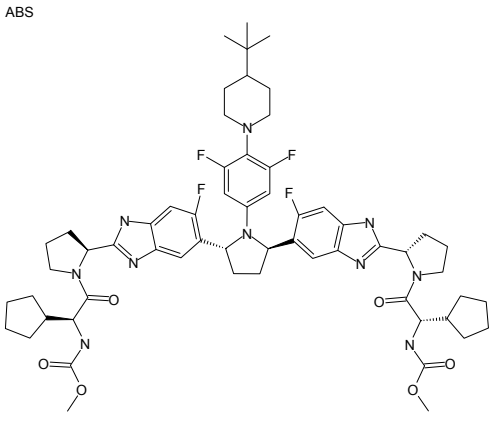
1H RMN (400 MHz, DMSO-d6) δ ppm 0,68 - 0,84 (m, 12 H), 0,98 - 1,30 (m, 8 H), 1,47 - 1,60 (m, 5 H), 1,63 - 2,07 (m, 9 H), 2,09 - 2,24 (m, 3 H), 2,78 (s, 4 H), 3,51 (s, 6 H), 3,71 - 3,87 (m, 4 H), 3,97 - 4,12 (m, 2 H), 5,03 - 5,17 (m, 2 H), 5,43 - 5,63 (m, 2 H), 5,78 - 5,96 (m, 2 H), 7,02 (dd, J=6,78, 2,33 Hz, 1 H), 7,08 - 7,19 (m, 4 H), 7,19 - 7,35 (m, 5 H), 7,39 (dd, J=11,28, 6,29 Hz, 1 H), 11,50 - 12,73 (m, 2 H); MS (ESI+) m/z 1105 (M+H)+; MS (ESI-) m/z 1103 (M-H)-.



Ejemplo 4.27

{(2S)-1-[(2S)-2-{5-[(2R,5R)-1-[4-(4-tert-butilpiperidin-1-il)-3,5-difluorofenil]-5-{6-fluoro-2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-benzimidazol-5-il}pirrolidin-2-il]-6-fluoro-1H-benzimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

1H RMN (400 MHz, DMSO-d6) δ ppm 0,69 - 0,76 (m, 4 H), 0,76 - 0,91 (m, 17 H), 1,13 - 1,27 (m, 3 H), 1,55 (d, J=11,39 Hz, 2 H), 1,67 - 2,09 (m, 9 H), 2,11 - 2,26 (m, 4 H), 2,72 - 2,94 (m, 4 H), 3,50 - 3,57 (m, 6 H), 3,62 - 3,86 (m, 5 H), 3,99 - 4,11 (m, 2 H), 5,03 - 5,17 (m, 2 H), 5,46 - 5,63 (m, 2 H), 5,87 (dd, J=12,52, 7,21 Hz, 2 H), 7,03 (d, J=6,40 Hz, 1 H), 7,13 (d, J=6,94 Hz, 1 H), 7,25 - 7,37 (m, 3 H), 7,40 (dd, J=11,17, 6,29 Hz, 1 H), 11,67 - 12,63 (m, 2 H); MS (ESI+) m/z 1043 (M+H)+; MS (ESI-) m/z 1041 (M-H)-.

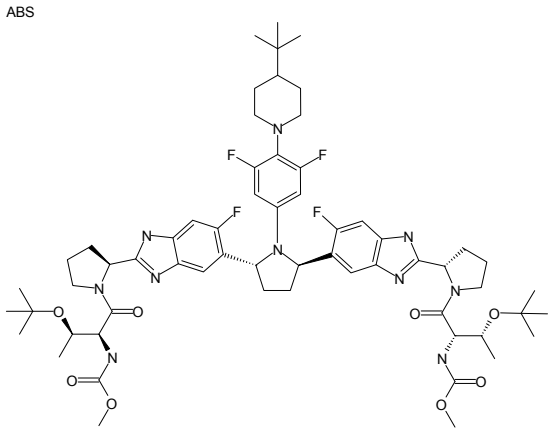


Ejemplo 4.28

({(2R,5R)-1-[4-(4-tert-butilpiperidin-1-il)-3,5-difluorofenil]pirrolidin-2,5-diil}bis{(6-fluoro-1H-benzimidazol-5,2-diil)(2S)pirrolidin-2,1-diil[(1S)-1-ciclopentil-2-oxoetano-2,1-diil]})biscarbamato de dimetilo

1H RMN (400 MHz, DMSO-d6) δ ppm 0,80 (s, 9 H), 1,08 - 1,63 (m, 24 H), 1,65 - 1,87 (m, 3 H), 1,92 - 2,25 (m, 10 H), 2,37 - 2,45 (m, 1 H), 2,73 - 2,93 (m, 4 H), 3,60 - 3,91 (m, 4 H), 4,13 (t, J=8,24 Hz, 2 H), 5,11 (d, J=6,83 Hz, 2 H), 5,45 - 5,63 (m, 2 H), 5,80 - 5,97 (m, 2 H), 6,95 - 7,08 (m, 1 H), 7,13 (d, J=6,61 Hz, 1 H), 7,34 (dd, J=10,25, 3,74 Hz, 1 H), 7,37 - 7,46 (m, 3 H), 11,73 - 12,50 (m, 2 H); MS (ESI+) m/z 1095 (M+H)+; MS (ESI-) m/z 1093 (M-H)-.

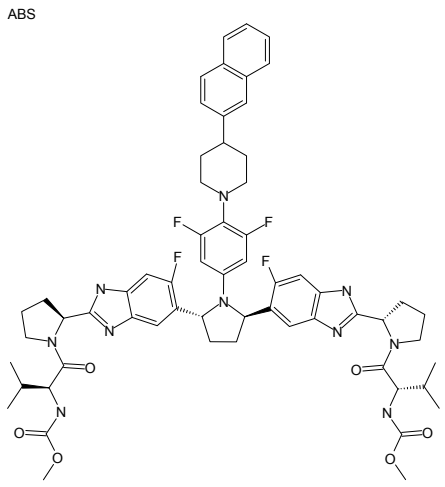
ABS



Ejemplo 4.29

{(2S,3R)-3-tert-butoxi-1-[(2S)-2-(5-{(2R,5R)-5-{2-[(2S)-1-{(2S,3R)-3-tert-butoxi-2-[(metoxicarbonil)amino]butanoil}pirrolidin-2-il]-6-fluoro-1H-benzimidazol-5-il}-1-[4-(4-tert-butilpiperidin-1-il)-3,5-difluorofenil]pirrolidin-2-il}-6-fluoro-1H-benzimidazol-2-il)pirrolidin-1-il]-1-oxobutan-2-il}carbamato de metilo

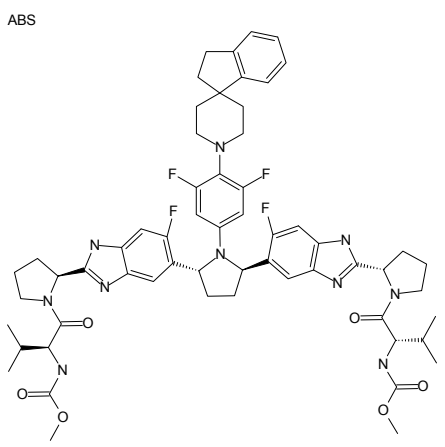
1H RMN (400 MHz, DMSO-d6) δ ppm 0,82 (d, J=14,64 Hz, 13 H), 0,88 - 0,96 (m, 4 H), 1,02 (s, 7 H), 1,12 (d, J=33,83 Hz, 11 H), 1,49 - 2,31 (m, 9 H), 2,69 - 2,93 (m, 4 H), 3,27 (s, 1 H), 3,50 - 3,57 (m, 6 H), 3,64 - 3,94 (m, 9 H), 4,03 - 4,31 (m, 3 H), 5,06 - 5,23 (m, 1 H), 5,38 - 5,69 (m, 2 H), 5,78 - 5,95 (m, 2 H), 6,46 - 6,63 (m, 1 H), 6,70 - 6,87 (m, 1 H), 6,92 - 7,04 (m, 1 H), 7,08 - 7,29 (m, 1 H), 7,34 (dd, J=10,63, 1,84 Hz, 1 H), 7,38 - 7,55 (m, 1 H), 11,40 - 12,88 (m, 2 H); MS (ESI+) m/z 1159 (M+H)+.



Ejemplo 4.30

{(2S)-1-[(2S)-2-{5-[(2R,5R)-1-{3,5-difluoro-4-[4-(2-naftil)piperidin-1-il]fenil}-5-{6-fluoro-2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-benzimidazol-5-il}pirrolidin-2-il]-6-fluoro-1H-benzimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

1H RMN (400 MHz, DMSO-d6) δ ppm 0,73 (d, J=6,51 Hz, 4 H), 0,76 - 0,85 (m, 8 H), 1,19 - 1,32 (m, 2 H), 1,69 - 2,08 (m, 12 H), 2,11 - 2,25 (m, 3 H), 2,67 - 2,78 (m, 1 H), 2,92 - 3,18 (m, 5 H), 3,52 (d, J=1,19 Hz, 6 H), 3,72 - 3,87 (m, 4 H), 3,99 - 4,11 (m, 2 H), 5,06 - 5,19 (m, 2 H), 5,49 - 5,67 (m, 2 H), 5,83 - 6,00 (m, 2 H), 7,01 - 7,09 (m, 1 H), 7,16 (d, J=7,05 Hz, 1 H), 7,25 - 7,37 (m, 3 H), 7,38 - 7,53 (m, 4 H), 7,68 - 7,93 (m, 4 H), 11,88 - 12,65 (m, 2 H); MS (ESI+) m/z 1113 (M+H)+; MS (ESI-) m/z 1111 (M-H)-.

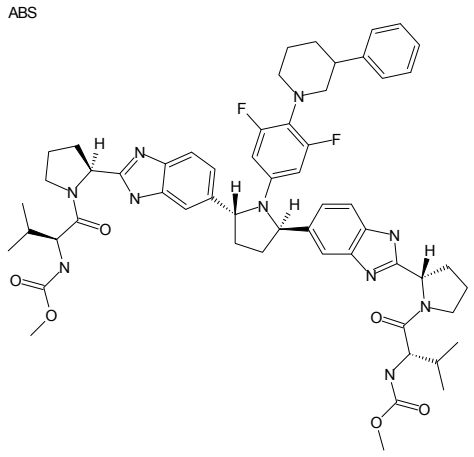


Ejemplo 4.31

{(2S)-1-[(2S)-2-{5-[(2R,5R)-1-[4-(2,3-dihidro-1'H-espiro[inden-1,4'-piperidin]-1'-il)-3,5-difluorofenil]-5-{6-fluoro-2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-benzimidazol-5-il}pirrolidin-2-il]-6-fluoro-1H-benzimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

1H RMN (400 MHz, CDCl3) δ ppm 10,53-10,63 (m, 1H) 10,31-10,41 (m, 1H) 7,43-7,52 (m, 1H) 7,30-7,40 (m, 1H) 7,10-7,25 (m, 5H) 6,92-7,00 (m, 1H) 5,86 (d, 2H) 5,23-5,51 (m, 6H) 4,26-4,40 (m, 2H) 3,77-3,91 (m, 2H) 3,68-3,72 (m, 6H) 3,56-3,66 (m, 2H) 2,83-3,26 (m, 8H) 1,81-2,61 (m, 16H) 0,71-1,10 (m, 12H); MS (ESI) m/z 1089 (M+H)+.

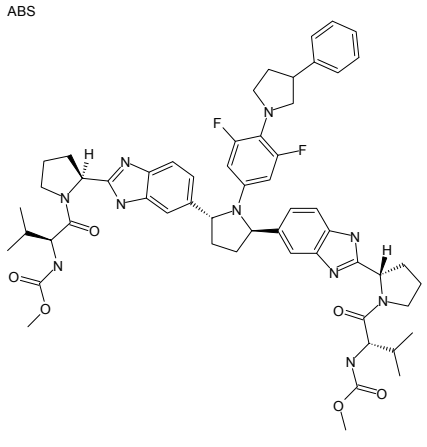
ABS



Ejemplo 4.32

{(2S)-1-[(2S)-2-{5-[(2R,5R)-1-[3,5-difluoro-4-(3-fenilpiperidin-1-il)fenil]-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-benzimidazol-6-il}pirrolidin-2-il]-1H-benzimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

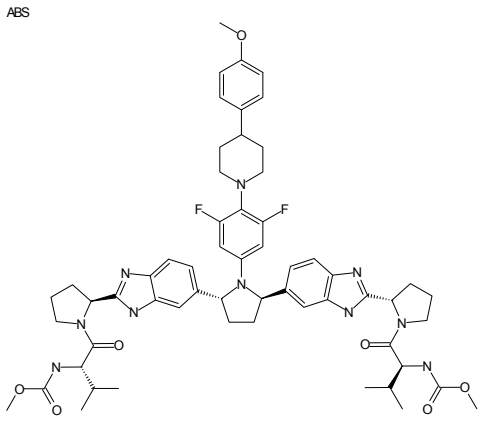
1H RMN (400 MHz, DMSO-d6) ppm 12,07 (s, 1 H), 12,01 (s, 1 H), 7,48 (d, J = 8,3 Hz, 1 H), 7,38 (m, 2 H), 7,20 (s, 8 H), 7,09 (m, 2 H), 5,90 (d, J = 12,9 Hz, 2 H), 5,36 (d, J = 7,5 Hz, 2 H), 5,14 (s, 2 H), 4,05 (t, J = 8,1 Hz, 2 H), 3,81 (s, 4 H), 3,54 (s, 6 H), 2,85 (s, 4 H), 2,18 (s, 5 H), 1,94 (m, 7 H), 1,61 (m, 5 H), 0,77 (m, 12 H); MS (ESI+) m/z (abundancia relativa) 1027 (100, M+H)+.



Ejemplo 4.33

{(2S)-1-[(2S)-2-{5-[(2R,5R)-1-[3,5-difluoro-4-(3-fenilpirrolidin-1-il)fenil]-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-benzimidazol-6-il}pirrolidin-2-il]-1H-benzimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

1H RMN (400 MHz, DMSO-d6) □ ppm 12,09 (d, J = 14,8 Hz, 2 H), 7,47 (m, 2 H), 7,45 (m, 2 H), 7,24 (m, 8 H), 7,08 (s, 2 H), 5,93 (d, J = 12,1 Hz, 2 H), 5,38 (s, 2 H), 5,15 (s, 2 H), 4,06 (t, J = 8,4 Hz, 2 H), 3,82 (s, 4 H), 3,53 (s, 6 H), 3,13 (m, 4 H), 2,19 (s, 4 H), 1,90 (m, 6 H), 1,70 (s, 2 H), 0,80 (m, 12 H); MS (ESI+) m/z (abundancia relativa) 1013 (100, M+H)+, 1014 (58).



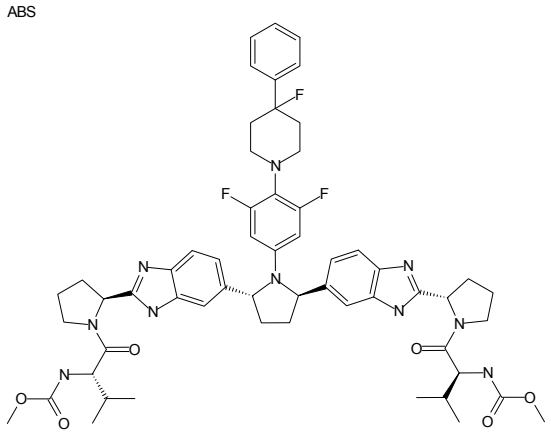
Ejemplo 4.34

{(2S)-1-[(2S)-2-{6-[(2R,5R)-1-{3,5-difluoro-4-[4-(4-metoxifenil)piperidin-1-il]fenil}-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-benzimidazol-6-

il}pirrolidin-2-il]-1H-benzimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

1H RMN (400 MHz, DMSO-d6) δ ppm 0,97 - 0,69 (m, 12H), 1,24 (s, 1H), 1,78 - 1,50 (m, 6H), 2,10 - 1,85 (m, 7H), 2,19 (s, 4H), 2,47 - 2,38 (m, 1H), 3,03 - 2,80 (m, 4H), 3,53 (s, 6H), 3,69 (s, 3H), 3,82 (s, 4H), 4,17 - 3,93 (m, 2H), 5,22 - 5,08 (m, 2H), 5,45 - 5,29 (m, 2H), 5,91 (d, J = 12,8, 2H), 6,81 (d, J = 8,7, 2H), 7,17 - 7,02 (m, 4H), 7,21 (s, 1H), 7,34 - 7,26 (m, 3H), 7,41 (d, J = 8,2, 1H), 7,50 (d, J = 8,2, 1H), 12,17 (dd, J = 19,9, 74,7, 2H); MS (ESI) m/z 1057 (M+H)+, 1055 (M-H)+.

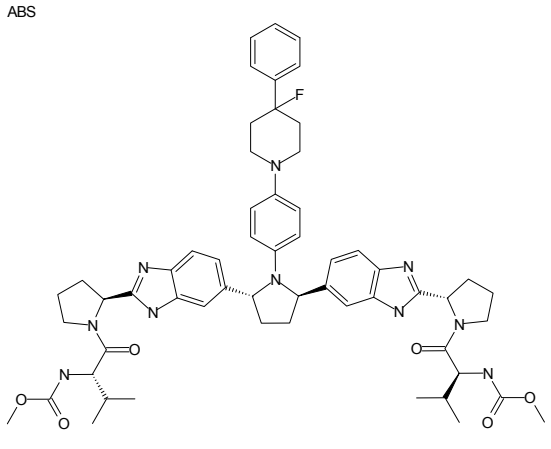
ABS



Ejemplo 4.35

{(2S)-1-[(2S)-2-{6-[(2R,5R)-1-[3,5-difluoro-4-(4-fluoro-4-fenilpiperidin-1-il)fenil]-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-benzimidazol-6-il}pirrolidin-2-il]-1H-benzimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

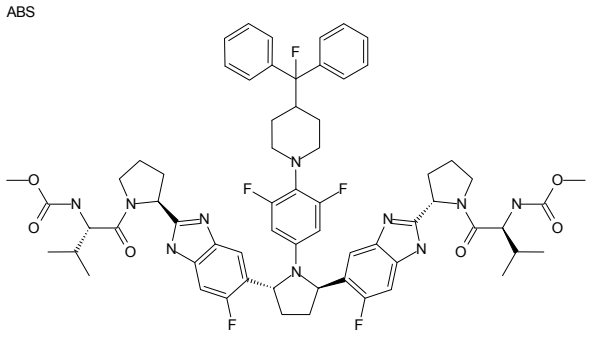
1H RMN (400 MHz, DMSO-d6) δ ppm 0,91 - 0,75 (m, 12H), 2,11 - 1,60 (m, 12H), 2,28 - 2,12 (m, 4H), 2,55 (d, J = 5,5, 2H), 2,84 - 2,71 (m, 2H), 3,28 - 3,06 (m, 2H), 3,53 (s, 6H), 3,83 (s, 4H), 4,11 - 3,99 (m, 2H), 5,19 - 5,09 (m, 2H), 5,45 - 5,30 (m, 2H), 5,94 (d, J = 12,8, 2H), 7,13 - 7,05 (m, 2H), 7,45 - 7,18 (m, 10H), 7,50 (d, J = 8,3, 1H), 12,11 (d, J = 15,2, 2H); MS (ESI) m/z 1045 (M+H)+, 1043 (M-H)+.



Ejemplo 4.36

{(2S)-1-[(2S)-2-{6-[(2R,5R)-1-[4-(4-fluoro-4-fenilpiperidin-1-il)fenil]-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-benzimidazol-6-il}pirrolidin-2-il]-1H-benzimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

1H RMN (400 MHz, DMSO-d6) δ ppm 0,92 - 0,74 (m, 12H), 1,23 (d, J = 3,9, 1H), 1,69 (d, J = 3,6, 2H), 2,09 - 1,80 (m, 9H), 2,26 - 2,09 (m, 5H), 2,81 - 2,69 (m, 2H), 3,26 - 3,10 (m, 3H), 3,53 (s, 6H), 3,89 - 3,74 (m, 4H), 4,05 (t, J = 8,4, 2H), 5,18 - 5,06 (m, 2H), 5,34 (d, J = 4,5, 2H), 6,27 (d, J = 8,7, 2H), 6,65 (dt, J = 4,2, 8,6, 2H), 7,06 (t, J = 7,8, 2H), 7,21 (s, 1H), 7,43 - 7,26 (m, 9H), 7,45 (d, J = 8,2, 1H), 12,04 (s, 2H); MS (ESI) m/z 1009 (M+H)+, 1007 (M-H)+.

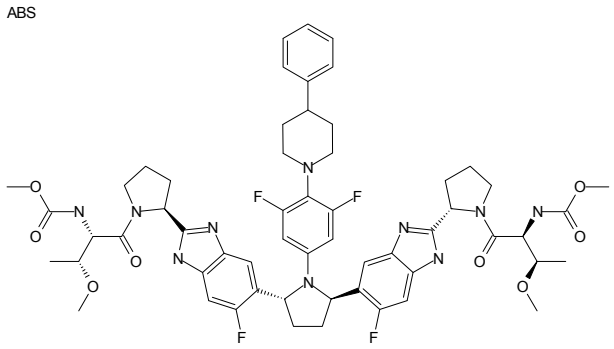


Ejemplo 4.37

{(2S)-1-[(2S)-2-{5-[(2R,5R)-1-(3,5-difluoro-4-{4-[fluoro(difenil)metil]piperidin-1-il}fenil)-5-{6-fluoro-2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-

benzimidazol-5-il}pirrolidin-2-il]-6-fluoro-1H-benzimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

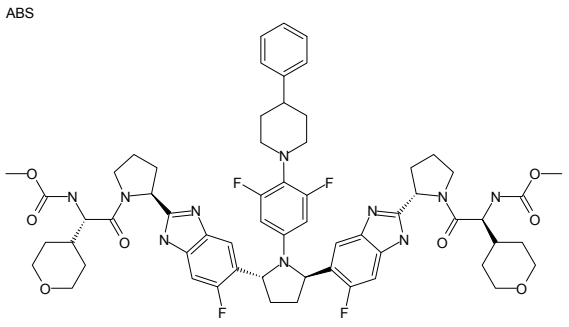
1H RMN (400 MHz, metanol-d4) δ ppm 0,99 - 0,69 (m, 12H), 1,42 - 1,26 (m, 3H), 1,55 (dd, J = 12,0, 24,4, 2H), 2,42 - 1,85 (m, 12H), 2,62 - 2,43 (m, 3H), 3,01 - 2,74 (m, 4H), 3,63 (s, 6H), 3,90 - 3,77 (m, 2H), 4,05 - 3,90 (m, 2H), 4,20 (d, J = 7,4, 1H), 5,24 - 5,08 (m, 2H), 5,52 (t, J = 5,8, 2H), 5,92 - 5,72 (m, 2H), 7,07 (s, 1H), 7,18 (t, J = 7,3, 2H), 7,29 (t, J = 7,5, 6H), 7,33 (s, 1H), 7,43 (d, J = 7,3, 4H); MS (ESI) m/z 1171 (M+H)+.



Ejemplo 4.38

{(2S,3R)-1-[(2S)-2-{5-[(2R,5R)-1-[3,5-difluoro-4-(4-fenilpiperidin-1-il)fenil]-5-(6-fluoro-2-{(2S)-1-[N-(metoxicarbonil)-O-metil-L-threonil]pirrolidin-2-il}-1H-benzimidazol-5-il)pirrolidin-2-il]-6-fluoro-1H-benzimidazol-2-il}pirrolidin-1-il]-3-metoxi-1-oxobutan-2-il}carbamato de metilo

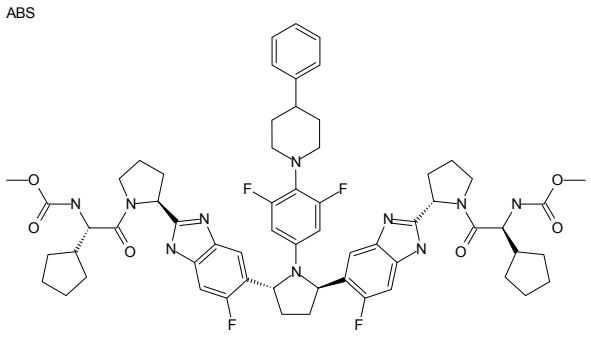
1H RMN (400 MHz, DMSO-d6) δ ppm 0,92 (d, J = 5,5, 2H), 1,04 (dd, J = 5,8, 12,0, 4H), 1,68 (s, 4H), 1,80 (s, 2H), 2,09 - 1,91 (m, 4H), 2,27 - 2,10 (m, 4H), 3,01 - 2,82 (m, 3H), 3,03 (s, 4H), 3,13 (s, 4H), 3,25 (s, 2H), 3,44 (dd, J = 6,5, 12,8, 3H), 3,53 (s, 6H), 3,81 (s, 3H), 4,31 - 4,14 (m, 2H), 5,17 - 5,02 (m, 2H), 5,66 - 5,41 (m, 2H), 5,97 - 5,80 (m, 2H), 7,13 - 6,99 (m, 2H), 7,19 - 7,13 (m, 2H), 7,31 - 7,19 (m, 5H), 7,38 (dd, J = 9,8, 26,3, 2H), 12,39 - 12,01 (m, 2H); MS (ESI) m/z 1095 (M+H)+, 1093 (M-H)+.



Ejemplo 4.39

({(2R,5R)-1-[3,5-difluoro-4-(4-fenilpiperidin-1-il)fenil]pirrolidin-2,5-diil}bis{(6-fluoro-1H-benzimidazol-5,2-diil)(2S)pirrolidin-2,1-diil[(1S)-2-oxo-1-(tetrahidro-2H-piran-4-il)etano-2,1-diil]})biscarbamato de dimetilo

1H RMN (400 MHz, DMSO-d6) δ ppm 1,37 - 1,07 (m, 6H), 1,56 - 1,36 (m, 4H), 1,73 - 1,60 (m, 4H), 1,78 (s, 4H), 2,06 - 1,93 (m, 4H), 2,26 - 2,06 (m, 4H), 3,26 - 2,81 (m, 8H), 3,52 (s, 6H), 3,91 - 3,60 (m, 8H), 4,12 (dd, J = 6,9, 15,8, 2H), 5,11 (s, 2H), 5,54 (d, J = 10,0, 2H), 5,99 - 5,81 (m, 2H), 7,05 (dd, J = 6,3, 23,5, 2H), 7,16 (t, J = 6,9, 1H), 7,31 - 7,20 (m, 5H), 7,45 - 7,30 (m, 4H), 12,23 (d, J = 83,3, 2H); MS (ESI) m/z 1147 (M+H)+.

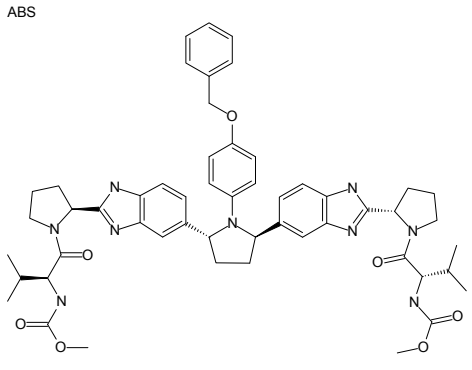


Ejemplo 4.40

({(2R,5R)-1-[3,5-difluoro-4-(4-fenilpiperidin-1-il)fenil]pirrolidin-2,5-diil}bis{(6-fluoro-1H-benzimidazol-5,2-diil)(2S)pirrolidin-2,1-diil[(1S)-1-ciclopentil-2-oxoetano-2,1-diil]})biscarbamato de dimetilo

1H RMN (400 MHz, DMSO-d6) δ ppm 1,61 - 1,10 (m, 18H), 1,67 (s, 4H), 1,90 - 1,72 (m, 2H), 2,13 - 1,93 (m, 6H), 2,18 (s, 4H), 3,08 - 2,86 (m, 4H), 3,17 (d, J = 5,1, 1H), 3,52 (s,

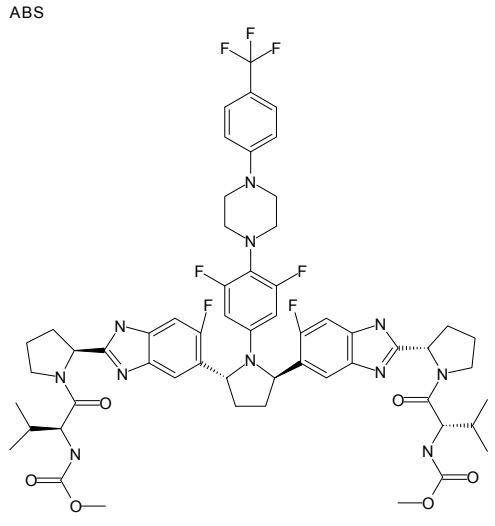
6H), 3,89 - 3,70 (m, 4H), 4,20 - 4,01 (m, 2H), 5,11 (s, 2H), 5,56 (d, J = 21,5, 2H), 5,96 - 5,83 (m, 2H), 7,04 (d, J = 6,7, 1H), 7,16 (t, J = 7,0, 2H), 7,31 - 7,20 (m, 4H), 7,39 (dt, J = 8,1, 25,5, 4H), 12,16 (d, J = 61,1, 2H); MS (ESI) m/z 1115 (M+H)+, 1113 (M-H)+.



Ejemplo 4.41

{(2S)-1-[(2S)-2-{5-[(2R,5R)-1-[4-(benciloxi)fenil]-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-benzimidazol-5-il}pirrolidin-2-il]-1H-benzimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

1H RMN (400 MHz, DMSO-d6) □ ppm 12,02 (s, 2H), 7,28 (m, 13H), 6,60 (m, 2H), 6,23 (m, 2H), 5,33 (m, 2H), 5,14 (m, 2H), 4,90 (m, 2H), 3,81 (m, 4H), 3,56 (s, 6H), 2,20 (m, 6H), 1,98 (m, 6H), 1,70 (m, 2H), 0,86 (m, 12H); MS (ESI) m/z 938 (M+H)+.

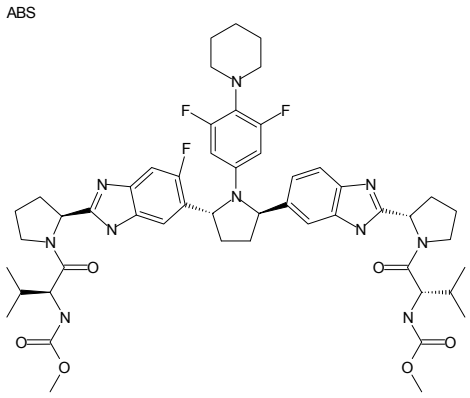


Ejemplo 4.42

{(2S)-1-[(2S)-2-{5-[(2R,5R)-1-(3,5-difluoro-4-{4-[4-(trifluorometil)fenil]piperazin-1-il}fenil)-5-{6-fluoro-2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-benzimidazol-5-il}pirrolidin-2-il]-6-fluoro-1H-benzimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

1H RMN (400 MHz, DMSO-d6) ppm 7,55 (m, 2H), 7,48 (d, J=8,8Hz, 2H), 7,34 (m, 2H), 7,18 (m, 2H), 7,04 (d, J=7,8Hz, 2H), 5,99 (m, 2H), 5,63 (m, 2H), 5,13 (m, 2H), 4,06 (m, 2H), 3,80 (m, 2H), 3,53 (s, 6H), 3,25 (m, 8H), 2,99 (m, 4H), 2,05 (m, 12H), 0,81 (m, 12H); MS (ESI) m/z 1132 (M+H)+.

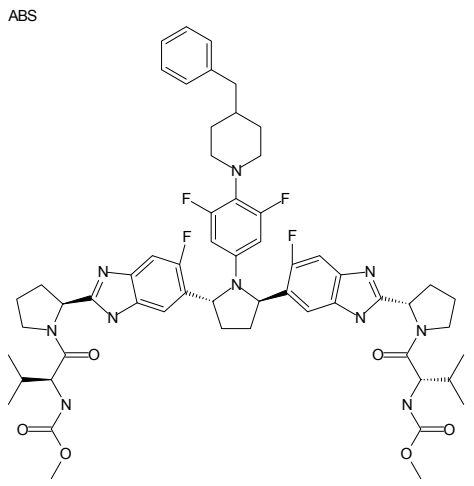
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Ejemplo 4.43

{(2S)-1-[(2S)-2-{6-[(2R,5R)-1-[3,5-difluoro-4-(piperidin-1-il)fenil]-5-{5-fluoro-2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-benzimidazol-6-il}pirrolidin-2-il]-1H-benzimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

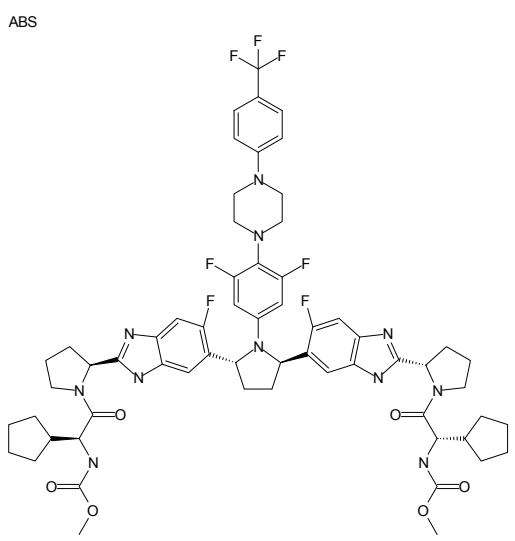
1H RMN (400 MHz, DMSO-d6) δ ppm 0,68 - 0,89 (m, 12 H) 1,34 - 1,50 (m, 6 H) 1,65 - 2,06 (m, 9 H) 2,12 - 2,24 (m, 4 H) 2,70 - 2,82 (m, 4 H) 3,52 (d, J=2,49 Hz, 6 H) 3,73 - 3,86 (m, 4 H) 3,99 - 4,08 (m, 2 H) 5,06 - 5,19 (m, 2 H) 5,26 - 5,43 (m, 1 H) 5,46 - 5,56 (m, 1 H) 5,86 (d, J=12,04 Hz, 2 H) 6,98 (d, J=6,51 Hz, 1 H) 7,02 - 7,11 (m, 1 H) 7,21 (d, J=6,94 Hz, 1 H) 7,26 - 7,35 (m, 2 H) 7,39 (d, J=8,35 Hz, 1 H) 7,45 - 7,51 (m, 1 H) 12,01 - 12,26 (m, 2 H); MS (ESI+) m/z 969 (M+H)+.



Ejemplo 4.44

{(2S)-1-[(2S)-2-{6-[(2R,5R)-1-[4-(4-bencilpiperidin-1-il)-3,5-difluorofenil]-5-{5-fluoro-2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-benzimidazol-6-il}pirrolidin-2-il]-5-fluoro-1H-benzimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

1H RMN (400 MHz, DMSO-d6) δ ppm 0,67 - 0,88 (m, 12 H) 1,22 (s, 12 H) 1,42 - 1,51 (m, 5 H) 1,73 - 2,04 (m, 12 H) 2,12 - 2,21 (m, 4 H) 2,72 - 2,81 (m, 5 H) 3,48 - 3,54 (m, 6 H) 3,72 - 3,83 (m, 3 H) 3,97 - 4,06 (m, 2 H) 5,05 - 5,13 (m, 2 H) 5,46 - 5,58 (m, 2 H) 5,79 - 5,89 (m, 2 H) 6,99 - 7,04 (m, 1 H) 7,09 - 7,16 (m, 5 H) 7,20 - 7,34 (m, 6 H) 7,35 - 7,42 (m, 1 H) 7,51 - 7,64 (m, 3 H) 12,10 (s, 1 H) 12,23 (s, 1 H); MS (ESI+) m/z 1077 (M+H)+.

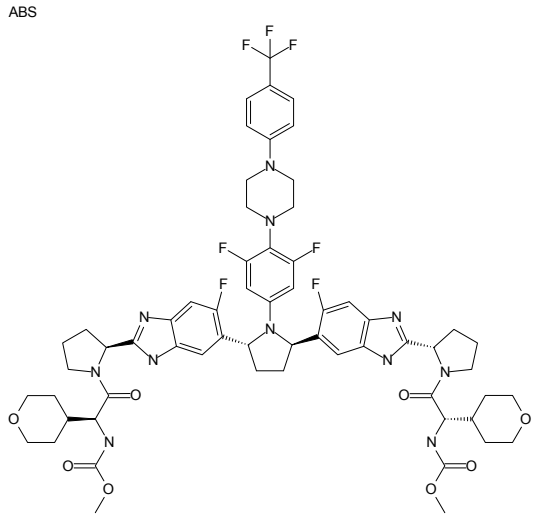


Ejemplo 4.45

([(2R,5R)-1-(3,5-difluoro-4-{4-[4-(trifluorometil)fenil]piperazin-1-il}fenil)pirrolidin-2,5-diil]bis{(5-fluoro-1H-benzimidazol-6,2-diil)(2S)pirrolidin-2,1-diil[(1S)-1-ciclopentil-2-oxoetano-2,1-diil]})biscarbamato de dimetilo

1H RMN (400 MHz, DMSO-d6) δ ppm 1,09 - 1,64 (m, 18 H) 1,71 - 1,86 (m, 2 H) 1,92 - 2,23 (m, 10 H) 2,91 - 3,03 (m, 5 H) 3,22 - 3,30 (m, 4 H) 3,52 (s, 6 H) 3,71 - 3,87 (m, 4 H) 4,12 (t, J=8,40 Hz, 2 H) 5,05 - 5,16 (m, 2 H) 5,48 - 5,65 (m, 2 H) 5,85 - 5,99 (m, 2 H) 7,03 (d, J=8,89 Hz, 3 H) 7,14 (d, J=6,29 Hz, 1 H) 7,30 - 7,38 (m, 1 H) 7,40 (d, J=9,54 Hz, 2 H) 7,46 (d, J=8,67 Hz, 2 H) 12,08 (s, 1 H) 12,20 (s, 1 H); MS (ESI+) m/z 1184 (M+H)+.

ABS

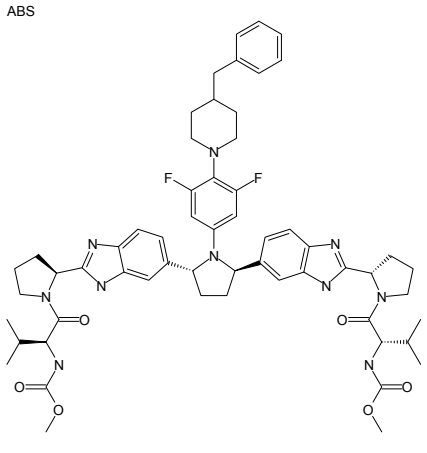


Ejemplo 4.46

([(2R,5R)-1-(3,5-difluoro-4-{4-[4-(trifluorometil)fenil]piperazin-1-il}fenil)pirrolidin-2,5-diil]bis{(5-fluoro-1H-benzimidazol-6,2-diil)(2S)pirrolidin-2,1-diil[(1S)-2-oxo-1-(tetrahidro-2H-piran-4-il)etano-2,1-diil]})biscarbamato de dimetilo

1H RMN (400 MHz, DMSO-d6) δ ppm 1,09 - 1,33 (m, 4 H) 1,38 - 1,54 (m, 4 H) 1,70 - 1,88 (m, 4 H) 1,92 - 2,05 (m, 4 H) 2,10 - 2,25 (m, 3 H) 2,95 - 3,03 (m, 4 H) 3,03 - 3,20 (m, 3 H) 3,21 - 3,29 (m, 4 H) 3,51 (s, 6 H) 3,62 - 3,89 (m, 6 H) 4,05 - 4,17 (m, 2 H) 5,06 - 5,15 (m, 2 H) 5,48 - 5,64 (m, 2 H) 5,83 - 5,98 (m, 2 H) 7,03 (d, J=8,67 Hz, 3 H) 7,07 (d, J=6,29 Hz, 1

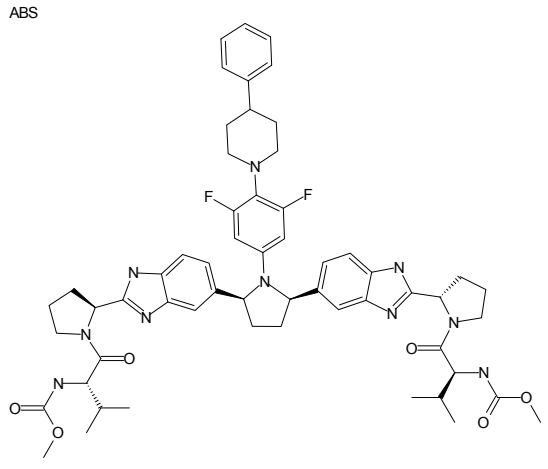
H) 7,29 - 7,42 (m, 3 H) 7,46 (d, J=8,78 Hz, 2 H) 12,11 (s, 1 H) 12,32 (s, 1 H); MS (ESI+) m/z 1216 (M+H)+.



Ejemplo 4.47

{(2S)-1-[(2S)-2-{6-[(2R,5R)-1-[4-(4-bencilpiperidin-1-il)-3,5-difluorofenil]-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-benzimidazol-6-il}pirrolidin-2-il]-1H-benzimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

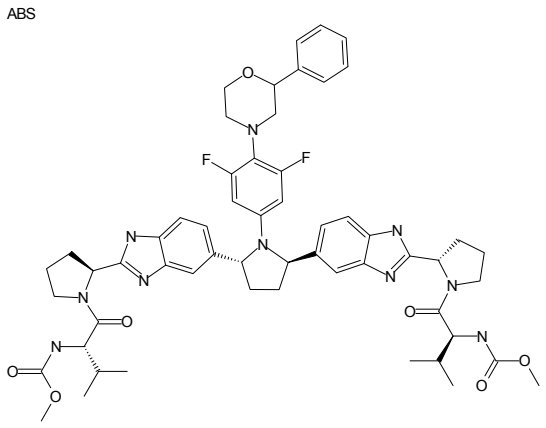
1H RMN (400 MHz, DMSO-d6) δ ppm 12,07 (d, J = 19,1, 2H), 7,48 (d, J = 8,3, 2H), 7,40 (d, J = 8,1, 2H), 7,34 – 7,10 (m, 8H), 7,07 (s, 2H), 5,87 (d, J = 12,3, 2H), 5,35 (s, 2H), 5,14 (s, 1H), 3,78 (d, J = 28,9, 2H), 3,54 (s, 6H), 2,76 (s, 3H), 2,19 (s, 4H), 2,07 – 1,80 (m, 6H), 1,68 (s, 2H), 1,46 (d, J = 10,4, 3H), 1,25 – 1,08 (m, 2H), 0,92 – 0,71 (m, 12H); MS (ESI+) m/z 1041,4 (M+H)+, (ESI-) m/z 1039,3 (M-H)-.



Ejemplo 4.48

{(2S)-1-[(2S)-2-{5-[(2S,5R)-1-[3,5-difluoro-4-(4-fenilpiperidin-1-il)fenil]-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-benzimidazol-5-il}pirrolidin-2-il]-1H-benzimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

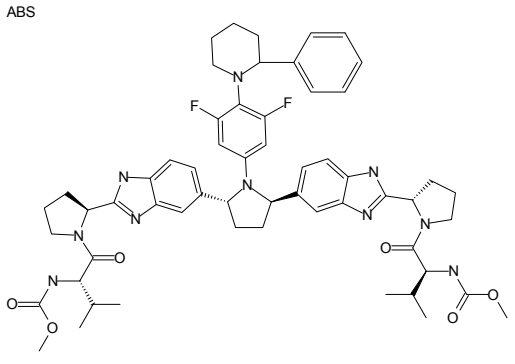
1H RMN (400 MHz, DMSO-d6) □ ppm 0,76 - 0,94 (m, 12 H), 1,60 - 2,30 (m, 14 H), 2,88 - 3,09 (m, 4 H), 3,54 (s, 6 H), 3,84 (s, 3 H), 4,02 - 4,15 (m, J=8,1, 8,1 Hz, 2 H), 4,77 - 4,97 (m, 2 H), 5,17 (d, J=2,9 Hz, 2 H), 5,95 - 6,10 (m, 2 H), 7,08 - 7,70 (m, 13 H), 12,09 - 12,23 (m, 2 H).



Ejemplo 4.49

{(2S)-1-[(2S)-2-{5-[(2R,5R)-1-[3,5-difluoro-4-(2-fenilmorfolin-4-il)fenil]-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-benzimidazol-5-il}pirrolidin-2-il]-1H-benzimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

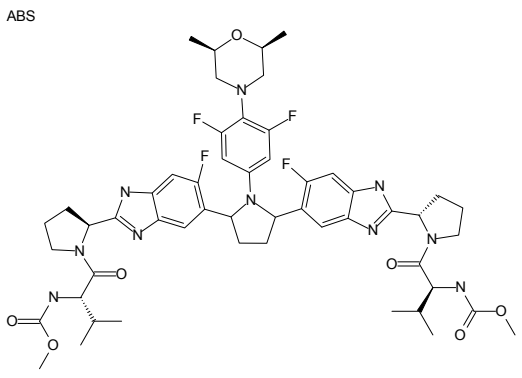
1H RMN (400 MHz, DMSO-d6) □ ppm 0,69 - 0,92 (m, 12 H), 1,69 (d, J=5,1 Hz, 2 H), 1,82 - 2,30 (m, 12 H), 2,70 - 3,16 (m, J=63,6 Hz, 6 H), 3,54 (s, 6 H), 3,81 (s, 3 H), 3,99 - 4,12 (m, 2 H), 4,47 (dd, J=9,1, 3,7 Hz, 1 H), 5,08 - 5,19 (m, 2 H), 5,29 - 5,48 (m, 2 H), 5,92 (d, J=13,4 Hz, 2 H), 7,07 (t, J=7,9 Hz, 2 H), 7,16 - 7,35 (m, J=0,8 Hz, 10 H), 7,40 (d, J=8,1 Hz, 1 H), 7,49 (d, J=8,3 Hz, 1 H), 12,06 (s, 1 H), 12,11 (s, 1 H); MS (APCI+) m/z 1030,1(M+H).



Ejemplo 4.50

{(2S)-1-[(2S)-2-{5-[(2R,5R)-1-[3,5-difluoro-4-(2-fenilpiperidin-1-il)fenil]-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-benzimidazol-5-il}pirrolidin-2-il]-1H-benzimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

1H RMN (400 MHz, DMSO-d6) □ ppm 0,81 - 1,01 (m, 12 H), 1,24 - 2,35 (m, 22 H), 3,60 (s, 6 H), 3,89 (s, 4 H), 3,94 - 4,20 (m, 3 H), 5,22 (s, 2 H), 5,30 (d, J=4,3 Hz, 2 H), 5,73 (dd, J=13,1, 3,6 Hz, 2 H), 6,92 - 7,44 (m, 13 H), 7,48 (d, J=8,1 Hz, 1 H), 12,08 (s, 1 H), 12,17 (s, 1 H); MS (APCI+) m/z 1028,2 (M+H)+.

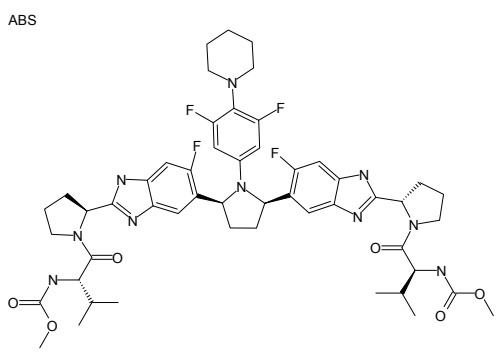


Ejemplo 4.51

[(2S)-1-{(2S)-2-[5-(1-{4-[(2R,6S)-2,6-dimetilmorfolin-4-il]-3,5-difluorofenil}-5-{6-fluoro-2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-benzimidazol-5-il}pirrolidin-2-il)-6-fluoro-1H-benzimidazol-2-il]pirrolidin-1-il}-3-metil-1-oxobutan-2-il]carbamato de metilo

1H RMN (400 MHz, DMSO-d6) □ ppm 0,67 - 0,90 (m, 12 H), 0,96 (s, 6 H), 1,01 - 1,31 (m, 2 H), 1,68 - 2,25 (m, 12 H), 3,51 (s, 6 H), 3,78 (s, 3 H), 4,01 (q, J=7,2 Hz, 2 H), 5,10 (d,

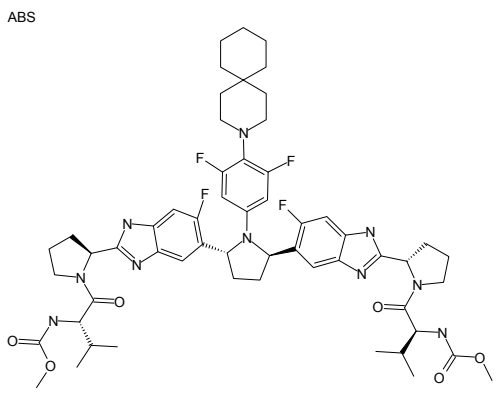
J=4,8 Hz, 2 H), 5,43 - 5,65 (m, 2 H), 5,79 - 5,97 (m, 2 H), 7,02 (d, J=5,3 Hz, 1 H), 7,11 (d, J=6,8 Hz, 1 H), 7,21 - 7,46 (m, 4 H), 12,11 (s, 1 H), 12,24 (s, 1 H); MS (ESI) m/z 1017,4 (M+H)+.



Ejemplo 4.52

{(2S)-1-[(2S)-2-{5-[(2S,5R)-1-[3,5-difluoro-4-(piperidin-1-il)fenil]-5-{6-fluoro-2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-benzimidazol-5-il}pirrolidin-2-il]-6-fluoro-1H-benzimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

1H RMN (400 MHz, DMSO-d6) ppm 0,72 - 0,94 (m, J=10,5, 10,5 Hz, 12 H), 1,36 - 1,58 (m, 6 H), 1,77 - 2,28 (m, 14 H), 2,83 (s, 4 H), 3,53 (s, 6 H), 3,82 (s, 4 H), 3,97 - 4,14 (m, 2 H), 4,92 - 5,07 (m, 2 H), 5,09 - 5,20 (m, 2 H), 5,83 - 6,02 (m, 2 H), 7,21 - 7,79 (m, 6 H), 12,14 - 12,44 (m, 2 H); MS (APCI+) m/z 987,8 (M+H)+.



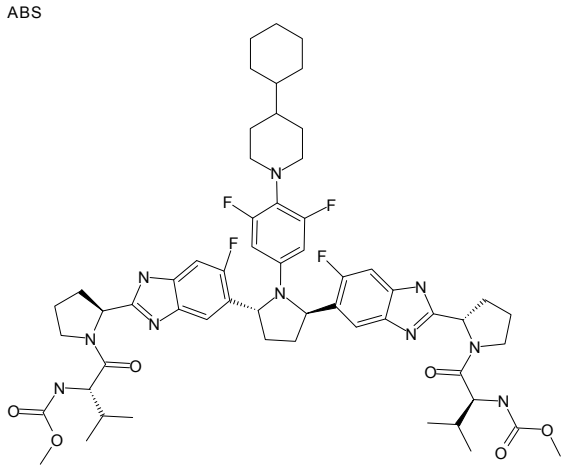
Ejemplo 4.53

{(2S)-1-[(2S)-2-{5-[(2R,5R)-1-[4-(3-azaespiro[5,5]undec-3-il)-3,5-difluorofenil]-5-{6-fluoro-2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-benzimidazol-5-

il}pirrolidin-2-il]-6-fluoro-1H-benzimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

1H RMN (400 MHz, DMSO-d6) □ ppm 0,64 - 0,94 (m, 12 H), 1,21 - 1,44 (m, 16 H), 1,68 - 2,25 (m, J=78,0 Hz, 12 H), 2,78 (s, 4 H), 3,53 (s, 6 H), 3,80 (s, 4 H), 4,04 (t, J=7,1 Hz, 2 H), 5,11 (s, 2 H), 5,55 (dd, J=19,8, 4,2 Hz, 2 H), 5,79 - 5,99 (m, 2 H), 7,03 (d, J=6,0 Hz, 1 H), 7,13 (d, J=6,5 Hz, 1 H), 7,24 - 7,48 (m, 4 H), 12,12 (s, 1 H), 12,24 (s, 1 H); MS (ESI) m/z 1055,4 (M+H)+.

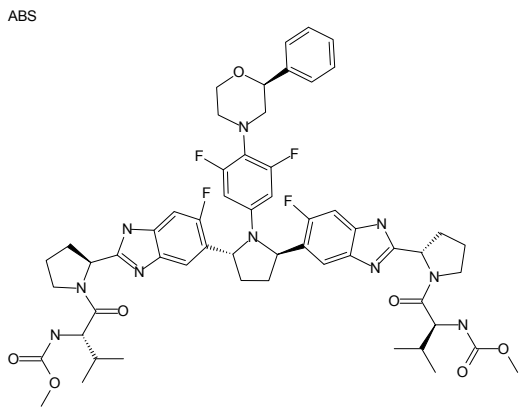
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Ejemplo 4.54

{(2S)-1-[(2S)-2-{5-[(2R,5R)-1-[4-(4-ciclohexilpiperidin-1-il)-3,5-difluorofenil]-5-{6-fluoro-2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-benzimidazol-5-il}pirrolidin-2-il]-6-fluoro-1H-benzimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

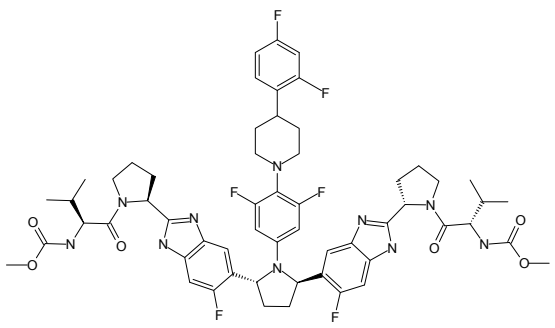
1H RMN (400 MHz, DMSO-d6) □ ppm 0,65 - 0,97 (m, 12 H), 0,98 - 1,33 (m, 10 H), 1,50 - 2,25 (m, 20 H), 2,72 - 2,91 (m, 4 H), 3,53 (s, 6 H), 3,79 (s, 4 H), 4,04 (t, J=8,1 Hz, 2 H), 5,11 (s, 2 H), 5,54 (dd, J=14,7, 6,7 Hz, 2 H), 5,79 - 5,97 (m, 2 H), 7,03 (d, J=6,7 Hz, 1 H), 7,13 (d, J=6,9 Hz, 1 H), 7,24 - 7,46 (m, 4 H), 12,11 (s, 1 H), 12,23 (s, 1 H); MS (ESI+) m/z 1069,5 (M+H)+.



Ejemplo 4.55

{(2S)-1-[(2S)-2-{5-[(2R,5R)-1-{3,5-difluoro-4-[(2S)-2-fenilmorfolin-4-il]fenil}-5-{6-fluoro-2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-benzimidazol-5-il}pirrolidin-2-il]-6-fluoro-1H-benzimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

1H RMN (400 MHz, DMSO-d6) □ ppm 0,60 - 0,95 (m, 12 H), 1,64 - 2,08 (m, 10 H), 2,09 - 2,25 (m, 4 H), 2,70 - 3,18 (m, 4 H), 3,53 (s, 6 H), 3,64 - 3,86 (m, 4 H), 3,91 (d, J=11,4 Hz, 1 H), 4,03 (t, J=8,2 Hz, 2 H), 4,48 (d, J=7,5 Hz, 1 H), 5,10 (s, 2 H), 5,43 - 5,69 (m, 2 H), 5,80 - 6,03 (m, 2 H), 7,03 (d, J=6,8 Hz, 1 H), 7,14 (d, J=6,7 Hz, 1 H), 7,20 - 7,45 (m, 10 H), 12,10 (s, 1 H), 12,24 (s, 1 H); MS (ESI+) m/z 1065,4 (M+H)+.

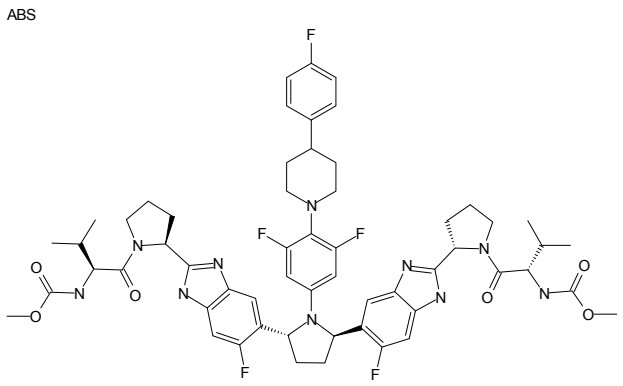


Ejemplo 4.56

{(2S)-1-[(2S)-2-{5-[(2R,5R)-1-{4-[4-(2,4-difluorofenil)piperidin-1-il]-3,5-difluorofenil}-5-{6-fluoro-2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-

benzimidazol-5-il}pirrolidin-2-il]-6-fluoro-1H-benzimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

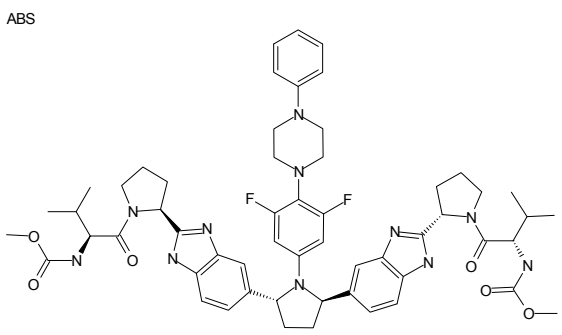
1H RMN (400 MHz, DMSO-d6) □ ppm 0,68 - 0,92 (m, 14 H), 1,58 - 2,08 (m, 11 H), 2,09 - 2,27 (m, 4 H), 2,71 - 3,14 (m, 6 H), 3,52 (s, 6 H), 3,68 - 3,89 (m, 4 H), 3,98 - 4,10 (m, 2 H), 5,05 - 5,17 (m, 2 H), 5,48 - 5,68 (m, 2 H), 5,83 - 5,99 (m, 2 H), 6,95 - 7,08 (m, 2 H), 7,09 - 7,21 (m, 2 H), 7,25 - 7,46 (m, 5 H), 12,06 - 12,39 (m, 2 H); MS (ESI+) m/z 1099,3 (M+H)+.



Ejemplo 4.57

{(2S)-1-[(2S)-2-{5-[(2R,5R)-1-{3,5-difluoro-4-[4-(4-fluorofenil)piperidin-1-il]fenil}-5-{6-fluoro-2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-benzimidazol-5-il}pirrolidin-2-il]-6-fluoro-1H-benzimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

1H RMN (400 MHz, DMSO-d6) □ ppm 0,67 - 0,93 (m, 14 H), 1,53 - 2,09 (m, 11 H), 2,10 - 2,25 (m, 4 H), 2,83 - 3,15 (m, 6 H), 3,53 (s, 6 H), 3,69 - 3,88 (m, 4 H), 3,98 - 4,10 (m, 2 H), 5,05 - 5,17 (m, 2 H), 5,48 - 5,67 (m, 2 H), 5,83 - 5,99 (m, 2 H), 6,99 - 7,20 (m, 4 H), 7,22 - 7,47 (m, 6 H), 12,02 - 12,47 (m, 2 H); MS (ESI+) m/z 1081,4 (M+H)+.

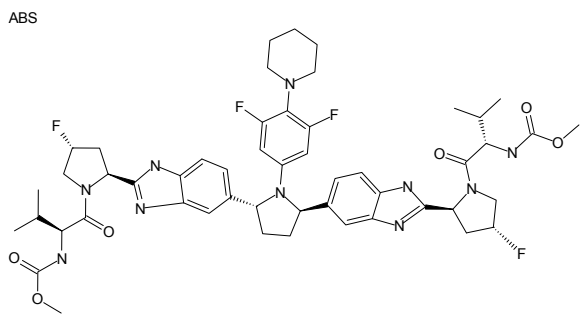


Ejemplo 4.58

{(2S)-1-[(2S)-2-{5-[(2R,5R)-1-[3,5-difluoro-4-(4-fenilpiperazin-1-il)fenil]-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-benzimidazol-5-il}pirrolidin-2-il]-1H-benzimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

1H RMN (400 MHz, DMSO-d6) ppm 0,72 - 0,95 (m, 12 H) 1,69 (s, 1 H) 1,84 - 2,11 (m, 2 H) 2,20 (s, 4 H) 2,97 (s, 4 H) 3,09 (s, 4 H) 3,54 (s, 6 H) 3,82 (s, 4 H) 4,03 (q, J=7,05 Hz, 6 H) 5,15 (s, 2 H) 5,39 (s, 2 H) 5,95 (s, 2 H) 6,75 (s, 2 H) 6,90 (d, J=8,24 Hz, 2 H) 7,08 (t, 2 H) 7,17 (t, J=7,92 Hz, 2 H) 7,30 (s, 2 H) 7,48 (s, 2 H) 7,66 (s, 2 H) 7,92 (s, 2 H) 12,09 (s, 2 H); MS (ESI+) m/z 1028,4, (ESI-) m/z 1026,4 (M-H)-.

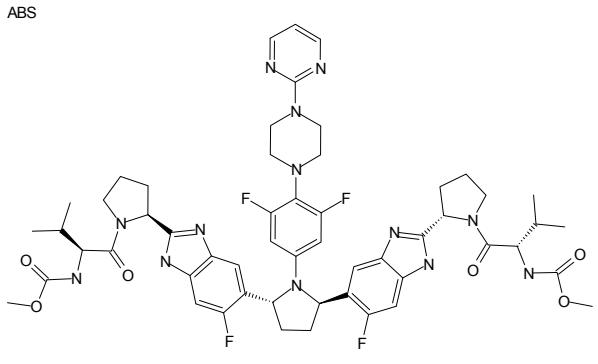
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Ejemplo 4.59

{(2S)-1-[(2S,4R)-2-{5-[(2R,5R)-1-[3,5-difluoro-4-(piperidin-1-il)fenil]-5-{2-[(2S,4R)-4-fluoro-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-benzimidazol-5-il}pirrolidin-2-il]-1H-benzimidazol-2-il}-4-fluoropirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

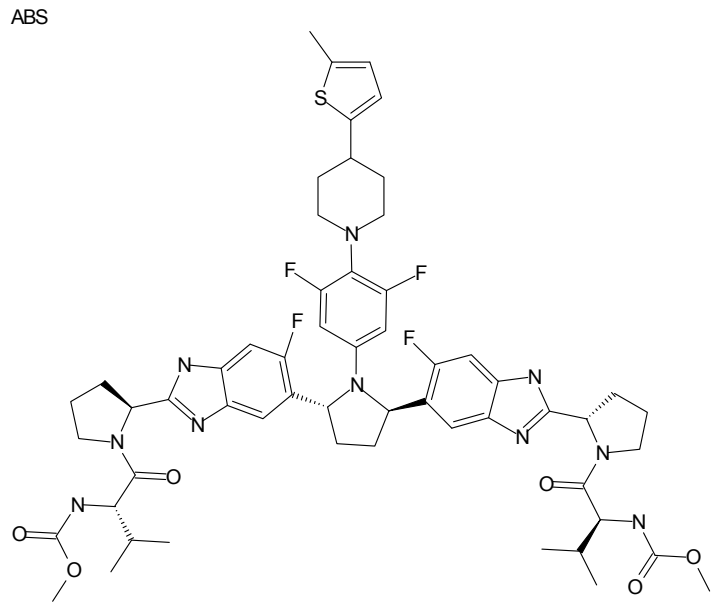
1H RMN (400 MHz, DMSO-d6) ppm 0,76 (m,16 H) 0,89 (m, 3 H) 1,45 (m, 5 H) 1,70 (m, 2 H) 1,85 (m, 1 H) 2,76 (d, 2 H) 3,17 (d, J=5,10 Hz, 2 H) 3,53 (s, 6 H) 3,87 - 4,13 (m, 4 H) 4,31 (m, 1 H) 5,17 (d, 2 H) 5,36 (m, 3 H) 5,57 (s, 1 H) 5,89 (d, 2 H) 7,09 (m, 2 H) 7,18 - 7,25 (m, 1 H) 7,29 (m, 3 H) 7,48 (m, 3 H) 12,22 (s, 2 H); MS (ESI+) m/z 987,4, (ESI-) m/z 985,2 (M-H)-.



Ejemplo 4.60

{(2S)-1-[(2S)-2-{5-[(2R,5R)-1-{3,5-difluoro-4-[4-(pirimidin-2-il)piperazin-1-il]fenil}-5-{6-fluoro-2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-benzimidazol-5-il}pirrolidin-2-il]-6-fluoro-1H-benzimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

1H RMN (400 MHz, DMSO-d6) ppm 0,67 - 0,93 (m, 12 H) 1,99 (m, 16 H) 2,18 (m, 4 H) 2,87 (m, 4 H) 3,53 (s, 6 H) 3,56 m, 2H) 3,74 (m, 10 H) 5,11 (m, 2 H) 5,53 (m, 2 H) 5,90 (m, 2 H) 6,60 (t, J=4,72 Hz, 1 H) 7,04 (m, 2 H) 7,32 (m, 4 H) 8,33 (d, J=4,77 Hz, 2 H) 12,14 (s, 1 H) 12,22 (s, 1H); MS (ESI+) m/z 1066,4, (ESI-) m/z 1064,1 (M-H)-.



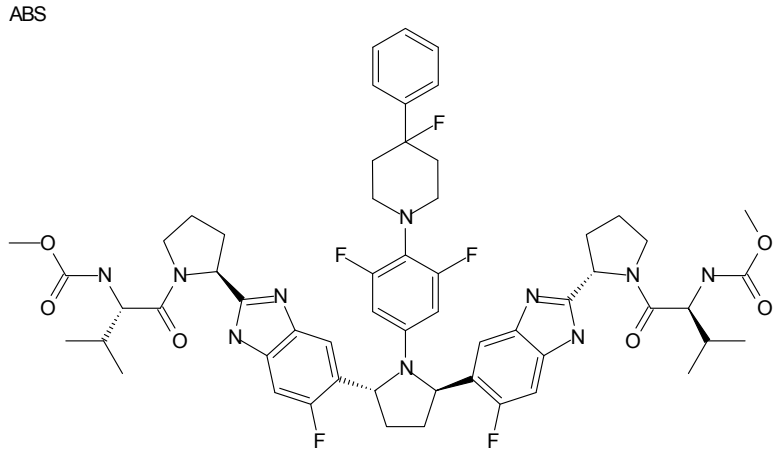
Ejemplo 4.61

{(2S)-1-[(2S)-2-{5-[(2R,5R)-1-{3,5-difluoro-4-[4-(5-metil-2-tienil)piperidin-1-il]fenil}-5-{6-fluoro-2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-

benzimidazol-5-il}pirrolidin-2-il]-6-fluoro-1H-benzimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

1H RMN (400 MHz, DMSO-D6) □ ppm 0,71 - 0,98 (m, 12 H), 1,49 - 2,31 (m, 18 H), 2,42 (s, 3 H), 2,87 - 3,11 (m, J=14,1 Hz, 5 H), 3,59 (s, 6 H), 3,77 - 3,94 (m, J=9,1 Hz, 4 H), 4,05 - 4,17 (m, 2 H), 5,08 - 5,26 (m, 2 H), 5,53 - 5,74 (m, 2 H), 5,89 - 6,05 (m, 2 H), 6,64 (d, J=2,4 Hz, 1 H), 6,68 (d, J=3,5 Hz, 1 H), 7,04 - 7,14 (m, 1 H), 7,16 - 7,25 (m, 1 H), 7,31 - 7,53 (m, 4 H), 12,09 - 12,23 (m, 1 H), 12,26 - 12,41 (m, 1 H); MS (ESI) m/z 1083,3 (M+H).

ABS

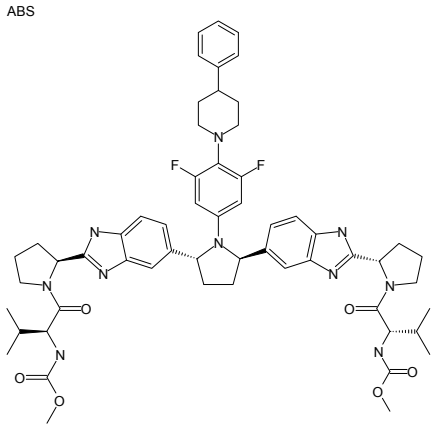


Ejemplo 4.62

{(2S)-1-[(2S)-2-{5-[(2R,5R)-1-[3,5-difluoro-4-(4-fluoro-4-fenilpiperidin-1-il)fenil]-5-{6-fluoro-2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-benzimidazol-5-il}pirrolidin-2-il]-6-fluoro-1H-benzimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

1H RMN (400 MHz, DMSO) δ 0,84 - 0,69 (m, 12H), 0,90 - 0,84 (m, 2H), 1,93 - 1,76 (m, 7H), 2,00 (dd, J = 6,8, 14,5, 8H), 2,23 - 2,12 (m, 5H), 3,52 (s, 6H), 3,87 - 3,73 (m, 4H), 4,08 - 3,97 (m, 2H), 5,16 - 5,06 (m, 2H), 5,65 - 5,48 (m, 2H), 5,99 - 5,86 (m, 2H), 7,06 (d, J = 6,7, 1H), 7,15 (d, J = 6,9, 1H), 7,31 (d, J = 7,0, 3H), 7,36 (d, J = 7,7, 2H), 7,41 (t, J = 7,6, 4H), 12,19 (d, J = 44,3, 2H). MS (ESI) m/z 1081 $(M+H)^+$.

ABS

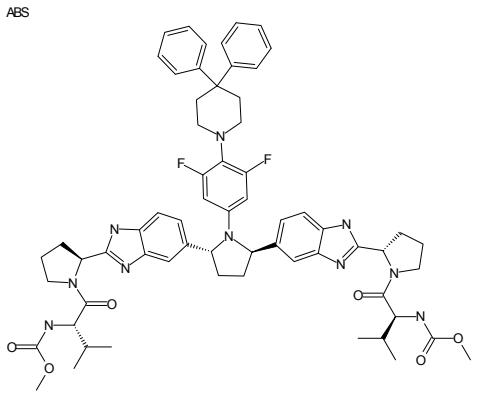


Ejemplo 5.1

{(2S)-1-[(2S)-2-{5-[(2R,5R)-1-[3,5-difluoro-4-(4-fenilpiperidin-1-il)fenil]-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-benzimidazol-5-il}pirrolidin-2-il]-1H-benzimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

En un balón de 250 ml enfriado en un baño de hielo se agregó (S)-6,6'-((2R,5R)-1-(3,5-difluoro-4-(4-fenilpiperidin-1-il)fenil)pirrolidin-2,5-diil)bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol) (2,57 mmol), ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico (0,945 g, 5,40 mmol) e hidrato de 1H-benzo[d][1,2,3]triazol-1-ol (0,984 g, 6,43 mmol) en DMF (25 mL) para dar una solución anaranjada. Se agregaron 4-Metilmorfolina (2,83 mL, 25,7 mmol) y clorhidrato de N1-((etilimino)metilen)-N3,N3-dimetilpropan-1,3-diamina (1,232 g, 6,43 mmol) , y la mezcla se agitó a temperatura ambiente durante 2 horas y luego se diluyó en EtOAc. La capa de EtOAc se lavó con NaHCO3 saturado acuoso, H2O, y NaCl saturado. La capa orgánica se trató con 3-mercaptopropilo silica durante 1 hora, se secó (Na2SO4), se filtró y se concentró hasta obtener una espuma amarilla (2,74 g). La purificación mediante cromatografía flash en un cartucho de 120 de sílice eluyendo con 2-5% metanol en diclorometano dio 1,7 g (61%) del compuesto del título como un polvo amarillo. El compuesto del título se puede volver a purificar por recristalización a partir de acetonitrilo. 1H RMN (400 MHz, DMSO-d6) □ ppm 0,73 - 0,91 (m, 12 H) 1,60 - 1,74 (m, 6 H) 1,86 - 2,04 (m, 6 H) 2,17 - 2,30 (m, 4 H) 2,52 - 2,53 (m, 4 H) 2,84 - 3,02 (m, 4 H) 3,52 - 3,56 (m, 6 H) 3,78 - 3,87 (m, 3 H) 4,00 - 4,12 (m, 2 H) 5,10 - 5,18 (m, 2 H) 5,32 - 5,42 (m,

2 H) 5,88 - 5,95 (m, 2 H) 7,05 - 7,33 (m, 11 H) 7,41 (d, J=8,24 Hz, 1 H) 7,50 (d, J=8,35 Hz, 1 H) 11,97 - 12,30 (m, 2 H); MS (ESI+) m/z 1027 (M+H)+.

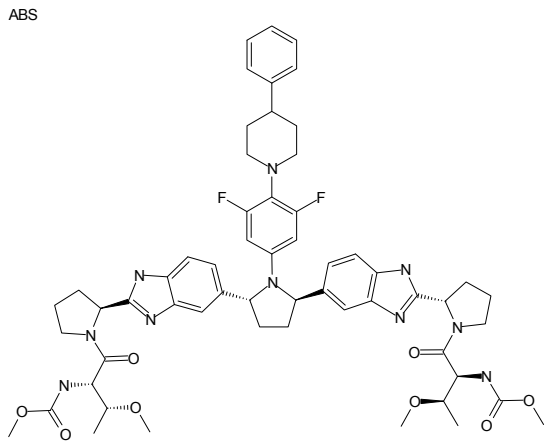


Ejemplo 5.2

{(2S)-1-[(2S)-2-{5-[(2R,5R)-1-[4-(4,4-difenilpiperidin-1-il)-3,5-difluorofenil]-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-benzimidazol-5-il}pirrolidin-2-il]-1H-benzimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

En un balón de 100 ml se agregó (S)-6,6'-((2R,5R)-1-(4-(4,4-difenilpiperidin-1-il)-3,5-difluorofenil)pirrolidin-2,5-diil)bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol) (0,385 g, 0,488 mmol), ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico (0,180 g, 1,025 mmol), e hidrato de 1H-benzo[d][1,2,3]triazol-1-ol (0,187 g, 1,220 mmol) en DMF (25 mL) para dar una solución anaranjada. Se agregaron 4-Metilmorfolina (0,537 mL, 4,88 mmol) y clorhidrato de N1-((etilimino)metilen)-N3,N3-dimetilpropan-1,3-diamina (0,234 g, 1,220 mmol) , y la mezcla se agitó a temperatura ambiente durante 2 horas y luego se diluyó con EtOAc. La solución orgánica se lavó en forma secuencial con NaHCO3 saturado, H2O, y NaCl saturado. La capa orgánica se trató con 3-mercaptopropilo silica durante 1 hora, se secó (Na2SO4), se filtró y se concentró hasta obtener una espuma amarilla. La purificación mediante cromatografía flash en un cartucho de sílice de 24 g eluyendo con 2-7% metanol en CH2Cl2 dio material 99% puro determinado por HPLC. Una segunda cromatografía de fracciones seleccionadas en un cartucho de 12 g de sílice eluyendo con

2-5% metanol en CH2Cl2 dio el compuesto del título como un sólido de color crema (100 mg, 17%). 1H RMN (400 MHz, DMSO-d6) ppm 0,76 - 0,91 (m, 12 H) 1,68 (d, J=4,01 Hz, 2 H) 1,85 - 2,07 (m, 6 H) 2,19 (s, 4 H) 2,38 (s, 4 H) 2,86 (s, 4 H) 3,54 (s, 6 H) 3,82 (s, 4 H) 4,06 (t, J=8,35 Hz, 2 H) 5,10 - 5,17 (m, 2 H) 5,34 (d, J=7,16 Hz, 2 H) 5,85 (d, J=12,79 Hz, 2 H) 6,84 - 7,54 (m, 20 H) 12,06 (d, J=18,98 Hz, 2 H); MS (ESI+) m/z 1103 (M+H)+.

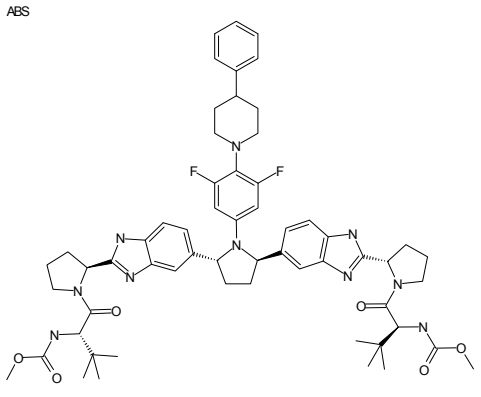


Ejemplo 5.3

{(2S,3R)-1-[(2S)-2-{5-[(2R,5R)-1-[3,5-difluoro-4-(4-fenilpiperidin-1-il)fenil]-5-(2-{(2S)-1-[N-(metoxicarbonil)-O-metil-L-treonil]pirrolidin-2-il}-1H-benzimidazol-5-il)pirrolidin-2-il]-1H-benzimidazol-2-il}pirrolidin-1-il]-3-metoxi-1-oxobutan-2-il}carbamato de metilo

Se disolvió clorhidrato de (S)-6,6'-((2R,5R)-1-(3,5-Difluoro-4-(4-fenilpiperidin-1-il)fenil)pirrolidin-2,5-diil)bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol) (0,12 g) en dimetil sulfóxido (2 mL) y se trató con diisopropiletilamina (0,195 mL, 1,12 mmol) a temperatura ambiente seguido por ácido (2S,3R)-3-metoxi-2-(metoxicarbonilamino)butanoico (0,059 g, 0,307 mmol) y HATU (0,112 g, 0,293 mmol). Luego de 1 hora, la solución se diluyó con agua y se extrajo con diclorometano, se concentró y se purificó mediante cromatografía, eluyendo con 0-8% metanol en diclorometano para dar 0,071 g de un sólido amarillo (48%). 1H RMN (400 MHz, DMSO-d6) ppm 1,03 (dd, J=18,22, 6,18 Hz, 6 H) 1,63 - 1,72 (m, 6 H) 1,99 - 2,08 (m, 6 H) 2,15 - 2,26 (m, 6 H) 2,87 - 3,00 (m, 2 H) 3,10 (s, 3 H) 3,15 (s, 3 H) 3,17 - 3,20 (m, 1 H) 3,43 - 3,52 (m, 2 H) 3,54 (s, 6 H) 3,79 - 3,89 (m, 4 H) 4,25 - 4,30

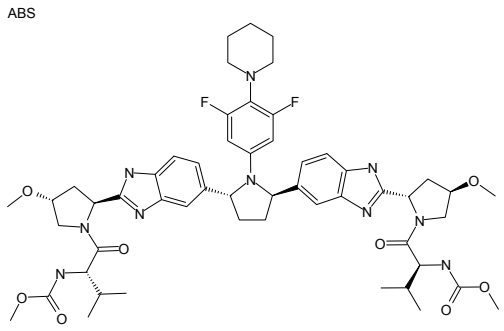
(m, 2 H) 5,11 - 5,18 (m, 2 H) 5,35 - 5,42 (m, 2 H) 5,87 - 5,95 (m, 2 H) 7,09 (t, J=8,19 Hz, 2 H) 7,12 - 7,32 (m, 9 H) 7,41 (d, J=8,35 Hz, 1 H) 7,49 (d, J=8,78 Hz, 1 H) 12,03 (s, 1 H) 12,10 (s, 1 H); MS (ESI+) m/z 1059,4 (M+H)+.



Ejemplo 5.4

{(2S)-1-[(2S)-2-{5-[(2R,5R)-1-[3,5-difluoro-4-(4-fenilpiperidin-1-il)fenil]-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3,3-dimetilbutanoil}pirrolidin-2-il]-1H-benzimidazol-5-il}pirrolidin-2-il]-1H-benzimidazol-2-il}pirrolidin-1-il]-3,3-dimetil-1-oxobutan-2-il}carbamato de metilo

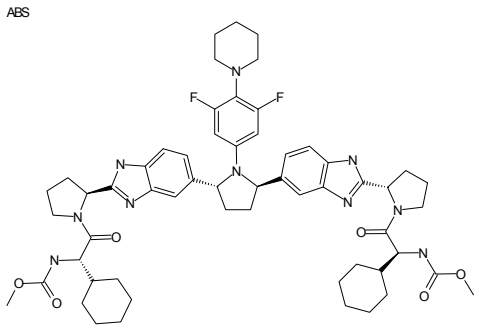
Se disolvió clorhidrato de (S)-6,6'-((2R,5R)-1-(3,5-Difluoro-4-(4-fenilpiperidin-1-il)fenil)pirrolidin-2,5-diil)bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol) (0,12 g) en dimetil sulfóxido (2 mL) y se trató con diisopropiletilamina (0,195 mL, 1,12 mmol) a temperatura ambiente seguido por ácido (S)-2-(metoxicarbonilamino)-3,3-dimetilbutanoico (0,058 g, 0,307 mmol) y HATU (0,112 g, 0,293 mmol). Luego de 1 hora, la solución se diluyó con agua y se extrajo con diclorometano. Las fases orgánicas se concentraron y se purificó mediante cromatografía, eluyendo con 0-6% metanol en diclorometano para dar el compuesto del título (0,065 g, 44%) como un sólido amarillo . 1H RMN (400 MHz, DMSO-d6) □ ppm 0,89 (d, J=13,88 Hz, 18 H) 1,61 - 1,73 (m, 8 H) 1,95 - 2,08 (m, 4 H) 2,15 - 2,24 (m, 6 H) 2,86 - 3,02 (m, 4 H) 3,55 (s, 6 H) 3,78 - 3,85 (m, 4 H) 4,23 (dd, J=8,89, 4,66 Hz, 2 H) 5,13 - 5,22 (m, 2 H) 5,33 - 5,43 (m, 2 H) 5,92 (dd, J=12,85, 2,98 Hz, 2 H) 7,05 - 7,18 (m, 4 H) 7,20 - 7,29 (m, 5 H) 7,33 (s, 1 H) 7,42 (d, J=8,13 Hz, 1 H) 7,49 (d, J=8,46 Hz, 1 H) 12,05 (d, J=1,63 Hz, 1 H) 12,09 (d, J=1,30 Hz, 1 H); MS (ESI+) m/z 1055,4 (M+H)+.



Ejemplo 5.5

{(2S)-1-[(2S,4R)-2-{5-[(2R,5R)-1-[3,5-difluoro-4-(piperidin-1-il)fenil]-5-{2-[(2S,4R)-4-metoxi-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-benzimidazol-5-il}pirrolidin-2-il]-1H-benzimidazol-2-il}-4-metoxipirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

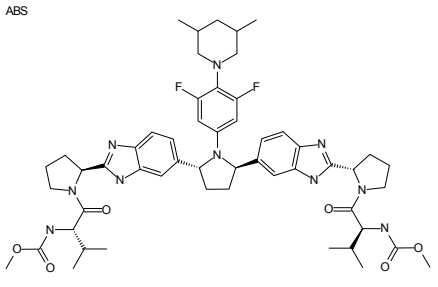
Se disolvió (S,R)-6,6'-((2R,5R)-1-(3,5-Difluoro-4-(piperidin-1-il)fenil)pirrolidin-2,5-diil)bis(2-((2S,4R)-4-metoxipirrolidin-2-il)-1H-benzo[d]imidazol) (0,20g, 0,287 mmol) en dimetil sulfóxido (3 mL) y se trató con diisopropiletilamina (0,400 mL, 2,29 mmol) a temperatura ambiente seguido por ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico (0,111 g, 0,631 mmol) y HATU (0,229 g, 0,603 mmol). Luego de 2 horas, la solución se diluyó con agua y se extrajo con diclorometano. La capa orgánica se concentró y se purificó mediante cromatografía, eluyendo con 0-6% metanol en diclorometano para dar el compuesto del título (0,163 g, 56%) como un sólido amarillo. 1H RMN (400 MHz, DMSO-d6) □ ppm 0,71 - 0,84 (m, 12 H) 1,35 - 1,49 (m, 8 H) 1,69 (d, J=5,42 Hz, 2 H) 1,83 - 1,94 (m, 2 H) 2,22 - 2,32 (m, 4 H) 2,76 (s, 4 H) 3,29 (s, 6 H) 3,54 (s, 6 H) 3,87 (dd, J=11,11, 3,85 Hz, 2 H) 4,03 (q, J=7,05 Hz, 4 H) 4,21 (s, 2 H) 5,02 - 5,15 (m, 2 H) 5,36 (d, J=3,25 Hz, 2 H) 5,84 - 5,94 (m, 2 H) 7,04 - 7,11 (m, 2 H) 7,19 (s, 1 H) 7,27 - 7,34 (m, 3 H) 7,41 (d, J=8,24 Hz, 1 H) 7,48 (d, J=8,24 Hz, 1 H) 12,13 (s, 1 H) 12,19 (s, 1 H); MS (ESI+) m/z 1011,6 (M+H)+.



Ejemplo 5.6

({(2R,5R)-1-[3,5-difluoro-4-(piperidin-1-il)fenil]pirrolidin-2,5-diil}bis{1H-benzimidazol-5,2-diil(2S)pirrolidin-2,1-diil[(1S)-1-ciclohexil-2-oxoetan-2,1-diil]})biscarbamato de dimetilo

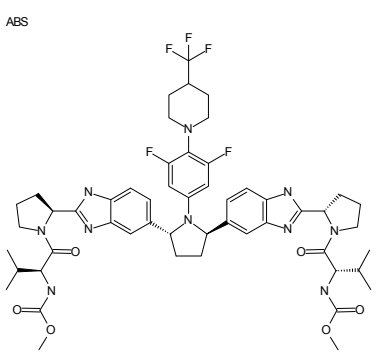
Se disolvió (S)-6,6'-((2R,5R)-1-(3,5-Difluoro-4-(piperidin-1-il)fenil)pirrolidin-2,5-diil)bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol) (0,192 g, 0,302 mmol) en dimetil sulfóxido (4 mL) y se trató con diisopropiletilamina (0,421 mL, 2,41 mmol) a temperatura ambiente seguido por ácido (S)-2-ciclohexil-2-(metoxicarbonilamino)acético (0,143 g, 0,663 mmol) y HATU (0,241 g, 0,633 mmol). Luego de 1 hora, la solución se diluyó con agua y se extrajo con diclorometano. La fase orgánica se concentró, y el residuo se purificó mediante cromatografía, eluyendo con 0-8% metanol en diclorometano para dar el compuesto del título (0,166 g, 53%) como un sólido amarillo. 1H RMN (400 MHz, DMSO-d6) □ ppm 0,80 - 1,12 (m, 8 H) 1,36 - 1,70 (m, 24 H) 1,98 (d, J=4,45 Hz, 4 H) 2,15 - 2,25 (m, 4 H) 2,75 (s, 4 H) 3,52 (s, 6 H) 3,81 (d, J=2,39 Hz, 4 H) 4,08 (q, J=8,57 Hz, 2 H) 5,14 (d, J=4,23 Hz, 2 H) 5,36 (d, J=3,58 Hz, 2 H) 5,82 - 5,93 (m, 2 H) 7,10 (dd, J=13,93, 8,30 Hz, 2 H) 7,15 - 7,28 (m, 4 H) 7,42 (d, J=7,37 Hz, 1 H) 7,48 (dd, J=8,35, 1,84 Hz, 1 H) 12,00 (s, 1 H) 12,16 (s, 1 H); MS (ESI+) m/z 1031,4 (M+H)+.



Ejemplo 5.7

{(2S)-1-[(2S)-2-{6-[(2R,5R)-1-[4-(3,5-dimetilpiperidin-1-il)-3,5-difluorofenil]-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-benzimidazol-6-il}pirrolidin-2-il]-1H-benzimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

Se agregó Diisopropiletilamina (3 mL, 17,18 mmol) a una suspensión de (S)-6,6'-((2R,5R)-1-(4-(3,5-dimetilpiperidin-1-il)-3,5-difluorofenil)pirrolidin-2,5-diil)bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol) (1,045 g, 1,572 mmol), ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico (0,6852 g, 3,91 mmol), y HATU (1,4995 g, 3,94 mmol) en diclorometano (20 mL). La mezcla de reacción se agitó a temperatura ambiente durante 30 minutos. La reacción se diluyó con diclorometano, se lavó con agua (2×), salmuera (1×), y se concentró. El residuo se purificó mediante cromatografía flash (2–5% metanol/diclorometano) para dar el compuesto del título (0,7107 g, 46%). ^{1}H RMN (400 MHz, DMSO-d6) δ ppm 0,50 (q, J = 11,9, 1H), 0,97 - 0,64 (m, 18H), 1,32 - 1,20 (m, 2H), 1,81 - 1,46 (m, 5H), 2,09 - 1,80 (m, 6H), 2,32 - 2,13 (m, 5H), 2,75 (dd, J = 10,0, 40,2, 2H), 3,18 - 3,05 (m, 1H), 3,54 (s, 6H), 3,82 (s, 4H), 4,14 - 3,95 (m, 2H), 5,14 (s, 2H), 5,36 (d, J = 7,2, 2H), 5,88 (d, J = 12,8, 2H), 7,14 - 7,02 (m, 2H), 7,19 (s, 1H), 7,33 - 7,23 (m, 3H), 7,41 (d, J = 8,2, 1H), 7,49 (d, J = 8,2, 1H), 12,37 - 11,98 (m, 2H); MS (ESI+) m/z 979 $(M+H)^+$.



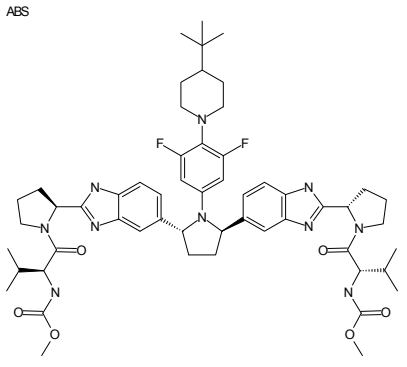
Ejemplo 5.8

{(2S)-1-[(2S)-2-{5-[(2R,5R)-1-{3,5-difluoro-4-[4-(trifluorometil)piperidin-1-il]fenil}-5-{2-[(2S)-

1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-benzimidazol-5-il}pirrolidin-2-il]-1H-benzimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

Se combinaron tetraclorhidrato de (S)-6,6'-((2R,5R)-1-(3,5-Difluoro-4-(4-(trifluorometil)piperidin-1-il)fenil)pirrolidin-2,5-diil)bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol) (250 mg, 0,294 mmol) y ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico (113 mg, 0,647 mmol) en DMF anhidro (3 mL) bajo nitrógeno. Se agregaron hidrato de HOBT (113 mg, 0,735 mmol) y EDAC (144 mg, 0,735 mmol) . La solución color ámbar se enfrió a 0 ºC. Se agregó 4-metilmorfolina (0,323 mL, 2,94 mmol) , el baño de frío se retiró, y la mezcla de reacción se agitó a 20 °C. Luego de 2 horas, la reacción se diluyó con EtOAc (50 mL) y se lavó con agua (3×25 mL) y salmuera (25 mL). La fase orgánica se secó sobre MgSO4 anhidro, se filtró, y se concentró mediante evaporación por rotación a un sólido color tostado (300 mg). Se disolvió una alícuota (50 mg) de material crudo en 2 mL de acetonitrilo y 2 mL 0,1% TFA en H2O, y se purificó mediante RP-C18 HPLC (Waters Prep LC, módulo de 40 mm con un cartucho Nova-Pak HR C18 6µm 40×100 mm Prep Pak) eluyendo con un gradiente de 30 minutos de 95:5 0,1% TFA en H2O/acetonitrilo a 25:75 0,1% TFA en H2O/acetonitrilo, luego 10 minutos al 100% de acetonitrilo a 20 mL/minuto (fracciones de 10 mL). Las fracciones puras se trataron con NaHCO3 sat acuoso (2 mL/tubo), cada tubo se centrifugó para neutralizar totalmente el TFA, y las soluciones neutralizadas se combinaron en un balón de 250 ml. El acetonitrilo se retiró por evaporación por rotación, y la fase acuosa remanente se extrajo con EtOAc (2×50 mL). Los extractos orgánicos combinados se secaron sobre MgSO4 anhidro, se filtró, y se concentró por evaporación por rotación para dar el compuesto del título como un sólido blanco (18 mg). Se volvieron a purificar otros 100 mg como se ha indicado por HPLC prep en dos inyecciones de 50-mg . La purificación mencionada dio el compuesto del título adicional como un sólido blanco (34 mg). 1H RMN (400 MHz, DMSO-d6) □ ppm 0,73 - 0,90 (m, 12 H), 1,23 (s, 1 H), 1,34 - 1,49 (m, 2 H),

1,63 - 1,76 (m, 4 H), 1,83 - 2,04 (m, 6 H), 2,11 - 2,25 (m, 4 H), 2,84 (m, 4 H), 3,52 (s, 6 H), 3,81 (br s, 4 H), 4,00 - 4,09 (m, 2 H), 5,08 - 5,18 (m, 2 H), 5,28 - 5,42 (m, 2 H), 5,89 (d, J=12,79 Hz, 2 H), 7,06 (t, J=7,26 Hz, 2 H), 7,16 - 7,32 (m, 4 H), 7,39 (d, J=8,24 Hz, 1 H), 7,47 (d, J=8,13 Hz, 1 H), 12,06 (dos s, 2 H); MS (ESI+) m/z 1019 (M+H)+.

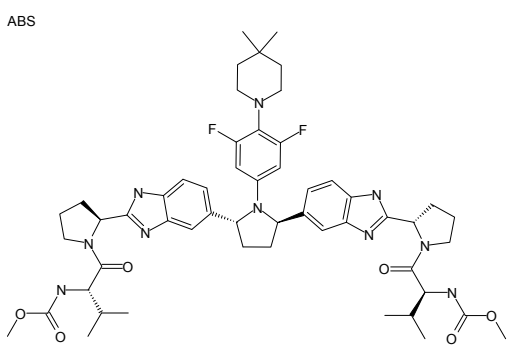


Ejemplo 5.9

{(2S)-1-[(2S)-2-{5-[(2R,5R)-1-[4-(4-tert-butilpiperidin-1-il)-3,5-difluorofenil]-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-benzimidazol-5-il}pirrolidin-2-il]-1H-benzimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

Se combinaron tetraclorhidrato de (S)-6,6'-((2R,5R)-1-(4-(4-tert-Butilpiperidin-1-il)-3,5-difluorofenil)pirrolidin-2,5-diil)bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol) (250 mg, 0,298 mmol) y ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico (115 mg, 0,656 mmol) en DMF anhidro (3 mL) bajo nitrógeno. Se agregaron hidrato de HOBT (114 mg, 0,745 mmol) y EDAC (146 mg, 0,745 mmol) , y luego la solución color ámbar se enfrió a 0 ºC. Se agregó 4-Metilmorfolina (0,328 mL, 2,98 mmol) , el baño de frío se retiró, y la mezcla de reacción se agitó a 20 °C. Después de 18 horas, la mezcla de reacción se diluyó con EtOAc (50 mL), se lavó con agua (3×25 mL) y salmuera (25 mL). La fase orgánica se secó sobre MgSO4 anhidro, se filtró, y se concentró mediante evaporación por rotación a un sólido amarillo. Se pre-purificó por Cromatografía flash en SiO2 (columna Alltech Extract-Clean™ , lecho de 10 g) eluyendo con 3% CH3OH/CH2Cl2 y se obtuvo un sólido amarillo (119 mg). Una alícuota (50 mg) del residuo se disolvió en 2 mL acetonitrilo y 2 mL 0,1%

TFA en H2O, y se purificó mediante RP-C18 HPLC (Waters Prep LC, Módulo de 40 mm con cartucho Nova-Pak HR C18 6 µm 40×100 mm Prep Pak) eluyendo con un gradiente de 30 minutos de 95:5 0,1% TFA en H2O/acetonitrilo a 25:75 0,1% TFA en H2O/acetonitrilo, luego de 10 minutos en acetonitrilo al 100% a 20 mL/minuto (fracciones de 10 ml). Las fracciones puras se trataron con NaHCO3 sat acuoso (2 mL/tubo), cada tubo se centrifugó para neutralizar totalmente el TFA, y las soluciones se combinaron en un balón de 250 ml. Los restantes 69 mg de material se purificaron mediante HPLC prep como se describe precedentemente. El las fracciones que contenían el producto puro se trataron con NaHCO3 sat acuoso como se ha descrito y se combinó en el mismo balón de 250-mL . El acetonitrilo se retiró por evaporación por rotación, la fase acuosa remanente se extrajo con EtOAc (2×50 mL). Los extractos orgánicos combinados se secaron sobre MgSO4 anhidro, se filtró, y se concentró por evaporación por rotación para dar el compuesto del título como un sólido blanco (56 mg). 1H RMN (400 MHz, DMSO-d6) □ ppm 0,68 - 0,93 (m, 22 H), 1,09 - 1,25 (m, 2 H), 1,53 (d, J=11,93 Hz, 2 H), 1,63 - 1,75 (m, 2 H), 1,80 - 2,08 (m, 7 H), 2,12 - 2,27 (m, 4 H), 2,71 - 2,91 (m, 5 H), 3,54 (s, 6 H), 3,82 (br s, 4 H), 4,06 (t, J=8,35 Hz, 2 H), 5,09 - 5,19 (m, 2 H), 5,30 - 5,44 (m, 2 H), 5,89 (d, J=12,69 Hz, 2 H), 7,02 - 7,11 (m, 2 H), 7,17 - 7,32 (m, 4 H), 7,40 (d, J=8,24 Hz, 1 H), 7,49 (d, J=8,13 Hz, 1 H), 12,07 (dos s, 2 H); MS (ESI+) m/z 1007 (M+H)+.



Ejemplo 5.10

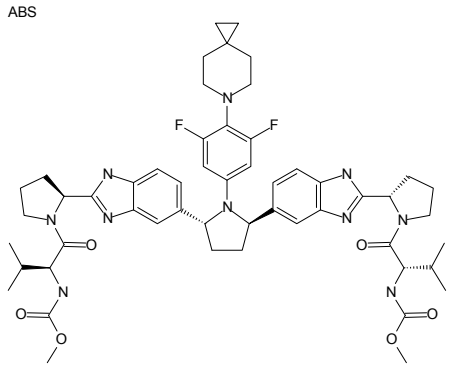
{(2S)-1-[(2S)-2-{5-[(2R,5R)-1-[4-(4,4-dimetilpiperidin-1-il)-3,5-difluorofenil]-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-benzimidazol-5-

il}pirrolidin-2-il]-1H-benzimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

Se combinaron pentaclorhidrato de (S)-6,6'-((2R,5R)-1-(4-(4,4-Dimetilpiperidin-1-il)-3,5-difluorofenil)pirrolidin-2,5-diil)bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol) (250 mg, 0,295 mmol) y ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico (109 mg, 0,620 mmol) en DMF anhidro (3 mL) bajo nitrógeno. Se agregaron hidrato de HOBT (104 mg, 0,679 mmol), y EDAC (133 mg, 0,679 mmol) , y luego la solución color ámbar se enfrió a 0 ºC. Se agregó 4-Metilmorfolina (0,325 mL, 2,95 mmol) , el baño de frío se retiró, y la mezcla de reacción se agitó a 20 °C. Luego de 2 horas, la mezcla de reacción se diluyó con EtOAc (50 mL), y se lavó con agua (3×25 mL) y salmuera (25 mL). La fase orgánica se secó sobre MgSO4 anhidro, se filtró, y se concentró mediante evaporación por rotación a un sólido color tostado. La purificación mediante cromatografía flash en SiO2 (3,8 cm×15 cm) eluyendo con un paso de gradiente de 3% a 4% CH3OH/CH2Cl2 dio el compuesto del título como un sólido (115 mg). Una alícuota (50 mg) se disolvió en 1,5 mL acetonitrilo y 1,5 mL 0,1% TFA en H2O, y se purificó mediante RP-C18 HPLC (Waters Prep LC, módulo de 40 mm con Cartucho Nova-Pak HR C18 6 µm 40x100 mm Prep Pak) eluyendo con un gradiente de 30 minutos de 95:5 0,1% TFA en H2O/acetonitrilo a 25:75 0,1% TFA en H2O/acetonitrilo, luego de 10 minutos a acetonitrilo al 100% a 20 mL/minuto (fracciones de 10 ml). Las fracciones puras se trataron con NaHCO3 sat acuoso (2 mL/tubo), cada tubo se centrifugó para neutralizar totalmente el TFA, y las soluciones se combinaron en un balón de 250 ml. El acetonitrilo se retiró por concentración al vacío. La fase acuosa remanente se extrajo con EtOAc (2×50 mL). Los extractos orgánicos combinados se secaron sobre MgSO4 anhidro, se filtró, y se concentró por evaporación por rotación para dar el compuesto del título como un sólido blanco (33 mg). Los restantes 65 mg de producto impuro (de la columna de gel de sílice) se purificaron por RP-C18 HPLC preparativa como se describe precedentemente para obtener compuesto del título adicional como un sólido blanco (33mg). 1H RMN (400 MHz, DMSO-d6) δ ppm 0,75 - 0,91

(m, 12 H), 0,87 (s, 6 H), 1,21 - 1,35 (m, 4 H), 1,63 - 1,77 (m, 2 H), 1,81 - 2,09 (m, 6 H), 2,11 - 2,29 (m, 4 H), 2,49 - 2,59 (m, 2 H), 2,76 (s, 4 H), 3,54 (s, 6 H), 3,82 (br s, 4 H), 4,06 (t, J=8,46 Hz, 2 H), 5,09 - 5,22 (m, 2 H), 5,30 - 5,44 (m, 2 H), 5,89 (d, J=12,79 Hz, 2 H), 7,03 - 7,11 (m, 2 H), 7,17 - 7,32 (m, 4 H), 7,41 (d, J=8,13 Hz, 1 H), 7,49 (d, J=8,02 Hz, 1 H), 12,07 (dos s, 2 H); (ESI+) m/z 979 (M+H)+; MS (ESI-) m/z 977 (M-H)-.

ABS

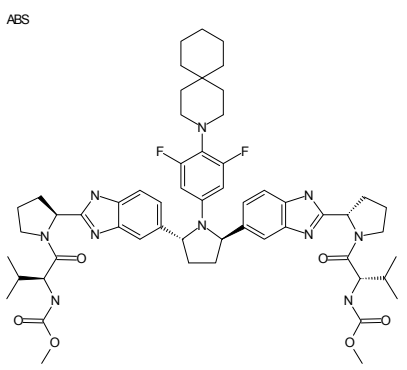


Ejemplo 5.11

{(2S)-1-[(2S)-2-{5-[(2R,5R)-1-[4-(6-azaespiro[2,5]oct-6-il)-3,5-difluorofenil]-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-benzimidazol-5-il}pirrolidin-2-il]-1H-benzimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

Se combinaron (S)-6,6'-((2R,5R)-1-(3,5-Difluoro-4-(6-azaespiro[2,5]octan-6-il)fenil)pirrolidin-2,5-diil)bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol) tetraclorhidrato de (250 mg, 0,309 mmol) y ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico (119 mg, 0,680 mmol) en DMF anhidro (3 mL) bajo nitrógeno. Se agregaron hidrato de HOBT (118 mg, 0,773 mmol) y EDAC (151 mg, 0,773 mmol), , y luego la solución color ámbar se enfrió a 0 ºC. Se agregó 4-Metilmorfolina (0,340 mL, 3,09 mmol) , el baño de frío se retiró, y la mezcla de reacción se agitó a 20 °C. Después de 16,5 horas, la mezcla de reacción se diluyó con EtOAc (50 mL), y se lavó con agua (3×25 mL) y salmuera (25 mL). La fase orgánica se secó sobre MgSO4 anhidro, se filtró, y se concentró mediante evaporación por rotación a un sólido amarillo. La prepurificación por Cromatografía flash en SiO2 (Columna Alltech Extract-Clean™ , lecho de 10 g) eluyendo con 3% CH3OH/CH2Cl2

para dar un sólido beige (172 mg). Una alícuota (50 mg) se disolvió en 1,5 mL acetonitrilo y 1,5 mL 0,1% TFA en H2O, y se purificó mediante RP-C18 HPLC (Waters Prep LC, módulo de 40 mm con cartucho Nova-Pak HR C18 6 µm 40×100mm Prep Pak) eluyendo con un gradiente de 30 minutos de 95:5 0,1% TFA en H2O/acetonitrilo a 25:75 0,1% TFA en H2O/acetonitrilo, luego de 10 minutos a acetonitrilo al 100% a 20 mL/minuto (fracciones de 10 ml). Las fracciones puras se trataron con NaHCO3 sat acuoso (2 mL/tubo), cada tubo se centrifugó para neutralizar totalmente el TFA, y las soluciones se combinaron en un balón de 250 ml. Se purificaron dos lotes adicionales de 50 mg por HPLC prep como se describe precedentemente, y las fracciones que contenían el producto puro se trataron con NaHCO3 sat acuoso de la misma forma y se combinaron en el mismo balón de 250 ml. El acetonitrilo se retiró por concentración al vacío, y la fase acuosa remanente se extrajo con EtOAc (2×50 mL). Las fases orgánicas combinadas se secaron sobre MgSO4 anhidro, se filtró, y se concentró por evaporación por rotación para dar el compuesto del título como un sólido blanco (42 mg). 1H RMN (400 MHz, DMSO-d6) δ ppm 0,22 (s, 4 H), 0,72 - 0,93 (m, 12 H), 1,21 - 1,36 (m, 5 H), 1,61 - 1,78 (m, 2 H), 1,83 - 2,08 (m, 7 H), 2,13 - 2,27 (m, 4 H), 2,81 (br s, 4 H), 3,53 (s, 6 H), 3,82 (br s, 4 H), 4,06 (t, J=8,40 Hz, 2 H), 5,10-5,19 (m, 2 H), 5,29 - 5,45 (m, 2 H), 5,90 (d, J=12,79 Hz, 2 H), 7,02 - 7,32 (m, 6 H), 7,41 (d, J=8,24 Hz, 1 H), 7,49 (d, J=8,24 Hz, 1 H), 12,07 (dos s, 2 H); MS (ESI+) m/z 977 (M+H)+.

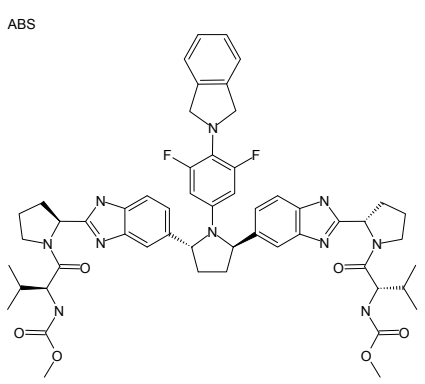


Ejemplo 5.12

{(2S)-1-[(2S)-2-{5-[(2R,5R)-1-[4-(3-azaespiro[5,5]undec-3-il)-3,5-difluorofenil]-5-{2-[(2S)-1-

{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-benzimidazol-5-il}pirrolidin-2-il]-1H-benzimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

Se combinaron tetraclorhidrato de (S)-6,6'-((2R,5R)-1-(3,5-Difluoro-4-(3-azaespiro[5,5]undecan-3-il)fenil)pirrolidin-2,5-diil)bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol) (250 mg, 0,294 mmol) y ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico (113 mg, 0,646 mmol) en DMF anhidro (3 mL) bajo nitrógeno. Se agregaron hidrato de HOBT (113 mg, 0,735 mmol) y EDAC (144 mg, 0,735 mmol), y luego la mezcla se enfrió a 0 ºC. Se agregó 4-Metilmorfolina (0,323 mL, 2,94 mmol) , el baño de frío se retiró, y la mezcla de reacción se agitó a 20 °C durante 18 horas. La mezcla de reacción se diluyó con EtOAc (50 mL) y se lavó con agua (3×25 mL) y salmuera (25 mL). La fase orgánica se secó sobre MgSO4 anhidro, se filtró, y se concentró mediante evaporación por rotación a una espuma color beige. El material crudo se purificó mediante cromatografía flash en SiO2 (3,8 cm×15 cm) eluyendo con 4% CH3OH/CH2Cl2 para dar el compuesto del título como un sólido blanco (82 mg). 1H RMN (400 MHz, DMSO-d6) δ ppm 0,72 - 0,93 (m, 12 H), 1,22 - 1,41 (m, 15 H), 1,63 - 1,74 (m, 2 H), 1,80 - 2,07 (m, 7 H), 2,12 - 2,27 (m, 4 H), 2,75 (s, 4 H), 3,54 (s, 6 H), 3,82 (s, 4 H), 4,06 (t, J=8,40 Hz, 2 H), 5,14 (d, J=1,19 Hz, 2 H), 5,27 - 5,42 (m, 2 H), 5,88 (d, J=12,69 Hz, 2 H), 7,03 - 7,11 (m, 2 H), 7,20 (s, 1 H), 7,29 (d, J=5,96 Hz, 3 H), 7,40 (d, J=8,24 Hz, 1 H), 7,49 (d, J=8,24 Hz, 1 H), 12,07 (m, 2 H); MS (ESI+) m/z 1019 (M+H)+, (ESI-) m/z 1017 (M-H)-.

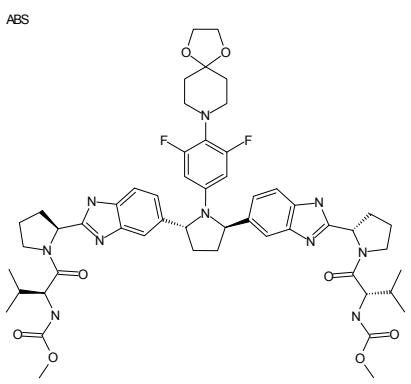


Ejemplo 5.13

{(2S)-1-[(2S)-2-{5-[(2R,5R)-1-[4-(1,3-dihidro-2H-isoindol-2-il)-3,5-difluorofenil]-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-benzimidazol-5-il}pirrolidin-2-il]-1H-benzimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

Tetraclorhidrato de (S)-6,6'-((2R,5R)-1-(3,5-Difluoro-4-(isoindolin-2-il)fenil)pirrolidin-2,5-diil)bis(2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol) (250 mg, 0,306 mmol) y ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico (118 mg, 0,673 mmol) se combinaron en DMF anhidro (3 mL) bajo nitrógeno. Se agregaron hidrato de HOBT (117 mg, 0,765 mmol) y EDAC (150 mg, 0,765 mmol) , luego la solución color ámbar se enfrió a 0 ºC. Se agregó 4-Metilmorfolina (0,337 mL, 3,06 mmol) , el baño de frío se retiró, y la mezcla de reacción se agitó a 20 °C durante 16 horas. La mezcla de reacción se diluyó con EtOAc (50 mL) y esta mezcla se lavó con agua (3×25 mL) y salmuera (25 mL). La fase orgánica a lo largo de se secó a sobre MgSO4 anhidro, se filtró, y se concentró mediante evaporación por rotación en un sólido amarillo verdoso. El sólido se purificó mediante cromatografía flash en SiO2 (3,8 cm×15 cm) eluyendo con 4% CH3OH/CH2Cl2 para dar un sólido blanco opaco (104 mg). Una alícuota (52 mg) se disolvió acetonitrilo (2 mL) y 0,1% TFA en H2O (2 mL) y se purificó mediante RP-C18 HPLC (Waters Prep LC, módulo de 40 mm con Cartucho Nova-Pak HR C18 6 µm 40x100 mm Prep Pak) eluyendo con un gradiente de 30 minutos de 95:5 0,1% TFA en H2O/acetonitrilo a 25:75 0,1% TFA en H2O/acetonitrilo, luego de 10 minutos a acetonitrilo al 100% a 20 mL/minuto (fracciones de 10 ml). Las fracciones puras se trataron con NaHCO3 sat acuoso (2 mL/tubo), cada tubo se centrifugó para neutralizar totalmente el TFA, y las soluciones se combinaron en un balón de 500 ml. Los restantes 52 mg de material se purificaron por HPLC prep como se describe precedentemente y las fracciones que contenían el producto puro se trataron con NaHCO3 sat acuoso como se describe precedentemente. Las fracciones que contenían el producto se combinaron en el mismo balón de 500 ml. El acetonitrilo se retiró por evaporación por rotación. La fase acuosa remanente se extrajo con EtOAc (2×50 mL). Las fases orgánicas combinadas se

secaron sobre MgSO4 anhidro, se filtró, y se concentró por evaporación por rotación para dar el compuesto del título como un sólido blanco (88 mg). 1H RMN (400 MHz, DMSO-d6) δ ppm 0,75 - 0,92 (m, 12 H), 1,61 - 2,08 (m, 8 H), 2,11 - 2,26 (m, 3 H), 2,57 (s, 2 H), 3,54 (s, 6 H), 3,83 (s, 4 H), 4,07 (t, J=8,29 Hz, 2 H), 4,26 - 4,43 (m, 4 H), 5,10 - 5,23 (m, 2 H), 5,33 - 5,50 (m, 2 H), 5,99 (d, J=12,79 Hz, 2 H), 7,09 (t, J=6,83 Hz, 2 H), 7,20 (s, 4 H), 7,22 - 7,37 (m, 4 H), 7,42 (d, J=8,24 Hz, 1 H), 7,50 (d, J=8,13 Hz, 1 H), 12,09 (m, 2 H); MS (ESI+) m/z 985 (M+H)+, (ESI-) m/z 983 (M-H)-.



Ejemplo 5.14

{(2S)-1-[(2S)-2-{5-[(2R,5R)-1-[4-(1,4-dioxa-8-azaespiro[4,5]dec-8-il)-3,5-difluorofenil]-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-benzimidazol-5-il}pirrolidin-2-il]-1H-benzimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

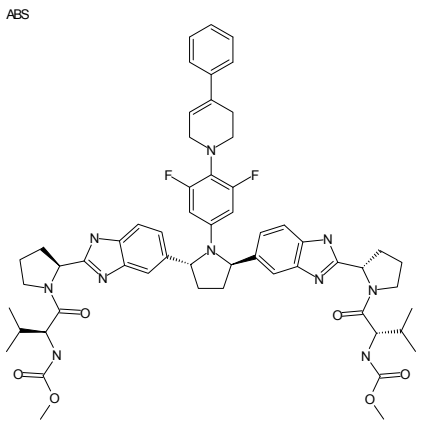
Parte A

El compuesto 8-(4-((2R,5R)-2,5-bis(4-cloro-3-nitrofenil)pirrolidin-1-il)-2,6-difluorofenil)-1,4-dioxa-8-azaespiro[4,5]decano puede transformarse siguiendo los métodos del Procedimiento General 8,1 y el Procedimiento General 9D (PtO2) para obtener (2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-((2R,5R)-1-(3,5-difluoro-4-(1,4-dioxa-8-azaespiro[4,5]decan-8-il)fenil)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 .

Parte B

En un balón de 10 ml secado en el horno, se disolvió (2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-((2R,5R)-1-(3,5-difluoro-4-(1,4-dioxa-8-azaespiro[4,5]decan-8-il)fenil)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 (200 mg, 0,191 mmol) en tolueno anhidro (2 mL) bajo nitrógeno. Se agregó ácido acético glacial (0,110 mL, 1,914 mmol) , y la solución se agitó en un baño de aceite a 60 °C. Después de 1,5 horas, la mezcla de reacción se enfrió a temperatura ambiente, se diluyó con EtOAc (50 mL), y se lavó con NaHCO3 sat acuoso (25 mL). La fase orgánica se secó sobre MgSO4 anhidro, se filtró, y se concentró por evaporación por rotación para dar el compuesto del título crudo como un sólido color tostado (185 mg). Una alícuota (93 mg) se disolvió en acetonitrilo (2 mL) y 0,1% TFA en H2O (2 mL) y se purificó mediante RP-C18 HPLC (Waters Prep LC, módulo de 40 mm con cartucho Nova Pak HR C18 6 µm 40x100 mm Prep Pak) eluyendo con un gradiente de 30 minutos de 95:5 0,1% TFA en H2O/acetonitrilo a 25:75 0,1% TFA en H2O/acetonitrilo, luego de 10 minutos a acetonitrilo al 100% a 20 mL/minuto. Las fracciones puras se trataron inmediatamente con NaHCO3 sat acuoso (2 mL/tubo), cada tubo se centrifugó para neutralizar totalmente el TFA, y las soluciones se combinaron en un balón de 500 ml. Los restantes 92 mg se purificaron por HPLC preparativa como se describe precedentemente y las fracciones que contenían el producto puro se trataron con NaHCO3 sat acuoso como se describe precedentemente. Las fracciones adicionales se combinaron en el mismo balón de 500 ml. El acetonitrilo se retiró por evaporación por rotación, y la fase acuosa remanente se extrajo con EtOAc (2×50 mL). Los extractos orgánicos combinados se secaron sobre MgSO4 anhidro, se filtró, y se concentró por evaporación por rotación para dar el compuesto del título como un sólido blanco (103 mg). 1H RMN (400 MHz, DMSO-d6) δ ppm 0,73 - 0,94 (m, 12 H), 1,51 - 1,61 (m, 4 H), 1,63 - 1,75 (m, 2 H), 1,83 - 2,10 (m, 8 H), 2,13 - 2,29 (m, 4 H), 2,86 (s, 4 H), 3,54 (s, 6 H), 3,83 (s, 8 H), 4,06 (t, J=8,51 Hz, 2 H), 5,09 - 5,21 (m, 2 H), 5,30 - 5,42 (m, 2 H), 5,90 (d, J=12,69 Hz, 2 H), 7,01 - 7,12 (m, 2 H), 7,17 - 7,32 (m, 4 H), 7,40 (s, 1 H), 7,49 (d, J=8,24

Hz, 1 H), 11,71 - 12,53 (m, 2 H); MS (ESI+) m/z 1009 (M+H)+, (ESI-) m/z 1007 (M-H)-.



Ejemplo 5.15

{(2S)-1-[(2S)-2-{5-[(2R,5R)-1-[3,5-difluoro-4-(4-fenil-3,6-dihidropiridin-1(2H)-il)fenil]-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-benzimidazol-5-il}pirrolidin-2-il]-1H-benzimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

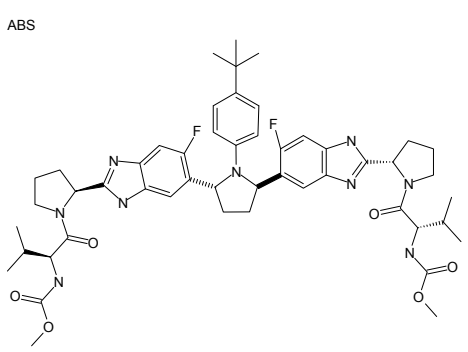
Parte A

El compuesto 1-(4-((2R,5R)-2,5-bis(4-cloro-3-nitrofenil)pirrolidin-1-il)-2,6-difluorofenil)-4-fenil-1,2,3,6-tetrahidropiridina puede transformarse siguiendo los métodos del Procedimiento General 8,1 y el Procedimiento General 9E para obtener (2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-((2R,5R)-1-(3,5-difluoro-4-(4-fenil-5,6-dihidropiridin-1(2H)-il)fenil)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 .

Parte B

En un recipiente de base redonda de 5 ml secado en el horno, se disolvió (2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-((2R,5R)-1-(3,5-difluoro-4-(4-fenil-5,6-dihidropiridin-1(2H)-il)fenil)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 (75 mg, 0,071 mmol) en tolueno anhidro (1 mL) bajo nitrógeno. Se agregó ácido acético glacial (0,041 mL, 0,707 mmol) , y la solución se agitó en un baño de aceite a 60 °C. Después de 1,5 horas, la

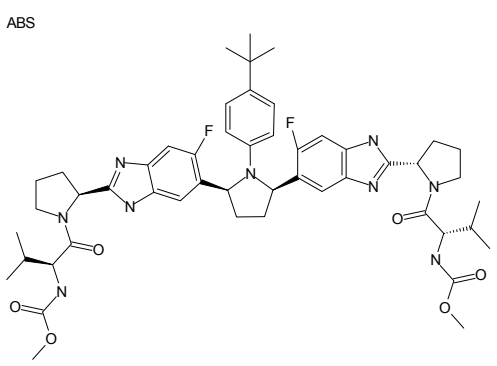
mezcla de reacción de color amarillo se enfrió a temperatura ambiente, se diluyó en EtOAc (50 mL), y se lavó con NaHCO3 sat acuoso (25 mL). La fase orgánica se secó sobre MgSO4 anhidro, se filtró, y se concentró mediante evaporación por rotación a un sólido amarillo (~80 mg). El residuo se disolvió en 2 mL acetonitrilo y 2 mL 0,1% TFA en H2O, y se purificó mediante RP-C18 HPLC (Waters Prep LC, módulo de 40 mm con Cartucho Nova-Pak HR C18 6 µm 40x100 mm Prep Pak) eluyendo con un gradiente de 30 minutos de 95:5 0,1% TFA en H2O/acetonitrilo a 25:75 0,1% TFA en H2O/acetonitrilo, luego de 10 minutos a acetonitrilo al 100% a 20 mL/minuto (fracciones de 10 ml). Las fracciones puras se trataron con NaHCO3 sat acuoso (2 mL/tubo), cada tubo se centrifugó para neutralizar totalmente el TFA, y las soluciones se combinaron en un balón de 250 ml. El acetonitrilo se retiró por evaporación por rotación, y la fase acuosa remanente se extrajo con EtOAc (2×50 mL). La fase orgánica se secó sobre MgSO4 anhidro, se filtró, y se concentró por evaporación por rotación para dar el producto como un sólido blanco opaco (34 mg). 1H RMN (400 MHz, DMSO-d6) δ ppm 0,76 - 0,94 (m, 12 H), 1,70 (d, J=4,55 Hz, 2 H), 1,83 - 2,10 (m, 6 H), 2,11 - 2,26 (m, 3 H), 2,44 (s, 1 H), 2,56 (s, 4 H), 3,09 (s, 2 H), 3,48 (s, 2 H), 3,54 (s, 6 H), 3,82 (s, 4 H), 4,07 (t, J=8,35 Hz, 2 H), 5,09 - 5,22 (m, 2 H), 5,30 - 5,46 (m, 2 H), 5,95 (d, J=12,90 Hz, 2 H), 6,09 (s, 1 H), 7,04 - 7,17 (m, 2 H), 7,19 - 7,25 (m, 2 H), 7,26 - 7,34 (m, 5 H), 7,36 - 7,45 (m, 3 H), 7,50 (d, J=8,35 Hz, 1 H), 11,71 - 12,63 (m, 2 H); MS (ESI+) m/z 1025 (M+H)+, (ESI-) m/z 1023 (M-H)-.



Ejemplo 6.1

{(2S)-1-[(2S)-2-{5-[(2R,5R)-1-(4-tert-butilfenil)-5-{5-fluoro-2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-benzimidazol-6-il}pirrolidin-2-il]-6-fluoro-1H-benzimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

A 6,6'-[(2R,5R)-1-(4-tert-butilfenil)pirrolidin-2,5-diil]bis{5-fluoro-2-[(2S)-pirrolidin-2-il]-1H-benzimidazol} se agregó DMF (1,0 mL) seguido por N-metilmorfolina (0,045mL, 0,41 mmol), ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico (15mg, 0,09 mmol), EDC (20mg, 0,1 mmol) y HOBT (16mg, 0,1 mmol). La solución se agitó a temperatura ambiente durante 18 horas. La mezcla de reacción se diluyó con EtOAc, se lavó con H2O y salmuera, se secó (Na2SO4), se filtró y se concentró. El producto se purificó mediante cromatografía HPLC en fase reversa (5-100% CH3CN/0,1%TFA-H2O); las fracciones deseadas se neutralizaron con solución acuosa de NaHCO3 , se extrajo con EtOAc, se secó, se filtró y evaporo el solvente para dar el compuesto del título (6,7mg, 7,2 µmol, 18%): 1H RMN (400 MHz, CDCl3) δ ppm 10,48 (m, 1H) 10,25 (m, 1H) 7,39 (m, 1H) 7,14 (m, 1H) 6,98 (m, 3H) 6,29 (m, 1H) 5,54 (br s, 1H) 5,34 (br s, 4H) 4,31 (m, 1H) 3,82 (m, 2H) 3,70 (s, 6H) 3,51-3,65 (m, 2H) 3,03 (br s, 2H) 2,51 (br s, 2H) 2,23-2,40 (m, 2H) 2,14 (m, 4H) 1,95 (m, 4H) 1,27 (m, 2H) 1,09-1,23 (m, 9H) 1,07 (m, 3H) 0,87 (m, 9H) 0,67-0,79 (m, 2H); MS (ESI) m/z 924 (M+H)+.



Ejemplo 6.2

{(2S)-1-[(2S)-2-{5-[(2R,5S)-1-(4-tert-butilfenil)-5-{5-fluoro-2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-benzimidazol-6-il}pirrolidin-2-il]-6-fluoro-1H-benzimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

Con la purificación por HPLC del Ejemplo 6.1, también se obtuvo el isómero cis (6,4mg, 6,9µmol, 17%) : 1H RMN (400 MHz, CDCl3) δ ppm 11,62 (s, 1H) 11,37 (s, 1H) 7,45-7,55 (m, 3H) 7,36 (d, 1H) 7,04 (d, 2H) 6,92 (d, 1H) 6,77 (d, 1H) 6,41 (d, 2H) 5,36-5,40 (m, 2H) 5,33 (m, 1H) 5,07 (t, 1H) 3,98-4,07 (m, 1H) 3,93 (m, 1H) 3,74-3,86 (m, 2H) 3,72 (m, 1H) 3,59 (m, 2H) 2,80 (m, 1H) 2,50 (s, 6H) 2,32 (s, 4H) 1,86-2,27 (m, 7H) 1,78 (m, 1H) 1,17 (s, 9H) 0,86-1,01 (m, 9H); MS (ESI) m/z 924 (M+H)+.

Los siguientes compuestos ejemplificativos 6,3-6,11 se pueden preparar a partir de la amina intermediaria apropiada que se indica siguiendo en general el método del Ejemplo 6.1:

Aminas intermediarias:

6,6'-[(2R,5R)-1-(4-tert-butilfenil)pirrolidin-2,5-diil]bis{7-fluoro-2-[(2S)-pirrolidin-2-il]-1H-benzimidazol} (Nomenclatura ACD v12);

6,6'-[(2R,5S)-1-(4-tert-butilfenil)pirrolidin-2,5-diil]bis{7-fluoro-2-[(2S)-pirrolidin-2-il]-1H-benzimidazol} (Nomenclatura ACD v12);

6,6'-[(2R,5R)-1-(4-tert-butilfenil)pirrolidin-2,5-diil]bis{7-cloro-2-[(2S)-pirrolidin-2-il]-1H-benzimidazol} (Nomenclatura ACD v12);

6,6'-[(2R,5S)-1-(4-tert-butilfenil)pirrolidin-2,5-diil]bis{7-cloro-2-[(2S)-pirrolidin-2-il]-1H-benzimidazol} (Nomenclatura ACD v12);

6,6'-[(2R,5R)-1-(4-tert-butilfenil)pirrolidin-2,5-diil]bis{7-metil-2-[(2S)-pirrolidin-2-il]-1H-benzimidazol} (Nomenclatura ACD v12);

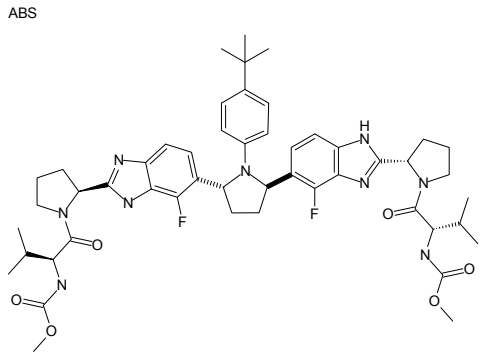
6,6'-[(2R,5S)-1-(4-tert-butilfenil)pirrolidin-2,5-diil]bis{7-metil-2-[(2S)-pirrolidin-2-il]-1H-benzimidazol} (Nomenclatura ACD v12);

6,6'-{(2R,5R)-1-[3-fluoro-4-(piperidin-1-il)fenil]pirrolidin-2,5-diil}bis{5-fluoro-2-[(2S)-pirrolidin-2-il]-1H-benzimidazol} (Nomenclatura ACD v12);

6,6'-{(2R,5R)-1-[3,5-difluoro-4-(piperidin-1-il)fenil]pirrolidin-2,5-diil}bis{5-fluoro-2-[(2S)-pirrolidin-2-il]-1H-benzimidazol} (Nomenclatura ACD v12); y

6,6'-{(2R,5R)-1-[3,5-difluoro-4-(4-fenilpiperidin-1-il)fenil]pirrolidin-2,5-diil}bis{5-fluoro-2-

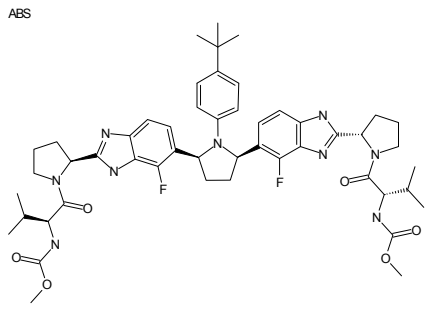
[(2S)-pirrolidin-2-il]-1H-benzimidazol} (Nomenclatura ACD v12).



Ejemplo 6.3

{(2S)-1-[(2S)-2-{5-[(2R,5R)-1-(4-tert-butilfenil)-5-{7-fluoro-2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-benzimidazol-6-il}pirrolidin-2-il]-4-fluoro-1H-benzimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

1H RMN (400 MHz, CDCl3) δ ppm 10,41-10,64 (m, 2H) 6,84-7,06 (m, 6H) 6,25-6,36 (m, 2H) 5,55-5,68 (m, 1H) 5,25-5,46 (m, 4H) 4,27-4,40 (m, 1H) 3,79-3,92 (m, 2H) 3,71 (s, 6H) 3,56-3,67 (m, 2H) 3,03-3,27 (m, 2H) 1,83-2,66 (m, 10H) 1,14 (s, 9H) 0,77-1,31 (m, 14H); MS (ESI) m/z 924 (M+H)+.

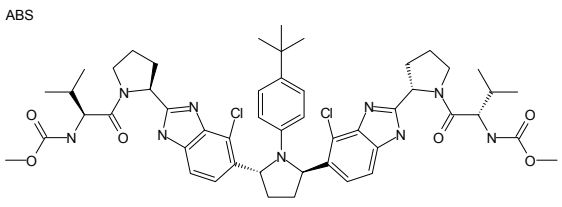


Ejemplo 6.4

{(2S)-1-[(2S)-2-{5-[(2R,5S)-1-(4-tert-butilfenil)-5-{7-fluoro-2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-benzimidazol-6-il}pirrolidin-2-il]-4-fluoro-1H-benzimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

1H RMN (400 MHz, CDCl3) δ ppm 10,54-10,71 (m, 2H) 7,54-7,68 (m, 2H) 7,00-7,21 (m, 4H) 6,43-6,54 (m, 2H) 5,27-5,50 (m, 4H) 5,20 (br s, 2H) 4,29-4,42 (m, 1H) 3,80-3,94 (m, 2H) 3,71 (s, 6H) 3,59-3,69 (m, 2H) 3,04-3,29 (m, 2H) 1,86-2,66 (m, 10H) 1,18 (s, 9H) 0,79-

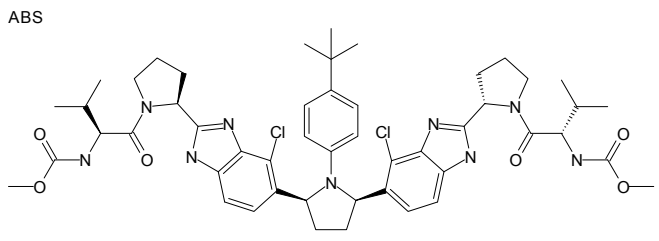
1,33 (m, 14H); MS (ESI) m/z 924 (M+H)+.



Ejemplo 6.5

{(2S)-1-[(2S)-2-{5-[(2R,5R)-1-(4-tert-butilfenil)-5-{4-cloro-2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-benzimidazol-5-il}pirrolidin-2-il]-4-cloro-1H-benzimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

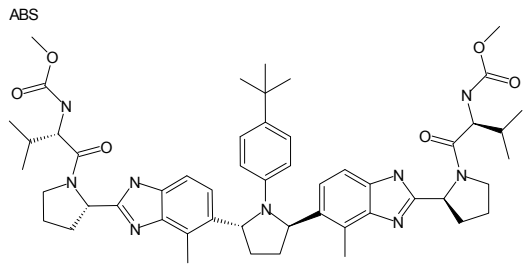
1H RMN (400 MHz, DMSO-d6) δ 12,70 (s, 0H), 12,39 (s, 1H), 8,07 (s, 1H), 7,32 (dd, J = 26,1, 8,1, 3H), 6,91 (d, J = 37,0, 4H), 6,08 (d, J = 7,9, 1H), 5,64 (s, 1H), 5,17 (s, 1H), 4,66 (s, 1H), 4,10 (d, J = 5,2, 1H), 3,86 (s, 3H), 3,52 (d, J = 14,1, 6H), 3,17 (d, J = 5,2, 1H), 2,30 – 2,10 (m, 2H), 2,00 (s, 4H), 1,77 (s, 1H), 1,23 (s, 1H), 1,18 – 1,01 (m, 9H), 1,01 – 0,72 (m, 11H); MS (APCI+) m/z 958,76 (M+H)+.



Ejemplo 6.6

{(2S)-1-[(2S)-2-{5-[(2R,5S)-1-(4-tert-butilfenil)-5-{4-cloro-2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-benzimidazol-5-il}pirrolidin-2-il]-4-cloro-1H-benzimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

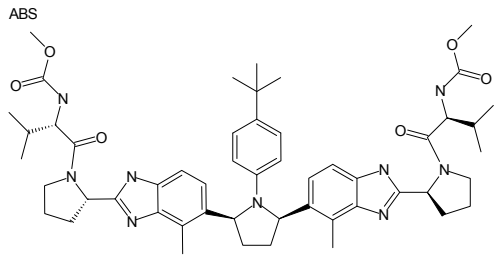
1H RMN (400 MHz, DMSO-d6) δ 12,45 (s, 1H), 8,06 (d, J = 3,3, 1H), 7,68 (d, J = 8,6, 2H), 7,48 (t, J = 12,5, 2H), 7,31 (d, J = 8,2, 2H), 7,00 (d, J = 8,1, 2H), 6,20 (d, J = 8,7, 2H), 5,16 (d, J = 32,0, 4H), 4,66 (s, 1H), 4,11 (s, 1H), 3,88 (s, 3H), 3,56 (d, J = 8,1, 6H), 2,30 – 2,09 (m, 5H), 2,02 (s, 7H), 1,80 (s, 2H), 1,23 (s, 2H), 1,09 (s, 9H), 1,00 – 0,78 (m, 12H); MS(APCI+) m/z 958,64 (M+H)+.



Ejemplo 6.7

{(2S)-1-[(2S)-2-{5-[(2R,5R)-1-(4-tert-butilfenil)-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-4-metil-1H-benzimidazol-5-il}pirrolidin-2-il]-4-metil-1H-benzimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

1H RMN (400 MHz, DMSO-d6) □ ppm 0,78 - 1,05 (m, 14 H), 1,06 (s, 9 H), 1,86 - 2,06 (m, 8 H), 2,09 - 2,31 (m, 4 H), 2,58 - 2,72 (m, 6 H), 3,54 (s, 6 H), 3,79 - 3,93 (m, 4 H), 4,02 - 4,17 (m, 2 H), 5,11 - 5,23 (m, 2 H), 5,42 - 5,51 (m, 2 H), 6,02 - 6,12 (m, 2 H), 6,71 - 6,83 (m, 2 H), 6,83 - 6,96 (m, 2 H), 7,04 - 7,19 (m, 2 H), 7,24 - 7,35 (m, 2 H), 11,84 - 12,26 (m, 2 H).

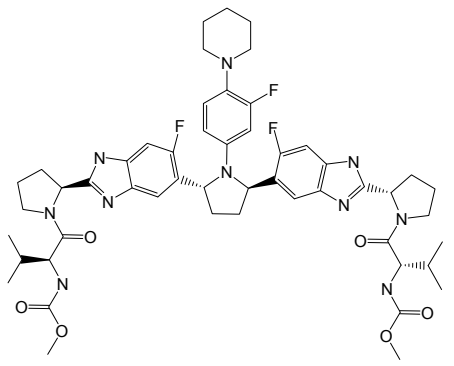


Ejemplo 6.8

{(2S)-1-[(2S)-2-{5-[(2R,5S)-1-(4-tert-butilfenil)-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-4-metil-1H-benzimidazol-5-il}pirrolidin-2-il]-4-metil-1H-benzimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

1H RMN (400 MHz, DMSO-d6) □ ppm 0,79 - 1,06 (m, 12 H), 1,23 (s, 9 H), 1,87 - 2,31 (m, J=30,69 Hz, 12 H), 2,58 - 2,65 (m, J=3,25 Hz, 6 H), 3,55 (s, 6 H), 3,81 - 3,96 (m, 4 H), 4,01 - 4,19 (m, 2 H), 4,92 (s, 2 H), 5,12 - 5,26 (m, 2 H), 6,14 - 6,26 (m, 2 H), 6,86 - 7,02 (m, 2 H), 7,22 - 7,39 (m, 4 H), 7,57 - 7,79 (m, 2 H), 11,90 - 12,32 (m, 2 H); MS (ESI) m/z =

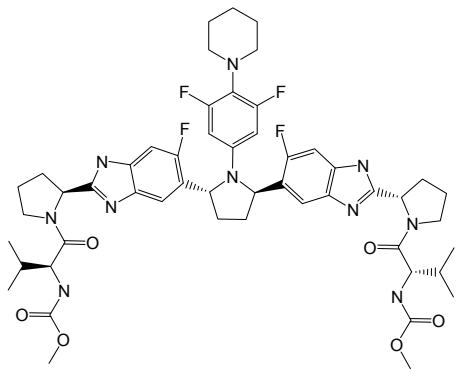
916,4 (M+H)+.



Ejemplo 6.9

{(2S)-1-[(2S)-2-(6-fluoro-5-{(2R,5R)-5-{6-fluoro-2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-benzimidazol-5-il}-1-[3-fluoro-4-(piperidin-1-il)fenil]pirrolidin-2-il}-1H-benzimidazol-2-il)pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

1H RMN (400 MHz, CDCl3) δ ppm 10,21-10,67 (m, 2H) 6,55-7,99 (m, 6H) 5,95-6,14 (m, 1H) 5,19-5,56 (m, 6H) 4,25-4,39 (m, 1H) 3,77-3,92 (m, 2H) 3,70 (s, 6H) 3,42-3,76 (m, 3H) 2,95-3,17 (m, 2H) 2,64-2,95 (m, 2H) 2,43-2,64 (m, 1H) 1,78-2,42 (m, 11H) 0,62-1,78 (m, 18H); MS (ESI) m/z 969 (M+H)+.

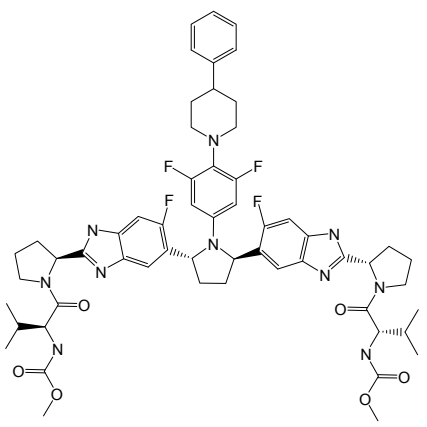


Ejemplo 6.10

{(2S)-1-[(2S)-2-{5-[(2R,5R)-1-[3,5-difluoro-4-(piperidin-1-il)fenil]-5-{6-fluoro-2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-benzimidazol-5-il}pirrolidin-2-il]-6-fluoro-1H-benzimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

A una solución de 6,6'-{(2R,5R)-1-[3,5-difluoro-4-(piperidin-1-il)fenil]pirrolidin-2,5-

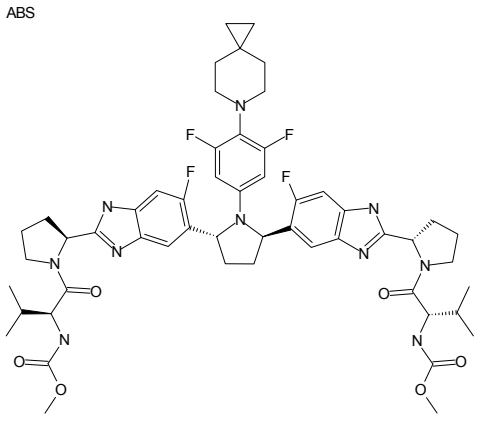
diil}bis{5-fluoro-2-[(2S)-pirrolidin-2-il]-1H-benzimidazol} (64 mg, 0,095 mmol) en DMF (2378 µL) se agrego ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico (35,0 mg, 0,200 mmol), EDC (45,6 mg, 0,238 mmol), HOBT (36,4 mg, 0,238 mmol) y N-metilmorfolina (105 µL, 0,951 mmol), y la solución resultante se agitó a temperatura ambiente durante la noche. La solución de la reacción se diluyó con EtOAc, se lavó con H2O y salmuera, se secó (MgSO4), se filtró y se concentró. El material crudo se disolvió en 1:1 CH3CN:0,1% TFA/H2O y se purificó mediante HPLC (C18, 0-100% CH3CN/0,1%TFA/H2O). Las fracciones que contenían el producto se combinaron, se basificaron con solución saturada de bicarbonato de sodio, y se extrajeron con EtOAc. La capa orgánica se secó (MgSO4), se filtró y se concentró para dar el compuesto del título (43,3 mg, 0,044 mmol, 46,1 % de rendimiento). El compuesto del título también se puede preparar de acuerdo con el procedimiento general 12C como se ha descrito. 1H RMN (400 MHz, CDCl3) δ ppm 10,25-10,70 (m, 2H) 6,83-7,53 (m, 4H) 5,70-5,91 (m, 2H) 5,20-5,52 (m, 4H) 4,21-4,42 (m, 2H) 3,70 (s, 6H) 3,53-3,94 (m, 6H) 1,75-3,17 (m, 16H) 0,63-1,74 (m, 18H); MS (ESI) m/z 987 (M+H)+.



Ejemplo 6.11

{(2S)-1-[(2S)-2-{5-[(2R,5R)-1-[3,5-difluoro-4-(4-fenilpiperidin-1-il)fenil]-5-{6-fluoro-2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-benzimidazol-5-il}pirrolidin-2-il]-6-fluoro-1H-benzimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

1H RMN (400 MHz, CDCl3) δ ppm 10,54 (br s, 2H) 7,09-7,33 (m, 9H) 5,77-5,92 (m, 2H) 5,23-5,52 (m, 4H) 4,24-4,39 (m, 2H) 3,79-3,91 (m, 2H) 3,70 (s, 6H) 3,55-3,67 (m, 2H) 2,92-3,21 (m, 5H) 1,73-2,65 (m, 10H) 0,97-1,74 (m, 8H) 0,76-0,96 (m, 12H); MS (ESI) m/z 1063 (M+H)+.

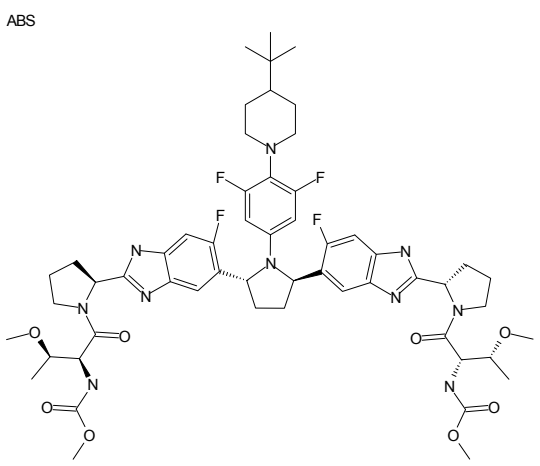


Ejemplo 6.12

{(2S)-1-[(2S)-2-{5-[(2R,5R)-1-[4-(6-azaespiro[2,5]oct-6-il)-3,5-difluorofenil]-5-{6-fluoro-2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-benzimidazol-5-il}pirrolidin-2-il]-6-fluoro-1H-benzimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

En un recipiente en forma de pera de 5 ml secado al horno , se disolvió ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico (56,6 mg, 0,323 mmol) en CH2Cl2 anhidro (1 mL) bajo nitrógeno, se agregó EDAC (63,2 mg, 0,323 mmol), y se agitó a 20 °C durante 20 min. La solución resultante se agregó por medio de una jeringa hermética al gas a una solución de clorhidrato de (S)-6,6'-((2R,5R)-1-(3,5-difluoro-4-(6-azaespiro[2,5]octan-6-il)fenil)pirrolidin-2,5-diil)bis(5-fluoro-2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol) (91 mg) y diisopropiletilamina (0,188 mL, 1,077 mmol) en CH2Cl2 anhidro (2 mL) bajo nitrógeno, se agregó hidrato de HOBT (49,5 mg, 0,323 mmol), y se agitó a 20 °C durante 1 hr. La reacción se diluyó con CH2Cl2 (50 mL), se lavó con agua (25 mL), se secó sobre Na2SO4 anhidro, se filtró, y se concentró mediante evaporación por rotación para dar una espuma de color amarillo oscuro (~140 mg). Se disolvieron 70 mg del material impuro en 2 mL

Acetonitrilo y 2 mL 0,1% TFA en H2O, y se purificó mediante RP-C18 HPLC (Waters Prep LC, módulo de 40mm con cartucho Nova Pak HR C18 6µm 40x100mm Prep Pak) eluyendo con un 30 min gradiente de 95:5 0,1% TFA en H2O/Acetonitrilo a 25:75 0,1% TFA en H2O/Acetonitrilo, luego 10 min con acetonitrilo al 100% a 20 mL/min. Las fracciones puras se trataron con NaHCO3 acuoso saturado (2 mL/tubo), se centrifugó cada tubo para neutralizar totalmente el TFA, y se combinaron las soluciones en un balón de 500 ml. Los 70 mg remanentes se purificaron por HPLC prep como se ha descrito y las fracciones que contenían el producto puro se trataron con NaHCO3 acuoso saturado como se ha descrito y se combinaron en el mismo balón de 500 ml. Removed el acetonitrilo por evaporación por rotación, la fase acuosa remanente se extrajo con EtOAc (2 x 50 mL), los extractos orgánicos combinados se secaron sobre MgSO4 anhidro, se filtró, y se concentró por evaporación por rotación para dar el producto como un sólido blanco (49 mg, 0,048 mmol). 1H RMN (400 MHz, DMSO-d6) δ ppm 0,24 (s, 4 H), 0,68 - 0,91 (m, 12 H), 1,21 - 1,35 (m, 5 H), 1,67 - 2,07 (m, 9 H), 2,13 - 2,24 (m, 4 H), 2,84 (s, 4 H), 3,53 (s, 6 H), 3,73 - 3,87 (m, 4 H), 3,99 - 4,11 (m, 2 H), 5,02 - 5,23 (m, 2 H), 5,45 - 5,65 (m, 2 H), 5,81 - 5,99 (m, 2 H), 7,04 (d, J=6,07 Hz, 1 H), 7,14 (d, J=6,94 Hz, 1 H), 7,26 - 7,36 (m, 3 H), 7,41 (dd, J=11,06, 6,18 Hz, 1 H), 11,73 - 12,63 (m, 2 H); MS (ESI+) m/z 1013 (M+H)+; MS (ESI-) m/z 1011 (M-H)-.



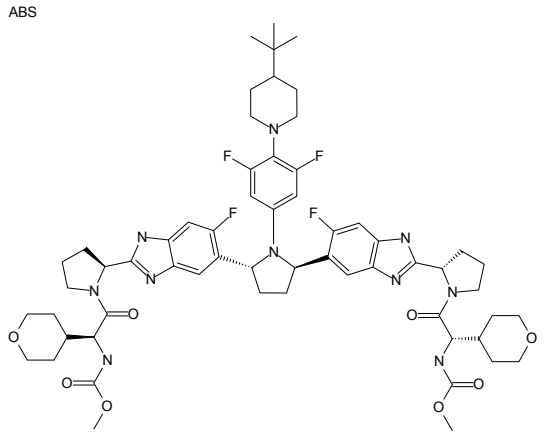
Ejemplo 6.13

{(2S,3R)-1-[(2S)-2-{5-[(2R,5R)-1-[4-(4-tert-butilpiperidin-1-il)-3,5-difluorofenil]-5-(6-fluoro-2-{(2S)-1-[N-(metoxicarbonil)-O-metil-L-treonil]pirrolidin-2-il}-1H-benzimidazol-5-il)pirrolidin-2-il]-6-fluoro-1H-benzimidazol-2-il}pirrolidin-1-il]-3-metoxi-1-oxobutan-2-il}carbamato de metilo

Se disolvió ácido (2S,3R)-3-Metoxi-2-(metoxicarbonilamino)butanoico (65,6 mg, 0,343 mmol) en CH2Cl2 anhidro (1 mL) bajo nitrógeno. Se agregó EDAC (67,1 mg, 0,343 mmol) , y la mezcla se agitó a 20 °C durante 20 minutos. La solución resultante se agregó en una solución de clorhidrato de (S)-6,6'-((2R,5R)-1-(4-(4-tert-butilpiperidin-1-il)-3,5-difluorofenil)pirrolidin-2,5-diil)bis(5-fluoro-2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol) (100 mg) y diisopropilamina (0,200 mL, 1,143 mmol) en CH2Cl2 anhidro (2 mL) bajo nitrógeno. Se agregó hidrato de HOBT (52,5 mg, 0,343 mmol) , y la mezcla se agitó a 20 °C durante 1 hora. La reacción se diluyó con CH2Cl2 (50 mL), se lavó con agua (25 mL), se secó sobre Na2SO4 anhidro, se filtró, y se concentró mediante evaporación por rotación para dar una espuma de color amarillo oscuro (140 mg). El material crudo (70 mg) se disolvió en acetonitrilo (2 mL) y 0,1% TFA en H2O (2 mL), y se purificó mediante RP-C18 HPLC (Waters Prep LC, módulo de 40 mm con cartucho Nova-Pak® HR C18 6µm 40×100mm Prep Pak) eluyendo con un gradiente de 10 min de 95:5 0,1% TFA en H2O/acetonitrilo a 25:75 0,1% TFA en H2O/acetonitrilo, luego de 10 minutos a acetonitrilo al 100% a 20 mL/minuto. Las fracciones puras se trataron con NaHCO3 acuoso saturado (2 mL/tubo), cada tubo se centrifugó para neutralizar totalmente el TFA, y las fracciones se combinaron en un balón de 500 ml. Los restantes 70 mg de material se purificaron mediante HPLC prep como se describe precedentemente y las fracciones que contenían el producto puro se trataron con NaHCO3 acuoso saturado como se ha descrito y se combinaron en el mismo balón de 500 ml. El acetonitrilo se retiró por evaporación por rotación, la fase acuosa remanente se extrajo con EtOAc (2×50 mL), los extractos orgánicos combinados se secaron sobre MgSO4 anhidro, se filtró, y se concentró por evaporación por rotación para dar el producto como un sólido blanco (62 mg, 0,057 mmol). 1H RMN (400 MHz,

DMSO-d6) δ ppm 0,80 (s, 9 H), 0,92 (d, J=6,07 Hz, 2 H), 0,98 - 1,09 (m, 4 H), 1,12 - 1,22 (m, 2 H), 1,44 - 1,63 (m, 3 H), 1,65 - 1,89 (m, 3 H), 1,91 - 2,10 (m, 4 H), 2,11 - 2,28 (m, 4 H), 2,73 - 2,92 (m, 4 H), 3,04 (d, J=1,73 Hz, 2 H), 3,13 (s, 3 H), 3,25 (d, J=3,47 Hz, 1 H), 3,41 - 3,50 (m, 3 H), 3,53 (s, 6 H), 3,72 - 3,92 (m, 4 H), 4,25 (q, J=7,99 Hz, 2 H), 5,02 - 5,17 (m, 2 H), 5,46 - 5,63 (m, 2 H), 5,79 - 6,00 (m, 2 H), 7,02 (d, J=6,72 Hz, 1 H), 7,08 - 7,18 (m, 2 H), 7,24 (d, J=8,02 Hz, 1 H), 7,33 (dd, J=10,36, 4,50 Hz, 1 H), 7,40 (dd, J=11,22, 6,23 Hz, 1 H), 11,84 - 12,63 (m, 2 H); MS (ESI+) m/z 1075 (M+H)+; MS (ESI-) m/z 1073 (M-H)-.

ABS



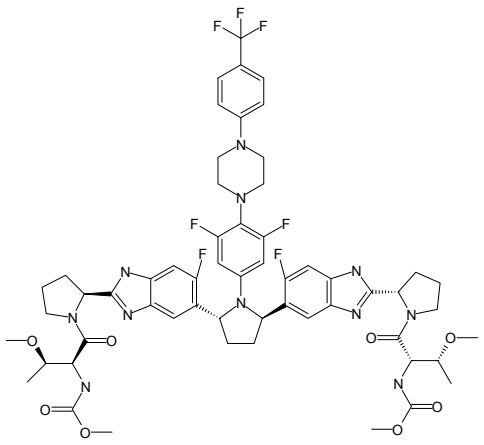
Ejemplo 6.14

({(2R,5R)-1-[4-(4-tert-butilpiperidin-1-il)-3,5-difluorofenil]pirrolidin-2,5-diil}bis{(6-fluoro-1H-benzimidazol-5,2-diil)(2S)pirrolidin-2,1-diil[(1S)-2-oxo-1-(tetrahidro-2H-piran-4-il)etan-2,1-diil]})biscarbamato de dimetilo

Se disolvió ácido (S)-2-(Metoxicarbonilamino)-2-(tetrahidro-2H-piran-4-il)acético (74,5 mg, 0,343 mmol) en CH2Cl2 anhidro (1 mL) bajo nitrógeno. Se agregó EDAC (67,1 mg, 0,343 mmol) , y la mezcla se agitó a 20 °C durante 20 minutos. La solución resultante se agregó a una solución de clorhidrato de (S)-6,6'-((2R,5R)-1-(4-(4-tert-butilpiperidin-1-il)-3,5-difluorofenil)pirrolidin-2,5-diil)bis(5-fluoro-2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol) (100 mg) y diisopropiletilamina (0,200 mL, 1,143 mmol) en CH2Cl2 anhidro (2 mL) bajo nitrógeno. Se agregó hidrato de HOBT (52,5 mg, 0,343 mmol) , y la mezcla se agitó a 20 °C durante 1 hora. La reacción se diluyó con CH2Cl2 (50 mL), se lavó con agua (25 mL),

se secó sobre Na2SO4 anhidro, se filtró, y se concentró mediante evaporación por rotación para dar un sólido amarillo oscuro (210 mg). El material impuro (70 mg) se disolvió en 2 mL de acetonitrilo y 2 mL 0,1% TFA en H2O, y se purificó mediante RP-C18 HPLC (Waters Prep LC, módulo de 40mm con cartucho Nova-Pak® HR C18 6µm 40×100mm Prep Pak) eluyendo con un gradiente de 30 minutos de 95:5 0,1% TFA en H2O/acetonitrilo a 25:75 0,1% TFA en H2O/acetonitrilo, luego de 10 minutos a acetonitrilo al 100% a 20 mL/minuto. Las fracciones puras se trataron con NaHCO3 acuoso saturado (2 mL/tubo), cada tubo se centrifugó para neutralizar totalmente el TFA, y las fracciones se combinaron en un balón de 500 ml. El material restante se purificó en dos inyecciones d 70 mg por HPLC prep como se describe precedentemente, y las fracciones que contenían el producto puro se trataron con NaHCO3 acuoso saturado como se ha descrito y se combinaron en el mismo balón de 500 ml. El acetonitrilo se retiró por evaporación por rotación, la fase acuosa remanente se extrajo con EtOAc (2×50 mL), los extractos orgánicos combinados se secaron sobre MgSO4 anhidro, se filtró, y se concentró por evaporación por rotación para dar el producto como un sólido blanco (69 mg, 0,060 mmol). 1H RMN (400 MHz, DMSO-d6) δ ppm 0,80 (s, 9 H), 0,89 - 1,01 (m, 1 H), 1,07 - 1,38 (m, 7 H), 1,39 - 1,63 (m, 6 H), 1,67 - 1,91 (m, 5 H), 1,92 - 2,05 (m, 4 H), 2,10 - 2,26 (m, 4 H), 2,71 - 2,95 (m, 5 H), 2,96 - 3,25 (m, 3 H), 3,52 (s, 6 H), 3,62 - 3,92 (m, 8 H), 4,06 - 4,23 (m, 2 H), 5,10 (t, J=6,23 Hz, 2 H), 5,39 - 5,65 (m, 2 H), 5,77 - 5,99 (m, 2 H), 7,01 (d, J=6,72 Hz, 1 H), 7,07 (d, J=7,05 Hz, 1 H), 7,28 - 7,49 (m, 4 H), 11,78 - 12,42 (m, 2 H); MS (ESI+) m/z 1127 (M+H)+; MS (ESI-) m/z 1125 (M-H)-.

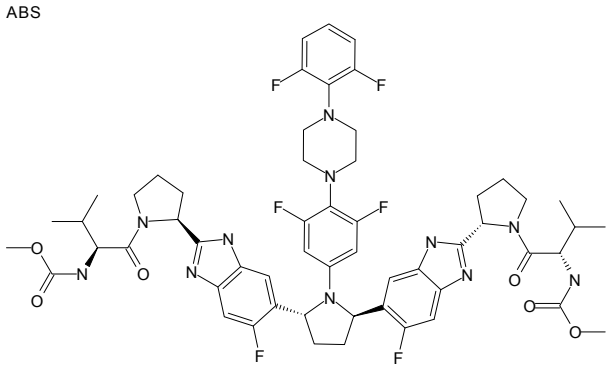
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Ejemplo 6.15

{(2S,3R)-1-[(2S)-2-{5-[(2R,5R)-1-(3,5-difluoro-4-{4-[4-(trifluorometil)fenil]piperazin-1-il}fenil)-5-(6-fluoro-2-{(2S)-1-[N-(metoxicarbonil)-O-metil-L-threonil]pirrolidin-2-il}-1H-benzimidazol-5-il)pirrolidin-2-il]-6-fluoro-1H-benzimidazol-2-il}pirrolidin-1-il]-3-metoxi-1-oxobutan-2-il}carbamato de metilo

Se disolvieron clorhidrato de (S)-6,6'-((2R,5R)-1-(3,5-Difluoro-4-(4-(4-(trifluorometil)fenil)piperazin-1-il)fenil)pirrolidin-2,5-diil)bis(5-fluoro-2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol) (88 mg), ácido (2S,3R)-3-metoxi-2-(metoxicarbonilamino)butanoico (41 mg, 0,216 mmol), clorhidrato de N-(3-dimetilaminopropil)-N'-etilcarbodiimida (46 mg, 0,238 mmol), hidrato de 1-hidroxibenzotriazol (36 mg, 0,238 mmol) y 4-metilmorfolina (0,095 mL, 0,864 mmol) en DMF (3,0 mL), y la mezcla se agitó a temperatura ambiente durante 3 horas. A continuación, se agregó una mezcla de alcohol isopropílico y cloroformo y luego se extrajo con ácido clorhídrico acuoso 1N. El extracto orgánico se secó, se filtró y se concentró, y luego el residuo se purificó mediante cromatografía (gel de sílice, metanol en diclorometano) para dar 71 mg del compuesto del título. 1H RMN (400 MHz, DMSO-d6) □ ppm 7,56 (m, 2H), 7,48 (d, J=8,8Hz, 2H), 7,34 (m, 2H), 7,18 (m, 2H), 7,04 (d, J=8,6Hz, 2H), 5,97 (m, 2H), 5,62 (m, 2H), 5,17 (m, 2H), 4,28 (m, 2H), 3,82 (m, 2H), 3,60 (m, 2H), 3,54 (s, 6H), 3,25 (m, 8H), 3,17 (s, 6H), 2,99 (m, 4H), 2,05 (m, 12H), 1,25 (m, 6H); MS (ESI) m/z 1164 (M+H)+.

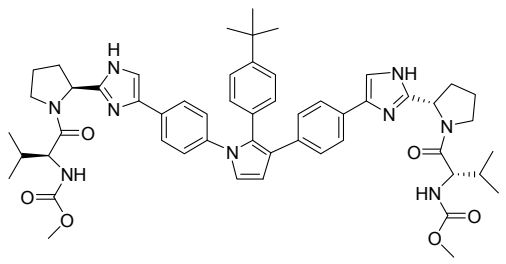


Ejemplo 6.16

{(2S)-1-[(2S)-2-{6-[(2R,5R)-1-{4-[4-(2,6-difluorofenil)piperazin-1-il]-3,5-difluorofenil}-5-{5-fluoro-2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-benzimidazol-6-il}pirrolidin-2-il]-5-fluoro-1H-benzimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

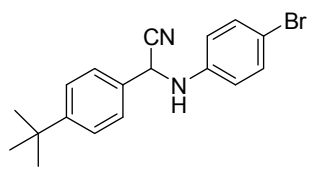
Se combinaron ácido (S)-2-(Metoxicarbonilamino)-3-metilbutanoico (0,072 g, 0,410 mmol) y HOBt (0,063 g, 0,410 mmol) en DMF (2 mL). A la solución traslúcida se agregó EDAC (0,079 g, 0,410 mmol) con un enjuague de 0,2 ml de DMF , y la solución límpida resultante se agitó a temperatura ambiente durante 20 minutos. Se disolvió clorhidrato de (S)-6,6'-((2R,5R)-1-(4-(4-(2,6-Difluorofenil)piperazin-1-il)-3,5-difluorofenil)pirrolidin-2,5-diil)bis(5-fluoro-2-((S)-pirrolidin-2-il)-1H-benzo[d]imidazol) (0,160 g) en 2 ml DMF, se trató con N-metilmorfolina (1,863 mmol, 0,205 ml), y luego se trató con la solución de aminoácido activado y la solución de color marrón claro resultante se agitó a temperatura ambiente durante 1 hora. El pH de la solución se determinó en 8 usando papel de medición de pH. El progreso de la reacción se determinó por LC-MS en 1 hora y el análisis determinó que se había completado la reacción. La mezcla de reacción se concentró al vacío para dar un aceite de color marrón. El aceite se diluyó con 50 ml EtOAc y se lavó con 30 mL 10% NaHCO3. Las capas se separaron y la capa acuosa se extrajo con otro 50 mL EtOAc. Los extractos orgánicos combinados se lavaron con 10% NaCl, se secó sobre Na2SO4 anhidro(s), se filtró y el solvente se eliminó al vacío dejando un residuo aceitoso de color marrón. El residuo se purificó en una columna de 12 g de gel de

sílice eluida con un gradiente de CH2Cl2/CH3OH, 99/1 a 95/5 a lo largo de 13 minutos, luego 95/5 a 90/10 a lo largo de 8 minutos. Las fracciones que contenían producto se combinaron y se volvieron a purificar en una columna de 12 g de oro eluida con un gradiente de CH2Cl2/CH3OH, 98/2 a 90/10 a lo largo de 15 minutos. Las fracciones se concentraron al vacío dejando un sólido marrón claro como el compuesto del título (50,3 mg). 1H RMN (400 MHz, DMSO-d6) □ ppm 0,82 (m, 12 H) 1,99 (m, 9 H) 2,18 (m, 2 H) 2,95 (m, 4 H) 3,05 - 3,17 (m, 5 H) 3,53 (s, 6 H) 3,79 (m, 4 H) 3,95 - 4,11 (m, 4 H) 5,11 (m, 2 H) 5,55 (m, 2 H) 5,91 (m, 2 H) 7,01 (m, 5 H) 7,29 (m, 4 H) 12,14 (m, 2 H); MS (ESI+) m/z 1100,3, (ESI-) m/z 1098,3(M-H)-.



Ejemplo 7.1

{(2S)-1-[(2S)-2-(4-{4-[2-(4-tert-butilfenil)-1-(4-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-4-il}fenil)-1H-pirrol-3-il]fenil}-1H-imidazol-2-il)pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

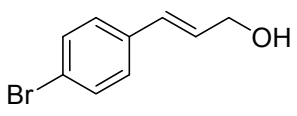


Ejemplo 7.1A

2-(4-bromofenilamino)-2-(4-tert-butilfenil)acetonitrilo

A una solución de 4-bromoanilina (10,0 g, 58,1 mmol) en THF (100 mL) se agregó 4-tert-butilbenzaldehido (9,72 mL, 58,1 mmol), ácido acético (13,3 mL, 233 mmol), cianuro de potasio (3,79 g, 58,1 mmol) y agua (50 mL). La mezcla resultante se agitó a temperatura ambiente durante 16 horas. El sólido resultante que se formó se recogió mediante filtración al vacío, se lavó con hexano, y luego se secó para dar 15,3 g, (77%)

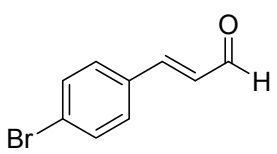
del compuesto del título. 1H RMN (400 MHz, CDCl3) ppm 7,49 (m, 4H), 7,37 (d, J=8,7 Hz, 2H), 6,66 (d, J=8,8 Hz, 2H), 5,34 (d, J=8,1 Hz, 1H), 4,02 (d, J=8,0 Hz, 1H), 1,34 (s, 9H).



Ejemplo 7.1B

(E)-3-(4-bromofenil)prop-2-en-1-ol

A una solución de (E)-etil 3-(4-bromofenil)acrilato (10,0 g, 39,2 mmol) en diclorometano (151 mL) enfriada a -78°C se agregó una solución de hidruro de diisobutilaluminio (1,0 M en diclorometano, 82 mL, 82 mmol) por goteo a lo largo de 15 minutos . La solución luego se agitó por otras 2 horas y luego se agregó una solución de 10% acuoso hidróxido de sodio (250 mL). La mezcla se dejó calentar a temperatura ambiente, y luego la mezcla se extrajo con diclorometano. La capa orgánica se secó y se concentró para dar 8,35 g (100%) del compuesto del título que se usaron directamente en la siguiente reacción.

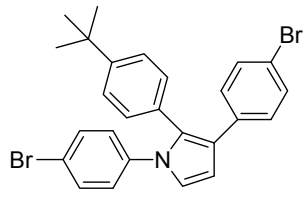


Ejemplo 7.1C

(E)-3-(4-bromofenil)acrilaldehido

Al producto del Ejemplo 7.1B (8,35 g, 39,2 mmol) disuelto en diclorometano (151 mL) se agregó dicromato de piridinio (22,11 g, 58,8 mmol), y la mezcla resultante se agitó durante 16 horas a temperatura ambiente. Una solución de hexano se agregó, y la mezcla resultante se filtró a través de tierras diatomeas, y luego se concentró. Agua se agregó agua al residuo, y la mezcla se extrajo con acetato de etilo. Las capas orgánicas se combinaron, se secó y luego se concentró. El residuo se purificó mediante cromatografía (gel de sílice, hexanos en acetato de etilo) para dar 5,5 g, (67%) del compuesto del título.

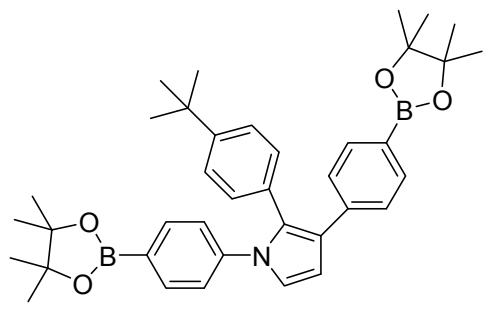
1H RMN (400 MHz, CDCl3) ppm 9,62 (d, J=7,6 Hz, 1H), 7,57 (d, J=8,5 Hz, 2H), 7,42 (m, 3H), 6,70 (dd, J=15,9, 7,6 Hz, 1H).



Ejemplo 7.1D

1,3-bis(4-bromofenil)-2-(4-tert-butilfenil)-1H-pirrol

Al producto del Ejemplo 7.1C (0,676 g, 3,2 mmol) y el producto del Ejemplo 7.1A (1,0 g, 2,91 mmol) se agregó etanol (30 mL) seguido por hidróxido de potasio (0,163 g, 2,91 mmol), y la mezcla se agitó a temperatura ambiente durante 16 horas. Luego la mezcla se concentró. El residuo se particionó entre agua y acetato de etilo. Las capas orgánicas se combinaron, se secó y luego se concentró. El residuo se purificó mediante cromatografía (gel de sílice, hexanos en acetato de etilo) para dar 150 mg, (10%) del compuesto del título. 1H RMN (400 MHz, CDCl3) ppm 7,37 (m, 3H), 7,32 (d, J=8,5, 2H), 7,21 (d, J=8,4 Hz, 2H), 7,06 (d, J=8,3 Hz, 2H), 6,93 (m, 4H), 6,51 (dd, J=2,9 Hz, 1H), 1,29 (s, 9H).

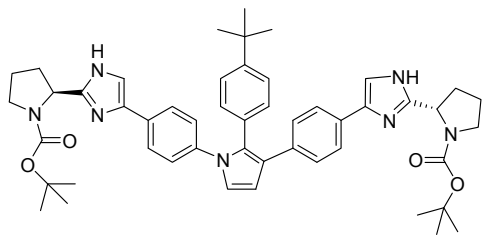


Ejemplo 7.1E

2-(4-tert-butilfenil)-1,3-bis(4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)-1H-pirrol

Una solución del producto del Ejemplo 7.1D (150 mg, 0,295 mmol), 4,4,4',4',5,5,5',5'-octametil-2,2'-bi(1,3,2-dioxaborolano) (165 mg, 0,648 mmol), acetato de potasio (87 mg, 8,84 mmol) y complejo de [1,1'-bis(difenilfosfino)ferrocen]dicloropaladio(II), con diclorometano (21,6 mg, 0,029 mmol) en

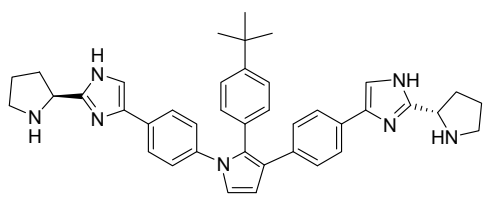
dioxano (5,5 mL) se calentó a 100°C durante 18 horas. La mezcla luego se filtró a través de tierras diatomeas y se concentró para dar un aceite que se disolvió en EtOAc y se extrajo con salmuera. El extracto orgánico se concentró para dar 230 mg del compuesto del título que se usó directamente en el siguiente paso.



Ejemplo 7.1F

(2S,2'S)-2,2'-{[2-(4-tert-butilfenil)-1H-pirrol-1,3-diil]bis(bencen-4,1-diil-1H-imidazol-4,2-diil)}dipirrolidin-1-carboxilato de di-tert-butilo (Nomenclatura ACD v12)

Se calentaron el producto del Ejemplo 7.1E (227 mg, 0,376 mmol), 2-(5-bromo-1H-imidazol-2-il)pirrolidin-1-carboxilato de (S)-tert-butilo o 2-(4-bromo-1H-imidazol-2-il)pirrolidin-1-carboxilato de (S)-tert-butilo (357 mg, 1,13 mmol), [1,1'-bis(difenilfosfino)ferrocen]dicloropaladio(II), complejizado con diclorometano (27,5 mg, 0,038 mmol), y una solución de carbonato de sodio (1,0 M en agua, 1,13 mL, 1,13 mmol) en una solución de etanol (3 mL) y tolueno (3 mL) a 85°C durante 18 horas. Se mezcló y luego se agregó agua (10 mL) seguido por extracción con EtOAc (2×10 mL). El extracto orgánico se secó, se filtró y se concentró, y luego el residuo se purificó mediante cromatografía (gel de sílice, metanol en diclorometano) para dar 29 mg, (9 %) del compuesto del título; MS (ESI) m/z 823 (M+H)+.



Ejemplo 7.1G

4,4'-{[2-(4-tert-butilfenil)-1H-pirrol-1,3-diil]dibencen-4,1-diil}bis{2-[(2S)-pirrolidin-2-il]-1H-imidazol} (Nomenclatura ACD v12)

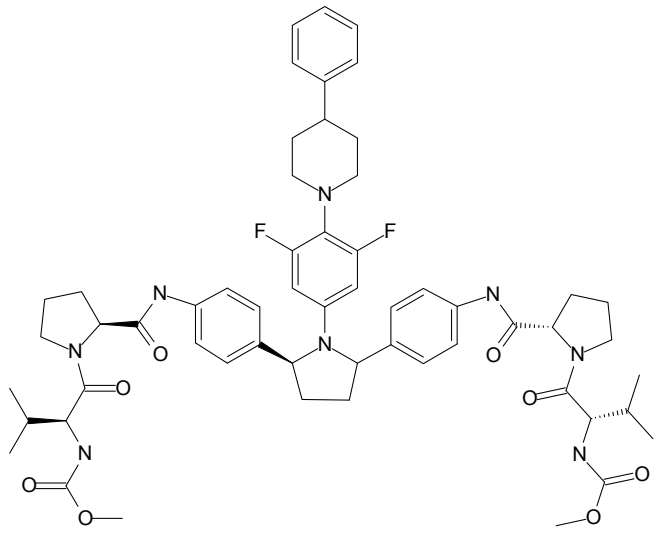
El producto del Ejemplo 7.1F (29 mg, 0,035 mmol) se disolvió en dioxano (0,5 mL) y se agregó ácido clorhídrico en dioxano (4,0 N, 0,14 mL, 0,54 mmol) . La mezcla se agitó a temperatura ambiente durante 4 horas. Luego la mezcla se concentró para dar el compuesto del título como una sal clorhidrato. MS (ESI) m/z 622 (M+H)+.

Ejemplo 7.1H

{(2S)-1-[(2S)-2-(4-{4-[2-(4-tert-butilfenil)-1-(4-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-4-il}fenil)-1H-pirrol-3-il]fenil}-1H-imidazol-2-il)pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

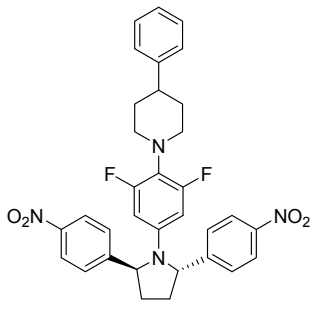
El producto del Ejemplo 7.1G (22 mg, 0,036 mmol), ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico (12,7 mg, 0,072 mmol), clorhidrato de N-(3-dimetilaminopropil)-N'-etilcarbodiimida (15,2 mg, 0,079 mmol), hidrato de 1-hidroxibenzotriazol (12,2 mg, 0,079 mmol) y 4-metilmorfolina (0,021 mL, 0,29 mmol) se disolvieron en DMF (0,7 mL), y la mezcla se agitó a temperatura ambiente durante 3 horas. A continuación, se agregó ácido clorhídrico acuoso 1N (5 mL) seguido por extracción con diclorometano (2×5 mL). El extracto orgánico se secó, se filtró y se concentró. Luego el residuo se purificó mediante cromatografía (gel de sílice, metanol en diclorometano) para dar 3,3 mg, (10 %) del compuesto del título. 1H RMN (400 MHz, DMSO-d6) □ ppm 10,57 (s, 1H), 10,26 (s, 1H), 7,62 (m, 4H), 7,20 (m, 8H), 6,99 (m, 4H), 5,37 (m, 2H), 5,24 (m, 2H), 4,30 (m, 2H), 3,80 (m, 2H), 3,08 (m, 1H), 2,96 (s, 3H), 2,88 (s, 3H), 2,30 (m, 2H), 2,19 (m, 2H), 2,08 (m, 2H), 1,92 (m, 2H), 1,23 (m, 9H), 0,85 (m, 12H); MS (ESI) m/z 936 (M+H)+.

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Ejemplo 8

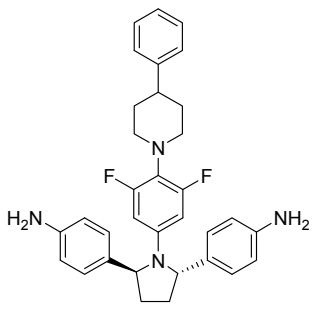
({(2S)-1-[3,5-difluoro-4-(4-fenilpiperidin-1-il)fenil]pirrolidin-2,5-diil}bis{4,1-fenilencarbamoil(2S)pirrolidin-2,1-diil[(2S)-3-metil-1-oxobutan-1,2-diil]})biscarbamato de dimetilo



Ejemplo 8A

1-(4-((2S,5S)-2,5-bis(4-nitrofenil)pirrolidin-1-il)-2,6-difluorofenil)-4-fenilpiperidina

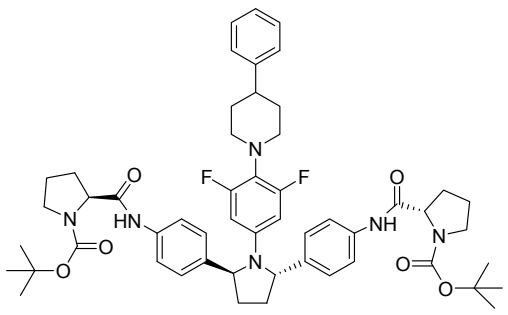
Una mezcla del Intermediario 6 (2,68 g, 5,49 mmol), 3,5-difluoro-4-(4-fenilpiperidin-1-il)anilina (1,90 g, 6,58 mmol) y diisopropiletilamina (9,58 mL, 54,9 mmol) en DMF (18,3 mL) se calentó a 60 °C durante 18 horas. Luego se agregó acetato de etilo a la solución seguido por extracción con agua. El extracto orgánico se secó, se filtró y se concentró y luego el residuo se purificó mediante cromatografía (gel de sílice, acetato de etilo en hexanos) para dar 197 mg, (6 %) del compuesto del título. MS (ESI) m/z 585 (M+H)+.



Ejemplo 8B

4,4'-((2S,5S)-1-(3,5-difluoro-4-(4-fenilpiperidin-1-il)fenil)pirrolidin-2,5-diil)dianilina

El producto del Ejemplo 8A (197 mg, 0,337 mmol) se disolvió en una mezcla de THF (3 mL), etanol (3 mL) y agua (0,5 mL), y luego hierro (95 mg, 1,69 mmol) y cloruro de amonio (27 mg, 0,506 mmol) se agregaron y la mezcla se calentó a 80 °C durante 3 horas. Luego se agregó acetato de etilo a la solución seguido por extracción con bicarbonato de sodio. El extracto orgánico se secó, se filtró y se concentró para dar 177 mg (100%) del compuesto del título. MS (ESI) m/z 525 (M+H)+.

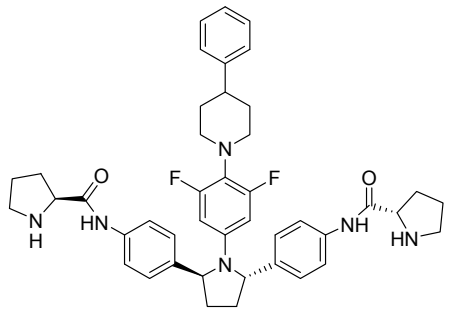


Ejemplo 8C

2,2'-(4,4'-((2S,5S)-1-(3,5-difluoro-4-(4-fenilpiperidin-1-il)fenil)pirrolidin-2,5-diil)bis(4,1-fenilen))bis(azandiil)bis(oxometilen)dipirrolidin-1-carboxilato de (2S,2'S)-tert-butilo

El producto del Ejemplo 8B (177 mg, 0,337 mmol), ácido (S)-1-(tert-butoxicarbonil)pirrolidin-2-carboxílico (160 mg, 0,742 mmol), clorhidrato de N-(3-dimetilaminopropil)-N'-etilcarbodiimida (162 mg, 0,843 mmol), hidrato de 1-hidroxibenzotriazol (129 mg, 0,843 mmol) y 4-metilmorfolina (0,370 mL, 3,37 mmol) se disolvieron en diclorometano (3,5 mL), y la mezcla se agitó a temperatura ambiente durante 19 horas. A continuación, se agregó bicarbonato de sodio acuoso seguido por

extracción con diclorometano. El extracto orgánico se secó, se filtró y se concentró, y luego el residuo se purificó mediante cromatografía (gel de sílice, metanol en diclorometano) para dar 130 mg, (42 %) del compuesto del título. MS (ESI) m/z 920 (M+H)+.



Ejemplo 8D

(2S,2'S)-N,N'-(4,4'-((2S,5S)-1-(3,5-difluoro-4-(4-fenilpiperidin-1-il)fenil)pirrolidin-2,5-diil)bis(4,1-fenilen))dipirrolidin-2-carboxamida

El producto del Ejemplo 8C (130 mg, 0,141 mmol) se disolvió en diclorometano (2,7 mL) y ácido trifluoroacético (0,27 mL, 3,5 mmol) y la mezcla se agitó a temperatura ambiente durante 1 hora. Luego la mezcla se concentró, el residuo se disolvió en una mezcla de alcohol isopropílico y cloroformo y luego se extrajo con bicarbonato de sodio acuoso. La fase orgánica luego se secó y se concentró para dar 100 mg (99%) del compuesto del título. MS (ESI) m/z 719 (M+H)+.

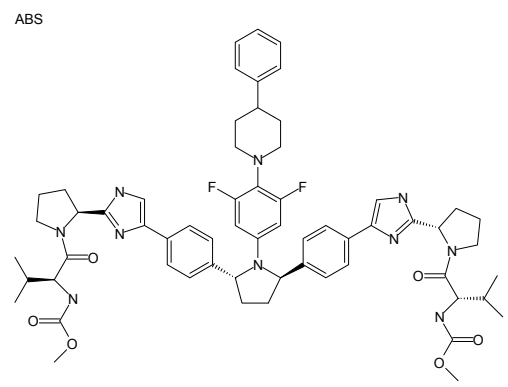
Ejemplo 8E

({(2S)-1-[3,5-difluoro-4-(4-fenilpiperidin-1-il)fenil]pirrolidin-2,5-diil}bis{4,1-fenilencarbamoil(2S)pirrolidin-2,1-diil[(2S)-3-metil-1-oxobutan-1,2-diil]})biscarbamato de dimetilo

El producto del Ejemplo 8D (100 mg, 0,142 mmol), ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico (60 mg, 0,341 mmol), clorhidrato de N-(3-dimetilaminopropil)-N'-etilcarbodiimida (68 mg, 0,355 mmol), hidrato de 1-hidroxibenzotriazol (54 mg, 0,355 mmol) y 4-metilmorfolina (0,156 mL, 1,42 mmol) se disolvieron en DMF (1,5 mL), y la mezcla se agitó a temperatura ambiente durante 19

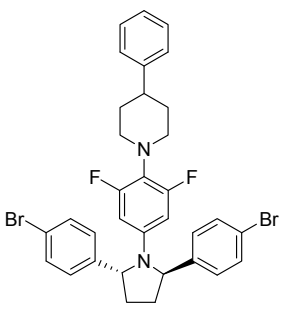
horas. A continuación, una mezcla de alcohol isopropílico y cloroformo se agregó y luego se extrajo con bicarbonato de sodio acuoso. El extracto orgánico se secó, se filtró y se concentró, y luego el residuo se purificó mediante cromatografía (gel de sílice, metanol en diclorometano) para dar 20 mg, (14 %) del compuesto del título. 1H RMN (400 MHz, DMSO-d6) □ ppm 10,03 (s, 2H), 7,53 (d, J = 8,5Hz, 4H), 7,30 (m, 9H), 5,83 (d, J= 12,6 Hz, 2H), 5,18 (m, 2H), 5,08 (m, 2H), 4,43 (m, 2H), 4,02 (m, 4H), 3,61 (m, 2H), 3,54 (s, 6H), 2,98 (m, 4H), 2,18 (m, 2H), 1,93 (m, 6H), 1,70 (m, 6H), 0,81 (m, 12H); MS (ESI) m/z 1033 (M+H)+.

ABS



Ejemplo 9

{(2S)-1-[(2S)-2-(4-{4-[(2R,5R)-1-[3,5-difluoro-4-(4-fenilpiperidin-1-il)fenil]-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

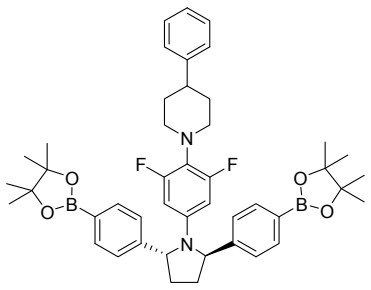


Ejemplo 9A

1-(4-((2R,5R)-2,5-bis(4-bromofenil)pirrolidin-1-il)-2,6-difluorofenil)-4-fenilpiperidina

Una mezcla del Intermediario 7 (2,35 g, 4,22 mmol), 3,5-difluoro-4-(4-fenilpiperidin-

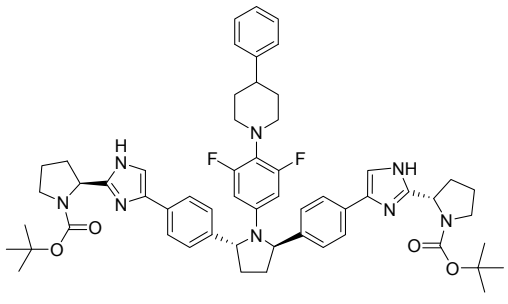
1-il)anilina (2,44 g, 8,45 mmol) y diisopropiletilamina (2,21 mL, 12,67 mmol) en acetonitrilo (25 mL) se calentó a 80°C durante 9 horas. Luego el sólido resultante se retiró mediante filtración y se purificó mediante cromatografía (gel de sílice, hexanos en acetato de etilo y luego diclorometano en hexanos) para dar 130 mg, (4,7%) del compuesto del título. MS (ESI+) m/z 653 (M+H)+.



Ejemplo 9B

1-(4-((2R,5R)-2,5-bis(4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)pirrolidin-1-il)-2,6-difluorofenil)-4-fenilpiperidina

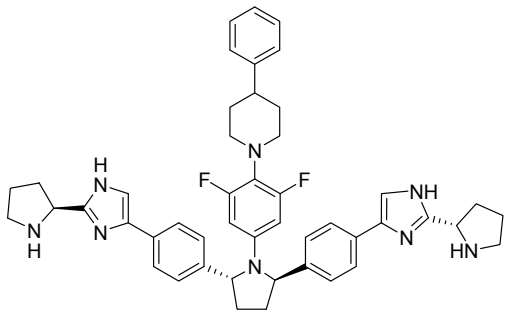
Una solución del producto del Ejemplo 9A (130 mg, 0,199 mmol), 4,4,4',4',5,5,5',5'-octametil-2,2'-bi(1,3,2-dioxaborolano) (121 mg, 0,478 mmol), acetato de potasio (59 mg, 0,598 mmol) y [1,1’-bis(difenilfosfino)ferrocen]dicloropaladio(II) (29 mg, 0,04 mmol) en dioxano (4,5 mL) se calentó a 100 °C durante 3 horas. La mezcla luego se filtró a través de tierras diatomeas y se concentró para dar un aceite que se disolvió en EtOAc y se extrajo con ácido clorhídrico acuoso 1N. El extracto orgánico se secó, se filtró y se concentró, y luego el residuo se purificó mediante cromatografía (gel de sílice, acetato de etilo en hexanos) para dar 50 mg, (34 %) del compuesto del título. MS (ESI) m/z 747 (M+H)+.



Ejemplo 9C

2,2'-(4,4'-(4,4'-((2R,5R)-1-(3,5-difluoro-4-(4-fenilpiperidin-1-il)fenil)pirrolidin-2,5-diil)bis(4,1-fenilen))bis(1H-imidazol-4,2-diil))dipirrolidin-1-carboxilato de (2S,2'S)-tert-butilo

El producto del Ejemplo 9B (50 mg, 0,067 mmol), el Intermediario 1 (64 mg, 0,201 mmol), [1,1'-bis(difenilfosfino)ferrocen]dicloropaladio(II) (6,1 mg, 0,0084 mmol), y carbonato de sodio (1,0 M en agua, 0,27 mL, 0,27 mmol) se calentaron en etanol (1,5 mL) y tolueno (1,5 mL) a 85 °C durante 17 horas. Se agregó agua (10 mL) a la mezcla seguida por extracción con diclorometano. El extracto orgánico se secó, se filtró y se concentró, y luego el residuo se purificó mediante cromatografía (gel de sílice, metanol en diclorometano) para dar 51 mg, (79 %) del compuesto del título. MS (ESI) m/z 966 (M+H)+.



Ejemplo 9D

1-(4-((2R,5R)-2,5-bis(4-(2-((S)-pirrolidin-2-il)-1H-imidazol-4-il)fenil)pirrolidin-1-il)-2,6-difluorofenil)-4-fenilpiperidina

El producto del Ejemplo 9C (50 mg, 0,052 mmol) se disolvió en dioxano (1,5 mL) y ácido clorhídrico en dioxano (4,0 N, 0,65 mL, 2,6 mmol), y la mezcla se agitó a temperatura ambiente durante 4 horas. Luego la mezcla se concentró para dar el compuesto del título como una sal clorhidrato. MS (ESI) m/z 765 (M+H)+.

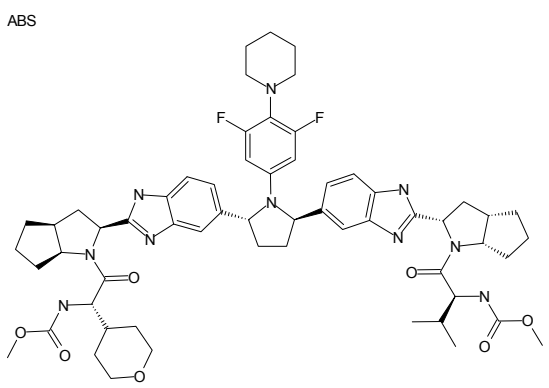
Ejemplo 9E

{(2S)-1-[(2S)-2-(4-{4-[(2R,5R)-1-[3,5-difluoro-4-(4-fenilpiperidin-1-il)fenil]-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 9D (40 mg, 0,052 mmol), ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico (18,3 mg, 0,105 mmol), clorhidrato de N-(3-dimetilaminopropil)-N'-etilcarbodiimida (22,1 mg, 0,115 mmol), hidrato de 1-hidroxibenzotriazol (17,6 mg, 0,115 mmol) y 4-metilmorfolina (0,046 mL, 0,418 mmol) se disolvieron en DMF (1,5 mL), y la mezcla se agitó a temperatura ambiente durante 19 horas. A continuación, se agregó ácido clorhídrico acuoso 1N seguido por extracción con diclorometano. El extracto orgánico se secó, se filtró y se concentró, y luego el residuo se purificó mediante cromatografía (gel de sílice, metanol en diclorometano) para dar 25 mg, (44 %) del compuesto del título. 1H RMN (400 MHz, DMSO-d6) □ ppm 7,64 (m, 5H), 7,23 (m, 11H), 5,89 (d, J= 12,8 Hz, 2H), 5,23 (m, 2H), 5,08 (m, 2H), 4,06 (m, 2H), 3,80 (m, 4H), 3,53 (s, 6H), 2,96 (m, 4H), 2,18 (m, 2H), 1,99 (m, 6H), 1,70 (m, 6H), 0,83 (m, 12H); MS (ESI) m/z 1080 (M+H)+.

A partir del producto del Procedimiento General 11C, se pueden obtener los compuestos de los Ejemplos 10,1 y 10,2 por medio de los siguientes pasos : (1) acoplamiento con ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico ; (2) remoción del único grupo protector de Boc; y (3) acoplamiento con un segundo carbamato seleccionado de-aminoácido protegido.



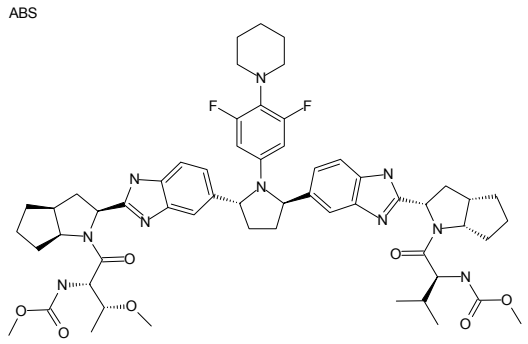
Ejemplo 10.1

[(1S)-2-[(2S,3aS,6aS)-2-{5-[(2R,5R)-1-[3,5-difluoro-4-(piperidin-1-il)fenil]-5-{2-

[(2S,3aS,6aS)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}octahidrociclopenta[b]pirrol-2-il]-1H-benzimidazol-5-il}pirrolidin-2-il]-1H-benzimidazol-2-il}hexahidrociclopenta[b]pirrol-1(2H)-il]-2-oxo-1-(tetrahidro-2H-piran-4-il)etil]carbamato de metilo

1H RMN (400 MHz, DMSO-d6) □ ppm 0,70 - 0,91 (m, 6 H) 1,10 - 1,27 (m, 2 H) 1,34 - 1,49 (m, 8 H) 1,50 - 1,64 (m, 4 H) 1,65 - 1,81 (m, 4 H) 1,84 - 2,03 (m, 6 H) 2,05 - 2,18 (m, 4 H) 2,36 - 2,46 (m, 4 H) 2,72 - 2,86 (m, 6 H) 3,02 - 3,21 (m, 2 H) 3,54 (s, 6 H) 3,70 - 3,89 (m, 2 H) 3,97 - 4,17 (m, 2 H) 4,72 - 4,86 (m, 2 H) 5,07 - 5,20 (m, 2 H) 5,32 - 5,43 (m, 2 H) 5,84 - 5,94 (m, 2 H) 7,07 (t, J=10,08 Hz, 2 H) 7,17 - 7,27 (m, 2 H) 7,30 - 7,56 (m, 4 H) 11,92 - 11,99 (m, 1 H) 12,03 - 12,13 (m, 1 H); MS (ESI+) m/z 1073,4 (M+H)+.

ABS



Ejemplo 10.2

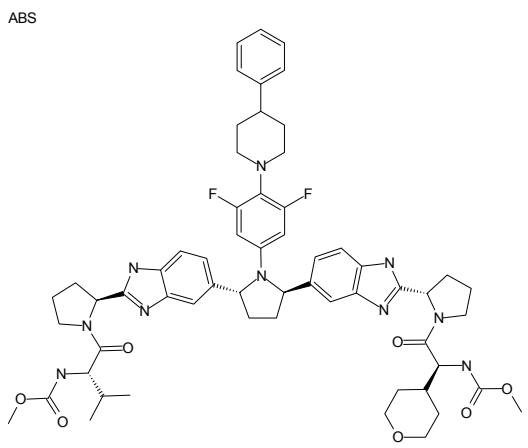
{(2S,3R)-1-[(2S,3aS,6aS)-2-{5-[(2R,5R)-1-[3,5-difluoro-4-(piperidin-1-il)fenil]-5-{2-[(2S,3aS,6aS)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}octahidrociclopenta[b]pirrol-2-il]-1H-benzimidazol-5-il}pirrolidin-2-il]-1H-benzimidazol-2-il}hexahidrociclopenta[b]pirrol-1(2H)-il]-3-metoxi-1-oxobutan-2-il}carbamato de metilo

1H RMN (400 MHz, DMSO-d6) □ ppm 0,70 - 0,89 (m, 6 H) 0,99 (ddd, J=34,43, 6,29, 3,31 Hz, 3 H) 1,35 - 1,48 (m, 6 H) 1,50 - 1,63 (m, 4 H) 1,66 - 1,80 (m, 6 H) 1,83 - 2,00 (m, 6 H) 2,05 - 2,16 (m, 4 H) 2,72 - 2,83 (m, 4 H) 3,17 (s, 3 H) 3,21 - 3,28 (m, 4 H) 3,54 (s, 6 H) 4,02 (t, J=7,48 Hz, 1 H) 4,20 - 4,30 (m, 1 H) 4,80 (t, J=7,97 Hz, 2 H) 5,08 - 5,17 (m, 2 H) 5,32 - 5,43 (m, 2 H) 5,83 - 5,94 (m, 2 H) 7,05 (dd, J=8,24, 1,30 Hz, 2 H) 7,21 (s, 1 H) 7,30

(d, J=3,14 Hz, 1 H) 7,40 (d, J=7,92 Hz, 1 H) 7,45 - 7,56 (m, 3 H) 11,99 (dd, J=9,87, 1,63 Hz, 1 H) 12,04 - 12,13 (m, 1 H); MS (ESI+) m/z 1047,5 (M+H)+.

A partir del producto del Procedimiento General 8B, Ejemplo 1B (mono-desplazamiento), se pueden obtener los compuestos de los Ejemplos 11,1 y 11,2 a través de los siguientes pasos: (1) reacción de Buchwald con una segunda amina apropiada (véase Procedimiento General 8); (2) nitrorreducción (véase Procedimiento General 9); y (3) ciclización (véase Procedimiento General 10).

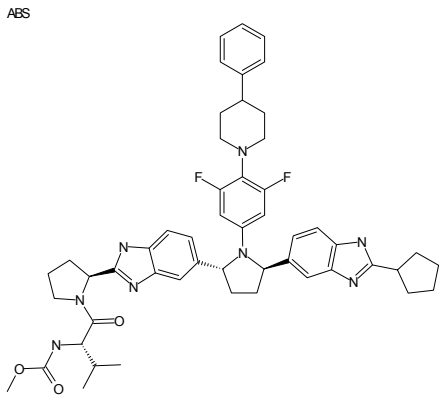
ABS



Ejemplo 11.1

[(1S)-2-[(2S)-2-{5-[(2R,5R)-1-[3,5-difluoro-4-(4-fenilpiperidin-1-il)fenil]-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-benzimidazol-5-il}pirrolidin-2-il]-1H-benzimidazol-2-il}pirrolidin-1-il]-2-oxo-1-(tetrahidro-2H-piran-4-il)etil]carbamato de metilo

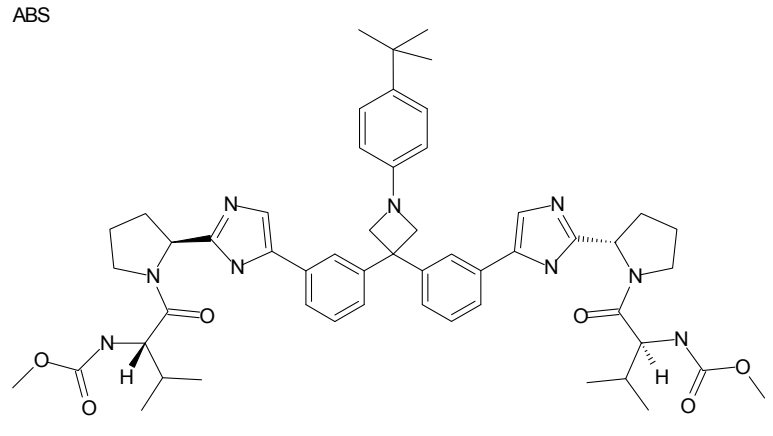
1H RMN (400 MHz, DMSO-d6) □ ppm 0,74 - 0,91 (m, 6 H) 1,44 - 1,56 (m, 2 H) 1,62 - 1,75 (m, 6 H) 1,82 - 1,95 (m, 2 H) 1,97 - 2,07 (m, 4 H) 2,16 - 2,26 (m, 4 H) 2,87 - 3,16 (m, 7 H) 3,43 - 3,50 (m, 2 H) 3,53 (s, 6 H) 3,58 - 3,66 (m, 2 H) 3,70 - 3,78 (m, 2 H) 3,80 - 3,89 (m, 4 H) 4,06 (t, J=8,51 Hz, 2 H) 5,11 - 5,19 (m, 2 H) 5,33 - 5,43 (m, 2 H) 5,86 - 5,95 (m, 2 H) 7,06 - 7,11 (m, 2 H) 7,12 - 7,37 (m, 9 H) 7,42 (dd, J=7,92, 1,73 Hz, 1 H) 7,46 - 7,53 (m, 1 H) 12,04 - 12,20 (m, 2 H); MS (ESI+) m/z 1069,4 (M+H)+.



Ejemplo 11.2

{(2S)-1-[(2S)-2-(5-{(2R,5R)-5-(2-ciclopentil-1H-benzimidazol-5-il)-1-[3,5-difluoro-4-(4-fenilpiperidin-1-il)fenil]pirrolidin-2-il}-1H-benzimidazol-2-il)pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

1H RMN (400 MHz, DMSO-d6) □ ppm 0,76 - 0,91 (m, 6 H) 1,59 - 1,73 (m, 10 H) 1,73 - 1,80 (m, 2 H) 1,83 - 1,94 (m, 4 H) 1,97 - 2,08 (m, 4 H) 2,16 - 2,24 (m, 1 H) 2,86 - 3,04 (m, 6 H) 3,19 - 3,29 (m, 1 H) 3,53 (s, 3 H) 3,79 - 3,87 (m, 2 H) 5,11 - 5,19 (m, 1 H) 5,34 - 5,42 (m, 2 H) 5,88 - 5,95 (m, 2 H) 7,03 - 7,11 (m, 2 H) 7,13 - 7,19 (m, 2 H) 7,20 - 7,27 (m, 4 H) 7,28 - 7,34 (m, 2 H) 7,40 (dd, J=13,88, 8,24 Hz, 1 H) 7,50 (d, J=8,02 Hz, 1 H) 12,05 (d, J=10,63 Hz, 1 H) 12,12 (d, J=3,90 Hz, 1 H); MS (ESI+) m/z 869,4 (M+H)+.



Ejemplo 12.1

{(2S)-1-[(2S)-2-(5-{3-[1-(4-tert-butilfenil)-3-(3-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-5-il}fenil)azetidin-3-il]fenil}-1H-imidazol-2-il)pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

Ejemplo 12.1A

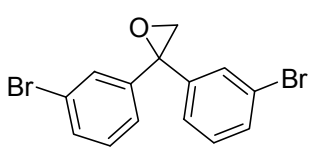
bis(3-bromofenil)metanol

Se agregó n-BuLi (26,5 mL, 42,4 mmol, 1,6M en hexano) a una solución de 1,3-dibromobenceno (10 g, 42,4 mmol) en THF (50 mL) a -78 oC. Después de agitar por 2 h a -78 oC, el 3-bromobenzaldehido (7,84 g, 42,4 mmol) se agregó a la mezcla de reacción. La mezcla de reacción se dejó calentar a temperatura ambiente y se agitó a 30 °C durante 12 h. La reacción se detuvo con NH4Cl acuoso (100 mL). La mezcla se extrajo con diclorometano (80 mLx5). Las capas orgánicas combinadas se secaron y se concentró. El residuo se purificó mediante cromatografía de columna (sobre gel de sílice, elución con Éter de petróleo ~Éter de petróleo: EtOAc=20:1) para dar 8,4 g del compuesto del título (24,5 mmol, 58%). LC/MS: [M-18+1] = 325. 1HRMN (DMSO-d6), 400MHz: δ 5,74 (d, 1H, J=4,0 Hz), 6,19 (d, 1H, J=4,4 Hz), 7,26-7,31 (m, 2H), 7,37-7,43 (m, 4H), 7,59 (s, 2 H).

Ejemplo 12.1B

bis(3-bromofenil)metanona

Se agregó MnO2 (21,61 g, 249 mmol) a una solución de bis(3-bromofenil)metanol (8,4 g, 24,5 mmol) en diclorometano (80 mL). La mezcla se agitó a 25 °C durante 12 h y luego se filtró. La torta de filtrado se lavó con diclorometano (60 mLx5). El material filtrado se concentró para dar 7,6 g del compuesto del título (22,3 mmol, 90%). LC/MS: [M+1] = 341. 1HRMN (DMSO-d6), 400MHz: δ 7,52-7,56 (m, 2H), 7,71 (d, 2H, J=7,2 Hz), 7,88-7,92 (m, 4H).

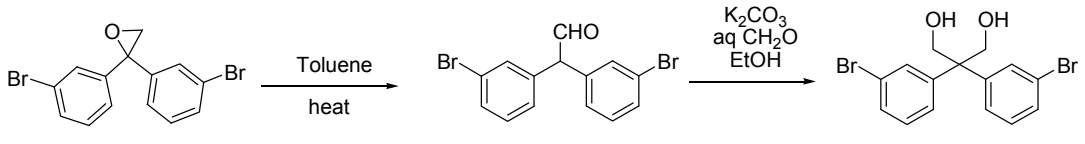


Ejemplo 12.1C

2,2-bis(3-bromofenil)oxirano

Se agregó KOt-Bu (2,72 g, 24,26 mmol) a una suspensión agitada de bis(3-bromofenil)metanona (7,5 g, 22,06 mmol) y yoduro de trimetilsulfonio (4,50 g, 22,06 mmol)

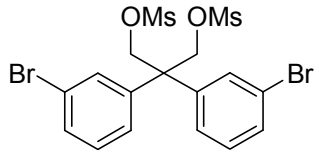
en DMSO (20 mL) y la mezcla resultante se agitó a 30 °C durante 8 h. La mezcla se diluyó con acetato de etilo (500mL), se lavó con agua (500 mL x 3) y salmuera (500 mL). La capa orgánica se separó y se evaporó al vacío para dar el compuesto del título el cual se usó directamente sin purificación adicional.



Ejemplo 12.1D

2,2-bis(3-bromofenil)propan-1,3-diol

Una mezcla del 2,2-bis(3-bromofenil)oxirano crudo (7,4 g, 20,90 mmol) y ácido p-toluensulfónico monohidratado (360 mg, 2,1 mmol) en tolueno (25 mL) se agitó a 95 °C durante 1 h. La solución se lavó con NaHCO3 aq (10 mL) y agua (20 mL). La capa orgánica se secó y se concentró. El residuo se disolvió en EtOH (20 mL). A la solución se agregó formaldehido (15,56 mL, 209 mmol, solución acuosa al 37%) y K2CO3 (1,44 g, 10,45 mmol). La mezcla se agitó a 85ºC durante 12h. Luego de enfriar a temperatura ambiente, la mezcla de reacción se diluyó con agua (50 mL) y se extrajo con diclorometano (60 mLx4). Las capas orgánicas combinadas se secaron y se concentró. El residuo se purificó mediante cromatografía de columna (sobre gel de sílice, elución con Éter de petróleo~Éter de petróleo: EtOAc=2:1) para dar 4,6 g de 2,2-bis(3-bromofenil)propan-1,3-diol (11,9 mmol, 57% después de dos pasos). LC/MS: [M-18+1] = 368. 1HRMN (CDCl3), 400MHz: δ 2,53 (brs, 2H), 2,41 (s, 4H), 7,09-7,20 (m, 4H), 7,36-7,40 (m, 4H).

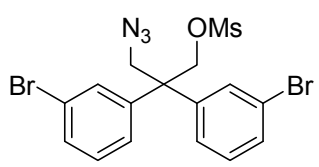


Ejemplo 12.1E

dimetansulfonato de 2,2-bis(3-bromofenil)propan-1,3-diilo

A una solución agitada de 2,2-bis(3-bromofenil)propan-1,3-diol (6,0 g, 15,54 mmol)

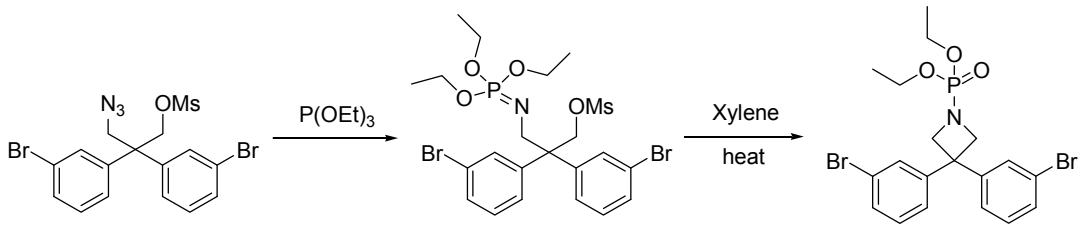
en diclorometano (50 mL) a 0oC se agregó cloruro metansulfónico (27,1 g, 155 mmol) y Et3N (17,3 mL, 124 mmol)para dar una solución anaranjada. La mezcla de reacción se agitó a 0 ºC durante 1h, luego a 40 °C durante 8 h. La reacción se lavó con NH4Cl acuoso (80 mL). La capa acuosa se extrajo con diclorometano (50 mLx3). Las capas orgánicas combinadas se secaron y se concentró. El residuo se purificó mediante cromatografía (sobre columna de gel de sílice, Éter de petróleo: EtOAc=2:1) para dar 3,2 g del compuesto del título (5,9 mmol, 38%). LC/MS: [M+18] = 560. 1HRMN (CDCl3), 400MHz: δ 2,93 (s, 6H), 4,49 (s, 4H), 7,15-7,48 (m, 8H).



Ejemplo 12.1F

metansulfonato de 3-azido-2,2-bis(3-bromofenil)propilo

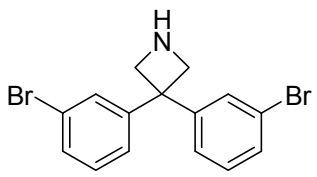
A una solución de dimetansulfonato de 2,2-bis(3-bromofenil)propan-1,3-diilo (3,6 g, 6,64 mmol) en DMPU (25 mL, 207 mmol) bajo N2 se agregó NaN3 (0,52 g, 7,97 mmol) con agitación. La mezcla se calentó a 110 °C durante 5 h. Luego de enfriar a temperatura ambiente, la mezcla de reacción se diluyó con EtOAc (100 mL), y se lavó con agua (30 mLx2) y salmuera (25 mL), se secó y se concentró. El residuo se purificó mediante cromatografía de columna (sobre gel de sílice, elución con Éter de petróleo: EtOAc=3:1) para dar 1,3 g del compuesto del título (2,66 mmol, 40%). LC/MS: [M+18] = 507. 1HRMN (CDCl3), 400MHz: δ 2,83 (s, 3H), 4,07 (s, 2H), 4,77 (s, 2H), 7,07-7,09 (m, 2H), 7,21-7,31 (m, 4H), 7,44-7,46 (m, 2H).



Ejemplo 12.1G

3,3-bis(3-bromofenil)azetidin-1-ilfosfonato de dietilo

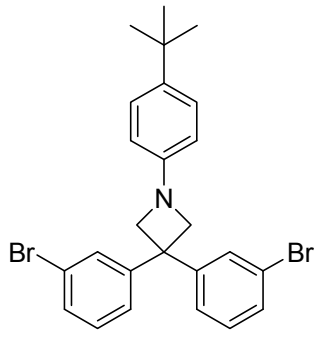
A una solución de metansulfonato de 3-azido-2,2-bis(3-bromofenil)propilo (1,3 g, 2,66 mmol) en tolueno anhidro (10 mL) y THF anhidro (5 mL) bajo N2 se agregó trietil fosfiita (0,49 mL, 2,79 mmol) a 25 °C. La mezcla se agitó durante 18 h. La reacción se concentró por evaporación por rotación en una secadora. El residuo se secó al vacío, y se usó en la siguiente reacción sin purificación adicional. El fosforimidato de trietilo crudo se disolvió en m-xileno anhidro (5 mL) bajo N2 y se calentó en un baño de aceite a 150 ºC durante 12h. Después de enfriar a temperatura ambiente, el solvente se eliminó por evaporación por rotación (con la ayuda de una bomba de vacío) para dar un aceite espeso de color anaranjado claro que se purificó mediante –TLC prep (elución con EtOAc: diclorometano=1:5) para dar 960 mg de 3,3-bis(3-bromofenil)azetidin-1-ilfosfonato de dietilo (1,9 mmol, 71% después de dos pasos). LC/MS: [M+1] = 504. 1HRMN (CDCl3), 400MHz: δ 1,25-1,36 (m, 6H), 4,05-4,39 (m, 4H), 4,40 (d, 2H, J=5,2 Hz), 7,09-7,11 (m, 2H), 7,20-7,27 (m, 2H), 7,40-7,42 (m, 4H).



Ejemplo 12.1H

3,3-bis(3-bromofenil)azetidina

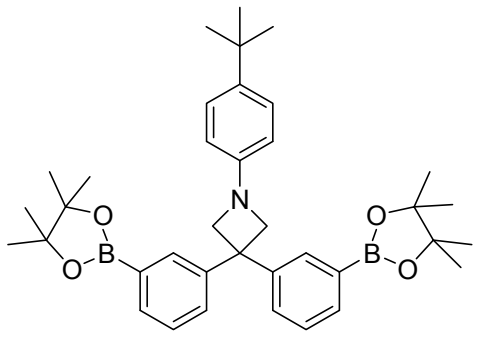
A una solución de 3,3-bis(3-bromofenil)azetidin-1-ilfosfonato de dietilo (960 mg, 1,9 mmol) en diclorometano anhidro (5 mL) bajo N2 se agregó TFA (5 mL). La mezcla se agitó a 20 °C durante 3 h, luego se concentró por evaporación por rotación. El residuo se disolvió en diclorometano (20 mL) y se lavó con acuoso NaHCO3 (30 mL). La capa orgánica se secó y se concentró para dar 595 mg del compuesto del título (1,6 mmol, 85%) como un aceite amarillo que se usó directamente en el siguiente paso sin purificación. LC/MS: [M+1] = 368.



Ejemplo 12.1I

3,3-bis(3-bromofenil)-1-(4-tert-butilfenil)azetidina

Una mezcla de 3,3-bis(3-bromofenil)azetidina (60 mg, 0,163 mmol), 1-tert-butil-4-yodobenceno (85 mg, 0,327 mmol), xantphos (9,46 mg, 0,016 mmol), Pd2(dba)3 (3,74 mg, 4,09 µmol) y tert-butóxido (18,85 mg, 0,196 mmol) en dioxano (5 mL) se agitó a 110 °C durante 12 h. Después de la reacción se enfrió a temperatura ambiente, se agregó agua (15 mL) y diclorometano (15 mL) . La fase acuosa se extrajo con diclorometano (15mLx3). Las capas orgánicas combinadas se secaron y se concentró. El residuo se purificó mediante HPLC prep (Instrumento waters 2767 PHW004 Columna YMC-Triart C18 150*20mm S-5um,12nm Fase móvil A: agua (0,05% NH4HCO3) B: ACN Gradiente 95-95% B en stop 8 min en 14 min Velocidad de flujo(ml/min) 20,00 Longitud de onda detective (nm) 214\254 Tiempo de retención(min) 7,4 para dar 26 mg del compuesto del título (0,052 mmol, 31,8 % de rendimiento). LC/MS: [M+1] = 500.



Ejemplo 12.1J

1-(4-tert-butilfenil)-3,3-bis(3-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)azetidina

Una mezcla de 3,3-bis(3-bromofenil)-1-(4-tert-butilfenil)azetidina (50 mg, 0,100

mmol), bis(pinacolato)diboro (65,9 mg, 0,260 mmol), KOAc (58,8 mg, 0,599 mmol) y el aducto PdCl2(dppf)-CH2Cl2 (20,39 mg, 0,025 mmol) se agitó a 100 °C durante 2 h bajo N2. Luego de enfriar a temperatura ambiente, se agregó agua (15 mL) y diclorometano (15 mL) . La capa acuosa se extrajo con diclorometano (15mLx3). Las capas orgánicas combinadas se secaron y se concentró. El residuo se purificó mediante prep-TLC (elución con diclorometano: hexano=1:1) para dar 50 mg del compuesto del título (0,078 mmol, 78 % de rendimiento). LC/MS: [M-C12H20+1] = 430; [M-C6H10+1] = 512.

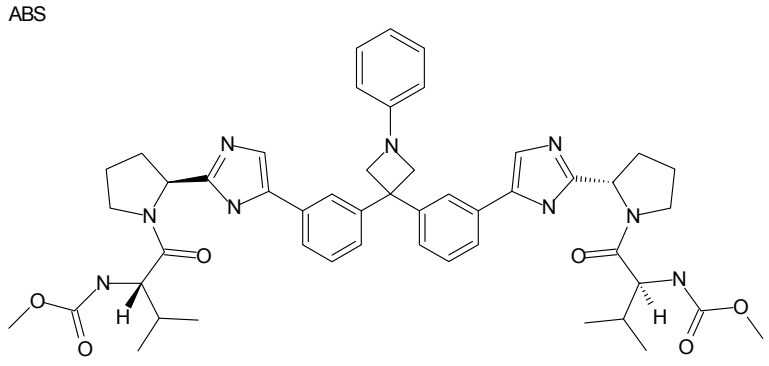
Ejemplo 12.1K

{(2S)-1-[(2S)-2-(5-{3-[1-(4-tert-butilfenil)-3-(3-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-5-il}fenil)azetidin-3-il]fenil}-1H-imidazol-2-il)pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

Una mezcla de 1-(4-tert-butilfenil)-3,3-bis(3-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)azetidina (50 mg, 0,084 mmol), el Intermediario 4 (66,0 mg, 0,177 mmol), el aducto PdCl2(dppf)-CH2Cl2 (13,76 mg, 0,017 mmol) y K2CO3 (69,9 mg, 0,506 mmol) en dioxano (5 mL) se agitó a 100 °C durante 2 h. Luego de enfriar a temperatura ambiente, la mezcla de reacción se diluyó con diclorometano (20 mL) y se lavó con NH4Cl acuoso (15 mLl). La capa acuosa se extrajo con diclorometano (15 mLx3), y las capas orgánicas combinadas se lavaron con salmuera (25 mL), se secó y se concentró. El residuo se purificó mediante HPLC prep: Instrumento Waters 2767 PHW003 Columna Boston C18 10um 21*250mm Fase móvil A:agua(0,05%NH4HCO3); B:ACN Gradiente 60-82% B en 8min, stop a los 14min Velocidad de flujo(ml/min) 30,00 Longitud de onda detective (nm) 214\254 Tiempo de retención(min) 8,32. La pureza era del 83% después de la primera purificación por HPLC prep. El compuesto se volvió a purificar por prep-TLC (elución con MeOH: diclorometano=1:15) para dar 22 mg del compuesto del título (0,024 mmol, 28,2 % de rendimiento). LC/MS: [M+1] = 926. 1HRMN (MeOD-d4), 400MHz: δ 0,77-0,85 (m, 12H), 1,18 (s, 9H), 1,88-2,23 (m, 10H), 3,07 (d, 2H, J= 6,4 Hz), 3,56 (s, 6H), 3,75-3,89 (m, 4H), 4,12-4,14 (m, 2H), 4,36-4,42 (m, 4H), 5,03-5,07 (m, 2H), 6,46-6,48 (m, 2H), 6,73-6,77

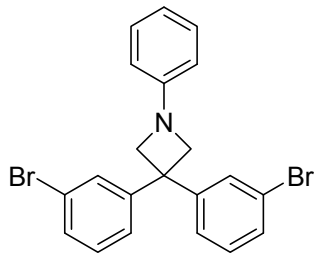
(m, 1H), 7,10-7,23 (m, 9H), 7,39-7,41 (m, 2H), 7,68-7,72 (m, 2H).

ABS



Ejemplo 12.2

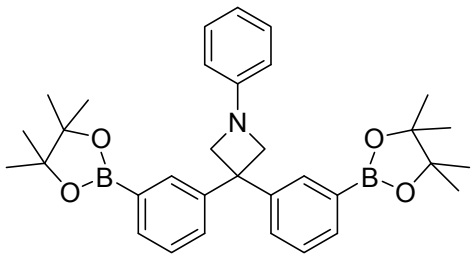
{(2S)-1-[(2S)-2-(5-{3-[3-(3-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-5-il}fenil)-1-fenilazetidin-3-il]fenil}-1H-imidazol-2-il)pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo



Ejemplo 12.2A

3,3-bis(3-bromofenil)-1-fenilazetidina

Una mezcla de 3,3-bis(3-bromofenil)azetidina (200 mg, 0,545 mmol), iodobenceno (222 mg, 1,090 mmol), xantphos (31,5 mg, 0,054 mmol), Pd2(dba)3 (12,47 mg, 0,014 mmol) y tert-butóxido de sodio (62,8 mg, 0,654 mmol) en dioxano (3 ml) se agitó durante 12 h a 100 °C. Luego de enfriar a temperatura ambiente, se agregó agua (15 mL) y diclorometano (15 mL) . La capa acuosa se extrajo con diclorometano (15mLx3). Las capas orgánicas combinadas se secaron y se concentró. El residuo se purificó mediante TLC prep (elución con diclorometano: EtOAc=5:1) para dar 140 mg del compuesto del título (0,31 mmol, 58%). LC/MS: [M+1] = 444, Ret. Time: 2,69 min. 1HRMN (CDCl3), 400MHz: 4,42 (s, 4H), 6,54 (d, 2H, J=7,6 Hz), 7,09-7,11 (m, 2H), 6,79 (t, 1H, J=7,2 Hz), 7,17-7,26 (m, 6H), 7,37-7,45 (m, 4H).



Ejemplo 12.2B

1-fenil-3,3-bis(3-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)azetidina

Una mezcla de 3,3-bis(3-bromofenil)-1-fenilazetidina (140 mg, 0,284 mmol), KOAc (167 mg, 1,705 mmol), aducto PdCl2(dppf)-CH2Cl2 (58,0 mg, 0,071 mmol) y bis(pinacolato)diboro (188 mg, 0,739 mmol) en dioxano (3 mL) se agitó a 110 °C durante 2h. Luego de enfriar a temperatura ambiente, la mezcla de reacción se diluyó con diclorometano (20 mL) y se lavó con NH4Cl acuoso (15 mL). La capa acuosa se extrajo con diclorometano (15 mLx3). Las capas orgánicas combinadas se lavaron con salmuera (25 mL). Las capas orgánicas se secaron y concentraron. El producto crudo se purificó mediante TLC prep (elución con diclorometano: Hexano=1:2) para dar 142 mg del compuesto del título (0,209 mmol, 73,6 % de rendimiento). LC/MS: [M+1] = 538.

Ejemplo 12.2C

{(2S)-1-[(2S)-2-(5-{3-[3-(3-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-5-il}fenil)-1-fenilazetidin-3-il]fenil}-1H-imidazol-2-il)pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

Una mezcla de 1-fenil-3,3-bis(3-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)azetidina (60 mg, 0,112 mmol), el Intermediario 4 (88 mg, 0,235 mmol), aducto PdCl2(dppf)-CH2Cl2 (18,24 mg, 0,022 mmol) y K2CO3 (93 mg, 0,670 mmol) en dioxano (5 mL) y agua (1 mL) se agitó a 100 °C durante 2 h bajo N2. La mezcla de reacción se diluyó con diclorometano (20 mL) y se lavó con NH4Cl acuoso (15 mL). La fase acuosa se extrajo con diclorometano (15 mLx3). Las capas orgánicas combinadas se lavaron con salmuera (25 mL). Las capas orgánicas se secaron y concentraron. El producto crudo se purificó mediante HPLC prep (Instrumento Waters 2767 PHW003 Columna Boston C18

10um 21*250mm Fase móvil A:agua (0,05%NH4HCO3);B:ACN Gradiente 45-70% B en 8min,stop a 14min Velocidad de flujo(ml/min) 30,00 Longitud de onda detective (nm) 214\254 Tiempo de retención(min) 8,47. Luego el compuesto se volvió a purificar por prep-TLC (elución con MeOH : diclorometano=1:15) para dar 20 mg del compuesto del título (0,022 mmol, 19,53 % de rendimiento). LC/MS: [M+1] = 870. 1HRMN (MeOD-d4), 400MHz: δ 0,86-0,97 (m, 12H), 1,97-2,33 (m, 10H), 3,07 (d, 2H, J= 6,4 Hz), 3,66 (s, 6H), 3,83-3,99 (m, 5H), 4,21-4,23 (m, 2H), 4,49-4,55 (m, 5H), 5,13-5,16 (m, 2H), 6,61-6,63 (m, 2H), 6,73-6,77 (m, 1H), 7,19-7,58 (m, 12H), 7,78-7,80 (m, 2H).

La presente invención también contempla las sales farmacéuticamente aceptables de cada compuesto del título descrito en los ejemplos anteriores. Todos los ejemplos divulgados en la publicación de la Solicitud de Patente de los EE.UU. N°: 2010/0317568 y las Solicitudes de Patente de los EE.UU. N° Acta: 12/903.822 y 12/964.027 también se incorporan en la presente a modo de referencia.

Cuando se evalúan usando ensayos del replicón 1b-Con1 del HCV en la presencia de FBS 5%, cada compuesto del título en 1,1, 1,3, 1,5, 1,6, 1,7, 1,8, 2,1, 2,2, 2,4, 2,5, 2,6, 2,9, 2,10, 2,11, 2,12, 2,13, 2,14, 2,15, 2,16, 2,17, 3,1, 3,2, 3,4, 3,5, 3,6, 3,7, 3,8, 3,11, 3,12, 3,13, 3,15, 3,17, 3,18, 3,19, 3,20, 3,21, 3,22, 3,23, 3,24, 3,25, 3,26, 3,27, 3,28, 3,29, 3,30, 3,31, 3,32, 3,33, 3,34, 3,35, 3,36, 3,37, 3,38, 3,39, 3,40, 3,41, 3,42, 3,43, 3,44, 3,45, 3,46, 3,47, 3,48, 3,49, 3,50, 3,51, 3,52, 3,53, 4,1, 4,2, 4,3, 4,4, 4,5, 4,6, 4,7, 4,8, 4,9, 4,10, 4,11, 4,12, 4,13, 4,14, 4,15, 4,16, 4,17, 4,18, 4,19, 4,20, 4,21, 4,22, 4,23, 4,24, 4,26, 4,27, 4,28, 4,29, 4,30, 4,31, 4,32, 4,33, 4,34, 4,35, 4,36, 4,37, 4,38, 4,39, 4,40, 4,41, 4,42, 4,43, 4,44, 4,45, 4,46, 4,47, 4,49, 4,50, 4,51, 4,52, 4,53, 4,54, 4,55, 4,56, 4,57, 4,58, 4,59, 4,60, 4,61, 4,62, 5,1, 5,2, 5,3, 5,4, 5,5, 5,6, 5,7, 5,8, 5,9, 5,10, 5,11, 5,12, 5,13, 5,14, 5,15, 6,1, 6,2, 6,3, 6,4, 6,5, 6,6, 6,7, 6,8, 6,9, 6,10, 6,11, 6,12, 6,13, 6,14, 6,15, 6,16, 7,1, 8, 9, 10,1, 10,2, 11,1 y 11,2 mostró un valor de EC50 menor que 0,1 nM aproximadamente. Cuando se evalúan usando ensayos del replicón 1b-Con1 del HCV en la presencia de FBS 5%, cada compuesto del título en los Ejemplos 1.4, 2,8, 3.3, 3.9, 3.10, 3.16 y 4.25 mostró un

valor de EC50 de entre aproximadamente 0,1 y aproximadamente 1 nM. Cuando se evalúan usando ensayos del replicón 1b-Con1 del HCV en la presencia de FBS 5%, cada compuesto del título en los Ejemplos 2.3, 2.7, 12.1 y 12.2 mostró un valor de EC50 de entre aproximadamente 1 y aproximadamente 10 nM. Los compuestos del título de los Ejemplos 1.2 y 3.14 mostraron un valor de EC50 mayor que 10 μM cuando se evalúan usando ensayos del replicón 1b-Con1 del HCV en la presencia de FBS 5%.

Cuando se evalúan usando ensayos del replicón 2a, 2b, 3a y 4a del HCV en la ausencia de plasma humano (HP), los valores de EC50 del Ejemplo 5.1 eran al menos 50 veces menores aproximadamente que los del Ejemplo 4.25 (aproximadamente 200-500 pM); y los valores de EC50 del Ejemplo 3.20 eran al menos 15 veces menores aproximadamente que los del Ejemplo 4.25. El valor AUC (definido previamente) del Ejemplo 5.1 era 30 veces mayor aproximadamente que el del Ejemplo 2.9. Cuando se evalúan usando ensayos del replicón 1a del HCV en la presencia de HP 40%, el valor EC50 del Ejemplo 6.1 contra el mutante L31M, Y93H o Y93N era al menos 5 veces menor que el del Ejemplo 109 (10-100 nM aproximadamente) de la publicación de la Solicitud de Patente de los EE.UU. N°: 2010/0317568 (Solicitud de Patente de los EE.UU. N° Acta: 12/813.301, de aquí en adelante la solicitud ‘301); y el valor AUC del Ejemplo 6.1 era 9 veces aproximadamente mayor que el del Ejemplo 109 de la solicitud ‘301. Cuando se evalúan usando ensayos del replicón 2a, 2b, 3a y 4a del HCV en la ausencia de HP, los valores EC50 del Ejemplo 4.15, así como del Ejemplo 302 de la solicitud ‘301, eran 2-4 veces menores aproximadamente que los del Ejemplo 163 (10-50 pM aproximadamente) de la solicitud ‘301. Cuando se evalúan usando ensayos del replicón 2b y 4a del HCV en la ausencia de HP, los valores EC50 del Ejemplo 251 de la solicitud ‘301 eran 2 veces menores aproximadamente que los del Ejemplo 163 de la solicitud ‘301. Cuando se evalúan usando ensayos del replicón 2a, 2b, 3a y 4a del HCV en la ausencia de HP, los valores de EC50 del Ejemplo 120 de la solicitud ‘301 eran al menos 2 veces menores aproximadamente que los del Ejemplo 164 (aproximadamente 300-1200 pM) de la

solicitud ‘301, y los valores de EC50 de los Ejemplos 245, 256 y 271 de la solicitud ‘301 eran al menos 10 veces menores aproximadamente que los del Ejemplo 164 de la solicitud ‘301; los valores AUC de los Ejemplos 245, 256 y 271 eran al menos 10 veces mayores aproximadamente que los del Ejemplo 164.

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 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 EC50 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 IA, IB, IC, ID IE, IF o IG).

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. Preferiblemente, 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, γ-interferón pegilado, lambda-interferón pegilado, ribavirina, viramidina, R-5158, nitazoxanida, amantadina, Debio-025, NIM-811, R7128, R1626, R4048, T-1106, PSI-7977 (Pharmasset) (inhibidor nucleosídico de polimerasa), PSI-7851 (Pharmasset) (inhibidor nucleosídico de polimerasa), PSI-938 (Pharmasset) (inhibidor nucleosídico de polimerasa), PF-00868554, ANA-598, IDX184 (inhibidor nucleosídico de polimerasa), IDX102, IDX375 (inhibidor no nucleosídico de polimerasa), GS-9190 (inhibidor no

nucleosídico de polimerasa), VCH-759, VCH-916, MK-3281, BCX-4678, MK-3281, VBY708, ANA598, GL59728, GL60667, BMS-790052 (inhibidor de NS5A), BMS-791325 (inhibidor de proteasa), BMS-650032, BMS-824393, GS-9132, ACH-1095 (inhibidor de proteasa), AP-H005, A-831 (Arrow Therapeutics) (inhibidor de NS5A), A-689 (Arrow Therapeutics) (inhibidor de NS5A), INX08189 (Inhibitex) (inhibidor de polimerasa), AZD2836, telaprevir (inhibidor de proteasa), boceprevir (inhibidor de proteasa), ITMN-191 (Intermune/Roche), BI-201335 (inhibidor de proteasa), VBY-376, VX-500 (Vertex) (inhibidor de proteasa), PHX-B, ACH-1625, IDX136, IDX316, VX-813 (Vertex) (inhibidor de proteasa), SCH 900518 (Schering-Plough), TMC-435 (Tibotec) (inhibidor de proteasa), ITMN-191 (Intermune, Roche) (inhibidor de proteasa), MK-7009 (Merck) (inhibidor de proteasa), IDX-PI (Novartis), BI-201335 (Boehringer Ingelheim), R7128 (Roche) (inhibidor nucleosídico de polimerasa), MK-3281 (Merck), MK-0608 (Merck) (inhibidor nucleosídico de polimerasa), PF-868554 (Pfizer) (inhibidor no nucleosídico de polimerasa), PF-4878691 (Pfizer), IDX-184 (Novartis), IDX-375 (Pharmasset), PPI-461 (Presidio) (inhibidor de NS5A), BILB-1941 (Boehringer Ingelheim), GS-9190 (Gilead), BMS-790052 (BMS), Albuferon (Novartis), ABT-333 (Abbott) (inhibidor no nucleosídico de polimerasa), ABT-072 (Abbott) (inhibidor no nucleosídico de polimerasa), ritonavir, otro inhibidor de 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, IA, IB, IC, ID IE, IF o IG (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.

En una forma de realización preferida, una composición farmacéutica de la invención comprende un compuesto de la invención (por ejemplo, un compuesto de la Fórmula I, IA, IB, IC, ID, IE, IF o IG, o, preferiblemente, un compuesto descrito precedentemente, o una sal, solvato o prodroga del mismo), y un inhibidor de proteasa del HCV. En otra forma de realización preferida, la composición farmacéutica de la invención comprende un compuesto de la invención (por ejemplo, un compuesto de la Fórmula I, IA, IB, IC, ID, IE, IF o IG, o, preferiblemente, un compuesto descrito precedentemente, o una sal, solvato o prodroga del mismo), y un inhibidor de polimerasa del HCV (por ejemplo, un inhibidor no nucleosídico de polimerasa o, preferiblemente, un inhibidor nucleosídico de polimerasa). En aún otra forma de realización preferida, una composición farmacéutica de la presente invención comprende (1) un compuesto de la invención (por ejemplo, un

compuesto de la Fórmula I, IA, IB, IC, ID, IE, IF o IG, o, preferiblemente, un compuesto descrito precedentemente, o una sal, solvato o prodroga del mismo), (2) un inhibidor de proteasa del HCV y (3) un inhibidor de polimerasa del HCV (por ejemplo, un inhibidor no nucleosídico de polimerasa o, preferiblemente, un inhibidor nucleosídico de polimerasa). Los ejemplos no limitativos de inhibidores de proteasa y de polimerasa se describieron previamente.

En aún otra forma de realización, una composición farmacéutica de la invención comprende (1) un compuesto de la Fórmula I, IA, IB, IC, ID, IE, IF o IG, o, preferiblemente, un compuesto seleccionado entre los compuestos de los títulos de los Ejemplos anteriores o de la Tabla 5, o una sal, solvato o prodroga de los mismos, y (2) uno o más inhibidores/moduladores del HCV seleccionados entre ABT-072 (Abbott), ABT-333 (Abbott), ACH-1095 (Achillion), ACH-1625 (Achillion), ACH-2684 (Achillion), ACH-2928 (Achillion), alisporovir, ANA-598 (Anadys), ANA-773 (Anadys), AVL-181 (Avila), AVL-192 (Avila), AZD2836 (Astra-Zeneca), AZD7295 (Astra-Zeneca), BCX-4678 (BioCryst), BI-201335 (Boehringer Ingelheim), BI-207127 (Boehringer Ingelheim), BILB-1941 (Boehringer Ingelheim), BMS-650032 (BMS), BMS-790052 (BMS), BMS-791325 (BMS), BMS-824393 (BMS), boceprevir, CTS-1027 (Conatus), danoprevir, EDP-239 (Enanta), filibuvir, GL59728 (Glaxo), GL60667 (Glaxo), GS-5885 (Gilead), GS-6620 (Gilead), GS-9132 (Gilead), GS-9256 (Gilead), GS-9451 (Gilead), GS-9620 (Gilead), GS-9669 (Gilead), GSK625433 (GlaxoSmithKline), IDX-102 (Idenix), IDX-136 (Idenix), IDX-184 (Idenix), IDX-316 (Idenix), IDX-320 (Idenix), IDX-375 (Idenix), INX-189 (Inhibitex), ITX-4520 (iTherx), ITX-5061 (iTherx), MK-0608 (Merck), MK-3281 (Merck), MK-5172 (Merck), narlaprevir, NM-811 (Novartis), PF-4878691 (Pfizer), PHX-1766 (Phenomix), PPI-1301 (Presidio), PPI-461 (Presidio), PSI-7977 (Pharmasset), PSI-938 (Pharmasset), RG7128 (Roche), RO5303253 (Roche), SCY-635 (Scynexis), tegobuvir, telaprevir, TMC-435 (Tibotec), TMC-647055 (Tibotec), TMC64912 (Medivir), vaniprevir, VBY708 (Virobay), VCH-759 (Vertex & ViraChem), VCH-916 (ViraChem), VX-222 (VCH-222) (Vertex & ViraChem), VX-500

(Vertex), VX-759 (Vertex), VX-813 (Vertex), VX-985 (Vertex) o una combinación de los mismos.

En otra forma de realización, una composición farmacéutica de la invención comprende (1) un compuesto de la Fórmula I, IA, IB, IC, ID, IE, IF o IG, o, preferiblemente, un compuesto seleccionado entre los compuestos de los títulos de los Ejemplos anteriores o de la Tabla 5, o una sal, solvato o prodroga del mismo, y (2) uno o más inhibidores de proteasa del HCV seleccionados entre ACH-1095 (Achillion), ACH-1625 (Achillion), ACH-2684 (Achillion), AVL-181 (Avila), AVL-192 (Avila), BI-201335 (Boehringer Ingelheim), BMS-650032 (BMS), boceprevir, danoprevir, GS-9132 (Gilead), GS-9256 (Gilead), GS-9451 (Gilead), IDX-136 (Idenix), IDX-316 (Idenix), IDX-320 (Idenix), MK-5172 (Merck), narlaprevir, PHX-1766 (Phenomix), telaprevir, TMC-435 (Tibotec), vaniprevir, VBY708 (Virobay), VX-500 (Vertex), VX-813 (Vertex), VX-985 (Vertex) o una combinación de los mismos.

En aún otra forma de realización preferida, una composición farmacéutica de la invención comprende (1) un compuesto de la Fórmula I, IA, IB, IC, ID, IE, IF o IG, o, preferiblemente, un compuesto seleccionado entre los compuestos de los títulos de los Ejemplos anteriores o de la Tabla 5, o una sal, solvato o prodroga del mismo, y (2) uno o más inhibidores de polimerasa del HCV seleccionados entre ABT-072 (Abbott), ABT-333 (Abbott), ANA-598 (Anadys), BI-207127 (Boehringer Ingelheim), BILB-1941 (Boehringer Ingelheim), BMS-791325 (BMS), filibuvir, GL59728 (Glaxo), GL60667 (Glaxo), GS-9669 (Gilead), IDX-375 (Idenix), MK-3281 (Merck), tegobuvir, TMC-647055 (Tibotec), VCH-759 (Vertex & ViraChem), VCH-916 (ViraChem), VX-222 (VCH-222) (Vertex & ViraChem), VX-759 (Vertex), GS-6620 (Gilead), IDX-102 (Idenix), IDX-184 (Idenix), INX-189 (Inhibitex), MK-0608 (Merck), PSI-7977 (Pharmasset), PSI-938 (Pharmasset), RG7128 (Roche), TMC64912 (Medivir), GSK625433 (GlaxoSmithKline), BCX-4678 (BioCryst) o una combinación de los mismos. El o los inhibidores de polimerasas pueden incluir (i) uno o más inhibidores nucleosídicos de polimerasa seleccionados entre GS-6620 (Gilead), IDX-

102 (Idenix), IDX-184 (Idenix), INX-189 (Inhibitex), MK-0608 (Merck), PSI-7977 (Pharmasset), PSI-938 (Pharmasset), RG7128 (Roche), TMC64912 (Medivir), o una combinación de los mismos; o (ii) uno o más inhibidores no nucleosídicos de polimerasa seleccionados entre ABT-072 (Abbott), ABT-333 (Abbott), ANA-598 (Anadys), BI-207127 (Boehringer Ingelheim), BILB-1941 (Boehringer Ingelheim), BMS-791325 (BMS), filibuvir, GL59728 (Glaxo), GL60667 (Glaxo), GS-9669 (Gilead), IDX-375 (Idenix), MK-3281 (Merck), tegobuvir, TMC-647055 (Tibotec), VCH-759 (Vertex & ViraChem), VCH-916 (ViraChem), VX-222 (VCH-222) (Vertex & ViraChem), VX-759 (Vertex), o una combinación de los mismos; o (iii) uno o más inhibidores nucleosídicos de polimerasa y uno o más inhibidores no nucleosídicos de polimerasa.

En una forma de realización adicional, una composición farmacéutica de la invención comprende (1) un compuesto de la Fórmula I, IA, IB, IC, ID, IE, IF o IG, o, preferiblemente, un compuesto seleccionado entre los compuestos de los títulos de los Ejemplos anteriores o de la Tabla 5, o una sal, solvato o prodroga del mismo, (2) uno o más inhibidores de proteasa del HCV seleccionados entre ACH-1095 (Achillion), ACH-1625 (Achillion), ACH-2684 (Achillion), AVL-181 (Avila), AVL-192 (Avila), BI-201335 (Boehringer Ingelheim), BMS-650032 (BMS), boceprevir, danoprevir, GS-9132 (Gilead), GS-9256 (Gilead), GS-9451 (Gilead), IDX-136 (Idenix), IDX-316 (Idenix), IDX-320 (Idenix), MK-5172 (Merck), narlaprevir, PHX-1766 (Phenomix), telaprevir, TMC-435 (Tibotec), vaniprevir, VBY708 (Virobay), VX-500 (Vertex), VX-813 (Vertex), VX-985 (Vertex), o una combinación de los mismos, y (3) uno o más inhibidores de polimerasa del HCV seleccionados entre ABT-072 (Abbott), ABT-333 (Abbott), ANA-598 (Anadys), BI-207127 (Boehringer Ingelheim), BILB-1941 (Boehringer Ingelheim), BMS-791325 (BMS), filibuvir, GL59728 (Glaxo), GL60667 (Glaxo), GS-9669 (Gilead), IDX-375 (Idenix), MK-3281 (Merck), tegobuvir, TMC-647055 (Tibotec), VCH-759 (Vertex & ViraChem), VCH-916 (ViraChem), VX-222 (VCH-222) (Vertex & ViraChem), VX-759 (Vertex), GS-6620 (Gilead), IDX-102 (Idenix), IDX-184 (Idenix), INX-189 (Inhibitex), MK-0608 (Merck), PSI-7977

(Pharmasset), PSI-938 (Pharmasset), RG7128 (Roche), TMC64912 (Medivir), GSK625433 (GlaxoSmithKline), BCX-4678 (BioCryst) o una combinación de los mismos. El o los inhibidores de polimerasas pueden incluir (i) uno o más inhibidores nucleosídicos de polimerasa seleccionados entre GS-6620 (Gilead), IDX-102 (Idenix), IDX-184 (Idenix), INX-189 (Inhibitex), MK-0608 (Merck), PSI-7977 (Pharmasset), PSI-938 (Pharmasset), RG7128 (Roche), TMC64912 (Medivir), o una combinación de los mismos; o (ii) uno o más inhibidores no nucleosídicos de polimerasa seleccionados entre ABT-072 (Abbott), ABT-333 (Abbott), ANA-598 (Anadys), BI-207127 (Boehringer Ingelheim), BILB-1941 (Boehringer Ingelheim), BMS-791325 (BMS), filibuvir, GL59728 (Glaxo), GL60667 (Glaxo), GS-9669 (Gilead), IDX-375 (Idenix), MK-3281 (Merck), tegobuvir, TMC-647055 (Tibotec), VCH-759 (Vertex & ViraChem), VCH-916 (ViraChem), VX-222 (VCH-222) (Vertex & ViraChem), VX-759 (Vertex), o una combinación de los mismos; o (iii) uno o más inhibidores nucleosídicos de polimerasa y uno o más inhibidores no nucleosídicos de polimerasa.

En aún otra forma de realización, una composición farmacéutica de la invención comprende (1) un compuesto de la Fórmula I, IA, IB, IC, ID, IE, IF o IG, o, preferiblemente, un compuesto seleccionado entre los compuestos de los títulos de los Ejemplos anteriores o de la Tabla 5, o una sal, solvato o prodroga del mismo, y (2) un inhibidor de ciclofilina (por ejemplo, alisporovir, NM-811 (Novartis), SCY-635 (Scynexis)), un inhibidor de entrada (por ejemplo, ITX-4520 (iTherx) o ITX-5061 (iTherx)), otro inhibidor de NS5A (por ejemplo,), o un agonista de TLR-7 (por ejemplo, GS-9620 (Gilead) o PF-4878691 (Pfizer)), y (3) opcionalmente uno o más inhibidores de proteasa o polimerasa del HCV descritos previamente.

Una composición farmacéutica que contiene múltiples ingredientes activos puede ser un producto co-formulado, un producto co-envasado o una combinación de los mismos.

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.

En una forma de realización preferida, un compuesto de la invención (por ejemplo, un compuesto de la Fórmula I, IA, IB, IC, ID, IE, IF o IG, o, preferiblemente, un compuesto descrito precedentemente, o una sal, solvato o prodroga del mismo) se formula en una dispersión sólida, donde el compuesto de la invención puede dispersarse molecularmente en una matriz amorfa que comprende un polímero hidrofilico, farmacéuticamente aceptable. La matriz también puede contener un agente tensioactivo farmacéuticamente aceptable. La tecnología de dispersión sólida adecuada para la formulación de un compuesto de la invención incluye, pero en un sentido no limitativo, extrusión por fusión, secado por aspersión, co-precipitación, secado por congelamiento u otras técnicas de evaporación de solventes, siendo preferidos la extrusión por fusión y el secado por aspersión. En un ejemplo, un compuesto de la invención se formula en una dispersión sólida que comprende copovidona y vitamina E TPGS. En otro ejemplo, un compuesto de

la invención se formula en una dispersión sólida que comprende copovidona y Span 20.

Una dispersión sólida descrita en la presente puede contener al menos un 30% en peso de un polímero hidrofilico farmacéuticamente aceptable o una combinación de dichos polímeros hidrofilicos. Preferiblemente, la dispersión sólida contiene al menos un 40% en peso de un polímero hidrofilico farmacéuticamente aceptable o una combinación de dichos polímeros hidrofilicos. Más preferiblemente, la dispersión sólida contiene al menos un 50% (incluyendo, por ejemplo, al menos un 60%, 70%, 80% o 90%) en peso de un polímero hidrofilico farmacéuticamente aceptable o una combinación de dichos polímeros. Una dispersión sólida descrita en la presente también puede contener al menos un 1% en peso de un agente tensioactivo farmacéuticamente aceptable o una combinación de dichos agentes tensioactivos. Preferiblemente, la dispersión sólida contiene al menos un 2% en peso de un agente tensioactivo farmacéuticamente aceptable o una combinación de dichos agentes tensioactivos. Más preferiblemente, la dispersión sólida contiene entre 4% y 20% en peso de uno o más agentes tensioactivo, tal como entre 5% y 10% en peso de uno o más agentes tensioactivos. Además, una dispersión sólida descrita en la presente puede contener al menos un 1% en peso de un compuesto de la invención, preferiblemente al menos un 5%, incluyendo, por ejemplo, al menos un 10%. En un ejemplo, la dispersión sólida comprende un 5% de un compuesto de la invención (por ejemplo, un compuesto de la Fórmula I, IA, IB, IC, ID, IE, IF o IG, o, preferiblemente, un compuesto descrito precedentemente, o una sal, solvato o prodroga del mismo), que está disperso molecularmente en una matriz amorfa que comprende un 7% de Vitamina E-TPGS y un 88% de copovidona; la dispersión sólida también se puede mezclar con otros excipientes tales como manitol/Aerosil (99:1), y la relación ponderal de la dispersión sólida frente a los demás excipientes puede variar en un rango entre 5:1 y 1:5, siendo preferida una relación de 1:1. En otro ejemplo, la dispersión sólida comprende un 5% de un compuesto de la invención (por ejemplo, un compuesto de la Fórmula I, IA, IB, IC, ID, IE, IF o IG, o, preferiblemente, un compuesto descrito precedentemente, o una

sal, solvato o prodroga del mismo), que está disperso molecularmente en a una matriz amorfa que comprende un 5% de Span 20 y un 90% de copovidona; la dispersión sólida también se puede mezclar con otros excipientes tales como manitol/Aerosil (99:1); la dispersión sólida también se puede mezclar con otros excipientes tales como manitol/Aerosil (99:1), y la relación ponderal de la dispersión sólida frente a los demás excipientes puede variar en un rango entre 5:1 y 1:5, siendo preferido una relación de 1:1.

También se pueden incluir o mezclar diversos aditivos con la dispersión sólida. Por ejemplo, se puede usar al menos un aditivo seleccionado entre reguladores del flujo, aglutinantes, lubricantes, rellenos, desintegrantes, plastificadores, colorantes o estabilizantes en la compresión de la dispersión sólida en tabletas. Estos aditivos se pueden mezclar con una dispersión sólida molida o triturada antes de la compactación. Los desintegrantes promueven una desintegración rápida del producto compactado en el estómago y mantienen a los gránulos liberados separados entre sí. Los ejemplos no limitativos de desintegrantes adecuados son polímeros entrecruzados tales como polivinilpirrolidona entrecruzada, carboximetilcelulosa de sodio entrecruzada o croscarmellosa de sodio. Los ejemplos no limitativos de rellenos adecuados (también conocidos como agentes para aumentar el volumen) son lactosa monohidrato, fosfato ácido de calcio, celulosa microcristalina (por ejemplo, Avicell), silicatos, en particular dióxido de silicio, óxido de magnesio, talco, almidón de papa o maíz, isomalta o alcohol polivinílico. Los ejemplos no limitativos de reguladores del flujo adecuados incluyen sílices altamente dispersos (por ejemplo, sílice coloidal tal como Aerosil), y grasas o ceras de origen animal o vegetal. Los ejemplos no limitativos de lubricantes adecuados incluyen polietilenglicol (por ejemplo, con un molecular peso de entre 1000 y 6000), estearatos de magnesio y calcio, estearilfumarato de sodio y semejantes. Los ejemplos no limitativos de estabilizantes incluyen antioxidantes, estabilizantes de luz, secuestrantes de radicales o estabilizantes contra ataques microbianos.

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, 3a o 4a 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. En una forma de realización, la presente invención está dirigida a métodos de tratamiento de una infección por HCV, en donde dichos métodos comprenden administrar un compuesto de la invención (por ejemplo, un compuesto de la Fórmula I, IA, IB, IC, ID, IE, IF o IG, o, preferiblemente, un compuesto descrito precedentemente, o una sal, solvato o prodroga del mismo), interferón y ribavirina a un paciente con HCV. El interferón preferiblemente es α-interferón, y más preferiblemente, interferón-α pegilado, tal como PEGASYS (PEG-interferón alfa-2a).

En otra forma de realización, la presente invención está dirigida a métodos de tratamiento de una infección por HCV, en donde dichos métodos comprenden administrar un compuesto de la invención (por ejemplo, un compuesto de la Fórmula I, IA, IB, IC, ID, IE, IF o IG, o, preferiblemente, un compuesto seleccionado entre los compuestos de los títulos de los Ejemplos anteriores o de la Tabla 5, o una sal, solvato o prodroga del mismo), y uno o más inhibidores/moduladores del HCV descritos previamente, con o sin

interferón.

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 composiciones de dosis única pueden contener estas cantidades o submúltiplos de las mismas para conformar la dosis diaria. Preferiblemente, 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

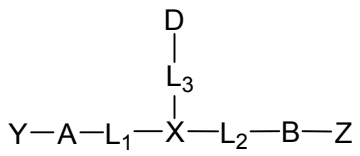
presente invención.

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, 13C, 15N o 18O. 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 5% molar (por ejemplo, al menos un 10% mol) 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 CARACTERIZADO PORQUE es de Fórmula I, o una sal aceptable farmacéuticamente del mismo,



I

donde:

X es C3-C12carbociclo o heterociclo de entre 3 y 12 miembros, y está opcionalmente sustituido con uno o más RA o RF;

L1 y L2 se seleccionan en forma independiente entre sí entre un enlace; o C1-C6alquileno, C2-C6alquenileno o C2-C6alquinileno, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más RL;

L3 es un enlace o –LS–K–LS'–, donde K se selecciona entre un enlace, –O–, –S–, –N(RB)–, –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(RB)–, –N(RB)C(O)–, –N(RB)C(O)O–, –OC(O)N(RB)–, –N(RB)S(O)–, –N(RB)S(O)2–, –S(O)N(RB)–, –S(O)2N(RB)–, –C(O)N(RB)C(O)–, –N(RB)C(O)N(RB')–, –N(RB)SO2N(RB')–, o –N(RB)S(O)N(RB')–;

A y B son en forma independiente entre sí C3-C12carbociclo o heterociclo de entre 3 y 12 miembros, y están opcionalmente sustituidos en forma independiente entre sí con uno o más RA;

D es C3-C12carbociclo o heterociclo de entre 3 y 12 miembros, y está opcionalmente sustituido con uno o más RA; o D es C3-C12carbociclo o heterociclo de entre 3 y 12 miembros que está sustituido con J y opcionalmente sustituido con uno o más RA, donde J es C3-C12carbociclo o

heterociclo de entre 3 y 12 miembros y está opcionalmente sustituido con uno o más RA, o J es –SF5; o D es hidrógeno o RA;

Y se selecciona entre –T'–C(R1R2)N(R5)–T–RD, –T'–C(R3R4)C(R6R7)–T–RD, –LK–T–RD, o –LK–E;

R1 y R2 son en forma independiente entre sí RC, y R5 es RB; o R1 es RC, y R2 y R5, tomados junto con los átomos a los cuales están unidos, forman un heterociclo de entre 3 y 12 miembros que está opcionalmente sustituido con uno o más RA;

R3, R4, R6, y R7 son en forma independiente entre sí RC; o R3 y R6 son en forma independiente entre sí RC, y R4 y R7, tomados junto con los átomos a los cuales están unidos, forman un carbociclo o heterociclo de entre 3 y 12 miembros que está opcionalmente sustituido con uno o más RA;

Z se selecciona entre –T'–C(R8R9)N(R12)–T–RD, –T'–C(R10R11)C(R13R14)–T–RD, –LK–T–RD, o –LK–E;

R8 y R9 son en forma independiente entre sí RC, y R12 es RB; o R8 es RC, y R9 y R12, tomados junto con los átomos a los cuales están unidos, forman un heterociclo de entre 3 y 12 miembros que está opcionalmente sustituido con uno o más RA;

R10, R11, R13, y R14 son en forma independiente entre sí RC; o R10 y R13 son en forma independiente entre sí RC, y R11 y R14, tomados junto con los átomos a los cuales están unidos, forman un carbociclo o heterociclo de entre 3 y 12 miembros que está opcionalmente sustituido con uno o más RA;

T y T' se seleccionan en forma independiente entre sí en cada caso entre un enlace, –LS–, –LS–M–LS'–, o –LS–M–LS'–M'–LS''–, donde M y M' se seleccionan en forma independiente entre sí en cada caso entre un enlace, –O–, –S–, –N(RB)–, –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(RB)–, –N(RB)C(O)–, –

N(RB)C(O)O–, –OC(O)N(RB)–, –N(RB)S(O)–, –N(RB)S(O)2–, –S(O)N(RB)–, –S(O)2N(RB)–, –C(O)N(RB)C(O)–, –N(RB)C(O)N(RB')–, –N(RB)SO2N(RB')–, –N(RB)S(O)N(RB')–, C3-C12carbociclo o heterociclo de entre 3 y 12 miembros, y donde dicho C3-C12carbociclo y heterociclo de entre 3 y 12 miembros están opcionalmente sustituidos en forma independiente entre sí en cada caso con uno o más RA;

LK se selecciona en forma independiente en cada caso entre un enlace, –LS–N(RB)C(O)–LS'– o –LS–C(O)N(RB)–LS'–; o C1-C6alquileno, C2-C6alquenileno o C2-C6alquinileno, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más RL; o C3-C12carbociclo o heterociclo de entre 3 y 12 miembros, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más RA;

E se selecciona en forma independiente en cada caso entre C3-C12carbociclo o heterociclo de entre 3 y 12 miembros, y está opcionalmente sustituido en forma independiente en cada caso con uno o más RA;

RD se selecciona en forma independiente en cada caso entre hidrógeno o RA;

RA se selecciona en forma independiente en cada caso entre halógeno, nitro, oxo, fosfonoxi, fosfono, tioxo, ciano, o –LS–RE, donde dos RA adyacentes, tomados junto con los átomos a los cuales están unidos y cualquier otro átomo entre los átomos a los cuales están unidos, pueden formar opcionalmente carbociclo o heterociclo;

RB y RB' se seleccionan en forma independiente entre sí en cada caso entre hidrógeno; o C1-C6alquilo, C2-C6alquenilo o C2-C6alquinilo, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano o carbociclo o

heterociclo de entre 3 y 6 miembros; o carbociclo o heterociclo de entre 3 y 6 miembros; donde cada carbociclo o heterociclo de entre 3 y 6 miembros en RB o RB' está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C1-C6alquilo, C2-C6alquenilo, C2-C6alquinilo, C1-C6haloalquilo, C2-C6haloalquenilo o C2-C6haloalquinilo;

RC se selecciona en forma independiente en cada caso entre hidrógeno, halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo o ciano; o C1-C6alquilo, C2-C6alquenilo o C2-C6alquinilo, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano o carbociclo o heterociclo de entre 3 y 6 miembros; o carbociclo o heterociclo de entre 3 y 6 miembros; donde cada carbociclo o heterociclo de entre 3 y 6 miembros en RC está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C1-C6alquilo, C2-C6alquenilo, C2-C6alquinilo, C1-C6haloalquilo, C2-C6haloalquenilo o C2-C6haloalquinilo;

RE se selecciona en forma independiente en cada caso entre –O–RS, –S–RS, –C(O)RS, –OC(O)RS, –C(O)ORS, –N(RSRS'), –S(O)RS, –SO2RS, –C(O)N(RSRS'), –N(RS)C(O)RS', –N(RS)C(O)N(RS'RS''), –N(RS)SO2RS', –SO2N(RSRS'), –N(RS)SO2N(RS'RS''), –N(RS)S(O)N(RS'RS''), –OS(O)–RS, –OS(O)2–RS, –S(O)2ORS, –S(O)ORS, –OC(O)ORS, –N(RS)C(O)ORS', –OC(O)N(RSRS'), –N(RS)S(O)–RS', –S(O)N(RSRS'), –P(O)(ORS)2, o –C(O)N(RS)C(O)–RS'; o C1-C6alquilo, C2-C6alquenilo o C2-C6alquinilo, cada

uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo o ciano; o C3-C6carbociclo o heterociclo de entre 3 y 6 miembros, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C1-C6alquilo, C2-C6alquenilo, C2-C6alquinilo, C1-C6haloalquilo, C2-C6haloalquenilo, C2-C6haloalquinilo, C(O)ORS, o –N(RSRS');

RF se selecciona en forma independiente en cada caso entre C1-C10alquilo, C2-C10alquenilo o C2-C10alquinilo, cada uno de los cuales contiene 0, 1, 2, 3, 4 o 5 herteroátomos seleccionados entre O, S o N y está opcionalmente sustituido con uno o más RL; o –(RX–RY)Q–(RX–RY'), donde Q es 0, 1, 2, 3 o 4, y cada RX es en forma independiente O, S o N(RB), donde cada RY es en forma independiente C1-C6alquileno, C2-C6alquenileno o C2-C6alquinileno cada uno de los cuales está opcionalmente sustituido en forma independiente con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo o ciano, y donde cada RY' es en forma independiente C1-C6alquilo, C2-C6alquenilo o C2-C6alquinilo cada uno de los cuales está opcionalmente sustituido en forma independiente con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo o ciano;

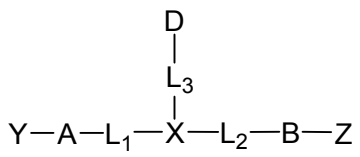
RL se selecciona en forma independiente en cada caso entre halógeno, nitro, oxo, fosfonoxi, fosfono, tioxo, ciano, –O–RS, –S–RS, –C(O)RS, –OC(O)RS, –C(O)ORS, –N(RSRS'), –S(O)RS, –SO2RS, –C(O)N(RSRS') o –N(RS)C(O)RS'; o C3-C6carbociclo o heterociclo de entre 3 y 6 miembros, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con

uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C1-C6alquilo, C2-C6alquenilo, C2-C6alquinilo, C1-C6haloalquilo, C2-C6haloalquenilo o C2-C6haloalquinilo; donde dos RL adyacentes, tomados junto con los átomos a los cuales están unidos y cualquier otro átomo entre los átomos a los cuales están unidos, pueden formar opcionalmente carbociclo o heterociclo;

LS, LS' y LS'' se seleccionan en forma independiente entre sí en cada caso entre un enlace; o C1-C6alquileno, C2-C6alquenileno o C2-C6alquinileno, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más RL; y

RS, RS' y RS'' se seleccionan en forma independiente entre sí en cada caso entre hidrógeno; C1-C6alquilo, C2-C6alquenilo o C2-C6alquinilo, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, –O–C1-C6alquilo, –O–C1-C6alquilen–O–C1-C6alquilo, o carbociclo o heterociclo de entre 3 y 6 miembros; o carbociclo o heterociclo de entre 3 y 6 miembros; donde cada carbociclo o heterociclo de entre 3 y 6 miembros en RS , RS' o RS' está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C1-C6alquilo, C2-C6alquenilo, C2-C6alquinilo, C1-C6haloalquilo, C2-C6haloalquenilo o C2-C6haloalquinilo.

2. Un compuesto CARACTERIZADO PORQUE es de Fórmula IE, o una sal aceptable farmacéuticamente del mismo,



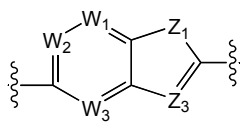
IE

donde:

X es heterociclo de entre 4 y 8 miembros, y está opcionalmente sustituido con uno o más RA;

L1 y L2 se seleccionan en forma independiente entre sí entre un enlace o C1-C6alquileno que está opcionalmente sustituido en forma independiente en cada caso con uno o más halo, hidroxi, –O–C1-C6alquilo, o –O–C1-C6haloalquilo;

L3 es un enlace o C1-C6alquileno;

A y B son en forma independiente entre sí fenilo, piridinilo, tiazolilo, o  donde Z1 se selecciona en forma independiente en cada caso entre O, S, NH o CH2, Z3 se selecciona en forma independiente en cada caso entre N o CH, y W1, W2, y W3 se seleccionan en forma independiente entre sí en cada caso entre CH o N; A y B están opcionalmente sustituidos en forma independiente entre sí con uno o más RA.

D es C6-C10carbociclo o heterociclo de entre 5 y 12 miembros, cada uno de los cuales está opcionalmente sustituido con uno o más RM;

Y es –T'–C(R1R2)N(R5)–T–RD;

Z es –T'–C(R8R9)N(R12)–T–RD;

R1 es hidrógeno, C1-C6alquilo, C1-C6haloalquilo, o carbociclo o heterociclo de entre 3 y 6 miembros, donde cada carbociclo o heterociclo de entre 3 y 6 miembros está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, C1-C6alquilo, C1-

C6haloalquilo, –O–C1-C6alquilo o –O–C1-C6haloalquilo;

R2 y R5 son en forma independiente entre sí hidrógeno, C1-C6alquilo, C1-C6haloalquilo, o carbociclo o heterociclo de entre 3 y 6 miembros, donde cada carbociclo o heterociclo de entre 3 y 6 miembros está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, C1-C6alquilo, C1-C6haloalquilo, –O–C1-C6alquilo o –O–C1-C6haloalquilo; o R2 y R5, tomados junto con los átomos a los cuales están unidos, forman un heterociclo de entre 3 y 12 miembros que está opcionalmente sustituido con uno o más RA;

R8 es hidrógeno, C1-C6alquilo, C1-C6haloalquilo, o carbociclo o heterociclo de entre 3 y 6 miembros, donde cada carbociclo o heterociclo de entre 3 y 6 miembros está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, C1-C6alquilo, C1-C6haloalquilo, –O–C1-C6alquilo o –O–C1-C6haloalquilo;

R9 y R12 son en forma independiente entre sí hidrógeno, C1-C6alquilo, C1-C6haloalquilo, o carbociclo o heterociclo de entre 3 y 6 miembros, donde cada carbociclo o heterociclo de entre 3 y 6 miembros está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, C1-C6alquilo, C1-C6haloalquilo, –O–C1-C6alquilo o –O–C1-C6haloalquilo; o R9 y R12, tomados junto con los átomos a los cuales están unidos, forman un heterociclo de entre 3 y 12 miembros que está opcionalmente sustituido con uno o más RA;

T se selecciona en forma independiente en cada caso entre un enlace o –C(O)–LS'–;

T' se selecciona en forma independiente en cada caso entre un enlace, –C(O)N(RB)–, –N(RB)C(O)–, o heterociclo de entre 3 y 12 miembros, donde dicho heterociclo de entre 3 y 12 miembros está opcionalmente sustituido en

forma independiente en cada caso con uno o más RA;

RD se selecciona en forma independiente en cada caso entre hidrógeno o RA;

RA se selecciona en forma independiente en cada caso entre halógeno, nitro, oxo, fosfonoxi, fosfono, tioxo, ciano, o –LS–RE;

RB y RB' se seleccionan en forma independiente entre sí en cada caso entre hidrógeno; o C1-C6alquilo que está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno o carbociclo o heterociclo de entre 3 y 6 miembros; o carbociclo o heterociclo de entre 3 y 6 miembros; donde cada carbociclo o heterociclo de entre 3 y 6 miembros en RB o RB' está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, C1-C6alquilo, C1-C6haloalquilo, –O–C1-C6alquilo, o –O–C1-C6haloalquilo;

RE se selecciona en forma independiente en cada caso entre –O–RS, –S–RS, –C(O)RS, –OC(O)RS, –C(O)ORS, –N(RSRS'), –S(O)RS, –SO2RS, –C(O)N(RSRS'), –N(RS)C(O)RS', –N(RS)C(O)N(RS'RS''), –N(RS)SO2RS', –SO2N(RSRS'), –N(RS)SO2N(RS'RS''), –N(RS)S(O)N(RS'RS''), –OS(O)–RS, –OS(O)2–RS, –S(O)2ORS, –S(O)ORS, –OC(O)ORS, –N(RS)C(O)ORS', –OC(O)N(RSRS'), –N(RS)S(O)–RS', –S(O)N(RSRS'), –C(O)N(RS)C(O)–RS', o =C(RSRS'); o C1-C6alquilo, C2-C6alquenilo o C2-C6alquinilo, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo o ciano; o C3-C12carbociclo o heterociclo de entre 3 y 12 miembros, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C1-C6alquilo, C2-

C6alquenilo, C2-C6alquinilo, C1-C6haloalquilo, C2-C6haloalquenilo o C2-C6haloalquinilo;

RL se selecciona en forma independiente en cada caso entre halógeno, nitro, oxo, fosfonoxi, fosfono, tioxo, ciano, –O–RS, –S–RS, –C(O)RS, –OC(O)RS, –C(O)ORS, –N(RSRS'), –S(O)RS, –SO2RS, –C(O)N(RSRS'), o –N(RS)C(O)RS'; o C3-C12carbociclo o heterociclo de entre 3 y 12 miembros, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C1-C6alquilo, C2-C6alquenilo, C2-C6alquinilo, C1-C6haloalquilo, C2-C6haloalquenilo o C2-C6haloalquinilo;

LS se selecciona en forma independiente en cada caso entre un enlace; o C1-C6alquileno, C2-C6alquenileno o C2-C6alquinileno, cada opcionalmente sustituido en forma independiente con halógeno;

LS' se selecciona en forma independiente en cada caso entre un enlace; o C1-C6alquileno, C2-C6alquenileno o C2-C6alquinileno, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más RL;

RS, RS' y RS'' se seleccionan en forma independiente entre sí en cada caso entre hidrógeno; C1-C6alquilo, C2-C6alquenilo o C2-C6alquinilo, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, –O–C1-C6alquilo, –O–C1-C6haloalquilo, o carbociclo o heterociclo de entre 3 y 12 miembros; o carbociclo o heterociclo de entre 3 y 12 miembros; donde cada carbociclo o heterociclo de entre 3 y 12 miembros en RS , RS' o RS'' está opcionalmente sustituido en forma independiente en cada caso con uno o más

sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C1-C6alquilo, C2-C6alquenilo, C2-C6alquinilo, C1-C6haloalquilo, C2-C6haloalquenilo o C2-C6haloalquinilo;

RM se selecciona en forma independiente en cada caso entre:

halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, ciano, SF5, –N(RSRS'), –O–RS, –OC(O)RS, –OC(O)ORS, –OC(O)N(RSRS'), –C(O)RS, –C(O)ORS, –C(O)N(RSRS'), –N(RS)C(O)RS', –N(RS)C(O)ORS', –N(RS)SO2RS', –S(O)RS, –SO2RS, –S(O)N(RSRS'), –SRS, –Si(RS)3, o –P(O)(ORS)2;

C1-C6alquilo, C2-C6alquenilo o C2-C6alquinilo, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, –N(RSRS'), –O–RS, –OC(O)RS, –OC(O)ORS, –OC(O)N(RSRS'), –C(O)RS, –C(O)ORS, –C(O)N(RSRS'), –N(RS)C(O)RS', –N(RS)C(O)ORS', –N(RS)SO2RS', –S(O)RS, –SO2RS, –S(O)N(RSRS'), –SRS, o –P(O)(ORS)2; o

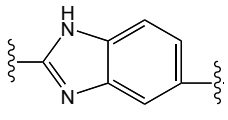
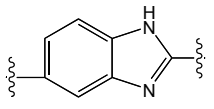
G2, donde G2 es un C3-C12carbociclo o heterociclo de entre 3 y 12 miembros, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más RG2, y cada RG2 se selecciona en forma independiente entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C1-C6alquilo, C2-C6alquenilo, C2-C6alquinilo, C1-C6haloalquilo, C2-C6haloalquenilo, C2-C6haloalquinilo, –O–RS, –C(O)ORS, –C(O)RS, –N(RSRS'), o –L4–G3;

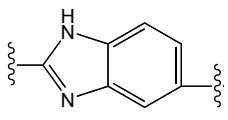
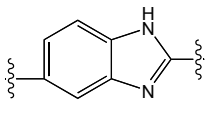
L4 es una unión, C1-C6alquileno, C2-C6alquenileno, C2-C6alquinileno, –O–, –S–, –N(RB)–, –C(O)–, –S(O)2–, –S(O)–, –C(O)O–, –OC(O)–, –OC(O)O–, –

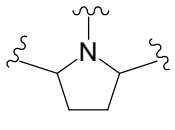
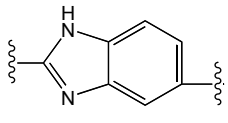
C(O)N(RB)–, –N(RB)C(O)–, –N(RB)C(O)O–, –OC(O)N(RB)–, –N(RB)S(O)–, –N(RB)S(O)2–, –S(O)N(RB)–, –S(O)2N(RB)–, –N(RB)C(O)N(RB')–, –N(RB)SO2N(RB')–, o –N(RB)S(O)N(RB')–;

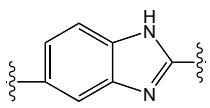
G3 es un C3-C12carbociclo o heterociclo de entre 3 y 12 miembros, y está opcionalmente sustituido con uno o más RG3; y

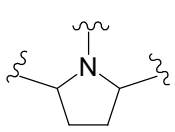
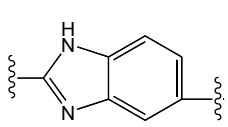
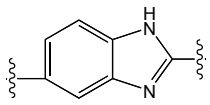
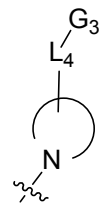
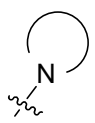
RG3 es cada en forma independiente, en cada caso, halógeno, –C1-C6alquilo, –C(O)C1-C6alquilo, –C1-C6haloalquilo, –O–C1-C6alquilo, –O–C1-C6haloalquilo, C3-C6carbociclo, o heterociclo de entre 3 y 6 miembros.

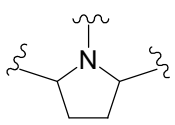
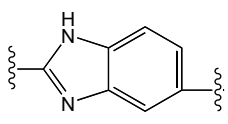
3. El compuesto o sal de acuerdo con la reivindicación 2, CARACTERIZADO PORQUE A es  y está opcionalmente sustituido con uno o más RA, y B es  y está opcionalmente sustituido con uno o más RA, y D es C6-C10arilo o heteroarilo de entre 5 y 10 miembros y está sustituido con uno o más RM.

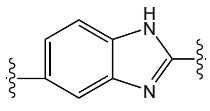
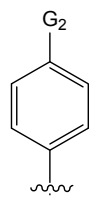
4. El compuesto o sal de acuerdo con la reivindicación 2, CARACTERIZADO PORQUE A es  y está opcionalmente sustituido con uno o más RA, y B es  y está opcionalmente sustituido con uno o más RA, y D es fenilo o piridilo y está sustituido con uno o más RM, donde al menos un RM es G2 que está sustituido con L4–G3 y opcionalmente sustituido con uno o más RG2.

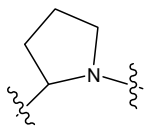
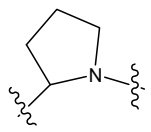
5. El compuesto o sal de acuerdo con la reivindicación 2, CARACTERIZADO PORQUE X es  y está opcionalmente sustituido con uno o más RA, A es  y está opcionalmente sustituido con uno o más RA, y B es

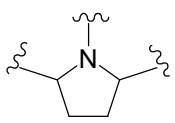
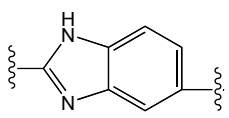
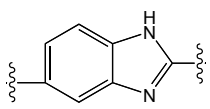
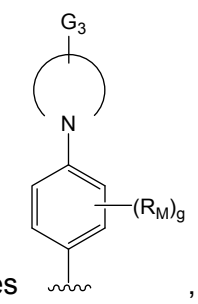
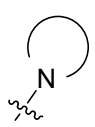
 y está opcionalmente sustituido con uno o más RA, y D es fenilo o piridilo y está sustituido con uno o más RM, y donde al menos un RM es  que es un heterociclo monocíclico que contiene nitrógeno de entre 4 y 8 miembros opcionalmente sustituido con uno o más RG2.

6. El compuesto o sal de acuerdo con la reivindicación 2, CARACTERIZADO PORQUE X es  y está opcionalmente sustituido con uno o más RA, A es  y está opcionalmente sustituido con uno o más RA, y B es  y está opcionalmente sustituido con uno o más RA, y D es fenilo o piridilo y está sustituido con uno o más RM, y al menos un RM es  , donde  es un heterociclo monocíclico que contiene nitrógeno de entre 4 y 8 miembros opcionalmente sustituido con uno o más RG2.

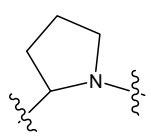
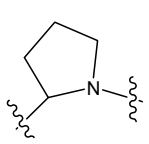
7. El compuesto o sal de acuerdo con la reivindicación 2, CARACTERIZADO PORQUE X es  y está opcionalmente sustituido con uno o más RA, A es  y está opcionalmente sustituido con uno o más RA, y B es

 y está opcionalmente sustituido con uno o más RA, y D es  y está opcionalmente sustituido con uno o más RM adicionales.

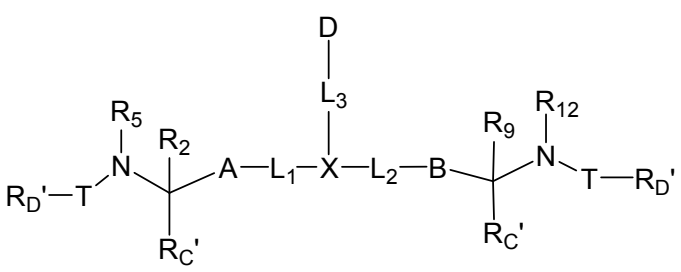
8. El compuesto o sal de acuerdo con la reivindicación 7, CARACTERIZADO PORQUE R1 es hidrógeno, y R2 y R5 tomados junto con los átomos a los cuales están unidos forman  que está sustituido con 0, 1, 2, 3, o 4 RA, donde R8 es hidrógeno, y R9 y R12 tomados junto con los átomos a los cuales están unidos forman  que está sustituido con 0, 1, 2, 3, o 4 RA, y donde cada T' es un enlace.

9. El compuesto o sal de acuerdo con la reivindicación 2, CARACTERIZADO PORQUE X es  y está opcionalmente sustituido con uno o más RA, A es  y está opcionalmente sustituido con uno o más RA, y B es  y está opcionalmente sustituido con uno o más RA, y D es  , donde G3 es fenilo opcionalmente sustituido con uno o dos RG3; g es 0, 1, o 2; RM es en forma independiente en cada caso fluoro, cloro, metilo, metoxi, trifluorometilo, o trifluorometoxi; y  es un heterociclo monocíclico que contiene nitrógeno de entre 4

y 8 miembros opcionalmente sustituido con uno o más RG2.

10. El compuesto o sal de acuerdo con la reivindicación 9, CARACTERIZADO PORQUE R1 es hidrógeno, y R2 y R5 tomados junto con los átomos a los cuales están unidos forman  que está sustituido con 0, 1, 2, 3, o 4 RA, donde R8 es hidrógeno, y R9 y R12 tomados junto con los átomos a los cuales están unidos forman  que está sustituido con 0, 1, 2, 3, o 4 RA, y donde cada T' es un enlace.

11. Un compuesto CARACTERIZADO PORQUE es de Fórmula IB, o una sal aceptable farmacéuticamente del mismo,



IB

donde:

RC' se selecciona en forma independiente entre RC;

RD' se selecciona en forma independiente entre RD;

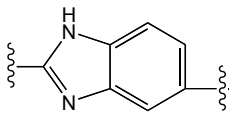
R2 y R5, tomados junto con los átomos a los cuales están unidos, forman un heterociclo de entre 3 y 12 miembros que está opcionalmente sustituido con uno o más RA;

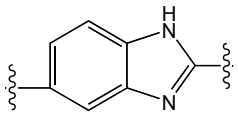
R9 y R12, tomados junto con los átomos a los cuales están unidos, forman un heterociclo de entre 3 y 12 miembros que está opcionalmente sustituido con uno o más RA;

X es C3-C12carbociclo o heterociclo de entre 3 y 12 miembros, y está opcionalmente sustituido con uno o más RA o RF;

L1 y L2 se seleccionan en forma independiente entre sí entre un enlace; o C1-C6alquileno, C2-C6alquenileno o C2-C6alquinileno, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más RL;

L3 es un enlace o –LS–K–LS'–, donde K se selecciona entre un enlace, –O–, –S–, –N(RB)–, –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(RB)–, –N(RB)C(O)–, –N(RB)C(O)O–, –OC(O)N(RB)–, –N(RB)S(O)–, –N(RB)S(O)2–, –S(O)N(RB)–, –S(O)2N(RB)–, –C(O)N(RB)C(O)–, –N(RB)C(O)N(RB')–, –N(RB)SO2N(RB')–, o –N(RB)S(O)N(RB')–;

A es  y está opcionalmente sustituido con uno o más RA;

B es  y está opcionalmente sustituido con uno o más RA;

D es C3-C12carbociclo o heterociclo de entre 3 y 12 miembros que está sustituido con J y opcionalmente sustituido con uno o más RA, donde J es C3-C12carbociclo o heterociclo de entre 3 y 12 miembros y está opcionalmente sustituido con uno o más RA;

T se selecciona en forma independiente en cada caso entre un enlace, –LS–, –LS–M–LS'–, o –LS–M–LS'–M'–LS''–, donde M y M' se seleccionan en forma independiente entre sí en cada caso entre un enlace, –O–, –S–, –N(RB)–, –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(RB)–, –N(RB)C(O)–, –N(RB)C(O)O–, –OC(O)N(RB)–, –N(RB)S(O)–, –N(RB)S(O)2–, –S(O)N(RB)–, –S(O)2N(RB)–, –C(O)N(RB)C(O)–, –N(RB)C(O)N(RB')–, –N(RB)SO2N(RB')–, –N(RB)S(O)N(RB')–, C3-C12carbociclo o heterociclo de entre 3 y 12 miembros,

y donde dicho C3-C12carbociclo y heterociclo de entre 3 y 12 miembros están opcionalmente sustituidos en forma independiente entre sí en cada caso con uno o más RA;

RD se selecciona en forma independiente en cada caso entre hidrógeno o RA;

RA se selecciona en forma independiente en cada caso entre halógeno, nitro, oxo, fosfonoxi, fosfono, tioxo, ciano, o –LS–RE, donde dos RA adyacentes, tomados junto con los átomos a los cuales están unidos y cualquier otro átomo entre los átomos a los cuales están unidos, pueden formar opcionalmente carbociclo o heterociclo;

RB y RB' se seleccionan en forma independiente entre sí en cada caso entre hidrógeno; o C1-C6alquilo, C2-C6alquenilo o C2-C6alquinilo, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano o carbociclo o heterociclo de entre 3 y 6 miembros; o carbociclo o heterociclo de entre 3 y 6 miembros; donde cada carbociclo o heterociclo de entre 3 y 6 miembros en RB o RB' está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C1-C6alquilo, C2-C6alquenilo, C2-C6alquinilo, C1-C6haloalquilo, C2-C6haloalquenilo o C2-C6haloalquinilo;

RC se selecciona en forma independiente en cada caso entre hidrógeno, halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo o ciano; o C1-C6alquilo, C2-C6alquenilo o C2-C6alquinilo, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano o

carbociclo o heterociclo de entre 3 y 6 miembros; o carbociclo o heterociclo de entre 3 y 6 miembros; donde cada carbociclo o heterociclo de entre 3 y 6 miembros en RC está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C1-C6alquilo, C2-C6alquenilo, C2-C6alquinilo, C1-C6haloalquilo, C2-C6haloalquenilo o C2-C6haloalquinilo;

RE se selecciona en forma independiente en cada caso entre –O–RS, –S–RS, –C(O)RS, –OC(O)RS, –C(O)ORS, –N(RSRS'), –S(O)RS, –SO2RS, –C(O)N(RSRS'), –N(RS)C(O)RS', –N(RS)C(O)N(RS'RS''), –N(RS)SO2RS', –SO2N(RSRS'), –N(RS)SO2N(RS'RS''), –N(RS)S(O)N(RS'RS''), –OS(O)–RS, –OS(O)2–RS, –S(O)2ORS, –S(O)ORS, –OC(O)ORS, –N(RS)C(O)ORS', –OC(O)N(RSRS'), –N(RS)S(O)–RS', –S(O)N(RSRS'), –P(O)(ORS)2, o –C(O)N(RS)C(O)–RS'; o C1-C6alquilo, C2-C6alquenilo o C2-C6alquinilo, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo o ciano; o C3-C6carbociclo o heterociclo de entre 3 y 6 miembros, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C1-C6alquilo, C2-C6alquenilo, C2-C6alquinilo, C1-C6haloalquilo, C2-C6haloalquenilo, C2-C6haloalquinilo, C(O)ORS, o –N(RSRS');

RF se selecciona en forma independiente en cada caso entre C1-C10alquilo, C2-C10alquenilo o C2-C10alquinilo, cada uno de los cuales contiene 0, 1, 2, 3, 4 o 5 herteroátomos seleccionados entre O, S o N y está opcionalmente sustituido con uno o más RL; o –(RX–RY)Q–(RX–RY'), donde Q es 0, 1, 2, 3 o 4, y cada

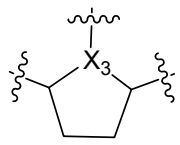
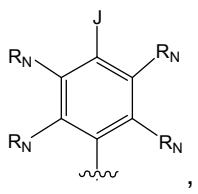
RX es en forma independiente O, S o N(RB), donde cada RY es en forma independiente C1-C6alquileno, C2-C6alquenileno o C2-C6alquinileno cada uno de los cuales está opcionalmente sustituido en forma independiente con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo o ciano, y donde cada RY' es en forma independiente C1-C6alquilo, C2-C6alquenilo o C2-C6alquinilo cada uno de los cuales está opcionalmente sustituido en forma independiente con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo o ciano;

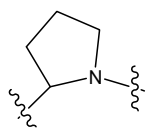
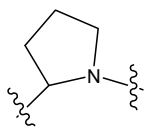
RL se selecciona en forma independiente en cada caso entre halógeno, nitro, oxo, fosfonoxi, fosfono, tioxo, ciano, –O–RS, –S–RS, –C(O)RS, –OC(O)RS, –C(O)ORS, –N(RSRS'), –S(O)RS, –SO2RS, –C(O)N(RSRS') o –N(RS)C(O)RS'; o C3-C6carbociclo o heterociclo de entre 3 y 6 miembros, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C1-C6alquilo, C2-C6alquenilo, C2-C6alquinilo, C1-C6haloalquilo, C2-C6haloalquenilo o C2-C6haloalquinilo; donde dos RL adyacentes, tomados junto con los átomos a los cuales están unidos y cualquier otro átomo entre los átomos a los cuales están unidos, pueden formar opcionalmente carbociclo o heterociclo;

LS, LS' y LS'' se seleccionan en forma independiente entre sí en cada caso entre un enlace; o C1-C6alquileno, C2-C6alquenileno o C2-C6alquinileno, cada uno de los cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más RL; y

RS, RS' y RS'' se seleccionan en forma independiente entre sí en cada caso entre hidrógeno; C1-C6alquilo, C2-C6alquenilo o C2-C6alquinilo, cada uno de los

cuales está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, –O–C1-C6alquilo, –O–C1-C6alquilen–O–C1-C6alquilo, o carbociclo o heterociclo de entre 3 y 6 miembros; o carbociclo o heterociclo de entre 3 y 6 miembros; donde cada carbociclo o heterociclo de entre 3 y 6 miembros en RS , RS' o RS' está opcionalmente sustituido en forma independiente en cada caso con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C1-C6alquilo, C2-C6alquenilo, C2-C6alquinilo, C1-C6haloalquilo, C2-C6haloalquenilo o C2-C6haloalquinilo.

12. El compuesto o sal de acuerdo con la reivindicación 11, CARACTERIZADO PORQUE X es  y está opcionalmente sustituido con uno o más RA o RF, y X3 es N y está directamente unido a –L3–D, donde L1, L2 y L3 son un enlace, donde D es  , y cada RN es en forma independiente RD, donde J es C3-C6carbociclo o heterociclo de entre 3 y 6 miembros y está sustituido con un C3-C6carbociclo o heterociclo de entre 3 y 6 miembros que está opcionalmente sustituido en forma independiente con uno o más sustituyentes seleccionados entre halógeno, hidroxi, mercapto, amino, carboxi, nitro, oxo, fosfonoxi, fosfono, tioxo, formilo, ciano, C1-C6alquilo, C2-C6alquenilo, C2-C6alquinilo, C1-C6haloalquilo, C2-C6haloalquenilo, C2-C6haloalquinilo, C(O)ORS o –N(RSRS'), y J está opcionalmente sustituido con uno o más RA, donde R2 y R5, tomados junto con los átomos a los cuales están unidos, forman

 que está opcionalmente sustituido con uno o más RA, donde R9 y R12, tomados junto con los átomos a los cuales están unidos, forman  que está opcionalmente sustituido con uno o más RA, donde -T-RD' es –C(O)–LY'–RD', –C(O)O–LY'–RD', –C(O)–LY'–N(RB)C(O)–LS''–RD', –C(O)–LY'–N(RB)C(O)O–LS''–RD', –N(RB)C(O)–LY'–N(RB)C(O)–LS''–RD', –N(RB)C(O)–LY'—N(RB)C(O)O–LS''–RD', o –N(RB)C(O)–LY'—N(RB)–LS''–RD', y donde LY' es en forma independiente en cada caso LS'.

13. Un proceso para preparar un compuesto de la invención, CARACTERIZADO PORQUE comprende un paso descrito en uno de los Esquemas, Procedimientos Generales o Ejemplos descritos en la presente.

14. Un intermediario CARACTERIZADO PORQUE se describe en uno de los Esquemas, Procedimientos Generales o Ejemplos descritos en la presente.

15. El compuesto CARACTERIZADO PORQUE es {(2S,3R)-1-[(2S)-2-{5-[(2R,5R)-1-{3,5-difluoro-4-[4-(4-fluorofenil)piperidin-1-il]fenil}-5-(6-fluoro-2-{(2S)-1-[N-(metoxicarbonil)-O-metil-L-treonil]pirrolidin-2-il}-1H-benzimidazol-5-il)pirrolidin-2-il]-6-fluoro-1H-benzimidazol-2-il}pirrolidin-1-il]-3-metoxi-1-oxobutan-2-il}carbamato de metilo, o una sal aceptable farmacéuticamente del mismo.

16. Una composición farmacéutica CARACTERIZADA PORQUE comprende el compuesto de la reivindicación 15 o dicha sal.17. El compuesto CARACTERIZADO PORQUE es {(2S)-1-[(2S)-2-{5-[(2R,5R)-1-[3,5-difluoro-4-(4-fenilpiperidin-1-il)fenil]-5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-benzimidazol-5-il}pirrolidin-2-il]-1H-benzimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo, o una sal aceptable farmacéuticamente del mismo.

18. Una composición farmacéutica CARACTERIZADA PORQUE comprende el

compuesto de la reivindicación 17 o dicha sal.19. El compuesto CARACTERIZADO PORQUE es {(2S,3R)-1-[(2S)-2-{5-[(2R,5R)-1-{4-[4-(2,6-difluorofenil)piperazin-1-il]-3,5-difluorofenil}-5-(6-fluoro-2-{(2S)-1-[N-(metoxicarbonil)-O-metil-L-treonil]pirrolidin-2-il}-1H-benzimidazol-5-il)pirrolidin-2-il]-6-fluoro-1H-benzimidazol-2-il}pirrolidin-1-il]-3-metoxi-1-oxobutan-2-il}carbamato de metilo, o una sal aceptable farmacéuticamente del mismo.

20. Una composición farmacéutica CARACTERIZADA PORQUE comprende el compuesto de la reivindicación 19 o dicha sal.21. El compuesto CARACTERIZADO PORQUE es {(2S)-1-[(2S)-2-{5-[(2R,5R)-1-(4-tert-butilfenil)-5-{5-fluoro-2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-benzimidazol-6-il}pirrolidin-2-il]-6-fluoro-1H-benzimidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo, o una sal aceptable farmacéuticamente del mismo.

22. Una composición farmacéutica CARACTERIZADA PORQUE comprende el compuesto de la reivindicación 21 o dicha sal.

COMPUESTOS ANTIVIRALES

RESUMEN

Compuestos eficaces para inhibir la replicación del virus de la hepatitis C (“HCV”); procesos de elaboración de tales compuestos, composiciones que los comprenden y métodos de uso de los mismos para tratar una infección por HCV.